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Physicochemical, Pharmacokinetics, and Toxicity of South Africa Leaf *(Vernonia amygdalina* Delile*)* Sesquiterpene Lactone Compounds by *In Silico*

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Abstract

Cancer is a disease caused by malignant growth that can occur in humans, animals and plants. Cancer treatment with chemotherapeutic agents is still the main option in cancer treatment. Various efforts to develop new treatment methods are needed for more effective cancer therapy one of them is cyclophosphamide. The sesquiterpene lactone compounds contained in South Africa Leaf (*Vernonia amygdalina* Delile) contribute to its pharmacological effects as anticancer for several cancers. This study aims to determine the pharmacokinetic profile and toxicity profile of various sesquiterpene lactone compounds contained in South Africa Leaf (*Vernonia amygdalina* Delile). This research begins with a search for the physicochemical properties and Canonical Simplified Molecular Input Line Entry System (SMILES) code with the assisted of the PubChem, followed by computational processing with the assisted of the pkCSM and ProTox-II. Analysis the physicochemical properties, pharmacokinetics profile, and toxicity profile in comparison with cyclophosphamide as the standard anticancer drug. The results showed that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds had physicochemical properties that met Lipinski's rule (rule of five). Analysis of the pharmacokinetic profile of the parameters of absorption, distribution, metabolism, and excretion; also the toxicity profile showed that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds had a similar to better profile than cyclophosphamide. The South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds meet Lipinski's rule (rule of five), have a better pharmacokinetic profile, and have a lower toxicity levels than cyclophosphamide.

Keywords: *Vernonia amygdalina* delile • Sesquiterpene lactone • Silico • Physicochemical • Pharmacokinetics • Toxicity

Introduction

Pharmacokinetics is the entire process experienced by drug molecules from the time the drug enters the body until the drug is released from the body. The drug action processes discussed in this pharmacokinetics sequentially are absorption, distribution, metabolism, and excretion which will affect the half-life. (T½), peak time (Tmax), onset of action, and duration of action [1]. Toxicity is the ability of a material to give a toxic effect (poison) for a certain period of time due to chemical interactions in the body physiologically. Toxicity testing on a material is specific or alternative in nature to determine risk factors [2]. The process of discovering new drugs to the market is very complex, including preclinical trials and clinical trials to prove safety, efficacy, and quality [3]. The safety of a developed drug compound must be proven by its low toxicity during preclinical trials and clinical trials [4]. Scientific and economic pressures to minimize chemical and biological experiments as well as to quickly and precisely screen new compounds with better pharmacokinetic profiles and toxicity profiles have led to accelerated processes and developments in computational chemical engineering in the pharmaceutical industry [5].

The South Africa Leaf (*Vernonia amygdalina* Delile) is a plant from the Asteraceae family originating from Africa, including Zimbabwe and Nigeria, which has a tropical climate, can be grown wild or planted. South Africa Leaf (*Vernonia amygdalina* Delile) has various pharmacological effects due to various phytochemical content, including sesquiterpenes, triterpenes, flavonoids, alkaloids, saponins, tannins, and glycosides [6]. The pharmacological content of sesquiterpene lactone compounds contained in South Africa Leaf (*Vernonia amygdalina* Delile) has been shown to contribute to its pharmacological effects as anticancer for several cancers, namely lung cancer, colorectal cancer, cervical cancer, and breast cancer [7,8]. The sesquiterpene lactone compounds contained in South Africa Leaf (*Vernonia amygdalina* Delile) were vernodalol, vernodalin, vernolepin, vernomygdin, vernolide, hydroxyvernolide [9].

Cancer is a disease caused by malignant growth that can occur in humans, animals and plants. Cancer is excessive cell proliferation, generally embryonic, pressing, and destroying the surrounding tissue (invasive). Cancer treatment with chemotherapeutic agents is still the main option in cancer treatment [10]. However, the existence of multiple drug resistance mechanisms results in reduced efficacy of chemotherapy drugs [11]. Various efforts to develop new treatment methods are needed for more effective cancer therapy one of them is cyclophosphamide [12]. Alternative medicine such as the use of medicinal plants in the treatment of degenerative diseases can reduce side effects [13].

