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Literature Review on the Ethnobotany, Phytochemistry, Pharmacological, Molecular Docking Study of *Vitex madiensis* Oliv. (Lamiaceae) and New Research Perspectives

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ABSTRACT

Introduction
Vitex madiensis (Lamiaceae) is a medicinal plant widely utilized in traditional African medicine for its antimicrobial, anti-inflammatory, and hepatoprotective properties. Its rich phytochemical diversity, including flavonoids, terpenoids, and iridoids, has garnered attention for its potential in combating antimicrobial resistance, particularly against β-lactamase-producing bacteria, which are major contributors to global antibiotic resistance.

Purpose
This study aims to review the ethnobotanical, phytochemical, and pharmacological properties of *Vitex madiensis*, evaluate the molecular docking potential of its bioactive compounds against β-lactamase (PDB ID: 1fco), and assess their pharmacokinetic and toxicological profiles to explore their viability as antimicrobial agents.

Methods
A total of 60 chemical compounds from *Vitex madiensis* and related *Vitex* species were analyzed. Molecular docking was performed using AutoDock Vina to evaluate interactions with β-lactamase, with gentamicin serving as the reference molecule. Pharmacokinetic and toxicological analyses were conducted on 54 compounds to predict drug-likeness, toxicity, and interaction profiles.

Results
Molecular docking revealed nine compounds with significant interactions. Among them, 3-epi-maslinic acid demonstrated the highest binding affinity (-8.8 kcal/mol), outperforming gentamicin (-8.3 kcal/mol). Other compounds, including kaempferol, luteolin, and vitetrifolin C, exhibited promising affinities (-7.9 to -8.2 kcal/mol). Pharmacokinetic analysis indicated that most compounds were non-toxic, with 8-epi-sclareol, citronellyl acetate, rotundifaran, vitexifolin E, and vitexifolin C exhibiting optimal drug-like properties. However, caution is warranted due to potential drug interactions observed in certain compounds.

Conclusion
This review highlights the therapeutic potential of *Vitex madiensis* as a cost-effective and accessible source for antimicrobial drug development, particularly against β-lactamase-producing bacteria. The integration of molecular docking with pharmacokinetic predictions provides novel insights into the synergistic potential of its bioactive compounds. Future research should further explore these findings through in vitro and in vivo studies.

INTRODUCTION

Infectious diseases remain a critical public health concern worldwide due to their prevalence, severity, and the limited accessibility to healthcare in many regions (Traoré et al., 2012; Aliyu et al., 2022). Antibiotics have historically served as a cornerstone in combating microbial infections. However, the rapid and widespread emergence of antimicrobial resistance (AMR) has undermined their efficacy, creating an urgent global health challenge (Dabur et al., 2007; N'tcha et al., 2017). The misuse and overuse of antibiotics in human and animal health are significant drivers of AMR, contributing to approximately 4.95 million deaths globally in 2019, which were linked to resistant bacterial infections (Public Health Agency of Canada, 2022; Kevin et al., 2024; Sayem et al., 2025). This rising resistance highlights the pressing need for alternative antimicrobial agents, including natural products derived from medicinal plants.

In traditional Congolese medicine, *Vitex madiensis* Oliv. (Lamiaceae) holds a central role in treating various ailments. Its fruits are consumed as a food source, while the plant's leaves, roots, and bark are widely used for therapeutic purposes, including the management of coughs, diarrhea, colds, dysentery, diabetes, and anemia. Across Africa, its applications extend to treating conjunctivitis, fever, jaundice, respiratory issues, and leprosy, among others (Latham, 2004; Lengbiye et al., 2018, 2020). The plant's reported anti-inflammatory and anthelmintic properties (Boungou-Tsona, 2023), along with its phytochemical richness—particularly in terpenoids and flavonoids—underscore its potential as a source of bioactive compounds with antioxidant, antiviral, anticancer, and antihyperglycemic effects (Vianney et al., 2023).

Despite these promising attributes, limited pharmacokinetic and molecular docking studies have been conducted on compounds from *Vitex madiensis* and the broader *Vitex* genus. This review seeks to address this gap by (1) synthesizing existing ethnobotanical, phytochemical, and pharmacological knowledge on *Vitex madiensis*, (2) performing molecular docking to elucidate key interactions between bioactive compounds and microbial targets, and (3) evaluating pharmacokinetic properties to enrich the databases of natural compounds. By integrating these insights, this study aims to provide a scientific foundation for the development of antimicrobial phytomedicines derived from *Vitex madiensis* and related species.

Molecular docking offers valuable atomistic insights into molecular recognition, making it a critical tool in medicinal chemistry and drug discovery. This review identifies *Vitex madiensis* as a promising candidate for antimicrobial drug development, warranting further exploration in preclinical and clinical studies.

METHODOLOGY

Literature Review

A literature review was conducted to gather information on the phytochemistry and pharmacological properties of *Vitex madiensis* Oliv. from scientific databases such as Google Scholar, PubMed, ScienceDirect, PubMed Central, and SciLEO. Keywords used included the scientific name of the plant (*Vitex madiensis*), along with terms such as "pharmacological" and "phytochemistry." Inclusion criteria focused on peer-reviewed scientific articles published in English or French between 2000 and 2024, specifically addressing the chemical composition and biological activities of *Vitex madiensis* and other species within the genus *Vitex*. Non-peer-reviewed sources and studies with incomplete data were excluded.

Justification for Choosing β-Lactamase as a Molecular Target

β-Lactamases (EC 3.5.2.6) are enzymes responsible for bacterial resistance to β-lactam antibiotics (penicillins, cephalosporins, monobactams, and carbapenems). They catalyze the hydrolysis of the amide bond in the β-lactam ring, rendering these antibiotics ineffective. The selection of β-lactamase (PDB ID: 1fco) as a molecular target is based on its critical role in bacterial resistance and the potential antibacterial properties of *Vitex madiensis*. The bioactive compounds in this plant, such as flavonoids and terpenes, may inhibit this enzyme, helping to restore antibiotic efficacy and disrupt bacterial cell wall synthesis.

Selection of Ligands

The chemical compounds of *Vitex madiensis*, known for their biological properties, were selected as potential ligands. These include flavonoids, terpenes, alkaloids, and iridoids, which are recognized for their antimicrobial

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activity. The selection was based on their relevance to the traditional uses of the plant and prior reports of bioactivity.

Preparation of Proteins and Ligands

The 3D crystal structure of β-lactamase (PDB ID: 1fco) was downloaded from the RCSB Protein Data Bank. Protein preparation involved removing water molecules (except those involved in protein-ligand interactions), adding hydrogen atoms, and verifying the integrity of amino acid residues. The structures of candidate molecules were drawn using ChemBioDraw Ultra 12.0 and optimized using PyRx with the UFF2 force field. The molecules were saved in PDBQT format for docking studies.

Molecular Docking

Molecular docking was performed using AutoDock Vina within Discovery Studio 2020 to evaluate interactions between bioactive compounds and β-lactamase. This structure-based method predicts the positions and conformations of ligands within the protein's active site. Scoring functions were used to calculate the ligand-receptor interaction affinity and identify the most stable complexes (Mpiana et al., 2020).

Validation and ADMET Analysis

The docking results were validated by cross-referencing the data with the SeamDock server to confirm the antibacterial properties of the compounds (Menga et al., 2024). The pharmacokinetic and toxicological properties (ADMET) of the selected compounds were analyzed using the pkCSM tool (Pires et al., 2015). This analysis identified promising compounds with favorable characteristics in terms of absorption, distribution, metabolism, excretion, and toxicity.

This rigorous methodology, integrating traditional knowledge, computational tools, and pharmacokinetic analyses, aims to explore the antimicrobial potential of *Vitex madiensis* compounds against β-lactamase.

BOTANICAL DESCRIPTION

In 1753, Linnaeus described the genus *Vitex* (Lamiaceae). Currently, this genus comprises between 250 and 300 species of shrubs and trees, with some rarely growing as lianas, and typically reaching heights of 1.5 to 3 m. These plants are distributed across tropical and subtropical regions (Ngbolua et al., 2014) and sometimes form shrubs or small trees, often as suffrutices less than 50 cm tall. The leaves are composed of three rigid leaflets, each up to 25 cm long. When cut, they emit a pleasant odour. The edges are shallowly serrated, with rounded teeth. The flowers are pinkish-white with violet or blue lobes.

The fruits are ellipsoid-oblong, fleshy, black, and often spotted with white, enclosed in a persistent calyx. They are approximately 2.5 cm long, with a shiny green exterior that turns blackish upon maturation. These fruits are edible, sweet, and thirst-quenching. They are typically small, succulent, and globular or ovoid drupes, measuring 0.2 to 2 cm in length (usually less than 2 cm). The hardened endocarp is divided into four pyrenees, each containing a single seed (de Kok, 2008). The fruits of different *Vitex* species share similar morphological characteristics, making differentiation challenging. The pulp of ripe fruits varies in colour from dark purple to brown (Chantaranothai et al., 2011).

Figure 1:
Leaves of *Vitex madiensis* Oliv. (www.google image.com)

GEOGRAPHICAL DISTRIBUTION

Vitex madiensis is found in tropical and subtropical regions, including the Democratic Republic of the Congo, Republic of the Congo, Senegal, Uganda, Gabon, Guinea-Bissau, Kenya, Mali, the Central African Republic, Somalia, Angola, Zambia, Zimbabwe, and Mozambique.

ETHNOBOTANY AND PHARMACOLOGY OF *Vitex madiensis* Oliv. AND *Vitex* spp.

Ethnobotany

Vitex madiensis is widely recognised for its therapeutic properties in traditional medicine, particularly for treating infections, malaria, and gastrointestinal disorders (Lengbiye et al., 2018, 2020). Historically, the *Vitex* genus

has been extensively used in traditional medicine and continues to have several ethnopharmacological applications. These include the treatment of bacterial infections, premenstrual and gynaecological ailments, venomous animal bites, gastrointestinal disorders, and inflammation. It has also been used as an insect repellent (Padmalatha et al., 2009).

Several *Vitex* species, including *V. mollis, V. pyramidata, V. pubescens, V. agnus-castus,* and *V. gaumeri*, exhibit analgesic, anti-inflammatory, antidysenteric, and antitumour properties. These species are traditionally used to treat scorpion stings and gastrointestinal disorders. In Ayurvedic and Unani medicine, the leaves and seeds of *V. negundo* are widely used to treat rheumatism and inflammatory joint disorders (Argueta et al., 1994). The insecticidal properties of *V. glabrata, V. leucoxylon, V. penduncularis, V. pinnata,* and *V. trifolia* have been demonstrated in India.

Ethanolic extracts of *V. leucoxylon Linn* have been found to significantly inhibit granulation tissue formation, while a cold aqueous infusion has been reported to reduce total serum cholesterol. However, although the flavonoid mixture of *V. leucoxylon* showed acute anti-inflammatory activity, it had no effect on chronic inflammation (Sarma et al., 1994).

