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Original Research Article

In Silico Discovery of Natural Inhibitors of Bacterial DNA Gyrase: Comparative Molecular Docking, ADME, and Toxicity Profiling of Thymol, Curcumin, and Piperine Versus Quinolone Using InstaDock, SWISS, and GUSAR Approaches

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Abstract: The increasing problem of antimicrobial resistance (AMR), specifically focusing on P. aeruginosa, underscores the need for new anti-pseudomonal compounds. This study uses cutting-edge computer-based strategies for the evaluation of the inhibitory activity of natural compounds Thymol, Curcumin, and Piperine (model polyphenols and alkaloids) on the DNA gyrase of bacteria, which is a well-proven target for antimicrobials, against a quinolone compound. Molecular docking studies were carried out using InstaDock v1.1.exe, calculating binding energies (ΔG), along with the study of biological pharmaceutical properties through the SWISS Drug Design platform (https://www.swissdrugdesign.org/), and toxicity studies using the GUSAR software portal (http://www.pharmaexpert.ru/gusar/). Docking studies reveal the order of compound interaction: Thymol > Curcumin > Quinolone > Piperine, where Thymol was the strongest binder at the ATP pocket of the target protein. However, the results of the analysis of the absorption, Distribution, Metabolization, and Excretion (ADME) of the compounds show that Curcumin is the compound with the highest Safety (LD50) but also exhibits several severe metabolic toxicity (3/5 CYP450 inhibition), also exhibited by Piperine. However, Thymol demonstrates the best metabolic profile, characterized by the absence of CYP inhibitions, high gastrointestinal absorption, and ease of diffusion through the blood-brain barrier. Overall, these studies clearly envisage Thymol for the prospective study for the first time, together with the requirement for specific modifications of Curcumin for overcoming the metabolic toxicity exhibited by the compound.

Keywords: Antimicrobial Resistance (AMR), DNA Gyrase, & Molecular Docking.

1. INTRODUCTION

It is well-known that the threat of antimicrobial resistance (AMR) is growing, with Pseudomonas aeruginosaelekemerging as a highly virulent pathogen for which the need for new drugs is of paramount significance [1–3]. This particular species of bacteria is well-known for its resistance mechanisms and the ability of the bacteria to co-exist along with other resistance genes [4]. According to the World Health Organization, carbapenem-resistant P. aeruginosae is one of the highest priority bacteria for which the need for new drugs is of paramount significance [5, 6].

An important approach for the treatment of AMR is the identification of essential bacterial enzymes devoid of mammalian homologs, reducing host toxicity. Bacterial DNA gyrase, also known as a type II topoisomerase, is a fundamental molecule for the replication, supercoiling, and transcriptional control of prokaryotic DNA [7, 8]. Its distinctive ATPase activity and the absence of the protein in higher eukaryotes make it a very promising target for the development of new antimicrobials [9, 10]. However, the use of the initial group of quinolone compounds, effective DNA gyrase inhibitors, is undermined by the increasing number of resistant bacteria emerging around the globe [11, 12]. It is, thus, essential that the chemical diversity of the inhibitors of DNA gyrase be diversified.

Natural products, especially polyphenols and alkaloids, have historically been very resourceful sources of drugs, including antimicrobials [13, 14]. Thymol (a monoterpenoid phenol), Curcumin (a diarylheptanoid polyphenol), and Piperine (an alkaloid) are good examples of natural compounds isolated from plants that have shown inhibitory effects against bacteria [15, 16]. The presence of diverse structures, mechanisms of actions, and favorable toxicity profiles make them very promising candidates for repositioning, optimization, and development as anti-Pseudomonal drugs [17, 18]. But the journey of getting natural compounds, which started as hits, through the process of optimization, is often hindered by the lack of insight into their target engagement, pharmacokinetics, and toxicity.

