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In Silico Exploration of Bioactive Compounds from *Dracaena cochinchinensis* as Potential Inhibitors of *Streptococcus pyogenes* Inosine-5'-Monophosphate Dehydrogenase (IMPDH)

Septi Handayani[1]*, Nawan[2], Agnes Immanuela Toemon[3]
[1]Departement of Biochemistry; [2]Departement of Microbiology; [3]Departement of Parasitology,
Faculty of Medicine, University of Palangka Raya, Indonesia.

Corresponding author*
septi@med.upr.ac.id

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Abstract

The emergence of multidrug-resistant *Streptococcus pyogenes* presents a significant global health threat, demanding the urgent discovery of novel antibacterial agents. This study utilized a comprehensive in silico framework to investigate 17 compounds from the traditional medicinal plant *Dracaena cochinchinensis* as potential inhibitors of Inosine-5'-monophosphate dehydrogenase (IMPDH), a validated antimicrobial drug target. The workflow included predictive modeling of physicochemical properties, pharmacokinetics (ADME), toxicity profiles, and molecular docking simulations to elucidate binding affinities and interaction patterns within the enzyme's active site. Physicochemical analysis revealed that 11 of the 17 compounds exhibited drug-like properties. Molecular docking identified several ligands with high binding affinities, notably Isopimaric acid (-8.2 kcal/mol) and Cochinchinenene D (-8.1 kcal/mol), whose stability was mediated by interactions with key catalytic residues. ADMET predictions indicated that most compounds possess favorable pharmacokinetic profiles. Crucially, Isopimaric acid demonstrated a superior safety profile, with a high LD50 (5000 mg/kg), no predicted mutagenicity, and no risk of drug-induced liver injury (DILI). This computational investigation successfully identified Isopimaric acid as a standout candidate, and its combination of strong target affinity and a favorable ADMET profile positions it as a promising scaffold for the development of novel antibacterial agents against S. pyogenes. These findings provide a strong impetus for experimental validation.

Keywords: ADMET; Antibiotic Resistance; *Dracaena cochinchinensis*; IMPDH; Molecular Docking; Streptococcus pyogenes.

Abbreviations: ADME: Absorption, Distribution, Metabolism, Excretion; DILI: Drug-Induced Liver Injury; IMPDH: Inosine-5'-monophosphate dehydrogenase; LD50: Lethal Dose 50.

INTRODUCTION

Streptococcus pyogenes remains a significant bacterial pathogen, responsible for a wide spectrum of human diseases ranging from mild localized infections to severe, life-threatening invasive conditions (Kanwal & Vaitla, 2023). This gram-positive bacterium is a primary cause of millions of cases of pharyngitis and invasive infections annually, contributing to substantial global morbidity and mortality (Kebede et al., 2021).

The primary line of treatment for S. pyogenes infections has traditionally been β-lactam antibiotics, such as penicillin. However, the emergence of strains with reduced susceptibility and outright resistance to multiple antibiotic classes, including macrolides and fluoroquinolones, poses a critical threat to public health (Cattoir, 2022; Ünübol et al., 2025). High rates of resistance have been documented globally, limiting therapeutic options and increasing the risk of treatment failure. This escalating crisis underscores the urgent need to explore and develop novel antibacterial agents with alternative mechanisms of action (Nawan et al., 2020; Nawan & Handayani, 2021).

Natural products, particularly those derived from medicinal plants, represent a rich reservoir for drug discovery. The red resin of *Dracaena cochinchinensis*, commonly known as "Dragon's Blood," has a long history of use in traditional Chinese medicine for treating various ailments. Modern scientific studies have validated its broad spectrum of bioactivities, including anti-inflammatory, anti-tumor, and antibacterial properties (Gupta & Gupta, 2011; He et al., 2021).

Effective antibacterial drug development hinges on the identification of essential molecular targets within the pathogen. Inosine-5'-monophosphate dehydrogenase (IMPDH) is a rate-limiting enzyme in the de novo biosynthesis of guanine nucleotides, which are

indispensable for bacterial DNA and RNA synthesis (Modi et al., 2021). Its critical role in pathogen viability and proliferation has established IMPDH as a validated and attractive target for novel antibacterial agents (Ramanujan, 2020).