In ethnomedicine, the fruits of *V. madiensis* are sweet, edible, and refreshing. A decoction of the young leaves is used to treat cough, fever, diarrhoea, and dysentery (Lengbiye et al., 2018). In other parts of Africa, the leaves, fruits, stems, and root bark of this species are used to treat conjunctivitis, malaria, cholera, headaches, respiratory problems, epilepsy, diabetes, oral candidiasis, sickle-cell anaemia, malnutrition, and jaundice (Boungou-Tsona, 2023).

The phytochemical profile of *V. madiensis* is rich in secondary metabolites, including anthraquinones, coumarins, flavonoids, terpenoids, iridoids, and phenolic acids. It also contains phytoecdysteroids such as 20-hydroxyecdysone, ajugasterone C, vitexirone, and pterosterone (Lengbiye et al., 2020; Boungou-Tsona, 2023). Additionally, this plant contains various diterpenes and flavonoids, which exhibit pharmacological and toxicological properties, including antifertility, antioxidant, antihyperglycaemic, antiviral, and anticancer activities. Some of these compounds also display cytotoxic effects (Vianney et al., 2023).

Nutritional Characteristics of Vitex Fruits

Fruits are essential components of the human diet, providing key nutrients such as vitamins, minerals, and fibre. Recently, functional foods and nutraceuticals, which offer health benefits beyond basic nutrition, have gained importance in the human diet. These include fruits such as grapes, cranberries, bilberries, and pomegranates, which are associated with improved health and longevity (Kaliora et al., 2007).

Many *Vitex* species produce edible fruits. Nearly 70 species have been documented in Africa alone, where they are commonly known as "chocolate berries." These wild berries play a crucial role in food security and sustainable development for several African communities. Some species, such as *V. madiensis, V. doniana, V. fischeri, V. grandifolia, V. payos, V. simplicifolia, V. mombassae, V. ferruginea,* and *V. pooara*, are commercially valuable in these regions (NRC, 2008).

Vitex fruits are consumed in various forms, including boiled preparations with sugar, as well as fresh or dried products (NRC, 2008). Research has explored new product developments based on these berries. For instance, Egbekun et al. (1996) demonstrated that the pulp of *V. doniana* is suitable for producing syrups with organoleptic properties comparable to those of honey. In Mexico, *V. mollis* is used for sweet preparations that can be consumed alone or mixed with milk, although the properties of these products remain largely unexplored (Montiel-Herrera et al., 2004).

Essential Oils from Vitex spp. Fruits

Fruits of the *Vitex* genus are a significant source of essential oils, with *Vitex agnus-castus* being the most extensively studied species. The primary constituents of its essential oil include 1,8-cineole, sabinene, and α-pinene. Notably, its chemical composition remains relatively consistent across different stages of fruit maturity (Novak et al., 2005; Stojkovic et al., 2011).

The therapeutic efficacy of *V. agnus-castus* essential oil varies depending on its source (leaf or fruit). However,

both extracts have been shown to alleviate symptoms associated with gynaecological disorders (Lucks et al., 2003).

Table 1:
Uses of *Vitex madiensis* Oliv. in Traditional African Medicine (Boungou-Tsona, 2023)

Organ Used	Pathology	Preparation Method	Treatment Dosage	Country	Reference
Bark, root, and stem leaves	Fever, malaria, antipyretic, and migraine	Maceration and decoction	Head wash with decoction	DRC, RCA, Gabon, and Mali	Ondo et al. (2012)
Trunk bark, flowers, and young leaves	Diarrhoea, dysentery, cholera, abdominal pain, and stomach ache	Maceration and decoction (1 L)	100 mL, 3x/day for adults; 1 teaspoon for children; chew and swallow juice	Congo, RCA, Uganda, and Mali	Diafouka (1997)
Leaves	Difficult childbirth and labour pains	Warm water	Bath	Angola	Boungou-Tsona (2023)
Leaves and bark	Fertility in women and men, sexual impotence, and oral candidiasis	Maceration	-	Congo	Lautenschläger et al. (2018)
Leaves juice, scraped bark, and root	Earaches, deafness, eye disorders, dental pain, and bleeding after tooth extraction	Juice and decoction	1 drop per ear, 1 drop per eye, cold gargle	Congo, RCA, Mali, and Angola	Lautenschläger et al. (2018)
Bark, leaves, and roots	Urogenital infection, urinary diseases, cystitis, tubal pain, and ovarian cysts	Maceration	-	Congo	Boungou-Tsona (2023)
Trunk bark and dried leaves	Anaemia, sickle cell disease, and malnutrition	Decoction and infusion	Bath	Congo and DRC	Delaude (1978)
Trunk bark and leaves	Nervous disorders, epilepsy, and insomnia	Decoction and sprinkling	Bath, juice, 2 drops in each nostril, 1x/day	Congo	Diafouka (1997)
Root powder, inner part of bark, root, and leaves	Lactation disorders, soiled breast milk, wounds, and scars	Dissolve in water and filter, decoction. Juice from the inner part of the bark on the wound	20 mL/day, rub breasts with crushed leaves, bath, local application	DRC and Guinea-Bissau	Kibungu (2003)
Leaves, stem, and bark	Back pain, arthritis, and rheumatism	Decoction (1 L of water), sprinkling, fumigation, and infusion	200 mL, 3x/day, steam bath, leaves massage	Congo and Angola	Diafouka (1997); Lautenschläger et al. (2018)
Root and bark	Diabetes	Decoction	100 mL, 3x/day for adults; 1 teaspoon for children	Congo and DRC	Kibungu (2003)
Fruit	Food	-	-	Mali	Malgas (1992)
Root and bark	Haemorrhoids	Burnt root and decoction	Ointment on the anus	Uganda and DRC	Makumbelo et al. (2008); Lautenschläger et al. (2018)
Leaves	Pregnancy disorders, pregnancy care, and menstrual disorders	Maceration	-	Guinea-Bissau and Mali	Catarino et al. (2016); Danton (2017)
Leaves	Arterial hypotension	Decoction	-	Congo	Kimpouni et al. (2018)

Table 2:
Pharmacological Activity of *Vitex madiensis* Oliv. and *Vitex* spp.

Plants or Extracts	Pathology	Micro-organisms or Biological Material	Bio-activities	Methods	Country	Reference
V. doniana, *V. keniensis*, and *V. fischeri* (methanol-acetone-water extracts 6:3:1 v/v)	-	-	Antioxidant activity	DPPH, FRAP, and NO scavenging	Kenya	Stojkovic et al. (2011)
Vitex agnus-castus essential oil	-	*Staphylococcus aureus*, *Micrococcus flavus*, *Bacillus subtilis*, *Salmonella typhimurium*, *Escherichia coli*, and	Antimicrobial (MIC = 44.5–445 µg/mL for bacteria; MIC = 44.5–219 µg/mL for fungi)	Micro-dilution	-	Lengbiye et al. (2018)

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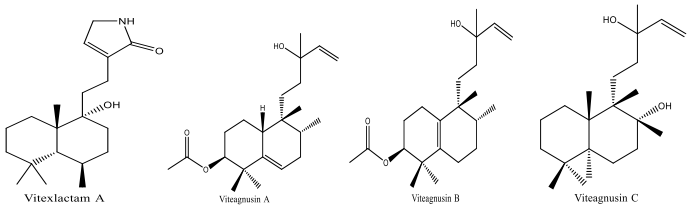
Plants or Extracts	Pathology	Micro-organisms or Biological Material	Bio-activities	Methods	Country	Reference
		fungi (*Alternaria alternata*, *Aspergillus flavus*, *Aspergillus niger*, etc.)				
Vitex madiensis Oliv. (CH_2Cl_2, *EtOAc*, *MeOH* extracts, and *Lbut* fraction of leaves and stem bark)	Malaria	*Plasmodium falciparum* (*MRC-5* and *THP1* cells for cytotoxicity activity)	Antiplasmodial activity (FCB strain and field isolates, IC50 = 0.53–4.87 µg/mL) and cytotoxicity	DELI assay (antiplasmodial activity) and MTT tetrazolium salt colorimetric assay (cytotoxicity)	Gabon	Lengbiye et al. (2018)
Vitex madiensis Oliv. (aqueous extracts)	Diabetes	*Cavia porcellus* (animal model)	Antihyperglycemic and hypoglycemic activities (43% reduction in normal blood glucose levels)	Oral glucose tolerance test (OGTT)	DRC	Lengbiye et al. (2018)
Vitex negundo and *Emblica officinalis* roots (methanolic extracts)	-	*Vipera russellii* and *Naja kaouthia*	Lethal antagonistic action	-	-	Lengbiye et al. (2018)
Vitex negundo Linn (petroleum ether and crude aqueous extracts of leaves)	Malaria	*Culex tritaeniorhynchus* larvae	Larvicidal activity	-	India	Guha et al. (2010)
Vitex negundo Linn	Helminthiasis	Indian earthworm *Pheretima posthuma*	Anthelmintic activity	-	India	Guha et al. (2010)
Vitex madiensis Oliv. (ethanolic and organic acid extracts)	Helminthiasis	DRC earthworm *Behamia rosea Michaelsen* and *Behamia itoliensis Michael*	Anthelmintic activity	-	DRC	Lengbiye et al. (2020)
Vitex madiensis Oliv. (ethanolic and organic acid extracts)	Bacterial infection	*Escherichia coli* ATCC 27195, *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 9027	Antibacterial activity (MIC ≥ 1000 µg/mL)	Micro-dilution method	DRC	Lengbiye et al. (2020)
Vitex madiensis Oliv. (ethanolic and organic acid extracts)	-	-	Antioxidant activity (*Organic acid extracts*: 40.74 ± 6.76 µg/mL with ABTS; *Ethanolic extracts*: 35.66 ± 4.80 µg/mL with ABTS and 59.70 ± 28.52 µg/mL with DPPH)	DPPH and ABTS methods	DRC	Lengbiye et al. (2020)
Vitex madiensis Oliv. (leaves, trunk bark, fruit, and root bark extracts)	Pain and inflammation	-	Antioxidant and anti-inflammatory activities (20-hydroxyecdysone significantly inhibited ROS production by 73% and COX-2 by 70%)	Anti-free radicals (DPPH), antioxidant (ROS)	Republic of the Congo	Boungou-Tsona (2023)

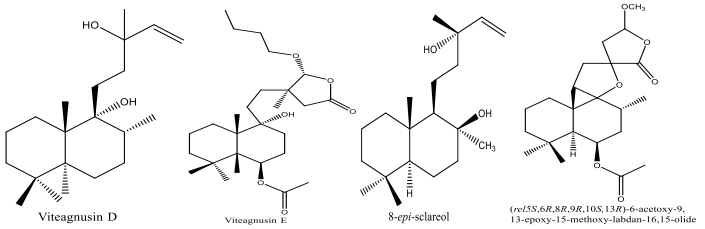
Phytochemical Study

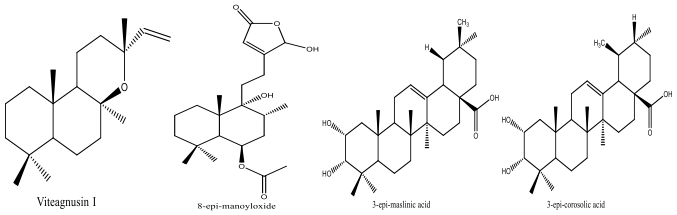
The phytochemical profile of *Vitex madiensis* is dominated by various secondary metabolites, including anthraquinones, coumarins, flavonoids, terpenoids, iridoids, phenolic acids, and phytoecdysteroids such as 20-hydroxyecdysone, ajugasterone C, vitexirone, and pterosterone (Lengbiye et al., 2020; Boungou-Tsona, 2023).

