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In Silico Study of Sesquiterpene Lactone Compounds from South Africa Leaves (*Vernonia amygdalina* Del.) as Antimalarial and Anticancer

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Abstract: Malaria due to the development of resistance by the most lethal causative parasitic species. New drugs required to treat sensitive and drug-resistant strains of malaria. Cancer is one of the main causes of death worldwide. The current tendency in the treatment of cancer pursues to increases its effectiveness and diminishes its adverse effects. Breast cancer is the most common among women. South africa leaves (*Vernonia amygdalina* Del.), contains sesquiterpene lactones, such as: hydroxyvernolide, vernolide, vernodalol, vernolepin, and vernodalin. Traditional medicine practitioners use the plant as an antimalarial and anticancer. The research was conducted by in silico docking of enzyme Plasmepsin I as antimalarial and enzyme 17 - β Hydroxysteroid Dehydrogenase I as anticancer with sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.). The objective research was to determine the activity of the sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) as a potential inhibitor for enzyme Plasmepsin I as antimalarial and enzyme 17 - β Hydroxysteroid Dehydrogenase I as anticancer by using in silico docking method. The models of protein enzyme enzyme Plasmepsin I and enzyme 17- β Hydroxysteroid Dehydrogenase I downloaded via Protein Data Bank (PDB) with code 3QS1 and 3HB5, then performed docking process using the PLANTS program and visualized by Yasara program. Docking score being evaluated as the docking process results. Docking score for hydroxyvernolide, vernolide, vernodalol, vernolepin, vernodalin, and chloroquine with enzyme Plasmepsin I respectively are – 71,1886; – 67,5105; – 80,5529; – 62,5758; – 71,4922; and – 80,5586. Docking score for hydroxyvernolide, vernolide, vernodalol, vernolepin, vernodalin, and tamoxifen with enzyme 17 - β Hydroxysteroid Dehydrogenase I respectively are – 71,1886; – 89,4629; – 99,0976; – 80,2207; – 90,3060; and – 87,9400. Vernodalol shown the better effect than hydroxyvernolide, vernolide, vernolepin, and vernodalin as antimalarial and anticancer. sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) can offer useful references for directing the molecular design of lead compound with improved activity.
Key Words: Docking, In Silico, *Vernonia amygdalina*, Antimalarial, Anticancer, Plasmepsin I, 17 - β Hydroxysteroid Dehydrogenase I.

Introduction

Target and lead discovery constitute the main components of today's early pharmaceutical research. In silico approaches contribute significantly to early pharmaceutical research and are especially important in target and lead discovery. With the near completion of the human genome sequencing, bioinformatics has established itself as an essential tool in target discovery and the in silico analysis of gene expression and gene function are now an integral part of it, facilitating the selection of the most relevant targets for a disease under study [1].

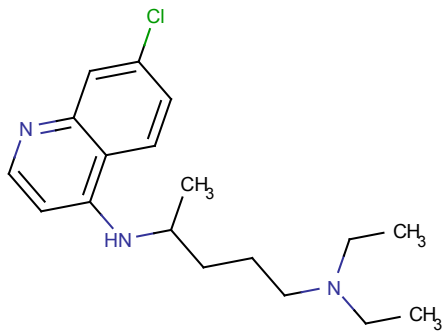
Malaria is a major public health problem mainly due to the development of resistance by the most lethal causative parasitic species, *Plasmodium falciparum* to the mainstay drugs like chloroquine. New drugs with unique structures and mechanism of action are urgently required to treat sensitive and drug-resistant strains of malaria. Antimalarial activity of several sesquiterpene lactones have been documented [2]. Enzyme Plasmepsin

I from *Plasmodium falciparum* are thought to initiate degradation of the native hemoglobin molecule. Enzyme Plasmepsin I could be blocked by chloroquine by by pH disrupting [4]. Specific inhibitor of enzyme Plasmepsin I, kill cultured *Plasmodium falciparum* parasites, most probably by blocking hemoglobin degradation [5].