This study aimed to investigate the potential of bioactive compounds from *D. cochinchinensis* as inhibitors of *S. pyogenes* IMPDH through a comprehensive computational approach. By integrating molecular docking simulations with predictions of pharmacokinetic (ADME) and toxicity profiles, we identify the most promising lead compounds that could serve as scaffolds for the development of new therapeutics against *S. pyogenes*.

MATERIALS AND METHODS

Software and Computational Resources

All computational tasks were performed on a PC equipped with an Intel® Core™ i7-5500U CPU @ 2.40GHz, 16 GB of RAM, running a Windows 11 Pro 64-bit operating system. The software suite included AutoDock Tools 1.5.7, Biovia Discovery Studio Visualizer 2021, and the online web servers pkCSM and ProTox-II for ADMET predictions.

Ligand Preparation

Three-dimensional (3D) structures of 17 selected bioactive compounds from D. cochinchinensis and the comparator drug, Penicillin G, were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in .sdf format. The structures were then imported into Biovia Discovery Studio Visualizer 2021, processed, and saved in .pdb format for further preparation.

Target Protein Preparation

The 3D crystal structure of S. pyogenes Inosine-5'-Monophosphate Dehydrogenase (IMPDH) was obtained from the RCSB Protein Data Bank (PDB ID: 1ZFJ). The protein was prepared for docking using AutoDock Tools 1.5.7. This process involved removing all water molecules and native co-crystallized ligands, followed by the addition of polar hydrogen atoms and Kollman charges to the protein structure. The final prepared receptor was saved in the .pdbqt file format.

Physicochemical and ADMET Predictions

The drug-likeness of each compound was evaluated based on Lipinski's Rule of Five (Molecular Weight ≤ 500 Da; Log P ≤ 5; H-bond donors ≤ 5; H-bond acceptors ≤ 10) using the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/). The same server was used to predict pharmacokinetic parameters (Absorption, Distribution, Metabolism, Excretion - ADME). Toxicity profiles, including LD50, Ames mutagenicity, and Drug-Induced Liver Injury (DILI), were predicted using both pkCSM and the ProTox-II server (https://tox-new.charite.de/protox_II/).

Molecular Docking Simulation

Molecular docking was conducted using AutoDock Tools 1.5.7 to analyze the binding interactions between the prepared ligands and the IMPDH receptor. A grid box was defined to encompass the active site of the enzyme. The docking simulations were performed to calculate the binding affinity (ΔG, in kcal/mol) for each ligand, and the lowest energy conformation was selected for further analysis.

Interaction Visualization and Analysis

Post-docking analysis was performed using Biovia Discovery Studio Visualizer 2021. The 2D and 3D interaction diagrams were generated to identify the specific amino acid residues involved in binding and to characterize the nature of the molecular interactions (e.g., hydrogen bonds, hydrophobic contacts, pi-interactions).

RESULTS AND DISCUSSION

Physicochemical Property Analysis and Candidate Filtering

The initial step in our virtual screening workflow involved assessing the drug-likeness of the 17 compounds based on Lipinski's Rule of Five to prioritize candidates with a higher probability of oral bioavailability (Lipinski et al., 2001). As detailed in Table 1, this analysis served as a critical filter.

Six compounds (Cochinchinenin, (2R)-8-Methylsocotrin-4'-ol, Cochinchinenene A, Cochinchinenene B, Cochinchinenin B, and Cochinchinenin C) were found to violate two or more of Lipinski's rules. Significant deviations, particularly in molecular weight (MW > 500 Da) and lipophilicity (LogP > 5), are strongly correlated with poor absorption and permeability, making them less desirable as oral drug candidates (Egbert et al., 2019; Nhlapho et al., 2024). Consequently, these six compounds were excluded from further investigation.

The remaining 11 compounds, which either fully complied with the rules or had only a single violation, were deemed promising and advanced to the subsequent stages of the analysis. This filtered set of candidates is predicted to possess more favorable pharmacokinetic properties.

Table 1. Physicochemical Property Prediction of Compounds from D. cochinchinensis based on Lipinski's Rule of Five.

