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# Phytochemicals from Philippine Medicinal Plants as Dual Inhibitors of *Acinetobacter baumannii* IMP-1 and OXA-24 β-Lactamases

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## Abstract

*Acinetobacter baumannii* is a gram-negative member of the ESKAPE group of pathogens and is recognized for causing severe hospital-acquired infections that are increasingly difficult to treat. Its carbapenem resistance is primarily driven by the production of β-lactamase enzymes, particularly the metallo-β-lactamase IMP-1 and the class D OXA-24 enzyme, which hydrolyze carbapenem antibiotics, rendering them ineffective. In this study, phytochemicals from ten Philippine-approved medicinal plants were explored as potential inhibitors of these key resistance enzymes. A total of 1,532 compounds were initially screened in ADMETlab 3.0, and twenty-three molecules met both the QED (quantitative estimate of drug-likeness) and ADMET (absorption, distribution, metabolism, excretion, toxicity) criteria. These selected compounds were then subjected to molecular docking using AutoDock 4, and several exhibited stronger binding affinities than the control drug. Among these, Kuguacin P, Negundol 1b, Negundoin E, Negundoin A, and Balsamiferine D emerged as the most promising candidates for further development of novel β-lactamase inhibitors.

**Keywords:** Multidrug resistance, Acinetobacter baumannii, β-lactamases, Phytochemicals

## Introduction

*Acinetobacter baumannii* is a gram-negative opportunistic pathogen and one of the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter cloaca*) organisms responsible for severe nosocomial infections, including ventilator-associated pneumonia (Pendleton *et al*., 2013; Lee *et al*., 2023). The World Health Organization designates *A. baumannii* a critical-priority pathogen due to its rapid acquisition of multidrug resistance (WHO, 2017; WHO, 2023). Central to this resistance is the production of carbapenemase enzymes, particularly metallo-β-lactamases (MBLs) and OXA-type class D β-lactamases, which are not inhibited by existing β-lactamase inhibitors, leaving few effective treatment options (Evans & Amyes, 2014; Bush & Bradford, 2016).

Among these enzymes, the IMP-type MBLs are encoded by the *blaIMP* gene and disseminated across gram-negative bacteria via integrons, enabling widespread resistance (Pongchaikul & Mongkolsuk, 2022). IMP enzymes hydrolyze β-lactams through zinc-dependent catalysis at their active site (Bebrone, 2007). Variants such as IMP-1, first reported in *Pseudomonas aeruginosa* (Watanabe *et al*., 1991), and subsequent forms display structural loop differences that influence substrate binding and catalytic efficiency (Walsh *et al*., 2005). Their broad distribution across *A. baumannii*, *K. pneumoniae*, and other pathogens underscores their clinical significance.

Similarly, OXA-24 β-lactamase, also known as OXA-40, represents a plasmid-encoded carbapenemase initially confined to *A. baumannii* but now found in other species (Bou & Martínez-Beltrán, 2000). Its active site is characterized by a hydrophobic barrier formed by Tyr112 and Met223, creating a tunnel-like entry for substrates (Santillana *et al*., 2007). A conserved STFK tetrad within the active site mediates nucleophilic attack on β-lactams, facilitating carbapenem hydrolysis (Rice *et al*., 2012). The structural adaptability of OXA enzymes has contributed to their success in conferring high-level resistance (Poirel *et al*., 2010; Mubayrik *et al*., 2022).

In the Philippines, *A. baumannii* isolates frequently carry IMP and OXA-24-like genes, with carbapenem resistance rates exceeding 50% (Chilam *et al*., 2021). To address this, plant-derived natural products offer a promising alternative. The ten Department of Health (DOH)-approved medicinal plants (*Vitex negundo*, *Blumea balsamifera* L., *Momordica charantia* L., *Allium sativum* L., *Psidium guajava*, *Carmona retusa*, *Mentha cordifolia*, *Quisqualis indica*, *Senna alata*, and *Peperomia pellucida*, known for antimicrobial activity, provide a rational starting point (Dantes *et al*., 2021; PITAHC, nd). Here, *in silico* ADMET screening and molecular docking were employed to identify phytochemicals with inhibitory potential against IMP-1 and OXA-24, aiming to highlight novel candidates for combating multidrug-resistant *A. baumannii*.