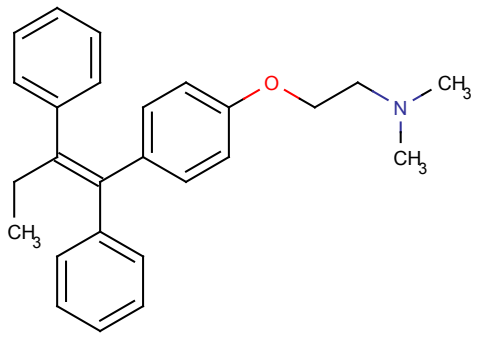
Cancer is considered at the moment one of the main causes of death worldwide. The current tendency in the treatment of cancer pursues to obtain a more successful treatment that do not increases alone its effectiveness but rather it diminishes its adverse effects. In these new therapeutic slopes the treatments are included that modify the biological answer, starting from emergent pharmacological agents able to modulate the transduction of signs inducing a selective death of the tumoral cells [3]. Breast cancer is the most common type of cancer among women. Treatment for breast cancer could be done by hormone therapy. Tamoxifen was effective hormone therapy that blocks estrogen's activity in the body [6]. Major risk factors for breast cancer are difficult to control at the individual level, and effective prevention of the disease is unlikely [7]. Enzyme 17 - β Hydroxysteroid Dehydrogenase I expressed in some breast cancer specimens. The presence of enzyme 17 - β Hydroxysteroid Dehydrogenase I in breast cancer cells may thus be an important factor regulating estrogen exposure and the estrogen responsive growth of breast cancer tissue. Another way to reduce the enzyme estrogen effect on breast cancer is to directly decrease the amount of synthesized enzyme estrogens. The most potent pathways for inhibition is enzyme 17 - β Hydroxysteroid Dehydrogenase I pathways. An interesting possibility in the prevention and treatment of enzyme estrogen dependent breast cancer is to use enzyme 17 - β Hydroxysteroid Dehydrogenase I inhibitors [8]. Sesquiterpene lactones constitute a large and diverse group of biologically active plant compounds that possess antitumor activity [9].

Vernonia amygdalina Del., is a perennial shrub that belongs to the family *Asteraceae* and grows throughout tropical Africa. It is probably the most used medicinal plant in the genus *Vernonia.* Traditional medicine practitioners use the plant as an antimalarial and anticancer [10]. *Vernonia amygdalina* Del., has been shown to have cancer cell inhibition and cytotoxic effects [11]. It is often utilised as edible vegetable. Their therapeutic potencies had relevance with phytochemical content of *Vernonia amygdalina* Del., and widely accepted anticancer properties of in traditional medicine [12]. The sesquiterpene lactones are related compounds were isolated were isolated as constituents of biological significance [13]. Some of the identified sesquiterpene lactones are hydroxyvernolide, vernolide, vernodalol, vernolepin, and vernodalin [10&13]. Table 1 below shown the structure of chloroquine (standard drug as antimalarial), tamoxifen (standard drug as antimalarial), and some of the identified sesquiterpene lactones from south africa leaves (*Vernonia amygdalina* Del.)

