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(RESEARCH ARTICLE)

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Bisabolene compound extracted from cassia fistula and docked as antioxidant and vitamin E alternative predicted drug design

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Abstract

Cis-Z-alpha-bisabolene epoxide (bisabolene) compound is extracted from *Cassia fistula* plant bark, which is a medicinal tree that contains many useful drug substances, the compound can act as a drug predictably similar to vitamin E, with the same function as an antioxidant which can act on pregnane X receptor on the body cells. The gas chromatography-mass spectrometry (GC-MS) analysis was used to identify the constituents of the n-hexane extract. Drug Bank was used to find similar compounds. The ID of the pregnane x receptor (PXR) was retrieved from the PDB database. Then the bisabolene ligand was used for docking with the receptor using Swiss Dock. Finally, the Swiss ADME was used to study and predict the pharmacological parameters. It was found that bisabolene can act as an antioxidant and alternative to vitamin E in the pregnane x receptor and with good pharmacological predicted results. When bisabolene is used as an effective ligand with pregnane X receptor alternative to vitamin E, care must be taken because the compound can penetrate the blood-brain barrier (BBB) with a specific amount.

Keywords: *Cassia fistula;* GC-MS analysis; *Cis-Z*-alpha- bisabolene epoxide; Pregnane X receptor; Swiss Dock; Swiss ADME

1. Introduction

Higher plants, a source of bioactive compounds and play a main role in the maintenance of human health since ancient times (Agnel RA and Mohan VR.) [1] (Amutha IDJ and Kottai MA.) [2]. Large numbers of modern clinical drugs are of natural plant origin and natural products play important role in drug discovery (Cragg GM and Newman DJ.) [3]. The medicinal value of plants lies in some bioactive constituents that possess a definite physiological action on the human body. The most important of these bioactive compounds are flavonoids, alkaloids, steroids, and phenolic. (Prashanth Kumar., *et.al.*) [4], (Agnel RA and Mohan VR.) [1].

One of the important medicinal plants is *Cassia fistula*, *Cassia* is a genus of *Fabaceae* in the subfamily Caesalpiniodeae commonly called cassias, "cassia" is also the English name of *Cinnamomun aromaticum*. *Cassia* is a green shrub or small tree, up to 15m tall (BGCI and IUCN SSC Global Tree Specialist Group) [5].

The *Cassia fistula* bark contains 1-4% essential oil. The bark oil is a colorless to brownish-yellow liquid, mainly consisting of cinnamaldehyde, and lacking eugenol. The leaf oil also mainly consists of cinnamaldehyde, but the main constituent of the root oil is camphor (Agnaniet H., *et.al.*) [6].

Using normal hexane solvent, the GC-MS result of *Cassia fistula* extract produces many important compounds around twenty five, one of the most important is bisabolene. This compound has a therapeutic effect and acts as a supplement

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or treatment for the specific type of lacking compounds or as an antioxidant mainly vitamin E, which is the most important antioxidant, also can be used as an alternative for vitamin E.

Vitamin E is known as an antioxidant that can neutralize endogenous free radicals (Niki E and Traber MG.) [7]. This biological action of vitamin E is the main reason for interest and study in whether or not its antioxidant abilities may be used to prevent or treat some different conditions like diabetes, cardiovascular disease, cancer, ocular conditions, and others. There is a lack of existing evidence to support any such additional uses for vitamin E (Sesso HD. *et.al*,) [8], (Shklar G and Oh SK.) [9].

Vitamin E Supplement is taken daily by more than thirty five million people in the US potential. Recent clinical studies showed that there are several effects of vitamin E that may be directly related to its hepatic metabolism in an *in vitro* system. Rifampicin is a known stimulator of xenobiotic metabolism, both vitamin E and rifampicin activated the pregnane X receptor (PXR). PXR/RXR which is responsible for regulating a constellation of genes involved in xenobiotic detoxification, including oxidation, conjugation, and transporters (Di Masi, A, *et.al*.) [10]. Importantly, the cytochrome P450 (CYP), CYP3A, is involved in the hepatic detoxification of more than 50% of prescription drugs and regulates by PXR/RXR (Lyubov.S., *et.al*.) [11]. Vitamin E acts as a PXR ligand and has the ability to alter these PXR-mediated reactions.

2. Material and methods

2.1. Preparation of hexane extract

20g of powdered air-dried plant sample was extracted with distilled hexane for forty-eight hours at room temperature. The hexane extract was filtered and then concentrated under reduced pressure. This prepared extract was used for GC-MS analysis of bioactive components.

