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In Silico Pharmacokinetic and Toxicity Analysis on *Clitoria Ternatea* Flower

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ABSTRACT

This article presents a pharmacokinetic analysis and in silico toxicity analysis of the flower of *C. ternatea*. *C. ternatea*, also known as "the butterfly flower," has long been used in traditional medicine and has significant pharmacological potential. In this study, we used computational methods to understand how the active compounds in the flower of *C. ternatea* can interact in the human body.

Study to predicted pharmacokinetic properties, including solubility, human intestinal absorption, distribution in the body, metabolism, and excretion. The results of this analysis provide insight into the potential of the compounds in the flower of *C. ternatea* as effective pharmacological agents. In addition, we also conducted an in silico toxicity assessment to identify the possible negative effects of these compounds on the human body.

The results of this research can provide a basis for the further development of the flowers of *C. ternatea* as a potential source for treatment and therapy. The results showed that most compounds have good bioavailability potential. Correlations between chemical structure and prediction of important parameters such as lipophilisity and P-gp substrate status were also explored. *C. ternatea* contains a compound with good pharmacological potential, but further research and experimental validation are needed to fully understand the pharmacologic and toxic properties of these compounds.

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1. INTRODUCTION

C. ternatea is a plant that has a long history of being used as a natural source of ingredients for a variety of health purposes. *C. ternatea* extract has potential pharmacological benefits, which have attracted the interest of academics and practitioners of traditional medicine. The compounds found in the flower are phenols, terpenoids, fatty acids, alkaloids, cyclotides, and vitamins[1], [2]. *C. ternatea* has a water content of 92.4%, the predominant component is fat, accounting for (32.9%), carbohydrates (29.3%), fiber (27.6%), and protein (4.2%). In addition, *C. ternatea* also contain calcium 3.09 mg/g, magnesium 2.23, potassium 1.25, zinc 0.59, sodium, and iron 0.14 mg/g, respectively[2], [3].

The flavonoids in *C. ternatea* consist of 87% of the flavonols (caempferol, quercetin, myricetin, and isorhamnetin)[4]. Anthocyanidins: 27% (ternatin A1-A3, B1-B4, C1-C5, D1-D3, petunidin, peonidin, delphinidin, malvidin, cyanidin)[5]. Flavanols (epicathechin) and flavones (scutellarin, baicalein, luteolin, and apigenin)[3]. Phenolic acid consists of chlorogenic, protocatechuic, and gallic acids[6]. Terpenoids (triterpenoid and taraxerol), tocopherol saponins (alpha and gamma tocopherols), and phytosterols (campesterol, stigmasterol, beta-sitosterol, and sitostanol)[7]. Fatty acids (palmitic, stearic, petroselinic, linoleic, arachidic, behenic, and phytanic)[8], alkaloid content (3-deoxy-3, 11-epoxy cephalotaxine)[9], and vitamins (inositol and pentanal)[2].

This content makes *C. ternatea* a promising natural ingredient in the field of medicines and health supplements. However, the study of the use of *C. ternatea* as a potential drug requires understanding related pharmacokinetic profiles and toxicity using in silico methods such as Swiss ADME and Protox II, as well as further validation through laboratory tests.

Pharmacokinetic analysis is correlate to bioavailability which can affect the pharmacology effect and the toxic effects of *C. ternatea* extract[10]. Conventional laboratory trials, however, can be expensive and time-consuming for pharmacokinetic and toxicity studies. As a result, we will use the in silico method with the Swiss ADME and Protox II programs in this study. The pharmacokinetics of a substance, including the processes of absorption, distribution, metabolism, and excretion, can be estimated with the help of software called Swiss ADME. Protox II is a toxicity predictor to assess the potential of chemical poisoning.

The objective of this study is to predict the potential pharmacological effects of *C. ternatea* extract so that it can study important details about how *C. ternatea* extract interacts with the human body, how the active ingredients are distributed within the body, and the potential toxic effects that may be caused by using the in silico method. The results of this research will further explain the potential applications of *C. ternatea* extracts as medications. The silico approach used in this study can also offer a faster and more cost-efficient alternative to understanding the pharmacokinetic properties and toxicity of natural compounds. The findings of this analysis could serve as a starting point for further research and potential advances in the pharmaceutical industry and the use of local wisdom as a herbal medicine.

