AMITY UNIVERSITY HARYANA

CENTRAL INSTRUMENT RESEARCH FACILITY

CENTRAL INSTRUMENT RESEARCH FACILITY (CIRF)
AMITY UNIVERSITY HARYANA

ABOUT CIRF

Central Instrument Research Facility (CIRF) was established at the Amity University, Haryana in Sep. 2019. The purpose of establishing this facility is to provide the scientific community (within Amity University and external researchers, both from academia and industry) with state-of-the-art analytical cutting edge access to Microscopy, Flow cytometry, Centrifuge, Chromatography and Spectrometric techniques for imaging, cell analysing, separation, identification and quantitation of biomolecules like protein, organic compound, drugs, food and pesticide etc. CIRF is working as Analytical Research and Development Division and provides:

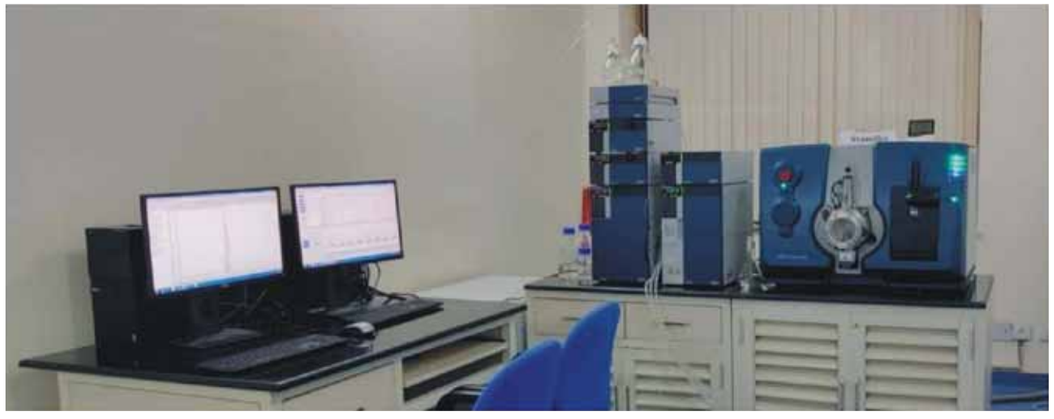
- A comprehensive, qualitative, and quantitative profiling of biomolecular species, organic samples with high sample throughput using FTIR, UV-Vis, Fluorescence spectrometric technologies, Chromatographic, Imaging, Flow-cytometric, DLS, DSC, Modular Spectrometer and Centrifugation technique.
- Helps with the experimental design, analysis, and data interpretation.
- Blended training to students/researchers/industries on general principles of imaging, cell analysing, separation, identification and quantitation through workshops organized at the regular intervals throughout the year with the full support of industries
- New analytical methods for different types of sample analysis to make full use of the technology for exploring new dimensions in research and development.

CIRF Houses following Functional Instruments:

Central Instrument Research Facility (CIRF) has installed LCMS (Q-Trap 4500 (SCIEX), Confocal microscope (Nikon A1 R HD 25 Model) Fluorescence microscope (TS2FL, Nikon), Flow cytometer (BD FACS), Gel-doc (GE- Health care), FTIR (630), UV-visible Spectrophotometer (Cary 100) and fluorimeter (Cary eclipse, Agilent), UPLC- PDA (Acuity H class, Waters), Cold and Ultra centrifuge (Beckman Coulter), DSC-STA 8000, Modular spectrophotometer (Trans/Abs/Ref),DLS(Zeta) and Uv-Vis spectrophotometer(solid).

Web page address:https://www.amity.edu/gurugram/central-instrument-research-facility.aspx

LIQUID CHROMATOGRAPHY WITH MASS SPECTROSCOPY



Liquid Chromatography with Mass spectroscopy: a triple stage quadrupole/linear ion trap mass spectrometer, Q-Trap 4500 (SCIEX), equipped with ion sources (turbo V) Electrospray ionization (ESI), and Atmospheric pressure chemical ionization (APCI), autosampler, column oven with HPLC (Exion LC-AC) system. The system is ideal for laboratories requiring ultimate robustness, ruggedness, and reliability for high-throughput screening of many compounds in many samples every day.

With the quantitative performance of a triple quad system and additional enhanced scan functionality of QTRAP, one is able to develop new methods and improve results for the existing workflows. The integrated linear ion trap (LIT) enables more accurate detection, quantification, and confirmation of your compounds – without added laborious or time-consuming sample prep. The enhanced product ion (EPI) functionality of QTRAP allows to acquire a complete MS/MS spectrum to accompany your MRM quantitation for every compound detected in your samples. Cross reference this 'compound fingerprint' with an integrated library and deliver ultimate confirmation and report your analysis without doubt. The unique ability to capture MRM and enhanced product ion confirmation scans in one injection, without the need for long and inefficient chromatography, enables reliable screening for more compounds in each analysis, without compromising data quality. This all leads to better throughput, without investing more time and resources. Liquid Chromatography with Mass spectroscopy offers the following services for internal and external users:

- ESI-MS based analysis (Nominal mass/ Molecular weight determination)
- MS/MS analysis, UPLC-MS analysis (qualitative)
- UPLC-MS/MS analysis (qualitative)
- UPLC-MS/MS for targeted analysis of lipids/small molecules
- UPLC-MS/MS for targeted analysis of lipids/small molecules including data analysis by Multi Quant Software
- UPLC-MS/MS for untargeted analysis of lipids/small molecules
- UPLC-MS/MS for untargeted analysis of lipids/small molecules including data analysis by Lipid-view Software.

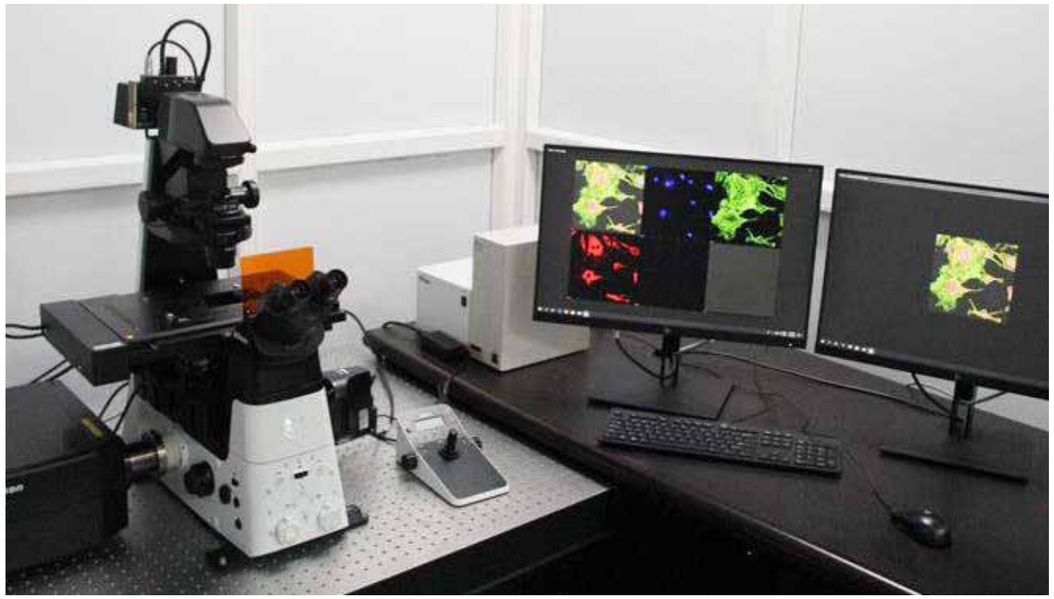
ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHY (UPLC)

The Ultra Performance Liquid Chromatography (UPLC) is used for separation of individual compounds in a mixture. It is equipped with PDA detector and quaternary solvent system . It is one of the widely used techniques in the fields like: clinical research, biochemical research and Industrial quality control, etc. The principle involved in UPLC testing is the separation of compounds in a mixture. Segregation of compounds is due to their relative differences in their retention time or RT. For example, all the monoamines like dopamine, epinephrine, and serotonin can be separated and estimated in a single run.

UPLC H- Class offers:

- Determination of Pesticides in Ground water,
- Improved Resolving Power in Peptide Maps,
- Rapid Dose Formulation Analysis,
- Analysis of Traditional Chinese Medicines (TCM),
- Identification of Metabolites and In Manufacturing / Quality Assurance (QA) / Quality Control (QC).

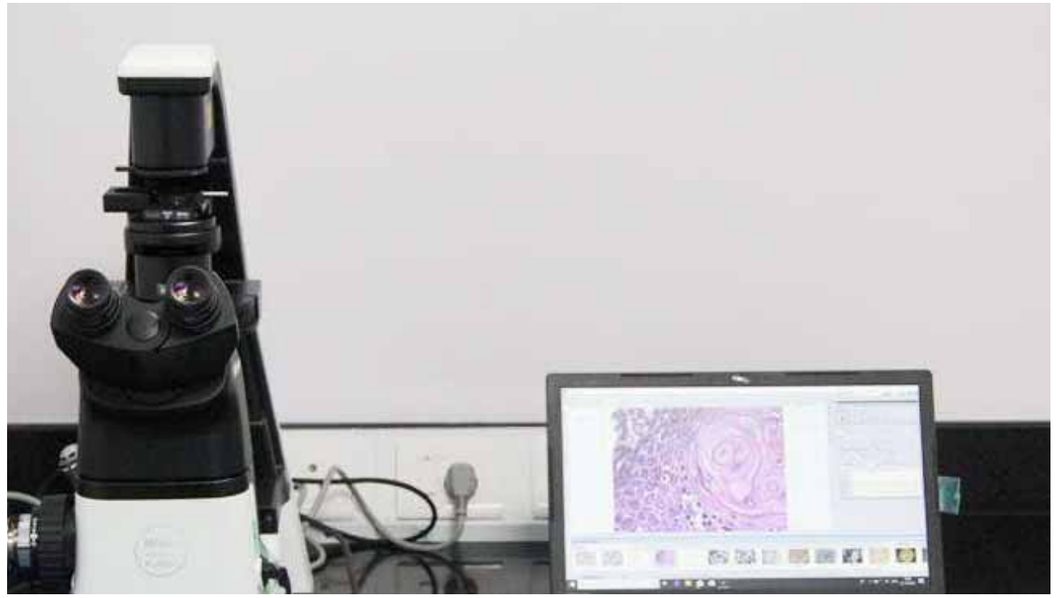
CONFOCAL MICROSCOPY



It has largest field of view (25 mm) in its field, when combined with the justified Ti 2-E inverted microscope, the imaging area of A1 R HD 25 is nearly twice the conventional FOV of 18 mm. High-definition imaging up to 1k x 1K, 1024 x 1024 pixels enables acquisition of high-resolution, high-quality images at lower magnification, enabling compatibility with a wide range of samples. High speed imaging capability up to 720 fps, in combination with a large field of view, dramatically increases imaging throughput. The scanning method reduces the exposure time of the sample to excitation light, minimizing photo toxicity and photo bleaching Capture large scale overview images as well as high magnification images with the same instrument. The 25 mm FOV of the A1R HD 25 is effective for observation of large samples, while its 1k x 1k high definition is ideal for the observation of minute structures. Highly sensitive detector options for various types of florescence labels. Confocal microscope offers the following services for internal as well as external users:

- 3D imaging,
- Colocalization,
- FLIP Fluorescence
- Fluorescence Recovery After Photobleaching Fluorescence Resonance Energy Transfer
- Photo activation, Time lapse Microscopy.

FLUORESCENCE MICROSCOPY

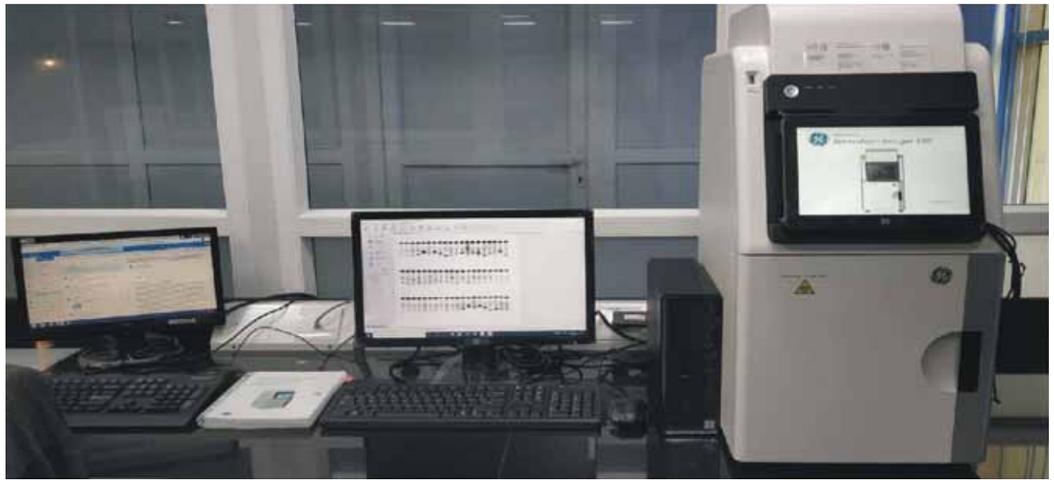


Fluorescence microscope uses fluorescence and phosphorescence instead of, or in addition to, reflection and absorption to study specimens. A sample is illuminated with light of a wavelength which excites fluorescence in the sample. Typical components of a fluorescence microscope are a light source, excitation filter, the dichroic mirror (or dichroic beam splitter), and emission filter. Fluorescence microscopes can be used for many different applications including localization of specific proteins, determining the shape of organs, cells, and intracellular structures, studying protein interactions or conformation, examining ion concentration and observing live cells. Look for ease of use, ergonomic features, multiple modes, high resolution and the possibility to upgrade.

It offers :

- Imaging structural components of small specimens, such as cells,
- Conducting viability studies on cell populations (are they alive or dead?),
- Imaging the genetic material within a cell (DNA and RNA)
- Viewing specific cells within a larger population with techniques such as FISH.

GEL DOCUMENTATION CENTRE



Gel doc has Camera Peltier cooled Fujifilm Super CCD, dynamic Range is 16-bit, 4.8 orders of magnitude, resolution of image 2048×1536 cum 3.2 megapixels (CCD) 2816×2048, 5.8 megapixels, max. (image) and Lens FUJINON Lens f/0.85 43 mm, W×D×H 360×485×785 mm.

It offers:

- The analysis of proteins and antibodies
- Analysis of nucleic acid immobilized in polyacrylamide or agarose gels
- Analysis of membranes or microarrays.

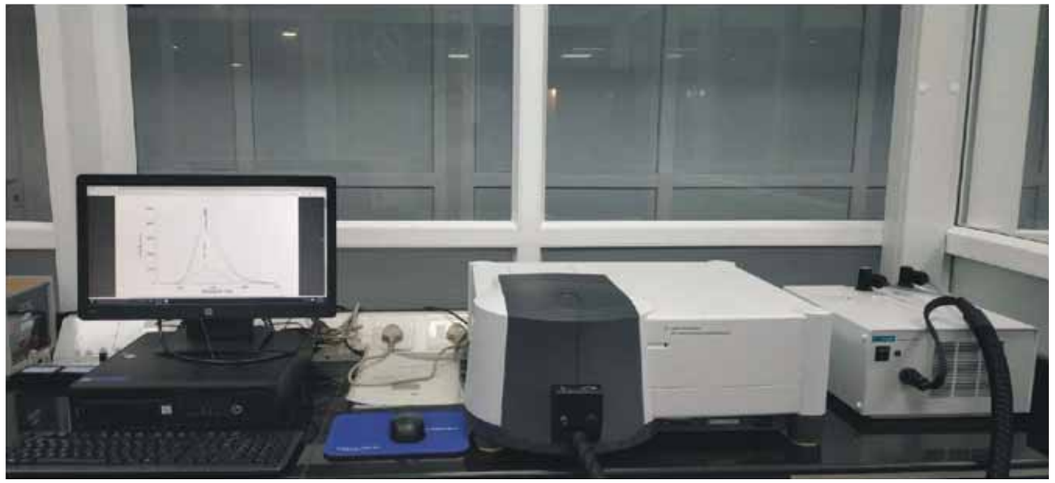
BD FACS FLOW CYTOMETER

BD FACS is a high-performance flow cytometer designed to support both routine clinical analysis and clinical research. With an integrated solution that combine instrument, software reagents and services, BD FACS lyric™ provides. clinicians and scientists with accurate, reliable and repeatable result -test to test, instrument to instrument and site to site, regardless of the assay complexity or operator experience level. Solid-state laser specifications is Blue laser: 488 nm, 20 mw, Red laser: 640 nm, 40 mw, Optics: excitation lasers up to 10 colour with below configuration, Six-colour: two-laser (blue, red) (4-2), Detection channels, Forward scatter (fsc), side scatter (ssc) and up to 10 fluorescence. A flexible, high-performance instrument in a compact footprint. The system is available in 4, 6, 8, 10 or 12 colours and equipped with a blue, red and violet laser depending on the configuration. Absorbance /excitation 488 nm (blue), 640 nm (red), 405 (violet). The fluidics design enables a large selection of sample input devices. For manual acquisition, choose from 12 x 75-mm tubes, microcentrifuge tubes (~500-µL) or large (up to 50-mL) conical tubes for continuous sample acquisition. For automated acquisition, the optional BD FACS™ Universal Loader provides walkaway operation with samples loaded in either microtiter plates or 12 x 75- mm tube racks. Runs at up to 35,000 events per second. It Can achieve sample carryover =0.05% and No limit on events acquired.

FACS offers:

- Cellular uptake studies,
- Cancer Studies,
- Detection of apoptosis with Annexin V labelling and Cell Cycle analysis.

FLUORESCENCE SPECTROPHOTOMETER



Fluorescence Spectrophotometer's measuring wavelength range of the instrument is 190-1100 nm. Manual polarizer holder accessory. Multi cell holder and Peltier system for heating up to 100 °Horizontal slit orientation for increased viewing. Light source: Xenon pulse lamp. Wavelength accuracy: 0.5 – 0.07 nm. Wavelength reproducibility: 0.1 nm and 2 bandpass filters in the range of 250–395 nm and 335–620 nm with WinFLR Software.

Fluorescence Spectrophotometer offers:

- Fluorescence measurements
- Phosphorescence measurements
- Chemiluminescence measurements
- Bioluminescence measurements

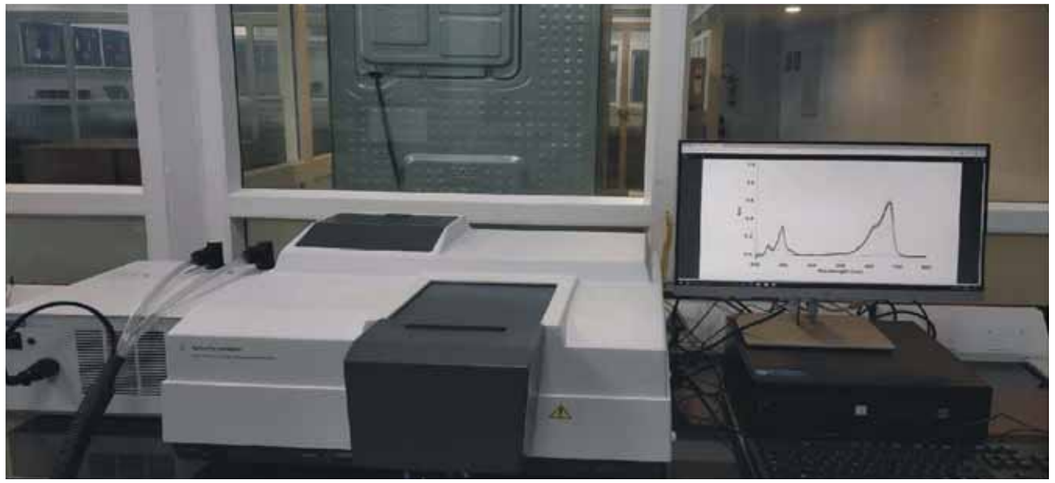
FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

FTIR has Spectral range 4000–650 cm-1 with KBr optics as well as ATR. Wavenumber reproducibility 0.005 cm 1. Single Reflection Diamond ATR for solid or liquid sample. (360° swivel press available) and Resolution Pro software and Spectral Libraries of 10,000 compounds including pharma, polymer etc.

FTIR offers:

- Quantitative and qualitative information of Functional groups of chemical compounds for routine analysis of solids and liquid sample.

UV-VIS SPECTROPHOTOMETER



UV-Visible spectrophotometer is a Double beam UV/Vis spectrophotometer, wavelength range is 190 to 1100 nm with R928 PMT detector. Versatile set of accessories including Peltier system, multicell liquid sample holders (cuvette as small as 8 µl). Wavelength accuracy ± 0.02 nm; UV Vis limiting resolution 0.189 nm. WinUV software – modular design provides a wide range of applications via a simple interface. UV-Visible spectrophotometer offers:

- Nanomaterial characterization,
- Detection of organic materials in water, food and agriculture, DNA and protein quantification and measuring small volumes,
- Monitoring kinetics of reactions that occur at sub-second rates and study of denaturation of biomolecules at elevated temperature

UV-VIS SPECTROPHOTOMETER

Beckman Coulter's Optima XPN-100 Ultracentrifuge is a high-performance centrifuge optimized for spinning its two rotors at speeds approaching 70,000 rpm and 40,000 rpm (swinging bucket). Maximum speed 100,000 rpm with speed control of +- 2 rpm of set speed (above 1,000 rpm). Large touch screen display, energy efficient and real time run graphing. Optima XPN boasts additional enhancement that will simplify use, optimize control, security and increase productivity. Ultra-centrifuge offers:

- To separate components of a sample using relative centrifugal force.
- A wide range of applications ranging from separating cell organelles to measuring conformational changes in proteins.

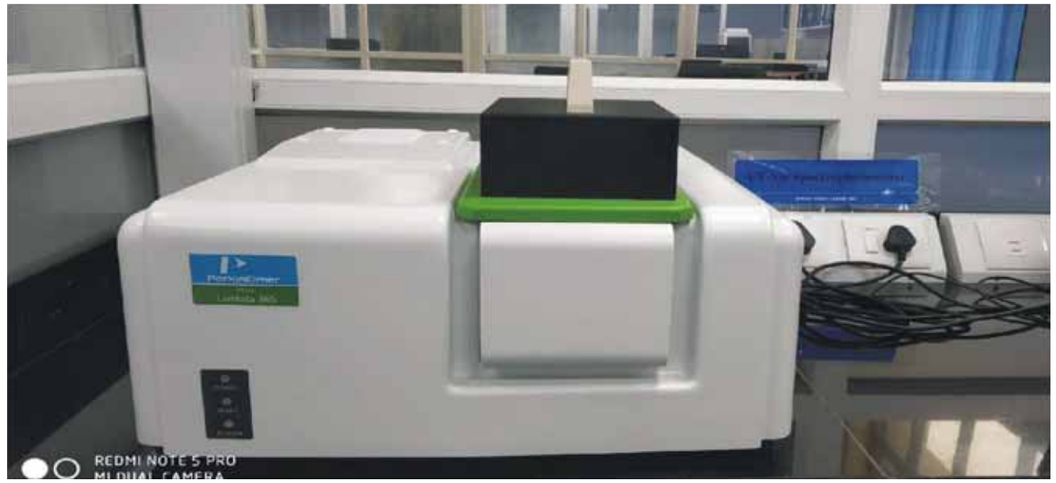
AVANTI JE BIOSAFE COLD CENTRIFUGE

Speed range is 300 to 20,000 rpm, refrigerated floor and temperature range is -10 °C to 40 °C. The Avanti J-E system generates maximum speeds up to 20,000 rpm and offers the capacity of processing from up-to 250 ml in under 10 minutes. It achieves a high degree of separation in a size compatible with your operations. The Avanti J-E's high torque switched reluctance (*SR) direct drive technology achieves faster acceleration and deceleration with gentle precision that delivers the fastest separations in the shortest run times, unattainable by standard high speed centrifuge systems. Shorter run times mean more discovery time for you. For clinical research applications tubes, and bottles for J 20 & J 16.2 rotors spin volumes of 50 and 250mL for effective blood component isolation with a variety of gradient kits.

It offers:

- Beside routine centrifuge applications such as cell pelleting from large volumes of cultures,
- Separation of macromolecules/ ligand binding kinetic studies
- Separation of various lipoprotein fractions from plasma
- Deprotonation of physiological fluids for amino acid analysis.

UV-VIS SPECTROPHOTOMETER



Lambda 365 is a double beam UV/Vis spectrophotometer which has an interface of Tungsten-halogen and Deuterium lamps. Operating Range is 190 - 1100 nm and temperature range is 15 °C to 35 °C. The system delivers a variable spectral bandwidth capability from 0.5 nm to 20 nm. It has a wide range of accessories, including multicell changers and a solid sample accessory for transmission and reflectance.

It offers:

- Used for characterizing nanoparticles in suspension
- Determine the absorption properties of metallic nanoparticles (through plasmonic absorbance)
- Study the sorption, diffusion and release properties of nanoparticles/nanomaterials
- Investigations in DLS have to be preceded by measurement of absorption spectrum of protein

MODULAR SPECTROMETER (ABS/REF/TRANS)

A Modular Spectrometer with 3648 pixels CCD linear array detector that has a high resolution of up to 0.03 nm (FWHM). The system includes an incident slit, collimating mirror, dispersion element (grating), focusing optical system and detector. Light is collected through the optical fibre into the spectrometer slit then the spectral information can be read out by the software.

It offers:

- Characterizing nanoparticles and thus has applications in the fields of Medical Sciences, Material Science, Nano Science, Food Safety, Environmental Sciences, Biological Science, Forensic Science and more
- In different modular setups user can perform Fluorescence, Photoluminescence, Absorbance, Transmittance, Reflection, Irradiance and more
- As the optical properties (absorbance, transmission etc.) depend on the surface defects, surface roughness, the prior knowledge of such properties in metal oxides using a Modular Spectrometer is very important in properly analyzing the information obtained from the Zeta sizer.

DLS-ZETA SIZER NANO SERIES

Zetasizer Nano ZS-Malvern can measure hydrodynamic size, zeta potential and molecular weight in particle dispersions, emulsions and molecular solutions. Works in size range maximum (diameter) 0.3nm - 10 microns even at a minimum sample volume of 12µL. Temperature control range is 0°C - 90°C +/- 0.1°C. Has a Reusable Dip cell for zeta potential measurements.

It offers:

- Estimating particle size distribution of the nanoparticles
- Calculate the average size for the entire population of nanoparticles (crystalline and amorphous)
- Surface charge in terms of electric potential (V) of the nanoparticle system which is an Important index of the stability of the nanoparticles
- Knowledge of surface charge of nanoparticles helps in designing nanocarriers for targeted drug delivery as it enables to determine the possible nature of drug receptor interactions
- It also helps us to understand the aggregated state of various biomolecules like protein, lipids etc.

DSC-STA 8000

STA 8000 has a sensor which is a pure platinum pan holder and there is a separate platform for sample and reference. Balance design is top loading, single beam with a resolution of 0.2 µg. Balance measurement range is up to 1500 mg and temperature range is 15 ˚C to 1600 ˚C. Heating rate from ambient to 1000 ˚C: 0.1 to 100 ˚C/min and 1000 to 1600 ˚C: 0.1 to 25 ˚C/min. Cooling rates from 1600 ˚C to 100 ˚C is under 35 minutes with cooling water at 5 ˚C. Temperature accuracy is from ambient to 1000˚C ±0.5 ˚C and 1000 ˚C to 1600 ˚C ±1.0 ˚C. Runs on an advanced Pyris software.

It offers:

- Measure thermal stability of synthesized nanoparticles of metallic oxides, polymeric nanoparticles, graphene-based materials, their hybrids and composites
- Determine the residual water in polymeric nanoparticles and nanofibers which is important for successful application of these polymeric nanomaterials in the field of biomedical sciences and to understand weight loss or degradation of materials with respect to temperature
- Nano-Bio interaction
- Protein unfolding studies and studies of their oligomeric states

AMITY UNIVERSITY HARYANA

CIRF AT A GLANCE (2019-TILL PRESENT)

New Funded Projects (Total Resource Mobilization)	Rs. 15.0 Crore
Equipment Acquired Under New Funded Projects (Total New Assets Created)	Rs. ~6.0
Crore Revenue Generated (User Charges, Symposiums, Workshops)	Rs.3.5 Lac
Total Manpower Trained	29
Total Ph.D.s Produced	41
Total Ongoing Ph.Ds	118
Total Publications	424
Total Patents	36
Total Workshops/ Symposiums organized	9

CIRF OFFERS THE FOLLOWING SERVICES ON CHARGE BASIS

CENTRAL INSTRUMENT RESEARCH FACILITY (CIRF)				
Equipment	**Experiment**	**Amity University**	**Academic & Research Institutions**	**Private Industries/ other Laboratories**
1. UHPLC Mass spectro metry	1. ESI-MS based analysis Nominal mass/MW. Determination*	Rs.400 per sample	Rs.800 per sample	Rs.1500 per sample
	2. MS/MS analysis*	Rs. 300 (per Precursorion)	Rs.600 (per Precursorion)	Rs.1500 (per Precursorion)
	3. UPLC-MS analysis (Qualitative)	Rs. 1000 (per Precursorion)	Rs.2000 (per Precursorion)	Rs.4000 (per Precursorion)
	4. UPLC-MS/MS Analysis (Qualitative)	Rs.2500/sample (5 peaks, Rs 200 per additional peak)	Rs.5000/ sample (5 peaks, Rs 300 per additional peak)	Rs.10000/ sample (5 peaks, Rs 400 per additional peak)
	5. UPLC-MS/MS for Targeted analysis of Lipids/Small molecules	Rs 1000/ MRM/ analytical lipid unit	Rs 2500 MRM/ analytical lipid unit	Rs 4000 MRM/ analytical lipid unit
	6. UPLC-MS/MS for Targeted analysis of Lipids/Small molecules including data analysis by MultiQuant Software	Rs 1500 MRM/ analytical lipid unit	Rs 4000 MRM/ analytical lipid unit	Rs 5000 MRM/ analytical lipid unit
	7. UPLC-MS/MS for Untargeted analysis of Lipids/Small molecules	Rs.1500 sample	Rs.2500/ sample	Rs.5000/ sample
	8. UPLC-MS/MS for untargeted analysis of Lipids/Small molecules including data analysis by Lipid view Software	Rs.2500/ sample	Rs.5,000/ sample	Rs.10,000/ sample

USER CHARGES LIST 2020*				
1. Equipment		**Amity University**	**Academic & Research Institutions**	**Private Industries/ other Laboratories**
2. Confocal Microscope		Rs. 500/ hour	Rs.2000/ hour	Rs.3000/ hour
3. Fluorescence Inverted Microscope		Rs. 100/ hour	Rs.500/ hour	Rs. 800/ hour
4. FACS		Rs. 150/ hour or Rs.1000/ day	Rs.400/ hour or Rs.2500/ day	Rs.1000/ hour
5. Spectrofluorometer		Rs. 200/hour	Rs.600/ hour	Rs.1000/ hour
6. UV–Vis. Spectrophotometer		Rs. 100/ hour	Rs.400/ hour	Rs. 750/ hour
7. FTIR		Rs. 300 per sample	Rs.1000 per sample	Rs.2000 per sample
8. Ultracentrifuge		Rs. 800/ day or 200/ hour	Rs. 1500/ day or 500/ hour	Rs. 3000/ day or 1000/ hour
9. Cold centrifuge		Rs. 100/ hour	Rs.500/ hour	Rs. 800/ hour
10. UPLC	UPLC- PDA (Qualitative Analysis) *	Rs. 500/ day	Rs. 1500/ day sample	Rs. 4000/ day sample
	UPLC- PDA (Quantitative Analysis) *	Rs. 500/ day	Rs. 2500/ day sample	Rs. 4000/ day sample

INTERNAL AND EXTERNAL USERS OF CIRF

Kaustuv Bandyopadhyay, AUH	**Vaishali Rana,** AUH	**Sudhir Kumar,** Premas biotech
Ujjaini Dasgupta, AUH	**Munish,** AUH	**Ambika Baru,** Premas biotech
Zeeshan Fatima, AUH	**Dipti Vyas,** AUH	**Savneet Kaur,** ILBS
Krishna Murari Sinha, AUH	**Suman Sharma,** AUH	**Vikas Lahariya,** AHU
Ranjita Ghosh, AUH	**Garima Singh,** AUH	**Deepika Yadav,** AHU
Manikandan, AUH	**Anshu Chauhan,** AUH	**Sujata Singh,** AUH
Gargi Bagchi, AUH	**Praveen Kumar,** AUH	**Pratibha Sharma,** AUH
Rajendra Prasad, AUH	**Manisha,** AUH	**Niti Srivastava,** AUH
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Juli Singh, AUH	**Anshu Rao,** AUH	**Ondrila,** AUH
Suresh Kalinga, AUH	Sandeep Hans, AUH	**Nihal Medhatwal,** AUH
Seema Pathak, AUH	**Akanksha Bhatt,** AUH	**Trishna Pani,** AUH
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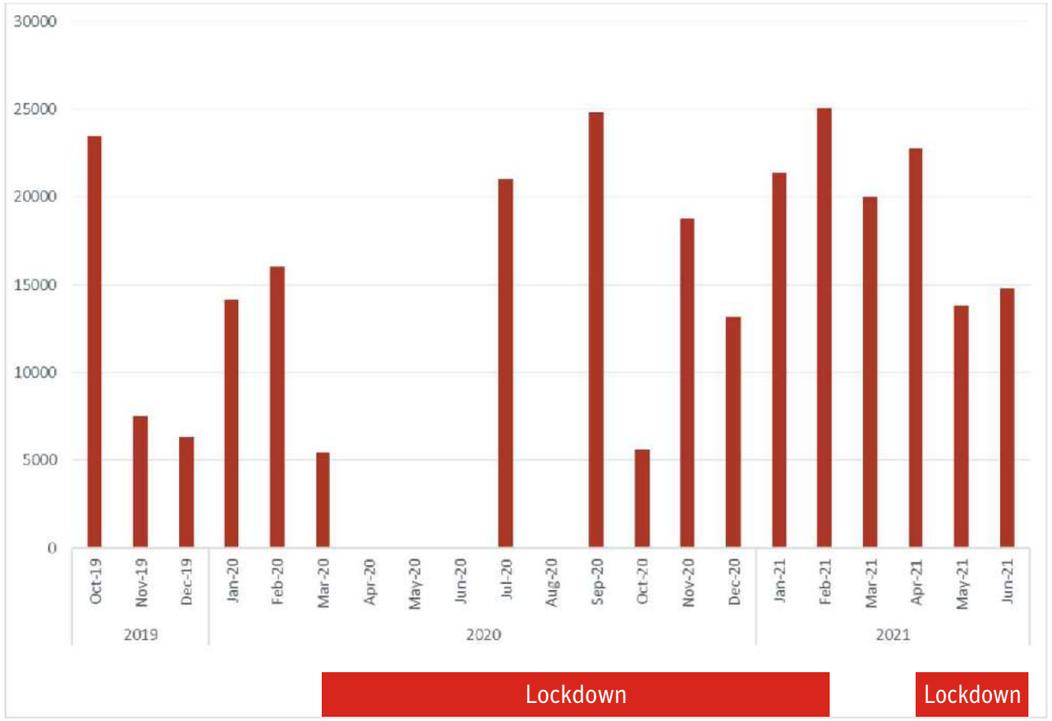
Basharat Ali, JNU	**Pankaj Sharma,** RCB	**Devashish Mehta,** AUH
Nootan Kaushik, AUUP	**Judith Berman,** TELAVIV, Israel	**Suman Kumari**
Amandeep Saini	**Syed Vilal Jilani,** AUH	**Meenu Yadav**
Durga Yadav	**Mamata**	**Rajnee Yadav**

REVENUE GENERATED FORM CIRF FACILITIES



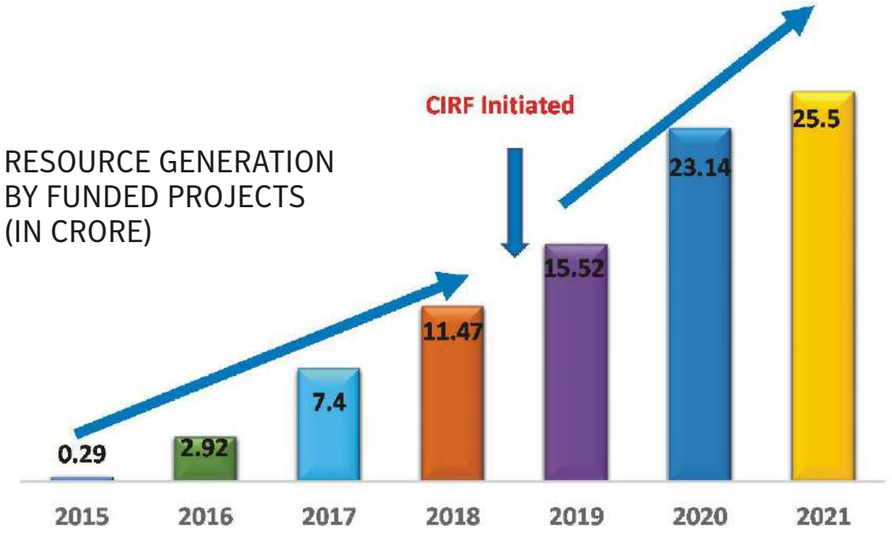
FROM USER'S CHARGES

Revenue generation was heavily affected by the lockdown (Mar 2020- Feb 2021), during which the facility was not functional. However, during partial lockdown only internal users were making use of the facility. The facility operates 24×7 out of which approximately 30% of the time is invested on maintenance of the machine.

- **The total revenue generated from internal and External Users Rs. 3,46,626.**
- **Revenue generated from Workshops and Organised Seminars Rs: 2,03,72**

EXTRAMURAL FUNDS

NEW ASSETS CREATED



RESOURCE GENERATION BY FUNDED PROJECTS (IN CRORE)

LIST OF FUNDED PROJECTS FUNDED BASED ON CIRF FACILITIES WORTH ~ 25 Cr. approx.

2019

Title of the Project:
Unraveling the molecular mechanism of lncRNAs involvement in Glioblastoma

Institute: AIB

Principal Investigator: Dr. Amit Kumar Pandey

Sponsor Agency: DST- RSF

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 71,74,032/-

Title of the Project:
Identifying the role of P53 regulated long non-coding RNAs (LncRNAs) by Crispr/Cas9 in ovarian cancer

Institute: AIB

Principal Investigator: Dr. Amit Kumar Pandey

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 59,97,000/-

Title of the Project:
Fabrication of the portable low cost point-of-care optical device for the screening of thalassemic career

Institute: AIB

Principal Investigator: Dr.Ranjita Ghosh Moulick

Sponsor Agency: DST

Duration of Project (In Yrs): 2 Years

Sanction Amount in INR: Rs. 14,60,000/-

Title of the Project:
A nanobionic approach for enhancement of plant photosynthesis and growth by augmenting chloroplast mediated photon absorption'

Institute: AIB

Principal Investigator:
Dr. Sumistha Das & Dr. Nitai Debnath

Sponsor Agency: DST

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 45,50,000/-

Title of the Project:
Developing small molecule inhibitors to target non-genomic androgen signalling and elucidating the role of GPR56 in Prostate Cancer

Institute: AIB

Principal Investigator: Dr. Gargi Bagchi

Sponsor Agency: DST-SERB

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 46,37,570/-

Title of the Project:
Mitigating the impact of antifungal resistance in the emerging pathogen candida auris by piggybacking its peptide permease as an antifungal delivery system

Institute: AIB

Principal Investigator: Dr. Atanu Banerjee

Sponsor Agency: DST

Duration of Project (In Yrs): 2 Years

Sanction Amount in INR: Rs. 32,32,312/-

Title of the Project:
Experimental validation of pre-identified candidate genes regulating protein storage in chicphea seeds

Institute: AIB

Principal Investigator: Dr. Kaustav Bandyopadhyay

Sponsor Agency: SERB

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 31,99,735/-

Title of the Project:
DNA biosensor for the diagnosis of Leptospirosis

Institute: AINT

Principal Investigator: Dr. Ankur Kaushal

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 12,39,000/-

Title of the Project:
Electrochemical DNA sensor for the diagnosis of Scrub Typhus

Institute: AIB

Principal Investigator: Dr.Ankur Kaushal

Sponsor Agency: DST, SYST

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 18,69,560/-

Title of the Project:
Identify Disease gene association using Google's Tensor Flow

Institute: AIB

Principal Investigator: Dr. Alok Srivastava

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 33,05,700/-

Title of the Project:
Understanding Wnt Pathway and LncRNAs interaction for the identification of novel therapeutic targets in triple-negative breast cancers

Institute: AIB

Principal Investigator: Dr. Amit Kumar Pandey

Sponsor Agency: DST

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 37,78,179/-

2020

Title of the Project:
Development of rare earth ions doped borate nanophosphors for solid state lighting and radiation dosimetry devices

Institute: ASAS

Principal Investigator: Dr. Ankush Vij

Sponsor Agency: RI Nano tech India

Duration of Project (In Yrs): 1 Year

Sanction Amount in INR: Rs. 2,30,000/-

Title of the Project:
Investigating of the role of Lnc RNAPANDAR in the progression and metastasis of ovarian cancer

Institute: AIB

Principal Investigator: Dr. Amit Pandey

Sponsor Agency: ICMR-EMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 30,00,000/-

Title of the Project:
System level meta-analysis of Type 2Diabetes to identify key regulator

Institute: AIB

Principal Investigator: Dr.Alok Srivastava

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 70,00,000/-

Title of the Project:
DHR-Identification of Sphingolipid-based Biomarkers for Triple Negative Breast Cancer (TNBC) and Luminal A Patients and their72Clinicopathological Correlation" Proposal id (GIA/2019/000170/PRCGIA)

Institute: AIB

Principal Investigator: Dr. Ujjaini Dasgupta

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 47,00,000/-

Title of the Project:
A low cost portable microfluidics embedded on chipr RT-PCR and microelectrode array coupled point-of care optoelectronic device for large scale screening of emerging viral disease like SARS COV2

Institute: AIB

Principal Investigator: Jaydeep Bhattacharya, Ravi Tandon, Dr. Ranjita Ghosh Moulick, Sameer Gulati, Subrata Sarkar and Souvik Pal

Sponsor Agency: BIRAC-DBT

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 90,00,000/-

Title of the Project:
PG Teaching in Biotechnology (M.Sc. in Biotechnology) approved by DBT for GAT-B national based admissions

Institute: AIB

Principal Investigator: Dr. Rajendra Prasad

Sponsor Agency: DBT

Duration of Project (In Yrs): 5 Years

Sanction Amount in INR: Rs. 1,30,00,000/-

Title of the Project:
Fabrication of Realtime in plantabiosensors for pre-symptomatic detection of heavy metal toxicity

Institute: AIB

Principal Investigator: Dr.Ranjita Ghosh Moulick and Kaustav

Sponsor Agency: DBT

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: 60,00,000/-

Title of the Project:
To study the dynamics of sickling inside blood capillary mimicking microfluidic system to fabricate a portable point-of-care electronic device for the detection of sickle cell disease

Institute: AIB

Principal Investigator: J. Bhattacharya, R.Ghosh Moulick and R. Chhabra

Sponsor Agency: ICMR-AEST

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 10,00,000/-

Title of the Project:
Human lacrimal gland regeneration: a study of the existing technological advancements and development of next generation solutions by tissue engineering and regenerative medicine,

Institute: ASET

Principal Investigator: Dr. Vimal Kishor Singh

Sponsor Agency: SERB

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 43,67,888/-

Title of the Project:
Differential Inhibition of Visfatin-PAK4 as a Novel Strategy inEsophageal Squamous Cell Carcinoma for Therapeutic Purpose

Institute: AIB

Principal Investigator: Manoj K Kashyap, Dr. Suresh Kr. Kalangi and Tessy Maliekal

Sponsor Agency: ICMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 45,00,000/-

Title of the Project:
Novel drug molecule discovery from Cannabis sativa and the irtherapeutic use as nanomedicine in pain management and non-healing ulcers had been approved

Institute: ASCI

Principal Investigator: Dr. Suresh Kr. Kalangi

Sponsor Agency: Stem Max Pvt. Ltd. India

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 40,00,000/-

Title of the Project:
Identification of biomarker candidate for early diagnosis of myocardial reperfusion injury and reoccurrence centralizing GSK3β using metanalysi

Institute: AIP

Principal Investigator: Dr.Arun Kumar, Dr Satish Sardana

Sponsor Agency: ICMR-EMR

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 49,00,000/-

Title of the Project:
Development of on spot diagnostic kit for COVID19 based on RT-LAMP Integrated CRISPR-Cas technique

Institute: AIB

Principal Investigator: Dr. Saif Hameed

Sponsor Agency: BRNS

Duration of Project (In Yrs): 1 Year

Sanction Amount in INR: Rs. 16,56,550/-

Title of the Project:
DBT-BUILDER Level-I

Institute: AIB

Principal Investigator: Dr. Rajendra Parsad

Sponsor Agency: DBT

Duration of Project (In Yrs): 5 Years

Sanction Amount in INR: Rs. 1,60,00,000/-

Title of the Project:
A Mass Spectrometric Approach to Unravel the Landscape of Sphingolipids as Major Signaling Determinants of Drug Resistance and Virulence in Emerging Human Fungal Pathogen Candida auris.

Institute: AIB

Principal Investigator: Dr. Rajendra Parsad, Co-PI, Dr. Atanu Banerjee, Dr. Ashutosh Singh

Sponsor Agency: DBT

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 84,25,600/-

Title of the Project:
Novel Nanoarchitectures for selective multistep catalysis

Institute: ASAS

Principal Investigator: Dr. Anirban Das

Sponsor Agency: SERB-DST

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 18,30,000/-

2021

Title of the Project:
DBT Skill Vigyan Programme under state partnership in Life Science and Biotechnology

Institute: AIB

Principal Investigator: Dr. Rajendra Parsad

Sponsor Agency: DBT

Duration of Project (In Yrs): 5 Years

Sanction Amount in INR: Rs. 1,23,00,000/-

Title of the Project:
Insights into the efflux pump arsenal of the emerging pathogen C.auris and its implication in high order of antifungal resistance and virulence

Principal Investigator: Dr. Atanu Banerjee, Co-PI Dr. Andrew M. Lynn, Dr.Rajendra Prasad

Sponsor Agency: DBT

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: 54,89,236/-

Title of the Project:
Regulation of ribosome biogenesis and SOS response by cyclic di-AMP in Mycobacterium

Institute: AIB

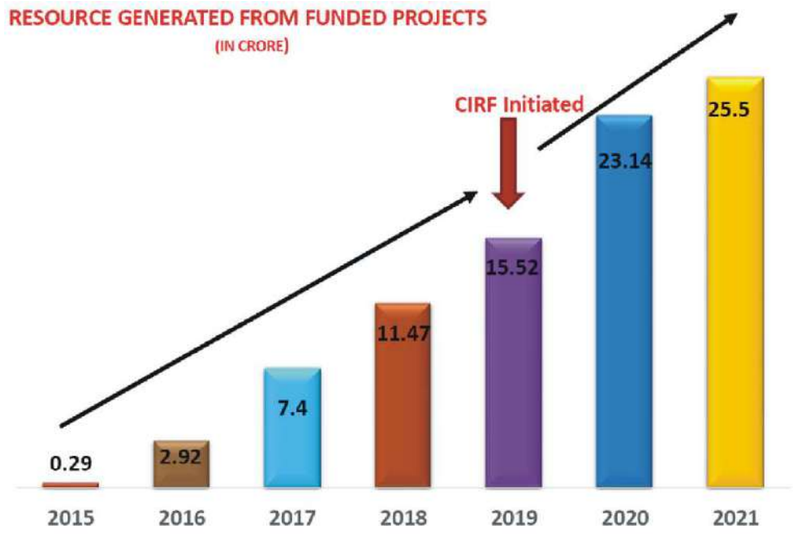
Principal Investigator: Dr. Krishna Murari Sinha (PI), Dr Aneesh Kumar NII (CO-PI)

Sponsor Agency: SERB

Duration of Project (In Yrs): 3 Years

Sanction Amount in INR: Rs. 57,86,258/-

NEW ASSETS CREATED



EQUIPMENT PURCHASED FROM ONGOING FIST FACILITY DEPENDENT PROJECTS

- AB SCIEX QTERAP 4500 SYSTEM, SCIEX
- Differential Thermal Analyzer (DTA) along with essential accessories, PERKIN ELMER
- HPTLC, CAMAG
- AKTA Pure with cold cabinet, GE
- Low Temp shaker/incubator, KUHNER
- HPE DL380 16G 8SFF Server, HP Pavilion Laptop (15–CX0144TX), TVS-682-i3-8G Qnap NAS ETC., EACEA (CABCIN), SIMBIAN SYSTEMS
- Centrifuge And PCR Machine, EPPENDORF
- Chemi Doc, DB, BIO-RAD
- Inverted Research Microscope, CARL ZEISS
- Real Time PCR (3) , BIO-RAD(1) , EPPENDORF (1),

- Fluorescent Microscope, OYLUMPUS CORPORATION
- RIUS Spectrometer RI INSTRUMENTS AND INNOVATION INDIA
- Centrifuge 5804 and Excella E24 bench top incubator, EPPENDORF
- REFRIGERATOR
- MATLAB and Toolbox, INTEGRATED PROGRESSIVE TECHNOLOGY
- CO2 incubator (4) with CO2 cylinder and Regulator, (1), KELVIN LIFESCIENCES, DBT THERMO (2), EPPENDORF (1)
- Microscope with camera, OLYMPUS
- Server PowerEdge, DELL, DELL THROUGH ARROW PC
- Oxygen Electrode System, HANSATECH INSTRUMENTS, UK
- Nanodrop (2), GINGER SCIENCE PVT. LTD.(1) THERMO (1)
- Plant growth chamber, A M BIOTECH
- Freezer (2), EPPENDORF (1) , -THERMO (1)
- Incubator, Shaker, Vortex Mixture, LACZENE BIOSCIENCE(!), DBT, LABNET (1)
- Fluorescence Phase Contrast Microscope, CHEMPEX INDUSTRIES (TOWA OPTICS INDIA PVT LTD)
- Dell laptop, HP laptop, AMAZON
- -80-degree Freezer, THERMO
- Fast Prep, MP BIOMEDICALS INDIA PVT. LTD.
- Potentiostat/Galvanostat with Impedance analyzer, SYST CLASS ONE SYSTEMS S&T PVT. LTD.
- Vacuum Thermal Coating Unit, SCIENTIFIC & ANALYTICAL INSTRUMENTS
- PCR Thermocycler, DISCOVERY BIONICS
- Elisa Reader, BIO-RAD
- PCR machine, EPPENDORF
- Biosafety cabinet, LABQUIP
- UV Visible Spectrophotometer, PERKINELMER PTE LTD, SINGAPORE
- Ferroelectric Loop Tracer, MARINE INDIA

NEW ASSETS CREATED: ~6 Cr.