A good pharmaceutical compound is not enough to be efficacious but also must have a good pharmacokinetic profile and good safety profile. Physicochemical analysis, pharmacokinetic analysis and toxicity analysis of the sesquiterpene lactone compounds of South Africa Leaf (*Vernonia amygdalina* Delile) *in silico* have not been reported. This study aims to determine the pharmacokinetic profile and toxicity profile of various sesquiterpene lactone compounds contained in South Africa Leaf (*Vernonia amygdalina* Delile).

Methodology

Hardware

The hardware used in this study is a laptop with a Processor specification

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with the type Advanced Micro Devices, Inc. (AMD) Ryzen 7-3700U with Radeon Vega Mobile Gfx 2.30 GHz, Random Access Memory (RAM) with a capacity of 8 GB, and Read Only Memory (ROM) with a capacity of 512 GB.

Sofware

The software used in this study is PubChem (https://pubchem.ncbi.nlm.nih.gov) for molecular structure of analysis compounds, pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) and ProTox-II (https://tox-new.charite.de/protox_II/index.php?site=compound_input) for pharmacokinetic analysis and toxicity analysis.

Prediction of the physicochemical properties, pharmacokinetic properties, and toxicity properties of the South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds (vernodalol, vernodalin, vernolepin, vernomygdin, vernolide, hydroxyvernolide) as a test compound and cyclophosphamide as a comparison compound (standard oral chemotherapy) begins with a search for the physicochemical properties and Canonical Simplified Molecular Input Line Entry System (SMILES) code with the assisted of the PubChem website, followed by computational processing with the assisted of the pkCSM website and ProTox-II websites. Ends with an analysis of the physicochemical properties, pharmacokinetic properties and toxicity properties of the computational data in comparison with cyclophosphamide as the standard anticancer drug.

Results and Discussion

The structure of the compound was obtained from PubChem in the Simplified Molecular Input Line Entry System (SMILES) format for physicochemical analysis, pharmacokinetic analysis, and toxicity analysis by *in silico* with pkCSM and ProTox-II. Figure 1 shows the structure of South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and Doxorubicin for pharmacokinetic analysis and toxicity analysis.

Preliminary analysis of the physicochemical properties was carried out to assess the fulfillment of Lipinski's rule (rule of five) of the compounds to be analyzed. Analysis of physicochemical properties includes hydrogen bond donors, hydrogen bond acceptors, molecular mass, and partition coefficient obtained from PubChem. Table 1 shows the results of the physicochemical analysis of South Africa Leaf (*Vernonia amygdalina* Delile) Sesquiterpene Lactone Compounds and Doxorubicin.

Lipinski's rule (rule of five) requires a molecular mass of less than 500 daltons; partition coefficient not more than 5; hydrogen bond donors not more than 5; hydrogen bond acceptors not more than 10. The above analysis is known as Lipinski's rule (rule of five) because all values are multiples of the number five. Active drugs with oral administration must comply with Lipinski's rule (rule of five) with the number of violations not more than 1 violation [14]. The results showed that both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide met Lipinski's rule (rule of five) so that all of them were candidates for active drugs with oral administration which is well absorbed through the gastrointestinal tract.

The number of rotating bonds is a parameter of the flexibility of a compound and is a parameter that is widely used in the process of discovering new drugs or drug candidates. A compound was declared to have good permeability and bioavailability having rotating bonds with an amount of less than 15. The results showed that both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide had the number of rotating bonds in the range of 1 to 8 so that all of them have good flexibility, permeability, and bioavailability [15].

Pharmacokinetic analysis was carried out by pkCSM with several parameters for absorption (intestinal absorption, and skin permeability), for distribution (distribution volume, fraction unbound, blood brain barrier permeability, and central nervous system permeability), for metabolism (CYP2D6 substrate CYP3A4 substrate CYP2D6 inhibitior, and CYP3A4 inhibitior), and for excretion (total clearance, and renal organic cation transporter substrate). Toxicity analysis was carried out with pkCSM with several parameters ames toxicity, hERG I inhibitor, hERG II inhibitor, median Lethal Dose (LD50), Lowest Observed Adverse Effect Level (LOAEL), and hepatotoxicity; also and ProTox-II with several parameters hepatotoxicity, carcinogenicity, immunotoxicity, and mutagenicity. Table 2 shows the results of the pharmacokinetic analysis and toxicity analysis of South Africa Leaf (*Vernonia amygdalina* Delile) Sesquiterpene Lactone Compounds and Doxorubicin.