2. METHOD

3D and Canonical SMILES structures were identified through the PubChem Database (National Library of Medicine). Analyze of the physiochemical descriptor as well as predict ADME parameters and drug-like properties (druglikeness) using SwissADME (Swiss Institute of Bioinformatics). Website Access http://www.swissadme.ch, upload SMILES compounds, SwissADME will provide results and ADME parameters. Toxicity of compounds tested using ProTox II (Prediction of Toxicity of Chemicals). Website Access https://tox-new.charite.de/protox_II/, upload SMILES compounds, select any additional models to predict and start Tox-Prediction. The dose of toxicity is based on LD50 in mg/kg of body weight. LD50 is a median lethal dose, which means a dose at which 50% of the test subjects die after exposure to a compound.

The toxicity class is determined by the globally harmonised chemical labeling classification system (GHS). The LD50 value is given in mg/kg. Class I: fatal if swallowed (LD50 ≤ 5). Class II: lethal if swelled (5 < LD50 ≥ 50). Class III: toxic if swallened (50 < LD 50 ≤ 300). Class IV: hazardous if swelted (300 < LD50) ≤ 2000). Class V: may be hazardous if swollen (2000 < LD50, ≤ 5000). Class VI: non-toxic (LD50 > 5000). Toxicity models analyze target hepatotoxicities, carcinogenicity, mutagenicity, and cytotoxics[10], [11]

3. RESULT and DISCUSSION

The solubility and bioavailability potential of a chemical compound in the human body are based on Lipinski's Rule. Lipinski's rule consists of four simple criteria that must be met by the chemical to be considered to have the potential to be a drug with good bioavailability, including: molecular weight less than 500 g/mol, Log P (octanol-water partition coefficient) less than 5, the number of hydrogen receptor atom donors from a bound hydrogen bond is less than or equal to 5, and the number of receptors of a hydrogen atom donor from a bonded hydrogen is less than or equivalent to 10. A compound meets at least four of the above criteria, so it is assumed that it has the potential to have good solubility in water and can easily pass through cell membranes. Compounds that meet Lipinski's Rule tend to have higher bioavailability, which means they are more likely to be absorbed by the body and produce the desired pharmacological effects[11], [12].

Table 1. Druglikeness *Clitoria Ternatea* Compounds

Compound	*Lipinski's Rule Parameter*				*Druglikeness* (Lipinski)
	Molecular Weight ≤500	MLOGP ≤4.15	Num H-bond acceptors ≤10	Num H-bond donors ≤5	
Kaempferol	286.24 g/mol	-0.03	6	4	Yes
Quercetin	302.24 g/mol	-0.56	7	5	Yes
Myricetin	318.24 g/mol	-1.08	8	6	Yes
Ternatin	374.34 g/mol	-0.12	8	2	Yes
Petunidin	317.27 g/mol	0.03	7	5	Yes
Peonidin	301.27 g/mol	0.57	6	4	Yes
Delphinidin	338.70 g/mol	0.03	7	6	Yes
Malvidin	331.30 g/mol	0.28	7	4	Yes
Cyanidin	287.24 g/mol	0.32	6	5	Yes
Epicatechin	290.27 g/mol	0.24	6	5	Yes
Scutellarin	462.36 g/mol	-2.12	12	7	No
Baicalein	270.24 g/mol	0.52	5	3	Yes