## Materials and Methods

The workflow of this study was adapted from Ahmed *et al*. (2023) and Etminani *et al*. (2023), with modifications suited to the available protein structures and software tools. The procedure was

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organized into five stages: (1) preparation of phytochemical ligands, (2) protein collection and refinement, (3) QED and ADMET screening, and (4) molecular docking.

*Preparation of Phytochemical Ligands*

Phytochemicals from the ten DOH-PITAHC medicinal plants (PITAHC, nd) were used as candidate ligands, yielding 1,532 compounds (Castro & Billones, 2024). Ligand SMILES and SDF files were obtained from PubChem; for unavailable compounds, structures were drawn using the RCSB PDB Chemical Sketch Tool. Structures were converted via OpenBabel v3.1.1 and geometry-optimized in Avogadro v1.2.0 using the MMFF94 force field (Steepest Gradient, convergence $10^{-7}$, 1000 steps). Optimized ligands were saved in Mol2 format.

*Protein Collection and Refinement*

The OXA-24 β-lactamase (PDB ID: 3G4P) was retrieved from RCSB PDB, while IMP-1 was modeled in SWISS-MODEL using UniProt Q6ZXZ6. Both structures were refined in ChimeraX v1.9 to remove water and heteroatoms, then processed in AutoDock Tools v1.5.7 by adding polar hydrogens, Kollman charges, and AD4 atom types. Final files were saved in PDBQT format.

*QED and ADMET Screening*

Ligands were screened in ADMETlab 3.0 for drug-likeness (QED ≥ 0.49) and pharmacokinetic parameters (absorption, distribution, metabolism, excretion, toxicity). Criteria included HIA, oral bioavailability, BBB penetration, hERG blockade, AMES toxicity, and hepatotoxicity. Only compounds meeting both QED and ADMET thresholds advanced to docking.

*Molecular Docking*

Docking was performed using AutoDock4 v4.2.6. Blind docking with sulbactam validated active sites in both targets (IMP-1: grid 100 × 100 × 100 Å, spacing 0.6 Å, center -11.002, 0.233, -20.063; OXA-24: grid 120 × 120 × 120 Å, spacing 0.6 Å, center 95.339, 27.065, 34.96). Subsequent site-directed docking was conducted for 23 screened ligands plus sulbactam as a control. Grid boxes encompassed the active sites (IMP-1: 70 × 70 × 70 Å, center -21.815, -1.523, -23.397; OXA-24: 70 × 70 × 70 Å, center 104.249, 27.118, 27.163). The Lamarckian genetic algorithm (10 runs, medium evaluation setting) was applied, and the lowest binding energy conformations were visualized in AutoDock Tools and BIOVIA Discovery Studio v25.1.0.24284.

## Results and Discussion

*QED and ADMET Screening of Phytochemical Ligands*

The present study commenced with an extensive in silico screening of 1,532 phytochemicals derived from Philippine-approved medicinal plants, serving as the initial ligand pool (PITAHC, n.d.). These natural products, traditionally employed for a wide range of ailments, are an underexplored source of potential anti-bacterial compounds. Their structural diversity, spanning alkaloids, flavonoids, terpenoids, coumarins, and phenolic compounds, provided a robust foundation for identifying inhibitors against two clinically important β-lactamases in *Acinetobacter baumannii*: the IMP-1 metallo-β-lactamase (class B) and OXA-24 β-lactamase (class D).