Table 1. Physicochemical results of South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and doxorubicin.

Compounds	Molecular mass	Partition coefficient	Hydrogen bond donors	Hydrogen bond acceptors	Rotatable bonds
Vernodalol	392.4	1.2	2	8	8
Vernodalin	360.4	1.6	1	7	5
Vernolepin	276.3	1.3	1	5	1
Vernomygdin	364.4	1	1	7	3
Vernolide	362.4	0.9	1	7	3
Hydroxyvernolide	378.4	–0.3	2	8	4
Cyclophosphamide	261.1	0.6	1	4	5

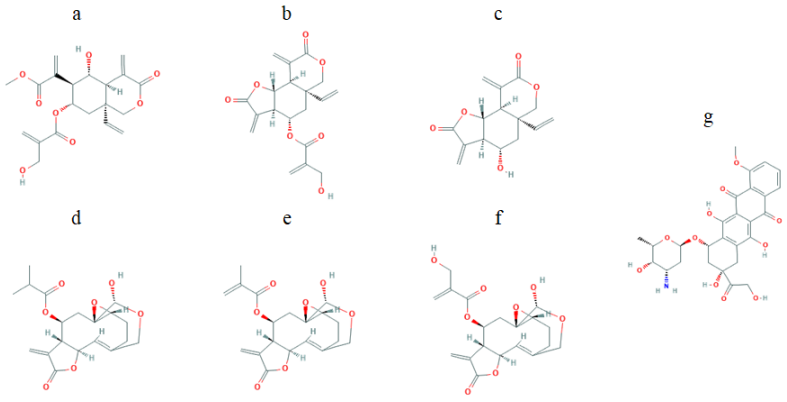

Figure 1. Structure of South Africa Leaf (*Vernonia amygdalina* Delile) Sesquiterpene Lactone Compounds and Doxorubicin for Pharmacokinetic Analysis and Toxicity Analysis.
*a: Vernodalol; b: Vernodalin; c: Vernolepin; d: Vernomygdin; e: Vernolide; f: Hydroxyvernolide; g: Cyclophosphamide

Table 2. Pharmacokinetic and toxicity results of South Africa Leaf (*Vernonia amygdalina Delile*) sesquiterpene lactone compounds and doxorubicin.

Property	Model name	A	B	C	D	E	F	G
Absorption	Intestinal absorption (human) (% Absorbed)	75.395	96.144	75.645	100	100	96.455	91.508
Absorption	Skin permeability (log Kp)	-3.447	-3.222	-3.867	-3.118	-3.086	-2.908	-2.281
Distribution	Vdss (human) (log L/kg)	-0.197	-0.236	0.017	0.107	0.156	0.198	-0.198
Distribution	Fraction unbound (human) (Fu)	0.509	0.419	0.491	0.404	0.452	0.551	0.586
Distribution	BBB permeability (log BB)	-0.48	-0.684	-0.193	-0.571	-0.566	-0.423	0.195
Distribution	CNS permeability (log PS)	-3.049	-3.061	-2.975	-3.072	-3.092	-3.179	-3.055
Metabolism	Cyp2d6 substrate (yes/no)	No	No	No	No	No	No	No
Metabolism	Cyp3a4 substrate (yes/no)	No	Yes	No	Yes	Yes	No	No
Metabolism	Cyp2d6 inhibitior (yes/no)	No	No	No	No	No	No	No
Metabolism	Cyp3a4 inhibitior (yes/no)	No	No	No	No	No	No	No
Excretion	Total clearance (log ml/min/kg)	0.747	0.725	0.665	1.053	1.184	1.267	0.628
Excretion	Renal oct substrate (yes/no)	No	No	No	No	No	No	No
Toxicity	Ames toxicity (yes/no)	Yes	Yes	Yes	Yes	No	No	Yes
Toxicity	Herg I inhibitor (yes/no)	No	No	No	No	No	No	No
Toxicity	Herg II inhibitor (yes/no)	No	No	No	No	No	No	No
Toxicity	Oral rat acute toxicity (LD50) (mol/kg) and (mg/kg_bw)	2.388	2.285	2.014	3.413	3.467	3.949	3.569
		937.051	823.514	556.468	1243.697	1256.44	1494.301	931.865
Toxicity	Oral rat chronic toxicity (LOAEL) (log mg/kg_bw/day)	1.971	1.768	1.405	1.134	1.107	2.087	0.518
Toxicity	Skin sensitisation (yes/no)	No	No	No	No	No	No	Yes
Toxicity	Hepatotoxicity (yes/no)	No	No	No	No	No	No	No
Toxicity	Carcinogenicity (yes/no)	No	No	No	Yes	No	No	Yes
Toxicity	Immunotoxicity (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes	No
Toxicity	Mutagenicity(yes/no)	No	No	No	Yes	Yes	Yes	Yes