LCMS Q-TRAP Mass-spec

Modular Spectrometer

STA 8000

UV-vis Lambda 365

Zetasizer Nano-Series

AKTA FPLC system

Cell culture incubator

Nanodrop spectrophotometer

HPTLC

Fluorescence microscope

PCR machine

RT-PCR machine

Cold centrifuge

AMITY UNIVERSITY HARYANA

PUBLICATION RESULTING USE OF CIRF FACILITIES

PUBLICATION RESULTING USE OF CIRF FACILITIES

1. The E-helix is a central core in a conserved helical bundle involved in Nucleotide binding and transmembrane domain intercalation in the ABC transporter superfamily, Poonam Vishwakarma, Atanu Banerjee, RituPasrija, Prasad R, Andrew Lynn, (International Journal of Biological Macromolecules). (127)95-106(2019) https://doi.org/10.1016/j.ijbiomac.2019.01. 030.

2. Vacuolar sequestration of azoles: A novel strategy of azole antifungal resistance conserved across pathogenic and non-pathogenic yeast. Khandelwal Nitesh,WasiMohd,Nair, Remya, Gupta Meghna, Mondal Alok Gaur Naseem, Prasad R. (Antimicrobial Agent and Chemotherapy).(63) 3 e01347-18 (2019)

3. Information theoretic measures and mutagenesis identify a novel linchpin for substrate specificity in an ABCG family exporter Cdr1p, Atanu Banerjee, Poonam Vishwakarma, Antresh Kumar, Andrew M. Lynn and Prasad R, (Archives of Biochemistry and Bipphysics).S0003-9861(18)30877-4, 2019 DOI:10.1016/j.abb. 2019.01.013.

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5. Lipidomics Approches: Applied to the Study of Pathogenesis in Candida Species, Prasad R and Ashutosh Singh invited contribution in Book “Yeast in Biotechnology and Human Health ", (Molecular and Subcellular Biology),978-3-030-13035-0,(58),195-215, (2019) https://link.springer.com/ chapter /10.1007/978-3-030-13035-08.

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HUMAN RESOURCE DEVELOPMENT

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5	Deepali Suhas Sarode	Dr. Sangeeta Singh	Multi Index, Multi Criteria and Fixed Charge Transportation Problem with Fuzzy Parameter	2019
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11	Rahul Pal	Dr. Zeeshan Fatima	Effect of iron deprivation on drug resistance of Mycobacterium tuberculosis"	2020
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13	Rahul Kumar Chandel	Dr. Manju Sharma	Study of Phosphine Resistance in Rhyzopertha Dominica Infesting Wheat	2020
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17	Kavita Kumari	Dr. Shailendra Kumar	Structural and Magnetic Properties of Diluted Oxide Magnetic Semiconductors for Spintronics Applications	2020
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Sr. No.	Scholar Name	Supervisor Name	Thesis Title	Convocation Year
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20	Nisha	Dr. Sunita Daniel	Mathematical Modelling of the Epidemiology of Malaria and Dengue	2020
21	Ved Prakash	Prof. (Dr.) Priti Singh	Analysis and design of Microstrip antenna for wireless Applications.	2020
22	Ganesh Gupta	Dr. Vivek Jaglan	An Investigation of on Demand power Management in AD Hoc Wireless Network	2020
23	Patel Nilam Kumari Ranchhodbhai	Dr. Khushboo Tripathi	Development of Secure AODV Protocol for Handling Network Layer Attacks in Wireless Ad hoc Networks	2020
24	Rashmi Goyal	Dr. Vivek Jaglan	Optimization of Software Testing Using Genetic Algorithm	2020
25	Malobi Nandi	Dr. Ravi Datta Sharma	"Insights into Mycobacterium tuberculosis dormancy adaptation in axenic culture and intracellular milieu from Transcriptome analysis"	2021
26	Deepak Kumar	Dr. Sangeeta Kumari	Analysis of major pollutant in Hindon river (tribu tary of Yamuna) and it's bioremediation by microbial contortium	2021
27	Rajesh M	Prof. Rajendra Prasad	Isolation, Characterization and Adjuvant Potential of Poly -a-L-glutamine from Cell Wall of Mycobacterium tuberculosis H37Rv	2021

Sr. No.	Scholar Name	Supervisor Name	Thesis Title	Convocation Year
28	Ashok Kumar	Prof. Rajendra Prasad	Molecular epidemiology, fungi biome and resistome and fungalisolates recovered from different cohort of patients from hospitals in Haryana	2021
29	Deepika Kulshreshtha	Dr. Narendra Kumar	Comparative study on compatible and incom patible interactions in wheat - puccinia striiformis f.sp. tritici	2021
30	Sharda Sharma	Dr. Zeeshan Fatima	Antimycobacterial potential of Vanillin & Geraniol against Mycobacterium	2021
31	Julie Pratibha Singh	Dr. Gargi Bagchi	Identification of molecular targets for the treatment of prostate cancer	2021
32	Shweta Singh	Dr. Saif Hameed	Antifungal potential of Terpenoid and Alkaloid compounds against 33 human fungal pathogen, Candida alb34icans	2021
33	Sunil Bhardwaj	Dr. Vijay Kumar	Relia 35 bility analysis of repairable systems 36 with respect to maintenan 3738 ce performance management	2021
34	Preeti	Dr. Chander Shekhar	Synthesis & Characterization of Lead Based Disordered Multi Ferric Ceramics	2021
35	Monika	Dr. Nahid Fatima	Analytical and numerical solution of Burgers; and time dependent differential equations in fluid using the homotopy perturbation method	2021
36	Sonal Dahiya	Dr. Karamjit Kaur Sekhon	A Petri Net Based Approach for Modelling and Simulation of Energy Consumption in Wireless Sensor Networks	2021

Sr. No.	Scholar Name	Supervisor Name	Thesis Title	Convocation Year
37	Quinton Chamunorwa Kanhukamwe	Prof. P. B. Sharma	Developing a model for systematic research, development and commercialisation of intellectual property - A crucial analysis of Harare Institute of Technology	2021
38	Abhishek Kumar Jain	Dr. Khushboo Tripathi	Handling unknown attacks through intrusion detection system	2021
39	Manjeet Kaur	Dr. Anil Kumar	Tuning of PID controllers for speed control of the drive using evolutionary algorithms	2021
40	Edmund Shingirayi Maputi	Dr. Rajesh Arora	Multistage gearbox design using advanced optimization techniques	2021
41	Kudzanayi Chiteka	Dr. Rajesh Arora	Installation and cleaning cycle optimization for fouling mitigation in non-tracking commercial Solar PV plants	2021

ONGOING Ph.D. THESIS USING CIRF FACILITY

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1	Kusum Yadav	Dr. Rajendra Prasad Professor, Amity Institute of Biotechnology	2019
2	Sonu Yadav	Dr. Zeeshan Fatima Associate Professor, Amity Institute of Biotechnology	2019
3	Praveen Kumar	Dr. Rajendra Prasad Professor, Amity Institute of Biotechnology	2019
4	Raj Laxmi Yadav	Dr. Rajendra Prasad Professor, Amity Institute of Biotechnology	2019
5	Nisha kumari	Dr. Jinny Tomar Assistant Professor	2019
6	Kansara Samarth	Dr Amit Pandey, Assistant Professor, Amity Institute of Biotechnology, Haryana	2019
7	Anshu Yadav	Dr. Gargi Bagchi, Associate Professor, Amity Institute of Biotechnology	2019
8	Trishana Pani	Dr. Ujjaini Dasgupta	2019
9	Himanshu Sharma	Dr. Saif Hameed, Associate Professor, Amity Institute of Biotechnology, Haryana	2019
10	Devashish Mehta	Dr. Ujjaini Dasgupta	2019
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12	Pooja	Dr. Sudeshna Ghosh Associate Prof, ASAS, AUH	2019
13	Deepika	Dr. Preeti Thakur, HOD Physics, ASAS, AUH	2019
14	Priya Goel	Dr. Dimple Singh, Assistant Professor, ASAS, AUH	2019
15	Ritu Malik	Dr. A. K. Yadav, HOI, Amity School of Applied Sciences, AUH	2019
16	Shilpa	Dr. Preeti Thakur, HOD Physics, ASAS, AUH	2019
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18	Vandana Rani	Dr. Vikas Lahariya, Assistant Professor, ASAS, AUH	2019
19	Durga Yadav	Dr. Joydeep Dutta, Professor, Amity School of Applied Science	2019

Sr. No.	Scholar Name	Supervisor Name	Batch
20	Monika K	Dr. Richa Rohatgi, Assistant Prof, ASAS, AUH	2019
21	Neelum Kumari	Dr. A. K. Yadav, HOI, Amity School of Applied Sciences, AUH	2019
22	Neha Kuhar	Dr. Monika Vats, Assistant Prof, ASAS, AUH	2019
23	Rekha Kumari	Dr. Sudeshna Ghosh, Associate Prof, ASAS, AUH	2019
24	Taruna Lodhi	Dr. Richa Rohatgi, Assistant Prof, ASAS, AUH	2019
25	Meena Yadav	Dr. Jyotsna Sharma, Associate Prof, ASAS, AUH	2019
26	Mohan Ganpatrao Bodkhe	Dr. Sanjeev Sharma, Associate Professor	2019
27	Bhavna Galhotra	Dr. Shalini Bhasker Bajaj, Professor, Amity School of Engineering of Technology	2019
28	Naresh Kumar Dahiya	Dr. Shalini Bhasker Bajaj, Professor, Amity School of Engnering of Technology	2019
29	K.N. Sanjeev Kumar	Dr. Sanjeev Sharma, Associate Professor	2019
30	Patil Anant Arun	Dr. S.N Sridhara	2019
31	Sukhvir Yadav	Dr. Sanjeev Sharma, Associate Professor	2019
32	Ajeet Kumar	Dr. Ravi Dutt, Assistant Professor, Amity Institute of Biotechnology	2019
33	Jasmine Kaur	Dr. Alok Kumar, Assistant Professor, Amity Institute of Biotechnology	2019
34	Harsh Sharma	Dr. Ravi Dutt, Assistant Professor, Amity Institute of Biotechnology	2019

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35	Dumpala Pradeep	Dr. Brijesh Kumar, Associate Professor, Amity Institute of Nanotechnology	2019
36	Jyoti Kumari	Dr Atul Thakur	2019
37	Amitendra Singh	Dr. Debashri Ghosh, Assistant Professor.	2019
38	Deepak Kala	Dr Ankur Kaushal	2019
39	Anshu Chauhan	Dr. Rajendra Prasad, Professor, Amity Institute of Biotechnology	2020
40	Nisha Goel	Dr. krishan Murari, Associate Professor, Amity Institute of Integrative Sciences, Haryana	2020
41	Prashant Yadav	Dr. Kaustav Bandhopadhyay, Assistant Professor, Amity Institute of Biotechnology, Haryana	2020
42	Ahana Mukharjee	Dr. Ranjita Ghosh, Assistant Prof. Amity Institute of Integrative Sciences, Haryana	2020
43	Bhupendra Yadav	Dr Amit Pandey, Assistant Professor, Amity Institute of Biotechnology, Haryana	2020
44	Sonali Pal	Dr Amit Pandey, Assistant Professor, Amity Institute of Biotechnology, Haryana	2020
45	Meenakshi	Dr. Zeeshan Fatima, Associate Professor, Amity Institute of Biotechnology	2020
46	Shikha Dhiman	Dr. Sumistha Das, Assistant Professor, Amity Institute of Biotechnology, Haryana	2020
47	Indu Kumari	Dr. Amresh Prakash, Associate Prof., Amity Institute of Integrative Sciences, Haryana	2020

Sr. No.	Scholar Name	Supervisor Name	Batch
48	Amit Kumar	Dr. Amresh Prakash, Associate Prof., Amity Institute of Integrative Sciences, Haryana	2020
49	Deepak Kushwaha	Dr. Ranjita Ghosh, Assistant Professor, Amity Institute of Integrative Sciences, Haryana	2020
50	Megha Yadav	Dr. Manju Sharma, Associate Professor, Amity Institute of Biotechnology, Haryana	2020
51	Shubhra Sharma	AIB	2020
52	Rosy Khatoon	AIB	2020
53	Varsha Dahiya	AIB	2020
54	Oindrila Bhattacharjee	AIB	2020
55	Chirag Dhankhar	Dr. A. K. Yadav, HOI, Amity School of Applied Sciences, AUH	2020
56	Vikas Kumar	Dr. Anupam Vyas, Assistant Prof, ASAS, AUH	2020
57	Manoj Kumar	Dr. Supreet, Assistant Prof, ASAS, AUH	2020
58	Rohit Yadav	Dr. Jyotsna Sharma, Associate Prof, ASAS, AUH	2020
59	Naveen Dhull	Dr. Shiv Poojan Kori, Assistant Prof, ASAS, AUH	2020
60	Meenu Yadav	Dr. Chander Mohan, Assistant Prof, ASAS, AUH	2020
61	Bharti Sheokhand	Dr. Monika Vats, Assistant Prof, ASAS, AUH	2020
62	Sonam Kumari	Dr. Preeti Thakur, HOD Physics, ASAS, AUH	2020
63	Salvi Anand Gatubhai	Dr. Manish Shandilya, Assistant Prof., ASAS, AUH	2020
64	Priya Kumari	Dr. Dipti Vaya, Associate Professor, ASAS, AUH	2020
65	Laxmi Devi	Dr. Anirban, Associate Professor, ASAS, AUH	2020
66	Komal	Dr. Kamal Nayan, ASAS, AUH	2020

Sr. No.	Scholar Name	Supervisor Name	Batch
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68	Rajnee Yadav	Dr. Vikas Lahariya, Assistant Prof, ASAS, AUH	2020
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78	Jiten	Dr. Atul Thakur	2020
79	Dinesh Kumar	Dr. Atul Thakur	2020
80	Saarthak Kharbanda	Dr. Atul Thakur	2020
81	Mohita Madaan	AIISH	2020
82	Neha Arora	AIISH	2020
83	Vikas Rana	AIISH	2020
84	Manjeet	AIISH	2020
85	Sapna	AIISH	2020
86	Annu Dhankhar	AIISH	2020
87	Jyothi Lakshmi	AIB	2021
88	Priya	AIB	2021
89	Akanksha Kumari	AIB	2021

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90	Tushar Goyal	AIB	2021
91	Prabha	ASAS	2021
92	Neetu	ASAS	2021
93	Neeraj Lather	ASAS	2021
94	Aman Sharma	ASAS	2021
95	Deepika Dubey	ASAS	2021
96	Bibi Shaguftah Khatoon	ASAS	2021
97	Gaurav Sharma	ASAS	2021
98	Rohit Yadav	ASAS	2021
99	Sudha	ASAS	2021
100	Anju Rani	ASAS	2021
101	Zomuanpuii	ASAS	2021
102	Varun	ASAS	2021
103	Deepika Yadav	ASAS	2021
104	Nisha Yadav	ASAS	2021
105	Arvind Kumar	ASAS	2021
106	Aditi Chauhan	ASAS	2021
107	Shanu	ASAS	2021
108	Ashima Jain	ASET	2021
109	Netake Renuka Bhaskar	ASET	2021
110	Mehetre Rupali Vasantrao	ASET	2021
111	Anmol Alawadhi	ASET	2021
112	Hement Kumar Upadhyay	ASET	2021
113	Gupta Mayank Rajat	ASET	2021
114	Jyoti Jangir	AIISH	2021
115	Ashish Kumar Chauhan	AIISH	2021
116	Ali Khan	AIISH	2021
117	Mohammad Nafees Ansari	AIISH	2021
118	Athira P Anil	AIISH	2021

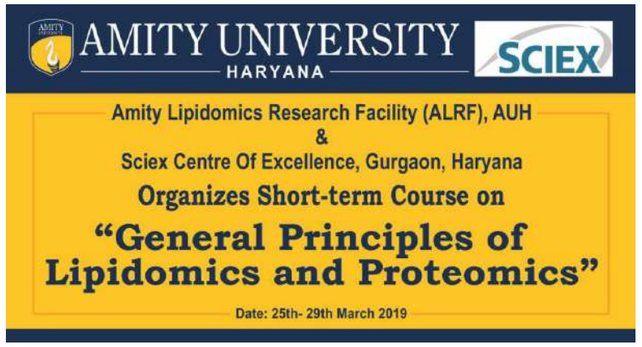
SKILLING

- The CIRF will regularly organize paid workshops on instrumentations to increase the skillsets of the students and researchers along with outside participants. Along with revenue generation, this will enhance the employability of Amity graduates.
- The ongoing DBT-sponsored M.Sc (BT) program has a mandatory skilling component, which will be covered by the instruments of CIRF.
- Our proposal for DBT-Skill Vigyan program has been technically approved by Haryana State Skill Council and CIRF will be heavily involved in the program (Money release awaited).
- AIB, AUH is in process of initiating a new skill-based program 'PG-diploma in quality control analysis and instrumentation'. The aim of this program will be to generate skilled manpower with 'QC specialists in industries' as target employment. The one-year program is being designed around the instruments housed at CIRF. We are trying to work with Life Science Sector Skill Development Council, GoI for joint certification in this course and the proposal is in the final stage of approval.

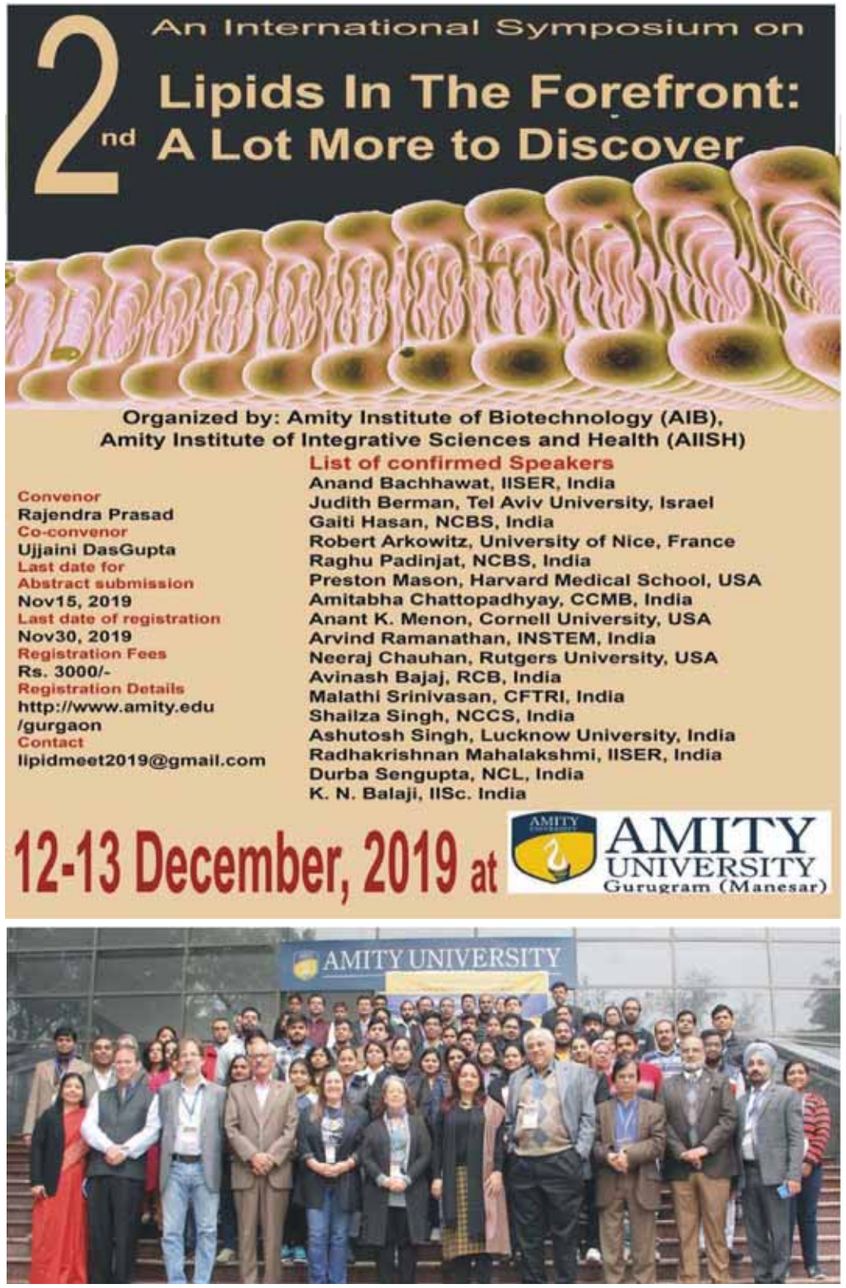
Skilling

- Workshops and Symposium supported by industry and organized by CIRF

SHORT-TERM COURSE ON "GENERAL PRINCIPLES OF LIPIDOMICS AND PROTEOMICS" AT AMITY LIPIDOMICS RESEARCH FACILITY (ALRF), AMITY UNIVERSITY HARYANA AND SCIEX, GURGAON, HARYANA WAS CONDUCTED FROM 25TH TO 29TH MARCH 2019.

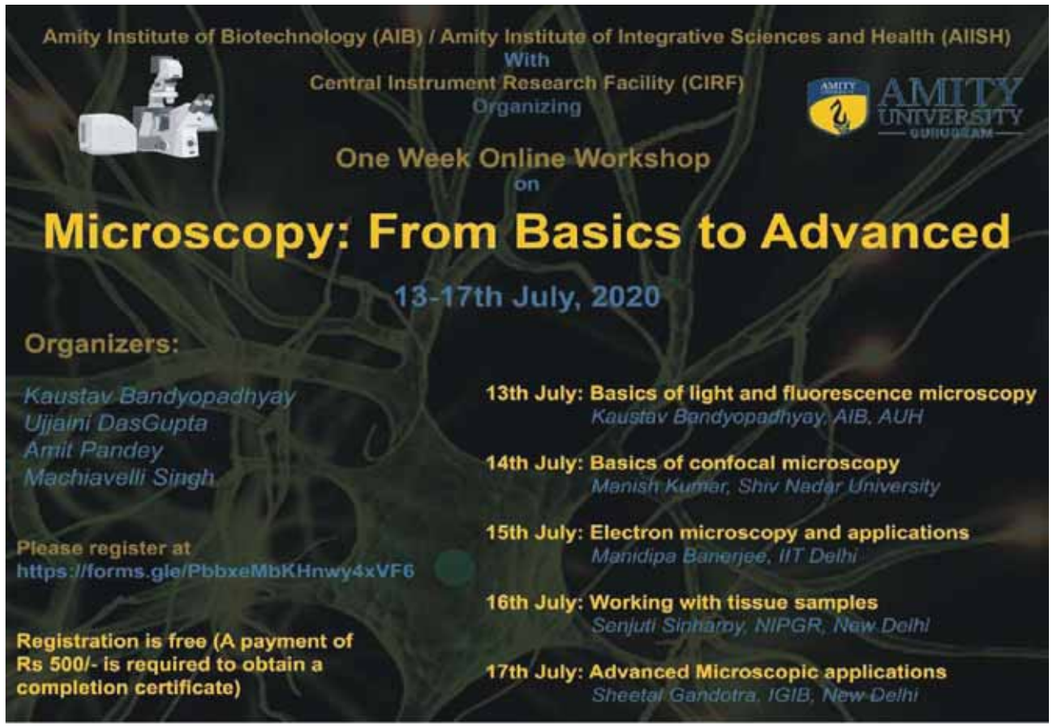


2nd International Symposium "Lipids in the Forefront: A Lot More to Discover", was conducted on 12th-13th December 2019



2-Days Workshop (18/02/2020 and 19/02/2020) on Principles and application of Flow Cytometry (FACS) at Central Instrumentation Research Facility (CIRF), Amity University

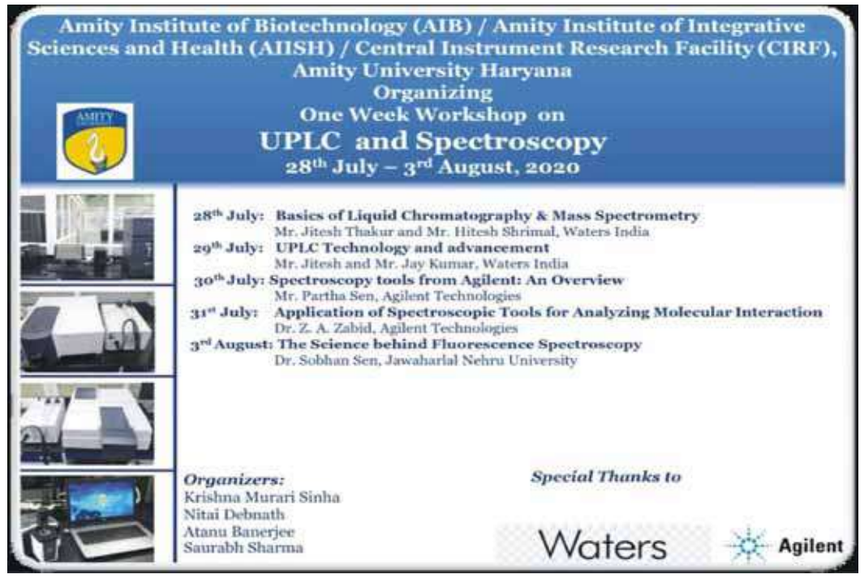
One-week online workshop (13-17th July 2020) on Microscopy: From basics to advanced

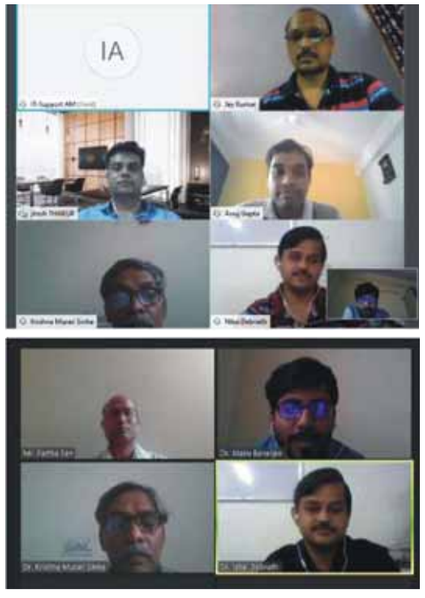


Dr. Manish Kumar, Shiv Nadar University on Basics of confocal microscopy

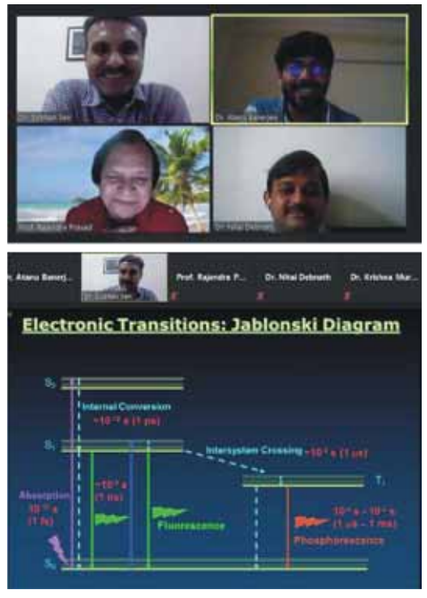
Dr. Senjuti Sinharoy, NIPGR Delhi on Working with tissue samples

One week Workshop on UPLC and Spectroscopy



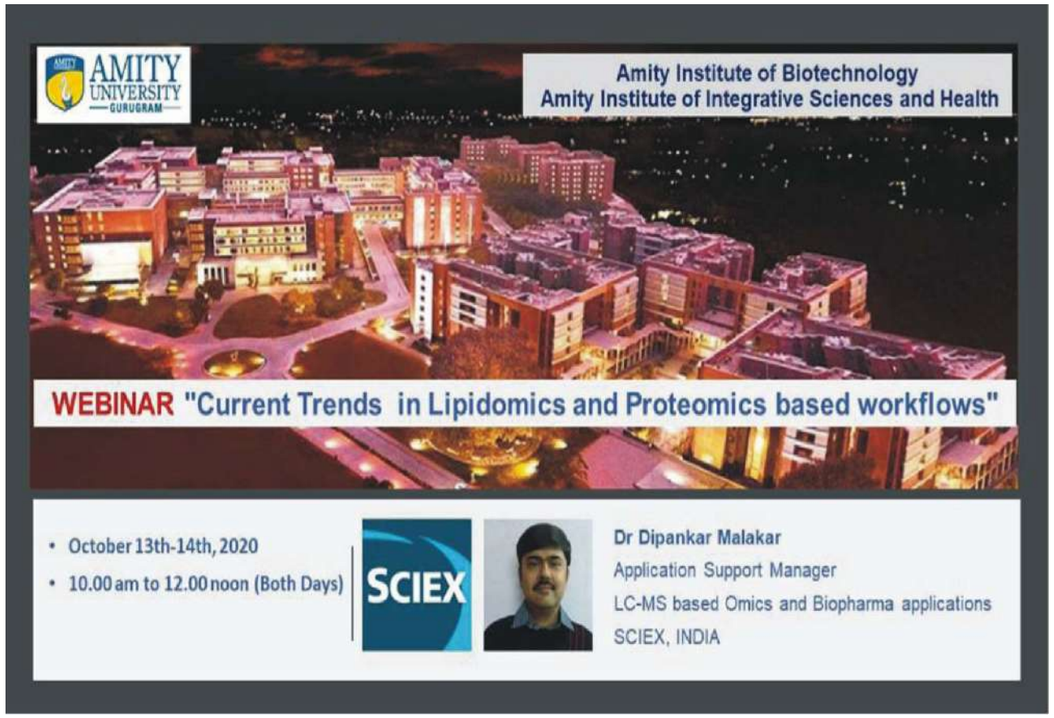


Organizers, scientists from Waters India and Mr. Partha Sen from Agilent technologies

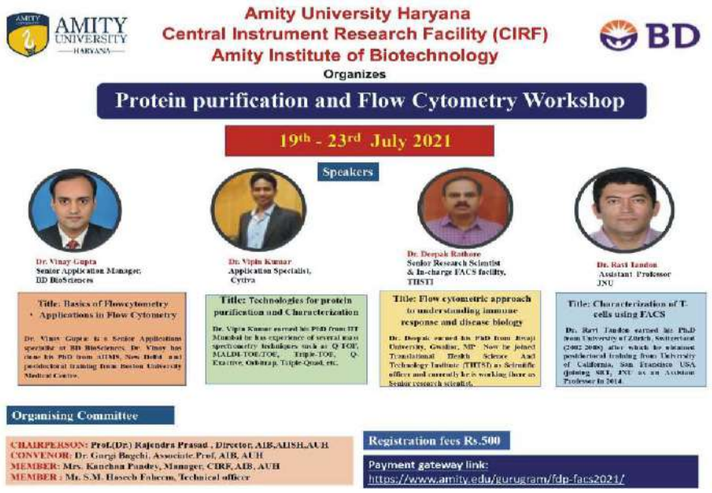


Organizers and Dr. Sobhan Sen from JNU on Fluorescence Spectroscopy and its Utility in Everyday Life

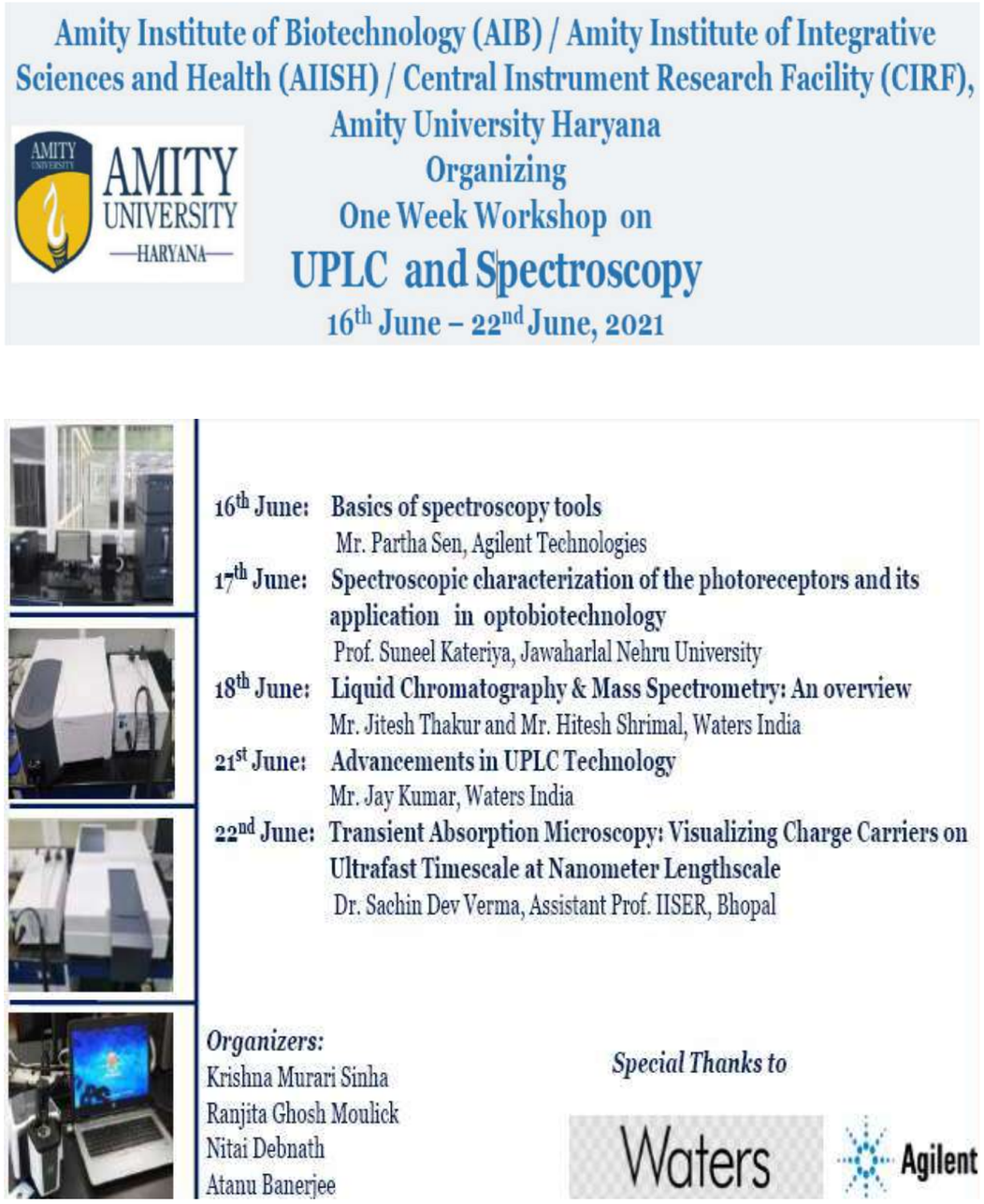
Webinar on Current trends in Lipidomics and Proteomics based workf



Protein Purification and Flow Cytometer Workshop



One Week online Workshop of UPLC and Spectroscopy



ROADMAP OF THE REVENUE GENERATION

The strategy for revenue generation is to provide Instrument based analysis on chargeable basis for research as well as commercial purposes. Both external and internal users can access the facility. Additional revenue can be generated by conducting workshops and seminars.

- Providing services to researchers from Amity University Haryana and other campuses on chargeable basis.
- Providing services to researchers from External Universities/Institutions on chargeable basis.
- Providing services to private industries on chargeable basis.
- Regularly conducting paid-workshops, seminars, and webinars on recent trends in chromatography, Imaging, Spectroscopy flow-cytometery,DSC and DLS, supported by the application scientists from industries and scientists researching in this area. These workshops will generate revenue. The seminars and webinars will give broader recognition to our CIRF as well as AUH as more students/ technical staff/scientists will be aware of the facility and more paid services will be sought.
- Conducting international symposiums, attended by scientists from the entire world specializing in the field of Lipidomics and Proteomics. This will help us to establish collaborations with other institutes, resulting in accomplishment of ongoing projects efficiently. This will lead to generation of revenue by acquiring extra mural grants.

Collecting sponsorship from vendors while organizing symposia of National and International repute. Some of these meetings may generate excess fund, and after spending the required money, rest may be added to AUH's fund.

- Preliminary data/data generated by using this facility is extremely pertinent for applying and successfully getting grants from national and international funding agencies. The sanctioned grants so achieved by the PI's add up to the overall revenue earned by the University along with prestige and recognition of Amity University by national/international science and technology platforms.
- Prestigious and high-impact factor publications made by the PIs (please check publication list on page no 8-10) using experimental data generated from CIRF also makes very significant contribution and impact in the national/international science and technology field that will add to the recognition and popularity of the University. The direct impact of this recognition will be harnessed by the University as this positive impact will encourage larger number of students to get enrolled for UG/PG/PhD programs.
- Circulating publications showcasing CIRF acknowledgement widely to make more people aware so that they avail the services of CIRF facility.
- Circulating Flyers and brochures of CIRF via email to PI'S across various institutes.

Offering skill-based new programs (like one-year diploma courses) which will utilize the instruments in CIRF to generate skilled manpower. This course may become very popular since the graduates may have better employability.

Applying for govt. funding to hold skilling workshops. We have already obtained the 'DBT Skill-Vigyan' funding (Money release awaited). We will apply for more such funding whenever a call is open.

PUBLICATIONS

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MECHANISMS OF RESISTANCE

Vacuolar Sequestration of Azoles, a Novel Strategy of Azole Antifungal Resistance Conserved across Pathogenic and Nonpathogenic Yeast

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ABSTRACT Target alteration and overproduction and drug efflux through overexpression of multidrug transporters localized in the plasma membrane represent the conventional mechanisms of azole antifungal resistance. Here, we identify a novel conserved mechanism of azole resistance not only in the budding yeast *Saccharomyces cerevisiae* but also in the pathogenic yeast *Candida albicans*. We observed that the vacuolar-membrane-localized, multidrug resistance protein (MRP) subfamily, ATP-binding cassette (ABC) transporter of *S. cerevisiae*, Ybt1, could import azoles into vacuoles. Interestingly, the Ybt1 homologue in *C. albicans*, Mlt1p, could also fulfill this function. Evidence that the process is energy dependent comes from the finding that a Mlt1p mutant version made by converting a critical lysine residue in the Walker A motif of nucleotide-binding domain 1 (required for ATP hydrolysis) to alanine (K710A) was not able to transport azoles. Additionally, we have shown that, as for other eukaryotic MRP subfamily members, deletion of the conserved phenylalanine amino acid at position 765 (F765Δ) results in mislocalization of the Mlt1 protein; this mislocalized protein was devoid of the azole-resistant attribute. This finding suggests that the presence of this protein on vacuolar membranes is an important factor in azole resistance. Further, we report the importance of conserved residues, because conversion of two serines (positions 973 and 976, in the regulatory domain and in the casein kinase I [CKI] consensus sequence, respectively) to alanine severely affected the drug resistance. Hence, the present study reveals vacuolar sequestration of azoles by the ABC transporter Ybt1 and its homologue Mlt1 as an alternative strategy to circumvent drug toxicity among pathogenic and nonpathogenic yeasts.

KEYWORDS ABC transporter, *Candida albicans*, *Saccharomyces cerevisiae*, azole, drug resistance

Fungi are among the most prevalent opportunistic pathogens and thereby pose a persistent threat to human life. The human fungal pathogen *Candida albicans* is frequently found in the oral cavity, gastrointestinal tract, and genital area of many individuals. In immunocompromised patients, it can lead to superficial oral infections. However, it also can cause vaginal infections in immunocompetent females (1, 2). Moreover, *Candida* infections can at times be fatal after gaining access to vital organs via the bloodstream, with mortality rates nearing 50% (1, 3, 4). Candidiasis, predominantly caused by *C. albicans*, is the fourth most common basis of hospital-acquired disease (5–7).

The number of antifungal agents employed clinically is restricted because of the

Citation Khandelwal NK, Wasi M, Nair R, Gupta M, Kumar M, Mondal AK, Gaur NA, Prasad R. 2019. Vacuolar sequestration of azoles, a novel strategy of azole antifungal resistance conserved across pathogenic and nonpathogenic yeast. Antimicrob Agents Chemother 63:e01347-18. https://doi.org/10.1128/AAC.01347-18.

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M.W. and R.N. contributed equally to this work.

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The E-helix is a central core in a conserved helical bundle involved in nucleotide binding and transmembrane domain intercalation in the ABC transporter superfamily

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ABSTRACT

ABC transporter proteins are involved in active transport, both in prokaryotes and eukaryotes. Sequence analysis of nucleotide binding domains (NBDs) of ABC proteins from all taxa revealed a well-conserved new motif having the signature: xT/ShxE/DNhxF, located between Q-loop and ABC signature sequence. A recent structure of an ABC transporter, ABCG5/G8 highlighted the motif as an essential structural determinant of inter-domain crosstalk and termed it as E-helix. We carried out an extensive computational analysis to unravel important structural entities alongside E-helix which plausibly play role in the interlocking mechanism of NBD with TMD. We identified E-helix to be a central structural moiety which interacts with three helices and an intracellular loop that leads to the transmembrane domain. Considering its wide occurrence, we examined the importance of this motif in one representative multidrug ABC transporter of *Candida albicans*, Cdr1p. The motif residues were replaced by alanines both individually as well as in combinations. The GFP-tagged versions of mutant proteins were overexpressed in *Saccharomyces cerevisiae*. Overall, our mutational data suggested that this motif plays a role in the maintenance of proper structural fold and/or inter-domain contacts in Cdr1p. We, thus, unveil an essential structural motif in ABC superfamily transporters.

1. Introduction

Transport systems play an indispensable role in the growth and survival of organisms ranging from microbes to higher organisms. To carry out the transport processes, there exists a vast array of proteins which are involved in the transport of ions and small or large macromolecules across biological membranes [1]. There are two basic mechanisms through which these proteins operate, i.e. passive transport and active transport [1]. Passive transport is the movement of molecules or ions along the concentration gradient, as a result of which energy is not required. Active transport is the movement of molecules or ions against a concentration gradient and thus, requires dedicated proteins and source of energy. Among all the transport proteins, the ABC superfamily constitutes the major membrane-bound proteins which are involved in active efflux/influx of a wide range of molecules [2,3]. ABC transporters work as exporters in case of the eukaryotes whereas in prokaryotic systems there exist both exporters as well as importers [4]. ABC transporter superfamily representatives work as primary active transporters because their transport mechanism relies on energy provided by the hydrolysis of ATP [4]. On the basis of the directionality of transport of substrates across the plasma membrane, ABC transporter proteins are classified as exporters and importers [5]. As importers, ABC transporter proteins mediate uptake of nutrients such as amino acids, peptides, sugars, and other hydrophilic molecules into the cell [5]. In contrast, the ABC exporters function as pumps that primarily extrude toxins, drugs out of the cells [6]. However, there are a number of exporters which are essential for the expulsion of some important biological macromolecules [6]. ABC proteins are an essential class of transporter proteins and have implications in several human inherited diseases such as CFTR and Tangier's disease [6]. Furthermore, overexpression of ABC exporters is a major mechanism of Multidrug resistance (MDR) in cancer cells as well as bacterial and fungal pathogens [7].

All ABC transporter proteins share a common structural architecture barring subtle differences. The core structure of an ABC transporter comprises of four domains, i.e. two NBDs (Nucleotide binding domains) and two TMDs (Transmembrane domains), wherein the NBD provides energy from the hydrolysis of ATP for transport of molecules and TMDs play role in the substrate recognition and transport [8]. Each TMD consists of membrane spanning alpha-helices which undergo

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COMMENTARY

Stable Positions of Epigenetically Inherited Centromeres in the Emerging Fungal Pathogen *Candida auris* and Its Relatives

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ABSTRACT *Candida auris* is an emerging fungal pathogen that is thermotolerant and often resistant to standard antifungal treatments. To trace its evolutionary history, the Sanyal lab conducted a comparative genomic study focusing on the positions of centromeres in *C. auris* and eight other species from the *Clavispora/Candida* clade of yeasts (A. Narayanan et al., mBio 12:e00905-12, 2021). These researchers discovered that these species possess small regional centromeres that are highly stable, having remained in the same syntenic positions for over 100 million years. This stability is remarkable, given the lack of a conserved sequence underlying the centromeres and the relative ease with which other yeasts form neocentromeres. Thus, this work provides an opportunity to investigate the molecular mechanism of centromere inheritance in a genetically tractable and medically important yeast.

KEYWORDS *Candida auris*, centromere, epigenetic inheritance

Centromeres, the points at which chromosomes attach to the mitotic spindle, promote genome integrity by ensuring equal segregation of sister chromatids upon cell division. However, they are also sites of chromosomal breaks and rearrangements, and this genomic instability is proposed to promote rapid adaptation to stress (1). These seemingly opposing aspects of centromeres have drawn attention to their properties in opportunistic and emerging fungal pathogens, raising the question of whether centromeres drive genomic changes that enhance virulence. A recent study from the Sanyal lab provides insights into this issue by identifying the locations and features of centromeres in the emerging fungal pathogen *Candida auris* and its relatives (2).

C. auris was first described in 2009 and is of increasing concern because of its thermotolerance and resistance to commonly used antifungal drugs, leading to high mortality for bloodstream infections (3). *C. auris* spreads easily in health care settings, where it primarily affects immunocompromised people. There have been hospital outbreaks in four geographic regions: India and Pakistan, Japan and Korea, South Africa, and Colombia and Venezuela. Isolates from a single region are highly similar in genome sequence, suggesting clonal propagation (4). However, there are substantial differences (tens of thousands of single nucleotide polymorphisms) between isolates from the four regions. These observations raise the conundrum of why these genetically distinct clades of *C. auris* all began causing infections at the same time (5, 6). Compared to other pathogenic *Candida* species, *C. auris* is most closely related to *Candida lusitaniae* and belongs to the *Clavispora/Candida* clade of the *Metschnikowiaceae* family (Fig. 1).

To identify centromeres in *C. auris*, the Sanyal group mapped the genomic distribution of the centromere-specific histone, Cse4, using chromatin immunoprecipitation followed by sequencing (ChIP-Seq). Cse4, also known as CENP-A or CenH3, replaces histone H3 in centromeric nucleosomes but is not found in other genomic locations. These researchers identified one site of Cse4 enrichment per chromosome. These

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PDR-like ABC systems in pathogenic fungi

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ABSTRACT

ABC transporters of the Pleiotropic Drug Resistance (PDR) family are the main actors of antifungal resistance in pathogenic fungi. While their involvement in clinical resistant strains has been proven, their transport mechanism remains unclear. Notably, one hallmark of PDR transporters is their asymmetry, with one canonical nucleotide-binding site capable of ATP hydrolysis while the other site is not. Recent publications reviewed here show that the so-called "deviant" site is of crucial importance for drug transport and is a step towards alleviating the mystery around the existence of non-catalytic binding sites.

1. Introduction

The *fungi* kingdom is estimated to be composed of more than five million species comprising both macroscopic and microscopic organisms [1]. Among them, 307 species are known to be pathogenic to humans but only a few are considered common pathogens [2]. Skin and nails diseases affect approximately 25% of the population worldwide and are mainly caused by dermatophytes. The second most common infections being mucosal infections of the genital and oral tracts named vulvovaginal and oral candidiasis or thrush caused by yeasts of the *Candida* genus [3]. While these remain benign in healthy individuals, invasive infections are a major threat for immunocompromised people for whom they are associated with poor prognosis and high morbidity. In a study based on the French national hospital database over the 2001–2010 period, the overall mortality rate of invasive fungal infections (IFIs) has been evaluated at more than 27% [4]. Globally, IFIs have been estimated to kill 1.5 million people per year [5]; the major causes being invasive candidiasis, aspergillosis, cryptococcosis, coccidioidomycosis, histoplasmosis and pneumocystis [6]. This high mortality is closely linked to the rise of antifungal resistance for which fungal ABC transporters of the Pleiotropic Drug Resistance (PDR) subfamily are major actors. Despite extensive characterization of yeast ABC proteins and significant advances in cryogenic electron microscopy (cryo-EM), no structural data exist for these transporters yet. However, recent mutagenesis and suppressor genetics studies have been shown to be powerful strategies towards the understanding of mechanisms underlying the functioning of PDR transporters.

2. Epidemiology of fungal invasive infections

Candidiasis is caused by human commensal yeast from the *Candida* species, mainly by *Candida albicans*, which become filamentous and grow biofilms in its infectious state. Bloodstream disseminated candidiasis, or candidemia, is the main IFI encountered in hospitals [4,7]. It is a major threat for immunocompromised people in hospital stay and often is the result of the dissemination of the patient's own endogenous *Candida* spp. after an act of invasive surgery. Because of the different trends in geographical species distribution and healthcare settings, great variations are observed in candidemia incidence and associated mortality. For instance, *Candida* ranked as the 4th most common pathogens in nosocomial bloodstream infections in the USA associated with a 39% crude mortality [8], the 6th in France with a 52% death rate in Intensive Care Unit (ICU) in contrast with 18% ICU deaths non-associated with candidemia [9], and the 7th in Brazil with a frightening crude mortality rate of 72% [10].

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Sphingolipidomics of drug resistant *Candida auris* clinical isolates reveal distinct sphingolipid species signatures

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ABSTRACT

Independent studies from our group and others have provided evidence that sphingolipids (SIs) influence the antimycotic susceptibility of *Candida* species. We analyzed the molecular SL signatures of drug-resistant clinical isolates of *Candida auris*, which have emerged as a global threat over the last decade. This included Indian hospital isolates of *C. auris*, which were either resistant to fluconazole (FLC^R) or amphotericin B (AmB^R) or both drugs. Relative to *Candida glabrata* and *Candida albicans* strains, these *C. auris* isolates were susceptible to SL pathway inhibitors such as myriocin and aureobasidin A, suggesting that SL content may influence azole and AmB susceptibilities. Our analysis of SLs confirmed the presence of 140 SL species within nine major SL classes, namely the sphingoid bases, Cer, αOH-Cer, dhCer, PCer, αOH-PCer, αOH-GlcCer, GlcCer, and IPC. Other than for αOH-GlcCer, most of the SLs were found at higher concentrations in FLC^R isolates as compared to the AmB^R isolates. SLs were at intermediate levels in FLC^R + AmB^R isolates. The observed diversity of molecular species of SL classes based on fatty acyl composition was further reflected in their distinct specific imprint, suggesting their influence in drug resistance. Together, the presented data improves our understanding of the dynamics of SL structures, their synthesis, and link to the drug resistance in *C. auris*.