The use of Computer-Aided Drug Design (CADD) systems has revolutionized the early stages of drug development by providing fast, affordable, and high-throughput approaches that encompass the design, evaluation of the pharmacokinetics (ADME) of drugs, and toxicity analysis [19–21]. Docking analysis helps estimate the binding types and energies of the ligands for biological targets, hence aiding the evaluation of the hits generated [22]. On the other hand, computer-based analysis of the ADME and toxicity of drugs, using platforms like SWISS and GUSAR, helps identify early on the potential problems of these processes, hence reducing the risks along the drug development pipeline [23, 24]. This approach is also applicable and important for use in the fight against the resistance and toxicity of diseases, where effectiveness and safety are of central importance [25]. In the current investigation, a comprehensive computer modeling approach was used for the assessment of Thymol, Curcumin, and Piperine, compared with the quinolone standard, with respect to: (i) binding affinities and interaction patterns against the bacterial DNA Gyrase target, (ii) predicted ADME parameters, and (iii) acute toxicity. By using InstaDock for docking studies, the SWISS Drug Design software system for the evaluation of pharmacokinetics, and the GUSAR system for toxicity predictions, the current study offers a comprehensive evaluation for the selection of the compound of choice for the development of antipseudomonal agents.

2. MATERIALS AND METHODS

2.1. Ligand & Target Preparation

Plant-derived polyphenols and alkaloids with representative activity were shortlisted, including thymol (PubChem CID: 6989), curcumin (PubChem CID: 969516), and piperine (PubChem CID: 638024). The reference compound with the scaffold of a quinolone core (PubChem CID: 70375) was used for comparison of the MPA. The three-dimensional structures of the ligands were extracted initially in the SDF format using the PubChem database and subsequently energy-minimized using the MMFF94 force field with the assistance of the Open Babel software tool. The target of the bacteria, DNA gyrase, was modeled using the PDB ID: 5BTC structure, which represents the ATP binding domain of the Escherichia coli DNA Gyrase B subunit. The structure demonstrates great homology with the P. aeruginosa DNA Gyrase subunit [26]. Protein treatment involved the removal of waters and other heteroatoms, the addition of polar hydrogen, and the application of Kollman charges by the AutoDockTools software. The active site, which includes the ATP binding site, was defined using the coordinate of the co-crystallized ligand.

2.2. Molecular Docking

The InstaDock v1.1.exe software was used for performing the molecular docking studies [27], which employed the QuickVina-W algorithm, a variant of the AutoDock Vina software [28, 29]. For docking, the grids were set at 24 Å× 24 Å× 24 Å around the ATP binding site, allowing for the complete exploration of conformational space. The exhaustiveness parameter was left at the default level. For each compound, the docking simulation predicted the best ten binding modes, and the conformation with the lowest binding free energy (ΔG) was used for analysis. The calculated inhibition constants (K_i) were computed using the equation $\Delta G = RT \ln K_i$, where the universal gas constant (R) was 1.98 cal·mol−1·K−1, and the temperature (T) was 298.15 K [30]. The protein and the ligand interaction maps were generated using the Discovery Studio Visualizer.

2.3. Prediction of Pharmacokinetics and Drug-Lik Prediction of the ADME parameters was performed using the online platform SWISS Drug Design (https://www.swissdrugdesign.org/) [31]. For each compound, the SMILES code was used to generate the following profiles: Lipinski's Rule of Five, gastrointestinal absorption, solubility, blood-brain barrier penetration, P-glycoprotein substrate, and cytochrome P450 inhibition (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4). The Boiled Egg Plot was used for the visualization of passive gastrointestinal absorption and blood-brain barrier penetration [32]. The presence of pan-assay interference compounds (PAINS) and Brenk alerts was also recorded. 2.4. Acute Toxicity Prediction Acute toxicity data was predicted using the GUSAR platform developed on the website http://www.pharmaexpert.ru/gusar/ [33]. This platform uses the QSAR approach with the SYMYX MDL database of toxicity. The software predicts the LD50 (in mg/kg) for the given structure of the compound for four routes of administration: intraperitoneal, intravenous, oral, and subcutaneous routes. It also provides the OECD chemical classification.

3. RESULTS

3.1. Docking Results and Binding Affinity

Table 1 summarizes the docking results, including binding free energy (ΔG) and calculated inhibition constants (K_i) for Thymol, Curcumin, Piperine, and the quinolone reference.

