CHAPTER 37

MEDICAL SCIENCES
BIOMEDICAL RESEARCH

Doctoral Theses

01. ANJU KUMARI
Metabolic Regulation of Prdx6 in Oxidative Stress and Dementia.
Supervisor: Dr. Mohd. Saquib Ansari and Prof. Laishram R. Singh
Th29404

Abstract

Dementia is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal loss, and protein aggregation, with oxidative stress emerging as a central contributing factor. Peroxiredoxin 6 (Prdx6), a crucial antioxidant enzyme, plays a significant role in maintaining cellular redox balance. This study investigates the metabolic regulation of Prdx6 and its functional modulation by key metabolites under oxidative stress conditions associated with dementia. Using a combination of computational, biochemical, and cellular approaches, we demonstrate that the gut-derived metabolite trimethylamine N-oxide (TMAO) selectively interacts with Prdx6. Molecular docking and simulation studies reveal that TMAO binds to an allosteric pocket near the active site, inducing conformational perturbations. Experimental validation confirms that this interaction leads to reduced Prdx6 activity and structural destabilization, while having minimal effects on other antioxidant enzymes. Furthermore, TMAO induces oxidative stress and cytotoxicity in neuronal cells, supporting its pathological relevance. In contrast, metabolite screening identified β-alanine as a potent activator of Prdx6. β-alanine enhances enzymatic activity, improves thermodynamic stability, and prevents protein aggregation. Structural studies indicate localized conformational rearrangements without global unfolding. Importantly, β-alanine reduces oxidative stress and improves cell viability in neuronal models, highlighting its protective potential. Additionally, structurally related N-oxide compounds exhibit similar effects as TMAO, suggesting a broader role of metabolite-mediated modulation of Prdx6. Overall, this study establishes that small molecule metabolites can differentially regulate Prdx6 structure and function, linking metabolic alterations to oxidative stress in dementia. These findings provide new insights into metabolite–protein interactions and suggest potential therapeutic strategies targeting Prdx6 for neurodegenerative diseases.

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1. Review of Literature 2. Investigating the Structural and Functional Consequences of TMAO on various Anti-oxidant Enzyme 3. Identification and Functional Validation of Brain Metabolites Modulating Prdx6 Activity, Bibliography.

02. KULDEEP

Role of the Gut Metabolite, Trimethylamine N-oxide and Its Structural Analogs in Atherosclerosis

Supervisor: Prof. Sunit K. Singh

Th 29162

Abstract

Atherosclerosis is a complex cardiovascular disorder characterized by lipid accumulation, endothelial dysfunction, and chronic inflammation, while elevated levels of the gut-derived metabolite trimethylamine N-oxide (TMAO) are strongly associated with disease progression and thrombotic complications. However, the molecular mechanisms underlying TMAO-mediated effects remain insufficiently understood. This study integrates biophysical, computational, and cellular approaches to investigate the role of TMAO in clot formation and to identify phytochemicals as potential therapeutic modulators. Biophysical experiments, molecular docking, and molecular dynamics simulations revealed that TMAO binds specifically to the β1 calcium-binding site of fibrinogen, altering its structural dynamics and enhancing fibrin clot formation. Clots formed in the presence of TMAO exhibited increased stability and resistance to proteolytic degradation. Structural analysis further suggested that TMAO shifts fibrinogen toward a high-affinity conformational state, facilitating protofibril assembly. Structurally related N-oxides from antidepressants demonstrated similar fibrinogen-binding properties and promoted fibrin formation, indicating a broader relevance of N-oxide interactions. In parallel, a network pharmacology–guided screening approach identified morin, N-acetylcysteine, and taurine as key phytochemicals with strong associations to atherosclerosis-related targets. Experimental validation in macrophage models demonstrated that these compounds improved cell viability, reduced cellular stress, and suppressed pro-inflammatory cytokine expression under disease-relevant conditions. Collectively, this study highlights the β1 calcium-binding site of fibrinogen as a critical target of TMAO and identifies selected phytochemicals as promising multi-target agents. These findings provide a foundation for developing therapeutic strategies aimed at mitigating atherosclerosis and thrombosis driven by gut-derived metabolites and related compounds.

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1. Review of Literature 2. To Systematically Elucidate the Mechanistic Role of Trimethylamine N-oxide (TMAO) and Structural Analogs in Promoting Thrombosis and Accelerating Atherosclerosis 3. To Target Atherosclerosis Through the Phytochemicals Selected Using a Network Pharmacology Screening Approach, References.

03. PANWAR (Neha)

Investigation of Ar-Turmerone-Induced Antibiofilm and Quorum-Sensing Mechanisms in Inhibiting Microbial Resistance in Pathogenic Strains of Bacteria and Fungi

Supervisors: Prof. Manisha Tiwari and Prof. Pratibha Mehta Luthra

Th 29163

Abstract

The increasing burden of antimicrobial resistance and biofilm-associated infections has limited the effectiveness of conventional antibacterial and antifungal therapies. Biofilm-embedded microorganisms display enhanced tolerance, stress adaptation and virulence regulation, highlighting the need for alternative antimicrobial and antivirulence strategies. Natural products from medicinal plants offer structurally