1. Introduction

Increasing antimicrobial resistance in pathogenic fungi is becoming a global health threat and eroding our ability to control fungal infections with a limited armamentarium of antifungals [1]. Most of the fungal infections associated with significant mortality and antimicrobial resistance are triggered by opportunistic human fungal pathogens [1,2]. The major pathogens, *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*, may survive in anatomically distinct locations within the host and are capable of fostering deep-seated infections in patients with compromised immune systems [3]. In contrast to the common *C. albicans*, non-albicans *Candida* (NAC) species are evolving as problematic drug resistance pathogens [1]. The recent emergence of multiple drug-resistant *Candida auris* clades within a short

Abbreviations: MDR, multidrug resistance; NAC, non-albicans *Candida*; FLC, fluconazole; AmB, amphotericin B; MS, mass spectrometry; SLs, sphingolipids; Liquid chromatography-tandem mass spectrometry, LC-MS/MS; FLC^S, FLC-resistant; AmB^S, AmB-resistant; FLC^R + AmB^R, both FLC and AmB resistant; MIPC, mannosyl-inositol-phosphoceramides; $M(IP)_2C$, mannosyl-diinositol-phosphoceramides; PDREs, Pdr1/Pdr3 response elements; PCA, principal component analysis; MYR, myriocin; AbA, aureobasidin A; SPT, serine palmitoyl-CoA transferase; IPC, inositolphosphorylceramide; GlcCer, glucosylceramide; DHS, dihydrosphingosine; SPH, sphingosine; S1P, sphingosine-1-phosphate; DHS1P, dihydrosphingosine-1-phosphate; PHS, phytosphingosine; PHS1P, phytosphingosine-1-phosphate; Glucosyl-SPH, glucosyl sphingosine; dhCer, dihydroceramide; Cer, ceramides; αOH-Cer, αhydroxy ceramides; PCer, phytoceramide; αOH-PCer, αhydroxy phytoceramide; αOH-GlcCer, αhydroxy glucosylceramide; IPCs, inositol phosphoryl ceramides

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Review

Multidrug transporters of *Candida* species in clinical azole resistance

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ABSTRACT

Over-expression of the human P-glycoprotein (P-gp) in tumor cells is a classic example of an ABC protein serving as a hindrance to effective chemotherapy. The existence of proteins homologous to P-gp in organisms encompassing the entire living kingdom highlights extrusion of drugs as a general mechanism of multidrug resistance. Infections caused by opportunistic human fungal pathogens such as *Candida* species are very common and has intensified in recent years. The typical hosts, who possess suppressed immune systems due to conditions such as HIV and transplantation surgery etc., are prone to fungal infections. Prolonged chemotherapy induces fungal cells to eventually develop tolerance to most of the antifungals currently in clinical use. Amongst other prominent mechanisms of antifungal resistance such as manipulation of the drug target, rapid efflux achieved through overexpression of multidrug transporters has emerged as a major resistance mechanism for azoles. Herein, the azole-resistant clinical isolates of *Candida* species utilize a few select efflux pump proteins belonging to the ABC and MFS superfamilies, to deter the toxic accumulation of therapeutic azoles and thus, facilitating cell survival. In this article, we summarize and discuss the clinically relevant mechanisms of azole resistance in *Candida albicans* and non-*albicans Candida* (NAC) species, specifically highlighting the role of multidrug efflux proteins in the phenomenon.

1. Introduction

Human pathogenic *Candida albicans* and certain non-*albicans Candida* (NAC) species, conventionally associated with healthy individuals as harmless commensals, are endowed with the propensity to transform into notorious pathogens in immunocompromised hosts (Robbins et al., 2017; Whaley et al., 2017). *Candida* species not only cause superficial infections but are also responsible for disseminated bloodstream and deep-tissue infections in hospitalized patients with incapacitated immunity (Prasad et al., 2015). Among the various *Candida* species that infect humans, *C. albicans* is the most prominent species, however, other emerging NAC species such as *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei*, etc. have recently gained epidemiological significance due to their increased prevalence globally (Lindberg et al., 2019; Whaley et al., 2017). Recently, a paradigm shift of candidiasis from *C. albicans* to NAC has been observed due to the emergence of another multi-drug resistant NAC species, *C. auris* (Chowdhary et al., 2017; Lindberg et al., 2019; Whaley et al., 2017). Its capability of nosocomial transmission and the ability to form adherent biofilms on clinically important substrates led to a high number of hospital outbreaks of *C. auris* globally (Chowdhary et al., 2017; Lockhart et al., 2016; Muñoz et al., 2018). The higher percentage of resistance to multiple classes of antifungal agents is the greatest challenge posed by this recently emerged NAC species. The unique features of *C. auris* make it challenging to diagnose, treat and eradicate from intensive care hospital wards as compared to other pathogenic *Candida* species (Forsberg et al., 2019).

The relentless use of antifungal drugs for prophylactic or empirical treatment has led to a change in the epidemiology of fungemia and the parallel emergence of fungal pathogens that manifest resistance to multiple, structurally unrelated drugs with different modes of action (Prasad et al., 2015). This phenomenon of multidrug resistance (MDR) is characterized by simultaneous resistance to at least two distinct classes of antifungal agents. The development of tolerance towards a particular drug mainly relies on the mode of action of that particular drug, however, other mechanisms which are largely uncharacterized also contribute to the emergence of drug tolerance (Dhamgaye et al., 2014; Hameed et al., 2011; Nair et al., 2017; Shapiro et al., 2011). Fungal species may either be intrinsically resistant to a class of drugs or may gradually develop tolerance upon constant exposure to a particular

Abbreviations: ABC, ATP-binding cassette; MFS, Major-Facilitator superfamily; MDR, Multidrug resistance; TMD, Transmembrane domain; NBD, Nucleotide-binding domain; TMHs, Transmembrane helices; NAC, non-*albicans Candida*; PM, Plasma membrane; CDR1, Candida drug resistance 1; MDR1, Multidrug resistance 1; FD, Facilitated diffusion; PDR, Pleiotropic drug resistance; DHA1, Drug/H^+ antiporter; MRP, Multidrug resistance protein; TOR1, Target of Rapamycin 1

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Hydrogel-mediated delivery of celastrol and doxorubicin induces a synergistic effect on tumor regression *via* upregulation of ceramides†

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The release of anticancer drugs in systemic circulation and their associated toxicity are responsible for the poor efficacy of chemotherapy. Therefore, the identification of new chemotherapeutic combinations designed to be released near the tumor site in a sustained manner has the potential to enhance the efficacy and reduce the toxicity associated with chemotherapy. Here, we present the identification of a combination of doxorubicin, a DNA-binding topoisomerase inhibitor, with a naturally occurring triterpenoid, celastrol, that induces a synergistic effect on the apoptosis of colon cancer cells. Hydrogel-mediated sustained release of a combination of doxorubicin and celastrol in a murine tumor model abrogates tumor proliferation, and increases the median survival with enhanced apoptosis and concurrent reduction in proliferation. Sphingolipid profiling (LC–MS/MS) of treated tumors showed that the combination of celastrol and doxorubicin induces global changes in the expression of sphingolipids with an increase in levels of ceramides. We further demonstrate that this dual drug combination induces a significant increase in the expression of ceramide synthase 1, 4, and 6, thereby increasing the level of ceramides that contribute to the synergistic apoptotic effect. Therefore, hydrogel-mediated localized delivery of a combination of celastrol and doxorubicin provides a new therapeutic combination that induces a sphingolipid-mediated synergistic effect against colon cancer.

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Introduction

Cancer chemotherapy is often challenged with low efficacy and high toxicity of anticancer drugs due to their lack of specificity for cancer cells leading to poor patient survival.[1] Therefore, combination therapy is usually preferred in clinical settings as it helps in reducing the toxicity owing to the lower dosage of chemotherapeutics.[2] Combination therapies also provide advantages of high efficacy, enhanced patient survival, and ability to combat drug resistance as a combination of drugs can modulate multiple signalling pathways in cancer cells.[3] However, numerous challenges are associated with the use of combination therapy like poor knowledge of an appropriate combination of drugs and their dosage, bioavailability of drugs in the desired ratio at the tumor site, their non-specific targeting, varying pharmacokinetics among different drugs, and lack of understanding of their mode of action.[4]

Many natural products like taxanes have been clinically approved for cancer treatment in combination with other therapeutic regimens.[5] Celastrol (CEL), a quinine methide triterpenoid extracted from *Tripterygium wilfordii* Hook. f., is a traditional Chinese medicine.[6,7] Recent studies have shown that CEL can enhance leptin sensitivity,[8] and can also activate the heat shock factor 1 (HSF1) that enhances the energy expenditure and mitochondrial functions for the treatment of obesity.[9] CEL is known to inhibit cancer cell proliferation by inducing the expression of pro-apoptotic proteins like Bax and cytochrome c, and by enhancing the Bax/Bcl-2 ratio.[10,11] CEL reduces the colon tumor progression where CEL-mediated activation of LKB1 activates AMPKα and phosphorylates YAP, leading to the degradation of β-catenin.[12] Administration of CEL also inhibits ulcerative colitis-induced colorectal cancer by preventing the upregulation of β-catenin, and downregulating the expression of inflammatory cytokines.[13] Therefore, a

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REVIEW

Potential use of nanotechnology in sustainable and 'smart' agriculture: advancements made in the last decade

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Abstract
Ever since mankind embraced technology, the largest number of inventions have been aimed at agricultural improvement, more than any other sectors where technology is used. Nonetheless, today we are struggling to meet the ever increasing hunger of a growing world population. We have almost exhausted the supply of traditional technological ammunitions in the arsenal of agricultural science. The only way forward is to embrace smart agricultural practice in a sustainable manner. Use of modern electronics and material science to increase production, without further increasing fertilizer or pesticide input, can be referred to as smart and sustainable agriculture. Scientists have made giant leaps in the field of 'biology at nanoscale' during the first decade of the present century. Nanoparticles and nanosensors have huge potential in agricultural advancements, if used wisely with proper caution. Nanoparticles can be used for getting higher yield and for crop protection. Nanoparticles can also aid in the rate limiting process of gene delivery during genetic improvement of crop species. Nanobiosensors can contribute to smart farming by growth monitoring, real time detection of pests, and continuous monitoring of local environment. In this review, we will update the readers with some of the advancements made in these directions during the last decade.

Keywords Nanopesticides · Nanosensor · Plant biosensor · Smart farming · Precision agriculture · Slow release

Introduction

Agricultural practice by human beings has evolved through centuries in time and space, and parallels evolution of our race from hunter gatherers to space explorers. The improvement of agriculture has been steady and exponential since its inception. The first half of the past century has seen rapid mechanization, while the second half can be attributed to technologies like transgenic crop production and marker-assisted breeding. This phenomenal rise of crop production has its own trade-offs in terms of decreasing nutritional quality of lands, increasing pathogen and pest problem, and finally adverse effects on environment. The decade before the last one has seen more research on biofertilizers, microbiome and soil health. While these advancements were necessary for the improvement of mankind, rapid use of technology has also led us to a situation where today we have almost reached the ceiling of crop production. Only a small room is still left for improvement with our current skillset and available technologies. To feed the projected population of 10 billion by 2050 (United-Nations 2019), we must further increase our crop production by sustainable approach. The only way to achieve this would be to acquire cutting edge technologies which were not hitherto applied in the agricultural sector. 'Smart agriculture' methods such as remote sensing, satellite technology, safe but effective pesticides, and next-generation bio-sensors to detect soil health must be employed. In this review, we shall discuss the recent advances and the prospects of nanoparticles and nanobiosensors in the area of agriculture (Fig. 1).

Use of nanoparticles and use of nanosensors for agricultural benefit are two completely different fields of research. Many biosensors are coated with particular proteins and work at nanoscale, but without any involvement of nanoparticles at the recognition level. On the other hand, biosensors can also use small particles (which can be called nanoparticles in true technical sense). A composite electrode coated with nanoparticles along with DNA or protein is an example of such biosensors (Gupta et al. 2020).

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Chapter 8
Lipidomics Approaches: Applied to the Study of Pathogenesis in *Candida* Species

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Abstract High rate of reported cases of infections in humans caused by fungal pathogens pose serious concern. Potentially these commensal fungi remain harmless to the healthy individuals but can cause severe systemic infection in patients with compromised immune system. Effective drug remedies against these infections are rather limited. Moreover, frequently encountered multidrug resistance poses an additional challenge to search for alternate and novel targets. Notably, imbalances in lipid homeostasis which impact drug susceptibility of *Candida albicans* cells do provide clues of novel therapeutic strategies. Sphingolipids (SPHs) are unique components of *Candida* cells, hence are actively exploited as potential drug targets. In addition, recent research has uncovered that several SPH intermediates and of other lipids as well, govern cell signaling and virulence of *C. albicans*. In this chapter, we highlight the role of lipids in the physiology of *Candida*, particularly focusing on their roles in the development of drug resistance. Considering the importance of lipids, the article also highlights recent high-throughput analytical tools and methodologies, which are being employed in our understanding of structures, biosynthesis, and roles of lipids in fungal pathogens.

Keywords Lipids · Pathogenic fungi · Functions · Mass spectrometry

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Information theoretic measures and mutagenesis identify a novel linchpin residue involved in substrate selection within the nucleotide-binding domain of an ABCG family exporter Cdr1p

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Substrate selection

ABSTRACT

ABC transporters are membrane-bound pumps composed of two major domains: the transmembrane domain(s) (TMDs) and the nucleotide-binding domain(s) (NBDs). Sequence analyses of the NBDs of key ABC exporters revealed a residue position within the H-loop to be differentially conserved in the ABCG family, wherein there lies glutamine instead of positively charged arginine/lysine as in non-ABCG members. Consequently, contrasting NBD sequences of fungal Pleiotropic Drug Resistance transporters (PDR/ABCG) with that of Cholesterol/Phospholipid and Retinal (CPR/ABCA) Flippase family revealed a high Cumulative Relative Entropy (CRE) score of this residue position implying its family-specific functional significance. Further, substitution of the glutamine by arginine in both the NBDs of a representative PDR/ABCG member, (*Candida* drug resistance 1 protein) Cdr1p led to selective susceptibility of the *Saccharomyces cerevisiae* strains overexpressing the corresponding mutant proteins (Q362R and Q1060R) towards antifungal substrates without any impact on the ATPase activity. Consistent with the findings from previous studies on H-loop motif of fungal PDR transporters, the current report points towards a role of the glutamine residue within both canonical and divergent H-loop of Cdr1p in conferring substrate selection in a precisely identical manner.

1. Introduction

ABC transporters with their wide range of physiological and clinical implications attract significant interest of medical professionals [1]. From a biochemical perspective, these proteins serve as key models to study nucleotide-catalysis. Structurally, these proteins are composed of the transmembrane domain(s) (TMDs) and the nucleotide-binding domain(s) (NBDs). While the purpose of the former is to act as the substrate interactive region, the latter provides the power to pump the substrates via ATP-binding and hydrolysis. Notably, there exists a significant proportion of ABC proteins which harbor unique substitutions in the core motifs of the NBDs that are highly conserved in the ABC superfamily [2,3]. As a result of these unique alterations, only one of the nucleotide-binding site (NBS) is canonical, while the other is non-canonical [4]. Even though, the latter has been referred to as non-catalytic, recent evidences suggest its key role in the transport mechanism [5,6]. Some noteworthy asymmetric ABC exporters include Cystic Fibrosis Transmembrane Conductance regulator (CFTR), Multidrug resistance protein 1 (MRP1), Transporter associated with antigen processing (TAP1/TAP2) and the yeast Pleiotropic drug resistance (PDR) transporters, Cdr1p of *Candida albicans* and Pdr5p of *Saccharomyces cerevisiae* [4,7,8]. Cdr1p is a prime contributor of azole resistance in the fungal pathogen *C. albicans* and hence serves as a prime target in the fungal pathogen [9]. One characteristic feature of the PDR family is that herein, the NBD precede the TMD [10]. With respect to the Human Genome Organisation (HUGO) nomenclature system, the PDR family members are included in the ABCG family [4]. Recent structural insights highlighted a novel structural organisation of the ABCG/PDR proteins which is in stark contrast with other groups of ABC proteins [11,12]. Hence, there exists every possibility of a distinct

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Review

Application of Core/Shell Nanoparticles in Smart Farming: A Paradigm Shift for Making the Agriculture Sector More Sustainable

Shikha Dhiman, Annu Yadav, Nitai Debnath, and Sumistha Das*

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ABSTRACT: Modern agriculture has entered an era of technological plateau where intervention of smarter technology like nanotechnology is imminently required for making this sector economically and environmentally sustainable. Throughout the world, researchers are trying to exploit the novel properties of several nanomaterials to make agricultural practices more efficient. Core/shell nanoparticles (CSNs) have attracted much attention because of their multiple attractive novel features like high catalytic, optical, and electronic properties for which they are being widely used in sensing, imaging, and medical applications. Though it also has the promise to solve a number of issues related to agriculture, its full potential still remains mostly unexplored. This review provides a panoramic view on application of CSNs in solving several problems related to crop production and precision farming practices where the wastage of resources can be minimized. This review also summarizes different classes of CSNs and their synthesis techniques. It emphasizes and analyzes the probable potential applications of CSNs in the field of crop improvement and crop protection, detection of plant diseases and agrochemical residues, and augmentation of chloroplast mediated photosynthesis. In a nutshell, there is enormous scope to formulate and design CSN-based smart tools for applications in agriculture, making this sector more sustainable.

KEYWORDS: *precision agriculture, controlled release, photosynthesis enhancement, nanosensor, nanotoxicity*

1. INTRODUCTION

Agriculture is the most promising and secure sector and is the primary source of food and feed supplies. Due to the ever-rising population, accelerated nitrogen mining, diminishing arable land, insufficient water supply, degrading organic soil, environmental issues, and so many other causes, the global food crisis is not getting addressed adequately. Although a huge number of advancements in sustainable agriculture through modern irrigation techniques, climate monitors, and chemical and biological pest control measures have played a huge role to meet the goal, pesticide resistance and leaching of harmful agrochemicals resulting in environmental pollution are the barriers in the way to meet the global food demand. In this present scenario, it is of utmost necessity to use advanced technologies such as nanotechnology in agricultural sciences. The nanoparticle's high surface area to volume ratio ensures higher efficacy and a tunable surface with multiple functionalities and makes them suitable for crop protection and growth promotion. Modification of the size, shape, surface moiety, and inner structure make the nanoparticles (NPs) ideal candidates for delivery of agrochemicals and genetic material to improve the quality and quantity of the crop yield. Moreover, nanotechnology can be utilized in precision farming, soil toxicity profiling, plant biosafety monitoring, soil and water quality improvement, climatic sensors, etc. The European Commission identified smart nanotechnology as one of the six key enabling technologies to impact the global market including the agriculture sector.[1]

A huge number of nanomaterials like silica, titanium dioxide, zinc oxide, and aluminum oxide NPs have been successfully experimented with as nanopesticides.[2,3] Nanoforms of sulfur,[4] iron,[5] manganese,[6] copper,[7] etc. have shown their efficiency as fertilizer. Nano silver[8] and nano zinc oxide[9] have the potential to protect the plants from several microbial phytopathogens. Apart from these inorganic nanocides, a good number of organic nanomaterials have also become popular either as nanocidal agent themselves, Chauhan et al. (2017), or as a carrier of agrochemicals.[10] Polymers like chitosan,[11] polycaprolactone,[12] amphiphilic block copolymers, etc. in their nanoform and lipid-based nanocarriers like liposomes proved to be very useful as an agrochemical carrier and helped in its controlled release. Nanomaterials can also be utilized in devising sensors which can monitor several important agricultural parameters like soil quality, etc.[13]

The main purpose of applying nanotechnology in agriculture is to reduce the dosage of toxic chemicals like pesticides, fungicides, minimize nutrient losses, and increase yield through pest and other phytopathogen management, promoting seed germination rate, crop vigor, managing beneficial microorganisms in soil, helping crop biofortification, etc.[14] Various

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RESEARCH ARTICLE

Functional and Comparative Analysis of Centromeres Reveals Clade-Specific Genome Rearrangements in *Candida auris* and a Chromosome Number Change in Related Species

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ABSTRACT The thermotolerant multidrug-resistant ascomycete *Candida auris* rapidly emerged since 2009 causing systemic infections worldwide and simultaneously evolved in different geographical zones. The molecular events that orchestrated this sudden emergence of the killer fungus remain mostly elusive. Here, we identify centromeres in *C. auris* and related species, using a combined approach of chromatin immunoprecipitation and comparative genomic analyses. We find that *C. auris* and multiple other species in the *Clavispora/Candida* clade shared a conserved small regional GC-poor centromere landscape lacking pericentromeres or repeats. Further, a centromere inactivation event led to karyotypic alterations in this species complex. Interspecies genome analysis identified several structural chromosomal changes around centromeres. In addition, centromeres are found to be rapidly evolving loci among the different geographical clades of the same species of *C. auris*. Finally, we reveal an evolutionary trajectory of the unique karyotype associated with clade 2 that consists of the drug-susceptible isolates of *C. auris*.

IMPORTANCE *Candida auris*, the killer fungus, emerged as different geographical clades, exhibiting multidrug resistance and high karyotype plasticity. Chromosomal rearrangements are known to play key roles in the emergence of new species, virulence, and drug resistance in pathogenic fungi. Centromeres, the genomic loci where microtubules attach to separate the sister chromatids during cell division, are known to be hot spots of breaks and downstream rearrangements. We identified the centromeres in *C. auris* and related species to study their involvement in the evolution and karyotype diversity reported in *C. auris*. We report conserved centromere features in 10 related species and trace the events that occurred at the centromeres during evolution. We reveal a centromere inactivation-mediated chromosome number change in these closely related species. We also observe that one of the geographical clades, the East Asian clade, evolved along a unique trajectory, compared to the other clades and related species.

KEYWORDS *Candida haemulonii*, fungal pathogen, centromere inactivation, geographical clades, karyotype evolution

First isolated from an infected ear of a patient in Japan in 2009, *Candida auris* emerged as a multidrug-resistant opportunistic fungal pathogen causing nosocomial infections worldwide in a short time span (1–5). It can survive at elevated temperatures and high salt concentrations, which otherwise act as physiological barriers to

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Review

Directed Mutational Strategies Reveal Drug Binding and Transport by the MDR Transporters of *Candida albicans*

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Abstract: Multidrug resistance (MDR) transporters belonging to either the ATP-Binding Cassette (ABC) or Major Facilitator Superfamily (MFS) groups are major determinants of clinical drug resistance in fungi. The overproduction of these proteins enables the extrusion of incoming drugs at rates that prevent lethal effects. The promiscuity of these proteins is intriguing because they export a wide range of structurally unrelated molecules. Research in the last two decades has used multiple approaches to dissect the molecular basis of the polyspecificity of multidrug transporters. With large numbers of drug transporters potentially involved in clinical drug resistance in pathogenic yeasts, this review focuses on the drug transporters of the important pathogen *Candida albicans*. This organism harbors many such proteins, several of which have been shown to actively export antifungal drugs. Of these, the ABC protein *Ca*Cdr1 and the MFS protein *Ca*Mdr1 are the two most prominent and have thus been subjected to intense site-directed mutagenesis and suppressor genetics-based analysis. Numerous results point to a common theme underlying the strategy of promiscuity adopted by both *Ca*Cdr1 and *Ca*Mdr1. This review summarizes the body of research that has provided insight into how multidrug transporters function and deliver their remarkable polyspecificity.

Keywords: *Candida albicans*; ABC transporters; MFS transporters; multidrug efflux pumps; *Ca*Cdr1; *Ca*Mdr1; polyspecificity; interdomain crosstalk; mutagenesis; suppressor genetics

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1. Introduction

Human pathogenic yeast that include *Candida albicans* and non-*albicans Candida* (NAC) species are commensal pathogens infecting individuals with compromised immunity [1]. The superficial infections caused by *C. albicans* and NAC species can also extend to disseminated bloodstream and deep-tissue infections [1]. Although *C. albicans* and a few NAC species (e.g., *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis*) are considered to be the most common fungi infecting immunocompromised patients, more recently, *Candida auris* has been recognized as a global health threat (https://www.cdc.gov/fungal/candida-auris/index.html) [2]. Besides the ability to spread nosocomially, its propensity to form adherent biofilms on medically relevant substrates has led to numerous hospital outbreaks of *C. auris* globally [3]. A higher percentage of clinical isolates resistant to multiple classes of antifungal agents is the greatest challenge posed by this recently emerged NAC species [4]. Apart from *C. auris*, the prophylactic or, prolonged use of antifungal drugs has allowed many other *Candida* species to manifest

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EXPERIMENTAL THERAPEUTICS

Cholic Acid-Peptide Conjugates as Potent Antimicrobials against Interkingdom Polymicrobial Biofilms

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ABSTRACT Interkingdom polymicrobial biofilms formed by Gram-positive *Staphylococcus aureus* and *Candida albicans* pose serious threats of chronic systemic infections due to the absence of any common therapeutic target for their elimination. Herein, we present the structure-activity relationship (SAR) of membrane-targeting cholic acid-peptide conjugates (CAPs) against Gram-positive bacterial and fungal strains. Structure-activity investigations validated by mechanistic studies revealed that valine-glycine dipeptide-derived CAP 3 was the most effective broad-spectrum antimicrobial against *S. aureus* and *C. albicans*. CAP 3 was able to degrade the preformed single-species and polymicrobial biofilms formed by *S. aureus* and *C. albicans*, and CAP 3-coated materials prevented the formation of biofilms. Murine wound and catheter infection models further confirmed the equally potent bactericidal and fungicidal effect of CAP 3 against bacterial, fungal, and polymicrobial infections. Taken together, these results demonstrate that CAPs, as potential broad-spectrum antimicrobials, can effectively clear the frequently encountered polymicrobial infections and can be fine-tuned further for future applications.

KEYWORDS antibacterial, antifungal, antimicrobials, bile acids, biofilms, membrane targeting

Biofilms formed on medical implants or infected tissues are usually complex, diverse, heterogenous, and polymicrobial in nature, where microbes from different species and genera evolve a mutualistic or synergistic relationship through physical and chemical interactions (1). These interactions help the microorganisms cohabit on epithelial surfaces and on indwelling medical devices (1). Sessile communities of microorganisms grown on a substratum or tissue can act as major mediators of systemic infections. These biofilms help in the enrichment of nutrients in their extracellular matrix and also enable them to evade the antibiotic treatment and host defense mechanism (2–4). Migration of detached microcolonies from biofilms to uninfected tissues can allow the formation of biofilms at distant sites and can cause persistent chronic recurrent systemic infections (5).

Candida albicans, the most prevalent of all fungal pathogens, is the fourth leading cause of bloodstream infections that readily forms biofilms on indwelling medical devices such as dental materials, stents, prostheses, implants, endotracheal tubes, pacemakers, and catheters (6). *C. albicans* is also a part of ~25% of wound infections and contributes to 50% of the overall microbial burden (7). The majority of nosocomial

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Cell Death & Disease

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Alternative splicing of *ceramide synthase 2* alters levels of specific ceramides and modulates cancer cell proliferation and migration in Luminal B breast cancer subtype

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Abstract
Global dysregulation of RNA splicing and imbalanced sphingolipid metabolism has emerged as promoters of cancer cell transformation. Here, we present specific signature of alternative splicing (AS) events of sphingolipid genes for each breast cancer subtype from the TCGA-BRCA dataset. We show that *ceramide synthase 2* (*CERS2*) undergoes a unique cassette exon event specifically in Luminal B subtype tumors. We validated this exon 8 skipping event in Luminal B cancer cells compared to normal epithelial cells, and in patient-derived tumor tissues compared to matched normal tissues. Differential AS-based survival analysis shows that this AS event of *CERS2* is a poor prognostic factor for Luminal B patients. As Exon 8 corresponds to catalytic Lag1p domain, overexpression of AS transcript of *CERS2* in Luminal B cancer cells leads to a reduction in the level of very-long-chain ceramides compared to overexpression of protein-coding (PC) transcript of *CERS2*. We further demonstrate that this AS event-mediated decrease of very-long-chain ceramides leads to enhanced cancer cell proliferation and migration. Therefore, our results show subtype-specific AS of sphingolipid genes as a regulatory mechanism that deregulates sphingolipids like ceramides in breast tumors, and can be explored further as a suitable therapeutic target.

Introduction

Sphingolipids help in maintaining the structural integrity of cell membranes, and also aid in numerous signaling processes in response to different stimuli[1–3]. Dysregulation of the sphingolipid pathway is one of the important contributing factors for breast cancer pathogenesis as it is implicated in various aspects of cancer initiation, progression, invasion, metastasis, and drug resistance[4,5]. Any alteration in the enzymes regulating the expression of sphingolipids play a vital role in cancer cell survival and apoptosis[6]. Therefore, dynamic metabolic interconversions among sphingolipids, attuning the cellular signaling mechanisms in cancer cells, make them a desirable yet challenging target for cancer therapy[7,8].

Ceramides are key precursors of complex sphingolipids that are synthesized via de novo as well as through salvage pathway. De novo pathway involves conjugation of specific fatty acyl chains to sphinganine using ceramide synthases, whereas salvage pathway involves degradation of sphingomyelins and complex sphingolipids to ceramides[9]. Human breast cancer tissues usually have high expression of ceramide species as compared to normal tissue samples[10]. There is an increased expression of

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Effect of synthetic route in particle size distribution of zinc oxide, silver and carbon nanoparticles and its role in controlling phytopathogenic fungus *Alternaria solani*

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ABSTRACT

There are plethoras of studies on antifungal effect of nanomaterials. But the effect of synthetic route on physico-chemical characteristics of nanoparticles and its corresponding effect on antifungal effect are not properly investigated. Though green synthesis is considered to be more eco-friendly and economical, mostly resultant nanomaterials have much broader size range in comparison with those prepared chemically. In this study three nanoparticles – zinc oxide, silver and carbon were prepared both by chemical and green routes and their efficacy was evaluated in controlling *Alternaria solani*, a phytopathogenic fungus. The average particle size of both zinc oxide and silver nanoparticles was smaller in case of chemical synthesis and these particles were much more potent antifungal agent than those particles that were synthesised by green route. In our study, there was no effect of synthetic route in size and shape of carbon nanoparticles and these particles were mostly not effective against *A. solani*.

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Introduction

Nanotechnology is the science and technology, which deals with extremely small materials that are in the size range of 1—100 nm (Bayda et al. 2019). The novel physico-chemical properties of nanoscale materials are now being exploited in all facets of human needs starting from manufacturing sector, electronics (Laurent et al. 2008), health care (Fatikow et al. 2012), energy harvesting (Kumar et al. 2015), wastewater treatment

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Cholic Acid-Derived Amphiphile which Combats Gram-Positive Bacteria-Mediated Infections via Disintegration of Lipid Clusters

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ABSTRACT: Inappropriate and uncontrolled use of antibiotics results in the emergence of antibiotic resistance, thereby threatening the present clinical regimens to treat infectious diseases. Therefore, new antimicrobial agents that can prevent bacteria from developing drug resistance are urgently needed. Selective disruption of bacterial membranes is the most effective strategy for combating microbial infections as accumulation of genetic mutations will not allow for the emergence of drug resistance against these antimicrobials. In this work, we tested cholic acid (CA) derived amphiphiles tethered with different alkyl chains for their ability to combat Gram-positive bacterial infections. In-depth biophysical and biomolecular simulation studies suggested that the amphiphile with a hexyl chain (**6**) executes more effective interactions with Gram-positive bacterial membranes as compared to other hydrophobic counterparts. Amphiphile **6** is effective against multidrug resistant Gram-positive bacterial strains as well and does not allow the adherence of *S. aureus* on amphiphile **6** coated catheters implanted in mice. Further, treatment of wound infections with amphiphile **6** clears the bacterial infections. Therefore, the current study presents strategic guidelines in design and development of CA-derived membrane-targeting antimicrobials for Gram-positive bacterial infections.

KEYWORDS: *antibacterial, bile acids, membrane interactions, MD simulations, antimicrobials*

■ INTRODUCTION

Infections caused by Gram-positive bacteria cause critical medical conditions such as abscesses, endocarditis, osteomyelitis, and pneumonia.[1] Treatment of these ailments faces extreme challenges due to the emergence of bacterial resistance toward existing antibiotic regimens.[2] Most of the commonly used antibiotics target the essential components of bacterial cellular machinery and become ineffective due to different genetic mutations.[3] Bacterial membranes are considered as the effective target for antimicrobial agents as physical damage of the membranes can directly kill the bacteria and disrupt other cellular functions of bacteria.[4,5] Therefore, the membrane-targeting bactericidal effect of antimicrobials mediated by electrostatic and hydrophobic interactions will not allow the bacteria to develop drug resistance as well.

Antimicrobial peptides (AMPs) are present in all organisms and act against different microbial infections by performing selective interactions with the microbial membranes.[6,7] The

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ABC-finder: A containerized web server for the identification and topology prediction of ABC proteins

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ABSTRACT

In view of the multiple clinical and physiological implications of ABC transporter proteins, there is a considerable interest among researchers to characterize them functionally. However, such characterizations are based on the premise that ABC proteins are accurately identified in the proteome of an organism, and their topology is correctly predicted. With this objective, we have developed ABC finder, i.e., a Docker-based package for the identification of ABC proteins in all organisms, and visualization of the topology of ABC proteins using a web browser. ABC-finder is built and deployed in a Linux container, making it scalable for many concurrent users on our servers and enabling users to download and run it locally. Overall, ABC-finder is a convenient, portable, and platform-independent tool for the identification and topology prediction of ABC proteins.

ABC-finder is accessible at http://abc-finder.osdd.jnu.ac.in.

1. Introduction

ABC proteins comprise one of the largest and most important protein families, most proteins being involved in active transport [1]. A typical ABC transporter is composed of a pair of nucleotide-binding domains (NBDs) and transmembrane domains (TMDs) [2]. While the NBDs are involved in fueling the transport process by means of ATP hydrolysis, the TMDs are responsible for substrate recognition and form the translocation channel [3]. NBDs have several conserved motifs, namely, Walker A, Walker B, Signature sequence (C-motif), H-loop, D-loop, and Q-loop [4]. Contrarily, the TMDs display poor conservation across different subfamilies. HUGO Gene Nomenclature Committee divided the ABC superfamily into 7 subfamilies from ABCA to ABCG. This classification was later extended for non-mammalian proteins with the addition of the ABCH subfamily found in insects [5] and fishes [6,7], and the ABCI subfamily found in plants [8]. ABC transporters can function both as importers as well as exporters, however, the former is restricted only to bacteria and plants and mediate the uptake of various nutrients, micronutrients, and phytohormones, etc. [9]. On the other hand, the ABC exporters facilitate the extrusion of a wide spectrum of substrates including ions, lipids, peptides, toxic xenobiotics, etc. [10]. Numerous studies have suggested the role of ABC transporters in various human diseases and chemoresistance [1]. Besides their role as transporters, some ABC proteins harbor just the NBDs, for instance, the ABCE and ABCF family representatives, and have implications in ribosome biogenesis, translation control, etc. [11,12], further adding to the immense biological relevance of this superfamily. The primary requirement for in-depth investigations pertaining to ABC proteins is their accurate identification from the genome/proteome and analysis of its topology. Even though programs performing certain steps in isolation exist, there is a need for a unified package to do the job with lesser hassles and more emphasis on reproducibility, keeping in view that reproducibility of research is the key element in modern science [13]. In an effort to make a simpler program available to the biology research community, we herein present "ABC-finder" as a simple and fast tool for identification and topology prediction of ABC proteins based on our previously established pipeline which led to the inventorization of ABC proteins in a number of yeast species [14–16]. ABC-finder combines stand-out methodologies, namely profile-HMM and TOPCONS for homology detection, and prediction of the topology of membrane proteins, respectively in a seamless manner whereby the users need to provide only the organism's name or the proteome file as an input. Our analysis

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ABC Transporter Genes Show Upregulated Expression in Drug-Resistant Clinical Isolates of *Candida auris*: A Genome-Wide Characterization of ATP-Binding Cassette (ABC) Transporter Genes

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ATP-binding cassette (ABC) superfamily members have a key role as nutrient importers and exporters in bacteria. However, their role as drug exporters in eukaryotes brought this superfamily member to even greater prominence. The capacity of ABC transporters to efflux a broad spectrum of xenobiotics represents one of the major mechanisms of clinical multidrug resistance in pathogenic fungi including *Candida* species. *Candida auris*, a newly emerged multidrug-resistant fungal pathogen of humans, has been responsible for multiple outbreaks of drug-resistant infections in hospitals around the globe. Our study has analyzed the entire complement of ABC superfamily transporters to assess whether these play a major role in drug resistance mechanisms of *C. auris*. Our bioinformatics analyses identified 28 putative ABC proteins encoded in the genome of the *C. auris* type-strain CBS 10913T; 20 of which contain transmembrane domains (TMDs). Quantitative real-time PCR confirmed the expression of all 20 TMD transporters, underlining their potential in contributing to the *C. auris* drug-resistant phenotype. Changes in transcript levels after short-term exposure of drugs and in drug-resistant *C. auris* isolates suggested their importance in the drug resistance phenotype of this pathogen. *CAUR_02725* orthologous to *CDR1*, a major multidrug exporter in other yeasts, showed consistently higher expression in multidrug-resistant strains of *C. auris*. Homologs of other ABC transporter genes, such as *CDR4*, *CDR6*, and *SNQ2*, also displayed raised expression in a sub-set of clinical isolates. Together, our analysis supports the involvement of these transporters in multidrug resistance in *C. auris*.

Keywords: *Candida auris*, multidrug resistance, ABC proteins, drug efflux pumps, fluconazole

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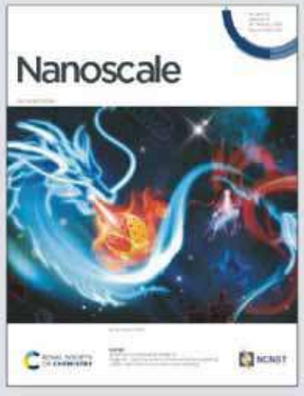

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REVIEW

Potential use of nanotechnology in sustainable and 'smart' agriculture: advancements made in the last decade

Ranjita Ghosh Moulick[1] · Sumistha Das[2] · Nitai Debnath[2] · Kaustav Bandyopadhyay[2]

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Abstract

Ever since mankind embraced technology, the largest number of inventions have been aimed at agricultural improvement, more than any other sectors where technology is used. Nonetheless, today we are struggling to meet the ever increasing hunger of a growing world population. We have almost exhausted the supply of traditional technological ammunitions in the arsenal of agricultural science. The only way forward is to embrace smart agricultural practice in a sustainable manner. Use of modern electronics and material science to increase production, without further increasing fertilizer or pesticide input, can be referred to as smart and sustainable agriculture. Scientists have made giant leaps in the field of 'biology at nanoscale' during the first decade of the present century. Nanoparticles and nanosensors have huge potential in agricultural advancements, if used wisely with proper caution. Nanoparticles can be used for getting higher yield and for crop protection. Nanoparticles can also aid in the rate limiting process of gene delivery during genetic improvement of crop species. Nanobiosensors can contribute to smart farming by growth monitoring, real time detection of pests, and continuous monitoring of local environment. In this review, we will update the readers with some of the advancements made in these directions during the last decade.

Keywords Nanopesticides · Nanosensor · Plant biosensor · Smart farming · Precision agriculture · Slow release

Introduction

Agricultural practice by human beings has evolved through centuries in time and space, and parallels evolution of our race from hunter gatherers to space explorers. The improvement of agriculture has been steady and exponential since its inception. The first half of the past century has seen rapid mechanization, while the second half can be attributed to technologies like transgenic crop production and marker-assisted breeding. This phenomenal rise of crop production has its own trade-offs in terms of decreasing nutritional quality of lands, increasing pathogen and pest problem, and finally adverse effects on environment. The decade before the last one has seen more research on biofertilizers, microbiome and soil health. While these advancements were necessary for the improvement of mankind, rapid use of technology has also led us to a situation where today we have almost reached the ceiling of crop production. Only a small room is still left for improvement with our current skillset and available technologies. To feed the projected population of 10 billion by 2050 (United-Nations 2019), we must further increase our crop production by sustainable approach. The only way to achieve this would be to acquire cutting edge technologies which were not hitherto applied in the agricultural sector. 'Smart agriculture' methods such as remote sensing, satellite technology, safe but effective pesticides, and next-generation bio-sensors to detect soil health must be employed. In this review, we shall discuss the recent advances and the prospects of nanoparticles and nanobiosensors in the area of agriculture (Fig. 1).

Use of nanoparticles and use of nanosensors for agricultural benefit are two completely different fields of research. Many biosensors are coated with particular proteins and work at nanoscale, but without any involvement of nanoparticles at the recognition level. On the other hand, biosensors can also use small particles (which can be called nanoparticles in true technical sense). A composite electrode coated with nanoparticles along with DNA or protein is an example of such biosensors (Gupta et al. 2020).

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SCIENCE ADVANCES | RESEARCH ARTICLE

MICROBIOLOGY

VapBC22 toxin-antitoxin system from *Mycobacterium tuberculosis* is required for pathogenesis and modulation of host immune response

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Virulence-associated protein B and C toxin-antitoxin (TA) systems are widespread in prokaryotes, but their precise role in physiology is poorly understood. We have functionally characterized the VapBC22 TA system from *Mycobacterium tuberculosis*. Transcriptome analysis revealed that overexpression of VapC22 toxin in *M. tuberculosis* results in reduced levels of metabolic enzymes and increased levels of ribosomal proteins. Proteomics studies showed reduced expression of virulence-associated proteins and increased levels of cognate antitoxin, VapB22 in the *ΔvapC22* mutant strain. Furthermore, both the *ΔvapC22* mutant and VapB22 overexpression strains of *M. tuberculosis* were susceptible to killing upon exposure to oxidative stress and showed attenuated growth in guinea pigs and mice. Host transcriptome analysis suggests upregulation of the transcripts involved in innate immune responses and tissue remodeling in mice infected with the *ΔvapC22* mutant strain. Together, we demonstrate that the VapBC22 TA system belongs to a key regulatory network and is essential for *M. tuberculosis* pathogenesis.

INTRODUCTION

Toxin-antitoxin (TA) systems are small genetic elements that compose of a stable toxin and an antitoxin that neutralizes the toxin activity (*1*, *2*). TA systems are widely distributed in prokaryotes in multiple copies and have been shown to contribute to stress adaptation, persisters, biofilm formation, or pathogenesis (*3*–*7*). The toxins are invariably translated into a protein, whereas the antitoxin can either be a protein or RNA (*1*, *8*). TA modules have been classified into six different types based on the nature of antitoxin and the mechanism by which antitoxin negates toxin activity (*8*). In type II TA systems, the most well-characterized family, the antitoxin negates the activity of the cognate toxin by forming a tight complex through direct interactions. The antitoxins belonging to type II TA systems have inherently disordered regions, which makes them susceptible to cleavage by cellular proteases (*9*, *10*). This proteolytic degradation results in the release of toxin that subsequently interferes with various cellular processes such as transcription, translation, DNA replication, cell wall synthesis, and cell division (*11*).

Various bioinformatics and phylogenetic analyses have revealed that the *Mycobacterium tuberculosis* genome encodes a notably large repertoire of TA systems (*12*, *13*). The conservation of these TA systems in species belonging to the *M. tuberculosis* complex suggests that they regulate metabolic pathways that are essential for bacterial pathogenesis. Mostly, the *M. tuberculosis* systems belong to type II TA systems such as VapBC, MazEF, ParDE, RelBE, and HigBA (*12*, *13*). VapC toxins belonging to VapBC TA systems contain a PilT N terminus (PIN) domain that has a ribonuclease H–like fold, and their activity is neutralized by cognate VapB antitoxins (*14*). Using ultraviolet-induced cross-linking and deep sequencing, Winther *et al.* (*15*) showed that these ribonucleases cleave either transfer RNA (tRNA) or the sarcin-ricin loop of 23S ribosomal RNA. The structures of various VapC toxins, either alone or in complex with their cognate antitoxins, have been solved, but the basis for their substrate specificity is poorly understood. Several studies have shown that TA systems are differentially expressed under stress conditions and ectopic expression of toxins inhibits growth in a bacteriostatic manner (*12*, *16*, *17*). It has also been reported that overexpression of toxins results in morphological changes that might lead to drug tolerance (*17*). Growth of *M. tuberculosis* strains with deletions in either toxins or TA systems is attenuated in guinea pigs and mice, but the exact mechanism by which these TA modules contribute to pathogenesis is poorly understood (*16*–*18*).

Here, we have functionally characterized the VapBC22 TA system from *M. tuberculosis*. We show that overexpression of VapC22 results in bacteriostasis and transcriptional reprogramming that is similar to that observed in *M. tuberculosis* exposed to nutrient-limiting and low-oxygen conditions. Proteome analysis revealed increased expression of VapB22 and reduced levels of various virulence-associated proteins in mid-log phase cultures of Δ*vapC22* strain. We also demonstrate that changes in the relative levels of antitoxin and toxin are essential for *M. tuberculosis* to adapt to oxidative stress and establish infection in host tissues. Host transcriptomic analysis revealed that in comparison to the parental strain, infection with Δ*vapC22* mutant strain resulted in enhanced innate immune response as evident by higher infiltration of neutrophils, eosinophils, dendritic cells, and suppressed T helper 1 cell (T_H1) response in lung tissues. Together, this study provides newer insights into the contribution of TA systems to bacterial pathogenesis.

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Original Article

Octyl gallate triggers dysfunctional mitochondria leading to ROS driven membrane damage and metabolic inflexibility along with attenuated virulence in *Candida albicans*

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Abstract

Recently the high incidence of worldwide *Candida* infections has substantially increased. The growing problem about toxicity of antifungal drugs and multidrug resistance aggravates the need for the development of new effective strategies. Natural compounds in this context represent promising alternatives having potential to be exploited for improving human health. The present study was therefore designed to evaluate the antifungal effect of a naturally occurring phenolic, octyl gallate (OG), on *Candida albicans* and to investigate the underlying mechanisms involved. We demonstrated that OG at 25 μg/ml could effectively inhibit *C. albicans*. Mechanistic insights revealed that OG affects mitochondrial functioning as *Candida* cells exposed to OG did not grow on non-fermentable carbon sources. Dysfunctional mitochondria triggered generation of reactive oxygen species (ROS), which led to membrane damage mediated by lipid peroxidation. We explored that OG inhibited glucose-induced reduction in external pH and causes decrement in ergosterol levels by 45%. Furthermore, OG impedes the metabolic flexibility of *C. albicans* by inhibiting the glyoxylate enzyme isocitrate lyase, which was also confirmed by docking analysis. Additionally, OG affected virulence traits such as morphological transition and cell adherence. Furthermore, we depicted that OG not only prevented biofilm formation but eliminates the preformed biofilms. *In vivo* studies with *Caenorhabditis elegans* nematode model confirmed that OG could enhance the survival of *C. elegans* after infection with *Candida*. Toxicity assay using red blood cells showed only 27.5% haemolytic activity. Taken together, OG is a potent inhibitor of *C. albicans* that warrants further structural optimization and pharmacological investigations.

Key words: *Candida*, mitochondria, ROS, membrane, glyoxylate cycle, morphogenesis, biofilm.

Introduction

Candida albicans is a common opportunistic microorganism known to cause both superficial and systemic infections in immunocompromised hosts. The morphological transition of *C. albicans* from budding yeast to hyphal form and subsequent biofilm formation further aggravates the pathogenecity associated with serious *Candida* infections.[1] Routinely used drugs include azoles (e.g., fluconazole) that inhibit ergosterol biosynthesis, polyenes (e.g., amphotericin B) that bind to ergosterol in the plasma membrane and the echinocandins (e.g., caspofungin) that inhibits glucan synthesis. However, the current therapeutics collectively suffers from shortfalls such as toxicity and resistance development.[2] Concomitantly, the emergence of multidrug-resistance in *Candida* isolates is only worsening the problem. Therefore, identification of new classes of safe, well-tolerated broad-spectrum antifungal drugs without a tendency for resistance are urgently needed.

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Multi-spectroscopic investigation on the inclusion complexation of α-cyclodextrin with long chain ionic liquid

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ABSTRACT

Host-guest interaction of ionic liquid (IL) 1-decyl-3-methylimidazolium tetrafluoroborate [Dmim][BF_4] within α-cyclodextrin (α-CD) has been studied by different spectroscopic techniques and our investigated system is significant in the field of supramolecular chemistry and medicine. Benesi-Hildebrand correlation is used to study the stoichiometry of the host-guest complexation. Here concurrence with FT-IR and dynamic light scattering (DLS) results, it is shown that α-CD interacts with [Dmim][BF_4], induces compositional and structural changes. Characterization of the [Dmim][BF_4]-α-CD inclusion complex (IC) by ^{1}H NMR spectroscopy provided information about the complexation among the [Dmim][BF_4] and α-CD molecules and the structure of the ICs. ^{1}H NMR results confirm the formation of inclusion complex (IC) while UV–vis spectroscopy, DLS and FTIR studies show development of IC with 1:1 stoichiometry. The present study can be highly applicable in the fields of pharmaceutical science, supra-molecular chemistry and material science.

1. Introduction

Host–guest interactions comprise one amongst the elemental areas in supra-molecular chemistry [1,2]. The host-guest chemistry between ionic liquids (ILs) and cyclodextrin is stable by non-covalent bonds and of vast importance for chemical and biological challenges [3]. The precise binding of a guest that is complementary to the host molecule to create host-guest complex by the non-covalent interactions is known as molecular recognition and is often applied within the area of molecular sensors and many other chemical processes [4,5].

Cyclodextrins (CDs) are simple branch chain of cyclic oligosaccharides molecules which are linked by 1–4 glycosides bond and are extremely biocompatible/biodegradable [6,7]. Cyclodextrins contain hydrophobic cavity and inter-glucose bonds which are arranged in a torus shaped molecular structure that can bind different guest molecules [8]. Cyclodextrins have two dimensional molecular configurations (i) the upper/wider rim is 2^0 -OH (secondary hydroxyl groups) and (ii) the lower/narrower rim having 1^0 –OH (primary hydroxyl groups) [9,10]. The macrocyclic host can contain the guests in its interior and hence they are generally classified as "endo receptors". Different types of macrocyclic hosts molecules are available *i.e.*, cucurbiturils, crown ethers, porphyrins, calixarenes and cyclodextrins etc [11–14].

Inclusion complexation (IC) of CDs with wide variety of guest molecules is of great interest because of their extensive application in various fields *i.e.*, food packing, sensor, drugs delivery, pharmaceutical and solubility of drugs etc. IL-CD IC are formed through the insertion of alkyl chain of the IL into CD cavity *via* various interactions resulting in the formation of different types of supramolecular self-assembled structures in aqueous solution with host molecules (α-, β- and γ-cyclodextrins) and find diverse applications in various fields *i.e.*, cosmetics, drug delivery and material science [15–17]. The α-cyclodextrin ring contains six glucopyranose units and its ring is more strained than that of β- and γ-cyclodextrins. Hence, it's more interesting to study the IC behavior of α-cyclodextrin with ILs.