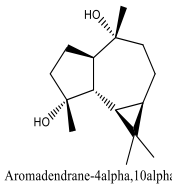
Molecules of Vitex spp.

1. Terpenoids





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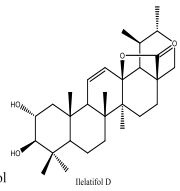
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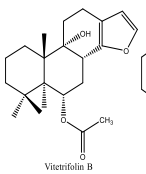
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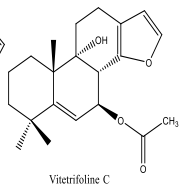
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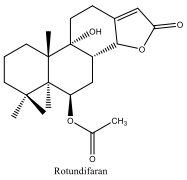
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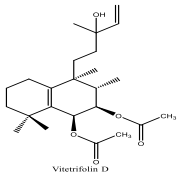
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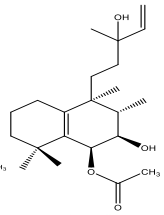
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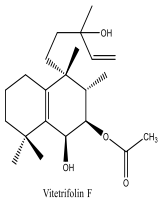
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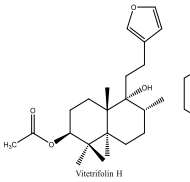
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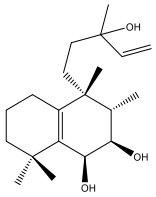
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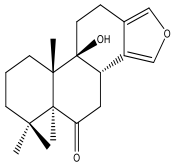
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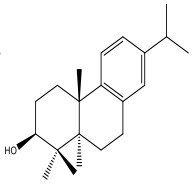
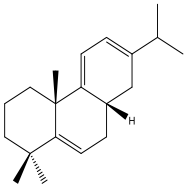
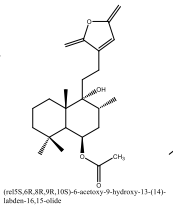
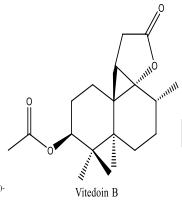
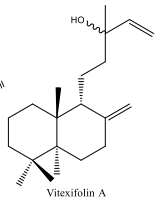
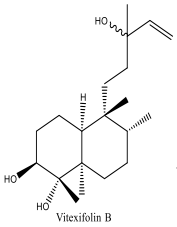

Abietatriene-3 beta-ol


Abietatriene


(re1S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13-(14)-labden-16,15-olide


Vitedoin B


Vitexifolin A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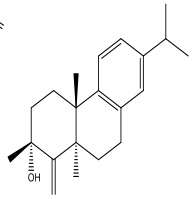
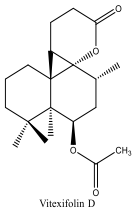
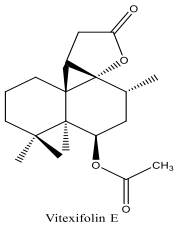
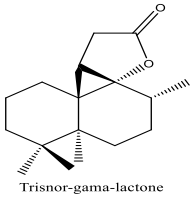
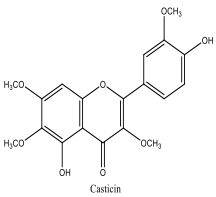

Vitexifolin C

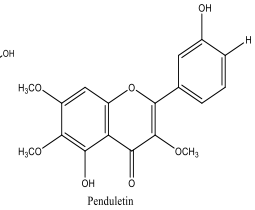

Vitexifolin D

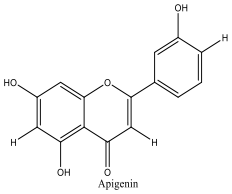

Vitexifolin E

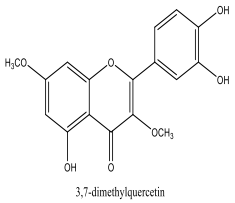

Trisnor-gama-lactone

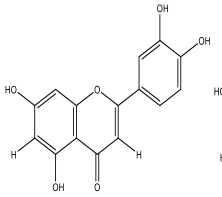
2. Flavonoids

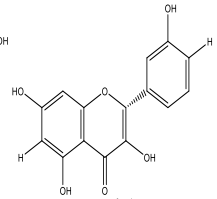

Casticin

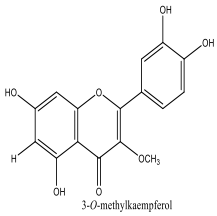

Penduletin

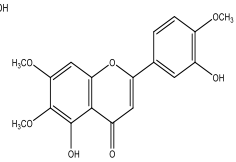

Apigenin

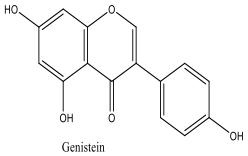

3,7-dimethylquercetin

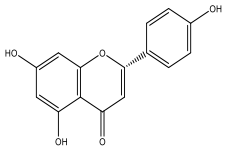

Luteolin

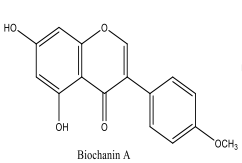

Kaempferol

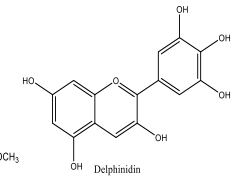

3-*O*-methylkaempferol

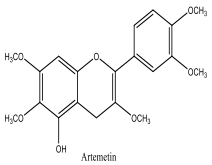

Eupatorin

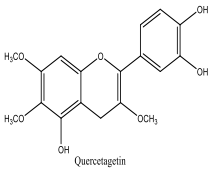

Genistein

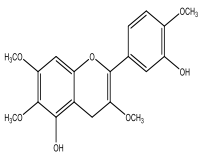

Naringenin


Biochanin A

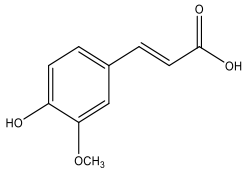

Delphinidin

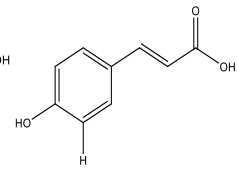

Artemetin

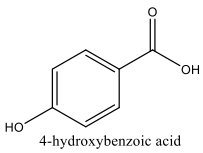

Quercetagetin

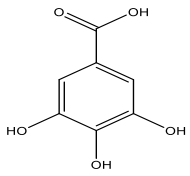

5,3'-dihydroxy-6,7,4'-Kotrimethoxyflavanone

3. Phenolics


Ferulic acid


p-Coumaric acide


4-hydroxybenzoic acid


Gallic acid

Chlorogenic acid

4. Essentials oils

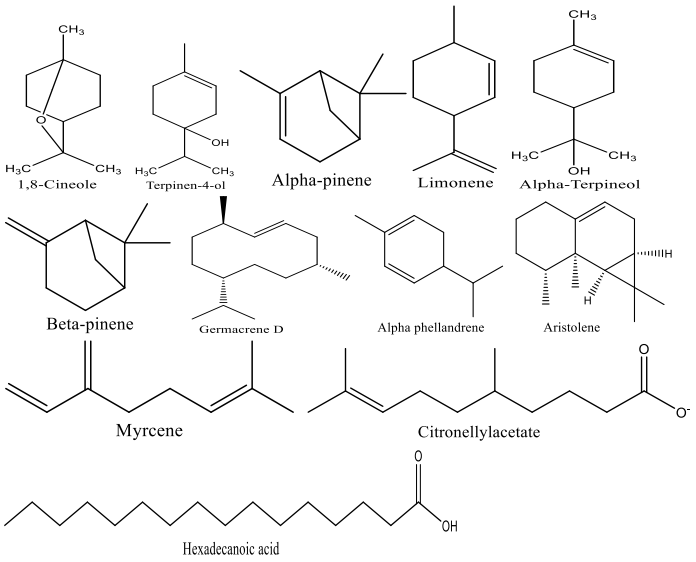


Table 3 presents a series of compounds with varying binding affinities (ΔG values) to β-lactamase, a key target for inhibiting bacterial resistance to antibiotics. Among these, 3-epi-maslinic acid (-8.8 kcal/mol) demonstrates the strongest binding affinity, suggesting its potential as a potent antimicrobial agent. Compounds such as gentamicin (-8.3 kcal/mol), a known antibiotic, serve as a benchmark, indicating that some compounds from *Vitex madiensis* may exhibit comparable antimicrobial activity. Additionally, kaempferol (-7.9 kcal/mol), luteolin (-7.9 kcal/mol), vitetrifolin C (-7.9 kcal/mol), and chlorogenic acid (-7.5 kcal/mol) also demonstrate promising affinities, reinforcing the potential antibacterial properties of *Vitex madiensis*.

Moreover, biochanin A (-7.2 kcal/mol), viteagnusin A (-7.4 kcal/mol), and vitexifolin C (-7.4 kcal/mol) further support the plant's potential for antibacterial applications. These compounds, with strong binding affinities to β-lactamase, may serve as valuable candidates for the development of novel antimicrobial treatments, particularly for combating bacterial infections resistant to conventional antibiotics. They could be explored as lead molecules for new drug development aimed at inhibiting β-lactamase activity and restoring the effectiveness of β-lactam antibiotics, contributing to the fight against antibiotic resistance.