Note: *A : Vernodalol; B : Vernodalin; C : Vernolepin; D : Vernomygdin; E : Vernolide; F : Hydroxyvernolide; G : Cyclophosphamide

Compounds that have absorption of more than 70% are declared as drugs with good absorption, while compounds that have absorption of less than 30% are declared as drugs with poor absorption. The intestine is the main site for absorption of the main drug in oral drug administration [16]. The results showed that the predicted intestinal absorption values for both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide were in the range of 75% to 100%. The predicted intestinal absorption values indicate that all of these compounds have good absorption.

The compound was declared to have good skin permeability with a log Kp (value of skin permeability) less than -2.5. The results showed that the predicted skin permeability value (log Kp) for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was in the range -2.908 to -3.867, while the predicted skin permeability value (log Kp) for cyclophosphamide was -2.281. The predicted skin permeability value (log Kp) shows that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds have better skin permeability than cyclophosphamide.

The volume of distribution is the theoretical volume of the total dose of drug required to be evenly distributed to give the same concentration as in blood plasma. A high volume of distribution indicates that many drugs are distributed at high concentrations in tissues and distributed at low concentrations in plasma [17]. Suatu senyawa dikategorikan mempunyai volume distribusi rendah bila logVD value less than -0,15, dan dikategorikan mempunyai volume distribusi tinggi bila logVD value less than 0.45 [18]. The results showed that the predicted logVD value for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was in the range -0.236 to 0.198 (vernodalin the lowest and hydroxyvernolide the highest), while the predicted logVD value for cyclophosphamide was -0.198. The predicted unbound fraction for vernodalin and vernodalol not significant difference to cyclophosphamide, so it is possible to have a similar distribution profile.

The concentration of unbound drug in the systemic circulation will determine the concentration of the active drug and exert a pharmacological effect [19]. The results showed that the predicted unbound fraction for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was in the range 0.404 to 0.551 (vernomygdin the lowest and hydroxyvernolide the highest), while the predicted unbound fraction for cyclophosphamide was 0.586. The predicted unbound fraction for hydroxyvernolide not significant difference to cyclophosphamide, so it is possible to have a similar pharmacological effect between South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide.

The ability of a drug to cross the brain (blood-brain barrier and central nervous system) is an important parameter to reduce the toxicity of a drug to the brain or to increase the efficacy of a drug to the brain [20]. The drug permeability to brain through the blood-brain barrier is expressed as logBB value, which is the logarithmic ratio of the drug concentration in the brain to the drug concentration in the plasma. The higher the logBB value, the higher the drug penetration ability [21]. The compound is declared easy to penetrate the blood brain barrier if the logBB value is higher than 0.3; and declared difficult to penetrate the blood brain barrier if the logBB is lower than -1.0 [22]. The results showed that the logBB values for both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide were in the range of -0.684 and 0.195. The overall predicted logBB value is in the range between -1.0 and 0.3, so it can be predicted that all of these compounds have are moderately to penetrate the blood brain barrier.