The stoichiometry of ICs mainly depends on particular chemical properties, shape and hydrophobicity of the guest as well as the dimension and the substituent of the cyclodextrin molecules [18–21]. Molecular modeling, simulation, X-ray crystallography, fluorescence, UV–vis, circular dichroism, NMR, FT-IR spectroscopy and thermal characterization techniques have been frequently used to verify the

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Data Article

GOLD standard dataset for Alzheimer genes

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ABSTRACT

Alzheimer disease is a genetically complex multigenic neurodegenerative disorder, resulting from the interaction between multiple genes. Most of the earlier studies reported only few specific genes that have involvement in Alzheimer. However more than hundreds of susceptible genes have been observed, that have significant role in the development and progression of Alzheimer. Among all the existing data resources, Genetic association database is the most popular data source that contains information about genes, their association classes into positive, negative and neutral class and supporting reference. However, it contains lot of false positives and negatives associations. We have taken this data as reference and performed the double fold cross validation to compile the comprehensive list of Alzheimer genes, their association class viz, positive, negative or ambiguous with the disease and reference sentence confirming the association. The data generated will be used as a GOLD standard reference data set for the training of machine learning classifier to predict the classification of published literature not only in Alzheimer but in other diseases as well. In addition, positive associated genes data can also be used for the system level modelling or meta analysis of Alzheimer.

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PLOS ONE

RESEARCH ARTICLE

Anti-neuroinflammatory potential of *Tylophora indica* (Burm. f) Merrill and development of an efficient *in vitro* propagation system for its clinical use

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Abstract

Neuroinflammation is a major risk factor associated with the pathogenesis of neurodegenerative diseases. Conventional non-steroidal anti-inflammatory drugs are prescribed but their long term use is associated with adverse effects. Thus, herbal based medicines are attracting major attraction worldwide as potential therapeutic candidates. *Tylophora indica* (Burm. f) Merrill is a valuable medicinal plant well known in Ayurvedic practices for its immunomodulatory, anti-oxidant, anti-asthmatic and antirheumatic activities. The present study aimed to elucidate the anti-neuroinflammatory potential of water and hydroalcoholic leaf extracts of micropropagated plants of *T. indica* using BV-2 microglia activated with lipopolysaccharide as an *in vitro* model system and development of an efficient reproducible protocol for its *in vitro* cloning. Non cytotoxic doses of the water and hydroalcoholic extracts (0.2μg/ml and 20μg/ml, respectively) were selected using MTT assay. α-Tubulin, Iba-1 and inflammatory cascade proteins like NFκB, AP1 expression was studied using immunostaining to ascertain the anti-neuroinflammatory potential of these extracts. Further, anti-migratory activity was also analyzed by Wound Scratch Assay. Both extracts effectively attenuated lipopolysaccharide induced microglial activation, migration and the production of nitrite via regulation of the expression of NFκB and AP1 as the possible underlying target molecules. An efficient and reproducible protocol for *in vitro* cloning of *T. indica* through multiple shoot proliferation from nodal segments was established on both solid and liquid Murashige and Skoog's (MS) media supplemented with 15μM and 10μM of Benzyl Amino Purine respectively. Regenerated shoots were rooted on both solid and liquid MS media supplemented with Indole-3-butyric acid (5–15μM) and the rooted plantlets were successfully acclimatized and transferred to open field conditions showing 90% survivability. The present study suggests that *T. indica* may prove to be a potential anti-neuroinflammatory agent and may be further explored as a potential therapeutic candidate for the management of neurodegenerative diseases. Further, the current study will expedite the conservation of *T. indica* ensuring ample supply of this threatened medicinal plant to fulfill its increasing demand in herbal industry.

OPEN ACCESS

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Growth Kinetics of Gold Nanoparticle Formation from Glycated Hemoglobin

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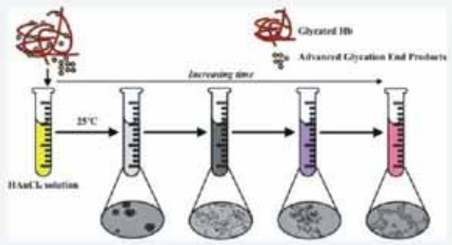
Supporting Information

ABSTRACT: Gold nanostructures have always been a subject of interest to physicists, chemists, and material scientists. Despite the extensive research associated with gold nanoparticles, their actual formation mechanism is still debatable. The nanoscale rearrangements leading to the formation of gold nanostructures of definite size and shape are contradictory. The study presented in here details out a mechanism for gold nanoparticle formation in the presence of a biological template. The kinetics of gold nanostructure formation was studied using glycated hemoglobin as a biological template as well as the reducing agent. Particle formation was studied in a time- and temperature-dependent manner using different biophysical techniques. Here, we report for the first time spontaneous formation of gold nanoflowers which gradually dissociates to form smaller spherical particles. In addition, our experiments conclusively substantiate the existing postulations on gold nanoparticle formation from relatively larger precursor structures of gold and contradict with the popular nucleation growth mechanism.



INTRODUCTION

Gold nanostructures find application in a range of fields of biological, physical, chemical, and medical sciences.[1−5] The in situ synthesis of gold nanoparticles (GNPs) involve two major reactions, reduction of gold ions to atomic gold and the stabilization of the resultant structures.[6] A number of chemical as well as biological agents are reported to be capable of synthesizing GNPs when used as a template or reducing agent. Among them, trisodium citrate is well studied and frequently employed owing to its use as both reducing agent and stabilizer for the fabrication of a range of gold nanostructures.[7−9] Recently, biological agents have gained popularity toward their use in GNP synthesis, principally for applications in the field of medical sciences because of its superior cytocompatibility and biocompatibility compared to other chemical reducing agents.[10−12]

In the bottom-up chemical synthesis of metallic nanomaterials, the post-reduction growth kinetics of nanostructures has drawn particular attention from scientists all over the world, ever since Turkevich studied the nucleation and growth in gold colloids.[12] Studying the growth kinetics of gold nanostructures is important owing to its versatile application potentials.

Biological and chemical sensing is an emerging application of GNPs considering its unique physical and optical properties. Taking into account the use of GNPs for sensing applications, the mechanism of sensing differs either by synthesis, aggregation, or interaction.[13−15] Here, aggregation and interaction studies are based on the already prepared GNPs, and sensing enabled through synthesis depends on the growth of GNPs from a template which is the target molecule. Different proteins are reported to carry out the formation of gold nanoclusters based on their activity towards the reduction of gold salt.[16,17] Extracts from different plant species' known to be rich in proteins, sugars, amino acids, and secondary metabolites including flavonoids and alkaloids can direct the growth of GNPs of different sizes and shapes.[18] Leng et al. in 2016 suggested that synthesis of GNPs using different proteins such as hemoglobin (Hb) and myoglobin can be used as a means for sensing of proteins on the basis of colorimetric profile of the formed GNPs.[13] GNPs which are found to be able to differentiate among structural and conformational alterations in proteins are also reported to be capable of sensing the protein conformational changes associated with glycation.[15,19−22] Nonenzymatic glycation is an important physiological phenomena having clinical significances in diabetes and associated complications. The products of nonenzymatic glycation are known to possess high reducing properties because of the formation of resultant molecules of a large number of functional groups.[23−26]

In a previous study, it was demonstrated that the color of colloidal GNPs when synthesized using the glycated Hb

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Research Paper

Vanillin confers antifungal drug synergism in *Candida albicans* by impeding CaCdr2p driven efflux

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ABSTRACT

Aim. – Among the most common mechanisms of multidrug resistance (MDR) in prevalent human fungal pathogen, *Candida albicans*, overexpression of drug efflux pumps remains the predominant mechanism. Hence to inhibit efflux pumps and chemosensitize *C albicans* against traditional antifungal drugs still represents an attractive approach. The present study aimed to analyze the effect of Vanillin (Van), a natural food flavoring agent, on drug efflux pump activity of *Candida albicans*.
Methods and results. – We observed that Van specifically inhibits *Candida* drug resistance protein 2 (CaCdr2p) activity belonging to ATP Binding Cassette (ABC) superfamily as revealed by abrogated rhodamine 6G efflux and nile red accumulation assay with CaCdr2p over expressing strain. Insight studies into the mechanisms suggested that abrogated efflux by CaCdr2p is due to competitive mode of inhibition by Van as depicted by Lineweaver-Burk plot. RT-PCR, western blot and confocal microscopy further unraveled that Van leads to reduced expression of *CDR2* and CaCdr2p mislocalization respectively. Furthermore, Van sensitizes the azole sensitive and resistant clinical matched pair of isolates Gu4/Gu5 and led to abrogated rhodamine 6G efflux and depleted ergosterol. Furthermore, Van synergizes with membrane targeting drugs fluconazole and amphotericin B as their fractional inhibitory coefficient index was less than 0.5.
Conclusion. – Van being a potent inhibitor of CaCdr2p and chemosensitizing of drug resistant *C. albicans* warrants further studies to be exploited as effective antifungal agent.

1. Introduction

Continuous deployment of antifungal drugs has led to emergence of multidrug resistance (MDR) in the prevalent human fungal pathogen *Candida albicans*. *C. albicans* resides in the mucocutaneous cavities of skin, vagina and intestine of humans as a commensal but can turn pathogenic under immunocompromised conditions [1,2]. The limited current armory of antifungal drugs is propelling MDR development which is a major hurdle against efficient therapeutics [3]. Despite the fact that MDR is a multifactorial phenomenon, resistance mediated by drug efflux pumps belonging to either ATP binding cassette (ATP) superfamily or major facilitator superfamily (MFS) remains the predominant mechanism [4,5]. Under such circumstances, it becomes pertinent to look for inhibitors targeting these drug efflux pumps.

In *C. albicans*, the major players involved in developing MDR are *Candida* drug resistance proteins CaCdr1p and CaCdr2p along with CaMdr1p which belongs to ABC and MFS super families respectively [4,6]. Despite sharing 84% similarity [7] evidence suggests that CaCdr1p contributes more towards drug resistance than CaCdr2p in *C. albicans*, however, recent studies have also depicted considerable role of CaCdr2p [8–10]. Even intracellular energy metabolism is known to correlate with the expression of *CDR1* and *CDR2* genes in drug resistance [11]. The activity of CDR genes, *CDR1* and *CDR2* is regulated by a common transcription factor, Tac1p [12].

Natural compounds have gained immense interest owing to their natural origin, cost effectiveness and lesser toxicity. Plants secondary metabolites are an enormous treasure, containing promising compounds targeting efflux pumps [13]. For instance, curcumin and geraniol modulates the expression of CaCdr1p efflux pump transporter [14,15]. The monoterpenes thymol and carvacrol, reverses azole resistance by inhibiting the expression of *CDR1* and *CDR2* genes along with synergism with known antifungal drug flucanozole (FLC) [16]. The extract from *Echinophora platyloba*

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MDPI

Article

Novel Carbazole-Piperazine Hybrid Small Molecule Induces Apoptosis by Targeting BCL-2 and Inhibits Tumor Progression in Lung Adenocarcinoma in Vitro and Xenograft Mice Model

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Abstract: Lung cancer is a type of deadly cancer and a leading cause of cancer associated death worldwide. BCL-2 protein is considered as an imperative target for the treatment of cancer due to their significant involvement in cell survival and death. A carbazole-piperazine hybrid molecule ECPU-0001 was designed and synthesized as a potent BCL-2 targeting agent with effective anticancer cancer activity. Interaction of ECPU-001 has been assessed by docking, molecular dynamics (MD) simulation, and thermal shift assay. Further, in vitro and in vivo anticancer activity was executed by cytotoxicity assay, FACS, colony formation and migration assay, western blotting, immunocyto/histochemistry and xenograft nude mice model. Molecular docking and MD simulation study confirmed that ECPU-0001 nicely interacts with the active site of BCL-2 by displaying a Ki value of 5.72 μM and binding energy (ΔG) of –8.35 kcal/mol. Thermal shift assay also validated strong interaction of this compound with BCL-2. ECPU-0001 effectively exerted a cytotoxic effect against lung adenocarnoma cells A459 with an IC_{50} value of 1.779 μM. Molecular mechanism of action have also been investigated and found that ECPU-0001 induced apoptosis in A459 cell by targeting BCL-2 to induce intrinsic pathway of apoptosis. Administration of ECPU-0001 significantly inhibited progression of tumor in a xenograft model without exerting severe toxicity and remarkably reduced tumor volume as well as tumor burden in treated animals. Our investigation bestowed ECPU-0001 as an effective tumoricidal agent which exhibited impressive anticancer activity in vitro as well as in vivo by targeting BCL-2 associated intrinsic pathway of apoptosis. Thus, ECPU-0001 may provide a valuable input for therapy of lung adenosarcoma in future, however, further extensive investigation of this compound will be needed.

Keywords: carbazole-piperazine hybrid molecule; ECPU-0001; tumor xenograft; mitochondrial mediated apoptosis; intrinsic pathway; molecular dynamics simulation

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Bi-functionalization of glass surfaces with poly-L-lysine conjugated silica particles and polyethylene glycol for selective cellular attachment and proliferation

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ABSTRACT

Fabrication of microstructured patterns serves as a powerful tool for studying the cellular responses toward synthetic materials at the material–cell interface for tissue engineering. Silica particles can effectively act as a substrate for cellular attachment and growth owing to its biocompatible nature and facile surface chemistry. In the current study, a non-lithographic microfabrication method for patterning of particles was devised using silica particles (~ 600 nm) and epoxy-silane-functionalized glass surfaces. Poly-L-lysine (PLL) was covalently attached to modified silica particles which were subsequently patterned onto the functionalized glass surfaces. PLL played a dual role. Firstly, it served as a bi-linker by covalently attaching modified particles on epoxy functionalized glass surfaces. Secondly, it facilitated cellular attachment on the pattern via electrostatic interactions. The vacant unpatterned regions were passivated with methoxy-polyethylene glycol-amino (MPA) to avoid non-specific cellular attachments. A549 cells were found to grow specifically on the monolayered silica patterns having lower packing density and exhibited stretched morphology, indicating cellular attachment to the substrate, whereas the MPA passivated areas were capable of blocking cell adhesion successfully. The highlight of the reported novel method lies in the dual use of PLL which not only provided necessary control over the surface chemistry by allowing fabrication of desired patterns but also facilitated selective cellular attachment on the generated patterns. Therefore, we report a simple process for micropatterning the cells on desired patterns via surface bi-functionalization for selective cellular attachment and proliferation.

Ajita Jindal and Neha Yadav have contributed equally to this work.

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ORIGINAL ARTICLE

Lipidomic insights to understand membrane dynamics in response to vanillin in *Mycobacterium smegmatis*

Sharda Sharma[1] · Saif Hameed[1] · Zeeshan Fatima[1]

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Abstract
Considering the emergence of multidrug resistance (MDR) in prevalent human pathogen, *Mycobacterium tuberculosis* (MTB), there is parallel spurt in development of novel strategies aimed to disrupt MDR. The cell envelope of MTB comprises a wealth of lipid moieties contributing towards long-term survival of pathogen that could be exploited as efficient antitubercular target owing to advancements made in mass spectrometry–based lipidomics technology. This study aimed to utilize the lipidomics approach to unveil several lipid associated changes in response to natural antimycobacterial compound vanillin (Van) in *Mycobacterium smegmatis*, a surrogate for MTB. Lipidomic analyses revealed that that Van alters the composition of fatty acid (FA), glycerolipid (GL), glycerophospholipid (GP), and saccharolipids (SL). Furthermore, Van leads to potentiation of ampicillin and displayed additive effect. The differential expressions of various lipid biosynthetic pathway genes by RT-PCR corroborated with the lipidomics data. Lastly, we demonstrated enhanced survival of *Mycobacterium*-infected *Caenorhabditis elegans* model in presence of Van. Thus, lipidomics approach provided detailed insight into mechanisms of membrane disruption by Van in *Mycobacterium smegmatis*. Our work offers the basis of further understanding the regulation of lipid homeostasis in MTB so that better therapeutic targets could be identified to combat MDR.

Keywords *Mycobacterium* · Vanillin · Lipids · Cell wall · Fatty acid · Glycerolipids · Glycerophospholipids

Introduction

The evolution of drug-resistant *Mycobacterium tuberculosis* (MTB) has established severe complications that are difficult to treat and generated considerable concern for developing effective strategies for the control of tuberculosis (TB). Although the current drug susceptibility testing is quite accurate and efficient, it is time-consuming. Identification of diagnostic biomarkers is, therefore, necessary to discriminate between infection from drug-resistant and drug-susceptible strains. One strategy that helps to effectively control TB is to understand the function of lipids that mycobacteria use to manipulate host cellular defenses. MTB has unique cell envelope architecture comprising several lipids between the outer and inner membrane which account for much of its impermeability to anti-TB drugs and confer unique staining properties to MTB (Jackson 2014).

The recent introduction of high-throughput analyses of lipids is accelerating our ability to analyze MTB lipid metabolism and signaling and the factors that regulate those pathways (Pal et al. 2017; Sharma et al. 2018). Several categories of lipid are present in MTB, e.g., fatty acids (FA), glycerolipids (GL), glycerophospholipids (GP), prenol (PR), polyketides (PK), and saccharolipids (SL). The outer membrane and capsular lipids of MTB play important roles in host–pathogen interactions. The innermost layer is the plasma membrane that seems typical of bacterial membrane while outside the plasma membrane is a massive cell wall core comprised of peptidoglycan (PG), in covalent attachment via phosphoryl-*N*-acetylglucosaminosyl-rhamnosyl linkage units with the heteropolysaccharide arabinogalactan (AG), which in turn is esterified at its non-reducing ends to α-alkyl, β-hydroxy long-chain (C_{60}-C_{90}) mycolic acids. The cell wall core, also referred to as the mycolyl arabinogalactan-peptidoglycan (mAGP) complex is required for

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SHORT COMMUNICATION

Fusarium solani causing stem rot and wilt of lucky Bamboo (*Dracaena sanderiana*) in India-first record

Narendra Kumar[1] · S. C. Dubey[2] · Pardeep Kumar[2] · S. M. Paul Khurana[1]

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Abstract
Lucky Bamboo (*Dracaena sanderiana* Sander ex Mast) is a tropical evergreen perennial woody, shrubby species. This is native of Cameroon area in tropical West Africa. This has flexible strap-shaped leaves and slender stems. Being an indoor house plant it grows very well under indirect lighting and have gained popularity because of adoption of new age culture. It multiplies readily by stem cuttings. In year 2014–2017, stem rot and wilt symptoms were observed in *D. sanderiana* cuttings. The first observed symptoms were yellowing in leaves with wilting. In due course of time the leaves turned dry and light brown with necrosis. On splitting open, rotted areas were seen in the middle with a visible brown discoloration in cortical region. The infected plants died within a few weeks. The fungal pathogen *Fusarium* was observed and isolated from the collar, roots, stems. This was morphologically confirmed as *Fusarium solani* and also through amplification and sequencing in ITS region, which showed cent percent similarity with the sequences of *F. solani* available in NCBI genbank. As per record in literature this is the first record of stem rot and wilt caused by *F. solani* in plants of *D. sanderiana* from India.

Keywords *Fusarium solani* · *Dracaena sanderiana* · Stem rot · Wilting

Dracaena sanderiana (Lucky Bamboo, Belgian Evergreen, Ribbon Dracaena or sometimes Ribbon Plant) is one of a group of small ornamental shrubby plants. This bears slender stems with strap shaped flexible leaves. They grow on surface ground of rainforests (Grewal et al. 1999) in the form of upright shrub reaching 1.5 m. The leaves come in the range of 15–25 cm (long) and 1.5–4 cm (broad) at base. It is marketed as "Lucky Bamboo" and a popular house plant used for decoration which survives under various indoor conditions. It can be easily propagated through stem cuttings. Literature records that some fungal species result into stem rot, in different parts of world viz., Tehran, Iran—*Aspergillus niger* (Abbasi and Aliabadi 2008), Bulgaria—*Colletotrichum dracaenophilum* (Bobev et al. 2008), Korea—*F. oxysporum*, *F. solani* and *F. moniliforme* (Choi et al. 2008), Iran—*F. solani* (Abedi-Tizaki et al. 2016) and leaf spot viz., *Cladosporium dracaenatum* and *Alternaria alternata* (Baka and Krzywinski 1996), *Fusarium* species viz., *F. equiseti*, *F. oxysporum*, *F. proliferatum*, *F. semitectum*, *F. solani*, *F. subglutinans* and *F. phyllophitum* (Choi et al. 2008; Thongkantha et al. 2008) from *Dracaena* plants.

Gurgaon District of Haryana state in southern most region (27°27′20″ and 28°32′25″ latitude and 76°39′39″ and 77°20′50″ longitude) and is among most valuable area where Lucky Bamboo are used as ornamental plants. It is propagated largely through stem cuttings/vegetative means. The pathogenic agents cause a lot of economic harm to many ornamental plants so it needs to identify for development of suitable control measures. Therefore present study was undertaken to find out the incitant of stem rot and wilt in *D. sanderiana*.

Potato dextrose agar medium (PDA) medium was prepared for culturing of associated fungi. Potato dextrose broth medium was used for DNA extraction. A total of 39.0 g Potato dextrose agar (HiMedia Laboratories Pvt Ltd, Mumbai) was suspended in double distilled water to make 1000 mL. It was heated till boiling to throughly mix the contents of medium. This was then autoclaved at 15 lbs pressure (121 °C) for 15 min (Kumar et al. 2016).

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Hindawi

Research Article

Anti-inflammatory Effects of *S. cumini* Seed Extract on Gelatinase-B (MMP-9) Regulation against Hyperglycemic Cardiomyocyte Stress

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Black berry (*Syzygium cumini*) fruit is useful in curing diabetic complications; however, its role in diabetes-induced cardiomyopathy is not yet known. In this study, we investigated the regulation of gelatinase-B (MMP-9) by *S. cumini* methanol seed extract (MSE) in diabetic cardiomyopathy using real-time PCR, RT-PCR, immunocytochemistry, gel diffusion assay, and substrate zymography. The regulatory effects of MSE on NF-κB, TNF-α, and IL-6 were also examined. Identification and estimation of polyphenol constituents present in *S. cumini* extract were carried out using reverse-phase HPLC. Further, *in silico* docking studies of identified polyphenols with gelatinase-B were performed to elucidate molecular level interaction in the active site of gelatinase-B. Docking studies showed strong interaction of *S. cumini* polyphenols with gelatinase-B. Our findings indicate that MSE significantly suppresses gelatinase-B expression and activity in high-glucose- (HG-) stimulated cardiomyopathy. Further, HG-induced activation of NF-κB, TNF-α, and IL-6 was also remarkably reduced by MSE. Our results suggest that *S. cumini* MSE may be useful as an effective functional food and dietary supplement to regulate HG-induced cardiac stress through gelatinase.

1. Introduction

Syzygium cumini, a seasonal perishable berry, commonly known as malabar plum, belongs to the family Myrtaceae. The plant is native to Asia and Oceanic regions, mainly India, China, and New Zealand. It is also grown in East Africa, South America, and tropical parts of the USA [1, 2]. The purple fruits of jamun are used for the processing of chips, vinegar, jams, smoothies, and squashes and hold a significant position in the functional food industry. Besides the fruits, other parts of the plant also have been found useful in treating chronic diseases including diabetes-related complications [3, 4]. The plant of *S. cumini*, especially its fruit, is considered a functional food, as it consists of plenty of polyphenols such as gallic acid, quercetin, β-sitosterol, eicosane, diphenic acid, ellagic acid, isoquercetin, and myricetin, which may facilitate healthy benefits against diabetes-induced detrimental changes and also reduce the risk of neurological and cardiovascular diseases (CVDs) [5]. These molecules are known for their anti-inflammatory, antihyperlipidemic, antioxidative, free radical scavenging, and antidiabetic potential [6]. Further studies have shown that *S. cumini* seed extracts function

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Studies on the antifungal activity of biotemplated gold nanoparticles over *Candida albicans*

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ABSTRACT

Green synthesis and applications of gold nanoparticles are more fascinating research area due to their unique optical properties and high X-ray attenuation power. In this study, we have synthesized gold nanoparticles of uniform size (5 nm) with spherical shape. UV–vis spectroscopy, Transmission Electron Microscopy and Atomic Force Microscopy were employed to characterize the synthesized gold nanoparticles. The biomedical applications of the synthesized gold nanoparticles were carried out against most prevalent human fungal pathogen, *Candida albicans*. Broth micro dilution assay was used to determine minimum inhibitory concentration (MIC). We observed that 0. 5 mM concentration was effective in inhibiting the growth of fungal cells which was later confirmed by spot assay.

1. Introduction

In the modern era of material science, nanoparticles have become the centre of attraction to the scientific community. In current years, nanotechnology is one of the most researched areas due to their noticeable performance in electronics, optics and photonics. Nanoparticles are the fundamental structures of nanotechnology. [1] Nanoscience and technology is an interdisciplinary broad area of research and development activity that has been growing dynamically worldwide in the past few years. Nanoparticles are the simplest form of structures with the range of 1–100 nm [2]. Nanoparticles have different physical and chemical properties such as higher surface area, mechanical strength and high reactivity. Gold nanoparticles are unique in optical property as gold is yellow in shading, strong in state where as gold nanoparticles are wine red shading arrangement against oxidant [3]. Gold nanoparticles display different sizes extending from 1 nm to 8 μm and they likewise show distinctive shapes, such as round, sub-octahedral, octahedral, decahedral, sporadic shape, tetrahedral, hexagonal platelets and nanorods. Among all these shapes, circular molded nanoparticles are most steady and show alluring optical properties when contrasted with the triangular formed nanoparticles [4].

Conventional physical and chemical methods are used to prepare metal nanoparticles from toxic chemicals [5]. Moreover, these methods are very expensive and not environmentally friendly [6]. Green synthesis of gold nanoparticles using various templates such as polysaccharides, fungi and plant extracts are found to be environmentally benign [7]. These attractive green strategies are free from toxic chemicals and toxic materials. Gold nanoparticle synthesized from bio templates offers a route for large scale production of different metallic nanoparticles [8].

Bio templated gold nanoparticles are utilized to detect cancer cells. Increased surface area of gold nanoparticles in solution which contribute to their enhanced physio-chemical properties which are useful in a variety of fields such as antimicrobial agents [9], bio-molecular detection, diagnostics, catalysis, biomedical and bio sensing devices. Gold nanoparticles are utilized as efficient materials for water purification [10]. These are also used in interface resistors, conductors and different components of an electronic chip. In photodynamic treatment, when light is connected to a tumor containing gold nanoparticles, the particles quickly warm up, executing tumor cells [11]. Gold nanoparticles are used as substrates to empower the estimation of vibrational energies of compound securities in surface upgraded Raman spectroscopy. Gold nanoparticles are very thick, consequently enabling them to be utilized as tests for transmission electron microscopy [12]. Gold nanoparticles can be readily dispersed, functionalized and are bio inert in nature. These particles have high X-ray attenuation power [13]. Gold nanoparticles have been generally utilized as a part of the field of radiation solution in radiation treatment due to the effective and

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Discovering Potential RNA Dependent RNA Polymerase Inhibitors as Prospective Drugs Against COVID-19: An in silico Approach

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COVID-19, caused by Severe Acute Respiratory Syndrome Corona Virus 2, is declared a Global Pandemic by WHO in early 2020. In the present situation, though more than 180 vaccine candidates with some already approved for emergency use, are currently in development against SARS-CoV-2, their safety and efficacy data is still in a very preliminary stage to recognize them as a new treatment, which demands an utmost emergency for the development of an alternative anti-COVID-19 drug *sine qua non* for a COVID-19 free world. Since RNA-dependent RNA polymerase (RdRp) is an essential protein involved in replicating the virus, it can be held as a potential drug target. We were keen to explore the plant-based product against RdRp and analyze its inhibitory potential to treat COVID-19. A unique collection of 248 plant compounds were selected based on their antiviral activity published in previous literature and were subjected to molecular docking analysis against the catalytic sub-unit of RdRp. The docking study was followed by a pharmacokinetics analysis and molecular dynamics simulation study of the selected best-docked compounds. Tellimagrandin I, SaikosaponinB2, Hesperidin and (-)-Epigallocatechin Gallate were the most prominent ones that showed strong binding affinity toward RdRp. All the compounds mentioned showed satisfactory pharmacokinetics properties and remained stabilized at their respective binding sites during the Molecular dynamics simulation. Additionally, we calculated the free-binding energy/the binding properties of RdRp-ligand complexes with the connection of MM/GBSA. Interestingly, we observe that SaikosaponinB2 gives the best binding affinity ($\Delta G_{binding}$ = −42.43 kcal/mol) in the MM/GBSA assay. Whereas, least activity is observed for Hesperidin ($\Delta G_{binding}$ = −22.72 kcal/mol). Overall our study unveiled the feasibility of the SaikosaponinB2 to serve as potential molecules for developing an effective therapy against COVID-19 by inhibiting one of its most crucial replication proteins, RdRp.

Keywords: COVID-19, RdRp, plant product, inhibitors, admet, free energy

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ORIGINAL ARTICLE

Understanding lipidomic basis of iron limitation induced chemosensitization of drug-resistant *Mycobacterium tuberculosis*

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Abstract
Under limited micronutrients condition, *Mycobacterium tuberculosis* (MTB) has to struggle for acquisition of the limited micronutrients available in the host. One such crucial micronutrient that MTB requires for the growth and sustenance is iron. The present study aimed to sequester the iron supply of MTB to control drug resistance in MTB. We found that iron restriction renders hypersensitivity to multidrug-resistant MTB strains against first-line anti-TB drugs. To decipher the effect of iron restriction on possible mechanisms of chemosensitization and altered cellular circuitry governing drug resistance and virulence of MTB, we explored MTB cellular architecture. We could identify non-intact cell envelope, tampered MTB morphology and diminished mycolic acid under iron restricted MDR-MTB cells. Deeper exploration unraveled altered lipidome profile observed through conventional TLC and advanced mass spectrometry-based LC–ESI–MS techniques. Lipidome analysis not only depicted profound alterations of various lipid classes which are crucial for pathogenecity but also exposed leads such as indispensability of iron to sustain metabolic, genotoxic and oxidative stresses. Furthermore, iron deprivation led to inhibited biofilm formation and capacity of MTB to adhere buccal epithelial cells. Lastly, we demonstrated enhanced survival of *Mycobacterium*-infected *Caenorhabditis elegans* model under iron limitation. The present study offers evidence and proposes alteration of lipidome profile and affected virulence traits upon iron chelation. Taken together, iron deprivation could be a potential strategy to rescue MDR and enhance the effectiveness of existing anti-TB drugs.

Keywords *Myobacterium* · Iron · Lipids · Membrane · Lipidomics · Glyoxylate cycle · Biofilm

Abbreviations

MTB	*Mycobacterium tuberculosis*
MDR	Multidrug resistance
ADC	Albumin dextrose catalase
OADC	Oleic albumin dextrose catalase
2,4 DNP	2,4 dinitrophenol
CFW	Calcoflour white
CV	Crystal violet
INT	Iodonitrotetrazolium chloride
SEM	Scanning electron microscopy
PI	Propidium iodide
DCFDA	2′,7′-dichlorofluorescin diacetate
DAPI	4′,6-diamidino-2-phenylindole
MS	Malate synthase
ICLI	Isocitrate lyase
ROS	Reactive oxygen species
EMB	Ethambutol
RIF	Rifampicin
INH	Isoniazid
STP	Streptomycin
2,2,-BP	2,2, Bipyridyl
FA	Fatty acid
GL	Glycerolipid
GPL	Glycerophospholipid
PK	Polykedide
PR	Prenol
SCL	Saccharolipide

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"Identification of Nafamostat and VR23 as COVID-19 drug candidates by targeting 3CL^{pro} and PL^{pro}."

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ABSTRACT

The sudden increase in the COVID-19 epidemic affected by novel coronavirus 2019 has jeopardized public health worldwide. Hence the necessities of a drug or therapeutic agent that heal SARS-CoV-2 infections are essential requirements. The viral genome encodes a large Polyprotein, further processed by the main protease/ 3C-like protease (3CL^{pro}) and papain-like proteases (PL^{pro}) into 16 nonstructural proteins to form a viral replication complex. These essential functions of 3CL^{pro} and PL^{pro} in virus duplication make these proteases a promising target for discovering potential therapeutic candidates and possible treatment for SARS-CoV-2 infection.

This study aimed to screen a unique set of protease inhibitors library against 3CL^{pro} and PL^{pro} of the SARS-CoV-2. A molecular docking study was performed using PyRx to reveal the binding affinity of the selected ligands and molecular dynamic simulations were executed to assess the three-dimensional stability of protein-ligand complexes. The pharmacodynamics parameters of the inhibitors were predicted using admetSAR. The top two ligands (Nafamostat and VR23) based on docking scores were selected for further studies. Selected ligands showed excellent pharmacokinetic properties with proper absorption, bioavailability and minimal toxicity. Due to the emerging and efficiency of remdesivir and dexamethasone in healing COVID-19 patients, ADMET properties of the selected ligands were thus compared with it. MD Simulation studies up to 100 ns revealed the ligands' stability at the target proteins' binding site residues. Therefore, Nafamostat and VR23 may provide potential treatment options against SARS-CoV-2 infections by potentially inhibiting virus duplication though more research is warranted.

1. Introduction

In December 2019, a new coronavirus caused an outbreak of the pulmonary disease in Wuhan, the capital of Hubei province in China, and has since spread globally [67,68,79]. The virus has been named SARS-CoV-2 [20], with 96% genome identical to a bat coronavirus and shares 79.6% sequence identity to SARS-CoV [43,67,79]. This pandemic spread worldwide with more than 104.9 million infections and more than 2.27 million deaths till 3rd February 2021 [https://www.worldometers.info/coronavirus/].

The genome size of coronaviruses is ~30,000 nucleotides in length with a 5′-cap structure and a 3′-poly (A) tail and consist of at least six open reading frames (ORFs) [27,13]. The first ORF (ORF 1a/b) is about two-thirds of the genome length, precisely translates two polyproteins, pp1a and pp1ab and are processed by the main protease, also known as the 3C-like protease (3CL^{pro}) and by one or two papain-like proteases (PL^{pro}), into 16 nonstructural proteins (NSPs) and develop into mature proteins which assist in the viral replication [7,26,24]. PL^{pro} facilitates cleavage at the first three polyproteins sites, whereas CL^{pro} facilitates the cleavage at 11 sites [14,29]. The 3CL^{pro} carries out cleavage at the polyproteins' C-terminal while, N-terminal of the polyproteins are cleaved by PL^{pro} [40]. These NSPs engaged in subgenomic RNAs construction that encodes four main structural proteins, namely envelope (E), membrane (M), spike (S), and nucleocapsid (N) proteins and other accessory proteins [56,57].

The ~306 aa long 3CL^{pro}, a key enzyme for coronavirus replication, is also encoded by the polypeptide and responsible for processing the polypeptide into functional proteins [67,77]. The 3CL^{pro}, also known as Nsp5, is the first to get automatically cleaved from polyproteins to produce mature enzymes, and then it further assists in the cleavage of downstream Nsps at 11 sites to release

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Case Study

Identifying the natural polyphenol catechin as a multi-targeted agent against SARS-CoV-2 for the plausible therapy of COVID-19: an integrated computational approach

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Abstract

The global pandemic crisis, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed the lives of millions of people across the world. Development and testing of anti-SARS-CoV-2 drugs or vaccines have not turned to be realistic within the timeframe needed to combat this pandemic. Here, we report a comprehensive computational approach to identify the multi-targeted drug molecules against the

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Covalent attachment of streptavidin to two dimensional magnetic nanocomposite enhances surface enhancement Raman spectroscopic signal

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ABSTRACT

In this work, we report that covalently attached protein to graphene oxide/magnetite (rGO-Fe_3O_4) nanocomposites can act as a substrate for surface-enhanced Raman spectroscopic studies. The substrate rGO-Fe_3O_4 synthesized by hydrothermal process was modified with a fluorescently labeled protein, streptavidin (Strp), using silane chemistry. The modification was confirmed by confocal fluorescence microscopy and Fourier-transform infrared spectroscopy, where the fluorescence of the conjugated protein and the presence of the additional peaks were visualized, respectively. The transmission electron microscopy demonstrated a wide distribution of Fe_3O_4 nanoparticles on rGO sheets. In addition, when the Raman peaks of these bio-nanocomposites (rGO-Fe_3O_4-Strp) were compared with the GO-Strp sheets and Fe_3O_4-Strp nanoparticles, an active substrate-mediated surface enhancement Raman spectroscopic effect was observed. It suggests that covalently attached protein on rGO-Fe_3O_4 nanocomposite substrates acts as a better platform for biosensing application than bare GO sheets or Fe_3O_4 nanoparticles.

I. INTRODUCTION

Graphene (G) and graphene oxide (GO) are the most significant two-dimensional (2D) materials used in different applications due to their unique physical and chemical properties. A combination of hydrophilic edges (due to the presence of functional groups) and a hydrophobic basal plane make the sheets amphiphilic in nature.[1,2] Furthermore, the GO sheets can be used as a progenitor for reduced graphene oxide (rGO) sheets when oxygen functional groups (COO^-, OH, and epoxy) from the sheets are removed by the reduction process. These rGO sheets have large applications not only in the field of electronics and materials science, but also in biology. These sheets have properties similar to graphene.[3–5] Upon decoration with inorganic materials such as metal or semiconductor nanoparticles, GO or rGO sheets form fascinating nanocomposites. Among other magnetic materials, Fe_3O_4 nanoparticles have been widely used to form such assemblies because they have been used in different diagnostics, imaging, and bioengineering applications since these nanoparticles showed high potential for surface functionalization.[6,7] It has also been shown that magnetic nanoparticles decorated on GO or rGO sheets create a biocompatible micro-environment and preserve the biological activities of the immobilized biomolecules.[8,9]

The GO-Fe_3O_4 (or rGO) nanocomposites synthesized by different methods display efficient adsorption performance in the biosensing fields.[10,11] High selectivity of Raman scattering has created an opportunity for the signal to be used as molecular fingerprinting, which is also related to the efficiency of the substrate. Surface enhancement

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Topical Perspectives

Virtual screening and free energy estimation for identifying Mycobacterium tuberculosis flavoenzyme DprE1 inhibitors

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ABSTRACT

In *Mycobacterium tuberculosis* (MTB), the cell wall synthesis flavoenzyme decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1) plays a crucial role in host pathogenesis, virulence, lethality and survival under stress. The emergence of different variants of drug resistant MTB are a major threat worldwide which essentially requires more effective new drug molecules with no major side effects. Here, we used structure based virtual screening of bioactive molecules from the ChEMBL database targeting DprE1, having bioactive 78,713 molecules known for anti-tuberculosis activity. An extensive molecular docking, binding affinity and pharmacokinetics profile filtering results in the selection four compounds, **C5 (ChEMBL2441313), C6 (ChEMBL2338605), C8 (ChEMBL441373)** and **C10 (ChEMBL1607606)** which may explore as potential drug candidates. The obtained results were validated with thirteen known DprE1 inhibitors. We further estimated the free-binding energy, solvation and entropy terms underlying the binding properties of DprE1-ligand interactions with the implication of MD simulation, MM/GBSA, MM/PBSA and MM/3D-RISM. Interestingly, we find that **C6** shows the highest ΔG scores (-41.28 ± 3.51, -22.36 ± 3.17, -10.33 ± 5.70 kcal mol^{-1}) in MM/GBSA, MM/PBSA and MM/3D-RISM assay, respectively. Whereas, the lowest ΔG scores (-35.31 ± 3.44, -13.67 ± 2.65, -3.40 ± 4.06 kcal mol^{-1}) observed for **CT319**, the inhibitor co-crystallized with DprE1. Collectively, the results demonstrated that hit-molecules: **C5**, **C6**, **C8** and **C10** having better binding free energy and molecular affinity as compared to **CT319**. Thus, we proposed that selected compounds may be explored as lead molecules in MTB therapy.

1. Introduction

Mycobacterium tuberculosis (MTB) is a slow growing and widely spread pathogen, survive in both, intra-cellular and extracellular systems of patients, and infection may result in chronic and complex disease state. During the treatment, it can go to latency which revert to exponential growth on the immune defiance conditions of hosts [1,2]. In recent years, WHO reports suggested that around 10.0 million (range, 9.0–11.1 million) individuals infected and 1.3 million (range, 1.2–1.4 million) people died from tuberculosis (TB) [1]. Moreover, the infection of MTB is one of the major causes of death worldwide, possessing the global health crisis, especially for the immunocompromised and HIV patients [3]. Although, the specific treatment may cure MTB, however, it requires multiple drug therapy for a longer period [1,3]. Furthermore, the development of multi- and extensively-drug-resistant (MDR-TB and XDR-TB) MTB strains are the big challenges to control TB infections [4,5]. In several conditions, it may turn into totally drug-resistant (TDR) tuberculosis which may worsen the condition of patients and therapy [2,6]. Thus, the potential drug candidates, having minimal or no side effects are highly sought in MTB therapy [1,2].

In recent years, several proteins involved in MTB survival and metabolism have been explored as potential drug targets and are progress in the drug development. During the evolution, mycobacteria have developed well-orchestrated and complex biosynthetic pathways to sustain a unique and thick cell wall which helps in maintaining the cellular integrity, survival under stress and dormancy, and eluding the host's immune systems. In MTB, the cell

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SHORT REPORTS

Development and utilization of *gyr*A and *gyr*B gene-based diagnostics for the phytoplasma classified under 16Sr I group in plants and insects

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Abstract
In the present study, a new set of primers of *gyr*A and *gyr*B genes of the phytoplasma genome were designed and validated for the successful detection and taxonomic classification of the previously identified phytoplasma strains of '*Candidatus* P. asteris' (16SrI-B subgroup) associated with Catharanthus leaf yellows, sesame phyllody and the leafhopper (*Hishimonus phycitis*). Our results suggested the ability and sensitivity of *gyrA* and *gyrB* genes as an alternative molecular marker to identify the *Ca*. P. asteris strain up to subgroup level associated both with plants and insects.

Keywords Multilocus genes · Validation · Phytoplasma detection · Leafhopper

Phytoplasma classification established using 16S ribosomal groups and '*Candidatus* Phytoplasma' taxon is mainly based on 16S rDNA properties and do not always provide molecular distinction of the closely related strains. More variable single copy genes, such as ribosomal proteins (*rpl22* and *rpS3*), *sec*Y, *sec*A, *tuf*, *dna*B and *gro*EL were employed for finer classification of phytoplasma and differentiation (Schneider et al. 1997; Langer and Maixner 2004; Lee et al. 2007; Martini et al. 2007; Hodgetts et al. 2008; Hodgetts and Dickinson 2010; Bertaccini et al. 2014).To further improve detection and taxonomic classification of phytoplasma, we have designed primers for PCR assays based on *gyr*A and *gyr*B genes and tested them on aster yellows phytoplasma strains (16SrI) from field-infected samples of periwinkle (*Catharanthus roseus*) and sesame (*Sesamum indicum*). The detection and validation of *gyr*A and *gyr*B gene specific primers were also attempted to detect the phytoplasma in samples of leafhopper (*Hishimonus phycitis*) collected from infected sesame fields.

The DNA was extracted from samples of two isolates of *Catharanthus* with symptoms of little leaf (one each from Gorakhpur, Cr-GKP isolate and Shahajahanpur, Cr-SJP isolate, Uttar Pradesh, India), sesame showing phyllody from Kushinagar (S-Kus isolate, Uttar Pradesh, India) and ten individual leafhoppers, *H. phycitis* collected from infected sesame fields at Kushinagar (HP-Kus). The protocol of Ahrens and Seemüller (1992) and Marzachi et al. (1998) was followed for total DNA extraction from the plants and leafhopper samples, respectively. The extracted DNAs from the earlier identified phytoplasma strains in our lab as 16SrI-B subgroup associated with the periwinkle (Cr-GKP and Cr-SJP), sesame (S-Kus) and *H. phycitis* (HP-Kus) (Madhupriya et al. 2015; Madhupriya 2016) were tested for the presence of phytoplasmas for direct PCR amplification with newly designed set of primers for *gyr*A and *gyr*B genes, *gyrA*F/R (5′-TGCTTATCACACCGGACAAG-3/5′-CCAAAGCCGTTTTCAGTCAT-3′) and *gyrB*F/R (5′-GGAGCCTCTGTGGTAAATGC-3′/5′-GCATCTTTGAGGCTTGCT TT-3′) that amplified an expected size amplicon of about 1.4 kb (*gyr*A) and 1.5 kb (*gyr*B) from all the four phytoplasma isolates of the plants and leafhopper samples. PCR assay was carried out in a thermal cycler (Eppendorf, Germany) and the cycling protocol used for the PCR assays was 94 °C for 5 min, followed by 35 cycles consisting of denaturation at 94 °C for 45 s, annealing at 55 °C (*gyrA*F/R) and 56 °C (*gyrB*F/R) for 1 min, and extension at 72 °C for 2 min, with extension in the final cycle for 10 min.

Expected amplified products of 1.4 kb (*gyr*A) and 1.5 kb (*gyr*B) were obtained with DNA extracted from both the test plants (periwinkle and sesame) and the leafhopper (*H. phycitis*) confirming the specificity of *gyr*A and *gyr*B

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Insights into the biased activity of dextromethorphan and haloperidol towards SARS-CoV-2 NSP6: in silico binding mechanistic analysis

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Abstract
The outbreak of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus continually led to infect a large population worldwide. SARS-CoV-2 utilizes its NSP6 and Orf9c proteins to interact with sigma receptors that are implicated in lipid remodeling and ER stress response, to infect cells. The drugs targeting the sigma receptors, sigma-1 and sigma-2, have emerged as effective candidates to reduce viral infectivity, and some of them are in clinical trials against COVID-19. The antipsychotic drug, haloperidol, exerts remarkable antiviral activity, but, at the same time, the sigma-1 benzomorphan agonist, dextromethorphan, showed pro-viral activity. To explore the potential mechanisms of biased binding and activity of the two drugs, haloperidol and dextromethorphan towards NSP6, we herein utilized molecular docking–based molecular dynamics simulation studies. Our extensive analysis of the protein-drug interactions, structural and conformational dynamics, residual frustrations, and molecular switches of NSP6-drug complexes indicates that dextromethorphan binding leads to structural destabilization and increase in conformational dynamics and energetic frustrations. On the other hand, the strong binding of haloperidol leads to minimal structural and dynamical perturbations to NSP6. Thus, the structural insights of stronger binding affinity and favorable molecular interactions of haloperidol towards viral NSP6 suggests that haloperidol can be potentially explored as a candidate drug against COVID-19.

Key messages
- Inhibitors of sigma receptors are considered as potent drugs against COVID-19.
- Antipsychotic drug, haloperidol, binds strongly to NSP6 and induces the minimal changes in structure and dynamics of NSP6.
- Dextromethorphan, agonist of sigma receptors, binding leads to overall destabilization of NSP6.
- These two drugs bind with NSP6 differently and also induce differences in the structural and conformational changes that explain their different mechanisms of action.
- Haloperidol can be explored as a candidate drug against COVID-19.

Keywords COVID-19 · NSP6 · Haloperidol · Dextromethorphan · Molecular docking · Molecular dynamics

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Introduction

The current outbreak of corona virus disease 2019 (COVID-19) caused by a novel coronavirus SARS-CoV-2 was first reported from Wuhan, China, in late December 2019 [1], which has subsequently affected the entire world, reporting nearly 26 million of confirmed cases of COVID-19 along with ~ 9.0-lakh deaths as per data recorded in September 1st week, 2020, posing a global threat for human health and economy. With so many novel studies and findings surfaced, since its inception, we are still lagging behind in development of an effective treatment strategy to control the virus spread and prevent the disease [2–7].

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Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an *in silico* study for drug development

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ABSTRACT

Spike glycoprotein, a class I fusion protein harboring the surface of SARS-CoV-2 (SARS-CoV-2S), plays a seminal role in the viral infection starting from recognition of the host cell surface receptor, attachment to the fusion of the viral envelope with the host cells. Spike glycoprotein engages host Angiotensin-converting enzyme 2 (ACE2) receptors for entry into host cells, where the receptor recognition and attachment of spike glycoprotein to the ACE2 receptors is a prerequisite step and key determinant of the host cell and tissue tropism. Binding of spike glycoprotein to the ACE2 receptor triggers a cascade of structural transitions, including transition from a metastable pre-fusion to a post-fusion form, thereby allowing membrane fusion and internalization of the virus. From ancient times people have relied on naturally occurring substances like phytochemicals to fight against diseases and infection. Among these phytochemicals, flavonoids and non-flavonoids have been the active sources of different anti-microbial agents. We performed molecular docking studies using 10 potential naturally occurring compounds (flavonoids/non-flavonoids) against the SARS-CoV-2 spike protein and compared their affinity with an FDA approved repurposed drug hydroxychloroquine (HCQ). Further, our molecular dynamics (MD) simulation and energy landscape studies with fisetin, quercetin, and kamferol revealed that these molecules bind with the hACE2-S complex with low binding free energy. The study provided an indication that these molecules might have the potential to perturb the binding of hACE2-S complex. In addition, ADME analysis also suggested that these molecules consist of drug-likeness property, which may be further explored as anti-SARS-CoV-2 agents.

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COVID-19; molecular docking; phytochemicals; flavonoids and non-flavonoids

Abbreviations: COVID-19: Coronavirus Disease 2019; SARS-CoV-2S: Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein; hACE2: Human Angiotensin Converting Enzyme-2; hACE2-S protein complex: Human Angiotensin Converting Enzyme-2 receptor and Severe Acute Respiratory Syndrome Coronavirus 2 Spike protein complex; HCQ: Hydroxychloroquine; CQ: Chloroquine; ACE2: Angiotensin-Converting Enzyme-2; MERS-CoV: Middle East Respiratory Syndrome coronavirus; PDB: protein data bank; ADME: absorption, distribution, metabolism and excretion

1. Introduction

The world population is facing a severe mass annihilation due to the rise of a global pandemic named Coronavirus Disease 2019 (COVID-19) (Boopathi et al., 2020; Chatterjee et al., 2020; Joshi et al., 2020; Kirchdoerfer et al., 2016). This pandemic is caused by a novel single-stranded RNA virus belonging to the β-coronavirus genera of the coronaviridae family (Elfiky & Azzam, 2020; Enmozhi et al., 2020; Khan et al., 2020; Rajarshi, Chatterjee & Ray 2020; Sarma et al., 2020; Sinha et al., 2020). As this virus shares significant phylogenetic similarity and structural familiarity (about 80% nucleotide identity and 89.10% nucleotide similarity) with the severe acute respiratory syndrome coronavirus (SARS-CoV), it has been named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and placed in the same lineage (Subgenus *Sarbecovirus*) (2020; Boopathi et al., 2020; Das et al., 2020; Khan et al., 2020; Ou et al., 2020; Rajarshi, Chatterjee & Ray 2020). To date, no effective regime of antivirals or vaccines is available for the use of the general public to combat the effect of COVID infections, which has put the population at a more vulnerable position (Aanouz

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Phospholipid biosynthesis disruption renders the yeast cells sensitive to antifungals

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Abstract

To understand the role of phospholipids on Cdr1p (drug exporter)-mediated drug resistance in yeast, the phospholipids biosynthesis genes *PSD1*, *PSD2*, *CHO2*, and *OPI3* were deleted in a strain of *Saccharomyces cerevisiae* already overexpressing Cdr1-GFP of *Candida albicans* as a heterologous system. The effect of phospholipids biosynthesis gene deletion was analyzed on Cdr1p-GFP-mediated drug resistance as well as its localization. The results indicate that phospholipids biosynthesis disruption makes the cell sensitive to several drugs including fluconazole (FLC), with Δ*psd1*/Cdr1-GFP being worst affected. Interestingly, unlike sterols and sphingolipids, the localization of Cdr1p was unaffected by phospholipid biosynthesis gene disruption. Concomitantly, phospholipids mutants also showed an increase in reactive oxygen species (ROS) generation, as verified by fluorescence probe 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) method. In addition, the sensitivity of phospholipid mutants with FLC was found to be synergistic to ROS generation, resulting in further reduction of growth. Thus, this study proposes phospholipid biosynthesis as a novel target for antifungal therapy.