Table 3:
Energetic Affinity Values for Enzyme Receptors and Ligands

N°	Compounds	Energy ΔG (kcal/moL)
01	3,7-dimethylquercetin	-7.3
02	3-epi-maslinic acid	-8.8
03	3-methylquercetin	-7.0
04	3-O-methylkaempferol	-7.3
05	4-hydroxybenzoic acid	-5.3
06	5,3'-dihydroxy-6,7,4'-Kotrimethoxyflavanone	-7.2
07	8-epi-manoyloxide	-7.8
08	8-epi-sclareol	-6.7
09	Abietatriene	-7.3
10	Abietatriene-3 beta-ol	-7.3
11	Alpha phellandrene	-5.0
12	Alpha-pinene	-4.6
13	Alpha-Terpineol	-5.3
14	Apigenin	-7.6
15	Aristolene	-5.6
16	Aromadendrane-4 alpha,10 alpha-diol	-6.1
17	Artemetin	-6.7
18	Bêta-pinene	-4.6
19	Biochanin A	-7.2
20	Casticin	-6.8
21	Chlorogenic acid	-7.5
22	Citronellylacetate	-5.2
23	Delphinidin	-7.7
24	Dihydrosolidagenone	-7.2
25	Eupatorin	-7.7
26	Ferulic acid	-6.2
27	Gallic acid	-5.5
28	Genistein	-7.5
29	Geracrene D	-5.8
30	Kaempferol	-7.9
31	Limonene	-4.7
32	Luteolin	-7.9
33	Naringenin	-7.6
34	p-Coumaric acide	-6.2
35	Penduletin	-6.7
36	Quercetagetin	-7.3
37	(rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13-(14)-labden-16,15-olide	-8.2
38	(rel5S,6R,8R,9R,10S,13R)-6-acetoxy-9, 13-epoxy-15-methoxy-labdan-16,15-olide	-8.1
39	Rotundifaran	-7.4
40	Terpinen-4-ol	-4.9
41	Trisnor-gama-lactone	-7.1
42	Viteagnusin A	-7.4
43	Viteagnusin B	-7.2
44	Viteagnusin C	-6.5
45	Viteagnusin D	-6.4
46	Viteagnusin E	-7.6
47	Viteagnusin I	-6.9
48	Vitedoin B	-7.1
49	Vitetrifolin C	-7.9
50	Vitetrifolin D	-6.5
51	Vitetrifolin E	-6.1
52	Vitetrifolin F	-7.0
53	Vitetrifolin H	-7.5
54	Vitetrifolin I	-6.4
55	Vitexifolin A	-6.3
56	Vitexifolin B	-6.9
57	Vitexifolin C	-7.4
58	Vitexifolin D	-7.3
59	Vitexifolin E	-7.2
60	Vitexlactam A	-7.0
61	Gentamicine	-8.3

Results of the Interaction Between Receptors and Ligands

Figure 2:
Types of interactions between Vitetrifolin C and receptor

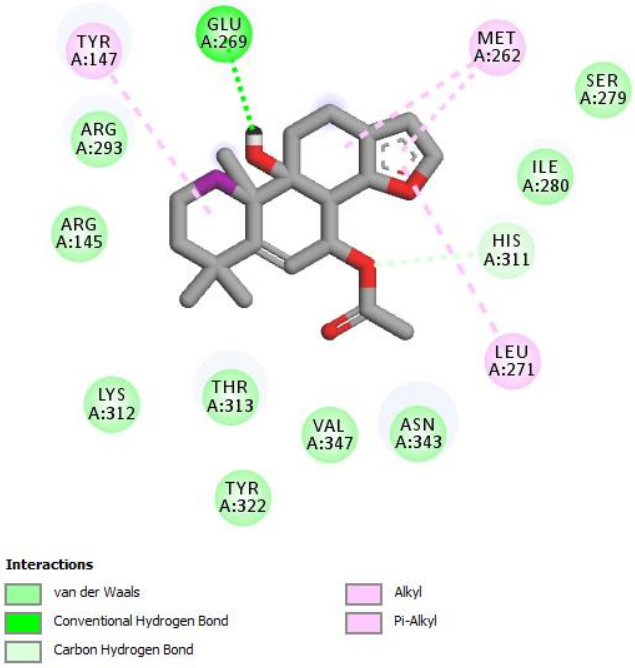


Figure 3:
Types of interactions between 3-epi-maslinic acid and receptor

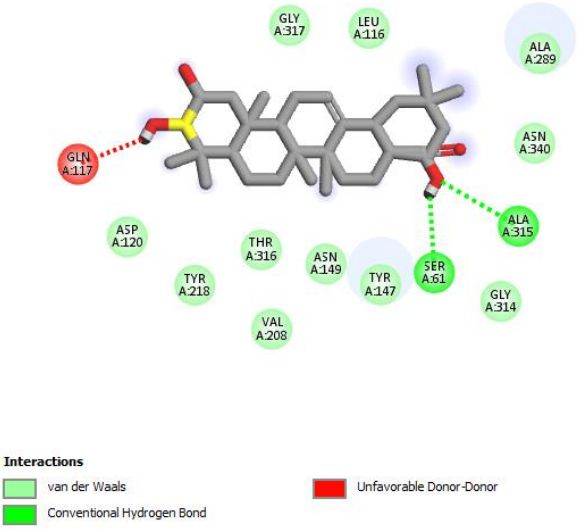


Figure 4:
Types of interactions between 8-epi-monoyloxide and receptor

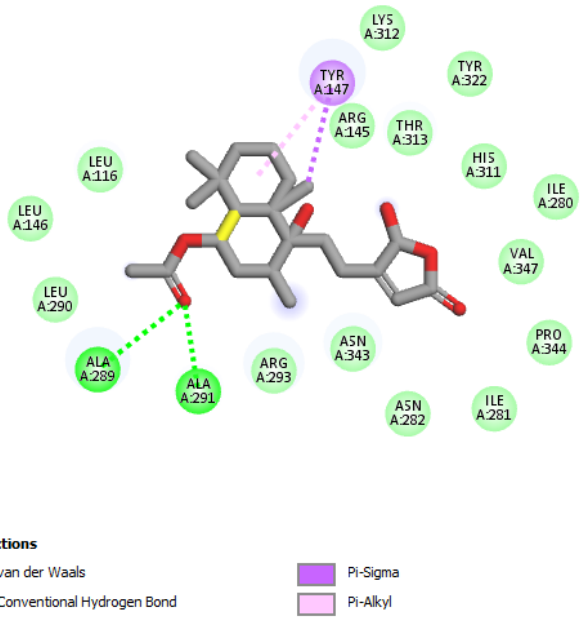
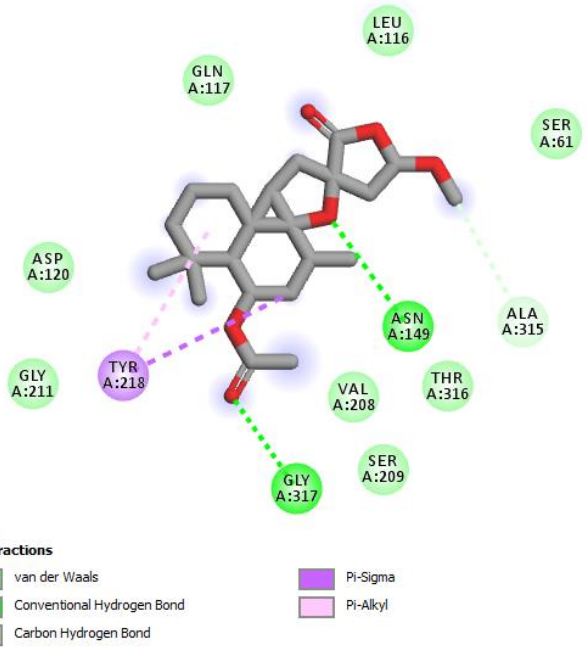


Figure 5:
Types of interactions between (rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13-(14)-labden-16,15-olide and receptor



https://dx.doi.org/10.4314/orapj.v6i2.17

Figure 6:
Types of interactions between Luteolin and receptor

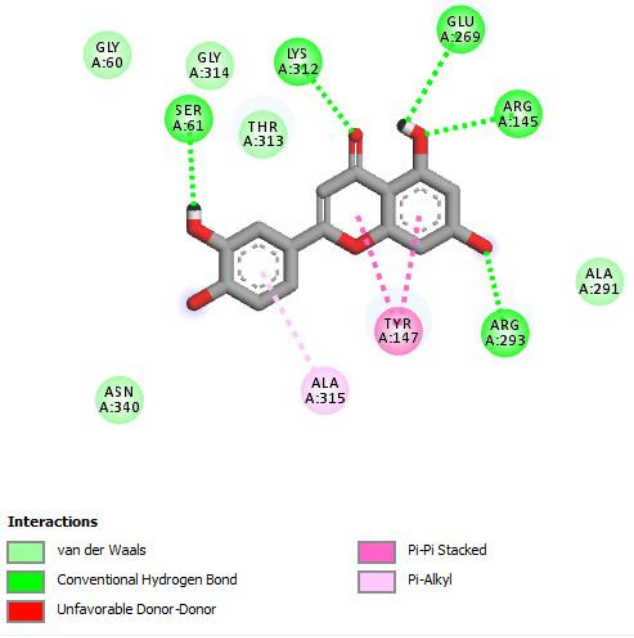
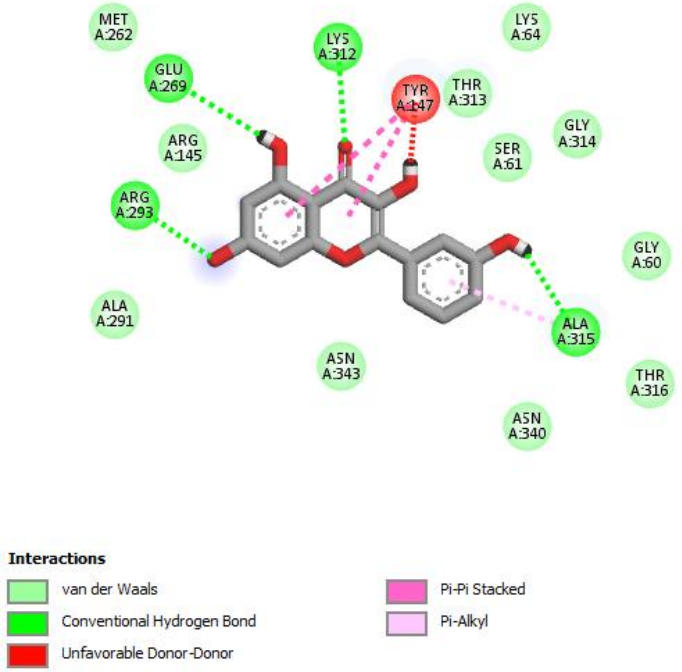


Figure 7:
Types of interactions between Kaempferol and receptor



These Figures illustrate the interactions of selected *Vitex* compounds at the active site of the β-lactamase receptor protein (PDB ID: 1fco) with amino acid residues. The key amino acid residues involved in receptor-ligand interactions include:

- **Vitetrifolin C**: GLU A269, TYR A147, MET A262, LEU A271
- **3-epi-maslinic acid**: GLN A171, ALA A314, SER A61
- **8-epi-manoyloxide**: TYR A147, ALA A289, ALA A291
- **(rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13-(14)-labden-16,15-olide**: ALA A315, ASN A149, GLY A317, TYR A218
- **Luteolin**: GLU A269, ARG A145, TYR A147, ALA A315, SER A61, LYS A312
- **Kaempferol**: LYS A312, TYR A147, ALA A315, ARG A293, GLU A269
- **Eupatorin**: GLU A269, LYS A312, SER A61, ALA A315, TYR A147, ALA A291, ARG A293, ARG A145

The main types of interactions observed include Van der Waals forces, hydrogen bonding, π–π interactions, π–σ interactions, π–alkyl interactions, alkyl interactions, and π–cation interactions.