No	Compound Name	Parameters of Lipinski's Law of Five				Application of Lipinski's Law of Five
		MW (g/mol)	Log P	HBA	HBD	
1	Isopimaric acid	302.458	5.206	2	1	Violate the Lipinski's RO5 (1 Time)
2	2'-O Methylisoliquiritigenin	270.284	3.003	4	2	Respect the Lipinski's RO5
3	Loureirin A	286.327	3.225	4	1	Respect the Lipinski's RO5
4	Davidigenin	258.273	2.619	4	3	Respect the Lipinski's RO5
5	4'-Hydroxy-2,6-dimethoxydihydrochalcone	286.327	3.225	4	1	Respect the Lipinski's RO5
6	4,4'-Dihydroxy-2,6-dimethoxydihydrochalcone	302.326	2.931	5	2	Respect the Lipinski's RO5
7	Cochinchinenin	514.574	5.803	7	5	Violate the Lipinski's RO5 (2 Times)
8	(2R)-8-Methylsocotrin-4'-ol	512.602	6.657	6	4	Violate the Lipinski's RO5 (2 Times)
9	Diphenolic acid	286.327	3.269	4	3	Respect the Lipinski's RO5
10	Cochinchinenene A	526.629	7.067	6	2	Violate the Lipinski's RO5 (2 Times)
11	Cochinchinenene B	512.602	6.764	6	3	Violate the Lipinski's RO5 (2 Times)
12	Cochinchinenene C	498.575	6.461	6	4	Violate the Lipinski's RO5 (1 Time)
13	Cochinchinenene D	484.548	5.515	6	4	Violate the Lipinski's RO5 (1 Time)
14	Cochinchinenin B	542.628	6.409	7	3	Violate the Lipinski's RO5 (2 Times)
15	Cochinchinenin C	542.628	6.409	7	3	Violate the Lipinski's RO5 (2 Times)
16	trans-3,5-Dihydroxy-4'-methoxystilbene	242.274	3.277	3	2	Respect the Lipinski's RO5
17	(2S)-5-Methoxy-6-methylflavan-7-ol	270.328	3.776	3	1	Respect the Lipinski's RO5
18	Penicillin G	334.397	0.861	6	2	Respect the Lipinski's RO5

Molecular Docking and Binding Affinity of Filtered Candidates

The 11 compounds that passed the physicochemical screening were docked into the active site of IMPDH (1ZFJ). The predicted binding affinities are presented in Table 2. All candidates exhibited strong binding energies, ranging from −6.7 to −8.2 kcal/mol. A lower, more negative binding energy correlates with higher binding affinity and a more stable ligand-receptor complex (Buchwald, 2019; Monteiro et al., 2022). Isopimaric acid (−8.2 kcal/mol), Cochinchinenene D (-8.1 kcal/mol), and 2'-O Methylisoliquiritigenin (−8.0 kcal/mol) emerged as the top three compounds with the most potent predicted binding to the target enzyme.

Table 2. Binding Affinities of Filtered Compounds against IMPDH (1ZFJ).

Protein-Ligand	Binding Affinity
1zfj _ Isopimaric acid	-8,2
1zfj_ Cochinchinenene D	-8,1
1zfj_2'-O Methylisoliquiritigenin	-8
1zfj_ Loureirin A	-7,7
1zfj_ Diphenolic acid	-7,7
1zfj_(2S)-5-Methoxy-6-methylflavan-7-ol	-7,7
1zfj_ Cochinchinenene C	-7,5
1zfj_ Davidigenin	-7,4
1zfj_ trans-3,5-Dihydroxy-4'-methoxystilbene	-7,4
1zfj_4,4'-Dihydroxy-2,6-dimethoxydihydrochalcone	-7,1
1zfj_4'-Hydroxy-2,6-dimethoxydihydrochalcone	-6,7

Pharmacokinetic (ADME) Profile of Prioritized Candidates

The ADME properties of the 11 prioritized compounds were predicted to assess their potential behavior in vivo (Table 3). All 11 compounds demonstrated high predicted human intestinal absorption (HIA > 85%), suggesting excellent absorption from the gastrointestinal tract. However, variability was noted in their distribution properties. For instance, only Isopimaric acid and (2S)-5-Methoxy-6-methylflavan-7-ol were predicted to penetrate the blood-brain barrier (BBB). In terms of metabolism, several compounds, including Loureirin A and the two dihydrochalcones, were predicted to be inhibitors of key cytochrome P450 enzymes (CYP3A4 or CYP2D6), which is a critical consideration for potential drug-drug interactions (Pires et al., 2015).