Keywords Antifungals · *Candida albicans* · Phospholipids · Drug resistance · Azoles · ROS · Mitochondria · Heterologous expression · Overexpression · pABC3

Introduction

Fungal pathogens including *Candida albicans* (*C. albicans*) can cause severe morbidity and mortality in immunocompromised patients (Kontoyiannis 2017). Eukaryotic pathogens already offer limited targets, and candidiasis further worsens with the emergence of drug resistance. This is due to either one or multiple mechanisms occurring simultaneously, such as alterations or up-regulation of the target, reduced intracellular accumulation of the drugs, and overexpression of drug efflux pumps including Cdr1p, Cdr2p [ATP Binding Cassette (ABC) Family], and Mdr1p (Major Facilitator Family) (Akins 2005; Tsao et al. 2009; Whaley et al. 2017; Robbins et al. 2017).

Hyper-expression of Cdr1p is a major reason for resistance against antifungals in *candidiasis*. Cdr1p, an ~ 170-kDa protein consist of two homologous halves, each half comprises of a nucleotide binding domain (NBD), followed by a transmembrane domain (TMD). Each TMD has six membrane helices, which are joined by interconnecting loops. NBDs are an indispensable region of ABC transporters and are responsible for ATP binding, followed by hydrolysis. Thus, this region serves as an engine for all the ABC proteins (Prasad et al. 2015). Additionally, plasma membrane (PM) lipid composition and imbalances also contribute to incidences of fungal drug resistance (Abe and Hiraki 2009; Rella et al. 2016). Azole-resistant fungal isolates from patients show altered lipid composition of sterols, sphingolipids, and phospholipids (Hitchcock et al. 1986; Loffler et al. 2000; Pasrija et al. 2005a; Singh and Prasad 2011; Singh et al. 2012, 2013). Thus, it is logical to observe that Cdr1p is affected by changes in membrane composition, especially sterols and sphingolipids. These lipids also gets attention due to their interactions, and subsequent formation of membrane rafts (micro-domains) in various organisms including yeast, mammals, plants, etc. (Xu et al. 2001; Malinska 2004; Prasad et al. 2005; Pasrija et al. 2008). Rafts are known to exist as a platform for initiating multiple events like entry of pathogen inside the target cell, virulence, signal transduction, and protein sorting (Moffett et al. 2000; Martin and Konopka 2004; Mollinedo

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Research Paper

Identification of potential inhibitors against SARS-CoV-2 by targeting proteins responsible for envelope formation and virion assembly using docking based virtual screening, and pharmacokinetics approaches

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ABSTRACT

WHO has declared the outbreak of COVID-19 as a public health emergency of international concern. The ever-growing new cases have called for an urgent emergency for specific anti-COVID-19 drugs. Three structural proteins (Membrane, Envelope and Nucleocapsid protein) play an essential role in the assembly and formation of the infectious virion particles. Thus, the present study was designed to identify potential drug candidates from the unique collection of 548 anti-viral compounds (natural and synthetic anti-viral), which target SARS-CoV-2 structural proteins. High-end molecular docking analysis was performed to characterize the binding affinity of the selected drugs-the ligand, with the SARS-CoV-2 structural proteins, while high-level Simulation studies analyzed the stability of drug-protein interactions. The present study identified rutin, a bioflavonoid and the antibiotic, doxycycline, as the most potent inhibitor of SARS-CoV-2 envelope protein. Caffeic acid and ferulic acid were found to inhibit SARS-CoV-2 membrane protein while the anti-viral agent's simeprevir and grazoprevir showed a high binding affinity for nucleocapsid protein. All these compounds not only showed excellent pharmacokinetic properties, absorption, metabolism, minimal toxicity and bioavailability but were also remain stabilized at the active site of proteins during the MD simulation. Thus, the identified lead compounds may act as potential molecules for the development of effective drugs against SARS-CoV-2 by inhibiting the envelope formation, virion assembly and viral pathogenesis.

1. Introduction

On 31st December 2019, China revealed to the world health organization (WHO) and the rest of the world, the occurrence of symptoms of unexplained pneumonia in a cluster of cases from Wuhan city (Rodriguez-Morales et al., 2020; Zhou et al., 2020a). The causative agent was later identified as a novel strain of coronavirus, named as 2019-nCOV and the disease as COVID-19 (Zhou et al., 2020a). On 30th January 2020, WHO declared the outbreak of COVID-19 as a public health emergency of international concern and also called a pandemic. The 2019-nCoV shared a 79.5% sequence identity to SARS-CoV. Recently, the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) renamed it SARS-CoV-2 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The ever-growing infections and the mortality rate across the globe have called an urgent emergency for specific anti-COVID-19 therapeutics and extensive screening of presently available drugs for the treatment and prevention of SARS-CoV-2. Coronaviruses (CoVs) are enveloped positive-stranded RNA viruses and Coronaviridae can be subdivided into four groups- *alpha-*, *beta-*, *gamma-* and *delta-* CoV (Perlman and Netland, 2009; Fehr and Perlman, 2015). Members of this virus family infect the mammalian respiratory organ from the upper respiratory tract (URTIs) to the lower respiratory tract (LRTIs) and gastrointestinal tract by incompletely understood mechanisms (Fehr and Perlman, 2015; Cong and Ren, 2014). SARS-COV-2 is the seventh-known SARS virus that will infect people after 229E, NL63, OC43, HKU1, MERS-CoV and the original SARS-CoV (Zhu et al., 2020). SARS-CoV-2 is a member of the subgenus Sarbecovirus (beta-

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Magnesium deprivation affects cellular circuitry involved in drug resistance and virulence in *Candida albicans*

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ABSTRACT

Objectives: Candida albicans has to struggle for the limited micronutrients present in the hostile host niche, including magnesium (Mg). The aim of this study was to examine the effect of Mg deprivation on drug resistance mechanisms and virulence traits of *C. albicans*.
Methods: The drug susceptibility of *C. albicans* strain SC5314 was determined by broth microdilution and spot assay. Efflux pump activity was measured using the substrate rhodamine 6G. Membrane intactness was studied by propidium iodide influx, and ergosterol levels were determined by the alcoholic KOH method. Metabolic flexibility was examined by studying the activity of glyoxylate cycle enzymes. Virulence factors were assessed by yeast-to-hyphae transition, biofilm formation and cell adherence. An in vivo study was also performed in a *Caenorhabditis elegans* infection model.
Results: Mg chelation leads to potentiation of membrane-targeting antifungals. The role of Mg on membrane homeostasis was explored and significant differences in ergosterol levels were found. Interestingly, it was also observed that Mg deprivation impedes the metabolic flexibility of *C. albicans* SC5314 by inhibiting glyoxylate cycle enzymes. Furthermore, Mg deprivation inhibited potential virulence traits, including morphological transition, biofilm formation and buccal epithelial cell adherence. All of the disrupted gene targets were validated by reverse transcription PCR. Lastly, enhanced survival of *C. elegans* infected with *C. albicans* SC5314 under Mg deprivation was observed.
Conclusion: In view of the restricted growth of *C. albicans* in a Mg-deficient environment, approaches could be utilised to boost the effectiveness of existing antifungals thereby improving the management of fungal infections.

1. Introduction

Candida albicans is an opportunistic human fungal pathogen causing both mucosal and invasive infections in immunocompromised patients [1]. The advent of multidrug resistance has led to a reduction in the effectiveness of antifungal drugs, commanding an urgent need to look for novel treatment strategies. One feature that pathogenic micro-organisms, including *C. albicans*, must surmount to establish successful infection is micronutrient stress, since micronutrients are not freely available in the host. Micronutrients are required for diverse enzymatic and structural roles. The host deliberately withholds metals such as Fe, Zn, Mn and Mg from invading microbes as a defence strategy known as nutritional immunity [2]. Thus, there is competition between the host and the pathogen for the limited amount of micronutrients. Pathogens have also evolved sophisticated machinery to precisely balance the fine line between acquiring essential micronutrients (Fe, Zn, Cu, Mg, etc.) and at the same time defending against micronutrient excess. Thus, pathogens must maintain proper micronutrient homeostasis for successful pathogenesis.

Among the micronutrients, magnesium (Mg) is one of the crucial elements for *C. albicans* that plays a significant role in cell signalling, energy production, oxidative phosphorylation, nucleic acid synthesis and glycolysis [3]. It has previously been shown that the antifungal activity of bovine pancreatic trypsin inhibitor (BPTI) and the metal chelator diethylenetriamine penta-acetic acid (DTPA) in inhibiting the growth of *C. albicans* is via hindrance of cellular Mg uptake [4,5]. However, a comprehensive study describing the cellular responses responsible for regulating drug resistance and virulence under Mg stress in *C. albicans* is still elusive. Thus, the aim of the present study was to determine the effect of Mg deprivation on drug susceptibility, antifungal targets, morphogenesis and virulence determinants of *C. albicans*. Here we

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Targeting virus–host interaction by novel pyrimidine derivative: an *in silico* approach towards discovery of potential drug against COVID-19

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ABSTRACT

The entire human population over the globe is currently facing appalling conditions due to the spread of infection from coronavirus disease-2019 (COVID-19). The spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present on the surface of the virion mediates the virus entry into the host cells and therefore is targeted by several scientific groups as a novel drug target site. The spike glycoprotein binds to the human angiotensin-converting enzyme-2 (hACE2) cell surface receptor abundantly expressed in lung tissues, and this binding phenomenon is a primary determinant of cell tropism and pathogenesis. The binding and internalization of the virus is the primary and most crucial step in the process of infection, and therefore the molecules targeting the inhibition of this process certainly hold a significant therapeutic value. Thus, we systematically applied the computational techniques to identify the plausible inhibitor from a chosen set of well characterized diaryl pyrimidine analogues which may disrupt interfacial interaction of spike glycoprotein (S) at the surface of hACE2. Using molecular docking, molecular dynamics (MD) simulation and binding free energy calculation, we have identified AP-NP (2-(2-amino-5-(naphthalen-2-yl)pyrimidin-4-yl)phenol), AP-3-OMe-Ph (2-(2-amino-5-(3-methoxyphenyl)pyrimidin-4-yl)phenol) and AP-4-Me-Ph (2-(2-amino-5-(p-tolyl) pyrimidin-4-yl)phenol) from a group of diaryl pyrimidine derivatives which appears to bind at the interface of the hACE2-S complex with low binding free energy. Thus, pyrimidine derivative AP-NP may be explored as an effective inhibitor for hACE2-S complex. Furthermore, *in vitro* and *in vivo* studies will strengthen the use of these inhibitors as suitable drug candidates against SARS-COV-2.

Abbreviations: 6-HB: six-helix bundle; ADME: absorption, distribution, metabolism and excretion; AP-NP: 2-(2-amino-5-(naphthalen-2-yl)pyrimidin-4-yl) phenol; AP-4-Me-Ph: 2-(2-amino-5-(p-tolyl)pyrimidin-4-yl) phenol; AP-3-OMe-Ph: 2-(2-amino-5-(3-methoxyphenyl)pyrimidin-4-yl) phenol; COVID-19: coronavirus disease 2019; CQ: chloroquine; hACE2: human angiotensin converting enzyme-2; hACE2-S protein complex: human angiotensin converting enzyme-2 receptor and severe acute respiratory syndrome coronavirus 2 spike protein complex; HR1: heptad repeat 1; HR2: heptad repeat 2; PDB: protein data bank; RBD: receptor-binding domain; SARS-CoV-2S: severe acute respiratory syndrome coronavirus 2 spike protein; TMPRSS-2: transmembrane protease serine 2

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KEYWORDS
hACE2; receptor; coronavirus; pyrimidine derivatives; binding site

1. Introduction

The world is currently going through a debilitating phase of acute health disaster attributed to the global pandemic brought about by the novel coronavirus disease-2019 (COVID-19) (Enayatkhani et al., 2020; Joshi et al., 2020; Kirchdoerfer et al., 2016; Muralidharan et al., 2020). Sequencing and simultaneous phylogenetic identification of the virus responsible for COVID-19 confirmed that it as a novel β-coronavirus that shared 88% sequence identity with two bat-derived SARS-like coronaviruses (Lu et al., 2020;; Pant et al., 2020; Wang et al., 2020). Additionally, it was shown that this coronavirus (CoV), termed as 2019-nCoV (Elfiky, 2020; Gorbalenya et al., 2020), shared 79.5% sequence identity with SARS-CoV (Elfiky & Azzam, 2020; Lu et al., 2020;; Wang et al., 2020; Xia et al., 2020) which caused the severe acute respiratory syndrome pandemic in 2012. Therefore, this newly identified virus was called as SARS-CoV-2 (Aanouz

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Toxicity assessment of anatase (TiO_2) nanoparticles: A pilot study on stress response alterations and DNA damage studies in *Lens culinaris* Medik

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ABSTRACT

The research was targeted to investigate the effect of nano-TiO_2 (anatase) on germination, vigour index, stress enzymes and mitotic cell cycle profile in lentils (*Lens culinaris* Medik.). Seed germination results indicated that TiO_2 NP (Nanoparticle) at lowest concentration promotes seed germination, vigour index and biomass; however, at higher concentrations, they showed significant reduction in growth parameters and photosynthetic pigments in concentration-dependent manner. NP treatments triggered an excessive formation of reactive oxygen species (ROS) which was evident from increased production of stress enzymes, lipid peroxidation, augmented DNA damage and aberrant mitotic cell division. The results exhibit a dose-dependent modification of NP- mediated oxidative stress and genotoxicity in lentil.

1. Introduction

Nanoscience is the study that deals in manipulation of materials at nanoscale, where properties differ significantly from the bulk material. Particle size and distribution are the most important characteristics of nanoparticle (NP) and are the major factors for the determination of it's *in vivo* distribution, biological fate, toxicity and the targeting ability of NP systems [1]. Effects of engineered nanoparticles on plants are of great concern because of their crucial interaction with the environment [2] and can have adverse effects on land and aquatic biota. Titanium oxide (TiO_2) is among the top ten most produced engineered nanomaterials (ENMs) by mass [3] and was included in the list of ENMs of priority for immediate testing by the Organization for Economic Cooperation and Development (OECD) [4]. Titanium oxide NPs (TiO_2) possesses many unique properties compared to it's bulk counterpart having high surface area. They have an ability to pass the cell membrane of living organisms because of their small size and are extensively used in cosmetics, printing ink, self-cleaning ceramics, sensing materials, glass, medicines, antiseptic, and a wide variety of industrial materials. The unproportionate use of these nanoparticles result into their accumulation in the soil, producers and ultimately entering the food chain since plants serve as a potential pathway for the transportation of Nanoparticles (NPs) [5] from primary producers (plants) to high trophic-level consumers [6]. Several studies have reported that injected or inhaled TiO_2 NPs can migrate to several organs through circulation and impose adverse effects on organisms [7]. Therefore potential effects of these NPs on plants, especially on edible crop plants, should be evaluated before their widespread application.

Zheng *et al.* [8], Gao *et al.* [9], have shown that nano-sized TiO_2 can have a positive effect on the growth of spinach when administered to the activity of several enzymes and to promote the adsorption of nitrate, acceleration of the transformation of inorganic into organic nitrogen. But at higher concentration of TiO_2, seed germination, plant growth and physiological activities related to it may be adversely affected.

Plants possess several tissue antioxidants for protection against the potentially cytotoxic forms of activated oxygen. The harmful effects of free radicals produced as a result of oxidation are neutralized by the enzymatic antioxidant defences such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). It is believed that nanoparticles increase the oxidative stress which mediates damage to cell structures, including lipids, membranes, proteins, and DNA. Ruffini Castiglione *et al.* [10] considered oxidative stress and oxidative damage as indicators of possible cytotoxicity caused by these nanoparticles.

The reports from previous studies have updated our knowledge regarding the toxicological impact of nanomaterial but still, the fate of release of these nanoparticles and their consequences on the plant system is poorly understood. There is also a paucity of literature regarding

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Development of novel *N*-(6-methanesulfonyl-benzothiazol-2-yl)-3-(4-substituted-piperazin-1-yl)-propionamides with cholinesterase inhibition, anti-β-amyloid aggregation, neuroprotection and cognition enhancing properties for the therapy of Alzheimer's disease†

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A novel series of benzothiazole–piperazine hybrids were rationally designed, synthesized, and evaluated as multifunctional ligands against Alzheimer's disease (AD). The synthesized hybrid molecules illustrated modest to strong inhibition of acetylcholinesterase (AChE) and $A\beta_{1-42}$ aggregation. Compound **12** emerged as the most potent hybrid molecule exhibiting balanced functions with effective, uncompetitive and selective inhibition against AChE (IC_{50} = 2.31 μM), good copper chelation, $A\beta_{1-42}$ aggregation inhibition (53.30%) and disaggregation activities. Confocal laser scanning microscopy and TEM analysis also validate the Aβ fibril inhibition ability of this compound. Furthermore, this compound has also shown low toxicity and is capable of impeding loss of cell viability elicited by H_2O_2 neurotoxicity in SHSY-5Y cells. Notably, compound **12** significantly improved cognition and spatial memory against scopolamine-induced memory deficit in a mouse model. Hence, our results corroborate the multifunctional nature of novel hybrid molecule **12** against AD and it may be a suitable lead for further development as an effective therapeutic agent for therapy in the future.

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1. Introduction

Alzheimer's disease (AD) is a predominant source of irreversible dementia, resulting in more than 75% of the dementia cases worldwide. It is known to be a multifactorial neurodegenerative disorder designated by progressive loss of memory and other cognitive functions. The main risk factor of AD is aging; however the mechanism underlying the foundation of AD due to aging is yet to be firmly elucidated. It is clinically marked by the progression from episodic memory problems to a slow global decline of cognitive function. Patients in end-stage AD become bedridden and are highly dependent on custodial care, with an average life span of 9 years after diagnosis.[1] AD leaves an enormous emotional and financial burden on patients, their families and society.

There are approximately 44 million people affected by Alzheimer's disease, and it is expected to increase three times by 2050; these perturbing numbers show that Alzheimer's disease (AD) remains a serious socio-economical problem.[2] AD is estimated to have cost the world $604 billion in 2010 alone.[3] These costs are staggering, particularly in light of worldwide increase in the number of AD cases. AD remains the most prevalent unmet medical need because of its chronicity, cost, severity, and lack of mechanism based treatment.[4]

Extensive research from several years has still not been able to establish the exact molecular-mechanistic aspects of AD. Clinically, AD is indicated by widespread neuronal cell death in the brain, which corresponds to deposition of abundant fibrillar plaques, primarily comprising the beta-amyloid (Aβ) peptide.[5,6] The identified pathological hallmarks of AD are senile plaques of amyloid beta protein, intracellular neurofibrillary tangles (NFTs), and neuronal degeneration. Accumulation of Aβ peptides encourages conformational changes that lead to further non-covalent polymerization into a heterogeneous

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† Electronic supplementary information (ESI) available: *In silico* study data, ^1H and ^{13}C spectra of all synthesized compounds have been kept as supplementary data. See DOI: 10.1039/d0ra00663g

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Development of novel *N*-(6-methanesulfonyl-benzothiazol-2-yl)-3-(4-substituted-piperazin-1-yl)-propionamides with cholinesterase inhibition, anti-β-amyloid aggregation, neuroprotection and cognition enhancing properties for the therapy of Alzheimer's disease†

Chandra Bhushan Mishra,‡[a] Shruti Shalini,‡[a] Siddharth Gusain,[a] Amresh Prakash,[b] Jyoti Kumari,[a] Shikha Kumari,[a] Anita Kumari Yadav,[a] Andrew M. Lynn[c] and Manisha Tiwari*[a]

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1. Introduction

Alzheimer's disease (AD) is a predominant source of irreversible dementia, resulting in more than 75% of the dementia cases worldwide. It is known to be a multifactorial neurodegenerative disorder designated by progressive loss of memory and other cognitive functions. The main risk factor of AD is aging; however the mechanism underlying the foundation of AD due to aging is yet to be firmly elucidated. It is clinically marked by the progression from episodic memory problems to a slow global decline of cognitive function. Patients in end-stage AD become bedridden and are highly dependent on custodial care, with an average life span of 9 years after diagnosis.[1] AD leaves an enormous emotional and financial burden on patients, their families and society.

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Extensive research from several years has still not been able to establish the exact molecular-mechanistic aspects of AD. Clinically, AD is indicated by widespread neuronal cell death in the brain, which corresponds to deposition of abundant fibrillar plaques, primarily comprising the beta-amyloid (Aβ) peptide.[5,6] The identified pathological hallmarks of AD are senile plaques of amyloid beta protein, intracellular neurofibrillary tangles (NFTs), and neuronal degeneration. Accumulation of Aβ peptides encourages conformational changes that lead to further non-covalent polymerization into a heterogeneous

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ORIGINAL ARTICLE

XopR T3SS-effector of *Xanthomonas oryzae* pv. *oryzae* suppresses cell death-mediated plant defense response during bacterial blight development in rice

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Abstract
Xanthomonas oryzae pv. *oryzae* (Xoo) causes bacterial blight disease that limits the rice production globally. The bacterium secretes effector proteins directly into plant cells through a type III secretion system (T3SS). Here, we examined the role of a conserved XopR T3SS-effector in the suppression of host basal defense response. Phylogenetic and sequence analysis showed that XopR is well conserved within Xoo strains but shares varying degree of similarity among the other *Xanthomonas* species. The expression of XopR was shown to be regulated by *hrpX*, a key regulator of *hrp* cluster. For functional analysis we employed two mutant strains of Xoo, one lacks *xopR* gene and other lacks *hrpX* gene (making the strain defective in T3SS). Programmed cell death (PCD) events was examined both in rice and tobacco leaves through trypan blue staining method. In XopR expressing tobacco leaves the PCD induction was compromised. We observed higher PCD on rice leaves inoculated with Xoo mutants lacking either *xopR* or functional T3SS as compared to wild type. Contrary, when *xopR* gene was complemented in mutated strain the PCD was suppressed which clearly suggests that XopR acts as suppressor of the PCD mediated defense response. The EYFP::XopR fusion protein was shown to be localized to the plasma membrane of *Nicotiana benthamiana* and onion epidermal cells. Altogether our study leads to the understanding that XopR T3SS-effector is essential for Xoo to suppress PCD, primarily to support the in planta colonization of Xoo during blight pathogenesis.

Keywords *Xanthomonas oryzae* · T3SS · Phylogenetic analysis · PCD · EYFP

Introduction

Rice is an important staple food crop grown in various agro-climatic regions all over world including India. *Xanthomonas oryzae* pv. *oryzae* (Xoo) causes bacterial blight that potentially threatens the rice production. *Xanthomonas* for its pathogenicity relies on the effector proteins that are secreted through the type III secretion system (T3SS) (Leyns et al. 1984; Tampakaki et al. 2004). Effectors are classified into two categories, one is TALE (transcription activation like effectors) of the avrBs3/pthA family and the other is Xop (*Xanthomonas* outer protein) effectors (Buttner and He 2009; Long et al. 2018; Medina et al. 2018; Mudgett 2005). Xop T3SS-effectors are known to play a vital role in disease induction. Pathogens use Xop T3SS-effectors to suppress PAMP (pathogen-associated molecular patterns) triggered immunity (PTI) in host plants (Bartetzko et al. 2009; Zhang et al. 2015). Genomic analysis revealed nine "core T3SS-effectors" present in all *Xanthomonas* species (Hajri et al. 2009; Jalan et al. 2011; Moreira et al. 2010; Potnis et al. 2011). The core T3SS-effectors are suggested to have a critical role in *Xanthomonas* pathology. Thus, in depth studies on these core T3SS-effectors may lead to strategies for disease mitigation (Dangl et al. 2013; Potnis et al. 2011).

Plants counteract the pathogen's invasion by activating various immune responses including PCD (programmed cell death), callose deposition, ROS production that often leads to effector-triggered immunity (ETI) (Spoel and Dong 2012). However, T3SS-effectors mediated plant immune system is of complex nature. The matching T3SS-effectors of the pathogen against the host receptors actually determine the outcome of a plant–pathogen interaction. Xoo strains

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Structural heterogeneity in RNA recognition motif 2 (RRM2) of TAR DNA-binding protein 43 (TDP-43): clue to amyotrophic lateral sclerosis

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ABSTRACT
Aberrant misfolding and aggregation of TAR DNA-binding protein 43 (TDP-43) and its fragments have been implicated in amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases. Within the protein, the second RNA recognition motif (RRM2) has recently been demonstrated to be a major contributor towards aggregation and the resultant toxicity. However, the physicochemical mechanism of its misfolding from the functional folded state is poorly understood. In the present work, we have used a cumulative ~2μs of molecular dynamics (MD) simulation to study the structural and thermodynamic characteristics of different unfolded intermediates of RRM2 domain of TDP-43. In 6 M GdmCl at 400 K, at RMSD around 1.5 nm, part of the secondary structure i.e. helix still does not melt without significant change in solvent accessibility and intra-protein hydrogen bonds. However, hydrophobic contacts disrupt significantly suggesting that unfolding proceeds through disruption of hydrophobic core of the protein.The temperature dependent free-energy landscapes (FELs) reveal the presence of multiple metastable intermediate states stabilized by hydrophobic (ILV) contacts and hydrogen bonds. These conformational states have all the native helices intact with significant loss of β-sheets. These partially unfolded states are quite compact and characterized by the exposure of aggregation-prone β-sheets, suggesting the increased aggregation propensity of the partially unfolded states. Our results will thus serve to uncover the structural properties of partially unfolded intermediate states that drive TDP-43 misfolding and aggregation. Elucidating the structural characterization of the misfolding and aggregation prone intermediate states of TDP-43 are important to understand its role in ALS and other neurodegenerative diseases.

Abbreviations: ALS: Amyotrophic lateral sclerosis; FEL: Free energy landscape; MD: Molecular dynamics; Nc: Fraction of native contacts; RRM2: RNA recognition motif 2; RMSD: Root mean square deviation; R_g: Radius of gyration; RMSF: Root mean square fluctuation; SASA: Solvent accessible surface area; TDP-43: TAR DNA-binding protein 43

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KEYWORDS
RNA recognition motifs; protein unfolding; unfolding intermediates; hydrophobic contacts; aggregation

Introduction

The 43 kDa human transactive response DNA-binding protein (TDP-43) pathology is a hallmark of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and other neurodegenerative diseases like Alzheimer's disease, and Parkinson's disease (Arai et al., 2006; Neumann et al., 2006; Pasinelli & Brown, 2006). Despite the involvement of TDP-43 in ALS and other neurodegenerative diseases, the molecular basis of the disease mechanism is still not completely understood (Kiernan et al., 2011; Kumar, Islam, Hassan, & Ahmad, 2016; Parakh & Atkin, 2016; Polymenidou & Cleveland, 2011).

TDP-43 is a 414-amino-acid protein with four functional domains, two RNA recognition motifs (RRM1 and RRM2), an N-terminal dimerization domain (NTD) and a prion-like glycine-rich, disordered C-terminal domain (CTD). The 25 kDaTDP-43 C-terminal fragments comprising a C-terminal part of RRM2 and the glycine-rich CTD has been identified as the pathological species in ALS and FTD (Igaz et al., 2008; 2009; Wang et al., 2013; Zhang et al., 2009). Also, both RRM2 and CTD are required for aggregate formation and toxicity in yeast (Johnson, McCaffery, Lindquist, & Gitler, 2008). These studies thus suggest the involvement of these two domains of TDP-43 in the aberrant cytoplasmic aggregation and pathology in FTD and ALS.

TDP-43 RRM2 is highly stable domain, as shown by previous thermal and chemical induced unfolding studies (Austin et al., 2014; Mackness, Tran, McClain, Matthews, & Zitzewitz, 2014; Morgan, Zitzewitz, & Massi, 2017; Pillai & Jha, 2019; Prakash, Kumar, Meena, Hassan, & Lynn, 2018; Tavella, Zitzewitz, & Massi, 2018; Zacco, Martin, Thorogate, & Pastore, 2018). The unfolding studies of RRM2 have established the presence of intermediate states in the unfolding pathway. As shown by Brian et al.(Mackness et al., 2014), the intermediate state is minimally populated under native conditions and the

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Delineating the conformational dynamics of intermediate structures on the unfolding pathway of β-lactoglobulin in aqueous urea and dimethyl sulfoxide

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ABSTRACT

The funnel shaped energy landscape model of the protein folding suggests that progression of folding proceeds through multiple pathways, having the multiple intermediates which leads to multidimensional free-energy surface. Herein, we applied all-atom MD simulation to conduct a comparative study on the structure of β-lactoglobulin (β-LgA) in aqueous mixture of 8 M urea and 8 M dimethyl sulfoxide (DMSO), at different temperatures. The cumulative results of multiple simulations suggest a common unfolding pathway of β-LgA, occurred through the stable and meta-stable intermediates (I), in both urea and DMSO. However, the free-energy landscape (FEL) analyses show that the structural transitions of I-states are energetically different. In urea, FEL shows distinct ensemble of intermediates, I1 and I2, separated by the energy barrier of ~3.0 kcal mol^{-1}. Similarly, we find the population of two distinct I1 and I2 states in DMSO, however, the I1 appeared transiently around ~30–35 ns and is short-lived. But, the I2 ensemble is observed structurally compact and long-lived (~50–150 ns) as compared to unfolding in urea. Furthermore, the I1 and I2 are separated through a high energy barrier of ~6.0 kcal mol^{-1}. Thus, our results provide the structural insights of intermediates which essentially bear the signature of a different unfolding pathway of β-LgA in urea and DMSO.

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KEYWORDS
Protein folding; β-lactoglobulin; urea; DMSO; free-energy landscape

Abbreviations: β-LgA: β-lactoglobulin; DMSO: dimethyl sulfoxide; FEL: free-energy landscape; GdmCl: guanidinium chloride; I: intermediate state; MG: molten globule state; PME: particle mesh Ewald; Q: fraction of native contacts; RMSD: root mean square deviation; RMSF: root mean square fluctuation; R_g: radius of gyration; SASA: solvent Accessible Surface Area: scSASA: the side chain SASA; Trp: tryptophan

Introduction

The funnel model of protein folding along with free energy landscape (FEL) analysis has been applied to find a generalized semi-quantitative picture of folding pathways (Lindorff-Larsen, Piana, Dror, & Shaw, 2011; Ghosh, Roy, & Bagchi, 2014; Roy & Bagchi, 2014; Eaton & Wolynes, 2017). This view largely suggests that protein folding occurs through different intermediate states, followed by the multiple paths and the nature of intermediate dictate the folding transition may exist during the folded to unfolded state and vice-versa. The folding pathway of a protein is influenced profoundly by the presence of solvent molecules around which is often water or an aqueous solution of different denaturants as co-solvents. Among the co-solvents, chemical denaturants like urea, GdmCl, DMSO, etc. are increasingly exploited in protein unfolding studies as they modulated the structural and functional properties of protein and enhanced the rate of unfolding (Baldwin, 1997; Camilloni et al., 2008; Rocco et al., 2008; Roy & Bagchi, 2014; Khan et al., 2016; Prakash, Kumar, Meena, & Lynn, 2018). However, it is a challenging task to chronicle the consequence of conformational reorganization which leads to the protein folding/unfolding (Lindorff-Larsen et al., 2011; Eaton & Wolynes, 2017). In this regards, molecular dynamics (MD) simulation is an efficient tool which has been applied successfully to characterize the structural details of protein unfolding at atomic resolution (Å) with the time evolution of picoseconds (ps) (Lindorff-Larsen et al., 2011; Prakash & Luthra, 2012; Ghosh et al., 2014; Kumar Thakur et al., 2014; Eaton & Wolynes, 2017; Prakash, Kumar, Lynn, & Haque, 2018; Kumar, Pandey, Idrees, Prakash, & Lynn, 2019).

To understand the protein folding, urea as chemical denaturant has been widely explored in both experimental and computational studies. However, the exact molecular mechanism of urea-induced protein denaturation is yet to

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cancers

MDPI

Article

Novel Carbazole-Piperazine Hybrid Small Molecule Induces Apoptosis by Targeting BCL-2 and Inhibits Tumor Progression in Lung Adenocarcinoma in Vitro and Xenograft Mice Model

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Abstract: Lung cancer is a type of deadly cancer and a leading cause of cancer associated death worldwide. BCL-2 protein is considered as an imperative target for the treatment of cancer due to their significant involvement in cell survival and death. A carbazole-piperazine hybrid molecule ECPU-0001 was designed and synthesized as a potent BCL-2 targeting agent with effective anticancer cancer activity. Interaction of ECPU-001 has been assessed by docking, molecular dynamics (MD) simulation, and thermal shift assay. Further, in vitro and in vivo anticancer activity was executed by cytotoxicity assay, FACS, colony formation and migration assay, western blotting, immunocyto/histochemistry and xenograft nude mice model. Molecular docking and MD simulation study confirmed that ECPU-0001 nicely interacts with the active site of BCL-2 by displaying a Ki value of 5.72 μM and binding energy (ΔG) of –8.35 kcal/mol. Thermal shift assay also validated strong interaction of this compound with BCL-2. ECPU-0001 effectively exerted a cytotoxic effect against lung adenocarnoma cells A459 with an IC_{50} value of 1.779 μM. Molecular mechanism of action have also been investigated and found that ECPU-0001 induced apoptosis in A459 cell by targeting BCL-2 to induce intrinsic pathway of apoptosis. Administration of ECPU-0001 significantly inhibited progression of tumor in a xenograft model without exerting severe toxicity and remarkably reduced tumor volume as well as tumor burden in treated animals. Our investigation bestowed ECPU-0001 as an effective tumoricidal agent which exhibited impressive anticancer activity in vitro as well as in vivo by targeting BCL-2 associated intrinsic pathway of apoptosis. Thus, ECPU-0001 may provide a valuable input for therapy of lung adenosarcoma in future, however, further extensive investigation of this compound will be needed.

Keywords: carbazole-piperazine hybrid molecule; ECPU-0001; tumor xenograft; mitochondrial mediated apoptosis; intrinsic pathway; molecular dynamics simulation

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SHORT REPORTS

Development and utilization of *gyr*A and *gyr*B gene-based diagnostics for the phytoplasma classified under 16Sr I group in plants and insects

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Received: 15 December 2018 / Accepted: 5 April 2019

Abstract
In the present study, a new set of primers of *gyr*A and *gyr*B genes of the phytoplasma genome were designed and validated for the successful detection and taxonomic classification of the previously identified phytoplasma strains of '*Candidatus* P. asteris' (16SrI-B subgroup) associated with Catharanthus leaf yellows, sesame phyllody and the leafhopper (*Hishimonus phycitis*). Our results suggested the ability and sensitivity of *gyrA* and *gyrB* genes as an alternative molecular marker to identify the *Ca*. P. asteris strain up to subgroup level associated both with plants and insects.

Keywords Multilocus genes · Validation · Phytoplasma detection · Leafhopper

Phytoplasma classification established using 16S ribosomal groups and '*Candidatus* Phytoplasma' taxon is mainly based on 16S rDNA properties and do not always provide molecular distinction of the closely related strains. More variable single copy genes, such as ribosomal proteins (*rpl22* and *rpS3*), *sec*Y, *sec*A, *tuf*, *dna*B and *gro*EL were employed for finer classification of phytoplasma and differentiation (Schneider et al. 1997; Langer and Maixner 2004; Lee et al. 2007; Martini et al. 2007; Hodgetts et al. 2008; Hodgetts and Dickinson 2010; Bertaccini et al. 2014).To further improve detection and taxonomic classification of phytoplasma, we have designed primers for PCR assays based on *gyr*A and *gyr*B genes and tested them on aster yellows phytoplasma strains (16SrI) from field-infected samples of periwinkle (*Catharanthus roseus*) and sesame (*Sesamum indicum*). The detection and validation of *gyr*A and *gyr*B gene specific primers were also attempted to detect the phytoplasma in samples of leafhopper (*Hishimonus phycitis*) collected from infected sesame fields.

The DNA was extracted from samples of two isolates of *Catharanthus* with symptoms of little leaf (one each from Gorakhpur, Cr-GKP isolate and Shahajahanpur, Cr-SJP isolate, Uttar Pradesh, India), sesame showing phyllody from Kushinagar (S-Kus isolate, Uttar Pradesh, India) and ten individual leafhoppers, *H. phycitis* collected from infected sesame fields at Kushinagar (HP-Kus). The protocol of Ahrens and Seemüller (1992) and Marzachi et al. (1998) was followed for total DNA extraction from the plants and leafhopper samples, respectively. The extracted DNAs from the earlier identified phytoplasma strains in our lab as 16SrI-B subgroup associated with the periwinkle (Cr-GKP and Cr-SJP), sesame (S-Kus) and *H. phycitis* (HP-Kus) (Madhupriya et al. 2015; Madhupriya 2016) were tested for the presence of phytoplasmas for direct PCR amplification with newly designed set of primers for *gyr*A and *gyr*B genes, *gyrA*F/R (5′-TGCTTATCACACCGGACAAG-3/5′-CCAAAGCCGTTTTCAGTCAT-3′) and *gyrB*F/R (5′-GGAGCCTCTGTGGTAAATGC-3′/5′-GCATCTTTGAGGCTTGCT TT-3′) that amplified an expected size amplicon of about 1.4 kb (*gyr*A) and 1.5 kb (*gyr*B) from all the four phytoplasma isolates of the plants and leafhopper samples. PCR assay was carried out in a thermal cycler (Eppendorf, Germany) and the cycling protocol used for the PCR assays was 94 °C for 5 min, followed by 35 cycles consisting of denaturation at 94 °C for 45 s, annealing at 55 °C (*gyrA*F/R) and 56 °C (*gyrB*F/R) for 1 min, and extension at 72 °C for 2 min, with extension in the final cycle for 10 min.

Expected amplified products of 1.4 kb (*gyr*A) and 1.5 kb (*gyr*B) were obtained with DNA extracted from both the test plants (periwinkle and sesame) and the leafhopper (*H. phycitis*) confirming the specificity of *gyr*A and *gyr*B

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Materials for life sciences

Bi-functionalization of glass surfaces with poly-L-lysine conjugated silica particles and polyethylene glycol for selective cellular attachment and proliferation

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ABSTRACT

Fabrication of microstructured patterns serves as a powerful tool for studying the cellular responses toward synthetic materials at the material–cell interface for tissue engineering. Silica particles can effectively act as a substrate for cellular attachment and growth owing to its biocompatible nature and facile surface chemistry. In the current study, a non-lithographic microfabrication method for patterning of particles was devised using silica particles (~ 600 nm) and epoxy-silane-functionalized glass surfaces. Poly-L-lysine (PLL) was covalently attached to modified silica particles which were subsequently patterned onto the functionalized glass surfaces. PLL played a dual role. Firstly, it served as a bi-linker by covalently attaching modified particles on epoxy functionalized glass surfaces. Secondly, it facilitated cellular attachment on the pattern via electrostatic interactions. The vacant unpatterned regions were passivated with methoxy-polyethylene glycol-amino (MPA) to avoid non-specific cellular attachments. A549 cells were found to grow specifically on the monolayered silica patterns having lower packing density and exhibited stretched morphology, indicating cellular attachment to the substrate, whereas the MPA passivated areas were capable of blocking cell adhesion successfully. The highlight of the reported novel method lies in the dual use of PLL which not only provided necessary control over the surface chemistry by allowing fabrication of desired patterns but also facilitated selective cellular attachment on the generated patterns. Therefore, we report a simple process for micropatterning the cells on desired patterns via surface bi-functionalization for selective cellular attachment and proliferation.

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Altered drug efflux under iron deprivation unveils abrogated MmpL3 driven mycolic acid transport and fluidity in mycobacteria

Rahul Pal · Saif Hameed · Zeeshan Fatima

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Abstract Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is a global threat to human health hence better understanding of the MTB pathogenesis for improved therapeutics requires immediate attention. Emergence of drug-resistant strains has stimulated an urgent need for adopting new strategies that could be implemented to control TB. One of the contributing mechanisms by which MTB evades drug doses is overexpression of drug efflux pumps. Thus blocking or modulating the functionality of efflux pumps represents an attractive approach to combat drug resistance. Iron is a critical micronutrient required for MTB survival and not freely available inside the host. In this study, we demonstrated that iron deprivation impairs drug efflux pump activity and confers synergism for anti-TB drugs in presence of efflux pump inhibitors against MTB. Mechanistic insights revealed that iron deprivation inhibit resistance nodulation division superfamily transporter activity. This was evident from enhanced Nile red accumulation and reduced expression of MmpL3, a transmembrane promising target involved in mycolic acid transport across membrane. Furthermore, iron deprivation led to abrogated MA transport particularly of class methoxy-MA which was confirmed by TLC and mass spectrometry based lipidome analysis. Additionally, iron deprivation leads to enhanced membrane fluidity in MTB. Together, MmpL3 being a promiscuous anti-TB target, metal chelation strategy could be adopted to boost the effectiveness of current anti-TB drug regimes to combat drug resistance TB.

Keywords *Mycobacterium* · Iron · Efflux pump · MmpL3 · Mycolic acid · Membrane fluidity

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) remains one of the important underlying causes of mortality worldwide. Widespread and prolonged deployment of anti-TB agents has led to emergence of drug resistance in MTB, which poses a serious threat to available therapy. Multidrug resistant tuberculosis (MDR-TB) results due to simultaneous resistance towards two frontline anti-TB drugs, isoniazid and rifampicin (Mezwa et al. 2018). Similarly, extensively drug resistant TB (XDR-TB) is caused by MTB strains which are resistant to isoniazid, rifampicin, a fluoroquinolone and one of the three second line

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Sphingolipidomics of drug resistant *Candida auris* clinical isolates reveal distinct sphingolipid species signatures

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Keywords:
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Sphingolipids
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Phytoceramide

ABSTRACT

Independent studies from our group and others have provided evidence that sphingolipids (SLs) influence the antimycotic susceptibility of *Candida* species. We analyzed the molecular SL signatures of drug-resistant clinical isolates of *Candida auris*, which have emerged as a global threat over the last decade. This included Indian hospital isolates of *C. auris*, which were either resistant to fluconazole (FLC^R) or amphotericin B (AmB^R) or both drugs. Relative to *Candida glabrata* and *Candida albicans* strains, these *C. auris* isolates were susceptible to SL pathway inhibitors such as myriocin and aureobasidin A, suggesting that SL content may influence azole and AmB susceptibilities. Our analysis of SLs confirmed the presence of 140 SL species within nine major SL classes, namely the sphingoid bases, Cer, αOH-Cer, dhCer, PCer, αOH-PCer, αOH-GlcCer, GlcCer, and IPC. Other than for αOH-GlcCer, most of the SLs were found at higher concentrations in FLC^R isolates as compared to the AmB^R isolates. SLs were at intermediate levels in FLC^R + AmB^R isolates. The observed diversity of molecular species of SL classes based on fatty acyl composition was further reflected in their distinct specific imprint, suggesting their influence in drug resistance. Together, the presented data improves our understanding of the dynamics of SL structures, their synthesis, and link to the drug resistance in *C. auris*.

1. Introduction

Increasing antimicrobial resistance in pathogenic fungi is becoming a global health threat and eroding our ability to control fungal infections with a limited armamentarium of antifungals [1]. Most of the fungal infections associated with significant mortality and antimicrobial resistance are triggered by opportunistic human fungal pathogens [1,2]. The major pathogens, *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*, may survive in anatomically distinct locations within the host and are capable of fostering deep-seated infections in patients with compromised immune systems [3]. In contrast to the common *C. albicans*, non-albicans *Candida* (NAC) species are evolving as problematic drug resistance pathogens [1]. The recent emergence of multiple drug-resistant *Candida auris* clades within a short

Abbreviations: MDR, multidrug resistance; NAC, non-albicans *Candida*; FLC, fluconazole; AmB, amphotericin B; MS, mass spectrometry; SLs, sphingolipids; Liquid chromatography-tandem mass spectrometry, LC-MS/MS; FLC^R, FLC-resistant; AmB^R, AmB-resistant; FLC^R + AmB^R, both FLC and AmB resistant; MIPC, mannosyl-inositol-phosphoceramides; $M(IP)_2C$, mannosyl-diinositol-phosphoceramides; PDREs, Pdr1/Pdr3 response elements; PCA, principal component analysis; MYR, myriocin; AbA, aureobasidin A; SPT, serine palmitoyl-CoA transferase; IPC, inositolphosphorylceramide; GlcCer, glucosylceramide; DHS, dihydrosphingosine; SPH, sphingosine; S1P, sphingosine-1-phosphate; DHS1P, dihydrosphingosine-1-phosphate; PHS, phytosphingosine; PHS1P, phytosphingosine-1-phosphate; Glucosyl-SPH, glucosyl sphingosine; dhCer, dihydroceramide; Cer, ceramides; αOH-Cer, αhydroxy ceramides; PCer, phytoceramide; αOH-PCer, αhydroxy phytoceramide; αOH-GlcCer, αhydroxy glucosylceramide; IPCs, inositol phosphoryl ceramides

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Protonophore FCCP provides fitness advantage to PDR-deficient yeast cells

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Abstract
Pleiotropic drug resistance (PDR) plasma membrane transporters mediate xenobiotic efflux from the cells and thereby help pathogenic microorganisms to withstand antimicrobial therapies. Given that xenobiotic efflux is an energy-consuming process, cells with upregulated PDR can be sensitive to perturbations in cellular energetics. Protonophores dissipate proton gradient across the cellular membranes and thus increase ATP spendings to their maintenance. We hypothesised that chronic exposure of yeast cells to the protonophores can favour the selection of cells with inactive PDR. To test this, we measured growth rates of the wild type *Saccharomyces cerevisiae* and PDR-deficient *Δpdr1Δpdr3* strains in the presence of protonophores carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (FCCP), pentachlorophenol (PCP) and niclosamide (NCA). Although the protonophore-induced respiration rates of these two strains were similar, the PDR-deficient strain outperformed the control one in the growth rate on non-fermentable carbon source supplemented with low concentrations of FCCP. Thus, active PDR can be deleterious under conditions of partially uncoupled oxidative-phosphorylation. Furthermore, our results suggest that tested anionic protonophores are poor substrates of PDR-transporters. At the same time, protonophores imparted azole tolerance to yeasts, pointing that they are potent PDR inducers. Interestingly, protonophore PCP led to a persistent increase in the levels of a major ABC-transporter Pdr5p, while azole clotrimazole induced only a temporary increase. Together, our data provides an insight into the effects of the protonophores in the eukaryotes at the cellular level and support the idea that cells with activated PDR can be selected out upon conditions of energy limitations.

Keywords Protonophores · Uncouplers · Multiple drug resistance · Niclosamide · Drug interactions

Introduction

Microbial drug resistance is an expanding problem for healthcare and agriculture (Fisher et al. 2018; Van Boeckel et al. 2019). While drug-resistant bacteria produce a major part of the pressure on the healthcare system (Roope et al. 2019), drug-resistant fungi are a specific threat to immunosuppressed patients (Kontoyiannis and Lewis 2002). Tens of thousands clinical cases are attributed to infections caused by drug-resistant *Candida* species (Centers for Disease Control and Prevention (U.S.) 2019).

In yeasts, drug resistance is usually mediated by plasma membrane transporters with broad substrate specificity (Tsao et al. 2009; Wasi et al. 2019; Zhang et al. 2020). These pleiotropic drug resistance (PDR) transporters efflux toxic compounds from yeast cytoplasm at the cost of ATP hydrolysis (ABC-transporters) or proton translocation in case of MFS transporters (Panwar et al. 2008). Moreover, some ABC transporters hydrolyse ATP even during futile catalytic cycles

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RESEARCH Open Access

Deletion of *pgi* gene in *E. coli* increases tolerance to furfural and 5-hydroxymethyl furfural in media containing glucose–xylose mixture

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Abstract

Background: Furfural and 5-hydroxymethyl furfural (5-HMF) are key furan inhibitors that are generated due to breakdown of lignocellulosic sugars at high temperature and acidic treatment conditions. Both furfural and 5-HMF act in a synergistic manner to inhibit microbial metabolism and resistance to both is a desirable characteristic for efficient conversion of lignocellulosic carbon to ethanol. Genetic manipulations targeted toward increasing cellular NADPH pools have successfully imparted tolerance against furfural and 5-HMF. In present study, deletion of *pgi* gene as a strategy to augment carbon flow through pentose phosphate pathway (PPP) was studied in ethanologenic *Escherichia coli* strain SSK101 to impart tolerance towards either furfural or 5-HMFor both inhibitors together.

Results: A key gene of EMP pathway, *pgi*, was deleted in an ethanologenic *E. coli* strain SSK42 to yield strain SSK101. In presence of 1 g/L furfural in minimal AM1 media, the rate of biomass formation for strain SSK101 was up to 1.9-fold higher as compared to parent SSK42 strain, and it was able to clear furfural in half the time. Tolerance to inhibitor was associated with glucose as carbon source and not xylose, and the tolerance advantage of SSK101 was neutralized in LB media. Bioreactor studies were performed under binary stress of furfural and 5-HMF (1 g/L each) and different glucose concentrations in a glucose–xylose mixture with final sugar concentration of 5.5%, mimicking major components of dilute acid treated biomass hydrolysate. In the mixture having 6 g/L and 12 g/L glucose, SSK101 strain produced ~ 18 g/L and 20 g/L ethanol, respectively. Interestingly, the maximum ethanol productivity was better at lower glucose load with 0.46 g/(L.h) between 96 and 120 h, as compared to higher glucose load where it was 0.33 g/(L.h) between 144 and 168 h. Importantly, parent strain SSK42 did not exhibit significant metabolic activity under similar conditions of inhibitor load and sugar concentration.

Conclusions: *E. coli* strain *SSK101* with *pgi* deletion had enhanced tolerance against both furfural and 5-HMF, which was associated with presence of glucose in media. Strain SSK101 also had improved fermentation characteristics under both hyperosmotic as well as binary stress of furfural and 5-HMF in media containing glucose–xylose mixture.