2.2. GC-MS analysis method

The spectrum was recorded by using a Shimadzu GC- 17A gas chromatography coupled to a Shimadzu GCMS- QP5050 mass Spectrometer with PBX-5 fused silica column (30.0m x 0.25mm, film thickness 0.25µm). The column temperature was programmed from 70-265 ℃ at 3°/min with helium as carrier gas at a flow rate/min. The temperature of the ion source was 170 ℃ and the electron energy of 70eV. Spectrum was acquired and processed by Nist 107 and Nist 21 GC-MS library.

2.3. Drug Bank

(https://go.drugbank.com/) is an online comprehensive database containing detailed information on drugs and drug targets. Information regarding similarities of bisabolene was obtained from Drug Bank.

2.4. Protein data bank (PDB)

The pregnane X receptor protein was used in this study. The three -dimensional crystal structure of this protein was downloaded from (https://www.rcsb.org/) (PDB) with a protein ID: 6S41.

2.5. Molecular Docking:

Docking was conducted using Swiss Dock **(**http:// www.swissdock.ch/) a web service) to predict the molecular interaction between the receptor (pregnane X) and the ligand (bisabolene). The final docking result can be visualized online and downloaded on the computer.

2.6. ADME Analysis

ADME (adsorption, distribution, metabolism, and excretion) analysis, physicochemical descriptors, pharmacokinetic properties, and drug-likeness were conducted by using the Swiss ADME server (http://www.swissadme.ch/.(Daina.A.*et.al*)[12].

3. Results and discussion

The Gas chromatography-mass spectrometry chromatogram of n-hexane extract (Fig. 1) exhibited the presence of twenty five compounds. Four major ((lines 2, 6, 8 and 20.) and eighteen ranked as moderately abundant compounds (lines 1,4,5,7,9,10,11,12,13,14,15,16,17,18,19,20,21 and 22), among these is bisabolene (line1, 1.04%). The remaining three compounds are of weak abundant. The MS spectrum of bisabolene is shown in (Fig. 2)

