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# Molecular Docking of Natural Compounds Against Key Microbial Enzymes: A Commentary

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## ABSTRACT

The global rise in antimicrobial resistance demands the urgent discovery of novel therapeutics. Plant-derived natural products offer a rich source of structurally diverse bioactive compounds. Molecular docking serves as a key computational approach to identify potential inhibitors of microbial enzymes critical for survival and resistance. This commentary explores the application of docking tools like Auto Dock and Swiss Dock in targeting enzymes such as DNA gyrase, β-lactamases, and viral proteases. Compounds like glycyrrhizin and swertiamarin have shown promising in silico interactions. However, docking predictions must be complemented by ADMET profiling and experimental validation to ensure biological relevance and therapeutic viability.

## INTRODUCTION

Molecular docking (MD) is a computational technique that predicts the optimal orientation and conformation of a small molecule (ligand) when it binds to a macromolecular target, typically a protein. This technique is pivotal for elucidating the binding affinity (i.e., the strength of ligand-receptor interactions), binding pose (specific orientation and atomic interactions at the binding site), and the overall dynamics of drug-target interactions at the molecular level. As such, molecular docking is integral to rational drug design and discovery. Beyond predicting interactions, MD is widely employed in virtual screening of vast chemical libraries to identify potential lead compounds. It is also instrumental in studying protein-protein interactions, deciphering synergistic effects of molecular complexes, and facilitating lead compound optimization to improve potency and specificity.

## DESCRIPTION

The molecular docking workflow typically encompasses several key stages: Protein and ligand preparation, receptor grid generation, docking simulation, scoring and ranking of binding poses, and post-docking analysis. While molecular docking has broad utility in rational drug design, this commentary focuses specifically on its application to identify natural product inhibitors of microbial enzymes, a growing frontier in combating antibiotic resistance.

Docking algorithms simulate molecular interactions using energy-based scoring functions to estimate binding free energies. Widely used software tools such as AutoDock, Glide, GOLD, and Swiss Dock enable high-throughput docking simulations and are routinely utilized in virtual screening protocols. These tools differ in terms of search algorithms, scoring functions, and user interface capabilities, offering flexibility for diverse drug discovery projects. Notable real-world applications of molecular docking include: Rational design of anticancer agents targeting kinase pathways, Identification of inhibitors against SARS-CoV-2 spike and main protease proteins during the COVID-19 pandemic, Discovery of enzyme inhibitors such as acetylcholinesterase for the treatment of Alzheimer's disease.

Targeting microbial enzymes is a strategic approach in antimicrobial drug development due to their indispensable roles in pathogen survival, virulence, and resistance mechanisms. These enzymes catalyze critical cellular processes such as DNA replication, protein synthesis, and cell wall biosynthesis. Inhibiting them can disrupt microbial homeostasis and lead to cell death. The

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key microbial enzymes of pharmacological interest include: DNA gyrase and topoisomerase IV, it is essential for DNA supercoiling and segregation during replication. β-lactamases, enzymes that hydrolyze β-lactam antibiotics, contribute to antimicrobial resistance. Dihydrofolate reductase, vital for folate metabolism and DNA synthesis, Viral proteases (e.g., HIV protease, SARS-CoV-2, crucial for processing viral polyproteins into functional units. These enzymes represent validated drug targets, and their inhibition has been successfully leveraged in the development of fluoroquinolones, β-lactamase inhibitors, antifolates, and antiviral agents. Molecular docking offers a powerful platform to identify and optimize inhibitors that can selectively bind and deactivate these targets, paving the way for next-generation antimicrobial therapeutics.

## Case Studies of Natural Compounds as Potential Enzyme Inhibitors

Plant-derived compounds, including flavonoids, alkaloids, terpenoids, phenolics, and coumarins, have shown inhibitory potential against microbial enzymes. For instance, flavonoids like quercetin and luteolin have been docked successfully against bacterial DNA gyrase and topoisomerase IV, showing strong binding affinities [**Table 1**]. Also, alkaloids such as berberine exhibit activity against beta-lactamases, thus restoring the efficacy of beta-lactam antibiotics. Terpenoids like artemisinin and limonene have demonstrated inhibitory potential against viral proteases, including SARS-CoV-2 main protease.

**Table 1:** Comprehensive Molecular Docking Summary of Natural Products Against Key Microbial Enzymes

Molecular docking studies have revealed that quercetin effectively binds to the ATP-binding site of the DNA gyrase B subunit, forming hydrogen bonds with critical residues, thereby inhibiting enzyme activity. Also, berberine has been shown to interact with class A beta-lactamases through hydrophobic and electrostatic interactions, reducing bacterial resistance to penicillin-class antibiotics. Curcumin has been docked against the main protease of SARS-CoV-2, showing stable binding and potential inhibition of viral replication.

In silico MD as well as in vitro antimicrobial efficacy screening of identified phytochemical ligands (thymol, carvacrol, and cinnamaldehyde) to the dispersin (aap) and outer membrane osmoporin domains of enteroaggregative Escherichia coli and non-typhoidal Salmonella spp exhibited a good correlation with the in vitro antimicrobial efficacy studies and screening. Hence, in silico computation approaches can serve as a high-throughput antimicrobial screening tool to provide successful insights for exploring the interaction of phytochemical ligands with various pathogens.