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ORIGINAL ARTICLE

Secretome produced by a newly isolated *Aspergillus flavus* strain in engineered medium shows synergy for biomass saccharification with a commercial cellulase

Mohit Kumar[1,2] · Ajay Kumar Pandey[1] · Sonam Kumari[1] · Shahid Ali Wani[1] · Shaik Jakeer[1] · Rameshwar Tiwari[1] · Rajendra Prasad[2] · Naseem A Gaur[1]

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Abstract

In this study, we evaluated the saccharification potential of the secretome produced by a new elephant faeces isolate *Aspergillus flavus* (AF-NGF1), alone as well as in combination with a commercial enzyme (CTec2). Medium engineering (involving sequential Taguchi design, response surface methodology and one factor at a time approaches) enhanced the cellulase (FPase) secretion in the secretome of isolate AF-NGF1 (AF-S) by 3.89-folds. AF-S showed a maximum increase of 7.1- and 8.69-folds in exo-glucanase (avicellase) and endo-glucanase (CMCase) activities, respectively. Equal enzyme loading (20 FPU/g of biomass) of AF-S and CTec2 showed comparable saccharification potential with acid pre-treated paddy straw (APPS). However, a 1:1 combination of AF-S and CTec2 showed 67.84% and 37.21% increased saccharification of APPS as compared with AF-S or CTec2 alone at 50 °C and 40 °C, respectively. During simultaneous saccharification and fermentation (SSF) at 40 °C, a 1:1 combination produced > 2-folds increased ethanol titre as compared with AF-S or CTec2 alone. When equal FPU of AF-S and CTec2 were mixed for a total of 20 FPU, the degree of synergy (DOS) for APPS saccharification was 1.79 ± 0.06 and ~ 30.49% increased FPase activity was detected, which suggested the synergistic correlation between AF-S and CTec2. Therefore, the combination of AF-S and CTec2 could be considered as a potential cellulolytic enzyme formulation for efficient biomass hydrolysis and SSF process for lignocellulosic ethanol production.

Mohit Kumar and Ajay Kumar Pandey contributed equally to this work as first author.

Highlights
- A 3.89-folds enhanced FPase activity was achieved by medium engineering in AF-S.
- Endo- and exo-glucanase activities were most influenced by medium engineering.
- AF-S and CTec2 (1:1) showed 67.84% enhanced saccharification than CTec2/AF-S.
- AF-S and CTec2 (1:1) produced 54.1% higher ethanol than CTec2/AF-S during SSF.
- AF-S showed synergy with CTec2 for FPase activity and APPS saccharification.

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Research Article

RESEARCH ARTICLE

A homologous overexpression system to study roles of drug transporters in *Candida glabrata*

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One sentence summary: Development of a strain containing seven ABC transporter deletion with overexpressed CgCDR1 locus and its expression system for characterizing membrane protein in pathogenic yeast Candida glabrata.

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ABSTRACT

Considering the relevance of drug transporters belonging to ABC and MFS superfamilies in pathogenic *Candida* species, there has always been a need to have an overexpression system where these membrane proteins for functional analysis could be expressed in a homologous background. We could address this unmet need by constructing a highly drug-susceptible *Candida glabrata* strain deleted in seven dominant ABC transporters genes such as *CgSNQ2*, *CgAUS1*, *CgCDR1*, *CgPDH1*, *CgYCF1*, *CgYBT1* and *CgYOR1* and introduced a GOF mutation in transcription factor (TF) *CgPDR1* leading to a hyper-activation of *CgCDR1* locus. The expression system was validated by overexpressing four GFP tagged ABC (*CgCDR1*, *CgPDH1*, *CaCDR1* and *ScPDR5*) and an MFS (*CgFLR1*) transporters genes facilitated by an engineered expression plasmid to integrate at the *CgCDR1* locus. The properly expressed and localized transporters were fully functional, as was revealed by their several-fold increased drug resistance, growth kinetics, localization studies and efflux activities. The present homologous system will facilitate in determining the role of an individual transporter for its substrate specificity, drug efflux, pathogenicity and virulence traits without the interference of other major transporters.

Keywords: ABC transporters; multi-deletion; azoles; GOF mutation; expression plasmid; *Candida glabrata*

INTRODUCTION

Candida glabrata, present as a commensal in the human microbiota, is the only second most common infectious agent to cause superficial skin infections to be severe and life-threatening bloodstream infections among genus *Candida* (Kasper, Seider and Hube 2015). The continuous use of antimycotic drugs, especially azoles, has led to an emergence of drug-resistant clinical strains (Ksiezopolska and Gabaldón 2018). *C. glabrata* exhibits intrinsically low susceptibility to azoles (Whaley *et al.* 2016). This clinically rising drug resistance in *C. glabrata* is a culmination of several mechanisms which also includes overexpression

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Research Article

RESEARCH ARTICLE

A detailed lipidomic study of human pathogenic fungi *Candida auris*

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One sentence summary: The present study determines the lipid composition of *Candida auris* and highlights alterations in lipids that may be correlated to high drug resistance in fungi.

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ABSTRACT

The present study is an attempt to determine the lipid composition of *Candida auris* and to highlight if the changes in lipids can be correlated to high drug resistance encountered in *C. auris*. For this, the comparative lipidomics landscape between drug-susceptible (CBS10913T) and a resistant hospital isolate (NCCPF.470033) of *C. auris* was determined by employing high throughput mass spectrometry. All major groups of phosphoglycerides (PGL), sphingolipids, sterols, diacylglycerols (DAG) and triacylglycerols (TAG), were quantitated along with their molecular lipid species. Our analyses highlighted several key changes where the NCCPF.470033 showed an increase in PGL content, specifically phosphatidylcholine, phosphatidylglycerol, phosphatidylserine, phosphatidylinositol, and phosphatidylethanolamine; odd chain containing lipids and accumulation of 16:1-DAG and 16:0-DAG; depletion of 18:1-TAG and 18:0-TAG. The landscape of molecular species displayed a distinct imprint between isolates. For example, the levels of unsaturated PGLs, contributed by both odd and even-chain fatty acyls were higher in resistant NCCPF.470033 isolate, resulting in a higher unsaturation index. Notwithstanding, several commonalities of lipid compositional changes between resistant *C. auris* and other *Candida* spp., the study could also identify distinguishable changes in specific lipid species in *C. auris*. Together, the data highlights the modulation of membrane lipid homeostasis associated with drug-resistant phenotype of *C. auris*.

Keywords: Lipids; pathogenic fungi; functions; mass spectrometry

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ORIGINAL ARTICLE

Assessment of antifungal resistance and associated molecular mechanism in *Candida albicans* isolates from different cohorts of patients in North Indian state of Haryana

Ashok Kumar[1] · Remya Nair[1] · Mohit Kumar[1,2] · Atanu Banerjee[1] · Arunaloke Chakrabarti[3] · Shivaprakash M. Rudramurthy[3] · Ruchika Bagga[4] · Naseem A. Gaur[2] · Alok K. Mondal[5] · Rajendra Prasad[1]

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Abstract

The present study examines the trend in distribution of *Candida* species and their antifungal resistance patterns in hospitals across Haryana, a North Indian state with poorly addressed epidemiology of fungal infections. In our collection of 228 *Candida* isolates, *Candida albicans* dominated in both high vaginal swab (HVS) and urine samples while *Candida glabrata* and *Candida tropicalis* were the second-highest non-albicans *Candida* species (NAC), respectively. Of note, in blood samples, *C. tropicalis* and *C. albicans* were present in equal numbers. All 228 isolates were subjected to antifungal susceptibility tests, whereby 51% of *C. albicans* recovered from HVS samples displayed fluconazole resistance. To understand its mechanistic basis, expression profiling of efflux pump genes CDR1, CDR2, MDR1 and azole drug target, ERG11 was performed in 20 randomly selected resistant isolates, wherein many isolates elicited higher expression. Further, ERG11 gene sequencing suggested that most of the isolates harbored mutations, which are not reported with azole resistance. However, one isolate, RPCA9 (MIC 64 μg/mL) harbored triple mutation (Y132C, F145L, A114V), wherein Y132 and F145 sites were previously implicated in azole resistance. Interestingly, one isolate, (RPCA61) having MIC > 128 μg/mL harbored a novel mutation, G129R. Of note, HVS isolates RPCA 21, RPCA 22, and RPCA 44 (MICs 64 to > 128 μg/mL) did not show any change in alteration in ERG11 or overexpression of efflux pump genes. Together, this study presents a first report of *Candida* infections in selected hospitals of Haryana State.

Abbreviations

HVS	High vaginal swab
NAC	Non-albicans *Candida*
RT-PCR	Reverse transcriptase polymerase chain reaction
YEPD	Yeast Extract Peptone Dextrose
SDA	Sabouraud dextrose agar
BAL	Bronchoalveolar lavage
CSF	Cerebrospinal fluid
VVC	Vulvo-vaginal candidiasis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12223-020-00785-6) contains supplementary material, which is available to authorized users.

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Introduction

Among the human pathogens, fungi are referred to as "hidden killers" as more people die from invasive fungal diseases than tuberculosis or malaria (Brown et al. 2012). Candidemia is considered as the major cause of invasive fungal infections worldwide (Chakrabarti et al. 2015; Pfaller and Diekema 2004). Developing countries are currently struggling with 4 to 15 times higher rates of candidemia (Giri and Kindo 2012). The overall mortality due to candidemia also remains quite high in these countries (> 50%) (Kaur and Chakrabarti 2017), while the Western world reports a much lower rate (Wisplinghoff et al. 2004). However, more recently non-albicans *Candida* (NAC) species are also being increasingly reported (Mullick et al. 2015; Kaur et al. 2016; Sanches et al. 2018).

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ORIGINAL ARTICLE

Assessment of antifungal resistance and associated molecular mechanism in *Candida albicans* isolates from different cohorts of patients in North Indian state of Haryana

Ashok Kumar[1] · Remya Nair[1] · Mohit Kumar[1,2] · Atanu Banerjee[1] · Arunaloke Chakrabarti[3] · Shivaprakash M. Rudramurthy[3] · Ruchika Bagga[4] · Naseem A. Gaur[2] · Alok K. Mondal[5] · Rajendra Prasad[1]

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Abbreviations

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BAL	Bronchoalveolar lavage
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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12223-020-00785-6) contains supplementary material, which is available to authorized users.

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Introduction

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Research article

Identification, evolutionary profiling, and expression analysis of F-box superfamily genes under phosphate deficiency in tomato

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Tomato

ABSTRACT

F-box genes are an integral component of the Skp1-cullin-F-box (SCF) complex in eukaryotes. These genes are primarily involved in determining substrate specificities during cellular proteolysis. Here we report that 410 members constitute the F-box superfamily in tomato. Based on the incidence of C-terminal domains, these genes fell into ten subfamilies, leucine-rich repeat domain-containing F-box members constituting the largest subfamily. The F-box genes are present on all 12 chromosomes with varying gene densities. Both segmental and tandem duplication events contribute significantly to their expansion in the tomato genome. The syntenic analysis revealed close relationships among F-box homologs within Solanaceae species genomes. Transcript profiling of F-box members identified several ripening-associated genes with altered expression in the ripening mutants. RNA-sequencing data analysis showed that phosphate (Pi) deficiency affected 55 F-box transcripts in the Pi-deficient seedlings compared to their control seedlings. The persistent up-regulation of eight members, including two *phloem protein 2B (PP2–B)* genes, *PP2–B15*, and *MATERNAL EFFECT EMBRYO ARREST 66 (MEE66)* homologs, at multiple time-points in the roots, shoot, and seedling, point towards their pivotal roles in Pi starvation response in tomato. The attenuation of such upregulation in sucrose absence revealed the necessity of this metabolite for robust activation of these genes in the Pi-deficient seedlings. Altogether, this study identifies novel F-box genes with potential roles in fruit ripening and Pi starvation response and unlocks new avenues for functional characterization of candidate genes in tomato and other related species.

1. Introduction

Protein turnover is an essential regulatory mechanism underlying the regulation of a plethora of cellular processes such as cell cycle, cell lineage specification, embryogenesis, circadian rhythms, fruit development, stress responses, and several signaling pathways. The ubiquitin-proteasome route is the principal regulatory circuit that degrades selective intracellular proteins (Smalle and Vierstra, 2004). This pathway mainly operates in three main steps: (i) activation of ubiquitin (Ub) moiety by Ub-activating enzyme (E1), (ii) relocation of activated Ub to Ub-conjugating enzyme (E2), and (iii) transfer of Ub to the target proteins, followed by their degradation via Ub-protein ligase (E3) complex. F-box proteins constitute one of the Skp1-cullin-F-box (SCF) E3-ligase complex subunits and confer their specificity for appropriate substrates (Lechner et al., 2006).

The presence of a highly conserved, approximately 60 amino acids long N-terminally located F-box domain is the characteristic feature of these proteins. In contrast, the C-terminal end of these proteins are less conserved and may possess one or more variable protein-protein interaction domains such as leucine-rich repeats (LRR), kelch repeat, tetratricopeptide repeat (TPR), and WD40 repeats (Jain et al., 2007). F-box genes have been identified in a range of organisms after their initial discovery in humans (Bai et al., 1994; Jain et al., 2007). Numerous studies have shown that more F-box genes are present in plant genomes than in any other organism. For example, in contrast to the 18 F-box genes available in yeast (*Schizosaccharomyces pombe*) and 33 genes in

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ORIGINAL PAPER

Tissue specific expression of sialic acid metabolic pathway: role in GNE myopathy

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Abstract
GNE myopathy is an adult-onset degenerative muscle disease that leads to extreme disability in patients. Biallelic mutations in the rate-limiting enzyme UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine-kinase (GNE) of sialic acid (SA) biosynthetic pathway, was shown to be the cause of this disease. Other genetic disorders with muscle pathology where defects in glycosylation are known. It is yet not clear why a defect in SA biosynthesis and glycosylation affect muscle cells selectively even though they are ubiquitously present in all tissues. Here we have comprehensively examined the complete SA metabolic pathway involving biosynthesis, sialylation, salvage, and catabolism. To understand the reason for tissue-specific phenotype caused by mutations in genes of this pathway, we analysed the expression of different SA pathway genes in various tissues, during the muscle tissue development and in muscle tissues from GNE myopathy patients (p.Met743Thr) using publicly available databases. We have also analysed gene co-expression networks with *GNE* in different tissues as well as gene interactions that are unique to muscle tissues only. The results do show a few muscle specific interactions involving *ANLN*, *MYO16* and *PRAMEF25* that could be involved in specific phenotype. Overall, our results suggest that SA biosynthetic and catabolic genes are expressed at a very low level in skeletal muscles that also display a unique gene interaction network.

Keywords Sialic acid · Glycoconjugates · GNE myopathy · Sialic acid metabolic pathway · Neuromuscular disorder · Skeletal muscles

Introduction

A large number of proteins and lipids display extensive glycosylation involving several different sugar groups such as mannose, glucose, galactose, fucose, and SA at multiple sites. The main types of protein glycosylation in humans include N-, O-linked glycans, phosphorylated glycans, glycosaminoglycan (GAG), and glypiation (GPI anchor attachment) whereas glycosphingolipids make up the majority of glycoconjugates in lipids (Spiro 2002). Therefore, the landscape of glycosylated molecules spans a vast array of cellular metabolites involved in multiple functions. Glycosylation plays a critical role in providing molecular diversity and regulating structure, function, localization, interactions, and stability of modified molecules (Shental-Bechor and Levy 2009; Fogel et al. 2010). SAs are a family (with more than 50 members) of derivatives of neuraminic acid, an acidic sugar with a nine-carbon backbone. Neu5Gc is the widely expressed SA in all non-human mammalian species (Varki 2007; Varki et al. 2009). Due to the deletion mutation of Cytidine

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Cdr1p highlights the role of the non-hydrolytic ATP-binding site in driving drug translocation in asymmetric ABC pumps

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ARTICLE INFO

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Antifungal drug resistance
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ABC signature sequence
Non-hydrolytic nucleotide-binding site

ABSTRACT

ATP-binding cassette (ABC) transporters couple ATP binding and hydrolysis to the translocation of allocrites across membranes. Two shared nucleotide-binding sites (NBS) participate in this cycle. In asymmetric ABC pumps, only one of them hydrolyzes ATP, and the functional role of the other remains unclear. Using a drug-based selection strategy on the transport-deficient mutant I529A in the transmembrane domain of the *Candida albicans* pump Cdr1p, we identified a spontaneous secondary mutation restoring drug-translocation. The compensatory mutation Q1005H was mapped 60 Å away, precisely in the ABC signature sequence of the non-hydrolytic NBS. The same was observed in the homolog Cdr2p. Both the mutant and suppressor proteins remained ATPase active, but remarkably, the single Q1005H mutant displayed a two-fold reduced ATPase activity and a two-fold increased drug-resistance as compared to the wild-type protein, pointing at a direct control of the non-hydrolytic NBS in substrate-translocation through ATP binding in asymmetric ABC pumps.

1. Introduction

ABC transporters constitute a large protein family present in all kingdoms of life [1,2]. They are central to many physiological processes, and some of them are also involved in multidrug resistance (MDR) phenomenon. Indeed, overexpression of the MDR ABC pumps is the prime cause of chemoresistance in cancer cells [3]. Similarly, pathogenic fungal species such as *Candida albicans* take advantage of their repertoire of ABC transporters to expel a wide range of antifungal drugs, hampering the treatment of fungal diseases [4,5].

The minimal functional unit of ABC transporters consists of two transmembrane domains (TMDs), each usually comprising six transmembrane helices (TMHs) linked with intracellular and extracellular loops (ICLs and ECLs) and two nucleotide binding domains (NBDs) [6]. Transport of compounds occurs through inward- to outward-facing conformational changes of the TMDs upon ATP binding and hydrolysis

Abbreviations: ABC, ATP-binding cassette; ANI, anisomycin; Cdr1p, *Candida* drug resistance 1 protein; Cdr2p, *Candida* drug resistance 2 protein; CFTR, cystic fibrosis transmembrane conductance regulator; CHX, cycloheximide; CnH, connecting helix; CpH, coupling helix; CTZ, clotrimazole; DMSO, dimethyl sulfoxide; ECL, extracellular loop; ICL, intracellular loop; ITR, itraconazole; KTZ, ketoconazole; MCZ, miconazole; MDR, multidrug resistance; MRP1, Multidrug Resistance Protein 1; NR, Nile red; NBD, nucleotide-binding domain; NBS, Nucleotide Binding Site; OM, oligomycin; Pdr5p, Pleiotropic drug resistance 5 protein; PBS, phosphate-buffered saline; PM, plasma membrane; PMSF, phenylmethanesulfonyl fluoride; RB, resuspension buffer; R6G, rhodamine 6G; R123, rhodamine 123; TAP, transporter associated with antigen processing; TMD, transmembrane domain; TMH, transmembrane helix; TLCK, p-tosyl-L-lysine chloromethyl ketone; TPCK, tosyl phenylalanyl chloromethyl ketone; TCSPC, time-correlated single photon counting; VOR, voriconazole; WT, wild-type

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Review

Multidrug transporters of *Candida* species in clinical azole resistance

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ARTICLE INFO

Keywords:
Azole resistance
MDR transporters
Candida albicans
Non-*albicans Candida* species
ABC superfamily
MFS superfamily

ABSTRACT

Over-expression of the human P-glycoprotein (P-gp) in tumor cells is a classic example of an ABC protein serving as a hindrance to effective chemotherapy. The existence of proteins homologous to P-gp in organisms encompassing the entire living kingdom highlights extrusion of drugs as a general mechanism of multidrug resistance. Infections caused by opportunistic human fungal pathogens such as *Candida* species are very common and has intensified in recent years. The typical hosts, who possess suppressed immune systems due to conditions such as HIV and transplantation surgery etc., are prone to fungal infections. Prolonged chemotherapy induces fungal cells to eventually develop tolerance to most of the antifungals currently in clinical use. Amongst other prominent mechanisms of antifungal resistance such as manipulation of the drug target, rapid efflux achieved through overexpression of multidrug transporters has emerged as a major resistance mechanism for azoles. Herein, the azole-resistant clinical isolates of *Candida* species utilize a few select efflux pump proteins belonging to the ABC and MFS superfamilies, to deter the toxic accumulation of therapeutic azoles and thus, facilitating cell survival. In this article, we summarize and discuss the clinically relevant mechanisms of azole resistance in *Candida albicans* and non-*albicans Candida* (NAC) species, specifically highlighting the role of multidrug efflux proteins in the phenomenon.

1. Introduction

Human pathogenic *Candida albicans* and certain non-*albicans Candida* (NAC) species, conventionally associated with healthy individuals as harmless commensals, are endowed with the propensity to transform into notorious pathogens in immunocompromised hosts (Robbins et al., 2017; Whaley et al., 2017). *Candida* species not only cause superficial infections but are also responsible for disseminated bloodstream and deep-tissue infections in hospitalized patients with incapacitated immunity (Prasad et al., 2015). Among the various *Candida* species that infect humans, *C. albicans* is the most prominent species, however, other emerging NAC species such as *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei,* etc. have recently gained epidemiological significance due to their increased prevalence globally (Lindberg et al., 2019; Whaley et al., 2017). Recently, a paradigm shift of candidiasis from *C. albicans* to NAC has been observed due to the emergence of another multi-drug resistant NAC species, *C. auris* (Chowdhary et al., 2017; Lindberg et al., 2019; Whaley et al., 2017). Its capability of nosocomial transmission and the ability to form adherent biofilms on clinically important substrates led to a high number of hospital outbreaks of *C. auris* globally (Chowdhary et al., 2017; Lockhart et al., 2016; Muñoz et al., 2018). The higher percentage of resistance to multiple classes of antifungal agents is the greatest challenge posed by this recently emerged NAC species. The unique features of *C. auris* make it challenging to diagnose, treat and eradicate from intensive care hospital wards as compared to other pathogenic *Candida* species (Forsberg et al., 2019).

The relentless use of antifungal drugs for prophylactic or empirical treatment has led to a change in the epidemiology of fungemia and the parallel emergence of fungal pathogens that manifest resistance to multiple, structurally unrelated drugs with different modes of action (Prasad et al., 2015). This phenomenon of multidrug resistance (MDR) is characterized by simultaneous resistance to at least two distinct classes of antifungal agents. The development of tolerance towards a particular drug mainly relies on the mode of action of that particular drug, however, other mechanisms which are largely uncharacterized also contribute to the emergence of drug tolerance (Dhamgaye et al., 2014; Hameed et al., 2011; Nair et al., 2017; Shapiro et al., 2011). Fungal species may either be intrinsically resistant to a class of drugs or may gradually develop tolerance upon constant exposure to a particular

Abbreviations: ABC, ATP-binding cassette; MFS, Major-Facilitator superfamily; MDR, Multidrug resistance; TMD, Transmembrane domain; NBD, Nucleotide-binding domain; TMHs, Transmembrane helices; NAC, non-*albicans Candida*; PM, Plasma membrane; CDR1, Candida drug resistance 1; MDR1, Multidrug resistance 1; FD, Facilitated diffusion; PDR, Pleiotropic drug resistance; DHA1, Drug/H^+ antiporter; MRP, Multidrug resistance protein; TOR1, Target of Rapamycin 1

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Data Article

GOLD standard dataset for Alzheimer genes

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ABSTRACT

Alzheimer disease is a genetically complex multigenic neurodegenerative disorder, resulting from the interaction between multiple genes. Most of the earlier studies reported only few specific genes that have involvement in Alzheimer. However more than hundreds of susceptible genes have been observed, that have significant role in the development and progression of Alzheimer. Among all the existing data resources, Genetic association database is the most popular data source that contains information about genes, their association classes into positive, negative and neutral class and supporting reference. However, it contains lot of false positives and negatives associations. We have taken this data as reference and performed the double fold cross validation to compile the comprehensive list of Alzheimer genes, their association class viz, positive, negative or ambiguous with the disease and reference sentence confirming the association. The data generated will be used as a GOLD standard reference data set for the training of machine learning classifier to predict the classification of published literature not only in Alzheimer but in other diseases as well. In addition, positive associated genes data can also be used for the system level modelling or meta analysis of Alzheimer.

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Chapter 15
Mechanisms of Drug Resistance in *Candida albicans*

Dominique Sanglard

Abstract Antifungal drug resistance in *Candida albicans* started to emerge with the introduction of antifungal agents in the treatment of diseases caused in human by this fungal pathogen. The decreased activity of these drugs in *C. albicans* as a result of resistance has been observed in different scales for every currently used drug classes. The occurrence of resistance, generally acquired by genetic alterations, can be considered as a natural defense mechanism of *C. albicans* against drugs introduced by humans. Several other mechanisms contribute to drug efficacy in *C. albicans*, one of which is being attributed to tolerance. Antifungal tolerance is rather an adaptive mechanism not necessarily requiring genome changes. Even though the incidence of antifungal resistance in *C. albicans* is still generally low, clinical samples have given the opportunity to dissect resistance mechanisms. Resistance mechanisms have resulted in a significant gain of knowledge in diverse cellular functions and also genome organization. This knowledge can now be implemented in other fields including clinical diagnostics and design of novel drugs or novel therapies. In this chapter, I will not only review the general principles mediating antifungal drug resistance and latest developments, but also update on the mechanisms mediating antifungal tolerance. Moreover, I will illustrate how the understanding of resistance mechanisms can help to establish novel approaches in detecting drug resistance and designing alternative treatment strategies.

15.1 Introduction

Candida albicans is among the most diagnosed fungal species in clinical samples. This fungal species lives as a commensal in the microbiome of healthy individuals, but can propagate as a pathogen in immunocompromised patients (Pfaller and

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Phytoremediation of Heavy Metals Contaminated Soil Using *Tegetes patula*

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ABSTRACT

Soils polluted with heavy metals have become common across the globe due to increase in geologic and anthropogenic activities. Plants growing on these soils show a reduction in growth, performance and yield. Bioremediation is an effective method of treating heavy metal polluted soils. It is a widely accepted method that is mostly carried out *in situ*; hence, it is suitable for the establishment/reestablishment of crops on treated soils. Microorganisms and plants employ different mechanisms for the bioremediation of polluted soils. Using plants for the treatment of polluted soils called phytoremediation is a more common approach in the bioremediation of heavy metal polluted soils. Phytoremediation of contaminated sites supports the goal of sustainable development by helping to conserve soil as a resource, bringing soil back into beneficial use, preventing the spread of pollution to air and water and reducing the pressure for development on green or agricultural field. In this study, an assessment of phytoremediation of contaminated soil was done using hyper accumulator plant species *Tegetes patula* having ability to absorb and accumulate heavy metals (Fe, Cr, Cu, Ni and Zn). *T. patula* can hyper accumulate Fe in higher rates from the multi-metal contaminated soil nevertheless Cd and Zn were phytoextracted in lower amounts and there was no absorption of Ni and Cr.

Key words : Phytoremediation, ornamental plants, hyper accumulator, heavy metal pollution

INTRODUCTION

The contamination of soil due to the heavy metals is a serious threat not only to the soil but also to the entire ecosystem which can cause agricultural damage, deterioration of the food chain, contamination of water resources, economic damage and finally serious human and animal health problems. Heavy metals are a major source of water and soil pollution, generated either through geogenic activities or industrial waste discharge (Chandra and Yadav, 2010). Most of heavy metals have noxious effect on living organisms and get bioaccumulated in the environment and create risk for human health when transferred to the food chain.

There are a number of conventional remediation technologies which are employed to remediate environmental contamination with heavy metals such as solidification/stabilization, soil flushing, soil washing, excavation, retrieval and offsite disposal. But a majority of these techniques require expensive equipment and monitoring systems, complex reagents and can cause further disturbance to the already damaged environment.

Phytoremediation is a very old, cost effective technique that employs the use of plants known as hyper-accumulators to metabolize, assimilate or adsorb hazardous materials in soil (Wu *et al.*, 2015). The plants have the tendency to accumulate heavy metals in their vegetative parts for the extraction and the removal of inorganic pollutants. They can accumulate the heavy metals through their root in higher amount to other plants and transfer it more quickly to their shoots and store large amounts in their leaves and roots. Phytoremediation involves several specific subsets, of which phytoextraction and phyto-degradation are currently the most developed for the phytoremediation of metals and organics in contaminated soils (Lee, 2013; Mani *et al.*, 2015).

Ornamental plants had always been in rich demand for the purpose of phytoremediation because of their major advantage that they are not edible thereby the pollutants accumulated in the ornamental plants can be separated from food chains, thus reducing the human health risk (Liu *et al.*, 2018). In contaminated urban

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Impact of Interactions among Water into Herbicide into Nutrient applications on grain yield in Wheat

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Abstract

A field experiment in split plot design using Bagci 2000 bread wheat variety was conducted at Selçuk University, Sarayönü-Konya, Turkey to evaluate impact of water application (rainfed vs irrigated) as main treatments and fertiliser, micronutrients and herbicides control plots (sub treatments) along with their interactive effects on grain yield. The comparisons of means 3for grain yield under different treatments revealed that the irrigation led to 35.5% increase in control plots over rainfed treatment. The yield increases up to 45.5% when 2,4-D ACID ISOOCTYLESTER (H1) herbicide was used with Zn whereas 46.5% increase was recorded when AMINOPYRALID + FLORASULAM (H2) herbicide was used with N. The results recorded the 37.7% increase in yield over control plots with PYROXSULAM + CLOQUINTOCET-METHYL (H3) herbicide used with nitrogen applications. While H3 herbicide along with Fe application exhibited maximum increase (24.6%) in grain yield under rainfed condition. The comparison of grain yield means over herbicides revealed that PYROXSULAM + CLOQUINTOCET-METHYL (H3) application recorded higher grain yield over 2,4-D ACID ISOOCTYLESTER (H1) and AMINOPYRALID + FLORASULAM (H2) particularly under rainfed conditions. The study revealed strong interactive effects among various treatments and the treatment responses were more evident under rainfed conditions.

Keywords: Wheat, fertiliser, rainfed, irrigation, herbicides.

Introduction

Wheat (*Triticum aestivum L.*) is one of the most important winter cereal crops of the world which meets caloric needs of about 35% world population (Wheeler *et al.*, 2013; FAOSTAT, 2019). Also, wheat is a major component of world food security (Shiferaw *et al*, 2013). Bread wheat is a natural hexaploid evolved through a combination of three genomes (A, B, D) from

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Effect of Nitrogen, Micronutrient and Herbicide Application on Grain Protein Content under Irrigated and Rainfed Conditions in Wheat

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Abstract

A field experiment in split plot design was conducted to evaluate impact of water application (rainfed vs irrigated) as main treatment and fertiliser, micronutrients and herbicides as sub treatments along with their interactive effects on grain protein content using Bagci 2000 bread wheat variety at Selçuk University, Sarayönü-Konya, Turkey The comparisons of means for grain protein content under different treatments revealed that the irrigation led to 11.4% increase in control plots over rainfed treatment. The grain protein content increases up to 35.8% when 2,4-D Acid Isooctylester (H1) herbicide was used with Zn and 50.2% increase in grain protein content with mixture (N+Fe+Zn) micronutrient application under irrigated conditions; whereas 33.78% increase was recorded when Aminopyralid + Florasulam (H2) herbicide was used with N. The results recorded the 47.19% increase in grain protein content over control plots with Pyroxsulam + Cloquintocet-Methyl (H3) herbicide used with nitrogen applications under rainfed conditions. While H3 herbicide along with mixture (N+Fe+Zn) micronutrient application exhibited maximum increase (55.4%) in grain protein content under rainfed condition. The comparison of grain protein content means over herbicides revealed that Pyroxsulam + Cloquintocet-Methyl (H3) application recorded higher grain protein content over 2,4-D Acid Isooctylester (H1) and Aminopyralid + Florasulam (H2) particularly under rainfed conditions. The study revealed strong interactive effects among various treatments and the treatment responses were more evident under rainfed conditions.

Keywords: *Wheat, grain protein content, fertiliser, rainfed, irrigation, herbicides.*

Introduction

Wheat (*Triticum aestivum* L.) is a natural hexaploid species derived through a combination of three genomes (AA, BB, DD) developed from three diploid species (Zhang *et al.*, 2014). Wheat is one of the most important winter cereal crops of the world which meets caloric needs of about 35% world population (Wheeler *et al.*, 2013; FAOSTAT, 2019). Also, wheat is a major component of world food security (Shiferaw *et al*, 2013). Wheat behaves genetically like amphidiploid and therefore breeds true to type as predominately self-pollinated crop. Due to its diverse genetic constitution wheat has very large adaptability from North and South America, Europe, Eurasia and Asia including countries like Turkey and India. Since the basic species have evolved on diverse agronomic conditions, they inherit

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Research Article

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Efficacy of Protein Hydrolysate (Plant Force Advance) Based Formulation on Cotton Yield

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ABSTRACT

A field experiment was conducted using Bt. hybrid cotton (var. RS2013) in Sri Ganganagar district of Rajasthan during Kharif 2017. The agronomic and biological parameters were studied in the cotton crop grown using protein hydrolysate (Plant Force Advance) from waste human hair. The test plots were given the foliar spray of liquid formulation (having approx. 8% (v/v) nitrogen and diluted 1:200 with water) after 25 days of seed germination followed by three consecutive sprays after interval of 30 days. The comparisons of means showed increase in height of the treated plants by 20.46%, enhancement in the chlorophyll content of plant leaves by 16.32%, increase in weight of balls per plant by 19.21% as well as 14.32% reduction in immature ball formation per plant as compared to control and the total yield showed an increase of 13.63%. The study concluded that the foliar application of protein hydrolysate along with recommended package of practices in Bt. hybrid cotton have promising results on the yield and growth of cotton under the field conditions.

Keywords: Bt. hybrid cotton, protein hydrolysate, amino acid-based bio-fertilizer.

Introduction

Cotton is the most important fibre crop of India and has the largest area under cotton cultivation in the world. Bt. hybrids constitute 87 per cent worldwide with increased yield of 8-10% till the release of Bollgard II (Sudha et al. 2011). The present hybrids though high yielding but are susceptible to pests like boll worms and number of viral infestations transmitted by the whitefly. Currently it is grown over 6 per cent of the net sown area and the coverage under Bt. hybrids in India is almost saturated and further improvement in cotton yield is not possible (Rao and Alapati, 2007) and presently the agronomists and cotton breeders are suggesting an alternative strategy to optimize cotton productivity by reducing production costs. The availability of most suitable cultivars, more efficient options of weed, pest and disease management to modify morpho physiological frame, planting/harvesting tools has rekindled an interest in developing new types of fertilizer and exploring novel application patterns to ensure high fertilizer-use efficiency.

The increased crop production largely relies on the type of fertilizers used to supplement essential nutrients for plants, which has also led to over exploitation of chemical fertilizers and emerging environmental issues. So, there is a dire need to switch to natural biological based organic inputs as an alternative to agro-chemicals and the search to explore the cheap waste materials as new resources. Amino acid-based bio-fertilizers are gaining the high input in agricultural market because the formulation of amino acid bio-fertilizers are cheaper than the chemical fertilizers. Amino acids are fundamental

Phospholipid biosynthesis disruption renders the yeast cells sensitive to antifungals

Deepika Kundu, Saif Hameed, Zeeshan Fatima & Ritu Pasrija

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Upregulation of NOX-2 and Nrf-2 Promotes 5-Fluorouracil Resistance of Human Colon Carcinoma (HCT-116) Cells

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Abstract—Altered expression of cellular redox genes and proteins contributes to invasion, metastasis, and drug resistance in cancer. NADPH oxidase (NOX) isoforms are the pro-oxidant enzymes that generate ROS as a primary product. Dysregulation of NOX activity and expression alters ROS generation, which either directly or indirectly modulates cell death and survival signaling during the progression of cancer. Nuclear factor erythroid 2-related factor 2 (Nrf-2) is an inducible transcription factor, which transcribes an array of antioxidant genes and protects cancer cells from the oxidative stress. Both NOXs and Nrf-2 participate in the regulation of cellular redox homeostasis; but their dysregulation promotes oxidative stress, which contributes to the progression of different types of cancer. Indeed, the role of NOX isoforms and Nrf-2 in developing the drug resistance in cancer is largely unknown. In the present study, we have explored the association of NOX isoforms and Nrf-2 signaling with the *MDR1* gene expression in colon carcinoma cells (HCT-116/R). The *MDR1* gene was overexpressed to develop resistant HCT-116/R cells and the NOX activation and ROS generation were monitored. We also assessed the role of NOX isoforms and Nrf-2 in the 5-fluorouracil (5-FU) mediated apoptotic cell death of HCT-116/R cells. The HCT-116/R cells demonstrated higher expression of HIF-1α, Nrf-2, and HO-1 and were highly resistant to 5-FU; they also displayed upregulated expression and activity of NOX-2, as well as elevated ROS levels. Interestingly, the treatment with HDC, a specific NOX-2 inhibitor, reduced the ROS levels in HCT-116/R cells. The treatment with HDC and ML-385 (specific inhibitor of Nrf-2) augmented the 5-FU-mediated apoptotic cell death of HCT-116/R cells, which suggests that NOX-2 and Nrf-2 are involved in the development of the chemoresistant phenotype of these cells. Taken together, NOX-2 and Nrf-2 are associated with developing drug resistance of colorectal cancer cells and might be potential targets to overcome drug resistance during cancer therapy.

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Keywords: 5-fluorouracil, drug resistance, HO-1, MDR1, NOX-2, Nrf-2, ROS

INTRODUCTION

Colon cancer is responsible for a higher mortality rate and one of the leading causes of death worldwide [1]. Chemotherapy and surgery are commonly offered against cancer, but cancer cells become chemoresistant over a short period of treatment with anticancer drugs. The acquisition of resistance to chemotherapy is a major hurdle in the successful application of cancer therapy [2].

Abbreviations: 5-FU, 5-fluorouracil; ABC, ATP-binding cassette; DPBS, Dulbecco's phosphate buffered saline; HCT-116/R, MDR resistant colon cancer cells; NOX, NADPH oxidase; Nrf-2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species;

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The development of drug resistance cancer cells has complex molecular mechanisms [3]. Mechanistically, the development of drug resistance is associated with various cellular phenomena and processes, such as drug inactivation, drug target alteration, drug efflux, DNA damage repair, cell death inhibition, epithelial to mesenchymal transition (EMT), inherent cell heterogeneity, epigenetic effects, or any combination of these mechanisms [4, 5].

Compelling evidence suggests that the development of drug resistance in cancer cells occurs via upregulation of drug efflux proteins or reduction in the cellular uptake of anti-cancer drugs. One of the most studied mechanisms of drug resistance in cancer involves the overexpression of the ATP-binding cassette (ABC) transporter

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Fusarium solani causing stem rot and wilt of lucky Bamboo (*Dracaena sanderiana*) in India-first record

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Abstract
Lucky Bamboo (*Dracaena sanderiana* Sander ex Mast) is a tropical evergreen perennial woody, shrubby species. This is native of Cameroon area in tropical West Africa. This has flexible strap-shaped leaves and slender stems. Being an indoor house plant it grows very well under indirect lighting and have gained popularity because of adoption of new age culture. It multiplies readily by stem cuttings. In year 2014–2017, stem rot and wilt symptoms were observed in *D. sanderiana* cuttings. The first observed symptoms were yellowing in leaves with wilting. In due course of time the leaves turned dry and light brown with necrosis. On splitting open, rotted areas were seen in the middle with a visible brown discoloration in cortical region. The infected plants died within a few weeks. The fungal pathogen *Fusarium* was observed and isolated from the collar, roots, stems. This was morphologically confirmed as *Fusarium solani* and also through amplification and sequencing in ITS region, which showed cent percent similarity with the sequences of *F. solani* available in NCBI genbank. As per record in literature this is the first record of stem rot and wilt caused by *F. solani* in plants of *D. sanderiana* from India.

Keywords *Fusarium solani* · *Dracaena sanderiana* · Stem rot · Wilting

Dracaena sanderiana (Lucky Bamboo, Belgian Evergreen, Ribbon Dracaena or sometimes Ribbon Plant) is one of a group of small ornamental shrubby plants. This bears slender stems with strap shaped flexible leaves. They grow on surface ground of rainforests (Grewal et al. 1999) in the form of upright shrub reaching 1.5 m. The leaves come in the range of 15–25 cm (long) and 1.5–4 cm (broad) at base. It is marketed as "Lucky Bamboo" and a popular house plant used for decoration which survives under various indoor conditions. It can be easily propagated through stem cuttings. Literature records that some fungal species result into stem rot, in different parts of world viz., Tehran, Iran—*Aspergillus niger* (Abbasi and Aliabadi 2008), Bulgaria—*Colletotrichum dracaenophilum* (Bobev et al. 2008), Korea—*F. oxysporum*, *F. solani* and *F. moniliforme* (Choi et al. 2008), Iran—*F. solani* (Abedi-Tizaki et al. 2016) and leaf spot viz., *Cladosporium dracaenatum* and *Alternaria alternata* (Baka and Krzywinski 1996), *Fusarium* species viz., *F. equiseti*, *F. oxysporum*, *F. proliferatum*, *F. semitectum*, *F. solani*, *F. subglutinans* and *F. phyllophitum* (Choi et al. 2008; Thongkantha et al. 2008) from *Dracaena* plants.

Gurgaon District of Haryana state in southern most region (27°27′20″ and 28°32′25″ latitude and 76°39′39″ and 77°20′50″ longitude) and is among most valuable area where Lucky Bamboo are used as ornamental plants. It is propagated largely through stem cuttings/vegetative means. The pathogenic agents cause a lot of economic harm to many ornamental plants so it needs to identify for development of suitable control measures. Therefore present study was undertaken to find out the incitant of stem rot and wilt in *D. sanderiana*.

Potato dextrose agar medium (PDA) medium was prepared for culturing of associated fungi. Potato dextrose broth medium was used for DNA extraction. A total of 39.0 g Potato dextrose agar (HiMedia Laboratories Pvt Ltd, Mumbai) was suspended in double distilled water to make 1000 mL. It was heated till boiling to throughly mix the contents of medium. This was then autoclaved at 15 lbs pressure (121 °C) for 15 min (Kumar et al. 2016).

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Article

A Comparative Estimation of Alprazolam in Pharmaceutical Formulations by Validated HPLC and HPTLC Techniques

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Abstract: The aim of present work is to develop and validate two simple and specific methods for the estimation of alprazolam hydrochloride (a psychoactive drug) in pharmaceutical formulations. The first method involves HPLC separation on the Cosmosil C-8 column using acetonitrile and potassium phosphate buffer (pH 6.0±0.1) (40:60 v/v) as mobile phase. The peak was obtained at 3.01±0.02 min. The effluent was monitored at 254 nm. The second method is based on HPTLC using Acetic acid: water: methanol: ethyl acetate (2:15:20:80 v/v/v/v) as mobile phase and detection of the spot was carried out at 254 nm. The R_f value was found to be 0.76±0.02. The methods were validated as per ICH guidelines. The linearity curves were found to be linear over the concentration range 50-150 µg/ ml for HPLC and 50-400 ng/spot for HPTLC with a high correlation coefficient (R^2 = 0.991 and 0.9987 respectively). The limit of detection and limit of quantification were found to be 1.66 and 5.04 µg/ml for HPLC and14.84 and 44.097 µg/ ml for HPTLC, respectively. The proposed methods are successfully used for the quality control of alprazolam in commercial form. Statistical analysis results confirmed that the methods are selective and precise.

Keywords: Alprazolam, HPLC, HPTLC, Phosphate buffer, validation, analysis.

Introduction

Psychotropic substances have several medical and scientific applications but they often bring about changes that are pleasant to users thus forcing the user to take them regularly. Hence, these psychoactive substances are abused i.e. they are used repeatedly despite health risks and negative consequences.Alprazolam, 8-Chloro-1-methyl-6-phenyl-4H-(1,2,4)triazolo(4,3-±)(1,4)-benzodiazepine (Figure 1), belongs to a class of the benzodiazepine. It is used to treat moderate to severe anxiety disorders and panic attacks by enhancing the effect of GABA, a neurotransmitter, in the body [1,2]. It is also known to possess sedative, hypnotic and anticonvulsant properties [3] and maybe habit-forming where long-term use is involved [4-6]. Although it is available as a generic medication but is also controlled by Narcotic Drug & Psychotropic substance Act as a controlled substance. These tablets dosage may be seized from illegal trafficking by antitrafficking control agencies and where claimed doses may vary from the declaration. Studies have shown the presence of these psychotropics in pharmaceutical formu-

Altered drug efflux under iron deprivation unveils abrogated MmpL3 driven mycolic acid transport and fluidity in mycobacteria

Rahul Pal, Saif Hameed & Zeeshan Fatima

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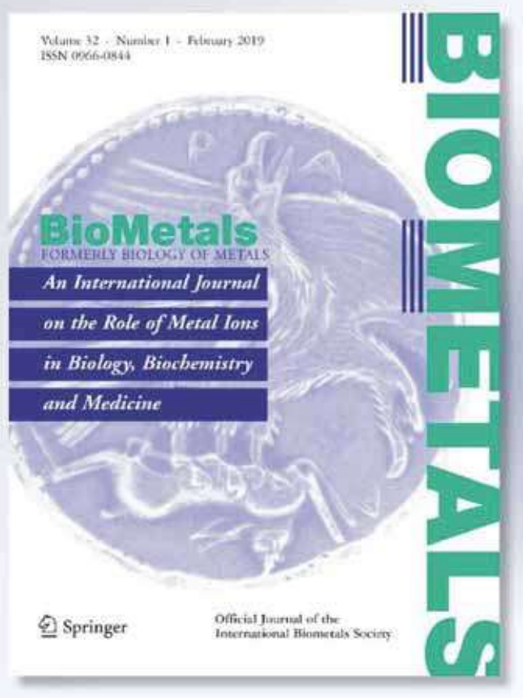

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Metabolic fitness of *Candida albicans* is indispensable for functional drug efflux, ergosterol, and chitin biosynthesis

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ABSTRACT

Background and Purpose: The increment in fungal infections, particularly due to *Candida* species, is alarming due to the emergence of multidrug resistance (MDR). Hence, the identification of novel drug targets to circumvent the problem of MDR requires immediate attention. The metabolic pathway, such as glyoxylate cycle (GC), which utilizes key enzymes (isocitrate lyase [ICL] and malate synthase [MLS]), enables *C. albicans* to adapt under glucose-deficient conditions. This study uncovers the effect of GC disruption on the major MDR mechanisms of *C. albicans* as a human pathogenic fungus.

Materials and Methods: For the purpose of the study, efflux pump activity was assessed by phenotypic susceptibilities in the presence of substrates rhodamine 6G (R6G) and Nile red, along with R6G extracellular concentration (527 nm). In addition, ergosterol content was estimated by the alcoholic potassium hydroxide hydrolysis method. The estimation of chitin was also accomplished by the absorbance (520 nm) of glucosamine released by acid hydrolysis.

Results: The results revealed that the disruption of ICL enzyme gene (Δicl1) led to the impairment of the efflux activity of multidrug transporters belonging to the ATP-binding cassette superfamily. It was further shown that Δicl1 mutant exhibited diminished ergosterol and chitin contents. In addition, all abrogated phenotypes could be rescued in the reverting strain of Δicl1 mutant.

Conclusion: Based on the findings, the disruption of GC affected efflux activity and the synthesis of ergosterol and chitin. The present study for the first time revealed that metabolic fitness was associated with functional drug efflux, ergosterol and chitin biosynthesis and validated GC as an antifungal target. However, further studies are needed to comprehend and exploit this therapeutic opportunity.

Keywords: *Candida*, Chitin, Efflux pump, Ergosterol, Glyoxylate cycle

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Introduction

Candida albicans is a prevalent human fungal pathogen and leading cause of nosocomial infections, particularly in individuals with immunocompromised conditions, such as HIV/AIDS, cancer, transplantations, and neonatal infections [1, 2]. The impeded progress in the development of new antifungal drugs and concomitant rise in multidrug resistance (MDR) have even worsened the problems associated with such infections [3, 4]. Therefore, it is pertinent to identify novel drug targets to circumvent the phenomenon of MDR. The pathogenicity of *C. albicans* mainly depends upon adaptability to combat diverse stress conditions existing inside the hostile niche by the activation of various stress-induced pathways. Regarding this, the in vitro analysis of these pathways and their roles in stress adaptation have generated considerable interest to identify potential antifungal targets.

Although *C. albicans* mainly utilizes six-carbon glucose as the key source of metabolism, they frequently encounter sites with low carbon compounds, such as acetate and citrate, which must be utilized to trigger virulence [5, 6]. Therefore, the metabolic fitness of *C. albicans* is a crucial factor, which is required as a strategy to adapt to nutrient-limited conditions and establish a successful infection. Glyoxylate cycle (GC) is one such pathway that operates under metabolic stress and acts as a homeostatic mechanism to adjust various metabolic activities in *C. albicans*.

In microorganisms, including *C. albicans*, GC acts as a metabolic shunt for tricarboxylic acid cycle to enable the consumption of the low number of carbon (C_2) compounds in a two-step process when glucose is not readily present as a carbon source. Therefore, this cycle not only utilizes C_2 compounds but also prevents the loss of the two carbons, bypassing the CO_2 generating steps

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RESEARCH ARTICLE

Monoterpenoid Geraniol Improves Anti-mycobacterial Drug Efficiency by Interfering with Lipidome and Virulence of Mycobacteria

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Abstract: ***Background***: Tuberculosis (TB) remains a global infectious disorder for which efficient therapeutics are elusive. Nature is a source of novel pharmacologically active compounds with many potential drugs being derived directly or indirectly from plants, microorganisms and marine organisms.

Objective: The present study aimed to elucidate the antimycobacterial potential of Geraniol (Ger), monoterpene alcohol, against *Mycobacterium smegmatis*.

Methods: Disrupted membrane integrity was studied by membrane permeability assay and PI uptake. Cell surface phenotypes were studied by colony morphology, sliding motility and cell sedimentation rate. Lipidome profile was demonstrated by thin-layer chromatography and liquid chromatography-electrospray ionization mass spectrometry. Amendment in iron homeostasis was assessed by using iron chelator ferrozine and ferroxidase assay while genotoxicity was estimated with EtBr and DAPI staining. Biofilm formation was measured by staining, dry mass and metabolic activity using crystal violet. Cell adherence was examined microscopically and spectrophotometrically.

Results: We found the antimycobacterial activity of Ger to be 500 µg/ml against *M. smegmatis*. Underlying mechanisms revealed impaired cell surface phenotypes. Lipidomics analysis exposed profound decrement of mycolic acids, phosphatidylinositol mannosides and triacylglycerides which are crucial for MTB pathogenicity. We further explored that Ger impairs iron homeostasis and leads to genotoxic stress. Moreover, Ger inhibited the potential virulence attributes such as biofilm formation and cell adherence to both polystyrene surface and epithelial cells. Finally, we have validated all the disrupted phenotypes by RT-PCR which showed good correlation with the biochemical assays.