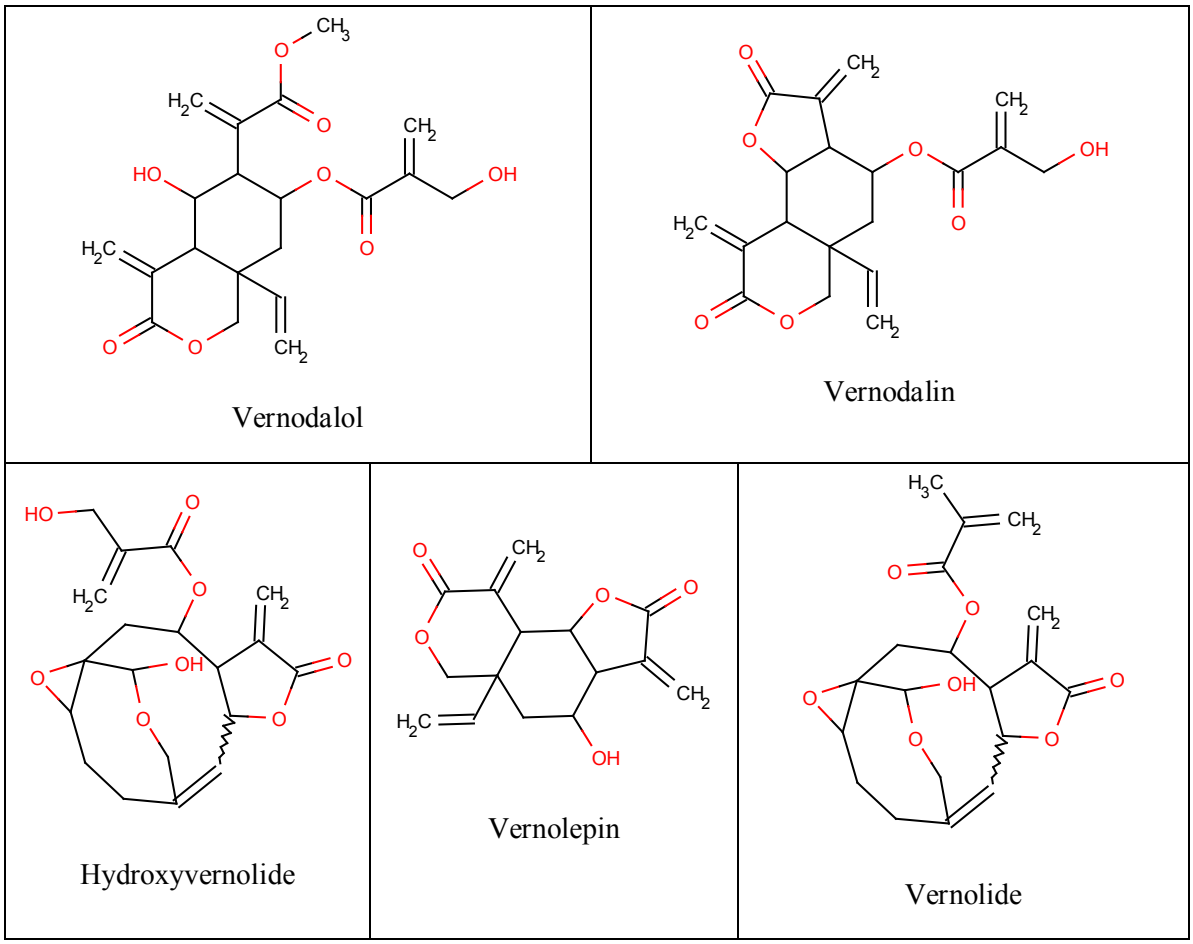
Table 1. Structure of chloroquine (standard drug as antimalarial), tamoxifen (standard drug as antimalarial), and some of the identified sesquiterpene lactones from south africa leaves (*Vernonia amygdalina* Del.)



Chloroquine



Tamoxifen



Therefore, there is an increased interest to identify potential activity of sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) to enzyme Plasmepsin I (as the antimalarial target) compared with chloroquine as the antimalarial standard compound and to enzyme 17 - β Hydroxysteroid Dehydrogenase I (as the anticancer target) compared with tamoxifen as the anticancer standard compound by in silico docking.