Compound	*Lipinski's Rule Parameter*				*Druglikeness* (Lipinski)
	Molecular Weight ≤500	MLOGP ≤4.15	Num H-bond acceptors ≤10	Num H-bond donors ≤5	
Luteolin	286.24 g/mol	-0.03	6	4	Yes
Apigenin	270.24 g/mol	0.52	5	3	Yes
Chlorogenic	354.31 g/mol	-1.05	9	6	Yes
Protocatechuic	154.12 g/mol	0.40	4	3	Yes
Gallic	170.12 g/mol	-0.16	5	4	Yes
Anthraquinone	208.21 g/mol	1.86	2	0	Yes
Taraxerol	426.72 g/mol	6.92	1	1	Yes
Alpha Tocopherol	430.71 g/mol	6.14	2	1	Yes
Gamma-Tocopherol	416.68 g/mol	5.94	2	1	Yes
Campesterol	400.68 g/mol	6.54	1	1	Yes
Stigmasterol	412.69 g/mol	6.62	1	1	Yes
Beta-Sitosterol	414.71 g/mol	6.73	1	1	Yes
Sitostanol	416.72 g/mol	6.88	1	1	Yes
Palmitic Acid	256.42 g/mol	4.19	2	1	Yes
Stearic Acid	284.48 g/mol	4.67	2	1	Yes
Petroselinic Acid	282.46 g/mol	4.57	2	1	Yes
Linoleic Acid	280.45 g/mol	4.47	2	1	Yes
Arachidic Acid	312.53 g/mol	5.13	2	1	Yes
Behenic Acid	340.58 g/mol	5.58	2	1	Yes
Phytanic Acid	312.53 g/mol	5.13	2	1	Yes
3-deoxy-3, 11-epoxy cephalotaxine	313.35 g/mol	1.56	5	0	Yes

Substance has a molecular weight greater than 500 and the log of the octanol/water partition coefficient (log P) is greater than +5, then the substance is impermeable and has low permeability. Groups O-H and N-H larger than 5 represent a donor of hydrogen binding (HBD), and the number of atoms O and N greater than 10 indicates a hydrogen-binding acceptor (HBA)[12]. Based on the above table, there is one compound with a status of no based on drug similarity based on Lipinski: a composite of scutellarine with a hydrogene binding donor > 5 is 7, and a receptor > 10 is 12. As for 33 other compounds, it is predictable that they meet the Lipinski Five Law, are readily absorbable, and have good premeability.

Forecasting absorption, distribution, metabolism, and excretion is then done by entering the SMILES code of the compound through the ADME Tools (Swiss ADME).

Table 2. ADME Prediction Analysis (Absorption, Distribution, Metabolism, Excretion)

Compounds	ADME Prediction				
	Absorption		Distribution (Lipophilicity-Log $P_{o/w}$)	Metabolism (Cytochrome metabolism)	Excretion (P-gp substrate)
	GI Absorption	Skin permeation (Log Kp)			
Kaempferol	High	-6.7	1.58	CYP1A2 CYP2D6 CYP3A4	No
Quercetin	High	-7.05	1.23	CYP1A2 CYP2D6 CYP3A4	No
Myricetin	Low	-7.4	0.79	CYP1A2 CYP3A4	No
Ternatin	High	-6.37	2.50	CYP1A2	No

Compounds	ADME Prediction				
	Absorption		Distribution	Metabolism	Excretion
	GI Absorption	Skin permeation (Log Kp)	(Lipophilicity-Log $P_{o/w}$)	(Cytochrome metabolism)	(P-gp substrate)
Petunidin	High	-6.88	0.63	CYP2C9 CYP3A4 CYP1A2	Yes
Peonidin	High	-6.53	0.97	CYP1A2	Yes
Delphinidin	High	-7.5	-0.98	No	Yes
Malvidin	High	-6.73	0.92	CYP1A2	Yes
Cyanidin	High	-7.51	0.32	CYP1A2	Yes
Epicatechin	High	-7.82	0.85	No	Yes
Scutellarin	Low	-8.59	-0.20	No	Yes
Baicalein	High	-5.7	2.24	CYP1A2 CYP2D6 CYP3A4	No
Luteolin	High	-6.25	1.73	CYP1A2 CYP2D6 CYP3A4	No
Apigenin	High	-5.8	2.11	CYP1A2 CYP2D6 CYP3A4	No
Chlorogenic	Low	-8.76	-0.38	No	No
Protocatechuic	High	-6.42	0.65	CYP3A4	No
Gallic	High	-6.84	0.21	CYP3A4	No
Anthraquinone	High	-5.16	2.64	CYP1A2 CYP2C19	No
Taraxerol	Low	-2.3	7.22	No	No
Alpha Tocopherol	Low	-1.33	8.27	No	Yes
Gamma-Tocopherol	Low	-1.51	7.95	No	Yes
Campesterol	Low	-2.5	6.90	No	No
Stigmasterol	Low	-2.74	6.97	CYP2C9	No
Beta-Sitosterol	Low	-2.2	7.19	No	No
Sitostanol	Low	-2.93	7.07	No	No
Palmitic Acid	High	-2.77	5.20	CYP1A2 CYP2C9	No
Stearic Acid	High	-2.19	5.93	CYP1A2	No
Petroselinic Acid	High	-2.6	5.70	CYP1A2 CYP2C9	No
Linoleic Acid	High	-3.05	5.45	CYP1A2 CYP2C9	No
Arachidic Acid	Low	-1.61	6.62	CYP1A2	No
Behenic Acid	Low	-1.01	7.40	CYP1A2	No
Phytanic Acid	High	-2.31	6.15	CYP2C9	Yes
3-deoxy-3, 11-epoxy cephalotaxine	High	-7.25	1.95	CYP2D6	No