Conclusion: Taken together, the current study demonstrates the antimycobacterial mechanisms of Ger, which may be exploited as an effective candidate of pharmacological interest.

Keywords: *Mycobacterium*, Anti-TB drugs, Geraniol, Membrane, Lipidome, Biofilm.

1. INTRODUCTION

Mycobacterium tuberculosis (MTB) is a life-threatening human pathogen that causes Tuberculosis (TB). It is estimated that about 10 million populations (5.8 million men, 3.2 million women and 1 million children) suffered from TB in 2017 [1]. The recommended standard anti-TB drugs are - isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) which have potential to sterilize both semi-dormant and actively multiplying mycobacterial bacilli. However, the current anti- TB drugs are becoming less effective due to the emergence of resistant strains of MTB resulting in patients remaining infectious for a longer period and requiring a prolonged course of treatment which has many side effects on human health [2]. In order to impede the problem of multidrug resistance (MDR), the pace of drug discovery needs to be enhanced. Nature represents a rich source of a still undiscovered plethora of compounds that are underutilized and could be better exploited [3]. Geraniol (Ger) is acyclic monoterpene alcohol which occurs in geranium, lemon and many other essential oils such as rose oil, palmarosa oil, citronella oil exhibiting various properties such as anticancer activity [4], anti-inflammatory activity [5] and antimicrobial activity [6]. Previous studies also suggested that Ger demonstrated antimicrobial activity against *Candida albicans*, *Saccharomyces cerevisiae*, *Enterobacter aerogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus agalactiae* and *Bacillus cereus*. In a preliminary study, Rajab *et al.* reported antimycobacterial activity of Ger however, its mechanism of

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Insights into the modulatory effect of magnesium on efflux mechanisms of *Candida albicans* reveal inhibition of ATP binding cassette multidrug transporters and dysfunctional mitochondria

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Abstract *Candida* infections pose a serious hazard to public health followed by widespread and prolonged deployment of antifungal drugs has which has led multidrug resistance (MDR) progress in prevalent human fungal pathogen, *Candida albicans*. Despite the fact that MDR is multifactorial phenomenon govern by several mechanisms in *C. albicans*, overexpression of drug efflux transporters by far remains the leading cause of MDR govern by ATP Binding Cassette (ABC) or major facilitator superfamily (MFS) transporters. Hence searching for strategies to target efflux pumps transporter still signifies a promising approach. In this study we analyzed the effect of magnesium (Mg) deprivation, on efflux pump action of *C. albicans*. We explored that Mg deprivation specially inhibits efflux of transporters (CaCdr1p and CaCdr2p) belonging to ABC superfamily as revealed by rhodamine 6G and Nile red accumulation. Furthermore, Mg deprivation causes mislocalization of CaCdr1p and CaCdr2p and reduced transcripts of *CDR1* and *CDR2* with no effect on CaMdr1p. Additionally, Mg deprivation causes depletion of ergosterol content in azole sensitive and resistant clinical matched pair of isolates Gu4/Gu5 and F2/F5 of *C. albicans*. Lastly, we observed that Mg deprivation impairs mitochondrial potential which could be the causal reason for abrogated efflux activity. With growing appreciation of manipulating metal homeostasis to combat MDR, inhibition of efflux activity under Mg deprivation warrants further studies to be utilized as an effective antifungal strategy.

Keywords *Candida albicans* · Magnesium · MDR · ABC transporters · Drug efflux · Ergosterol · Mitochondria

Introduction

The incidence of *Candida* infections has increased intensely in the course of recent decades due to the rise in number of immunocompromised patients suffering from surgery, chemotherapy, HIV disease and organ transplant etc. (Pfaller and Diekema 2007; Spampinato and Leonardi 2013). *Candida albicans* is an opportunistic fungal pathogen that can rapidly change from a harmless resident of mucocutaneous to an extremely pathogenic entity accomplished of killing its host under suitable circumstances. The restricted arsenal of antifungal drugs for the treatment of

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RESEARCH ARTICLE

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Interaction of glutathione-s-transferase genotypes with environmental risk factors in determining susceptibility to head and neck cancer and treatment response and survival outcome

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Abstract

The present case-control study aimed to investigate the role of interaction of glutathione-s-transferase (GST) genotypes with environmental risk factors in determining susceptibility to head and neck squamous cell carcinoma (HNSCC) involving 1,250 cases and equal number of healthy controls. An increase in the risk of HNSCC and its subsites (larynx, pharynx, and oral cavity) was observed among the cases with null genotypes of GSTM1 (odds ratio [OR] = 1.87) or GSTT1 (OR = 1.39) while reduced risk (OR = 0.81) was observed the cases with variant genotype of GSTP1. Tobacco use in the form of smoking or chewing interacted multiplicatively with GSTM1 or GSTT1 to increase the risk several folds (3–10 folds) in HNSCC and its subsites. Alcohol use also increased the risk (2–3 folds) to HNSCC and its subsites in cases with null or variant genotypes of GSTs, though this risk was of lesser magnitude when compared to the tobacco users. A synergistic effect of both, tobacco smoking and alcohol drinking, led to several folds (25-folds) increased risk to HNSCC among the cases with null genotype of GSTM1 and GSTT1 when compared to non-smokers and nondrinkers with wild genotype of GSTM1 and GSTT1 in controls. Furthermore, cases with variant genotypes of GSTP1 (Val/Val) showed superior treatment response with improved survival rate and lower risk of death when compared to the patients with wild type genotype (Ile/Ile). The data suggest that though polymorphism in GSTs may be a modest risk factor for determining HNSCC risk, gene-environment interactions significantly modify the susceptibility to HNSCC by several folds.

KEYWORDS
GSTs, HNSCC, interaction, polymorphism, risk, tobacco

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Highly Surface Active Anisotropic Silver Nanoparticles as Antimicrobial Agent Against Human Pathogens, *Mycobacterium smegmatis* and *Candida albicans*

Ananya S. Agnihotri,[a] Zeeshan Fatima,[b] Saif Hameed,[b] and M. Nidhin*[a]

Rapid synthesis of anisotropic silver nanoparticles via cost-effective, non-hazardous, and eco-friendly methods using naturally available gums are of greater significance as their chemical synthesis is associated with high toxicity. This study aims to synthesize highly surface-active anisotropic silver nanoparticles and evaluate their antimicrobial efficacy against human pathogens, *Mycobacterium smegmatis* and *Candida albicans*. Anisotropic silver nanoparticles were synthesized using silver nitrate as the metal precursor and gum arabic as the template. The synthesized silver nanoparticles were characterized by UV-visible spectroscopy, fourier transformation infrared (FTIR) spectroscopy, dynamic light scattering (DLS) analysis, high-resolution transmission electron microscopy and selected area electron diffraction (HRTEM-SAED) analysis and thermogravimetric analysis (TGA). TEM analysis showed the anisotropy and monodispersed nature of silver nanoparticles with an average size of less than 20 nm. The antibacterial and antifungal properties of the anisotropic silver nanoparticles were also studied keeping rifampicin and fluconazole as the reference. The minimum inhibitory concentration (MIC) was found to be 1 mM silver nanoparticles for both *M. smegmatis* and *C. albicans*. Synthesized anisotropic silver nanoparticles can be used as an alternative to antibiotics to treat the infections caused by *M. smegmatis* and *C. albicans*. Further, the effect of silver nanoparticles on haemolytic activity was also studied.

1. Introduction

In modern material sciences, nanotechnology is one of the most important fields that identify nano-substances with diverging applications in various fields like biomedicine and pharmaceutics.[1] Silver nanoparticles are well known for their biocompatibility, non-toxicity, find numerous applications in biotechnology and can be used as an alternate therapy to treat multiple drug-resistant microbes.[2-4] The increased emergence of drug-resistant microbes is a major confront for the scientific community in the struggle for the successful development of therapeutics.[5] Hence, designing efficient therapeutics from novel sources is the need of the hour.[6] The disinfecting, antimicrobial, antioxidant and medicinal properties of AgNPs make them potential materials for various biotechnological applications in addition to their thermal, electrical, magnetic and catalytic characteristics.[7-10] The high reactivity of AgNPs leads to surface oxidation and aggregation of AgNPs over time. Thus, it is crucial to stabilize the AgNPs during and after the synthesis. Since the concept of green synthesis of nanoparticles has emerged, there is a rise in the demand for the production of biocompatible and eco-friendly nanoparticles.[11-12]

Though literature reports several chemical and physical methods to produce pure and well-defined nanoparticles, these methods are expensive and involve physical processes. The toxicity and probable risk on human health and the environment are the major drawbacks of this approach. Furthermore, the use of surfactants as stabilizers limits the use of nanoparticles as they may present cellular toxicity.[13] Besides, these methods produce isotropic AgNPs with particle sizes ranging from 1 nm–1000 nm. Though particle size is a significant factor that affects size distribution and cellular uptake of nanomedicine, it is not the only parameter that is considered while designing nano-medicines and therapeutics.[13] Interest in developing AgNPs with different shapes has been increased in the recent years. The use of morphologically different nanoparticles is a novel strategy to enhance the efficacy of nanomedicine by controlling the interface between biological systems and nanoparticles.[14] Shape specificity and anisotropy are significant parameters at molecular, cellular and tissue levels.[15] The presence of asymmetric axes in anisotropic nanoparticles gives rise to noteworthy physical properties in metals. The anisotropic nanoparticles have been an interesting subject in fundamental and application-driven research as they provide target sites for regiospecific functionalization. To facilitate the best interaction between a nanoparticle and target, the shape of the nanoparticle should be fine-tuned based on the bio-function.[16]

Gums are well known for their ability to fine-tune the size, shape and provide very good stability to the synthesized nanoparticles.[17] The stabilization provided by gum depends on the presence of multiple binding sites along the skeletal carbon

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Octyl gallate reduces ABC multidrug transporter CaCdr1p expression and leads to its mislocalisation in azole-resistant clinical isolates of *Candida albicans*

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ABSTRACT
Objectives: Fungal pathogens pose a serious threat to public health. Widespread and prolonged use of antifungal drugs has led to the development of multidrug resistance in the human fungal pathogen *Candida albicans*. Among several mechanisms leading to drug resistance in *C. albicans*, overexpression of drug efflux transporters remains by far the leading cause of multidrug resistance, facilitated by overexpression of ATP-binding cassette (ABC) and major facilitator superfamily (MFS) transporters. Hence, targeting efflux pumps still represents a promising approach to combat multidrug resistance. In this study, the effect of octyl gallate (OG), a natural food additive, on drug efflux pump activity of *C. albicans* was analysed.
Methods: Drug efflux pump activity was determined by rhodamine 6G (R6G) efflux and Nile red accumulation assay in a *Candida* drug resistance protein 1 (CaCdr1p)-overexpressing strain. Gene expression and protein expression and localisation were studied by RT-PCR, Western blot and confocal microscopy. Ergosterol content was measured by the alcoholic KOH method.
Results: OG specifically inhibits the activity of CaCdr1p, belonging to the ABC superfamily. The underlying mechanism was confirmed as competitive mode of inhibition by OG as revealed by Lineweaver–Burk plot. Furthermore, OG leads to reduced expression of *CDR1* and CaCdr1p and mislocalisation of CaCdr1p. Additionally, OG sensitises azole-susceptible and -resistant clinical matched-pair isolates Gu4 & Gu5 and leads to impeded R6G efflux and depleted ergosterol content.
Conclusion: The ability of OG as a potent inhibitor of CaCdr1p that chemosensitises drug-resistant *C. albicans* warrants further studies to be exploited as an effective antifungal agent.

1. Introduction

Candida albicans is among the most common opportunistic human fungal pathogens and the rate of infections has considerably increased [1,2]. *Candida albicans* resides in the mucocutaneous cavities of the skin, vagina and intestine of humans as a commensal but may become pathogenic under immunocompromised conditions such as organ transplantation, burn and chemotherapy. The limited available antifungal regimens belongs to three classes, namely azoles, polyenes and echinocandins; however, continuous deployment of antifungal drugs has led to the emergence of multidrug resistance, which is a major hurdle against efficient therapeutics [3]. Despite the fact that multidrug resistance is a multifactorial phenomenon contributed by many factors, resistance mediated by drug efflux pumps belonging to either the ATP-binding cassette (ABC) superfamily or major facilitator superfamily (MFS) remains the predominant mechanism [4]. Under such circumstances, it becomes worthwhile to discover inhibitors targeting these drug efflux pumps.

In *C. albicans*, the major players involved in developing multidrug resistance are *Candida* drug resistance proteins CaCdr1p and CaCdr2p as well as CaMdr1p, which belong to the ABC and MFS superfamilies, respectively [3,5]. Despite sharing 84% similarity [6], evidence suggests that CaCdr1p contributes more to drug resistance than CaCdr2p in *C. albicans* [7,8]. Plant secondary metabolites are an enormous treasure comprising promising compounds targeting efflux pumps [9]. Octyl gallate (OG) is a globally recognised antioxidant that is widely used as a food additive [10]. A previous study established OG as an efficient antifungal compound that affects mitochondrial activity, metabolic flexibility and virulence of *C. albicans* [11]. The present study aimed to add to the existing

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Studies on the antifungal activity of biotemplated gold nanoparticles over *Candida albicans*

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ABSTRACT

Green synthesis and applications of gold nanoparticles are more fascinating research area due to their unique optical properties and high X-ray attenuation power. In this study, we have synthesized gold nanoparticles of uniform size (5 nm) with spherical shape. UV–vis spectroscopy, Transmission Electron Microscopy and Atomic Force Microscopy were employed to characterize the synthesized gold nanoparticles. The biomedical applications of the synthesized gold nanoparticles were carried out against most prevalent human fungal pathogen, *Candida albicans*. Broth micro dilution assay was used to determine minimum inhibitory concentration (MIC). We observed that 0. 5 mM concentration was effective in inhibiting the growth of fungal cells which was later confirmed by spot assay.

1. Introduction

In the modern era of material science, nanoparticles have become the centre of attraction to the scientific community. In current years, nanotechnology is one of the most researched areas due to their noticeable performance in electronics, optics and photonics. Nanoparticles are the fundamental structures of nanotechnology. [1] Nanoscience and technology is an interdisciplinary broad area of research and development activity that has been growing dynamically worldwide in the past few years. Nanoparticles are the simplest form of structures with the range of 1–100 nm [2]. Nanoparticles have different physical and chemical properties such as higher surface area, mechanical strength and high reactivity. Gold nanoparticles are unique in optical property as gold is yellow in shading, strong in state where as gold nanoparticles are wine red shading arrangement against oxidant [3]. Gold nanoparticles display different sizes extending from 1 nm to 8 μm and they likewise show distinctive shapes, such as round, sub-octahedral, octahedral, decahedral, sporadic shape, tetrahedral, hexagonal platelets and nanorods. Among all these shapes, circular molded nanoparticles are most steady and show alluring optical properties when contrasted with the triangular formed nanoparticles [4].

Conventional physical and chemical methods are used to prepare metal nanoparticles from toxic chemicals [5]. Moreover, these methods are very expensive and not environmentally friendly [6]. Green synthesis of gold nanoparticles using various templates such as polysaccharides, fungi and plant extracts are found to be environmentally benign [7]. These attractive green strategies are free from toxic chemicals and toxic materials. Gold nanoparticle synthesized from bio templates offers a route for large scale production of different metallic nanoparticles [8].

Bio templated gold nanoparticles are utilized to detect cancer cells. Increased surface area of gold nanoparticles in solution which contribute to their enhanced physio-chemical properties which are useful in a variety of fields such as antimicrobial agents [9], bio-molecular detection, diagnostics, catalysis, biomedical and bio sensing devices. Gold nanoparticles are utilized as efficient materials for water purification [10]. These are also used in interface resistors, conductors and different components of an electronic chip. In photodynamic treatment, when light is connected to a tumor containing gold nanoparticles, the particles quickly warm up, executing tumor cells [11]. Gold nanoparticles are used as substrates to empower the estimation of vibrational energies of compound securities in surface upgraded Raman spectroscopy. Gold nanoparticles are very thick, consequently enabling them to be utilized as tests for transmission electron microscopy [12]. Gold nanoparticles can be readily dispersed, functionalized and are bio inert in nature. These particles have high X-ray attenuation power [13]. Gold nanoparticles have been generally utilized as a part of the field of radiation solution in radiation treatment due to the effective and

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Rec A disruption unveils cross talk between DNA repair and membrane damage, efflux pump activity, biofilm formation in *Mycobacterium smegmatis*

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ABSTRACT

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) has emerged in recent decades as one leading causes of mortality worldwide. The burden of TB is alarmingly high, with one third affected population as reported by WHO. Short-course treatment with an antibiotic is a powerful weapon to tr fection of susceptible MTB strain, however; MTB has developed resistance to anti-TB drugs, which is ar lating global health crisis. Thus there is urgent need to identify new drug targets. RecA is a 38 kilodalton p required for the repair and maintenance of DNA and regulation of the SOS response. The objective of this st to understand the effect of disruption of RecA gene (deletion mutant ΔdisA from previous study) in a sur model for MTB, *Mycobacterium smegmatis*. This study demonstrated that disruption of RecA causes enh susceptibility towards rifampicin and generation of ROS leading to lipid peroxidation and impaired mem homeostasis as depicted by altered cell membrane permeability and efflux pump activity. Mass spectro based lipidomic analysis revealed decreased mycolic acid moieties, phosphatidylinositol mannosides Phthiocerol dimycocerosate (DIM). Furthermore, biofilm formation was considerably reduced. Additional have validated all the disrupted phenotypes by RT-PCR which showed a good correlation with the biochs assays. Lastly, RecA mutant displayed reduced infectivity in *Caenorhabditis elegans* illustrating its vulnerabi antimycobacterial target. Together, present study establishes a link between DNA repair, drug efflux and b formation and validates RecA as an effective drug target. Intricate studies are needed to further understar exploit this therapeutic opportunity.

1. Introduction

Despite the improvement of tuberculosis (TB) regimen, TB remains the second public severe health problem and a leading cause of death due to an infectious disease after HIV infection [51]. The treatment of TB caused by *Mycobacterium tuberculosis* (MTB) requires at least six months duration, but multidrug-resistant MTB entails second-line drugs that are generally toxic for a longer period usage [36]. Currently, the main obstacle in TB research is limited understanding of the mechanisms by which MTB evades both the host immune response and the emergence of multidrug resistance (MDR). Hence we need to identify novel drug targets to be employed in therapeutic strategies.

The RecA proteins are structurally conserved among eubacteria and archaea [37]. However, the functional connection among RecA proteins is poorly implicit. In comparison to the most-studied *Escherichi* RecA, which is essential for several processes related to DNA me lism, MTB RecA displays many unique, distinctive features [11,2 vitro studies have revealed that the MTB RecA protein exhibit merous differences from other bacterial RecA homologs. Apart fr *coli* RecA (EcRecA), homologous pairing and strand exchange pror by MTB RecA (MtRecA) is greatly dependent on the pH of the me [48]. The MtRecA protein also displays a reduced affinity for AT reduced efficiency of ATP hydrolysis [19]. First time [10] functi the MTB RecA protein in DNA repair and integration of exog nucleic acids was demonstrated by its ability to fully restore the notype of *M. smegmatis* RecA mutants. RecA also has a regul function in response to DNA damage, due to the ability of nucleop filament created on regions of single-stranded DNA to stimulat

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Research Perspective

Alternative splicing of CERS2 promotes cell proliferation and migration in luminal B subtype breast cancer cells

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Breast cancer is broadly categorised into four different clinical subtypes, Luminal A, Luminal B, Triple-negative (TNBC), and HER2$^+$ based on histological and molecular characterizations, distinct gene expression profiles and alternative splicing patterns that impact the choice and response to treatment [1]. Based on the unique molecular portrait, among the Estrogen receptor (ER) positive and responsive subtypes, Luminal A manifests less aggressive cell proliferation, better response to endocrine therapy, lower lung and liver metastatic rate, and higher recurrence free survival (RFS) compared to Luminal B subtype. In contrast, ER-negative TNBC and HER2$^+$ subtypes show poor prognosis, diverse resistance patterns to different cytotoxic agents, high invasion and metastasis to brain, lung or visceral organs, and significantly reduced overall survival [2]. Therefore, each of these subtypes need a robust array of dependable histopathological and molecular markers that can be exploited to predict prognosis, and response to treatment.

Sphingolipids are a group of bioactive lipids, well-known for their diverse signalling roles in cellular regulatory circuits including inflammation, migration, proliferation, apoptosis and multiple drug resistance. All sphingolipids have a sphingosine backbone with varied polar headgroups and variable fatty-acyl chains with their functional diversity contingent to the carbon chain length and degree of saturation. The most prominent sphingolipids like ceramides, ceramide-1-phosphate, sphingosine-1-phosphate, and glucosylceramides have been reported to modulate different phenotypic hallmarks of cancer like proliferation, invasion, and migration [3]. Alteration in expression of sphingolipid metabolic enzymes affect the lipid homeostasis leading to dysregulation of the cellular signalling pathways involved in oncogenesis. Differential sphingolipid gene expression patterns are reported for each subtype that contribute to their distinct phenotypes [4]. Microarray analysis has shown that enzymes like *SPHK1*, *UGT8*, *ST8SIA1* are upregulated in ER-negative tumors whereas ER-positive tumors showed an increase in expression of *UGCG*, *CERS4*, *CERS6*, *ASAH1* [5]. In recent years, alternative splicing (AS) has emerged as a crucial post-transcriptional regulatory mechanism as the relative ratio of different splice isoforms of genes reveal imbalance in their abundance, many of which were not evident by conventional gene expression analysis alone [6]. The differentially expressed transcript isoforms of various oncogenic or growth pathways are unique to each breast cancer subtype, and therefore have high potential to be developed as valuable targets for cancer therapy [7]. On the same ground, it is likely that the RNA splicing signature for genes of sphingolipid pathway are distinct for all breast cancer subtypes, an area less ventured till now.

To elucidate the role of AS in sphingolipid metabolizing genes in cancer, we used bioinformatic approach, and identified AS events in sphingolipid genes for different breast cancer subtypes from TCGA BRCA dataset. The AS signature for sphingolipid genes predicted a unique *ceramide synthase 2* (*CERS2*) cassette exon event for exon 8 in Luminal B breast cancer subtype generating an AS transcript that was not identified before. Ceramide, the metabolic hub of the sphingolipid pathway is an antiproliferative, proapoptotic tumor suppressor lipid. Mammalian *ceramide synthase* (*CERS*) has six isoforms and each of them synthesizes a distinct chain-length ceramide. Expression of *CERS2*, *CERS4* and *CERS6* are found to be high in malignant breast tumors [8]. *CERS2* is the only *CERS* that synthesises very long chain ceramides (C22:0, C24:0, C24:1) involved in preventing cell invasion and metastasis by impairing the role of matrix metalloproteinases [9]. Exon 8 of CERS2, corresponds to almost the entire Lag1p motif that imparts acyl chain substrate specificity to the protein, and is a part

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RESEARCH ARTICLE Open Access

Identification of the conserved long non-coding RNAs in myogenesis

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Abstract

Background: Our understanding of genome regulation is ever-evolving with the continuous discovery of new modes of gene regulation, and transcriptomic studies of mammalian genomes have revealed the presence of a considerable population of non-coding RNA molecules among the transcripts expressed. One such non-coding RNA molecule is long non-coding RNA (lncRNA). However, the function of lncRNAs in gene regulation is not well understood; moreover, finding conserved lncRNA across species is a challenging task. Therefore, we propose a novel approach to identify conserved lncRNAs and functionally annotate these molecules.

Results: In this study, we exploited existing myogenic transcriptome data and identified conserved lncRNAs in mice and humans. We identified the lncRNAs expressing differentially between the early and later stages of muscle development. Differential expression of these lncRNAs was confirmed experimentally in cultured mouse muscle C2C12 cells. We utilized the three-dimensional architecture of the genome and identified topologically associated domains for these lncRNAs. Additionally, we correlated the expression of genes in domains for functional annotation of these trans-lncRNAs in myogenesis. Using this approach, we identified conserved lncRNAs in myogenesis and functionally annotated them.

Conclusions: With this novel approach, we identified the conserved lncRNAs in myogenesis in humans and mice and functionally annotated them. The method identified a large number of lncRNAs are involved in myogenesis. Further studies are required to investigate the reason for the conservation of the lncRNAs in human and mouse while their sequences are dissimilar. Our approach can be used to identify novel lncRNAs conserved in different species and functionally annotated them.

Background

Recent transcriptomic studies of mammalian genomes have revealed the presence of a substantial population of non-coding RNA (ncRNA) molecules among the transcripts expressed in cells. More than 90% of the human genome encodes ncRNAs [1–3], and the presence of such a large collection of ncRNAs indicates the regulatory potential of these molecules [4–6] . Based on size, ncRNAs are grouped into two classes: short ncRNAs and long ncRNAs. Short ncRNAs, fewer than 200 bp in length, include microRNAs or piwi-interacting RNAs; long ncRNAs (lncRNAs) are greater than 200 nucleotides and transcribed mostly by RNA polymerase II. Similar to messenger RNAs, lncRNAs contain a 5′7-methylguanosine cap and a 3′ poly(A) tail; however, lncRNAs lack coding potential. This new class of genes has recently been identified in various tissues [7–10]. Although the functions of microRNAs are well studied [11], the mode of action of lncRNAs in gene regulation is not well understood. Previous studies in X-chromosomal dosage compensation underscore the regulatory potential of lncRNAs, whereby the mechanism is carried out via concerted action of the lncRNA Xist and protein complexes [12, 13]. Recent

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Research Paper

Vanillin confers antifungal drug synergism in *Candida albicans* by impeding CaCdr2p driven efflux

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ABSTRACT

Aim. – Among the most common mechanisms of multidrug resistance (MDR) in prevalent human fungal pathogen, *Candida albicans*, overexpression of drug efflux pumps remains the predominant mechanism. Hence to inhibit efflux pumps and chemosensitize *C. albicans* against traditional antifungal drugs still represents an attractive approach. The present study aimed to analyze the effect of Vanillin (Van), a natural food flavoring agent, on drug efflux pump activity of *Candida albicans*.

Methods and results. – We observed that Van specifically inhibits *Candida* drug resistance protein 2 (CaCdr2p) activity belonging to ATP Binding Cassette (ABC) superfamily as revealed by abrogated rhodamine 6G efflux and nile red accumulation assay with CaCdr2p over expressing strain. Insight studies into the mechanisms suggested that abrogated efflux by CaCdr2p is due to competitive mode of inhibition by Van as depicted by Lineweaver-Burk plot. RT-PCR, western blot and confocal microscopy further unraveled that Van leads to reduced expression of *CDR2* and CaCdr2p mislocalization respectively. Furthermore, Van sensitizes the azole sensitive and resistant clinical matched pair of isolates Gu4/Gu5 and led to abrogated rhodamine 6G efflux and depleted ergosterol. Furthermore, Van synergizes with membrane targeting drugs fluconazole and amphotericin B as their fractional inhibitory coefficient index was less than 0.5.

Conclusion. – Van being a potent inhibitor of CaCdr2p and chemosensitizing of drug resistant *C. albicans* warrants further studies to be exploited as effective antifungal agent.

1. Introduction

Continuous deployment of antifungal drugs has led to emergence of multidrug resistance (MDR) in the prevalent human fungal pathogen *Candida albicans*. *C. albicans* resides in the mucocutaneous cavities of skin, vagina and intestine of humans as a commensal but can turn pathogenic under immunocompromised conditions [1,2]. The limited current armory of antifungal drugs is propelling MDR development which is a major hurdle against efficient therapeutics [3]. Despite the fact that MDR is a multifactorial phenomenon, resistance mediated by drug efflux pumps belonging to either ATP binding cassette (ATP) superfamily or major facilitator superfamily (MFS) remains the predominant mechanism [4,5]. Under such circumstances, it becomes pertinent to look for inhibitors targeting these drug efflux pumps.

In *C. albicans*, the major players involved in developing MDR are *Candida* drug resistance proteins CaCdr1p and CaCdr2p along with CaMdr1p which belongs to ABC and MFS super families respectively [4,6]. Despite sharing 84% similarity [7] evidence suggests that CaCdr1p contributes more towards drug resistance than CaCdr2p in *C. albicans*, however, recent studies have also depicted considerable role of CaCdr2p [8–10]. Even intracellular energy metabolism is known to correlate with the expression of *CDR1* and *CDR2* genes in drug resistance [11]. The activity of CDR genes, *CDR1* and *CDR2* is regulated by a common transcription factor, Tac1p [12].

Natural compounds have gained immense interest owing to their natural origin, cost effectiveness and lesser toxicity. Plants secondary metabolites are an enormous treasure, containing promising compounds targeting efflux pumps [13]. For instance, curcumin and geraniol modulates the expression of CaCdr1p efflux pump transporter [14,15]. The monoterpenes thymol and carvacrol, reverses azole resistance by inhibiting the expression of *CDR1* and *CDR2* genes along with synergism with known antifungal drug flucanozole (FLC) [16]. The extract from *Echinophora platyloba*

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Efficiency of vanillin in impeding metabolic adaptability and virulence of *Candida albicans* by inhibiting glyoxylate cycle, morphogenesis, and biofilm formation

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ABSTRACT

Background and Purpose: *Candida albicans* is the fourth most common cause of nosocomial fungal infections across the world. The current drug regimens are suffering from such drawbacks as drug resistance, toxicity, and costliness; accordingly, they highlight the need for the discovery of novel drug agents. The metabolic adaptability under low-carbon conditions and expression of functional virulence traits mark the success of pathogens to cause infection. The metabolic pathways, such as glyoxylate cycle (GC), enable *C. albicans* to survive under glucose-deficient conditions prevalent in the hostile niche. Therefore, the key enzymes, namely isocitrate lyase (ICL) and malate synthase (MLS), represent attractive agents against *C. albicans*. Similarly, virulence traits, such as morphogenesis and biofilm formation, are the crucial determinants of *C. albicans* pathogenicity. Regarding this, the present study was conducted to uncover the role of vanillin (Van), a natural food flavoring agent, in inhibiting GC, yeast-to-hyphal transition, and biofilm formation in human fungal pathogen *C. albicans*.

Materials and Methods: For the determination of hypersensitivity under low-glucose conditions, phenotypic susceptibility assay was utilized. In addition, enzyme activities were estimated based on crude extracts while in-silico binding was confirmed by molecular docking. The assessment of morphogenesis was accomplished using hyphal-inducing media, and biofilm formation was estimated using calcofluor staining, MTT assay, and biomass measurement. Additionally, the in vivo efficacy of Van was demonstrated using *Caenorhabditis elegans* nematode model.

Results: Based on the results, Van was found to be a potent GC inhibitor that phenocopied *ICL1* deletion mutant and displayed hypersensitivity under low-carbon conditions. Accordingly, Van facilitated the inhibition of ICL and MLS activities in vitro. Molecular docking analyses revealed the in-silico binding affinity of Van with *Icl*1p and *Mls*1p. Those analyses were also confirmative of the binding of Van to the active sites of both proteins with better binding energy in comparison to their known inhibitors. Furthermore, Van led to the attenuation of such virulence traits as morphogenesis, biofilm formation, and cell adherence. Finally, the antifungal efficacy of Van was demonstrated by the enhanced survival of *C. elegans* with *Candida* infection. The results also confirmed negligible hemolytic activity on erythrocytes.

Conclusion: As the findings of the present study indicated, Van is a persuasive natural compound that warrants further attention to exploit its anticandidal potential.

Keywords: Biofilm, *Caenorhabditis elegans*, *Candida*, Glyoxylate cycle, Morphogenesis, Vanillin

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Introduction

Candida albicans is among the most common fungal microflora that resides in the mucocutaneous cavities of the skin, vagina, and intestine of humans as commensal organisms. However, they can turn pathogenic after the alteration of the immune system [1]. With a substantial rise in the number of immunocompromised patients, the potential risk implicated in the occurrence of fungal diseases has considerably been alarming [2]. Widespread use of the existing limited antifungals, as well as the impeding progress in the development of new antifungal drugs, has led to a rise in multidrug

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ORIGINAL ARTICLE

Lipidomic insights to understand membrane dynamics in response to vanillin in *Mycobacterium smegmatis*

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Abstract
Considering the emergence of multidrug resistance (MDR) in prevalent human pathogen, *Mycobacterium tuberculosis* (MTB), there is parallel spurt in development of novel strategies aimed to disrupt MDR. The cell envelope of MTB comprises a wealth of lipid moieties contributing towards long-term survival of pathogen that could be exploited as efficient antitubercular target owing to advancements made in mass spectrometry–based lipidomics technology. This study aimed to utilize the lipidomics approach to unveil several lipid associated changes in response to natural antimycobacterial compound vanillin (Van) in *Mycobacterium smegmatis*, a surrogate for MTB. Lipidomic analyses revealed that that Van alters the composition of fatty acid (FA), glycerolipid (GL), glycerophospholipid (GP), and saccharolipids (SL). Furthermore, Van leads to potentiation of ampicillin and displayed additive effect. The differential expressions of various lipid biosynthetic pathway genes by RT-PCR corroborated with the lipidomics data. Lastly, we demonstrated enhanced survival of *Mycobacterium*-infected *Caenorhabditis elegans* model in presence of Van. Thus, lipidomics approach provided detailed insight into mechanisms of membrane disruption by Van in *Mycobacterium smegmatis*. Our work offers the basis of further understanding the regulation of lipid homeostasis in MTB so that better therapeutic targets could be identified to combat MDR.

Keywords *Mycobacterium* · Vanillin · Lipids · Cell wall · Fatty acid · Glycerolipids · Glycerophospholipids

Introduction

The evolution of drug-resistant *Mycobacterium tuberculosis* (MTB) has established severe complications that are difficult to treat and generated considerable concern for developing effective strategies for the control of tuberculosis (TB). Although the current drug susceptibility testing is quite accurate and efficient, it is time-consuming. Identification of diagnostic biomarkers is, therefore, necessary to discriminate between infection from drug-resistant and drug-susceptible strains. One strategy that helps to effectively control TB is to understand the function of lipids that mycobacteria use to manipulate host cellular defenses. MTB has unique cell envelope architecture comprising several lipids between the outer and inner membrane which account for much of its impermeability to anti-TB drugs and confer unique staining properties to MTB (Jackson 2014).

The recent introduction of high-throughput analyses of lipids is accelerating our ability to analyze MTB lipid metabolism and signaling and the factors that regulate those pathways (Pal et al. 2017; Sharma et al. 2018). Several categories of lipid are present in MTB, e.g., fatty acids (FA), glycerolipids (GL), glycerophospholipids (GP), prenol (PR), polyketides (PK), and saccharolipids (SL). The outer membrane and capsular lipids of MTB play important roles in host–pathogen interactions. The innermost layer is the plasma membrane that seems typical of bacterial membrane while outside the plasma membrane is a massive cell wall core comprised of peptidoglycan (PG), in covalent attachment via phosphoryl-*N*-acetylglucosaminosyl-rhamnosyl linkage units with the heteropolysaccharide arabinogalactan (AG), which in turn is esterified at its non-reducing ends to α-alkyl, β-hydroxy long-chain (C_{60}-C_{90}) mycolic acids. The cell wall core, also referred to as the mycolyl arabinogalactan-peptidoglycan (mAGP) complex is required for

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Structural characterization of starch capped ZnO nanoparticles

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Abstract. Zinc oxide nanoparticles have been synthesized by a simple green synthesis route using soluble starch as a capping agent in an aqueous medium. The results of structural investigation of ZnO nanoparticles using various techniques such as X-ray diffraction, scanning electron microscope and Fourier transforms spectroscopy have been presented. XRD confirms the formation of c-axis orientated hexagonal wurtzite crystalline structure of ZnO with average particle size in the range of 21 nm to 25 nm. The morphology of the ZnO samples were determined by SEM images, indicating nano rod like structure with hexagonal phase for starch capped ZnO nanoparticles. Further, the presence of starch and different functional group in synthesized ZnO nanoparticles have been studied by Fourier transform spectroscopy approve the different bonding between starch with Zn.

1. Introduction

The Metal oxide nanostructured materials have been identified for their notable optical, electronic properties and versatile applications. Zinc oxide has been emerged as favorable metal oxide for optoelectronic and biological applications. It is a wide bandgap compound semiconductor material having the bandgap 3.37eV, and large exciton binding energy 60meV.[1] High thermal and chemical stability and excellent optoelectronic properties, making it useful in large-scale studies and in many optoelectronic and biological applications. Also, high electrical conductivity and optical transparency in the visible region makes it beneficial as a transparent electrode for flat panel display, short-wavelength LED, and Solar cell [2-4]. It has been used as a buffer electrode for LED applications. Many research papers have reported ZnO as a good conducting electrode with better transparency [4,5]. Moreover, antibacterial and antifungal properties of ZnO have been utilized for cosmetic and biological applications, it can be used as a photocatalyst, biosensor, biomarkers, since its fluorescence in the visible region [6,7]. Furthermore, the preparation of zinc oxide nanoparticles by various chemical methods have been reported [2-8]. Organic capping agent or polymeric encapsulations has been used to prevent aggregation of nanoparticles. The environmentally benign synthetic way

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Synthesis and application of copper ferrite-graphene oxide nanocomposite photocatalyst for the degradation of malachite green

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ABSTRACT

The magnetic graphene oxide (GO) nanocomposites possess unique physicochemical properties, high surface area, high chemical stability, and the ease with which they can be modified and functionalized. In the present work, a nanocomposite of copper ferrite and GO was synthesized through a facile hydrothermal method and their photocatalytic efficiency with dye removal was studied. X-ray diffraction (XRD) was used to characterize the synthesized nanocomposite. The UV–Vis spectrophotometer was used to compare the photocatalytic efficiency for degradation of malachite green dye by using GO/$CuFe_2O_4$ nanocomposite, GO and copper ferrite. GO/$CuFe_2O_4$ nanocomposite could be recycled and possessed of magnetic and photocatalytic properties hence it can be developed as an inexpensive and alternative photocatalyst for dye removal from wastewater.

Selection and peer-review under responsibility of the scientific committee of Cutting-edge Research in Material Science and Chemistry (CRMSC-2021).

1. Introduction

In current scenario, there has been the freshwater shortage all over the world. Water contamination is considered as foremost worrying problem that requires an instant and practical solution. Globally, 748 million people face the shortage of fresh drinking water. This problem become severe in coming years as water need increase to 400% till 2050 [1].Water contamination majorly caused by microbes, organic & inorganic pollutants, and heavy metals. Organic pollutants include dyes, pesticides, and antibiotics. Dyes are released by textile industry effluents and, due to their higher stability, long term exposure in water sources generates to toxic impact on flora and fauna. Various dyes for instance methyl orange, malachite green, bromophenol blue, when expelled in large amount causes severe pollution in water reservoirs [2]. Various remedial techniques have already used for the pollutants removal from the wastewater that include adsorption, flocculation, coagulation, physical and biological treatments, ozonation, chlorination, ozone, UV radiation, chemical oxidation and advanced filtration process etc. [3,4]. All of the above-mentioned techniques involve serious limitations, such as generation of by product as secondary pollutants and incomplete degradation of pollutants that leads to generate more hazardous material, low efficiency of system. To solve these problems photocatalysis is good choice due to its eco-friendly process with no generation of secondary pollutants or minimize the waste [5–11].

Due to two-dimensional nature along with associated band structure, graphene and its composites are utilized in various applications like electronics, supercapacitors, photocatalysis and biosensing. Graphene and its derivative form graphene oxide (GO) and reduced-graphene oxide (rGO) is obtained from graphite [12]. GO; a functionalized graphene which has varying oxygen containing groups on the surface, found as plausible material in several field especially in water remediation. The problem associated with these is their recyclability. To solve these problems, exploration of hybrid materials in photocatalysis is found to be an interesting area by researchers. These materials exhibit synergetic or complementary properties which usually do not exist in the individual component. Hence, they offer enhanced applications in wastewater system. Recently, the numerous work has been done on the use of semiconductor magnetic oxide, $CuFe_2O_4$hybrid material due to economical synthesis process, excellent photochemical steadiness as well as magnetic properties and sensitivity towards visible light [13]. $CuFe_2O_4$based hybrid has been investigated, with C_3N_4[14], TiO_2[15], GO[16] and AgBr[17]. These hybrid

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ORIGINAL ARTICLE

Deciphering the potent application of nanobentonite and α-Fe_2O_3/bentonite nanocomposite in dye removal: revisiting the insights of adsorption mechanism

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Abstract
Clays are widely accepted for dye removal from wastewater. Here, in this work, nanobentonite was synthesized by a simple, rapid, and cost-effective chemithermal method. Additionally, nanobentonite was coupled with hematite nanoparticles via thermal coupling to prepare a nanocomposite with enhanced surface absorption. Surface morphology, compositional and structural analysis of synthesized samples were done using various characterization techniques. Results suggested that nanobentonite and nanocomposite having an average diameter of 35.36 and 21.85 nm respectively were synthesized. Nanocomposite exhibited increased surface area. Additionally, the ability of all samples as an adsorbent for removal of methylene blue (MB) and Congo red (CR), from an aqueous solution was investigated under various optimization conditions. Adsorption kinetics revealed that Pseudo II order equation fits well for the adsorption process following intraparticular diffusion mechanism for both the dyes. The adsorption equilibrium data of MB and CR was fitted well by the Langmuir and Freundlich adsorption isotherm model, respectively. The thermodynamic parameters suggested adsorption process is endothermic and spontaneous in nature with increased entropy value.

Keywords Bentonite clay · Acid activation · Nanocomposite · Dye degradation · Adsorption studies

Introduction

In effluents, the presence of dyes is one of the major concerns because of their adverse effects on many forms of life (Bulut and Karaer 2015). The discharge of dyes into the environment is important to be looked after for both esthetical and toxicological reasons (Raffatulah et al. 2010; Santhi and Manonmani 2011). Wastewaters are the major contributors of colored effluents released from the industries like textile, printing, food coloring, dyeing, papermaking, cosmetics, etc. (Wang et al. 2011). Releasing even a small amount of dye in the water produces carcinogenic and mutagenic effects and thus affects aquatic life and the food webs (Liu et al. 2010). Thus it becomes environmentally important to remove these dyes from wastewater effluents (Chen and Huang 2010). Azo dyes are the most common dyes used for dying silk, cotton, and wool and can cause adverse health issues to both animals and humans (Raffatulah et al. 2010; Ghosh and Bhattacharyya 2002; Tan et al. 2008). Therefore, the treatment of effluents containing such dyes is of great concern because of its harmful impacts on receiving waters. Conventional methods of treatment such as precipitation, coagulation and flocculation, electrochemical destruction, photocatalytic oxidation, ozonation, biological treatment, and adsorption are developed for water decontamination applications (Santhi and Manonmani 2011; Huang et al. 2011). Adsorption is found to be the most efficient

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Efficient photocatalytic degradation of Malachite green dye using facilely synthesized cobalt oxide nanomaterials using citric acid and oleic acid

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ABSTRACT

Citric acid and oleic acid modified cobalt oxide nanomaterials successfully fabricated by sol-gel process and used to remove malachite green (MG) by photocatalytic degradation. The synthesized nanomaterials were characterized by powder X-ray diffraction (P-XRD), Scanning electronic microscopy (SEM), Transmission electron microscopy (TEM), UV–Visible spectrophotometer, Fourier transform infrared spectroscopy (FT-IR) and Thermogravimetric Analysis (TGA) in order to investigate their structural, morphological, optical, functional and thermal properties, respectively. The PXRD gave the crystalline nature with average crystallite size of 29 and 42 nm for citric acid and oleic acid modified cobalt oxide nanomaterials, respectively. SEM images indicate layered porous aggregates morphology having higher porosity. Optimum condition for photocatalytic degradation of MG dye were found at pH 6.84, dose 0.5 gL^{-1} for 1×10^{-5} M concentrated dye. Citric acid modified cobalt oxide catalyst exhibited 91.2% photocatalytic degradation of MG dye while in oleic acid modified sample exhibited 66.6% under simulated light due to greater chelating power of citric acid as compare to oleic acid. Kinetics results for MG dye degradation follow to pseudo-second-order kinetics with rate constants 0.00653, 0.084 and 0.00633 $mol^{-1}L^{1}min^{-1}$ for CoCA, CoOA and Co NPs, respectively. In addition, possible mechanism for the photodegradation of MG dye is also proposed.

1. Introduction

Recently, due to rapid development of industries and social economy, non-biodegradable pollutants in aqueous system becomes more and more serious and greatly influenced the health people and animals [1]. Also, toxicity of pollutants could be assessed by using bacterial and plant bioassay such as Vibrio fischeri and Vicia faba respectively [2–4]. Dyes are also included in this category which are released from industrial sectors such as printing, food, textile, leather, paper, cosmetics, rubber, and pharmaceutical, and become a serious threat to the human health and environmental safety. These are carcinogenic in nature and are responsible for potential health hazards to living being. Among the different dyes, MG a synthetic cationic dye for both laboratory research as well as industrial products, and show higher toxicity [5]. Since MG capable to enter into cells due to its easy interaction with membranes [6]. It is widely used as an additive in food colouring and dye in varieties of industries [7,8]. Therefore, it is highly recommended to degrade the dyes into nontoxic forms. Different chemical, biological and physical processes have been used for the treatment of wastewater to get rid from dyes and related toxic pollutants. Some of the physico-chemical water treatment methods like flocculation, precipitation, membrane filtration, coagulation, ion-exchange and adsorption techniques are extensively used for removal pollutants, however, these are not ideal to remove he pollutants completely [9–13]. Heterogeneous photocatalysis is carried out using semiconductor oxides for complete mineralization of organic pollutants to CO_2, H_2O and inorganic ions [14]. Photocatalysis gets good position as compared to other conventional methods in water treatment due to solar energy [15].

The nanomaterials possess unique physical and chemical properties such as higher surface aren, surface defects etc. And, would be utilized in the photocatalytic process. Nanomaterials exhibit unique optical properties which usually dependent upon size and shape [16,17]. Cobalt oxides are utilized in various form such as lithium ion batteries, heterogeneous catalysts, gas sensor, ceramics, energy storage devices etc. [18–20].

Efficiency of heterogeneous catalyst increases by altering size,

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REVIEW
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Signature of Candidate:

Rationalizing the Role of Monosodium Glutamate in the Protein Aggregation Through Biophysical Approaches: Potential Impact on Neurodegeneration

Ishfaq Ahmad Ahanger[1,2], Sania Bashir[2], Zahoor Ahmad Parray[2], Mohamed F. Alajmi[3], Afzal Hussain[3], Faizan Ahmad[2], Md. Imtaiyaz Hassan[2], Asimul Islam[2] and Anurag Sharma[1]**

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Monosodium glutamate (MSG) is the world's most extensively used food additive and is generally recognized as safe according to the FDA. However, it is well reported that MSG is associated with a number of neurological diseases, and in turn, neurological diseases are associated with protein aggregation. This study rationalized the role of MSG in protein aggregation using different biophysical techniques such as absorption, far-UV CD, DLS, and ITC. Kinetic measurements revealed that MSG causes significant enhancement of aggregation of BSA through a nucleation-dependent polymerization mechanism. Also, CTAB-BSA aggregation is enhanced by MSG significantly. MSG-induced BSA aggregation also exhibits the formation of irreversible aggregates, temperature dependence, non-Arrhenius behavior, and enhancement of hydrodynamic diameter. From the isothermal titration calorimetry measurement, the significant endothermic heat of the interaction of BSA-MSG indicates that protein aggregation may be due to the coupling of MSG with the protein. The determined enthalpy change (ΔH) is largely positive, also suggesting an endothermic nature, whereas entropy change (ΔS) is positive and Gibbs free energy change (ΔG) is largely negative, suggesting the spontaneous nature of the interaction. Furthermore, even a low concentration of MSG is involved in the unfolding of the secondary structure of protein with the disappearance of original peaks and the formation of a unique peak in the far-UV CD, which is an attention-grabbing observation. This is the first investigation which links the dietary MSG with protein aggregation and thus will be very instrumental in understanding the mechanism of various MSG-related human physiological as well as neurological diseases.

Keywords: monosodium glutamate, protein aggregation, nucleation-dependent polymerization, isothermal titration calorimetry measurement, neurodegeneration

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Article

Heparin Accelerates the Protein Aggregation via the Downhill Polymerization Mechanism: Multi-Spectroscopic Studies to Delineate the Implications on Proteinopathies

Ishfaq Ahmad Ahanger, Zahoor Ahmad Parray, Khalida Nasreen, Faizan Ahmad, Md. Imtaiyaz Hassan, Asimul Islam,* and Anurag Sharma

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ABSTRACT: Heparin is one of the members of the glycosaminoglycan (GAG) family, which has been associated with protein aggregation diseases including Alzheimer's disease, Parkinson's disease, and prion diseases. Here, we investigate heparin-induced aggregation of bovine serum albumin (BSA) using different spectroscopic techniques [absorption, 8-anilino-1-naphthalene sulfonic acid (ANS) and thioflavin T (ThT) fluorescence binding, and far- and near-UV circular dichroism]. Kinetic measurements revealed that heparin is involved in the significant enhancement of aggregation of BSA. The outcomes showed dearth of the lag phase and a considerable change in rate constant, which provides conclusive evidence, that is, heparin-induced BSA aggregation involves the pathway of the downhill polymerization mechanism. Heparin also causes enhancement of fluorescence intensity of BSA significantly. Moreover, heparin was observed to form amyloids and amorphous aggregates of BSA which were confirmed by ThT and ANS fluorescence, respectively. Circular dichroism measurements exhibit a considerable change in the secondary and tertiary structure of the protein due to heparin. In addition, binding studies of heparin with BSA to know the cause of aggregation, isothermal titration calorimetry measurements were exploited, from which heparin was observed to promote the aggregation of BSA by virtue of electrostatic interactions between positively charged amino acid residues of protein and negatively charged groups of GAG. The nature of binding of heparin with BSA is very much apparent with an appreciable heat of interaction and is largely exothermic in nature. Moreover, the Gibbs free energy change (ΔG) is negative, which indicates spontaneous nature of binding, and the enthalpy change (ΔH) and entropy change (ΔS) are also largely negative, which suggest that the interaction is driven by hydrogen bonding.