Table 3. Predicted Pharmacokinetic (ADME) Profile of the Filtered Candidate Compounds.

Compound Name	HIA (%)	Skin Permeability (log Kp)	BBB Penetrant	VDss (log L/kg)	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Total Clearance (log ml/min/kg)
Isopimaric acid	95.8	-2.04	Yes	0.39	No	No	1.27
2'-O Methylisoliquiritigenin	92.1	-2.06	No	0.98	No	No	4.28
Loureirin A	93.3	-2.76	No	0.76	No	Yes	5.65
Davidigenin	90.1	-1.98	No	0.81	No	No	5.43
4'-Hydroxy-2,6-dimethoxydihydrochalcone	92.5	-2.53	No	1.09	No	Yes	6.59
4,4'-Dihydroxy-2,6-dimethoxydihydrochalcone	93.1	-2.58	No	1.37	Yes	Yes	8.10
Diphenolic acid	85.9	-1.53	No	0.47	No	No	3.21
Cochinchinenene C	88.3	-0.57	No	0.66	Yes	Yes	7.40
Cochinchinenene D	87.5	0.52	No	0.64	Yes	Yes	6.81
trans-3,5-Dihydroxy-4'-methoxystilbene	91.2	-2.20	No	1.38	No	Yes	4.54
(2S)-5-Methoxy-6-methylflavan-7-ol	93.5	-2.32	Yes	2.15	Yes	No	7.10
Penicillin G (Control)	89.9	-3.64	No	0.26	No	No	5.47

HIA: Human Intestinal Absorption; BBB: Blood-Brain Barrier; VDss: Volume of Distribution at steady state.

Toxicity Profile of Prioritized Candidates

The safety profiles of the 11 candidate compounds were assessed using several key toxicity endpoints (Table 4). A crucial finding was that all compounds were predicted to be non-mutagenic in the Ames test, a highly desirable attribute for any drug candidate. In terms of acute oral toxicity, the compounds ranged from Class 4 to Class 5, with Isopimaric acid (LD50 5000 mg/kg, Class 5) being predicted as the least acutely toxic. The prediction for Drug-Induced Liver Injury (DILI) identified several compounds, including Davidigenin and Cochinchinenene D, as potentially "Toxic." Conversely, Isopimaric acid and Loureirin A were predicted to be "Safe." Significantly, the computational model also accurately classified the control drug, Penicillin G, as "Safe" for DILI, which is consistent with its well-established clinical safety profile and supports the reliability of the predictions for the test compounds.

Table 4. Predicted Toxicity Profiles of the Filtered Candidate Compounds.

No.	Compound Name	LD50 (mg/kg)	Toxicity Class*	Ames Toxicity	DILI**
1	Isopimaric acid	5000	4	Safe	Safe
2	2'-O Methylisoliquiritigenin	1190	4	Safe	Toxic
3	Loureirin A	500	4	Safe	Safe
4	Davidigenin	500	4	Safe	Toxic
5	4'-Hydroxy-2,6-dimethoxydihydrochalcone	1190	4	Safe	Safe
6	4,4'-Dihydroxy-2,6-dimethoxydihydrochalcone	1190	4	Safe	Safe
7	Diphenolic acid	1320	4	Safe	Toxic
8	Cochinchinenene C	302	4	Safe	Toxic
9	Cochinchinenene D	302	4	Safe	Toxic
10	trans-3,5-Dihydroxy-4'-methoxystilbene	2090	5	Safe	Toxic
11	(2S)-5-Methoxy-6-methylflavan-7-ol	2500	5	Safe	Safe
12	Penicillin G (Control)	1000	4	Safe	Safe

**Toxicity Class based on Globally Harmonized System (GHS): Class 4 (300 < LD50 ≤ 2000, Warning) & Class 5 (2000 < LD50 ≤ 5000, Warning - May be harmful).*
***DILI: Drug-Induced Liver Injury.*

Analysis of Ligand-Receptor Interactions

To understand the molecular basis for the high binding affinities observed in docking, the specific interactions between the ligands and the IMPDH active site were analyzed. Table 5 provides a summary of the key interacting residues for each of the 11 compounds, while Figure 1 illustrates the binding modes of the top three candidates.