GI (gastrointestinal) absorption gives an estimate of the potential absorption of a compound through the digestive tract. High: If a compound is categorized as "high" in GI absorption, this indicates that the compound has a high potential for good absorption through the digestive tract. These compounds tend to be easily absorbed by the intestinal walls and enter the bloodstream. Moderate: If a compound is categorized as "moderate" in GI absorption, this indicates that the compounds have a potential for moderate or moderate absorptions through the digestive tract. The absorption rate of the compound may not be as efficient as "high," but it is also not as bad as low. Low: If a compound is categorized as "low" in GI absorptions, this indicates that the composition has a low gastrointestinal absorptive potential. Compounds in the "low" category may have a barrier to intestinal absorption, so a significant amount of such compounds may not be absorbed efficiently into the systemic circulation[11], [13].

Based on the ADME prediction table, the GI absorption prediction results are 22 compounds in the "high" category (kaempferol, quercetin, ternatin, petunidin, peonidin, delphinidin, malvidin, cyanidin, epicatechin, isorhamnetin, hainicale, luteolin, apigenin, protocatechuic, gallic, anthraquinone, palmitic acid, stearic acid, petroselinic acids, linoleic acides, phytanic acidos, 3-deoxy-3, 11-epoxy cephalotaxine). There are 12 compounds in the category "low" (myricetin, scutellarin, chlorogenic, taraxerol, alpha-tocopherol, gamma-tocopherol, campesterol, stigesterol, beta-sitosterol, sitstigostanol/mastanol, arachidic acid, and behenic acid).The GI absorption category is important in drug pharmacokinetics as it can affect the degree and duration of the effect of a drug in the body. Compounds with high GI absorbtion tend to have better bioavailability, which means they are more efficient in reaching the target tissue and producing the desired therapeutic effect[11], [12].

The octanol-water partition coefficient (Log Kp) is one of the parameters used to predict how far a compound can penetrate or absorb through the skin. Compounds with high skin permeation potential can affect drug administration route choices, such as transdermal or topical. Transdermal delivery allows the compound to penetrate the skin and reach the bloodstream without passing through the digestive tract, thus providing a more stable pharmacokinetic profile and avoiding excessive metabolism in the liver. In general, compounds with relatively high log Kp values are more likely to be developed as transdermal drugs than for topical applications. Topical application focuses on local effects on the surface area of the skin and does not require efficient absorption into the bloodstream[13], [14].

The level of skin permeability that is considered good for transdermal patches is usually in the range of about -3 to -1 cm/s. A higher level of permeability in this range indicates that the compound is more easily penetrating the skin and has the potential to provide an effective therapeutic dose. Compounds with a low log Kp value tend to remain on the skin surface without penetrating deeper. Composites with a positive log kp value (values above zero) tend to have the potential to penetrate or absorb through the skin better than compounds with a negative log kp value (values below zero). A positive Log K p value indicates that the compound is more prone to transitioning from the water (skin) phase to the non-polar phase (such as the skin layer)[11], [14]. There are 13 compounds that are predicted to be developed into transdermal patches of ternate clitoral, including taraxerol, alpha-tocopherol, gamma-tocopherol, campesterol, stigmasterol, beta-sitosterol, sitostanol/stigmastanol, palmitic acid, stearic acid, petroselinic acids, arachidic acids, behenic acid, and phytanic acid.