Drug-likeness was assessed using the QED index, with a cutoff of ≥ 0.50, consistent with established thresholds for drug-like molecules (Bickerton *et al*., 2012). Many rejected ligands were excluded because they failed basic physicochemical constraints, such as excessive molecular weight, poor solubility, or unfavorable polarity. The QED-passing compounds underwent further evaluation for Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties using ADMETlab 3.0. Parameters included human intestinal absorption (HIA), oral bioavailability, plasma protein binding (PPB), blood–brain barrier penetration, and cardiotoxicity (hERG inhibition). In addition, hepatotoxicity and genotoxicity were considered, as these remain common liabilities in drug development.

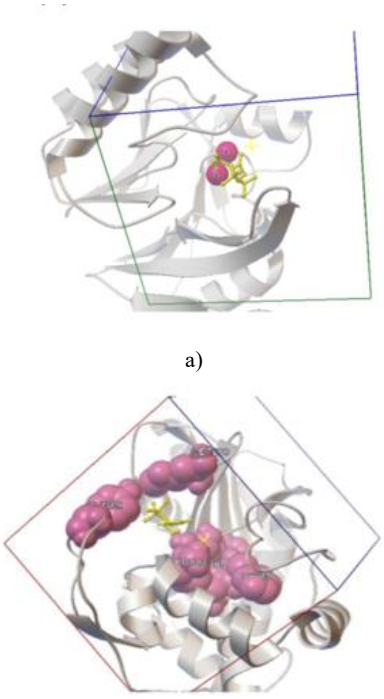
Twenty-three (23) compounds passed the full panel of ADMET and QED criteria. These included flavonoid derivatives (e.g., negundoin analogues), terpenoid lactones (e.g., kuguacin P), and alkaloid scaffolds (e.g., balsamiferine D). Importantly, these 23 compounds displayed favorable oral bioavailability and low predicted toxicity **(Table 1)**, supporting their candidacy for downstream docking studies.

**Table 1.** Quantitative Estimate of Druglikeness (QED) and Predicted ADMET Profiles of Top Hits

| Compound | HIA (%) | BBB Penetration | Oral Bioavailability | hERG Risk | Hepatotoxicity | QED |
|---|---|---|---|---|---|---|
| **Kuguacin P** | High | Low | Moderate | None | None | 0.62 |
| **Negundol 1b** | High | Negligible | High | None | None | 0.69 |
| **Negundoin A** | High | Low | High | None | Low | 0.53 |
| **Negundoin E** | Moderate | Low | High | Low | None | 0.70 |
| **Balsamiferine D** | High | Low | Moderate | None | None | 0.61 |

*Validation of Docking Protocol*

To ensure the reliability of docking simulations, blind docking was performed using the control drug sulbactam—a known β-lactamase inhibitor (Penwell, 2015). The docking reproduced experimentally reported active sites in both IMP-1 and OXA-24 **(Figure 1)**, confirming the robustness of the grid box parameters and search algorithm (Lamarckian Genetic Algorithm, AutoDock4). For IMP-1, sulbactam docked within the zinc-coordinated catalytic groove, interacting with key residues (His116, His118, His196, Asp120) that stabilize the two zinc ions essential for hydrolysis (Pongchaikul & Mongkolsuk, 2022). For OXA-24, sulbactam localized within the STFK tetrad-centered active site, forming hydrogen bonds with Ser81 and stacking interactions with Tyr112 and Met223 side chains, consistent with crystallographic data (Santillana *et al*., 2007).



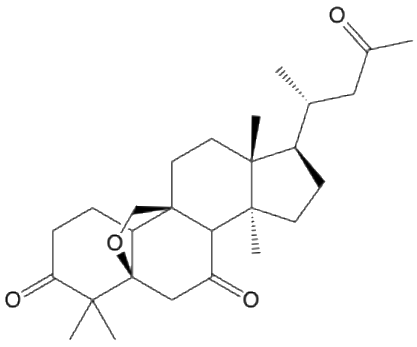
a)

b)

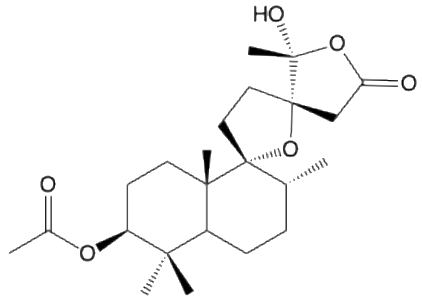
**Figure 1**. Docking pose of sulbactam from blind docking with a) IMP-1 metallo-β-lactamase and b) OXA-24 β-lactamase, showing alignment within the predefined grid box corresponding to literature-identified active sites.