The potent binding of Isopimaric acid (-8.2 kcal/mol) is anchored by three conventional hydrogen bonds with the side chains of THR312 and CYS310. Similarly, Cochinchinenene D (-8.1 kcal/mol) achieves its stable pose through an extensive network of hydrogen bonds

with residues such as LYS208 and TYR120, complemented by multiple hydrophobic contacts. The consistent interaction of multiple high-affinity ligands with residues like TYR120 and GLY124 suggests these residues are critical for ligand recognition and stabilization within the catalytic pocket.

Table 5. Summary of Key Molecular Interactions of Filtered Ligands with the IMPDH (1ZFJ) Active Site.

Compound Name	Binding Affinity (kcal/mol)	Key Interacting Residues
Isopimaric acid	-8.2	**THR312, CYS310**, ILE309
Cochinchinenene D	-8.1	**LYS208, TYR120**, ARG67, SER93, LYS60, ILE63, VAL97
2'-O Methylisoliquiritigenin	-8.0	**VAL97, GLY124**, GLY96, ILE122, ARG92, LEU200
Loureirin A	-7.7	**GLY124, VAL97**, GLY96, LYS89, ARG92, ILE122
Diphenolic acid	-7.7	**TYR13, GLU467, ALA463**, VAL466, TYR327, PHE465
(2S)-5-Methoxy-6-methylflavan-7-ol	-7.7	**GLY303**, MET53, CYS310, ALA51
Cochinchinenene C	-7.5	MET368, LYS347, PRO488, LYS430, TYR348
Davidigenin	-7.4	**GLY96, GLY124, TYR120**, VAL97, ILE122, LYS187
trans-3,5-Dihydroxy-4'-methoxystilbene	-7.4	**SER308**, MET53, CYS310, ALA255
4,4'-Dihydroxy-2,6-dimethoxydihydrochalcone	-7.1	**GLY96, LYS204, TYR120**, GLY124, THR202, LYS187
4'-Hydroxy-2,6-dimethoxydihydrochalcone	-6.7	**ASP253**, CYS310, PHE465, TYR327, TYR13

*Residues predominantly involved in hydrogen bonding are highlighted in **bold**.*

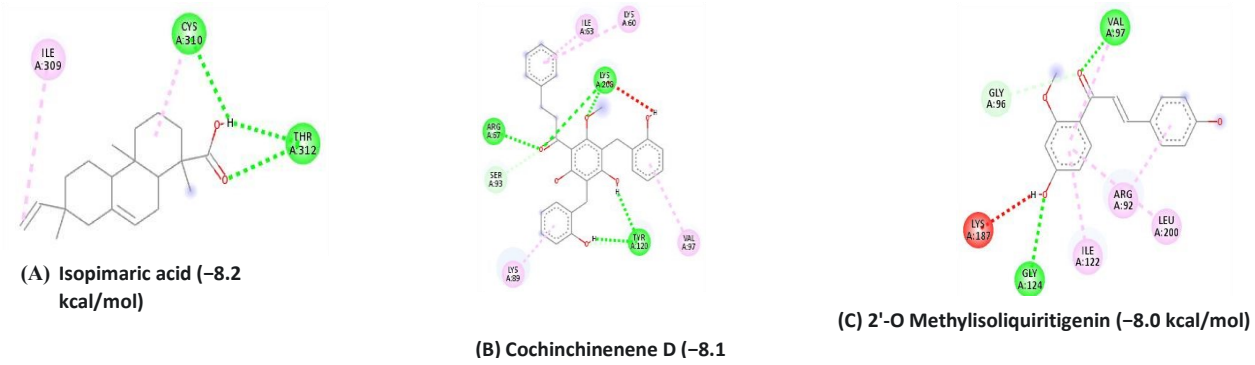

Figure 1. 2D plots illustrating the molecular interactions between the top three candidate compounds and the active site of IMPDH (1ZFJ). The diagrams depict the binding modes for (A) Isopimaric acid, (B) Cochinchinenene D, and (C) 2'-O Methylisoliquiritigenin. Conventional hydrogen bonds are shown as green dashed lines with arrows pointing from donor to acceptor. Hydrophobic interactions (e.g., Alkyl, Pi-Alkyl) are represented by light green splashes. Key interacting amino acid residues are labeled with their three-letter code and sequence number.