In addition to the logBB value, there is another gold standard for measuring permeability in the brain, namely logPS value. The logPS value is considered a more informative data [23]. The drug permeability to brain to the central nervous system is expressed as logPS value, which is the logarithmic of permeability surface-area product to central nervous system. The higher the logPS value, the higher the drug penetration ability [24]. The

compound is declared easy to penetrate the central nervous system if the logPS value is higher than -2; and declared difficult to penetrate the blood brain barrier if the logPS is lower than -3 [25]. The results showed that the logPS values for both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide were in the range of -3.179 and -2.975. The overall predicted logPS value is lower than -3 (except vernolepin), so it can be predicted that all of these compounds have are moderately to penetrate the central nervous system.

Metabolic enzymes in the liver that act as biomarkers to determine the effect of drug response are Cytochrome P450 (CYP450) enzymes which oxidatively metabolize endogenous substrates and foreign compounds. There are 10 types of Cytochrome P450 (CYP450) enzymes that are major in the human liver which is a group of CYP1, CYP2 and CYP3 isoenzyme families involved in drug metabolism. The most dominant types of Cytochrome P450 (CYP450) enzymes found in humans are CYP2D6 (20.0%) and CYP3A4 (30.2%) [26].

One of the metabolic pathways for drugs that enter the body is through the conversion pathway by cytochrome P450 enzymes. Metabolism by Cytochrome P450 (CYP450) enzymes requires a substrate; drugs as substrates will be converted into metabolites that can be excreted [27]. The results predict that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds are not CPY2D6 substrates and CYP3A4 substrates, except vernodalin, vernomygdin, dan vernolide, so that it is predicted not to be rapidly metabolized and not quickly excreted.

Inhibition of Cytochrome P450 (CYP450) enzymes can lead to clinically adverse drug interactions [28]. If a drug is not a substrate in the metabolic process by the cytochrome P450 enzyme, the process of drug washout from the body becomes slower and the dose of the drug can be minimized [29]. The results predict that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds do not inhibit CPY2D6 enzymes and CYP3A4 enzymes, so that it is predicted not to cause clinically adverse drug interactions.

The total clearance parameter is combination of hepatic clearance (metabolism in the liver and bile) and renal clearance (excretion through the kidneys). This is related to bioavailability, and it is important to determine the dose level in achieving steady-state concentrations [30]. The results showed that the predicted total clearance value (log mL per minute per kg body weight) for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was in the range 0.665 to 1.267, while the predicted total clearance value (log mL per minute per kg body weight) for cyclophosphamide was 0.628. The predicted total clearance value (log mL per minute per kg body weight) shows that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds have faster excretion than cyclophosphamide.

Kidney has Organic Cation Transporter (OCT) is a transporter that plays an important role in the disposition and excretion of drug compounds that have been known to play a role in drug entry by bridging the transport of several cation compounds from basolateral to apical renal tubular cells [31]. The isoform Organic Cation Transporter 2 (OCT2) is the Organic Cation Transporter (OCT) that is most responsible for drug accumulation in the kidney. The isoform Organic Cation Transporter 1 (OCT2) is the Organic Cation Transporter (OCT) that is most responsible for drug accumulation in the liver [32]. Drug compounds which are organic cation transporter substrates in tissues can cause drug toxicity in certain organs. Prediction results indicate that both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide are not substrates for Organic Cation Transporters (OCT), so they do not cause drug toxicity to organs.

Mutagenic test is a primary screening test to determine the possibility of mutagenicity of a drug compound. Ames test is one of the methods used to detect the mutagenic effect of a drug substance based on a reverse mutation system. From several studies, substances that are mutagenic may be carcinogenic [33]. Mutations are permanent changes and are chemical reactivity between genes and chemicals. Mutations in genes can cause many genetic disorders that result in certain cancers or syndromes [34]. Cancer is a disease that is characterized by the presence of abnormal cells/tissues that are malignant, grow quickly and uncontrollably and can spread to other places in the patient's body [35]. From the research, it is predicted that vernolide and hydroxyvernolide were negative on ames toxicity; vernodalol, vernodalin, and vernolepine were negative for mutagenicity and carcinogenicity; only vernomygdin and cyclophosphamide were positive in ames toxicity, mutagenicity, and carcinogenicity.