Molecular docking is employed primarily to predict the binding positions that a ligand can adopt within the active site of a receptor and to determine the conformation of the complex when receptor flexibility is considered. Additionally, scoring functions are used to calculate the interactions between the ligand and receptor in the identified docking positions, leading to a score representative of their binding affinity.

However, compounds that demonstrate high receptor affinities and favourable pharmacokinetic and toxicological properties can undergo further validation, such as molecular dynamics simulations, to refine docking predictions and gain a deeper understanding of molecular interactions.

The *in silico* study of plant-derived chemical compounds, particularly from *Vitex madiensis*, is crucial for understanding the fate of these molecules within the body. From a pharmacokinetic perspective, the journey of these compounds is categorised under Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET).

The absorption phase is directly linked to the mode of administration, ensuring that the molecule reaches its target via systemic circulation. For instance, intravenous

administration ensures direct and complete absorption, whereas oral administration may involve delayed or incomplete absorption (bioavailability). Certain drugs must pass through the intestinal lumen, the portal system, and the liver before reaching systemic circulation. Some compounds may undergo metabolic transformations via enzymatic systems, converting inactive molecules into active forms or facilitating their elimination.

According to the literature, *Vitex madiensis* is considered less toxic (Vianney et al., 2023) and is rich in secondary metabolites. Additionally, it is consumed as an edible plant in the Democratic Republic of the Congo.

Table 4a:
Results of pharmacokinetic properties analysis of compounds from *Vitex* spp.

Propriétés	3,7dq	3epa	3mq	3Omk	4hba	5,3'd6kf	8-epm	8-eps	Abt	Abt3b	AT	Apg	Atl	Aroma	Art	BioA	Cast
Absorption																	
Water solubility	-3.9	-3.35	-3.436	-1.997	-4.381	-3.852	-3.851	-7.247	-5.408	-3.849	-2.039	-3.025	-5.751	-2.613	-4.502	-3.478	-3.792
Caco2 permeability	0.926	0.71	0.452	1.147	1.253	1.004	1.38	1.445	1.605	1.414	1.489	0.952	1.418	1.183	1.355	1.115	0.543
Intestinal absorption (human)	100	77.566	71.181	74.467	93.914	83.053	94.741	97.981	95.181	96.548	94.183	92.532	96.464	94.733	96.619	96.274	69.98
Skin Permeability (log Kp)	-2.729	-2.744	-2.738	-2.434	-2.9	-3.737	-2.82	-2.198	-2.621	-1.508	-2.418	-2.751	-1.742	-2.707	-2.75	-2.757	-2.753
P-glycoprotein substrate	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
P-glycoprotein I inhibitor	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes
P-glycoprotein II inhibitor	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes
Distribution																	
VDss (human, log L/kg)	-1.315	0.024	-0.047	-1.229	0.087	-0.095	0.212	0.821	0.748	0.408	0.207	-0.13	0.77	0.269	-0.305	-0.198	0.001
Fraction unbound (human) (Fu)	0	0.126	0.1	0.541	0.154	0.176	0.105	0	0	0.427	0.565	0.163	0.164	0.365	0.093	0.152	0.143
BBB permeability (log BB)	-0.617	-1.114	-1.308	-0.31	-0.803	-0.197	-0.071	0.82	0.346	0.761	0.305	-1.007	0.828	0.373	-0.938	-0.314	-0.542
CNS permeability (log PS)	-1.481	-2.345	-3.251	-2.896	-2.923	-2.849	-1.672	-1.71	-0.985	-2.049	-2.807	-2.259	-1.785	-2.356	-3.156	-2.226	-3.206
Metabolism																	
CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	No	Yes	No	Yes
CYP1A2 inhibitior	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	Yes	No
CYP2C19 inhibitior	No	No	No	No	Yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes
CYP2C9 inhibitior	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No
CYP2D6 inhibitior	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No
CYP3A4 inhibitior	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes
Excretion																	
Total Clearance (log ml/min/kg)	-0.071	0.356	0.598	0.64	0.641	0.735	0.914	0.954	0.789	0.2	1.219	0.439	0.917	0.792	0.727	0.285	0.709
Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
AMES toxicity	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No
Max. tolerated dose (human)	0.234	0.638	0.756	1.603	0.899	-0.631	-0.606	-0.153	-0.352	0.754	0.886	0.698	0.179	-0.006	1.04	0.809	0.379
hERG I inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
hERG II inhibitor	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No

***Legend**: 3,7dq: 3,7-dimethylquercetin, 3epa: 3-epi-maslinic acid, 3mq: 3-methylquercetin, 3Omk: 3-O-methylkaempferol, 4hba: 4-hydroxybenzoic acid, 5,3'd6kf: 5,3'-dihydroxy-6,7,4'-Kotrimethoxyflavanone, 8-epm: 8-epi-manoyloxide, 8-eps: 8-epi-sclareol, Abt : Abietatriene, Abt3b: Abietatriene-3-bêta-ol, AT: Alpha-Terpineol, Apg: Apigenin, Atl: Aristolene, Aroma: Aromadendrane-4 alpha,10-alpha-diol, Art: Artemetin, BioA: Biochanin A, Cast: Casticin.*

The **Table** includes several important compounds with distinct pharmacokinetic properties, such as 3-epimaslinic acid (3epa), which demonstrates high intestinal absorption (77.566%) and good Caco2 permeability (0.71), indicating potential for oral administration, though it is a substrate for P-glycoprotein, suggesting possible interactions with other drugs. 3-methylquercetin (3mq), with moderate Caco2 permeability (0.452) and high intestinal absorption (71.181%), shows promise for both oral and topical applications. 4-hydroxybenzoic acid (4hba), with a high intestinal absorption rate (93.914%) and significant skin permeability (-2.9), appears suitable for dermatological formulations. 8-epimicrosporin (8-epm) stands out for its very high intestinal absorption (97.981%) and good skin permeability (-2.198), suggesting potential for both systemic and topical therapeutic uses. Lastly, Aptigel (Abt), with moderate absorption (94.183%) and distribution properties, and good blood-brain barrier (BBB) permeability (0.305), could be explored for central nervous

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system applications. These compounds, with their favorable pharmacokinetic profiles and minimal toxicity, offer promising prospects for drug development, with particular attention needed for drug interactions due to P-glycoprotein involvement.

Analysis of the results in Table 4a reveals that eight chemical compounds exhibit good pharmacokinetic and toxicological properties. These compounds are as follows:

1. **3,7dq**: This compound demonstrates low water solubility (log -3.9), but good Caco-2 permeability (0.926) with high human intestinal absorption (100%). It has low skin permeability (log Kp -2.729), is neither a P-glycoprotein substrate nor a P-glycoprotein II inhibitor. The compound exhibits a low volume of distribution (VDss log -1.315), an undetectable unbound fraction (Fu 0), low blood-brain barrier (BBB) permeability (log BB -0.617), and moderate permeability to the central nervous system (CNS) (log PS -1.481). In terms of metabolism, it is a substrate of CYP3A4 and does not inhibit the main CYP enzymes. It has low total clearance (log -0.071) and is not an OCT2 substrate. The compound is non-toxic according to the AMES test, but it exhibits moderate acute toxicity (LD50 2.734) and moderate chronic toxicity (LOAEL 2.018). It is hepatotoxic.
2. **3epa**: This compound has moderate water solubility (log -3.35), moderate Caco-2 permeability (0.71), and average human intestinal absorption (77.566%). It has very low skin permeability (log Kp -2.744) and is a P-glycoprotein substrate, but not a P-glycoprotein inhibitor. It has near-neutral volume of distribution (VDss log 0.024), moderate unbound fraction (Fu 0.126), low BBB permeability (log BB -1.114), and very low CNS permeability (log PS -2.345). It is a CYP1A2 inhibitor but does not inhibit other CYP enzymes. The compound shows moderate total clearance (log 0.356) and is not an OCT2 substrate. It is non-toxic in the AMES test, with moderate acute toxicity (LD50 2.342) and moderate chronic toxicity (LOAEL 1.88). It is not hepatotoxic.
3. **3mq**: This compound demonstrates low water solubility (log -3.436), low Caco-2 permeability (0.452), and moderate intestinal absorption (71.181%). It exhibits very low skin permeability (log Kp -2.738), is a P-glycoprotein substrate, but not a P-glycoprotein inhibitor. It has a low volume of distribution (VDss log -0.047), moderate unbound fraction (Fu 0.1), very low BBB permeability (log BB -1.308), and extremely low CNS permeability (log PS -3.251). It is a CYP1A2 inhibitor and does not inhibit other CYP enzymes. The compound has moderate total clearance (log 0.598) and is not an OCT2 substrate. It is non-mutagenic according to the AMES assay, with moderate acute toxicity (LD50 2.297) and moderate chronic toxicity (LOAEL 1.89). It is not hepatotoxic.
4. **3Omk**: This molecule has moderate solubility (log -1.997), good Caco-2 permeability (1.147), and high intestinal absorption (74.467%). It has low skin permeability (log Kp -2.434) and is neither a P-glycoprotein substrate nor an inhibitor. The volume of distribution is low (VDss log -1.229), and it has a high unbound fraction (Fu 0.541). It demonstrates moderate BBB permeability (log BB -0.31) and very low CNS permeability (log PS -2.896). It is not an inhibitor of the main CYP enzymes. The compound has moderate total clearance (log 0.64) and is not an OCT2 substrate. It is non-mutagenic according to the AMES test, with moderate acute toxicity (LD50 2.014) and high chronic toxicity (LOAEL 2.989). It is not hepatotoxic.
5. **4hba**: This compound has very low water solubility (log -4.381), good Caco-2 permeability (1.253), and high intestinal absorption (93.914%). It has very low skin permeability (log Kp -2.9). It inhibits P-glycoprotein I but is a P-glycoprotein substrate. The volume of distribution is moderate (VDss log 0.087), with a low unbound fraction (Fu 0.154). It demonstrates moderate BBB permeability (log BB -0.803) and very low CNS permeability (log PS -2.923). In terms of metabolism, it is a substrate of CYP3A4 and an inhibitor of CYP2C19 and CYP3A4. The compound has moderate total clearance (log 0.641) and is not an OCT2 substrate. It is non-mutagenic in the AMES test, with moderate acute toxicity (LD50 2.417) and moderate chronic toxicity (LOAEL 2.021). It is not hepatotoxic.
6. **5,3'd6kf**: This compound has poor water solubility (log -3.852), good Caco-2 permeability (1.004), and moderate intestinal absorption (83.053%), which

limits its absorption. It has very low skin permeability (log Kp -3.737) and is a P-glycoprotein substrate, but not a P-glycoprotein I inhibitor. The volume of distribution is moderate (VDss log -0.095), with a moderate unbound fraction (Fu 0.176). It shows moderate BBB permeability (log BB -0.197) and very low CNS permeability (log PS -2.849). The compound is not a substrate or inhibitor of the main CYP enzymes. Its total clearance is moderate (log 0.735), and it is not an OCT2 substrate. It is non-toxic according to the AMES test, with moderate acute toxicity (LD50 3.229) and moderate chronic toxicity (LOAEL 1.785). It is not hepatotoxic.