*Molecular Docking of Phytochemicals*

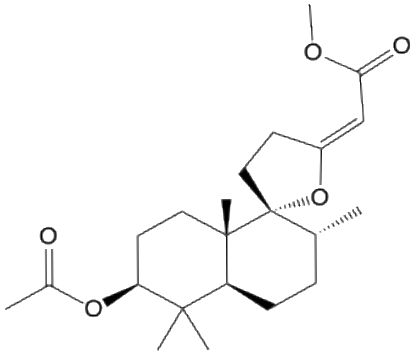
The 23 screened ligands were docked into the validated binding pockets of IMP-1 and OXA-24. Average binding energies reached as high (i.e., most negative) as –10.9 kcal/mol, with several ligands outperforming sulbactam (–6.7 kcal/mol). The top hits **(Figure 2)** included Kuguacin P, Negundol 1b, Negundoin A, Negundoin E, and Balsamiferine D, listed in decreasing order of average binding energy against the two targets **(Table 2)**.



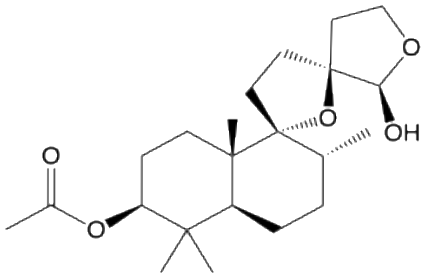
Kuguacin P



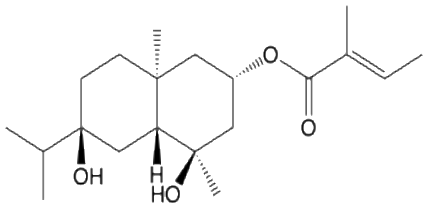
Negundol 1b



Negundoin A



Negundoin E



Balsamiferine D

**Figure 2.** Chemical structures of the top five hits from molecular docking studies.

**Table 2.** Molecular Docking Results of Top Five Compounds vs. Control Drug

| Compound | Plant Source | Docking Score (kcal/mol) with IMP-1 | Docking Score (kcal/mol) with OXA-24 | Average Docking Score (kcal/mol) |
|---|---|---|---|---|
| **Kuguacin P** | *Momordica charantia* | –11.4 | –10.3 | –10.9 |
| **Negundol 1b** | *Vitex negundo* | –7.0 | –8.0 | –7.5 |
| **Negundoin A** | *Vitex negundo* | –7.2 | –7.6 | –7.4 |

| | | | | |
|---|---|---|---|---|
| **Negundoin E** | *Vitex negundo* | –7.0 | –7.7 | –7.4 |
| **Balsamiferine D** | *Blumea balsamifera* | –7.7 | –6.9 | –7.3 |
| **Sulbactam*** | synthetic | –7.2 | –6.1 | –6.7 |

* Control

*In silico* analysis of several IMP-type metallo-β-lactamases (MBLs) revealed that the conserved sequence in the active site consists of His95, Phe96, His97, Asp99, Ser100, His157, Cys176, and His215. These enzymes contain two zinc (II) ions bound to the active site (Palacios *et al*., 2020; Chidambaranathan & Culathur, 2022; Pongchaikul *et al*., 2022; Macrì *et al*., 2023; Fiodorova, 2024), which were included in the binding site set for molecular docking analysis with IMP-1. The docking results showed that the active site residues interacted with the top 5 docked ligands, which were identified based on binding energies. Notably, His157 and His215 were consistently involved in interactions across all top hits. Although their direct role in IMP-1 resistance remains unclear, both are coordinated with one of the zinc atoms in the active site (Shakibaie *et al*., 2017; Chidambaranathan & Culathur, 2022; Pavithra *et al*., 2023).