Research Method

Fujitsu T Series (T4310) operated by Windows 7 Home Premium, Intel® Core™ 2 Duo CPU T660 @ 2.20 GHz, 32-bit, harddisk 320 GB, and RAM memory 4.00 GB was used to run molecular docking processes. In silico docking used PLANTS program and visualized by Yasara program. Connector for Windows Operation System to Linux Operation System was done by Co Pendrive Linux KDE program. Model of three dimensions enzyme structures used in this research were enzyme Plasmepsin I (Protein Data Bank code 3QS1) and enzyme 17 - β Hydroxysteroid Dehydrogenase I (Protein Data Bank code 3HB5) obtained through the Protein Data Bank in the download RSCB (PDB) website (http://www.rcsb.org/pdb). Two and three dimensions model of lactone compounds from south africa leaves (*Vernonia amygdalina* Del.), chloroquine as the antimalarial standard compound, and tamoxifen as the anticancer standard generated by using the Marvin Sketch program.

Result and Discussion

KNI which was cocrystallized in the structure of 3QS1 enzyme Plasmepsin I was extracted and redocked into its original binding pockets. The Root Mean Square Deviation values resulted from these ligands redocking was 1.7099 Å. E2B which was cocrystallized in the structure of 3HB5 enzyme 17 - β Hydroxysteroid Dehydrogenase I was extracted and redocked into its original binding pockets. The Root Mean Square Deviation values resulted from these ligands redocking was 0,7452 Å. Both of Root Mean Square Deviation obtained was less than 2.0000 Å, a value typically used in evaluating the success of docking algorithms, indicating the docking methods was valid [14]. Figure 1 shown the redocking of KNI into the binding pocket 3QS1 enzyme Plasmepsin I and Figure 2 shown the redocking of E2B into the binding pocket 3HB5 enzyme 17 - β Hydroxysteroid Dehydrogenase I.

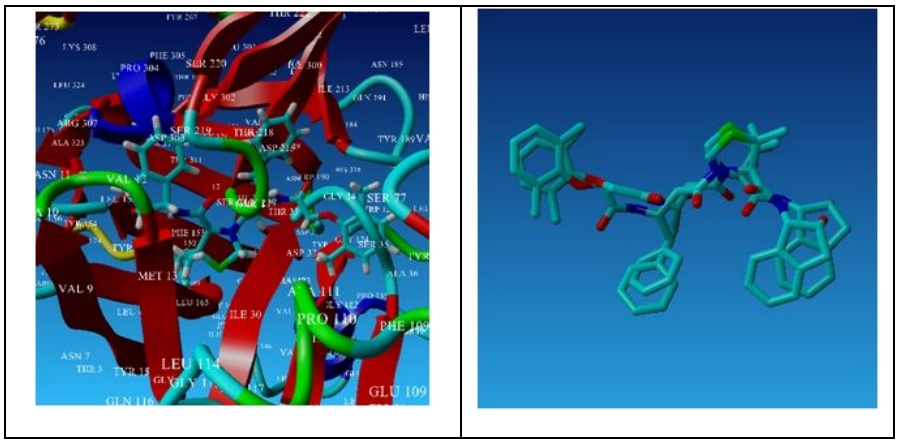


Figure 1. Redocking of KNI into the binding pocket 3QS1 enzyme Plasmepsin I

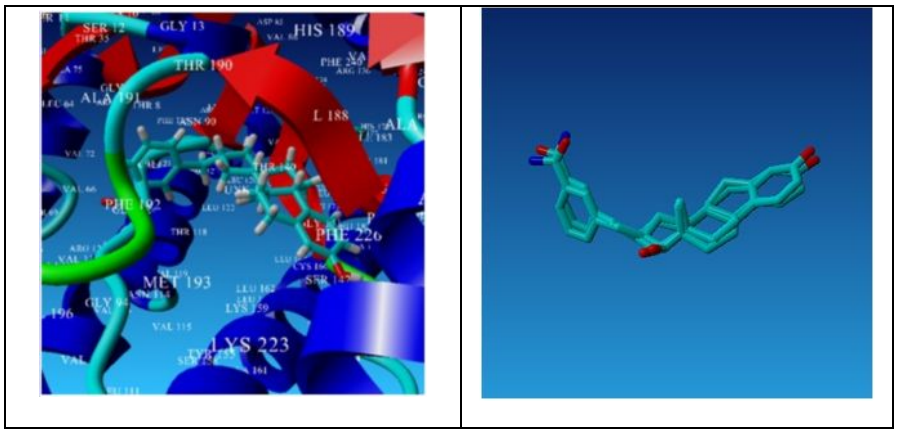


Figure 2.Redocking of E2B into the binding pocket 3HB5 enzyme 17 - β Hydroxysteroid Dehydrogenase I.