7. **8-epm**: This compound has low water solubility (log -3.851), high Caco-2 permeability (1.38), and high intestinal absorption (94.741%). It has low skin permeability (log Kp -2.82) and is a P-glycoprotein substrate but not a P-glycoprotein inhibitor. The volume of distribution is moderate (VDss log 0.212), with a low unbound fraction (Fu 0.105). It demonstrates moderate BBB permeability (log BB -0.071) and moderate CNS permeability (log PS -1.672). The compound is neither a substrate nor an inhibitor of the main CYP enzymes. It has moderate total clearance (log 0.914), is a non-substrate of OCT2, and is non-toxic according to the AMES test. It exhibits moderate acute toxicity (LD50 2.532) and moderate chronic toxicity (LOAEL 2.115). It is not hepatotoxic.
8. **8-eps**: This compound has very low water solubility (log -7.247), high Caco-2 permeability (1.445), and high intestinal absorption (97.981%). It has low skin permeability (log Kp -2.198). Metabolically, it is not a P-glycoprotein substrate but a P-glycoprotein II inhibitor. The volume of distribution is high (VDss log 0.821), with an undetectable unbound fraction (Fu 0). It demonstrates high BBB permeability (log BB 0.82) and moderate CNS permeability (log PS -1.71). It is a substrate of CYP3A4 and a CYP1A2 inhibitor.

Among the eight compounds analyzed, **8-eps** stands out for its excellent pharmacokinetic and toxicological properties. This compound has very low water solubility (log -7.247) but high Caco-2 permeability (1.445) and optimal intestinal absorption (97.981%). Its low skin permeability (log Kp -2.198) is offset by a high volume of distribution (VDss log 0.821) and an undetectable unbound fraction (Fu 0), facilitating efficient distribution throughout the body. Furthermore, it exhibits high permeability to the BBB (log BB 0.82) and moderate permeability to the CNS (log PS -1.71). Metabolically, it is a substrate of CYP3A4 and inhibits CYP1A2, indicating a favorable metabolic profile. Although it is not a P-glycoprotein substrate, it inhibits P-glycoprotein II, potentially minimizing adverse drug interactions. Regarding toxicity, this compound is non-mutagenic according to the AMES test, and although it is not specifically mentioned for hepatotoxicity, its overall profile suggests better tolerance compared to the other compounds tested, making it the most promising candidate for drug development.

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Table 4b:
Results of pharmacokinetic properties analysis of compounds from *Vitex* spp.

Propriétés	ChloA	Citro	Delp	Dihso	Eup	Fera	Gala	Gen	Ger	Kae	Lut	Nari	p-Cou	Pend	Quer	relhyd	relep
Absorption																	
Water solubility	-2.684	-3.696	-5.098	-3.555	-2.075	-2.283	-3.208	-5.853	-3.122	-3.083	-3.122	-2.046	-3.837	-3.527	-4.739	-4.764	-4.685
Caco2 permeability	-0.708	1.454	1.41	0.653	0.507	0.023	1.146	1.426	0.528	0.333	1.118	1.152	0.916	0.862	1.518	1.228	1.357
Intestinal absorption (human)	12.805	97.366	94.621	81.738	93.721	44.599	92.893	94.378	79.903	76.09	91.433	95.221	71.67	63.903	100	97.54	99.138
Skin Permeability (log Kp)	-2.735	-2.54	-3.138	-2.773	-2.245	-2.668	-2.736	-1.386	-2.735	-2.74	-2.737	-2.413	-2.785	-2.909	-3.785	-3.363	-4.275
P-glycoprotein substrate	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
P-glycoprotein I inhibitor	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes
P-glycoprotein II inhibitor	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Distribution																	
VDss (human, log L/kg)	-0.531	-0.269	0.432	0.067	-1.281	-0.689	-0.39	0.55	-0.005	-0.272	-0.308	-0.931	0.098	0.326	0.205	0.24	0.223
Fraction unbound (human) (Fu)	0.43	0.352	0.138	0.129	0.395	0.602	0.144	0.257	0.071	0.13	0.162	0.472	0.149	0.209	0.125	0.207	0.194
BBB permeability (log BB)	-1.57	-0.012	0.237	-0.584	-0.245	-1.103	-1.023	0.704	-1.312	-1.207	-1.069	-0.255	-0.235	-1.297	-0.056	-0.488	-0.136
CNS permeability (log PS)	-3.948	-2.009	-1.557	-3.054	-2.558	-3.433	-2.221	-2.118	-2.387	-2.37	-2.185	-2.39	-3.044	-3.056	-2.82	-2.778	-2.798
Metabolism																	
CYP2D6 substrate	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes
CYP1A2 inhibitior	No	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No
CYP2C19 inhibitior	No	No	Yes	Yes	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No
CYP2C9 inhibitior	No	No	No	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	No
CYP2D6 inhibitior	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitior	No	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No
Excretion																	
Total Clearance (log ml/min/kg)	0.369	1.562	0.63	0.693	0.623	0.572	0.236	1.251	0.302	0.569	0.592	0.674	0.352	0.579	0.622	0.45	0.609
Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Toxicity																	
AMES toxicity	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No
Max. tolerated dose (human)	0.796	0.003	-0.576	0.577	0.993	1.128	0.902	0.357	0.867	0.73	0.925	1.018	0.565	0.371	-0.361	-0.138	-0.089
hERG I inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
hERG II inhibitor	No	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No
Oral Rat Acute Toxicity (LD50)	2.347	1.602	2.518	2.207	2.122	2.211	2.291	1.593	2.417	2.338	2.397	2.293	2.007	2.031	2.846	2.149	2.559

***Legend**: ChloA: Chlorogenic acid, Citro: Citronellylacetate, Delp: Delphinidin, Dihso: Dihydrosolidagenone, Eup: Eupatorin, Fera: Ferulic acid, Gala: Gallic acid, Gen: Genistein, Ger: Geracrene D, Kae: Kaempferol, Lut: Luteolin, Nari: Naringenin, p-Cou: p-Coumaric acid, Pend : Penduletin, Quer: Quercetagetin, relhyd: (rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13-(14)-labden-16,15-olide, relep: (rel5S,6R,8R,9R,10S,13R)-6-acetoxy-9, 13-epoxy-15-methoxy-labdan-16,15-olide.*

This Table presents a detailed overview of various compounds, focusing on their pharmacokinetic properties, distribution, metabolism, excretion, and toxicity. **Water solubility** ranges from -5.853 for **Delp** to -2.046 for **Eup**, indicating variability in their solubility. **Caco2 permeability** shows a wide range, with **Citro** having the highest permeability at 1.454 and **Eup** at 0.023, suggesting different potential for absorption across cell membranes. **Intestinal absorption** is high for most compounds, notably **Nari (99.138%)** and **ChloA (12.805%)**, indicating differences in their oral bioavailability. The **skin permeability** values vary significantly, with **Ger** (-1.386) being the most permeable, suggesting it could be more suitable for topical formulations. Regarding **P-glycoprotein** interactions, compounds like **ChloA**, **Dihso**, and **Fera** are substrates, while **Pend** and **Quer** act as inhibitors. The **distribution** parameters show **Gala** (0.55) and **Gen** (0.704) with higher **BBB permeability**, implying potential central nervous system (CNS) effects. **Metabolism** profiles indicate compounds like **Dihso** and **Pend** as substrates for CYP enzymes, including **CYP2C19**, **CYP2C9**, and **CYP3A4**. **Excretion** properties, such as **renal OCT2 substrate**, are observed for **Pend** and **Quer**. Regarding **toxicity**, **ChloA**, **Citro**, and **Dihso** show lower acute and chronic toxicity, while **Fera** demonstrates higher toxicity potential, particularly in **T.Pyriformis** toxicity and **minnow** toxicity. These data provide insights into the pharmacokinetic and toxicological profiles of the compounds, crucial for evaluating their therapeutic and safety potential.

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Analysis of the results in Table 4b indicates that 17 chemical compounds exhibit good pharmacokinetic and toxicological properties. These compounds are:

1. **ChloA**: This compound has moderate water solubility (log -2.684) and low intestinal permeability (12.805%), which limits its absorption. It is a substrate for P-glycoprotein, which may affect its elimination. It has a moderate volume of distribution (log VDss -0.531) and is likely to cross the BBB (log BB -1.57), but with low permeability to the CNS (log PS -3.948). It is also a CYP2D6 substrate, which may influence its metabolism. The compound presents a risk of liver toxicity, potentially limiting its use.
2. **Citro**: This compound has very good water solubility (-3.696) and excellent intestinal absorption (97.366%). It is not a P-glycoprotein substrate and has good permeability across the blood-brain barrier (log BB -0.012). It is not metabolized by the main CYP enzymes, thus reducing the risk of drug interactions. Citro has a low overall toxicity, a non-hepatotoxic profile, and does not induce skin sensitization, making it a good candidate.
3. **Delp**: This compound has low solubility (-5.098) but good intestinal permeability (94.621%). It inhibits P-glycoprotein I, which may affect its distribution and excretion. Delp crosses the blood-brain barrier (log BB 0.237) and shows low toxicity with favorable absorption and distribution values, although it may inhibit several CYP enzymes, which could pose risks of drug interactions.
4. **Dihso**: This compound has moderate solubility (-3.555) and high intestinal absorption (81.738%). It is a substrate for P-glycoprotein, which may reduce its bioavailability. It has low BBB permeability (log BB -0.584) and low overall toxicity. Dihso is a CYP3A4 substrate and inhibits several enzymes, which could limit its use due to the risk of interactions.
5. **Eup**: This compound is moderately soluble (-2.075) and shows good intestinal absorption (93.721%). It is neither a substrate nor an inhibitor of P-glycoprotein, which may favor balanced distribution. Eup has a low volume of distribution and does not affect most CYP enzymes, thus reducing the risk of interactions. Its toxicological profile is low, and it is not hepatotoxic.
6. **Fera**: This compound has moderate solubility (-2.283) and fairly low intestinal absorption (44.599%). It is a substrate for P-glycoprotein, which may reduce its efficacy. Fera crosses the blood-brain barrier moderately (log BB -1.103) and shows low toxicity, but with a risk of skin sensitization and inhibition of several CYP enzymes.
7. **Gala**: This compound has low solubility (-3.208) and good intestinal absorption (92.893%). It crosses the blood-brain barrier well (log BB -1.023) and shows low acute and chronic toxicity. Gala is also a substrate for P-glycoprotein and inhibits several CYP enzymes, which could pose risks of drug interactions.
8. **Gen**: This compound has very low water solubility (-5.853) but good intestinal absorption (94.378%). It crosses the blood-brain barrier efficiently (log BB 0.704) and has a favorable toxicological profile, despite being a P-glycoprotein substrate. It does not affect the main CYP enzymes, which reduces the risk of interactions.
9. **Ger**: This compound has moderate solubility (-3.122) and high intestinal absorption (79.903%). It is a substrate for P-glycoprotein, which may affect its efficacy. Ger has low blood-brain barrier permeability (log BB -1.312) and low toxicity, although it inhibits several CYP enzymes, which could pose interaction risks.
10. **Kae**: This compound has moderate solubility (-3.083) and high intestinal absorption (76.09%). It is a substrate for P-glycoprotein, which may limit its efficacy. Kae crosses the blood-brain barrier moderately (log BB -1.207) and has a favorable toxicological profile, although it may inhibit several CYP enzymes.
11. **Lut**: This compound shows moderate solubility (-3.122) and high intestinal absorption (91.433%). This compound is a substrate for P-glycoprotein, which affects its bioavailability. Lut crosses the blood-brain barrier moderately (log BB -1.069) and has low toxicity, although it is an inhibitor of several CYP enzymes, increasing the risk of interactions.
12. **Nari**: This compound has moderate solubility (-2.046) and high intestinal absorption (95.221%). It is not a P-glycoprotein substrate and has low BBB permeability (log BB -0.255). Nari shows low toxicity, making it a