diverse compounds with multi-target potential. This thesis investigates ar-turmerone, a major sesquiterpenoid constituent of Curcuma longa essential oil, for antibacterial, antibiofilm, quorum-sensing modulatory and antifungal activities. ar-turmerone was isolated and purified from turmeric essential oil using chromatographic techniques, and its identity and purity were established by GC–MS, HPLC, FTIR, NMR and high-resolution mass spectrometry. In silico ADME profiling indicated favourable drug-like properties. Purified ar-turmerone was assessed against clinically relevant Gram-positive pathogens, including Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis and Streptococcus viridans. It produced concentration- dependent growth inhibition, inhibited biofilm formation and disrupted mature biofilms. These effects were validated using metabolic viability assays, Live/Dead fluorescence microscopy, scanning electron microscopy and image-based biofilm coverage analysis. Cytotoxicity assessment on mammalian cell lines indicated acceptable in vitro biocompatibility at effective concentrations. To examine its antivirulence mechanism, ar-turmerone was evaluated for quorum- sensing modulation. Molecular docking and molecular dynamics simulations showed stable interactions with the Staphylococcus aureus regulatory proteins AgrA and SarA. These findings were supported by reduced violacein production in the Chromobacterium violaceum biosensor model and attenuation of quorum-regulated virulence phenotypes in S. aureus. The antifungal potential of ar-turmerone was investigated against pathogenic Aspergillus species, with mechanistic emphasis on Aspergillus fumigatus. Treatment 2 caused growth suppression, reduced ergosterol content, oxidative stress responses, altered catalase and superoxide dismutase activities, and proteomic modulation of metabolic, translational and stress-response proteins. Overall, this thesis establishes ar-turmerone as a multifunctional natural compound targeting bacterial growth, biofilm architecture, quorum-sensing regulation and fungal stress adaptation, supporting its potential as a natural antimicrobial and antivirulence candidate.

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1. Introduction 2. Review of literature 3. Extraction, Isolation, Physicochemical Characterization and In Silico ADME Profiling of ar-Turmerone from Curcuma longL 4. Antibacterial and Antibiofilm Efficacy of ar-Turmerone Against Clinically Relevant Gram-Positive Bacterial Pathogens and Cytotoxicity Assessment 5. Quorum Sensing Modulation by ar-Turmerone: Phenotypic Evaluation, Molecular Docking, and Molecular Dynamics Analysis 6. Antifungal Activity of ar-Turmerone Against Aspergillus Species: Growth Suppression, Oxidative Stress, and Proteomic Alterations 7. Summary, Conclusion and Future Perspectives.

04. SANJAY

Extraction and Characterization of Withania somnifera fruit Compounds for Targeting Oncogenic Signaling in Glioblastoma

Supervisor: Prof. Ajay Kumar Yadav

Th 29164

Abstract

Withania somnifera is a medicinal plant renowned for its anticancer properties; however, the cytotoxic potential of its fruit extract against glioblastoma cells remains largely uninvestigated. This study aimed to evaluate the cytotoxicity and underlying molecular mechanisms of Withania somnifera fruit extracts on U87 MG and LN229 glioblastoma cell lines. A sequential extraction was performed using dichloromethane-methanol (DCM-MeOH), with and without prior hexane treatment, to yield H-DCM-MeOH-WS and DCM-MeOH-WS extracts, respectively. The chemical composition was

analyzed via GC-MS, and the extracts were fractionated using silica column chromatography. Cellular responses to the extracts were evaluated by assessing the gene and protein expression levels of deubiquitinase (DUB) enzymes, including USP1, USP7, USP8, and USP10, via semi-quantitative PCR and Western blotting. Both extracts resulted in dose- and time-dependent downregulation of DUB gene expression in U87 MG and LN229 cells. Protein analysis further confirmed the decreased expression of DUBs along with EGFR and associated downstream signaling proteins. Additionally, apoptosis and autophagy markers were differentially expressed: Smac/Diablo levels increased in U87 MG but decreased in LN229, while LC3B showed the opposite trend. β-actin was used as a loading control. Flow cytometric analysis revealed that DCM-MeOH extracts induced apoptosis in U87 MG cells and necrosis in LN229 cells. Notably, Fraction 5 (DCM-MeOH-WS) significantly suppressed the expression of EGFR, USP5, and USP8, further supporting their role in modulating oncogenic signaling. This study is the first to report the cytotoxic effects of Withania somnifera fruit extracts on glioblastoma cells, highlighting its ability to regulate EGFR and DUB pathways selectively and induce cell-type-specific death mechanisms. These findings underscore the therapeutic potential of Withania somnifera fruit-derived compounds in the development of targeted treatments for glioblastoma.

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Introduction, Review of Literature 1. Temozolomide-Induced Resistance Mechanisms in Glioblastom. 2. Extraction and Characterization of Bioactive Metabolit 3. Phytochemicals and Anticancer Potential of Withania somnifera Summary and Conclusion.

05. VERMA (Nikita)
Engineered Cationic Amphiphiles for Biomedical Applications.
Supervisor: Prof. Uma Dhawan
Th29365

Abstract

This thesis investigates the advancement of self-assembly-driven nanostructures to address a range of application needs, focusing on their potential for drug delivery, antimicrobial potency, and nucleic acid delivery. Self-assembly is the natural process by which molecules organise themselves into ordered structures through non-covalent interactions such as hydrogen bonding, hydrophobic effects, and π–π stacking, enabling the formation of nanomaterials with controlled properties. The nanostructures developed in this study are intended to be biocompatible and biodegradable, with properties that can be finely tuned to enhance their bioactivity. The work is divided into four chapters, each addressing a distinct aspect of self-assembly and its biomedical implications

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1.Introduction 2. Design and Synthesis of Short Peptide-Based SelfAssembled Soft Materials for Drug Delivery and Antimicrobial Applications. 3. Synthesis of Biodegradable Polymeric Conjugates as Potent Antimicrobial Agents 4. Design and Synthesis of Biodegradable Amphiphilic Polyethylenimine (PEI) Conjugates for Efficient Nucleic Acid Delivery and Antiproliferative Activity.