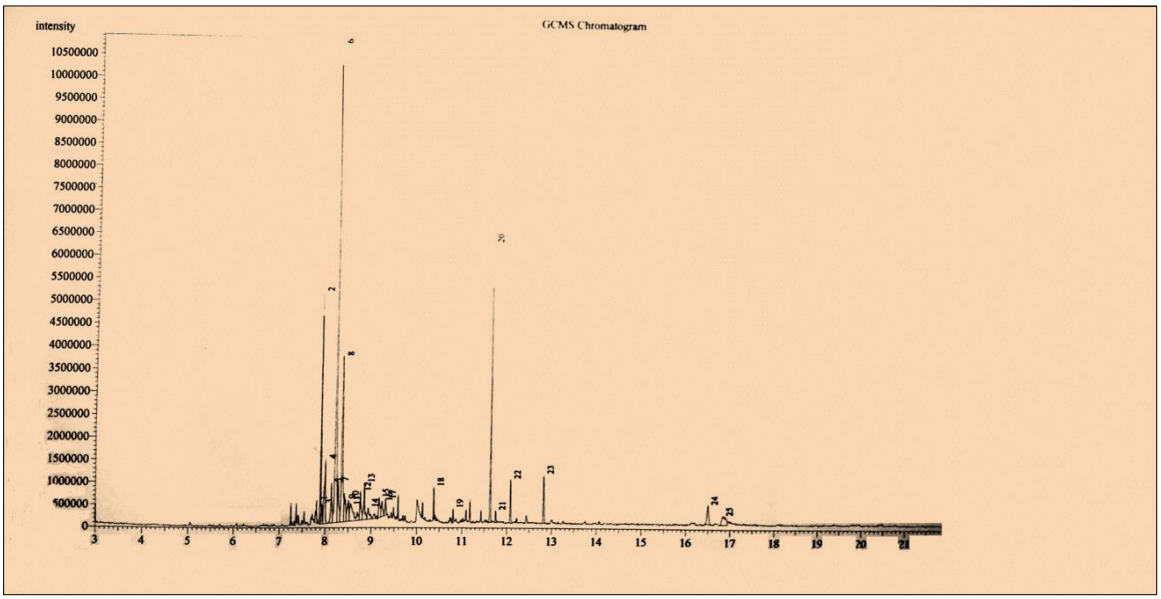


Figure 1 Gas chromatography-Mass spectrometry chromatogram of n-hexane extract

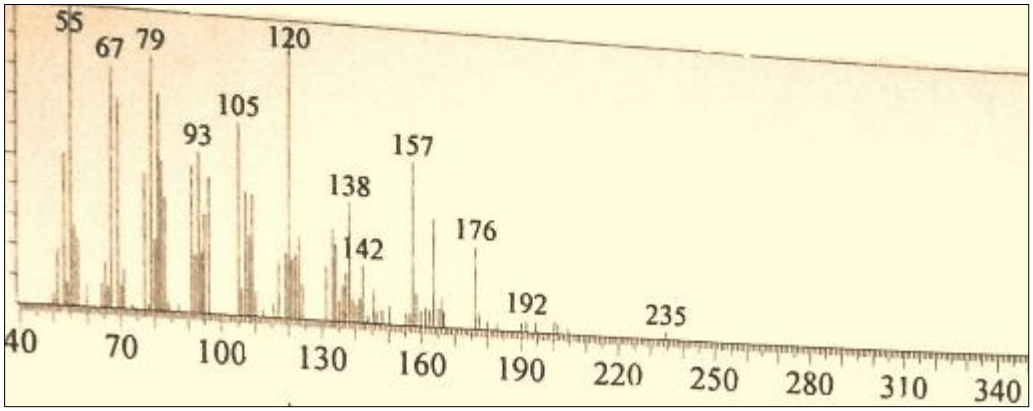
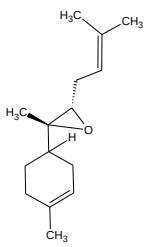
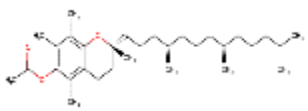


Figure 2 MS spectrum of bisabolene

Table 1 Structure of bisabolene and Tocopherol acetate differences and similarities

Compound name	Structure	Compound name	Structure
Cis-Z-alpha-Bisabolene epoxide		D-alpha-Tocopherol acetate	

Using Drug bank the compound bisabolene has similar chemical compound that use as a drug which is D-alpha-Tocopherol acetate, it is the primary form of vitamin E that is used as dietary supplements.

(Table1) shows the structures of Bisabolene and D-alpha-Tocopherol acetate differences and similarities.

Using swissDock the pregnane x receptor (PXR) protein (PDB ID: 6S41) in the cell and bisabolene compound were dock together (Fig. 3). The docking result shows how can the compound bisabolene bind to the receptor of pregnane x and acts as antioxidant.

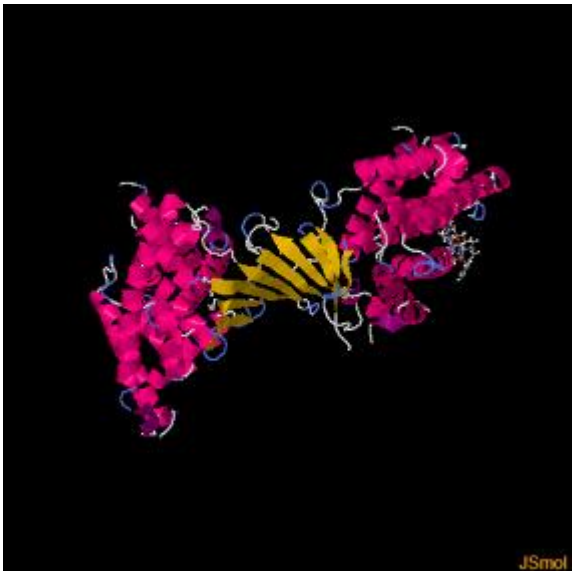


Figure 3 Docking result between PXR protein and Bisabene

In the Swiss ADME water solubility results (Table 2) bisabolene is found to be soluble compound in all classes and has log S (ESOL) = -3.41. In the first class the solubility 8.60e-02 mg/ml :3.90e-04 mol/I, second class log S (Aii) = -3.77 with solubility 3.76e-02 mg/ml : 1.7e-04 mol/I and third class log S(SILCOS-IT)= -3.17 with solubility1.50e-01 mg/ml, 6.79e-04 mol/l.

Table 2 Swiss ADME water solubility results

Solubility	**Bisabolene Result**
Log S (ESOL)	-3.41
Solubility	8.60e-0.02 mg/ml , 3.90e-0.04 mol/l
Class	Soluble
Log S (Aii)	-3.77
Solubility	3.76e-0.02 mg/ml , 1.71e-0.4 mol/l
Class	Soluble
Log S (SILICOS-IT)	-3.17
Solubility	1.50e-01mg/ml , 6.79e- 04 mol/l
Class	Soluble

In the Swiss ADME Pharmacokinetics results bisabolene (Table 3) revealed high GI absorption indicates that it can pass the blood brain barrier which in this case have to take care when use it as drug. The P-gp is essential in drug assimilation

(Ekins S.) [13] (Ekins,*et al*) [14]. An important role of p-gp is to protect the CNS from xenobiotic and if the molecule can act as an inhibitor, it reinforces the possibility of crossing the blood brain barrier (Maltrollo,V,G,*et al*,) [15].