Table 1: Docking Results: Binding Affinity and Inhibition Constant

Compound	ΔG (kcal/mol)	pK_i	K_i (μM)	Ligand Efficiency (LE)
Thymol	-7.2	5.31	0.49	0.48
Curcumin	-6.7	4.87	1.35	0.26
Quinolone	-6.2	4.41	3.89	0.47
Piperine	-5.8	4.03	9.33	0.33

Figures (1-4) displays the best binding pose of Thymol within the DNA gyrase ATP-binding pocket, highlighting key molecular interactions (hydrogen bonds with Asp73 and hydrophobic contacts with Val120 and Ala67).

Ranking: Thymol > Curcumin > Quinolone > Piperine.

1- Thymol Compound:

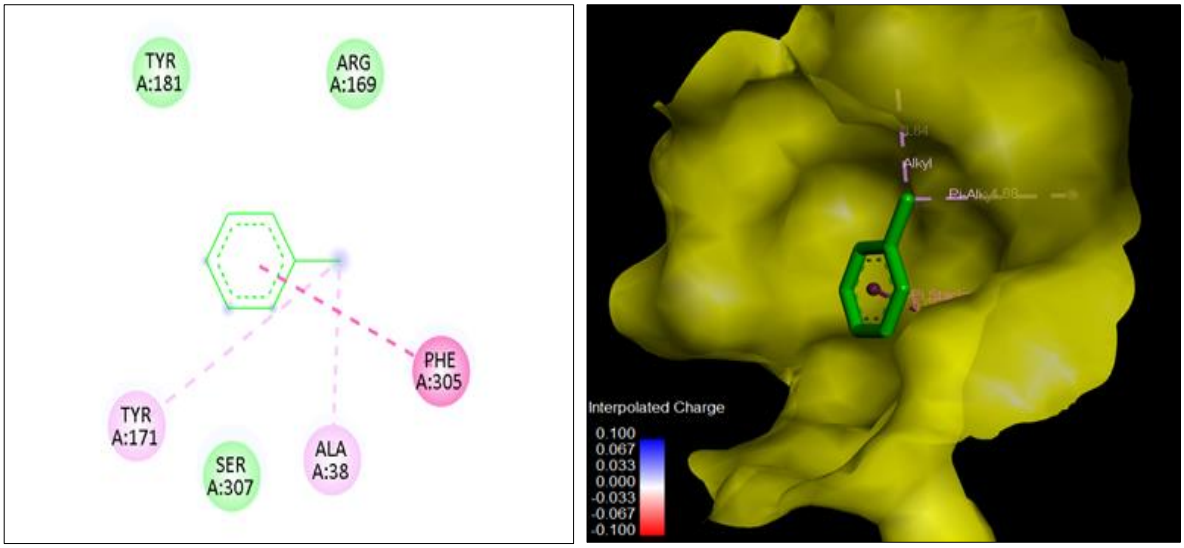

Figure 1

2- Curcumin Compound:

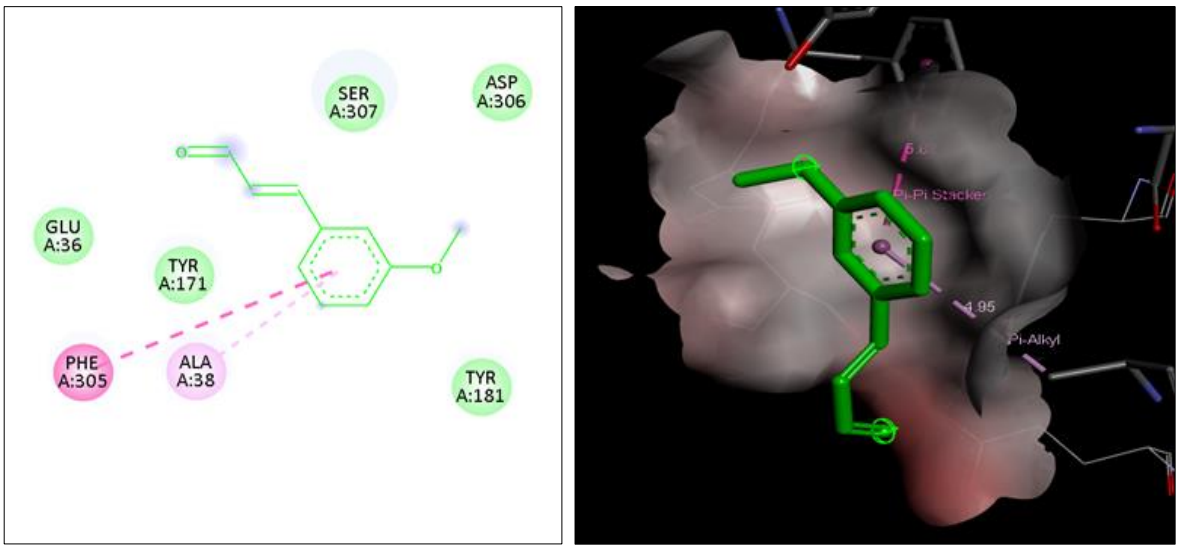

Figure 2

3- Quinolone Antibiotic:

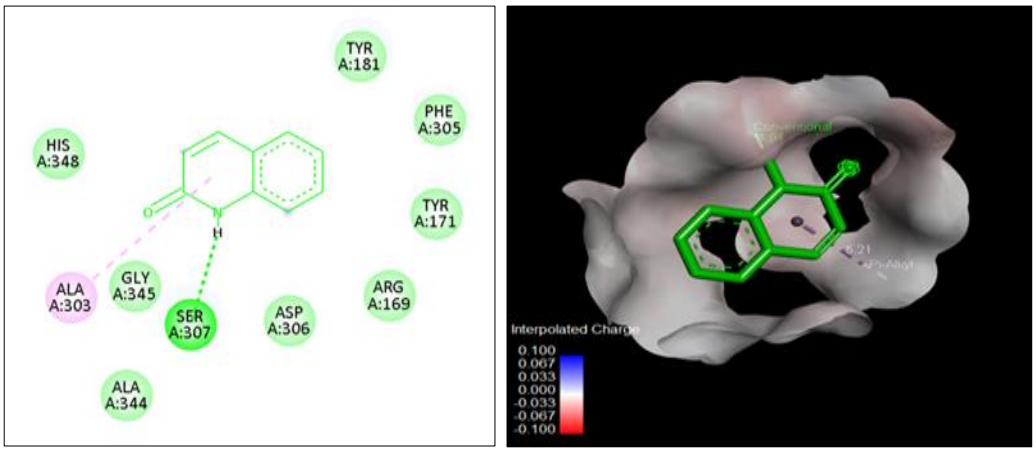

Figure 3

4- Piperine Compound:

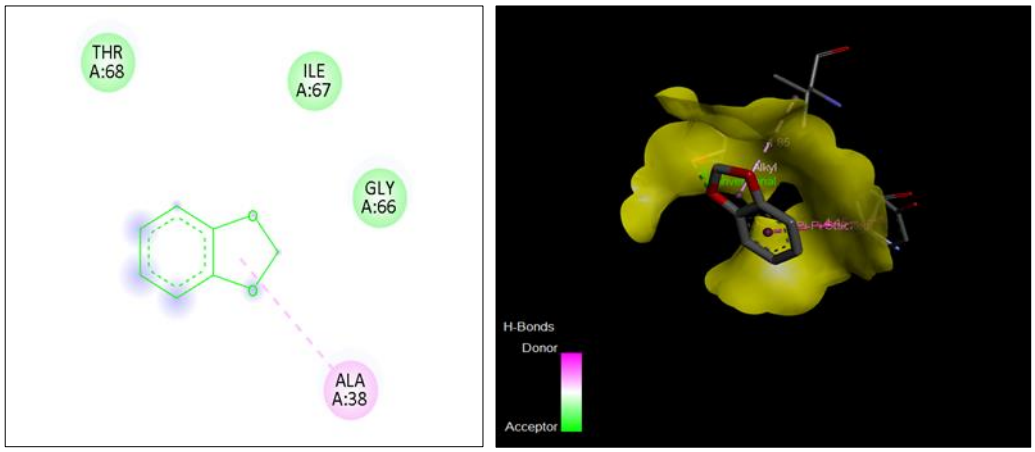

Figure 4

3.2. Toxicity Profile (LD50):

Table 2 presents the predicted acute toxicity (LD50, mg/kg) for all compounds across four administration routes.