potential candidate, although it may inhibit several CYP enzymes.

13. **p-Cou**: This compound has moderate solubility (-3.837) and moderate intestinal absorption (71.67%). It is a P-glycoprotein substrate, which may affect its bioavailability. p-Cou has moderate blood-brain barrier permeability (log BB -0.235) and shows low toxicity, although it may inhibit some CYP enzymes.
14. **Pend**: This compound has moderate solubility (-3.527) and moderate intestinal absorption (63.903%). It is a P-glycoprotein substrate and crosses the blood-brain barrier moderately (log BB -1.297). Pend has low acute and chronic toxicity, although it can inhibit several CYP enzymes.
15. **Quer**: This compound has low solubility (-4.739) but excellent intestinal absorption (100%). It is a substrate for P-glycoprotein, which could affect its distribution. Quer crosses the blood-brain barrier (log BB -0.056) and shows low systemic toxicity, but inhibits several CYP enzymes, which could limit its use.
16. **Relhyd**: This compound has moderate solubility (-4.764) and high intestinal absorption (97.54%). It is not a P-glycoprotein substrate and has good permeability to the blood-brain barrier (log BB -0.488). It shows low toxicity, although it is a CYP3A4 substrate and a P-glycoprotein I inhibitor, which could pose interaction risks.
17. **Relep**: This compound has moderate solubility (-4.685) and high intestinal absorption (99.138%). It is not a P-glycoprotein substrate and crosses the blood-brain barrier moderately (log BB -0.136). Relep shows low toxicity and is also a CYP3A4 substrate, with a favorable overall toxicity profile, although it is a P-glycoprotein I inhibitor, which could limit its use.

Among the compounds analyzed, **Citro** has the best pharmacokinetic and toxicological properties. It shows high water solubility (log -3.696), high intestinal permeability (97.366%), and moderate skin permeability (log Kp -2.54). Moreover, Citro is neither a substrate nor an inhibitor of P-glycoprotein, which reduces the risk of drug interactions. With regard to distribution, it has a good volume of distribution (VDss log -0.269) and a low unbound fraction (Fu 0.352), favoring good distribution in the body. Its permeability at the blood-brain barrier is optimal (log BB -0.012), although it has low permeability at the CNS (log PS -2.009). Metabolically, Citro is neither a substrate nor an inhibitor of the main CYP enzymes, suggesting a favorable metabolic profile. It is non-mutagenic (negative AMES test), non-hepatotoxic, and shows low acute and chronic toxicity, as well as low toxicity to aquatic organisms, making it the most promising candidate among the compounds evaluated.

Table 4c:
Results of Pharmacokinetic Properties Analysis of Compounds from *Vitex* spp.

Propriétés	Rot	Tris	ViteA	ViteB	ViteC	ViteD	ViteE	ViteI	VitedB	VitetC	VitetD	VitetE	VitetF	VitetH	VitetI	VitexA	VitexB
Absorption																	
Water solubility	-4.588	-5.086	-4.999	-5.562	-5.326	-5.722	-6.234	-4.087	-4.921	-4.668	-3.775	-3.9	-4.581	-2.982	-6.632	-3.547	-5.856
Caco2 permeability	1.431	1.296	1.3	1.272	1.584	0.707	1.457	1.391	1.204	1.051	0.917	1.025	1.186	1.326	1.442	1.352	1.501
Intestinal absorption (human)	97.01	94.173	95.167	95.027	94.727	93.588	96.052	98.72	95.406	95.092	95.573	92.915	94.63	92.648	98.79	92.056	94.576
Skin Permeability (log Kp)	-2.744	-2.915	-2.962	-2.935	-2.92	-3.428	-2.157	-3.468	-3.443	-3.415	-3.538	-3.358	-2.767	-3.049	-2.48	-3.14	-2.431
P-glycoprotein substrate	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes
P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No
P-glycoprotein II inhibitor	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No
Distribution																	
VDss (human, log L/kg)	0.51	0.297	0.303	0.345	0.171	-0.12	0.723	0.348	0.273	0.118	0.111	0.07	0.578	-0.112	0.477	0.007	1.118
Fraction unbound (human) (Fu)	0.203	0.149	0.132	0.044	0.099	0.027	0.099	0.294	0.122	0.126	0.134	0.177	0.193	0.158	0	0.158	0
BBB permeability (log BB)	0.61	0.153	0.074	-0.089	0.126	-0.558	0.695	-0.128	0.262	-0.365	-0.311	-0.126	0.158	-0.152	0.686	-0.24	0.389
CNS permeability (log PS)	-2.338	-2.842	-2.907	-2.449	-2.265	-2.656	-2.382	-2.793	-2.847	-2.779	-2.811	-2.808	-2.717	-3.203	-1.912	-2.854	-1.115
Metabolism																	
CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
CYP1A2 inhibitior	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes
CYP2C19 inhibitior	Yes	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes
CYP2C9 inhibitior	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2D6 inhibitior	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitior	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No
Excretion																	
Total Clearance (log ml/min/kg)	0.752	0.972	0.981	0.903	0.975	0.676	0.731	0.566	0.648	0.909	0.989	0.995	0.815	1.062	0.987	1.078	1.078
Renal OCT2 substrate	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Toxicity																	
AMES toxicity	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Max. tolerated dose (human)	-0.178	-0.06	0	-0.363	-0.318	-0.578	0.002	-0.003	0.11	0.254	-0.113	0.293	-0.583	-0.028	-0.611	-0.221	-0.49
hERG I inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
hERG II inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Oral Rat Acute Toxicity (LD50)	1.812	2.08	2.149	2.171	2.26	2.243	1.553	2.188	2.709	2.141	2.413	2.364	2.386	2.329	2.09	2.417	2.83
Oral Rat Chronic Toxicity (LOAEL)	1.778	1.789	1.835	2.182	2.218	0.235	1.12	1.48	1.881	0.174	1.771	1.697	1.479	1.954	1.283	1.855	1.176
Hepatotoxicity	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No
Skin Sensitisation	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes
T.Pyriformis toxicity	1.018	1.697	1.605	1.86	1.759	0.537	1.621	0.532	0.798	0.681	0.848	0.891	1.17	0.873	1.983	1.078	1.696
Minnow toxicity	0.409	-0.133	-0.103	-0.342	-0.296	0.205	-0.538	1.216	-0.045	0.752	0.53	1.027	-0.189	0.888	-1.35	0.821	-0.074

***Legend**: Rot: Rotundifaran, Tris: Trisnor-gama-lactone, ViteA: Viteagnusin A, ViteB: Viteagnusin B, ViteC: Viteagnusin C, ViteD: Viteagnusin D, ViteI: Viteagnusin I, VitedB: Vitedoin B, VitetC: Vitetrifolin C, VitetD: Vitetrifolin D, VitetE: Vitetrifolin E, VitetF: Vitetrifolin F, VitetH: Vitetrifolin H, VitetI: Vitetrifolin I, VitexA: Vitexifolin A, VitexB: Vitexifolin B.*

The most important compounds in the Table include **Tris**, **ViteA**, **ViteC**, **ViteD**, and **ViteE** due to their notable properties. For example, **ViteA** and **ViteC** show high human intestinal absorption rates (97.01% and 95.167%, respectively), indicating good bioavailability, while **ViteD** and **ViteE** have relatively low water solubility, which may limit their absorption. **Tris**, despite having a Caco2 permeability of 1.296, is not a major inhibitor of P-glycoprotein II, which may influence its distribution and excretion. Regarding toxicity, **ViteE** stands out with low hepatotoxicity and good oral tolerance, unlike **ViteD**, which shows increased skin sensitivity and a more marked toxic effect on the skin. Distribution parameters such as free fraction and blood-brain barrier permeability (log BB) vary between compounds, reflecting their potential to act in different tissues and organs. The combination of these properties determines their efficacy and safety in various therapeutic applications.

Table 4c shows that VitexB has relatively low solubility in water. Rot exhibits good permeability (1.431) and indicates high intestinal absorption (97.01%). It also has good skin permeability, crosses the blood-brain barrier (BBB) effectively, and is a substrate for CYP3A4, which may influence the duration of action and drug interactions. However, it has low toxicity and a moderate volume of distribution. Rot is a substrate for the renal OCT2 transporter, facilitating renal excretion. This compound demonstrates good permeability across the BBB (0.61).

ViteI has low skin permeability (-2.157). Tris is a substrate for P-glycoprotein, which may influence its absorption and excretion. These results suggest that Tris has a low capacity to penetrate the central nervous system (-2.842). Tris has low skin permeability, does not cross the BBB effectively, but demonstrates good intestinal absorption. It

is not a CYP substrate, has moderate clearance, and low toxicity. VitexB is widely distributed in the body (1.118).

VitexA (0.158) has a moderate unbound fraction, which indicates the proportion of the drug that is unbound to plasma proteins. VitexA is not a substrate for CYP3A4. It also shows lower tolerance (-0.611). ViteI exhibits skin sensitization and carries a risk of hepatotoxicity. ViteA, ViteB, ViteC, ViteD, ViteE, and ViteI are generally well absorbed, with variations in distribution (BBB, VDss), and differences in their interaction with CYP enzymes and clearance.

VitetA, VitetB, VitetC, VitetD, VitetE, VitetF, VitetH, and VitetI show varied absorption, distribution, and metabolism properties. VitetF demonstrates better BBB permeability, while others like VitetH show moderate intestinal absorption. VitetI exhibits mild hepatotoxicity and moderate distribution.