Cardiotoxicity is a condition of the occurrence of heart damage and dysfunction due to exposure to toxic chemical compounds or drug compunds [36]. The cardiotoxicity of the drug arises as a result of inhibition of the human ether-a-go-go related gene (hERG) that causes blockage of potassium ion channels. The blockage will cause a prolongation of the QT interval of the heart, which is a severe life-threatening cardiac side effect [37]. Hepatotoxicity (from the word hepatic toxicity) is injury or damage to the liver caused by chemicals or drugs. Hepatotoxicity caused by the use of the inappropriate medicine both type and dose [38]. The results of the prediction of cardiotoxicity showed that both South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds and cyclophosphamide did not inhibit human ether-a-go-go related gene (hERG) so it did not cause toxicity to the heart.

Immunotoxicity is a side effect that occurs in the immune system caused by exposure to foreign agents both chemical compounds and drug substances [39]. The presence of foreign agents or xenobiotic agents that enter the body will interfere with the work of the endocrine system in producing hormones, interfere with the work of the liver for activation of hepatotropic comolement protein factors, and disrupt the nervous system. Then xenobiotic agents produce cytokines that cause suppression of the immune system in the host and cause an increase in immune allergy or immunoallergy [40].

The Lowest Observed Adverse Effect Level (LOAEL) is the lowest concentration of a substance or drug that can cause adverse effects. The lower value of Lowest Observed Adverse Effect Level (LOAEL), the more toxic the compound [41]. The prediction results for the lowest observed adverse effect level (LOAEL) showed that the dose range for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was 1.107 mg per kg body weight to 2,087 mg per kg body weight, while for cyclophosphamide was 0.518 mg/kg body weight. Overall Lowest Observed Adverse Effect Level (LOAEL) obtained from South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds has a higher value than cyclophosphamide, this value indicated that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds are less toxic than cyclophosphamide. All the South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds are predicted not to cause skin sensitization, while cyclophosphamide predicted to cause skin sensitization. So that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds are of higher safety on the skin and lower toxicity to the skin.

Median lethal dose (LD50) is the dose of a substance or drug that can cause death to 50% of test animals. The lower value of median lethal dose (LD50), the less safety the compound [42]. Prediction results for the median lethal dose (LD50) obtained that the dose range for South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds was 556,469 mg per kg body weight per day to 1494,301 mg per kg body weight per day, while for cyclophosphamide was 931,865 mg per kg body weight per day. Overall median lethal dose (LD50) obtained from South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds has a higher value than cyclophosphamide (except vernodalin and vernolepine has a lower value than cyclophosphamide), this value indicated that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds are more safety than cyclophosphamide.

South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds have lower toxicity and better safety than cyclophosphamide. South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds were only more toxic in terms of immunotoxicity, whereas cyclophosphamide was more toxic in terms of ames toxicity, mutagenicity, carcinogenicity, and hepatotoxicity. Although there are several compounds in the South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds which also have toxicity, ames toxicity, mutagenicity, carcinogenicity, and hepatotoxicity [43]. However, the content of sesquiterpene lactone compounds in South Africa Leaf (*Vernonia amygdalina* Delile) is in small and varied amounts and is used in small doses. This is because the pharmacological effects caused by South Africa Leaf (*Vernonia amygdalina* Delile) are the result of addition or synergism between one sesquiterpene lactone compound and other sesquiterpene lactone compound. The use of natural ingredients has higher safety and lower toxicity than pure medicinal chemical compounds which are the result of synthesis [44].

Conclusion

The results of the research for prediction on the physicochemical profile, pharmacokinetic profile and toxicity profile of the South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds compare to cyclophosphamide can be concluded that South Africa Leaf (*Vernonia amygdalina* Delile) sesquiterpene lactone compounds meet Lipinski's rule (rule of five), have a better pharmacokinetic profile, and have a lower toxicity levels than cyclophosphamide.

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Conflict of Interest

The authors declare there is no conflict of interest in this research and there is no onflict of interest in this article.

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