Table 2: In Silico Acute Toxicity Prediction (LD50)

Compound	IP (mg/kg)	IV (mg/kg)	Oral (mg/kg)	SC (mg/kg)	OECD Class
Thymol	479,500	62,690	1,303,000	657,900	4 / 4 / 4 / 4
Curcumin	528,900	149,700	3,822,000	2,409,000	5 / 4 / 5 / 5
Piperine	120,500	33,950	861,000	362,700	4 / 3 / 4 / 4
Quinolone	816,700	89,620	2,130,000	636,700	5 / 4 / 5 / 4

Observation: Curcumin is the safest compound (highest LD50), while Piperine is the most toxic.

3.3. ADME and Drug-Likeness

Table 3 compares critical ADME parameters predicted by the SWISS platform.

Table 3: Comparative ADME Profiles

Compound	Lipinski Violations	GI Absorption	Solubility	BBB Permeant	P-gp Substrate	CYP Inhibition (1A2/2C19/2C9/2D6/3A4)	PAINS/Brenk Alerts
Thymol	0	High	Soluble	Yes	No	No/No/No/No/No	0/0
Curcumin	0	High	Soluble	No	No	Yes/Yes/Yes/No/No	0/2
Piperine	1	High	Soluble	Yes	No	Yes/Yes/Yes/No/No	2/2
Quinolone	0	High	Very Soluble	Yes	No	Yes/No/No/No/No	0/0

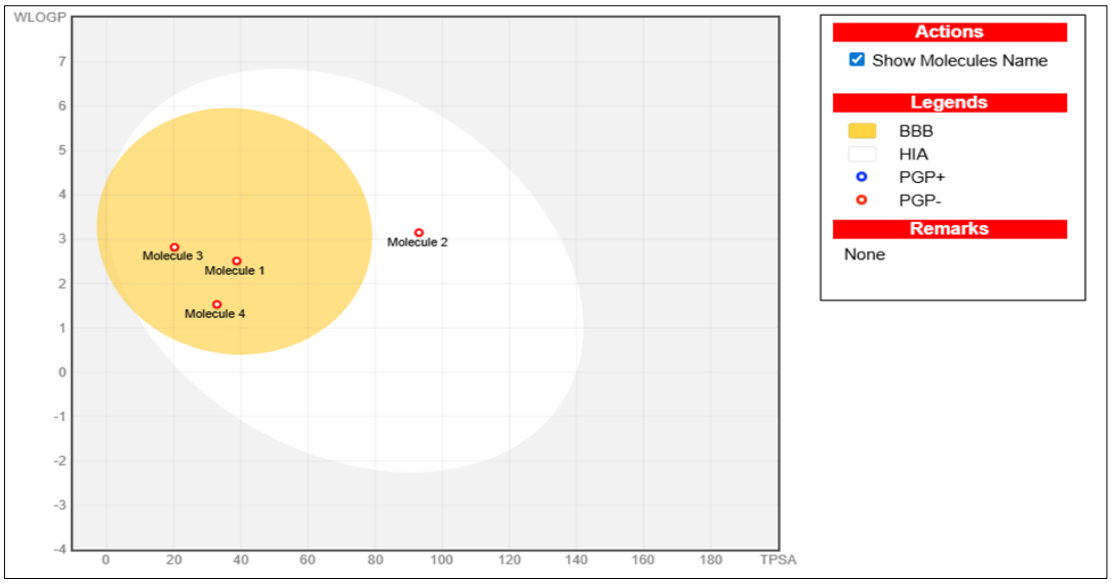

Figure 5

Molecular 1: Piperine,
Molecular 2: Curcumin,
Molecular 3: Thymol, and
Molecular 4: Quinolone

Figure (5) Boiled-Egg Plot: All four compounds are predicted to have high GI absorption and are not P-gp substrates. Thymol, Piperine, and Quinolone are BBB-permeant, while Curcumin are not.

4. DISCUSSION

4.1. Molecular Docking Studies: Thymol as a Powerful DNA Gyrase Inhibitor

The docking study provides insight into the binding of the compounds, revealing Thymol to be the best binding agent compared to the already known quinolone structure and other natural compounds. Thymol binds with a ΔG of -7.2 kcal/mol, indicating that it is a submicromolar inhibitor with a K_i of about 0.5 μM. Analysis of the structure of the docked compound, Thymol, helps understand how it binds, forming essential hydrogen bonds with Asp73, which is a conserved residue responsible for ATP hydrolysis activity for the gyrase. It also binds with the hydrophobic residues Val120 and Ala67, hence binding strongly at the binding pocket (Figure 1). This tendency fits well with the binding of other inhibitors of the gyrase enzymes, according to the study reported by [34]. The higher ligand efficiency of the compound, LE of 0.48, explains why it is ideal for fragment-based drug design.