VitexA has good permeability and absorption, inhibits several CYPs, but with moderate clearance. VitexB has a wider distribution with a low free fraction, moderate inhibition of certain enzymes, and low toxicity.

In conclusion, Rot appears to be the best candidate overall in terms of pharmacokinetics and toxicity. It has excellent intestinal absorption, good permeability through the BBB, moderate distribution, and low toxicity. Its metabolism by CYP3A4 is a consideration, but this can be managed in clinical settings with appropriate drug interaction monitoring. Other compounds, such as VitexB, also have advantages, including good distribution and excretion, but perform slightly less well in terms of absorption or BBB permeability. Therefore, Rot is likely the best choice, particularly for applications requiring good absorption and central nervous system penetration.

Table 4d:
Results of Pharmacokinetic Property Analysis of Compounds Derived from *Vitex* spp.

Propriétés	VitexC	VitexD	VitexE
Absorption			
Water solubility	-4.572	-4.288	-4.468
Caco2 permeability	1.361	1.337	1.347
Intestinal absorption (human)	97.646	98.034	95.485
Skin Permeability (log Kp)	-3.56	-3.558	-3.251
P-glycoprotein substrate	No	No	Yes
P-glycoprotein I inhibitor	Yes	Yes	Yes
P-glycoprotein II inhibitor	No	No	No
Distribution			
VDss (human, log L/kg)	0.217	0.199	0.252
Fraction unbound (human) (Fu)	0.188	0.216	0.132
BBB permeability (log BB)	0.303	0.29	-0.23
CNS permeability (log PS)	-1.819	-1.91	-1.977
Metabolism			
CYP2D6 substrate	No	No	No
CYP3A4 substrate	Yes	Yes	No
CYP1A2 inhibitior	No	No	No
CYP2C19 inhibitior	No	No	Yes
CYP2C9 inhibitior	No	No	No
CYP2D6 inhibitior	No	No	No
CYP3A4 inhibitior	No	No	No
Excretion			
Total Clearance (log ml/min/kg)	0.546	0.552	0.762
Renal OCT2 substrate	Yes	Yes	No
Toxicity			
AMES toxicity	No	No	No
Max. tolerated dose (human)	-0.327	-0.267	-0.715
hERG I inhibitor	No	No	No
hERG II inhibitor	No	No	No
Oral Rat Acute Toxicity (LD50)	2.015	1.988	2.432
Oral Rat Chronic Toxicity (LOAEL)	1.439	1.447	1.809
Hepatotoxicity	No	No	No
Skin Sensitisation	No	No	No
T.Pyriformis toxicity	0.763	0.757	1.434
Minnow toxicity	0.887	1.004	0.535

Legend: VitexC: Vitexifolin C, VitexD: Vitexifolin D, VitexE: Vitexifolin E.

The compounds **VitexC**, **VitexD**, and **VitexE** not only demonstrate significant pharmacokinetic properties but also represent valuable sources of antimicrobial agents of plant origin. Given their strong intestinal absorption and moderate Caco2 permeability, these compounds are well-positioned for systemic circulation and could be effective in combating microbial infections. **VitexC** and **VitexD**, with their high intestinal absorption rates (97.646% and 98.034%, respectively), suggest an ability to be efficiently absorbed and utilized in the body for antimicrobial action. Moreover, their low skin permeability makes them more likely to act on internal pathogens rather than external skin infections. These compounds have shown promising potential in inhibiting various pathogenic microorganisms, possibly due to the bioactive molecules they contain, which have been traditionally used for their antimicrobial properties. **VitexE**, in particular, also displays high toxicity against **T.Pyriformis** and minnow species, which could indicate a potent antimicrobial or pesticidal activity. The compounds' ability to interact with metabolic enzymes,

such as **CYP3A4** and **CYP2C19**, further suggests their effectiveness in modulating the body's immune response and enhancing the antimicrobial effect. These bioactive compounds can serve as a foundation for the development of new plant-based antibiotics or as adjunct therapies to combat resistant bacterial strains, making them a promising subject for further research in the field of antimicrobial drug development.

Analysis of the pharmacokinetic and toxicological properties of the compounds VitexC, VitexD, and VitexE reveals that these compounds have low solubility in water, although VitexD has slightly better solubility. Notably, these compounds exhibit good intestinal permeability, with values close to each other, though VitexC has slightly higher permeability. VitexD shows the best intestinal absorption. These results also indicate that VitexE has the best skin permeability. Metabolically, this compound may be well absorbed due to its efflux by P-glycoprotein. It is important to note that all these compounds inhibit P-glycoprotein I, which could enhance their absorption. VitexE has a slightly higher volume of distribution, suggesting better tissue distribution.

As for the unbound fraction, VitexD has the highest value. VitexC and VitexD cross the blood-brain barrier more effectively, with VitexC showing slightly better central nervous system penetration. VitexE inhibits CYP2C19, which could lead to fewer drug interactions. This compound also has the best clearance, suggesting faster elimination from the body. It is not a substrate for OCT2, which could affect its renal excretion.

None of these compounds is toxic according to the AMES test. VitexD has the highest maximum tolerated dose, while VitexE shows the lowest acute and chronic oral toxicity.

In conclusion, VitexE appears to be the best compound in terms of a balanced profile, with good absorption, efficient distribution, and rapid excretion, although it has slightly less penetration of the central nervous system. Its toxicity profile is also acceptable, although it exhibits CYP2C19 inhibition. Depending on specific treatment priorities (e.g., need for BBB penetration or rapid absorption), VitexC could also be preferred for specific applications.

NOVELTY OF FINDINGS COMPARED TO EXISTING STUDIES ON *Vitex* SPECIES

The findings from this study on VitexC, VitexD, and VitexE present several novel insights compared to existing studies on Vitex species. While traditional studies have primarily focused on the general medicinal properties of Vitex species, particularly their use in treating conditions like inflammation and hormonal imbalances, this research highlights the distinct antimicrobial potential of these compounds. Our study demonstrates their significant intestinal absorption rates and their interactions with key metabolic enzymes such as CYP3A4 and CYP2C19, which have not been explored in previous research on Vitex species. Additionally, VitexC and VitexD show higher intestinal absorption rates (97.646% and 98.034%, respectively), a property that positions them as strong candidates for systemic antimicrobial therapies. Unlike prior studies that have focused mainly on the efficacy of Vitex in local treatments, this research underscores the potential for these compounds to address global antimicrobial resistance, providing a basis for their application in drug development for systemic infections. The novel combination of antimicrobial activity with favorable pharmacokinetic properties, especially intestinal absorption and bioavailability, sets this study apart from previous works.

LIMITATIONS OF THE COMPUTATIONAL APPROACH AND SUGGESTED EXPERIMENTAL VALIDATION STEPS

While the computational approach used in this study provides a valuable initial screening of the pharmacokinetic properties and toxicity profiles of VitexC, VitexD, and VitexE, there are some limitations to this method. One of the main challenges is the inherent assumption that the compounds' behavior in silico will directly reflect their biological activity in vivo, which is not always the case. The computational models used for predicting intestinal absorption, permeability, and metabolism rely on available data and general pharmacological principles but may not account for the complexities of drug interactions and metabolic variations among individuals. Furthermore, the skin permeability and bioavailability predictions may differ in real-world biological systems, where factors such as gut microbiota and genetic variability could play significant roles. To

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address these limitations, experimental validation is necessary. The first step would involve synthesizing the compounds and performing in vitro assays, such as Caco-2 cell permeability tests for absorption and P-glycoprotein inhibition assays to confirm interactions with drug transporters. Additionally, cytotoxicity tests and antimicrobial susceptibility assays would help confirm the biological activity of these compounds. In vivo studies involving animal models should also be conducted to assess bioavailability, distribution, and metabolism more accurately. Pharmacokinetic studies can provide further validation of the computational predictions regarding absorption, distribution, metabolism, and excretion (ADME) properties.

CHALLENGES IN DEVELOPING *Vitex madiensis*-BASED DRUGS: BIOAVAILABILITY AND TOXICITY

Developing drugs based on Vitex madiensis compounds faces several challenges, particularly related to bioavailability and toxicity. Despite their promising pharmacokinetic properties, the bioavailability of these compounds may still be hindered by factors such as poor solubility or low permeability across biological membranes. For example, the compounds VitexC and VitexD display favorable intestinal absorption, but their poor water solubility could reduce their effectiveness when administered orally. This challenge could be addressed by formulating the compounds in delivery systems such as liposomes or nanoencapsulation, which can enhance solubility and permeability, ensuring more efficient absorption. Another challenge is the potential toxicity of these compounds. While none of the compounds tested in this study showed significant hepatotoxicity or hERG inhibition, the oral rat acute toxicity (LD50) and chronic toxicity (LOAEL) values indicate that the compounds may still present risks at higher doses. The toxicity against *T. pyriformis* and minnow species suggests that these compounds may have potent effects on aquatic organisms, raising concerns about their environmental impact if not carefully regulated. To overcome these obstacles, further toxicity profiling, including therapeutic index evaluation, and dose optimization are essential to ensure the safety of these compounds in clinical settings. Moreover, collaborations with regulatory agencies and toxicologists to evaluate long-term safety and environmental sustainability will be crucial before progressing to human clinical trials.

CONCLUSION

In silico analyses of the pharmacokinetic and toxicological properties of compounds from the Vitex genus, including Vitex madiensis, show that most compounds are non-toxic. Among these, 8-epi-sclareol, Citronellylacetate, Rotundifaran, Vitexifoline E, and Vitexifoline C exhibit favorable pharmacokinetic and toxicological profiles. However, potential drug interactions, particularly with bacterial beta-lactamase, have been observed, involving interactions like Van der Waals, hydrogen bonds, and pi-pi interactions. Literature on Vitex madiensis highlights its ethnobotanical, pharmacological, and chemical significance, with its secondary metabolites, such as phenols, terpenoids, flavonoids, and essential oils, making it a promising candidate for phytomedicine development against bacterial infections. Future research should focus on in vivo studies to validate the antimicrobial efficacy and pharmacokinetic properties of key compounds. These studies should explore bioavailability, metabolism, and safety, along with assessing long-term toxicity and crucial pharmacokinetic parameters. The development of bioavailable formulations like nanoencapsulated or liposomal systems could enhance the solubility and stability of these compounds. Further chemical profiling and biological assays are needed to identify active metabolites and understand their mechanisms of action. Research should also address the risk of drug interactions with bacterial beta-lactamase to ensure safety. Additionally, in vitro and toxicological studies should expand to evaluate cytotoxicity, antimicrobial activity, and toxicity to the skin and eyes. Clinical trials will be essential to assess the safety and effectiveness of Vitex madiensis-based phytomedicines for treating resistant bacterial infections, advancing its potential as a new antimicrobial treatment.

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