Discussion

The application of a hierarchical virtual screening workflow, as employed in this study, represents a rational and efficient strategy in modern drug discovery (van de Waterbeemd & Gifford, 2003). By first filtering a compound library based on fundamental drug-like properties, we effectively focused our computational efforts on candidates with a higher intrinsic probability of success, thereby streamlining the discovery process.

The initial screening using Lipinski's Rule of Five (Table 1) proved to be a decisive first step. The exclusion of six compounds with significant physicochemical liabilities allowed us to concentrate on 11 candidates possessing more favorable profiles for oral administration (Hughes et al., 2011; Leeson & Springthorpe, 2007). This approach is crucial for mitigating the risk of late-stage failures due to poor pharmacokinetics (Kola & Landis, 2004).

Among the filtered candidates, the molecular docking results (Table 2) provided strong evidence of potential inhibitory activity. The high binding affinities of Isopimaric acid (−8.2 kcal/mol) and Cochinchinenene D (−8.1 kcal/mol) are particularly noteworthy. The analysis of their binding modes (Table 5 and Figure 1) provides a structural rationale for this potency. The formation of specific hydrogen bonds and hydrophobic interactions with key residues within the IMPDH active site suggests a well-defined mechanism of binding. For example, the interactions of Isopimaric acid with THR312 and CYS310 are significant, as these residues are located in regions critical for enzymatic function (Braun-Sand & Peetz, 2010).

However, high potency must be balanced with an acceptable safety and pharmacokinetic profile. The ADMET analysis (Table 3 and Table 4) was instrumental in differentiating the top-binding compounds. Here, Isopimaric acid clearly distinguished itself as a superior lead candidate. It not only possesses the highest binding affinity but also exhibits an exemplary predicted safety profile: low acute toxicity (Class 5), a non-mutagenic

prediction, and no risk of hepatotoxicity (DILI). This combination of potent activity and predicted safety is the hallmark of a promising drug candidate (Waring et al., 2015).

In contrast, other potent binders like Cochinchinenene D, while showing strong target engagement, were flagged for potential DILI risk (Table 4). This finding does not outright disqualify them but indicates that they may carry a higher risk of adverse effects and would require careful toxicological evaluation or structural modifications to mitigate this liability. This comparative analysis demonstrates the critical importance of integrating ADMET profiling early in the discovery pipeline to prioritize compounds that balance efficacy with safety (van de Waterbeemd & Gifford, 2003).

While these in silico findings are highly encouraging, it is essential to acknowledge their predictive nature. Computational models are powerful tools for hypothesis generation but are not a substitute for empirical data (Agu et al., 2023). The next crucial phase will be the experimental validation of these predictions. This should involve in vitro assays to confirm the IMPDH inhibitory activity of the prioritized compounds and to determine their Minimum Inhibitory Concentrations (MICs) against clinical isolates of S. pyogenes. The compelling computational profile of Isopimaric acid, in particular, provides a strong justification for its advancement into these more resource-intensive stages of the drug discovery process (Lionta et al., 2014).

CONCLUSIONS

This in silico investigation has successfully employed a hierarchical virtual screening workflow to explore the therapeutic potential of compounds from *Dracaena cochinchinensis* against *Streptococcus pyogenes* IMPDH. Through a systematic evaluation of drug-likeness, target affinity, pharmacokinetics, and safety, this study has identified several promising lead candidates. Notably, Isopimaric acid emerged as a superior candidate, distinguished by its potent binding affinity for the target enzyme, compliance with key drug-like properties, and an excellent predicted safety profile free from mutagenic and hepatotoxic liabilities. These comprehensive computational findings strongly support the prioritization of Isopimaric acid for subsequent experimental validation, including in vitro enzymatic and antibacterial assays, to confirm its potential as a novel scaffold for developing new antibacterial agents against *S. pyogenes*.

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