Other active site residues, including His95, Phe96, His97, and Asp99, also demonstrated interactions with the ligands. Some ligands exhibited a higher number of interacting residues compared to the control drug, suggesting stronger binding affinity and a potentially greater inhibitory effect against IMP-1. These findings underscore the importance of further investigation into the functional significance of conserved residues and their role in ligand binding and enzyme inhibition.

The binding site for molecular docking with OXA-24 was defined to include the STFK tetrad and the tunnel-like entrance formed by Tyr112 and Met223. The conserved Ser residue within the STFK tetrad is crucial for catalytic activity, and ligand interaction with this residue may indicate probable inhibition of OXA-24 (Palacios *et al*., 2020). Docking results showed that all top 5 phytochemical ligands interacted with Ser81, while also engaging Tyr112 and Met223, which help orient inhibitors toward the active center. Previous in silico studies demonstrated that occupying this tunnel-like entrance, as in the case of QPX7728, contributes to vigorous inhibitory activity (Lence *et al*., 2021). Additionally, multiple residues interacted with the ligands, suggesting stronger binding affinity and inhibitory potential compared to the control drug.

Kuguacin P, a cucurbitane triterpenoid, ranked first for both IMP-1 and OXA-24 and has been reported to show weak anti-HIV-1 activity *in vitro* (Chen *et al*., 2009; Pavithra *et al*., 2023). Negundoin A, negundoin E, and negundol 1b are derived from *Vitex negundo*(lagundi), a plant with documented antimicrobial activity, including bactericidal effects of its ethyl acetate leaf extract against multidrug-resistant *Klebsiella pneumoniae* (Palaninathan *et al*., 2022). Meanwhile, balsamiferine D is a sesquiterpene derived from Blumea balsamifera (sambong), a plant renowned for its anti-bacterial properties against both Gram-positive and Gram-negative pathogens (Ismail *et al*., 2022). Balsamiferine compounds have also been shown to inhibit LPS-induced nitric oxide production in microglial BV-2 cells (Xu *et al*., 2012). These findings support the potential of the identified phytochemicals as lead compounds for the development of further inhibitors.

The discovery that natural phytochemicals can inhibit both class B (IMP-1) and class D (OXA-24) β-lactamases holds strong clinical promise against carbapenem-resistant *A. baumannii*. Compounds such as Kuguacin P exhibit favorable ADMET properties—high intestinal absorption, low plasma protein binding, and non-hepatotoxic predictions—supporting their potential as druggable adjuvant inhibitors, akin to clavulanic acid in combination with amoxicillin. Unlike conventional synthetic scaffolds, these phytochemicals derive from traditional medicinal plants, offering ethnopharmacological validation and a novel chemical space. This study is the first to highlight Kuguacin P, negundoin derivatives, and Balsamiferine D as dual inhibitors of IMP-1 and OXA-24, expanding the landscape of plant-derived β-lactamase inhibitors beyond prior flavonoid-based reports.

## Conclusion

This study systematically identified and evaluated phytochemicals from the Philippines' *10 Halamang Gamot* (Medicinal Plants) as potential inhibitors of two critical β-lactamases in *A. baumannii*. Through QED and ADMET filtering, molecular docking, and interaction analyses, five phytochemicals emerged as promising candidates, with Kuguacin P consistently demonstrating the strongest dual inhibitory potential against IMP-1 and OXA-24. These findings underscore the untapped potential of Philippine medicinal plants in antimicrobial drug discovery, offering a compelling rationale for experimental validation and further optimization.

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**Conflict of interest:** None

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**Ethics statement:** None

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