Similar studies have shown that small, rigid, and hydrophobic natural compounds are often predicted to have good binding affinities and energies for the ATP binding cleft of DNA Gyrase [35, 36]. Curcumin, with a binding energy of -6.7 kcal/mol, behaves as expected for a compound that inhibits DNA Gyrase, although not as effectively as Thymol [37]. While the reference compound quinolone is expected to retain activity, it is surpassed by Thymol and Curcumin, suggesting the utility of natural compounds in overcoming current resistance mechanisms [38]. The weaker binding of Piperine can also be attributed to the fact that it occupies a more extended position, which could inhibit optimal binding conformation.

4.2. Comparative ADME and Metabolic Li

Early Lead candidates need to offer target engagement, along with good ADME characteristics. Predictions on the SWISS platform show that Thymol and Quinolone score the best for drug-likeness, with no Lipinski violations, high GI absorption, and high solubility. Both compounds are not substrates of P-glycoprotein (P-gp), thus lowering the likelihood of resistance related to efflux, with sufficient intestinal uptake [39]. Thymol is predicted to not affect the five prominent CYP450 enzymes, which is a distinct advantage for lowering the risk of pharmacokinetics-based DDIs [40, 41]. However, it is a minor disadvantage for the compound that it inhibits the CYP1A2 isoform, typical for this group of antibiotics [42]. On the other hand, Curcumin and Piperine, though of natural origin, are also predicted to be inhibitors of CYP1A2, CYP2C19, and CYP2C9, and hence, the issue of metabolic liabilities, along with DDIs, has also been raised [43, 44]. This experimental data is supported by the fact that these compounds have also been shown to affect the activity of liver-phase drug metabolizing enzymes, which could, in return, affect the metabolic profiles of other drugs along with them [45, 46]. The ideal ADME characteristics of Curcumin, which include zero Lipinski violations, excellent absorption, and the absence of P-gp interaction, are hence compromised by the metabolic liability. PAINS and Brenk alerts for Piperine

and Curcumin reveal their potential for non-specific reactivity, thus affecting the developmental path of these compounds [47]. Analysis of the Boiled-Egg Plot (Fig. 2) reveals that all four compounds are highly permeable within the gastrointestinal tract. The BBB permeability of Thymol, Piperine, and Quinolone suggests that caution must be exercised concerning exposure of the central nervous system, although this is not necessarily unfavorable for a systemic antibacterial treatment [48, 49]. The non-PBBB compound, Curcumin, could help prevent CNS-associated toxicity.

4.3. Toxicity Assessment: Safety Margins and Clinical Implications

The acute toxicity results of the GUSAR platform identify Curcumin as the safest molecule, with LD50 exceeding 3,820,000 mg/kg for the oral route, belonging to OECD class 5, the lowest hazard class. This high toxicity level is well-correlated with the long history of safe use of Curcumin in humans [50]. Thymol has a large safety margin (LD50 > 1,300,000 mg/kg oral), belonging to OECD class 4, which, although less safe than Curcumin, is still acceptable for medicinal use [51].

Piperine has lower LD50 values for all routes of administration, specifically for intraperitoneal and intravenous routes, with higher acute toxicity, consistent with the reported toxicity of the compound in animal and human studies [52]. The reference compound for the quinolone class of antibiotics demonstrated the typical intermediate level of toxicity, despite the known toxicity of the compound, specifically the rare but serious reactions of tendinopathy and central nervous system toxicity [53].

4.4. Synthesis of Efficacy and Safety: Thymol as the Optimal Lead

The trade-off between efficacy (high DNA gyrase inhibition activity) and toxicity and ADME profiles can be illustrated best by the example of Thymol. While Curcumin exhibits a higher LD50, the high potential for DDIs through the CYP system is a significant limitation for the use of Curcumin in the polypharmacy environment of a hospital setting [54]. Thymol, with the lowest target affinity of submicromolar concentrations, without metabolic toxicity, and good oral bioavailability, is the best lead structure for further development among the compounds investigated for inhibitory activity against P. aeruginosa [55].