The Log Po/w value is used to predict the extent to which a compound will dissolve in fat (hydrophobicity) and how easily such compounds can penetrate biological membranes, including the cell membrane, to reach biological or systemic

targets in the body. These measurements are used to understand how the composition behaves within the body and influences interactions with biological targets, as well as to design compounds with desired pharmacokinetic properties. If the Log Po/w value is positive (Log Po/w > 0), the compound has a higher affinity to be dissolved in octanols or fat solvents than water. This indicates the hydrophobic or lipophilic properties of the composite, which means that the composition is more soluble in the fat phase than the water phase. Compounds with a high Log Po/W value tend to be more readily penetrating through cell membranes and tissues, as well as having a higher probability of distribution in the fatty tissue and other non-polar organs. If the log Po/w value is negative (LOG PO/w < 0), such compounds have a greater affinity for dissolving in the water than the octanol or the fat solver, indicating the hydrofobic and lipophobic characteristics of the compound, meaning that such a composite is more likely to be solvent in the aquatic phase rather than the fat phase [11], [12], [14]

All compounds are lipophobic, except the three hydrophilic. (delphinidin, scutellarin, chlorogenic) One of the important elements in pharmacokinetics and drug effects on the body is lipophilia. Better membrane and biological tissue penetration is characteristic of compounds with high lipophilicity, which allows for more effective distribution to various organs and tissues of the body. However, excessive lipophilization can also lead to an accumulation of substances in certain fat tissues and organs, which can affect the way the body distributes and removes those substances. Therefore, determining lipophilicity is an important component of pharmaceutical research and drug design[13].

Cytochrome metabolism is an important biochemical process in the human body involving the enzyme cytochrome P450, which is responsible for the breakdown and modification of compounds in the body. Information about the possible cytochrome metabolism of various compounds in natural substances such as C. ternatea can help understand how these compounds are processed by the body and their potential to interact with drugs or other substances. Some compounds, such as kaempferol, quercetin, ternatin, petunidin, peonidin, malvidin, and cyanidin, have predictions of metabolism by the CYP1A2 enzyme, which is one of the most active cytochrome P450 enzymes in the human body, suggesting that these compounds may undergo significant breakdown and modification in the body. The compounds baicalein, luteolin, and apigenin have predictions of metabolism by CYP2D6 and cYP3A4, which are other P450 cytochrome enzymes that are important in the breakdown of different compounds[14].

However, some compounds, such as delphinidine, epicatechin, scutellarin, chlorogenic, alpha-tocopherol, gamma-tocopherol, taraxerol, and a number of other compounds, have no prediction of metabolism by a particular cytochrome P450 enzyme. This may indicate that these compounds are less susceptible to breakdown in the body by these enzymes. Understanding the metabolism of these natural compounds can have an impact on the development of new medicines or health supplements, as well as a further understanding of how these natural substances can affect human health. Although this is an initial prediction, this information could serve as a basis for further research on the potential health effects of these natural compounds[14].

P-gp (P-glycoprotein) is an active transport protein found in the cell membranes of many organs, including the intestines, liver, kidneys, and brain. Drug pharmacokinetics and therapeutic outcomes can be affected by Pgp interactions. When a substance that is a Pgp substrate interacts with Pgp, there will be an increase in elimination from target tissue or a decrease in levels in the bloodstream, which reduces the expected therapy effect. Furthermore, some substances that inhibit Pgp

activity can increase the level of Pgp substrates in the body, which can result in drug interactions and a higher risk of side effects. When considering potential drug interactions or pharmacokinetic problems that may arise from the use of several drugs at once, it is important to know the status of the Pgp compound when designing the drug and providing patient care[14], [15].

There are 10 compounds (peonidin, delphinidin, malvidin, petunidin, cyanidin, epicatechin, scutellarin, alpha-tocopherol, gamma-tocopherol, and phytanic acid) with Pgp substrate status "yes", as well as 24 compounds with "no" status. For Pgp substrates with "no" status, it can be understood that the compounds evaluated in the analysis are not considered P-glycoprotein (Pgp) substrates. These compounds have little or no affinity to interact with Pgp and will not undergo elimination or a decrease in the level of the target cell protein by Pgp. The compounds are predicted to have no significant interaction with Pgp, and therefore, their transportation out of the cell by Pgp is not a problem to be taken into account in its pharmacokinetic or pharmacological effects. This can be useful information in pharmaceutical design because they do not have a substratum in the body that can be regarded as a bio-distributed substrated substrates[13]–[15].