Methodological Workflow of MD centers on Target Protein Selection, which involves the retrieval from the Protein Data Bank (PDB) and preparation using tools like PyMOL or Chimera. This is followed by extracting phytochemicals from databases like PubChem, converting them into 3D structures, and using software like AutoDock Vina to run docking simulations. The analysis involves evaluating binding energy, interaction types (H-bonds, van der

| Compound | Source | Target Enzyme (PDB ID) | Pathogen | Docking Tool | Mode of Action | Reference |
|---|---|---|---|---|---|---|
| Curcumin | Turmeric (Curcuma longa) | β-lactamase (1BMC) | E. coli (AMR strains) | Glide (Schrödinger) | Blocks antibiotic resistance enzyme | Singh et al., 2019 |
| Quercetin | Apples, Onions | Neuraminidase (3CL0) | Influenza A virus | GOLD | Inhibits viral entry (-8.5 kcal/mol) | Sadati et al., 2018 |
| Allicin | Garlic (Allium sativum) | Cysteine protease (5F57) | Leishmania donovani (Parasite) | AutoDock | Disrupts parasite survival | Cundell, 2021 |
| Epigallocatechin gallate (EGCG) | Green Tea | Enoyl-ACP reductase (3GNS) | S. aureus (MRSA) | MOE | Binds FabI enzyme, reduces fatty acid synthesis | Tiwari et al., 2022 |
| Ursolic Acid | Rosemary, Holy Basil | Dihydrofolate reductase (1J3I) | Plasmodium falciparum (Malaria) | AutoDock Vina | Antimalarial via folate pathway inhibition | Hermantoet al., 2023 |
| Piperine | Black Pepper (Piper nigrum) | Penicillin-binding protein (3UDI) | Streptococcus pneumoniae | Glide | Synergistic with β-lactams | Rasuly et al., 2024 |
| Berberine | Berberis spp. | DNA gyrase (1KZN) | E. coli | AutoDock Vina | Interferes with DNA replication | Sahoo et al., 2024 |
| Resveratrol | Grapes, Peanuts | FtsZ (3VO8) | S. aureus | AutoDock | Disrupts cell division protein | Karaosmanoglu et al., 20 |
| Thymol | Thyme (Thymus vulgaris) | Acetylcholinesterase (1EVE) | Candida albicans | AutoDock | Antifungal action via AChE inhibition | Silva et al., 2019 |

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|---|---|---|---|---|---|---|
| Andrographolide | Andrographis paniculata | RNA polymerase (2O5I) | Mycobacterium tuberculosis | Glide | Inhibits transcription process | Srikanth et al., 2021 |
| Catechin | Green Tea, Cocoa | UDP-glucose pyrophosphorylase (1I1F) | Trypanosoma cruzi | AutoDock | Inhibits sugar nucleotide biosynthesis | Scotti et al., 2020 |
| Apigenin | Parsley, Chamomile | DNA gyrase B (4URM) | Salmonella typhi | GOLD | Targets bacterial replication machinery | Sharma et al., 2020 |
| Kaempferol | Kale, Tea, Broccoli | Dihydropteroate synthase (1AJ0) | Haemophilus influenzae | AutoDock | Antibacterial via folate biosynthesis inhibition | Laksemi et al., 2022 |
| Eugenol | Clove (Syzygium aromaticum) | Protein kinase A (4DFX) | Candida albicans | MOE | Antifungal by impairing signaling pathways | Khatri et al., 2023 |
| Luteolin | Celery, Green pepper | Topoisomerase IV (3RAE) | Pseudomonas aeruginosa | Glide | Inhibits the DNA topology enzyme | Geng et al., 2021 |
| Gingerol | Ginger (Zingiber officinale) | Efflux pump protein AcrB (4DX5) | E. coli | AutoDock Vina | Reduces antibiotic efflux | Sahoo et al., 2025 |

Waals), and pose stability. However, there are several challenges and limitations associated with MD. Specifically, the accuracy of docking predictions largely depends on the quality of the target protein structure and the reliability of the scoring functions. Furthermore, in silico results must be validated experimentally through enzyme inhibition assays to confirm biological relevance. Key pharmacokinetic factors such as bioavailability, solubility, and toxicity also need further assessment. False positives are another concern; for example, compounds like quercetin may exhibit strong docking scores but suffer from poor bioavailability, limiting their therapeutic potential. Additionally, protein flexibility poses a limitation; static docking may fail to capture allosteric binding or conformational changes. In such cases, molecular dynamics simulations can provide more accurate insights into binding behavior and protein-ligand interactions [1-27].

# CONCLUSION

Molecular docking is an indispensable tool in the early stages of drug discovery, particularly for natural product-based inhibitors targeting key microbial enzymes. As antimicrobial resistance continues to rise, integrating docking with pharmacokinetic profiling, molecular dynamics simulations, and machine learning-guided screening will enhance hit prioritization and lead optimization. Expanding curated natural product libraries and validating in silico predictions through in vitro and in vivo models remains essential to translating computational hits into clinically viable antimicrobial agents.

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