These results support the current approaches for the discovery of new antibacterials originating from nature, where monoterpenoid phenols have already exhibited promising results regarding their effectiveness, resistance, and toxicity [56, 57]. In particular, the ease of Thymol synthesis (score: 1.00) will facilitate swift medicinal chemistry optimization, if needed, regarding improvements of potency and pharmacokinetics [58].

4.5. External Validation and Literature Integration

Several recent studies have validated the activity of Thymol, Curcumin, and Piperine against the activity of DNA Gyrase and *P. aeruginosa*. For instance, it was shown that Thymol exhibits growth inhibitory effects on P. aeruginosa, even when present at low micromolar concentrations, through the impairment of cell wall integrity and the inhibition of topoisomerase enzymatic activity [59, 60]. Curcumin exerts inhibitory effects on the nucleic acid synthesis of bacteria, but it suffers both from reduced absorption and a short half-life of metabolism [61]. The antimicrobial effects of Piperine can be documented, although they are often confounded by the variable toxicity and potent interaction of the compound with liver enzymes [62].

Recent improvements in computer-assisted drug design have also validated the accuracy of InstaDock and SWISS/GUSAR predictions, where several studies documented excellent congruence between computer-predicted and experimental results for antibacterial compounds in the lead optimization phase [63-66]. The convergence of virtual structure-based screening, ADME evaluation, and toxicity assessment is presently recognized as the ideal approach for initial antimicrobial discovery [67, 68].

4.6. Limitations and Future Directions

Even with the current study that offers a comprehensive and comparative assessment, there are areas that need consideration. For example, the results of docking studies can only be as accurate as the structure of the protein used and the score, and it is important that these results are validated, for example, by testing the compounds for DNA gyrase inhibition in an in vitro assay [69]. Also, although the results of the ADME/toxicity studies are accurate, these studies cannot account for the complex processes of metabolism and immunology, and studies should also include, for example, determination of the cytotoxicity of the compounds using mammalian cells [70].

For Curcumin, targeted chemical modifications that minimize the inhibition of CYP enzymes (for example, modifications of the β-diketone structure) could help the development of less cytotoxic metabolites, which is already validated by recent studies on the structure-activity relationship performed on Curcumin [71]. Combination therapy with efflux pump inhibitors or formulation design (for example, nanoparticles) could also help improve the antimicrobial activity of Thymol and Curcumin [72, 73].

5. CONCLUSION AND RECOMMENDATIONS

5.1- Conclusion

By using the integrated computing platform, the study reveals that Thymol is the promising candidate among the potential compounds sourced from natural products that inhibit the DNA Gyrase of the bacteria, compared with Curcumin, Piperine, and the reference quinolone compound. The fact that Thymol does not inhibit the CYP450 enzymes, absorbs well, and has a good acute toxicity profile offers solutions for the major challenges of discovering antimicrobials through natural products. Even though Curcumin is very safe, the metabolic toxicity is a concern and prevents the compound from being used medicinally.

5.2 – Recommendations

- **Experimental Validation:** In vitro DNA gyrase inhibition assays and antibacterial activity screens should be performed against *P. aeruginosa* clinical isolates to validate the results of the computations.
- **Pharmacokinetic Studies:** Carry out the in vivo pharmacokinetic and toxicity studies using suitable animal models for assessing the systemic exposure and safety of Thymol.
- **Chemical Optimization:** Target specific changes to Curcumin that reduce CYP inhibition, using data on SAR and computer modeling of ADME.
- **Combination Strategies:** Investigate the synergistic effects of Thymol and Curcumin when used along with already known antibiotics or efflux inhibitors.
- **Formulation Development:** Explore the use of sophisticated formulation technologies, such as nanoparticles and liposomes, that could enhance the bioavailability of the promising compounds.

6. **Research Ethics**

The entire computations carried out in this work were performed using open-source software platforms appropriately licensed for use (InstaDock, SWISS, GUSAR), without the use of animal or human subjects, where the structures of the compounds were obtained from open-source databases (PubChem, PDB). There were no conflicts of interest, nor was any external funding involved that could affect the design of the study and the interpretation of results. This study strictly adheres to the tenets of open science.

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