In silico docking between sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) to enzyme Plasmepsin I (as the antimalarial target) compared with chloroquine as the antimalarial standard compound resulting the docking score. Table 2 shows docking score result between ligand with the receptor enzyme Plasmepsin I.

Table 2.Docking score result between ligand with the receptor enzyme Plasmepsin I.

Number	Ligand	Docking Score
1	Vernolide	– 67,5105
2	Vernolepin	– 62,5758
3	Vernodalol	– 80,5529
4	Vernodalin	– 71,4922
5	Hydroxyvernolide	– 71,1886
6	Chloroquine	– 80,5586

Docking score of most sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) have higher docking score than chloroquine as the antimalarial standard compound. Only vernodalol has the most similar docking score to chloroquine; it means that has equal antimalarial activity on inhibition to enzyme Plasmepsin I compared to chloroquine. Hydroxyvernolide, vernolide, vernolepin, and vernodalin have the higher docking score than chloroquine; it means that have lower antimalarial activity on inhibition to enzyme Plasmepsin I compared to chloroquine.

Significant level of research for the development of antimalarial agents has reduced the spread and mortality of malaria. But still the pathogen continues to cause pathogenesis all over the world. The emergence of drug resistant species has made the situation more vulnerable. Plasmepsins have emerged into a potential drug targets for the purpose[15]. Sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) with the lower or equal inhibition to enzyme Plasmepsin I compared to chloroquine could

provide a base for the development of novel leads with better affinity and specificity against Plasmepsin I. Figure 3 shown visualisation of interaction between vernodalol and enzyme Plasmepsin I.

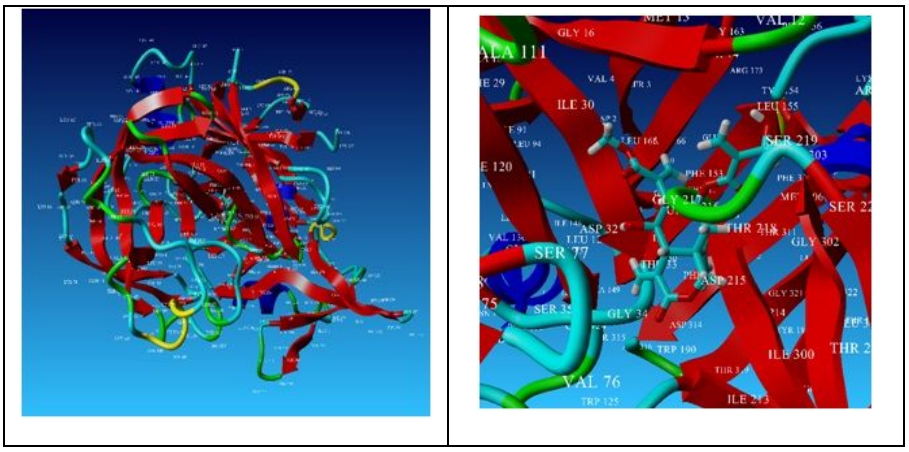


Figure 3.Visualisation of interaction between interaction between vernodalol and enzyme Plasmepsin I.

In silico docking between sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) to enzyme 17 - β Hydroxysteroid Dehydrogenase I (as the antimalarial target) compared with tamoxifen as the anticancer standard compound resulting the docking score. Table 3 shows docking score result between ligand with the receptor enzyme 17 - β Hydroxysteroid Dehydrogenase I.

Table 3. Docking score result between ligand with the receptor enzyme 17-β Hydroxysteroid Dehydrogenase I.