A Pgp substrate with "yes" status means that the compound evaluated in the analysis is considered to be a P-glycoprotein (Pgp) substrate. Such compounds have an affinity to interact with Pgp and are likely to experience elimination or reduction of the level of target cells by the Pgp protein. Pgp is an active transport protein that removes foreign compounds, including drugs, from cells into the lumen of the intestine, bile, or urine. If a compound is a Pgp substrate, there may be a decrease in the concentration of active compounds in the blood or target tissue as a result of elimination by Pgp. Interactions with Pgp can have important implications for drug design and patient treatment, especially when using drugs simultaneous. Compounds that are Pgp substrats may experience pharmacokinetic changes when interacting with Pgp, or if there are other drugs that cause inhibition or induction of Pgp, this may affect the required dosage, therapeutic effects, or the possibility of unwanted drug interactions[13], [14].

The ability of a compound or substance to harm living creatures is known as toxicity. The level of toxicity of a substance is determined by general toxicities, which include natural substances found in plants, animals, and other natural resources. The toxicity of natural compounds, including hepatotoxicity, carcinogenity, mutagenity, and cytotoxics, is critical for many pharmaceutical, medical, and environmental applications. Toxicity testing of compounds from natural ingredients is crucial because it can help in identifying potentially hazardous or toxic substances and provide guidance for safe and effective drug design [15], [16]

Table 3. Toxicity Test Results of *Clitoria Ternatea* Compound

Compounds	Toxicity						
	LD50 (mg/kg)	*Toxicity Class*	*Hepatotoxicity*	*Carcinogenicity*	*Immunotoxicity*	*Mutagenicity*	*Cytotoxicity*
Kaempferol	3919	5	Inactive	Active	Inactive	Active	Inactive
Quercetin	159	3	Inactive	Active	Inactive	Active	Inactive
Myricetin	159	3	Inactive	Active	Inactive	Active	Inactive
Ternatin	5000	5	Inactive	Inactive	Active	Inactive	Inactive
Petunidin	5000	5	Inactive	Active	Active	Inactive	Inactive
Peonidin	5000	5	Inactive	Inactive	Inactive	Inactive	Inactive
Delphinidin	5000	5	Inactive	Inactive	Inactive	Inactive	Inactive
Malvidin	5000	5	Inactive	Inactive	Active	Inactive	Inactive
Cyanidin	5000	5	Inactive	Active	Inactive	Inactive	Inactive
Epicatechin	10000	6	Inactive	Inactive	Inactive	Inactive	Inactive

Compounds	Toxicity						
	LD50 (mg/kg)	*Toxicity Class*	*Hepatotoxicity*	*Carcinogenicity*	*Immunotoxicity*	*Mutagenicity*	*Cytotoxicity*
Scutellarin	5000	5	Inactive	Active	Inactive	Inactive	Inactive
Baicalein	3919	5	Inactive	Active	Inactive	Active	Inactive
Luteolin	3919	5	Inactive	Inactive	Inactive	Inactive	Inactive
Apigenin	2500	5	Inactive	Inactive	Inactive	Inactive	Inactive
Chlorogenic	5000	5	Inactive	Inactive	Active	Inactive	Inactive
Protocatechuic	2000	4	Inactive	Active	Inactive	Inactive	Inactive
Gallic	2000	4	Inactive	Active	Inactive	Inactive	Inactive
Anthraquinone	5000	5	Inactive	Inactive	Inactive	Active	Inactive
Taraxerol	70000	6	Inactive	Inactive	Active	Inactive	Inactive
Alpha Tocopherol	5000	5	Inactive	Inactive	Inactive	Inactive	Inactive
Gamma-Tocopherol	5000	5	Inactive	Inactive	Inactive	Inactive	Inactive
Campesterol	890	4	Inactive	Inactive	Active	Inactive	Inactive
Stigmasterol	890	4	Inactive	Inactive	Active	Inactive	Inactive
Beta-Sitosterol	890	4	Inactive	Inactive	Active	Inactive	Inactive
Sitostanol	500	4	Inactive	Inactive	Active	Inactive	Inactive
Palmitic Acid	900	4	Inactive	Inactive	Inactive	Inactive	Inactive
Stearic Acid	900	4	Inactive	Inactive	Inactive	Inactive	Inactive
Petroselinic Acid	48	2	Inactive	Inactive	Inactive	Inactive	Inactive
Linoleic Acid	100000	6	Inactive	Inactive	Inactive	Inactive	Inactive
Arachidic Acid	900	4	Inactive	Inactive	Inactive	Inactive	Inactive
Behenic Acid	900	4	Inactive	Inactive	Inactive	Inactive	Inactive
Phytanic Acid	900	4	Inactive	Inactive	Inactive	Inactive	Inactive
3-deoxy-3, 11-epoxy cephalotaxine	28	2	Inactive	Active	Active	Inactive	Active