1. INTRODUCTION

Heparin [glycosaminoglycan (GAG) or heteropolysaccharides] is an extremely acidic sulfur-containing polysaccharide, composed of linear chains of repeating units of disaccharides comprising glucosamine and uronic acid.[1,2] It belongs to the family of GAGs or heteropolysaccharides and occurs in the liver, kidney, spleen, lungs including basophils and mast cells in the blood vessels, etc. It acts as the blood thinner that prevents blood from coagulation or blood clotting.[1,2] Structurally, heparin is formed from alternating units of *N*-sulfo D-glucosamine 6-sulfate and glucoronate 2-sulfate.[1]

Heparin has been suggested to accelerate the formation of amyloid fibrils of Aβ peptides which are the major agents involved in Alzheimer's disease.[3] It has also been found to increase the aggregation of tau protein, which is one of the major aggregating proteins responsible for causing Alzheimer's disease.[4] GAGs are consistently observed to be related with amyloid deposition in major amyloidosis diseases.[5] In vitro studies suggest that GAGs including heparin induce the phenomenon of amyloid formation in α-synuclein, which is the main aggregating protein in Parkinson's disease.[5] Prion is a proteinaceous infectious isoform present ubiquitously throughout the mammalian body, especially in neurons, which can get converted into either misfolded protein or amyloids or amorphous aggregates through altering the conformation or shape.[6] The diseases associated with prions and affect the brain (encephalopathies) are called prion diseases or transmissible spongiform encephalopathies (TSEs).[7,8] Heparin has been related to misfolding and aggregation of prion protein.[9] Besides these instances, there is promotion of fibrillation rate

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Multiple putative methemoglobin reductases in *C. reinhardtii* may support enzymatic functions for its multiple hemoglobins

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ABSTRACT

The ubiquitous nature of hemoglobins, their presence in multiple forms and low cellular expression in organisms suggests alternative physiological functions of hemoglobins in addition to oxygen transport and storage. Previous research has proposed enzymatic function of hemoglobins such as nitric oxide dioxygenase, nitrite reductase and hydroxylamine reductase. In all these enzymatic functions, active ferrous form of hemoglobin is converted to ferric form and reconversion of ferric to ferrous through reduction partners is under active investigation. The model alga *C. reinhardtii* contains multiple globins and is thus expected to have multiple putative methemoglobin reductases to augment the physiological functions of the novel hemoglobins. In this regard, three putative methemoglobin reductases and three algal hemoglobins were characterized. Our results signify that the identified putative methemoglobin reductases can reduce algal methemoglobins in a nonspecific manner under *in vitro* conditions. Enzyme kinetics of two putative methemoglobin reductases with methemoglobins as substrates and *in silico* analysis support interaction between the hemoglobins and the two reduction partners as also observed *in vitro*. Our investigation on algal methemoglobin reductases underpins the valuable chemistry of nitric oxide with the newly discovered hemoglobins to ensure their physiological relevance, with multiple hemoglobins probably necessitating the presence of multiple reductases.

1. Introduction

Globins are heme-containing proteins with a characteristic three-dimensional structure containing alpha-helical globin fold [1]. Hemoglobins are known to be attached covalently to the prosthetic group by a conserved histidine residue and have the ability to bind oxygen and other gaseous ligands reversibly. The oxygen transport function is considered as one of the most distinctly understood physiological role of hemoglobins. Increased genome sequence information has revealed that hemoglobins are present in all forms of life [2]. The ubiquitous nature of hemoglobins implies that these proteins must have some other significant physiological function that needs further investigation.

Most of the newly discovered globins do not function as oxygen transporters [3,4]. Several studies on diverse animal globins have proposed roles of cytoglobins as tumor suppressors and neuroglobins as neuroprotective agent in neurodegenerative diseases [5,6] One of the most widely accepted roles of hemoglobins in plants and bacterial cells is nitric oxide (NO) scavenging [3,7–11]. Nitric oxide is an important signaling free radical that can act as a potential toxin to cells beyond a certain concentration [3]. Many organisms have evolved various strategies for NO detoxification, including enzymes like NO reductases and NO dioxygenases [7,12]. Oxidative enzymatic functions for low abundance hemoglobin and oxidative reactions of nitrogen-containing diatomic radicals with hemoglobins have been reported earlier by many researchers [13,14]. It was hypothesized that the blood hemoglobin/myoglobin might have functioned as an enzyme utilizing bound activated oxygen to dioxygenate NO or other substrates in microbes. Flavo hemoglobins reported in *E.coli* and yeast are known to have a hybrid protein with a globin domain performing the NO dioxygenase function, while the reductase domain helps in the reduction of ferric to ferrous form to repeat the reaction cycle [7,15].

Although the novel hemoglobins lack the reductase domain, they showed NO dioxygenase function *in-vitro* [3,15]. However, for these globins to act as NO dioxygenase *in vivo*, they would need association

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A convenient 5-*exo*-*dig* cyclization route to diastereomerically pure methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate

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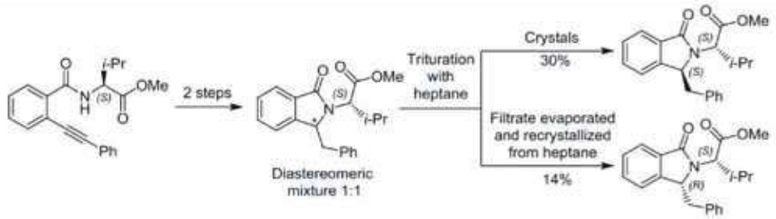

A robust method toward the synthesis of diastereomerically pure methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate has been described. The key reactions in the synthesis are: HATU-mediated coupling, Pd-catalyzed Sonogashira coupling, base-mediated 5-*exo*-*dig* cyclization, and catalytic hydrogenation. The diastereomeric mixture is subjected to trituration with heptane to furnish both diastereomers in moderate yields. The relative stereochemistry was confirmed by the single crystal X-ray diffractometry. The key feature of the method is the simplicity of the diastereomeric separation.

Keywords: oxoisoindoline, cyclization, diastereoselectivity, enantioselectivity, Sonogashira coupling.

Isoindolin-1-one is a common moiety present in many natural products like nuevamine,[1] magallanesine,[2] staurosporine etc.[3] More specifically, 3-substituted isoindolin-1-ones are found in pharmacologically important synthetic drugs such as pazinaclone,[4] renin inhibitors,[5] antiarrhythmic agents,[6] and HIV reverse transcriptase inhibitor[7] (Fig. 1). Organic compounds possessing isoindolin-1-one moiety display wide range of biological activities such as antiviral,[8] antibacterial,[9] HIV-1 inhibiting,[10] sedative, and hypnotic.[11] Numerous scientific studies claim that some isoindolin-1-ones help in the treatment of cancer,[12] CNS diseases,[13] diabetes,[14] obesity, and hyperlipidemia.[15] Isoindolin-1-ones have also been employed as pivotal substrates in the variety of organic transformations[16–18] such as Diels–Alder reaction, asymmetric synthesis, etc. Due to the vast range of medicinal activities of isoindolin-1-ones, a variety of approaches have been developed for the synthesis of these significant motifs.[19–21] However, synthetic strategies toward the synthesis of asymmetric 3-substituted isoindolin-1-ones have been limited. Few notable mentions include (a) asymmetric Michael reaction of 3-substituted isoindolinones using quinine-derived phase-transfer catalyst[22] with moderate enantiomeric excess, (b) Pd-catalyzed hydrogenation of *N*-substituted 3-methylene-isoindolin-1-ones with poor diastereoselectivity,[23] (c) multi-component reaction involving 2-formylbenzoic acid, chiral methylbenzylamine, and dimethyl phosphite, under solvent- and catalyst-free conditions, with good yield and high diastereoselectivity (95:5 *dr*),[24] (d) diastereoselective reductive alkylation approach to *N*-protected (*R*)-3-alkyl-isoindolin-1-ones using $BF_3{\cdot}OEt_2/Et_3SiH$,[25] (e) asymmetric alkylation of indolin-1-ones through the formation of unstabilized carbanion using LDA or NaHMDS.[26]

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Microwave assisted $Pd(OAc)_2$-catalyzed chemoselective reduction of aryl α,β-unsaturated esters with triethylsilane

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ABSTRACT

In this communication, we have reported that the $Pd(OAc)_2$–Et_3SiH-DMF system promotes the microwave-assisted chemoselective reduction of aryl α,β-unsaturated esters in good yields. The protocol affords a convenient reduction of aryl-conjugated double bonds even in presence of other functional groups like esters, phenols, and ethers.

Keywords: *Chemoselective; Microwave; Palladium; Reduction; Triethylsilane.*

1. Introduction

In recent years microwave assisted reactions have emerged as an increasingly popular field in organic chemistry [1]. This non-conventional heating approach uses the electromagnetic radiation ranging from 1 meter to 1 mm, with frequencies between 0.3 and 300 GHz. Microwave heating provides a straightforward and inexpensive reaction condition for carrying out a variety of organic transformations. Other advantages of this method include homogenized heating leading to accelerated reactions and better yields.

Palladium catalyzed reduction of carbon-carbon multiple bonds forms an important organic transformation relevant to both academic and industrial research [2]. Although Pd/C is known to be the most ubiquitous catalyst for hydrogenation, its reaction often proceeding in good yields but the use of elevated pressure along with poor selectivity makes this approach unappealing. Other literature known procedure for the reduction of carbon-carbon multiple bonds include the use of expensive catalyst or pyrophoric hydrides [3].

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For instance, Zhou *et. al.* demonstrated the application of a nickel catalyst supported by Me-DuPhos, a chiral bisphopshine in combination with DMF for chemo- and stereoselective reduction of α,β-unsaturated esters [3l]. Andersson's group reported a iridium-catalyzed asymmetric 1,4-hydrogenation of conjugated esters [3m]. Very recently, Sawamura's group developed a novel enantioselective conjugate reduction reaction utilizing chiral phenol–NHC/copper catalyst systems [3n]. Using a similar protocol Teichert's group had earlier reported a catalytic reduction of α,β-unsaturated esters with a NHC-Cu(I)-H_2 combination [3o]. Most of these methods use one or more expensive reagents which are not very selective.

In the past Pd/Et_3SiH has been used for the reduction of alkyl halides and functionalities like azide, imine, conversion of aromatic carbonyls and benzyl alcohols to corresponding methylenes and alcohols [4]. Previously, Mirza-Aghayan's group have reported the use of $PdCl_2/Et_3SiH$/EtOH system for reduction of alkenes to alkanes [5], isomerization of alkenes [6] and chemoselective reduction of α,β-unsaturated ketones to corresponding saturated ketones [7]. Even though

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ARTICLE

Organochalcogen ligands in catalysis of oxidation of alcohols and transfer hydrogenation

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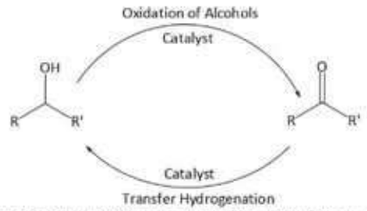
In the Honor of Dr. Ajai K. Singh, Professor Emeritus, Department of Chemistry, I.I.T. Delhi (India) on His 67th Birthday

Organochalcogen compounds have been used as the building blocks for the development of a variety of catalysts that have been studied comprehensively during the last two decades for several chemical transformations. Transfer hydrogenation (reduction of carbonyl compounds to alcohols) and oxidation of alcohols (conversion of alcohols to their respective ketones and aldehydes) are also among such chemical transformations. Some compilations are available in the literature on the development of catalysts, based on organochalcogen ligands, and their applications in Heck Reaction, Suzuki Reaction, and other related aspects. Some review articles have also been published on different aspects of oxidation of alcohols and transfer hydrogenation. However, no such article is available in the literature on the syntheses and use of organochalcogen ligated catalysts for these two reactions. In this perspective, a survey of developments pertaining to the synthetic aspects of such organochalcogen (S/Se/Te) based catalysts for the two reactions has been made. In addition to covering the syntheses of chalcogen ligands, their metal complexes and nanoparticles (NPs), the emphasis has also been laid down on the efficient conversion of different substrates during catalytic reactions, diversity in catalytic potential and mechanistic aspects of catalysis. It also includes the analysis of comparison (in terms of efficiency) between this unique class of catalysts and efficient catalysts without chalcogen donor. The future scope of this area has also been highlighted.

1. Introduction

The catalytically important transition metal complexes of organochalcogen ligands were synthesized and structurally characterized in the year 1980 for the first time.[1,2] During the last two decades, such complexes have constituted a new class of catalysts which are known for their efficiency, air-stability and moisture insensitivity.[3–83] Their application in catalysis was reported in the year 1999 probably for the first time when Bergbreiter and co-workers used a Pd(II) complex of an (S,C,S) pincer ligand as a catalyst in catalyzing heck coupling of various aryl iodides and alkenes.[84] Subsequently, Yao and co-workers reported a very interesting example of such complexes in the year 2004. They used palladium complex of an organoselenium ligand as a catalyst for the Heck coupling reaction.[85] In this case, the selenium ligated palladium complex was reported to be more efficient than its sulphur and phosphorous counterparts.[85] However, the catalytic potential of such complexes remained unexplored for the oxidation of alcohols and transfer hydrogenation reactions until the year 2009. Ligand systems considered in this perspective, dedicated to designing the catalysts for oxidation of alcohols and transfer hydrogenation, will refer only to the species containing at least one sulphur, selenium or tellurium atom bound to a transition metal (Ru, Rh, Ir) and the complexes containing just oxygen-metal bonds are not discussed here.



Scheme 1. Oxidation of alcohols and transfer hydrogenation of ketones

Oxidation of alcohols (Scheme 1) is a reaction in which alcohols are transformed into their carbonyl counterparts. This reaction has a fundamental importance in organic synthesis.[86–90] Likewise, transfer hydrogenation (Scheme 1) also holds an important place in organic syntheses. It involves the reduction of carbonyl compounds (ketones and aldehydes)

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Capping agent-induced variation of physicochemical and biological properties of α-Fe_2O_3 nanoparticles

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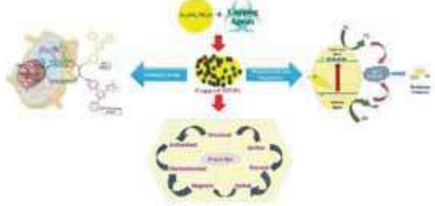
HIGHLIGHTS

- Hematite nanoparticles (HNPs) were successfully capped using Starch, PVP and citrate as capping agent.
- Variation in structural, Physiochemical and biological properties due to different capping agents were analyzed.
- Cytotoxic Potential of all the nanoparticles was assessed against MDA-MB-231 breast cancer cell line.
- Significant variation of properties in hematite nanoparticle was observed due to capping.

GRAPHICAL ABSTRACT



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DPPH assay

ABSTRACT

Capping agents play a vital role in controlling the size, morphology, and monodispersity of nanoparticles. To understand a comprehensive overview of the influence of capping on the structure and properties of hematite nanoparticles (HNPs), we have synthesized hematite nanoparticles (HNPs) with narrow size distribution by an economic co-precipitation method using capping agents like sodium citrate, Polyvinyl Pyrrolidone (PVP) and starch. A comparative in-depth study of structure, morphology, and surface analysis along with thermal, optical, magnetic and electrochemical properties of synthesized capped and uncapped HNPs has been performed. The effect of capping agents on photocatalytic and antioxidant activities along with cytotoxicity of all fabricated nanoparticles was studied against MDA-MB-231 cell line causing breast cancer along with flow cytometry. Results revealed a definite improvement in grain size, crystallinity, optical, thermal and magnetic properties of

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Role of EDTA capped cobalt oxide nanomaterial in photocatalytic degradation of dyes

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Abstract: Dyes released from textile, paint, and various other industries in wastewater have posed long term environmental damage. Functional nanomaterials provide a hope and opportunities to treat these effluent wastes in a rapid and efficient way due to their large surface area to volume ratios. Synthesis of 2,2',2",2"'-(Ethane-1,2-diyldinitrilo)tetraacetic acid (EDTA) capped cobalt oxide nanomaterial as a photocatalyst has been investigated and utilized for the rapid and efficient removal of malachite green (MG) and crystal violet (CV) dyes. The morphological, structural, optical, chemical and thermal properties of the synthesized nanomaterial were investigated using different characterization tools such as Scanning electron microscopy(SEM), Transmission electron microscopy (TEM), X-ray diffraction (XRD), Ultra violet visible (UV-Vis), Fourier transform infrared (FT-IR) spectroscopy and Thermogravimetric analysis (TGA) *etc*. The prepared EDTA capped Cobalt oxide nanomaterials display better photocatalytic degradation, 56.3 % for MG and 37.9 % for CV in comparison to the pure Cobalt oxide, 47.7 and 27.6 %, respectively under visible light illumination. The kinetics study followed the pseudo-first order kinetic model and Freundlich adsorption isotherm model. The incremental photodegradation of these two dyes was attributed by morphology of the nanomaterial which favour effective electron/hole separation.

Keywords: photocatalytic activity; crystal violet; malachite green; adsorption isotherm.

INTRODUCTION

Dye stuffs represent a class of synthetic organic pigments; these are one of the many causes for growing ecological issues. Colored dyeing wastewaters emanating from industries are largely non-biodegradable and also carcinogenic in nature. They also create problems to the aquatic creatures and adversely affect water ecosystem.[1] Therefore, degradation of dyes has attracted attention and substantial efforts have been committed to the specific remediation techniques.

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Time-dependent study of graphene oxide-trypsin adsorption interface and visualization of nano-protein corona

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ABSTRACT

Understanding of interactions of nanomaterials with biomolecules (especially proteins) is of great importance to the area of nanobiotechnology. Graphene and its derivative such as graphene oxide (GO), are two-dimensional (2-D) nanomaterials with remarkable physical and chemical properties and have been broadly explored in biotechnology and biomedical application. Here, we have reported the nature of adsorption of trypsin on the GO surface, considering its biomedical implications. A simple incubation of trypsin on GO surface exhibits varying resistance to autolysis. The structural morphology of trypsin on the GO surface was studied by using atomic force microscopy (AFM), circular dichroism (CD), fluorescence, and total internal reflection fluorescence (TIRF) microscopies. Results suggest that the trypsin follows the Freundlich Isotherm. By the Langmuir model, the maximum adsorption capacity was found to be 100 mg/g. From protein assay results we have concluded that the native trypsin exhibits the highest catalytic efficiency ($33.97*10^4$ L mol^{-1} min^{-1}) in comparison to other Trp-GO constructs. We have further visualized morphological change on GO-trypsin interface throughout the adsorption process by taking samples at definite time intervals, which suggests that the interaction of trypsin with GO is an example of the soft corona. Our findings may be implicated in enzyme engineering as well as enzyme-based biosensing applications.

1. Introduction

Over the last few decades, nanotechnology and biotechnology have become an integral part of society and civilization due to their extensive application in medical and allied health sciences; therefore, it is necessary to understand the actual mode of nanoparticle-biomolecule interaction [1]. As the proteins constituent arguably the most important class of biomolecule, to understand their mode of interaction with nanoparticles have drawn considerable interest. Hinerwarth et al. [2] reported that even without chemical conjugation simple mixing and incubation between enzymes and nanoparticles can significantly increase protein activity. On the other hand, the ratio of nano-protein incubation mixture is important as the higher concentration of nanoparticles can have a detrimental effect on protein conformation. Due to these encouraging results, the study of the interaction of nanoparticles with proteins has currently become popular among the researchers considering the biological significance of proteins in the living system. It is believed that protein- nanoparticle interaction takes place through corona formation, the nano-protein complex is usually considered as nanoparticles-protein corona (NP-PC) [3–14]. Depending on the nature of the interaction, it can be soft corona or hard corona [15]. Although there are some reports on these studies, very little is known about the actual mechanism and dynamic nature of interaction that happens at the nano-protein interface.

Here, we have reported the nature of adsorption of trypsin on the GO surface, this particular system was taken considering the huge importance of GO in current nanoscience. Graphene and its derivative graphene oxide (GO) have attracted colossal consideration due to their diversified physiochemical and biological properties over the last two decades [16–18]. GO, this star material possesses a single-layered, two dimensional, sp^2 hybrid structure, having a large specific surface area with sufficient functional surface groups, which can work as a perfect matrix for stacking of small organic and biomacromolecules with no surface adjust mentor any coupling reagents. GO exhibits high conductivity and shows diverse applications in various scientific and

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Green Synthesis of Copper Oxide Nanoparticles using *Cucumis sativus* (cucumber) Extracts and their Bio-physical and Biochemical Characterization for Cosmetic and Dermatologic Applications

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Abstract:

Background & Objective: Nanoparticles are used in cosmetic and dermatologic products, due to better skin penetration properties. Incorporation of natural products exhibiting medicinal properties in nano-preparations could significantly improve efficacy of these products and improve the quality of life without the side effects of synthetic formulations.

Methods: We here report green synthesis of Copper Oxide nanoparticles, using Cucumber extract, and their detailed bio-physical and bio-chemical characterization.

Results & Conclusion: These Copper Oxide-Cucumber nanoparticles exhibit significant anti-bacterial and anti-fungal properties, Ultra Violet-radiation protection ability and reactive-oxygen species inhibition properties. Importantly, these nanoparticles do not exhibit significant cellular toxicity and, when incorporated in skin cream, exhibit skin rejuvenating properties. Our findings have implications for nanoparticle-based cosmetics and dermatologic applications.

Introduction:

Human body gets exposed to environmental, physical as well as biological insults, and skin serves as a protective barrier against these exposures. In addition, skin also harbours Langerhans cells,

biomolecules

MDPI

Article

Zinc Oxide Nanoparticles Functionalized on Hydrogel Grafted Silk Fibroin Fabrics as Efficient Composite Dressing

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Abstract: Recent advances in woundcare is targeted towards developing active-dressings, where multiple components are combined to provide a suitable environment for rapid healing. The aim of the present research is to study the preparation of biomimic composite wound dressings by the grafting of hydrogel on silk fibroin fabric. The swelling ability of hydrogel grafted silk fibroin fabric was optimized by changing the initiator concentration. In order to impart antimicrobial properties, these dressing are further coated sono-chemically with zinc oxide nanoparticles. The water vapor transmission rate of the prepared samples was measured. The conformation of silk fibroin proteins after grafting with hydrogel was also confirmed using Fourier Transform Infrared Spectroscopy (FTIR). The morphology of the zinc oxide-coated silk fibroin fabric and hydrogel-coated silk fibroin was studied using Scanning Electron Microscope (SEM). The antimicrobial activity of the zinc oxide-coated samples was studied against *E coli*. The cytocompatibility of the prepared dressing materials were evaluated using L929 fibroblast cells. MTT assay and phase contrast microscopic studies showed that the adherence, growth, and proliferation of the L929 fibroblast cells that were seeded on zinc oxide nanoparticles on the functionalized hydrogel-coated silk fibroin dressing was significantly higher than that of pure silk fibroin due to the highly porous, bio-mimic structure that allowed ease of passage of nutrients, growth factors, metabolites, and the exchange of gases which is beneficial for successful regeneration of damaged tissues. The expression of TNF-α and IL-2 were not significantly higher than that of control. The proposed composite dressing would be a promising material for wound dressing and regenerative medicine but in order to prove the efficacy of these materials, more in vivo experiments and clinical tests are required to be conducted in future.

Keywords: silk fibroin; zinc oxide nanoparticles; hydrogel; antimicrobial activity; cytocompatibility

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Probing defects and electronic structure of Eu doped *t*-$Mg_2B_2O_5$ nanocrystals using X-ray absorption near edge spectroscopy and luminescence techniques

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ABSTRACT

We report here the defects and electronic structure study of Eu (1%,3%,5%) doped *t*-$Mg_2B_2O_5$ nanocrystals synthesized using low temperature combustion method, and probed using x-ray diffraction (XRD), transmission electron microscopy (TEM), X-ray absorption near edge spectra (XANES), photoluminescence (PL) and thermoluminescence (TL). The XRD analysis of all samples shows single phase triclinic crystal structure and average crystallite size decreases with Eu doping in $Mg_2B_2O_5$. The experimental XANES spectra of each sample acquired at Eu $M_{3,4}$-edges were compared with simulated absorption edges using atomic-multiplet calculations, which clearly shows the presence of Eu^{2+} in $Mg_2B_2O_5$. The O K-edge spectra of Eu doped $Mg_2B_2O_5$ predicts the formation of O and Mg defects upon increasing Eu concentrations. The photoluminescence of $Mg_{2-x}Eu_xB_2O_5$ nanocrystals at an excitation of 325 nm comprises of a group of sharp peaks owing to intra-4f transitions in Eu^{3+} and confirms the lowering of local symmetry with Eu concentration in $Mg_2B_2O_5$. The effect of Eu doping on the trapping states was probed using TL after irradiating $Mg_2B_2O_5$ with ultra-violet radiations (365 nm), which shows the presence of shallow and deep level trapping states. The corresponding activation energies of trapping states were determined using glow curve deconvolution method based on Kitti's general order equation.

1. Introduction

Borate based compounds are of great interest for generation of functional materials having applications in optical and electronic disciplinary owing to its good solubility of rare earth ions, good transparency, thermal and mechanical stability etc. [1,2]. Researchers have also reported defects or dopant induced magnetic behavior in some borates [4,5]. Amongst diverse borates family, pyroborates constitutes a group of compounds with chemical formula $MM'B_2O_5$, where M, M' stands for Mg, Ca or divalent 3d transition element, having triclinic crystal structure with P(-1) space group. Pyroborates are thermally and mechanically quite stable, thus used as ferroelastic, anti-wear materials etc [6,7]. In general, magnesium borates exist as MgB_4O_7, $Mg_3B_2O_6$ and $Mg_2B_2O_5$. In the present work we have investigated magnesium pyroborate i.e. $Mg_2B_2O_5$ ($2MgO{\cdot}B_2O_3$) nanocrystals. $Mg_2B_2O_5$ is a wide band gap (~5.1–5.5 eV) material which generally exists in monoclinic as well as triclinic crystal structure. Cheng et al. [8] have investigated electronic structure of monoclinic $Mg_2B_2O_5$ theoretically and found that the top of the valence band consists of mostly the O-2p orbitals and the bottom of the conduction band consists of cationic orbitals. Li et al. [9] reported the synthesis of single crystal $Mg_2B_2O_5$ nanowires on MgO substrates. Qasrawi et al. [10] synthesized bulk triclinic $Mg_2B_2O_5$ using partial precipitation technique and discussed their optical properties, which primarily are related to defects. Further, defects in $Mg_2B_2O_5$ may also be created by suitable doping with certain impurities. Kwano et al. [11] synthesized bulk triclinic $Mg_{1-x}Mn_xB_2O_5$ using conventional solid state method and discussed the effect of Mn doping on structural and optical properties which they correlated with defects depicted through rietveld refinement and optical spectroscopy. Most of techniques found in literature use high temperature treatment to synthesize triclinic $Mg_2B_2O_5$. We have used optimized combustion method, for the first time, to synthesize triclinic $Mg_2B_2O_5$ nanocrystals relatively at a much lower temperature [12].

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ORIGINAL ARTICLE Open Access

Novel C stain-based chemical method for differentiating real and forged fingerprints

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Abstract

Background: Fingerprints are useful evidence for establishing identities. Development and detection of fingerprints are of immense help in criminal investigation. However, forged fingerprints identical to the real ones are emerging as a worldwide problem. Existing methods for development of fingerprints (powder method/iodine fuming method/ninhydrin test/$AgNO_3$) fail to distinguish between real and forged fingerprints when forged fingerprints are fortified with salts and amino acids. The present study was conducted with the objective to test applicability of C stain for real and forged fingerprint differentiation.

Methodology: C stain was applied on real and forged fingerprints in combination with conventional methods and was evaluated on the basis of development and differentiation of real and forged fingerprints.

Results: The proposed technique is successful in differentiating between real and forged fingerprints. Colour difference between real and forged fingerprints was observed by taking a combination of C stain with ninhydrin, black powder and iodine fuming, one at a time.

Conclusion: C stain method is an effective technique for distinguishing forged fingerprints from the real ones. It works as a distinction tool even when used in combination with existing development methods.

Keywords: C stain, Forensic Science, Forged fingerprints, Non-porous surface, Porous surface, Real fingerprints

Introduction

Fingerprint technology has been used in forensic science and practiced for more than hundred years now. Due to its uniqueness, fingerprint identification is one of the most widely used biometric techniques. However, it is important to elucidate the use of forgery of fingerprints for the fabrication of evidence involving fake use of genuine marks (Bonebreak 1976). Forged fingerprints are generally used by individuals who intend to commit a crime and then employ forged fingerprints to frame an innocent person or to divert attention of investigating agencies (Champod and Espinoza 2014).

According to a survey of 152 forensic professionals conducted by Geller et al. (2001), 85% of them were aware of the possibility to forge fingerprints. Further, 57% indicated that the threat was credible, and 45% admitted their inability to distinguish genuine fingerprints from forged fingerprints. In another study, Champod and Espinoza (2014) investigated the risks posed by forgeries and inability of forensic practitioners to detect them. In their study, practitioners reported more than 53% forged fingerprints as genuine and 45% of genuine fingerprints as forged.

Powder method is the most commonly used approach for development of latent fingerprints with the help of glass fibre or camel hair brush (Sodhi and Kaur 2001). Other commonly used methods include ninhydrin, $AgNO_3$ and iodine fuming (Oden and Von Hofsten 1954; Lennard et al. 1986; Bassam et al. 1991; Jasuja et al. 2012; Somanchi 2018). Several methods exist for preparation of forged fingerprints and are easily available online. This along with easy availability of raw material facilitates development of forged fingerprints to bypass biometric scanners or to implant on a crime scene with

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Article

A Novel Synthesis of the Graphene Oxide-Silver (GO-Ag) Nanocomposite for Unique Physiochemical Applications

Sujata Kumari, Pratibha Sharma, Sunny Yadav, Jitender Kumar, Ankush Vij, Pooja Rawat, Shalendra Kumar, Chittaranjan Sinha, Jaydeep Bhattacharya, Chandra Mohan Srivastava,* and Sudip Majumder*

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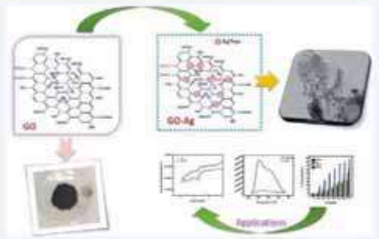
ABSTRACT: Graphene oxide-silver nanocomposite (GO-Ag) was fabricated via the sonochemical method, which shows unique physiochemical properties. Graphene oxide (GO) and silver nanoparticles (AgNPs) were synthesized by modified Hummer's and Chemical reduction methods, respectively. The synthesized nanocomposite was characterized using powder X-ray diffraction, Raman spectroscopy, and Fourier-transform infrared spectroscopy. The surface morphology of synthesized nanoparticles was studied using scanning electron microscopy and transmission electron microscopy. The thermoluminescence property of the nanocomposite was analyzed by irradiating the samples in gamma radiation at 1 kGy. Electrochemical reversibility of the GO-Ag nanocomposite was examined by cyclic voltammetry. The photocatalytic application of the nanocomposite was studied using degradation of methylene blue dye. Results reveal that doping of AgNPs on the GO surface not only improves its dye degradation property but also enhances its thermoluminescence property. This knowledge will be helpful in determining the antibacterial property of the GO-Ag nanocomposite in the future.



1. INTRODUCTION

Over the last few decades with the advent of nanotechnology, scientists have drawn extreme research interest regarding nanomaterial development. Among the nanomaterials, graphene and related compounds have emerged as a distinctive class of materials because of their unique structure and functionalities. Graphene oxide (GO), a monolayer sheet of graphite, serves as a precursor for the synthesis of reduced graphene oxide (rGO).[1] Like graphene, GO has a similar hexagonal carbon structure with hydroxyl (−OH), alkoxy (C−O−C), carbonyl (C−O), carboxylic acid (−COOH), and other oxygen-based functional groups as shown in Figure 1.[2,3] Due to the presence of these functional groups, GO exhibits hydrophilic character that makes it a water-soluble nanomaterial.[4] Moreover, the surface functionalization of GO has presented many opportunities regarding its application in the development of nanocomposite materials. GO has high conductivity and shows diverse applications in the field such as sensors, anticancer properties, electronics, biomedicine antibacterial coatings, photocatalytic activity, water decontamination, solar desalination, and drug delivery.[5−21] However, the nanocomposite enhances GO properties. Among all transition elements, silver (Ag) is the most conductive and reactive material and has also been used recently in fabricating silver-

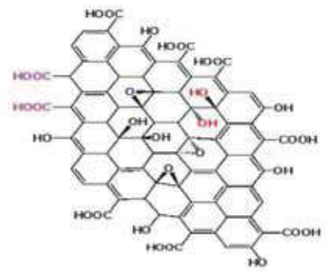


Figure 1. Pictorial representation of graphene oxide.

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RNA targeting by an anthracycline drug: spectroscopic and *in silico* evaluation of epirubicin interaction with tRNA

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ABSTRACT

Anthracyclines are putative anticancer agents used to treat a wide range of cancers. Among these anthracyclines, epirubicin is derived from the doxorubicin by the subtle difference in the orientation of C4-hydroxyl group at sugar molecule. Epirubicin has great significance as it has propitious anticancer potential with lesser cardiotoxicity and faster elimination from the body. The present study is done to understand the molecular aspect of epirubicin binding to tRNA. We have used various spectroscopic techniques like Fourier transform infrared spectroscopy (FTIR), absorption spectroscopy and circular dichroism to illustrate the binding sites, the extent of binding and conformational changes associated with tRNA after interacting with epirubicin. From infrared studies, we infer that epirubicin interacts with guanine and uracil bases of tRNA. Results obtained from infrared and CD studies suggest that epirubicin complexation with tRNA does not result in any conformational change in tRNA structure. Binding constant (2.1×10^5 M^{-1}) calculated from the absorbance data illustrates that epirubicin has a weak interaction with tRNA molecule. These spectroscopic results like the binding site of epirubicin and binding energy of epirubicin-tRNA complex were also verified by the molecular docking. Results of the present study provide information that aids in the development of efficient RNA targeted drugs from the existing drugs by certain chemical modification in their structure resulting in lesser side effects and better efficacy.

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KEYWORDS
Anthracycline; epirubicin; tRNA; infrared spectroscopy; CD spectroscopy; absorption spectroscopy; autodock

1. Introduction

The detailed study on understanding the interaction mechanism between ligand and nucleic acid is a fascinating area of research. The motivation behind studying the interactions among drug-nucleic acid is the aspiration to decipher drug action at a molecular level. Several anticancer drugs have been developed which possess the property of binding specifically to DNA (Afzal, Al-Lohedan, Usman, & Tabassum, 2019; Bandyopadhyay et al., 2017; Demeunynck, Bailly, & Wilson, 2006; Froehlich, Mandeville, Weinert, Kreplak, & Tajmir-Riahi, 2012; Gao, Sriram, & Wang, 1993; Hadian Rasanani et al., 2018; Hurley, 2002; Moradi, Khorasani-Motlagh, Rezvani, & Noroozifar, 2019). There are various proposed mechanisms by which these drugs are known to exert their biological activity which includes intercalation of drug between DNA strands, binding to grooves, crosslinking between DNA strands (Chaires, 2006; Fiebig, Wan, Kelley, Barton, & Zewail, 1999; Hamilton & Arya, 2012; Karami, Mehri Lighvan, Farrokhpour, Dehdashti Jahromi, & Momtazi-borojeni, 2018; Kosiha, Parthiban, Ciattini, Chelazzi, & Elango, 2018; Lyles & Cameron, 2002; Mansouri-Torshizi, Zareian-Jahromi, Abdi, & Saeidifar, 2018; Moradi, Khorasani-Motlagh, Rezvani, & Noroozifar, 2018; Patra, Paul, Sepay, Kundu, & Ghosh, 2018; Rajski & Williams, 1998; Shahabadi, Shadkam, & Mansouri, 2018). This molecular level understanding of drug binding modes has significantly resulted in the development of more efficacious drugs.

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PAPER

Revisiting the physiochemical properties of Hematite (α-Fe_2O_3) nanoparticle and exploring its bio-environmental application

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Keywords: Hematite nanoparticle, annealing temperature, grain size, photocatalytic degradation, biocompatibility assay

Abstract

Aim of present study is to understand the change in structural, magnetic, electrical, and optical properties as well as the thermal stability of hematite nanoparticles with variation in annealing temperature. Additionally its application for dye removal and in thrombolytic activity has also been explored. The α form of Fe_2O_3 nanoparticles were synthesized by co-precipitation method followed by annealing for 5 h at different temperatures from 300 °C, 500 °C, and 700 °C. The formation and properties of α-Fe_2O_3 were analyzed by using Powder x-ray Diffraction (PXRD), Dynamic Light Scattering (DLS), Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), Superconducting Quantum Interference Device magnetometer (SQUID), Thermo Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC), DC electrical resistivity and Ultraviolet–Visible Spectroscopy). Results suggest that there is definite correlation of annealing temperature with grain size, crystallinity, electric and magnetic properties, optical band gap, purity level, and crystallization temperature of α-Fe_2O_3 nanoparticle. The effectiveness of α-Fe_2O_3 as a photocatalyst, as well as biocompatible material was also established.

1. Introduction

Transition metal oxide nanoparticles have drawn a significant interest of researchers in recent past due to their wide range of applications in various fields, such as anti-cancer and anti-microbial agents, optical materials, adsorbents, electronics and electrical materials, heat transfer fluids, magnetic substances, and so on [1–7]. Iron oxide exists in different compositions and phases like FeO, α-Fe_2O_3, β- Fe_2O_3, γ- Fe_2O_3, and Fe_3O_4 etc. Amongst them α-Fe_2O_3 is most stable under ambient conditions. α-Fe_2O_3 nanoparticles or more commonly known as hematite nanoparticles are one of most popular transition metal oxide nanoparticles due to the ease of synthesis, cost effectiveness, non-toxic nature, environmental friendly, and a wide range of applications. In earlier literature, α-Fe_2O_3 nanoparticles were used in light-induced water splitting, catalysis, solar cells, field emission devices, Magnetic Resonance Imaging (MRI), tissue engineering, drug delivery, etc [8–14]. α-Fe_2O_3 exhibits rhombohedrally centered hexagonal structure of corundum type with a closely packed oxygen lattice in which two-third of the octahedral sites are occupied by Fe^{3+} ions [15].

Several methods have been adopted for the synthesis of nanoparticles of α-Fe_2O_3 that includes sol–gel, chemical precipitation, forced hydrolysis, hydrothermal, sonochemical, solution combustion, high-energy ball milling, etc [16–24]. However, controlling the size and monodispersity of the synthesized α-Fe_2O_3 nanoparticle has remained some sort of a challenge until now. Controlling size, shape, and monodispersity of the nanoparticles are extremely significant as the magnetic, optical, resistivity, and other physical properties seems to be greatly affected by these parameters. Uses of capping agents, optimization of reaction pH, and variation in annealing temperature have been found to play an important role in determining above-mentioned properties

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Facile synthesis of $CuFe_2O_4$ doped polyacrylic acid hydrogel nanocomposite and its application in dye degradation

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ABSTRACT

Polyacrylic acid hydrogel doped with copper ferrite nanoparticles has been prepared and studied for the removal and degradation of organic dye (methylene blue) from wastewater. Phase purity of nanoparticles was confirmed by powder X-ray diffraction and EDX analysis. Raman spectra showed three bands at E_g, F_{2g} and A_{1g}, attributing the formation of spinel phase with a band gap of 2.12 eV. Hydrogel composite showed an increase in weight by 1771% when soaked in water. Degradation and absorption studies of methylene blue dye solution with copper ferrite nanoparticles as well as hydrogel nanocomposite suggest absorption of dye by hydrogel and degradation with copper ferrite nanoparticles. Such hydrogel nanocomposites could be a promising material for mitigation of water pollution caused by organic dyes discharged by small and medium scale industries.

1. Introduction

Treatment of polluted water caused by industrial waste continues to be a major challenge for Chemists. Organic dyes used by various industries like textiles, printing, pulp mills, food, and plastics cause water pollution. The stability of dye molecules and their resistance towards biodegradation are the main cause of environmental pollution [1,2]. Several technologies have been used for the waste water management which include biological treatment, coagulation/flocculation, ozone treatment, chemical oxidation, ion exchange, photocatalysis, and adsorption [3,4]. The adsorption of pollutant using eco-friendly materials is considered to be superior over other techniques because of their low cost, the simplicity of design, and ease of operation. Dye removal by activated carbon, zeolite, clay, H_2O_2, sodium hypochlorite and other chemical agents has been widely practiced in the textile industries [5,6]. Superabsorbent polymers (SAP), such as hydrogels containing different types of functional groups, biocompatible and superior absorption capacity have been investigated for their dye removal, drug design, and photothermal properties [7–10]. In recent past, poly(acrylamide)/sepiolite-hydrogel composites, poly(acrylicacid-co-vinyl-2-pyrrolidone)/laponite hydrogel, and polysaccharide-based magnetic nanocomposite hydrogels have been reported for the removal of various dyes [11–13]. The cationic dye molecules are known to escape into the hydrogels matrices due to electrostatic and hydrophilic interactions [14].

Despite having good dye absorption capacity, a major disadvantage of hydrogels is their disposal after use. Hence, degradation of absorbed dye seems to be the optimal solution. Nanomaterials have been used in various fields ranging from materials to medicines [15,16]. Nano-crystalline Copper ferrite ($CuFe_2O_4$), have been reported to show significant dye degradation properties and can separate easily due to their magnetic nature. Thus, it was thought worthwhile to explore the absorption and degradation properties of $CuFe_2O_4$ incorporated hydrogel poly(acrylic acid-acrylamide-methacrylate) nanocomposite for dye using a selected dye model, methylene blue (MB).

2. Experimental procedure

2.1. Materials

$CuCl_2{\cdot}2H_2O$, $FeCl_3{\cdot}6H_2O$, NaOH, acrylic acid, ammonium persulphate and MB were purchased from CDH Chemicals. N,N′-methylene bisacrylamide was purchased from Sigma Aldrich.

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REVIEW

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Revisting the synthesis and applications of graphene oxide

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Over the last two decades, graphene and its derivatives have attracted lots of attention because of its peculiar properties. In this review, a general introduction, history, synthesis and applications of graphene and graphene oxide have been provided. However, we have emphasized the different synthetic routes adopted for synthesizing graphene oxide (GO). Till now, several methods have been developed for the synthesis of graphene oxide such as micro-mechanical, exfoliation of pyrolytic graphite; CVD, epitaxial growth, etc. Here in this review paper, we have discussed four methods for the synthesis of graphene oxide, namely Brodie's method, Staudenmaier method, Hofmann method, and Hummer's method. Mostly, graphene oxide has been synthesized by graphite oxidation. Because of excellent properties, chemical functionalization and ease of production graphene and its derivatives have made their way to various applications. Few of the applications of graphene oxide like in electronic devices, energy storage devices, biosensors, coating technology, and graphene oxide composites and paper-like materials have also been incorporated into this paper.

Keywords: Graphite oxide, graphene oxide, graphene.

1. Introduction

Graphene is a name given to the flat monolayer of carbon atoms tightly packed into two-dimensional (2D) honeycomb lattice and is a basic building block for graphitic materials of all other dimensionalities. Graphene is the origin compound of some carbon allotropes, along with graphite, carbon nanotubes and fullerenes[1,2]. In Graphite, each carbon is sp^2 hybridized and the atomic layers of carbon are stacked over each other by van der Waal's interactions and its one-atom-thick layer of carbon is known as "Graphene". For the first time in 1994, Boehm[3] introduced the name Graphene. Graphene is known as a wonder material because of its amazing properties. Owing to the special two-dimensional structure, graphene possessed many unique properties different than other carbon materials, including a high specific surface area[4], extraordinary electronic properties, and electron transport capabilities[5], and high thermal conductivity[6]. Graphene grasp a great compact for use in energy storage materials[7,8], drug delivery systems[9,10], biosensors[11,12], polymercomposites[13,14], liquid crystal devices[15], supercapacitors[16–18], nanoelectronics[19–21] and other areas, whereas, Graphene oxide shows potential in various industrial applications like capacitors, sensors, photovoltaic cells, and transparent electrodes[22,23].

In graphite, perpendicularly aligned graphene layers prove it to be a poor conductor due to weak van der Waals forces of attraction between them whereas shows good conductivity within the plane (i.e. a direction parallel to graphene layers) due to in-plane metallic character[24]. Graphene is an expensive material which is difficult to synthesis and various cost-effective methods have been tried to synthesize derivatives of Graphene.

Graphene oxide is one such material formed by the strong oxidation of Graphite in acidic medium due to its ability to disperse in water and other solvents. On one side, Graphene can be synthesized by the methods like micro-mechanical exfoliation of pyrolytic graphite[25], Chemical Vapour Deposition (CVD)[26,27] and epitaxial growth[28–30]. On the other side, Staudenmaier, Hofmann, Brodie, and Hummers method have been used for the synthesis of graphene oxide[31]. Various functional groups like epoxy, carbonyl, hydroxyl, and carboxyl are attached to graphene oxide. The oxygen-containing functional groups like epoxy and hydroxyl are present on the upper and lower surface of graphene layers or a plane and other functional groups like carbonyl and carboxyl on the edges of

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Optoelectronic Study on Starch Capped Cadmium Sulfide Nanoparticles

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Green synthesis method using soluble starch as a stabilizing agent in an aqueous medium is used to prepare CdS nanoparticles. It has an advantage over the conventional method involving toxic reagents. Here in, a study on the optical properties of CdS nanoparticles prepared by green synthesis method with different pH values is being reported. The samples were prepared by chemical route and characterized by scanning electron microscopy, UV-Vis absorption spectroscopy, Fourier transform infrared spectroscopy, and photoluminescence spectroscopy. The experimental results showed a blue shift in absorption wavelength with respect to bulk CdS that indicates small size formation of particles and quantum confinement effect with increase in the effective energy band gap. The size was estimated by the Brus equation and empirical Yu model. Photoluminescence spectra show band edge emission and deep trap states emission. The CIE coordinates verify the emission of CdS in visible region. The blue shift in band edge emission and red shift in trap state emission are observed with lower pH values. The existence of functional groups was identified by Fourier transform infrared spectroscopy, it confirms the presence of starch as a stabilizing agent. Variation in pH modifies the optical properties and reduction in the size of cadmium sulfide nanoparticles.

Keywords: Soluble Starch, Cadmium sulfide, UV-Vis Absorption, Photoluminescence, FTIR spectroscopy.

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1. INTRODUCTION

Semiconductor nanomaterials have received considerable attention due to their distinct photophysical properties and wide range of application in biology, biosensing and optoelectronic fields. Tunable band gap and narrow band width emission make them versatile materials. They have been extensively used as fluorescent bio labeling, biological assay, photo catalytic, sensors, LEDs, biological imaging and many more applications [1-3]. Semiconductor nanoparticles have been synthesized by variety of ways like chemical precipitation method, ion exchange reaction, orgenometallic precursor, sol-gel method [4].With the wide and diversified applications, the synthesis of semiconductor nanoparticles is drawing attention on an issue of environment safety and eco-friendly. There have been different capping agents like thiols groups, phosphines organic, mercapto accetate, etc. used to synthesize semiconductor nanoparticles [4, 5]. In which thiol group (R-SH) coordinates with functional group and provides good surface stability of the nanoparticles. Nanoparticles prepared with toxic reagents by various methods are not environment-friendly and not applicable in medical or biological purpose. In order to remove or reduce toxicity, the green synthesis of nanomaterials is an alternative method, which can be helpful for various applications and is more reliable and environmentally benign.

Environmentally benign synthetic route has become important aspect of fundamental research. Use of nontoxic chemicals, environmentally benign solvent and renewable stabilizing agent is an approach towards green synthesis. Green capping agents like starch, leaf extract, enzyme, biopolymers etc. are used to stabilize the surface of nanoparticles [1, 6-8]. In 1718, Helcher applied natural starch to stabilize gold nanoparticles. Later, Raveendran et al. have shown that hydroxyl group of starch acts as passivation centers for stabilization of metal nanoparticles [9]. Nowadays, synthetic polymers are commonly used to stabilize different types of nanoparticles. In which the steric force keeps the nucleated legends separated from each other. The soluble starch $(C_6H_{10}O_5)_n$ is a polymeric carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. This polysaccharide is produced by most green plants as energy storage. It is a mixture of amylopectin and amylose; amylose is soluble and known as soluble starch. It has been used as a capping agent or stabilizer in the synthesis of semiconductor or metal nanoparticles. Several reports are available on starch capped metal or semiconductor nanoparticles and used for different optical or biological applications [1, 6, 10]. Among all semiconductors, CdS has been subject of great interest due to its importance in various applications. It is an *n*-type direct band gap semiconductor having band gap of 2.42 eV at 300 K with exciton Bohr radius of 2.7 nm. This corresponds to visible radiation with a wavelength of 512 nm. Moreover, great interest has focused on synthesized CdS nanoparticles due to the wide band gap, good optoelectronic properties and thermal stability. Various parameters like reaction time, pH, temperature, concentration of the capping agent, molar ratio etc. are controlling the reaction and show a considerable effect on the size, shape, morphology and optical properties [3-5]. pH has a great importance in green synthesis route; it has a strong effect on the formation of metal as well semiconductor nanoparticles. pH affects the distribution of starch hydroxyl groups and the hydrolysis and condensation processes of solution during gelatinization, therefore it influences the shape, size, growth mechanism and morphology of the crystals. Uchil et al. have studied the effect of pH on the size of the CdS nanoparticles synthesized in chicken egg membrane by diffusion method. They observed that size of nanoparticles and yield strongly depend on pH in alkaline medium [11]. Sergiel results have presented stable light emission

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Semiconductor based photocatalytic degradation of pesticides: An overview

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ABSTRACT

Pesticides are a mixture of substances and widely used for destroying, combating, or controlling pests Various technologies used to control pesticide concentration in nature include photolysis, photo-Fenton, semiconductor-based photocatalysis and photoelectrocatalysis, etc. Among them semiconductor based photocatalysis has attracted huge attention due to its more feasible and higher rate of degradation which further leads to a great charge of mineralization. This review mainly focuses to discuss and summarize numerous characteristics of photocatalytic elimination of pesticides. The discussion includes the mechanism of semiconductor photocatalytic degradation, modifications over semiconductors that are available in the literature to increase the efficiency of the degradation process, and finally optimization of different parameters of a process for enhancement in the degradation course. The parameters elaborated in this study are pH of the system, amount of semiconductor catalyst, initial concentration of pesticides, calcination temperature of catalyst, and wavelength as well as the intensity of light.

Contents

1. Introduction 2
2. Overview of chemical treatment technologies for pesticides in wastewater treatment 3
 2.1. Photolysis process 3
 2.2. Photolysis combined with oxidants (H_2O_2/O_3) 4
 2.3. Photo-Fenton process 4
 2.4. Semiconductor based photocatalysis 4
 2.5. Photosensitized induced process 5
 2.6. Photoelectrocatalysis process 5
3. Semiconductor based photocatalytic degradation of pesticides 6
 3.1. Working principle and mechanism 6
 3.2. Progression of semiconductor photocatalysis 7
  3.2.1. Metal oxide semiconductors 7
  3.2.2. Doped and hybrid metal oxide semiconductor 8
  3.2.3. Supported metal oxide semiconductor 8
  3.2.4. Additional photocatalytic materials 10
 3.3. Kinetics of photocatalytic degradation process 10
 3.4. Photocatalytic degradation pathways of different pesticides 11

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