Number	Ligand	Docking Score
1	Vernolide	– 89,4629
2	Vernolepin	– 80,2207
3	Vernodalol	– 99,0976
4	Vernodalin	– 90,3060
5	Hydroxyvernolide	– 90,7054
6	Tamoxifen	– 87,9400

Docking score of most sesquiterpene lactone compounds from south africa leaves (*Vernonia amygdalina* Del.) have lower docking score than tamoxifen as the anticancer standard compound. Vernodalol, vernodalin, hydroxyvernolide, and vernolide have the lower docking score to tamoxifen; it means that has better anticancer activity on inhibition to enzyme 17-β Hydroxysteroid Dehydrogenase I compared to tamoxifen. Only Vernolepin has the higher docking score than chloroquine; it means that has lower anticancer activity on inhibition to enzyme 17 - β Hydroxysteroid Dehydrogenase I compared to tamoxifen.

Docking score represents binding affinity of the ligand to the enzyme, smaller docking score value shows stronger interaction [16]. These research results can offer useful references for directing the molecular design of lead compound with improved activity [17]. Increasing costs of drug development and reduced number of new chemical entities have been a growing concern for new drug development in recent years. Therefore, there is a need for the use of alternative tools to get answers on efficacy and safety faster, with more certainty and at lower cost. One such alternative tool is the *in silico* drug design or the computer aided drug design (CADD). *In silico* drug design can play a significant role in all stages of drug development from the preclinical discovery stage to late stage clinical development [18]. Figure 3 shown visualisation of interaction between vernodalol and enzyme 17 - β Hydroxysteroid Dehydrogenase I.

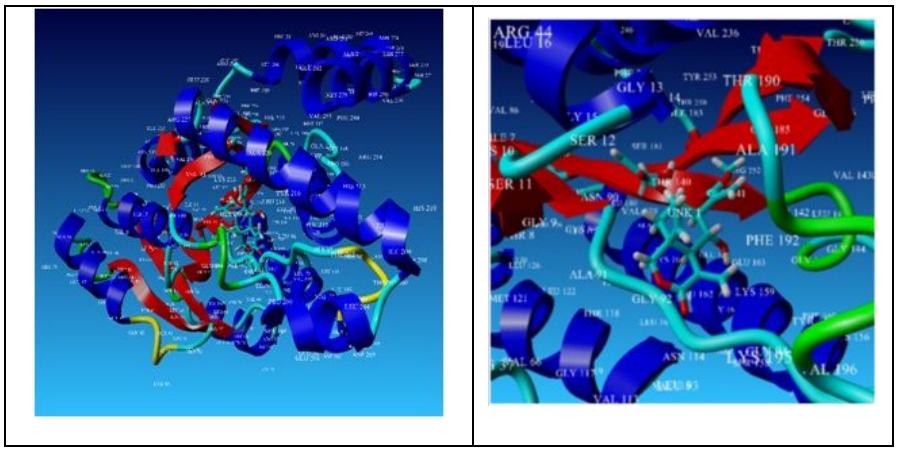


Figure 3.Visualisation of interaction between vernodalol and enzyme 17 - β Hydroxysteroid Dehydrogenase I.

Conclusion

Result show that some of the identified sesquiterpene lactones from south africa leaves (*Vernonia amygdalina* Del.), such as: hydroxyvernolide, vernolide, vernodalol, vernolepin, and vernodalin have the potential as antimalarial by inhibitors of enzyme Plasmepsin I, and have the potential as anticancer by inhibitors of enzyme 17 - β Hydroxysteroid Dehydrogenase I. Vernodalol shown the better effect than hydroxyvernolide, vernolide, vernolepin, and vernodalin as antimalarial and anticancer. Vernodalol with the lower docking score of bond means more stable and better for drug design because have the higher affinity. Hydroxyvernolide, vernolide, vernodalol, vernolepin, and vernodalin can offer useful references for directing the molecular design of lead compound with improved activity.

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