A huge amount of research and toxicity testing should be done on any natural ingredient intended to be used in pharmaceutical products, food supplements, or medicines. Toxicity studies help determine safe doses and help in the development of products that are safe for human health. Compounds found in natural products can vary in toxicity depending on their chemical and biological properties. Plants that are traditionally used as medicines contain compounds with low toxicity or even beneficial effects on health, but certain ingredients of natural products can also be highly toxic and harmful to humans[15].

The results of the analysis showed large variations in the LD50 of various compounds, with the highest value being 100,000 mg/kg (linoleic acid) and the lowest being 28 mg/kg. (3-deoxy-3, 11-epoxy cephalotaxine). Test results of LD50 compounds petroselinic acid and 3-deoxy-3, 11-epoxy cephalotaxine in class 2 compounds with LD50 class 2 considered to be toxic with high potential to cause negative effects on test organisms in moderate doses. These compounds have the ability to cause damage or disruption to the body's functions when consumed or exposed in sufficiently high doses. The LD50 test results of compounds in class 3 are quercetin and myricetin. Compounds with class 3 LD50 are considered to be toxic, with a moderate level of toxicity. Although its toxicity is lower than that of compounds with grade 1 and 2 LD50s, the compound still has the potential to cause negative effects on test organisms at higher doses. Even higher doses are needed to cause death in 50% of the test animals, but they still have the potential to cause toxic effects if swallowed in significant doses[16].

The LD50 test results of the compounds in class 4 are: protocatechuic, campesterol, stigmasterol, beta-sitosterol, sitostanol/stigmastanol, palmitic acid, stearic acid, arachidic acids, behenic acids, phytanic acid, and gallic acid. This classification suggests that much higher doses are needed to cause death or toxic effects, but we still need to be cautious as it can be dangerous if swallowed in significant doses. The LD50 test results of compounds in class 5 are: kaempferol, ternatin, sinensetin, peonidin, petunidin, delphinidin, malvidin, cyanidin, isorhamnetin, scutellarin, baicalein, luteolin, apigenin, chlorogenic, anthraquinone, alpha-tocopherol, and gamma-tocopherol. This category indicates that the compound has a low to moderate toxicity potential if swallowed. The doses required to cause toxicity effects in 50% of the test animals are within a sufficiently high range, so the compounds tend to be less harmful at doses commonly used in human applications or exposures. The LD50 test results of the compounds epicatechin, taraxerol, and linoleic acid fall into the class 6 category. Very high doses are required to cause toxicity effects, and this classification suggests that such a compound is considered non-toxic at commonly used doses. The majority of the compounds in *C. ternatea* are classified in classes 4 and 5, which show moderate to low levels of toxicity.[15], [16].