Bisabolene inhibits all the p350 (CYC) enzymes except CYP2C9 and CYP2C19. The skin permeation result of bisabolene is log k = -4.94cm/s which means it can be delivered using water or other substances in the body (Prasanna,S,& Dorksen,R,J.) [16] (Donker,J,M. *et al*.) [17].

Table 3 Swiss ADME pharmacokinetic results

Pharmacokinetic	**Bisabolene Result**
G1 absorption	High
BBB permeate	Yes
P- gap substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.94 cm/s

The drug likeness results of bisabolene (Table 4) are evaluated using Lipinski, Ghose, Veber, Egan and Muegge rules using different parameters, all results showed bisabolene as a very good drug to use. (Burley,S,K.*et. al.*) [18]. The bioavailability score which measure the permeability of a compound as a good drug F<10(Grosdidier,A,*et.al*.) [19], bisabolene gives bioavailability score of 0.55.

Table 4 Swiss ADME Drug likeness results

Drug likeness	**Bisabolene result**
Lipinski	Yes, 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No, 1 violation , heteroatoms< 2
Bioavailability score	0.55

Medicinal chemistry helps the discovery of drugs and to find any problematic fragments in the molecule (Daiana, A, et al) [12].The medicinal chemistry results of bisabolene (Table 5) showed that according to Brenk bisabolene structure has two alerts, that is isolated alkene and three-member ring heterocycle, the structural alerts indicated by Brenk are purely based on the knowledge of a chemical parts known to be responsible for poor pharmacokinetics (Chen, X, *et al*) [20]. Bisabolene has a molecular weight of less than 220.35 With a 4.23 synthetic bioavailability score, it shows that bisabene compound is not a difficult drug to synthesize molecule (Ekins, S) [13]. The score is defined between 1 (easy synthesis) and 10 (very difficult to synthesize).

In the lipophilicity (logP) results (Maltorollo, V, G.*et al*) [15] (Table 6) bisabene showed a presented average of 3.90 for logP classified as optimal for good intestinal absorption. Some evidence showed that controlling lipophilicity among all physiochemical properties within a defined ideal range enhances the quality of a molecule and increases the probability of therapeutic success (Prasanna,S,& Dorksen.R.J.) [21].

Table 5 Swiss ADME Medicinal chemistry results

Medicinal Chemistry	Bisabolene Result
PAINS	0 alert
Brenk	2 alerts: Three membered heterocycle, isolated alkene
Lead likeness	No, 2 violations: MW. < 250 , X log P3> 3.5
Synthetic Accessibility	4.23

Table 6 Swiss ADME Lipophlicity results

Lipophlicity	Bisabolene Result
Log $P_{o/w}$ (iLogP)	3.58
Log $P_{o/w}$ XLogP3)	3.81
Log $P_{o/w}$ (WLogP)	4.25
Log $P_{o/w}$ (MLogP)	3.56
Log $P_{o/w}$ (SILICOS-IT)	4.31
Consensus Log $P_{o/w}$	3.90

4. Conclusion

Bisabolene compound is an organic compound extracted from *Cassia fistula* bark plant and can be used as an antioxidant and replace vitamin E action in pregnane x receptor that taking out free radicals from the body and regulates xenobiotic detoxification which include most of cell process like oxidation, conjugation and transport and mainly by regulate the two cytochromes p450, CYP3A involved in the hepatic detoxification. Bisabolene can act as a PXR ligand and altering the PXR- mediated reactions.

In this study the predicted pharmacological properties of bisabolene compound show it as a good ligand for pregnane x receptor and can be synthetic as a drug with little care from penetrating the blood brain barrier (BBB) and its metabolism. Noticeably it can replace vitamin E action or use as drug to treat its missing on shelf.

Recommendation

In this study the *Cis*-Z-alpha-bisabolene epoxide (Bisabolene) compound can be act as a drug ligand for pregnane x receptor and it must be under supervisor or specialist due to its action that can penetrate the blood brain barrier and its hepatic metabolism action so recommended that many other studies must done especially in pharmacological drug effect and how can specific and effective dose can be taken with revision of all metabolic action and assimilation, also recommended further studies must apply on wet lab before transfer the compound as a ligand drug. This way of drug designing and discovery become booming in the late years, so as to design and predict how is going to be the pharmacological and pharmacokinetics effect.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

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