Analysis suggests that the compound *C. ternatea* is predicted to have no hepatotoxic activity, which can damage the liver. Some compounds are predicted to have carcinogenic potential, which means they can cause cancer. Compounds such as kaempferol, quercetin, myricetin, petunidin, cyanidin, scutellarin, baicalein, protocatechuic, gallic, and 3-deoxy-3, 11-epoxy cephalotaxine are classified as active in terms of carcinogenicity, so use or exposure to these compounds should be cautious. Some compounds are predicted to have immunotoxic potential, which can affect the immune system. These compounds, such as ternatin, petunidin, chlorogenic, taraxerol, campesterol, stigmasterol, beta-sitosterol, cytostanol, and 3-deoxy-3, 11-epoxy cephalotaxine, may affect the body's immune response to infection or disease. Mutagenicity refers to the ability of a compound to cause mutations in genetic material. Some compounds in this study are classified as active in terms of mutagenicity, such as kaempferol and quercetin, myricetin, baicalein, and anthraquinone, suggesting that these compounds can cause potentially harmful genetic changes. The compounds 3-deoxy-3, 11-epoxy cephalotaxine are predicted to have cytotoxic potential, which can affect the health of cells in the body. Further studies may be needed to confirm these predictions and identify more detailed toxic mechanism[15], [17].

Almost all the compounds in *C. ternatea* have a molecular weight that is well below the 500 g/mol limit recommended by Lipinski's Rule. A lower molecular weight tends to facilitate solubility in water and absorption by the body. Most of the compounds in *C. ternatea* have a negative log P value, showing their hydrophilic properties. Although some compounds, such as anthraquinone and taraxerol, have a positive log P value that shows higher hydrofobic qualities, this can affect the absorption and distribution of these compounds in the body. Compounds that have the potential to form more hydrogen bonds (more H-bond recipients and H-binders) have stronger interactions with molecules in the body. Most of the compounds in *C. ternatea* have a number of H-bounds that correspond to Lipinski's Rule criteria. Most compounds in *C. ternatea* have a high colon absorption prediction, which corresponds to predictions based on Log P parameters and a lower molecular weight, suggesting that these compounds have a good absorptive potential through the digestive tract. Some compounds, such as taraxerol, alpha-tocopherol, and gamma-tocoferol, have predictions of high levels of skin permeability, consistent with positive Log P values that indicate higher hydrophobic properties, making these compounds potential for use in transdermal formulations.

Some compounds in *C. ternatea* are predicted to undergo metabolism by various cytochrome P450 enzymes such as CYP1A2, CYPs2D6, and CYPS3A4, which can affect the rate of elimination and potential interactions with other drugs in the body. Some compounds in *C. ternatea* are predicted to be P-glycoprotein (P-gp) substrates, which can affect the elimination of target tissue and drug interactions. These compounds may require dose adjustments or consider potential drug interactions. Compounds with specific functional groups, such as phenol groups in kaempferol, quercetin, and others, can have certain toxic activities, including carcinogenic and mutagenic activity. Some compounds of certain functional groups can also have hepatotoxic or immunoxic potential. In this analysis, predictions of physiochemical parameters can provide initial clues about the potential pharmacokinetic properties and toxicity of the compounds in *C. ternatea*. However, it is important to remember that these predictions still require further experimental validation to confirm these relationships and identify potential side effects or more detailed health benefits of these compounds. In addition, other factors such as dosage, administration route, and interaction with other compounds can also influence the body's response to these compounds.

4. CONCLUSSION

The compounds in *C. ternatea* have a molecular weight that conforms to Lipinski's Rule, indicating good absorption potential. The hydrophobic properties of some compounds affect their distribution and permeability. Predicting metabolism and P-gp status provides insight into the pharmacokinetic effects. Experimental validation is required for confirmation.

5. ACKNOWLEDGEMENT

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P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

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Wrong Article You may have used the wrong article or pronoun. Proofread the sentence to make sure that the article or pronoun agrees with the word it describes.

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Prep. You may be using the wrong preposition.

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Missing "," Review the rules for using punctuation marks.

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Article Error You may need to use an article before this word. Consider using the article **the**.

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Wrong Article You may have used the wrong article or pronoun. Proofread the sentence to make sure that the article or pronoun agrees with the word it describes.

Verb This verb may be incorrect. Proofread the sentence to make sure you have used the correct form of the verb.

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Possessive Review the rules for possessive nouns.

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Proofread This part of the sentence contains an error or misspelling that makes your meaning unclear.

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P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

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Article Error You may need to use an article before this word.

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Article Error You may need to use an article before this word.

Missing "," Review the rules for using punctuation marks.

Sp. This word is misspelled. Use a dictionary or spellchecker when you proofread your work.

Article Error You may need to remove this article.

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Article Error You may need to use an article before this word. Consider using the article **the**.

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