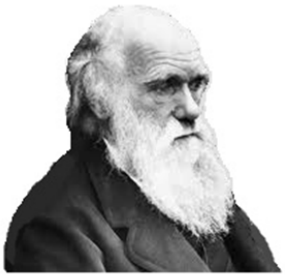
Available online at www.worldnewsnaturalsciences.com



World News of Natural Sciences

An International Scientific Journal

WNOFNS 55 (2024) 119-153 EISSN 2543-5426

Insilico Studies of activities of compounds from *Ricinodendron heudelotii* against inflammatory and oxidant enzymes Carbonic anhydrase

Ujupaul J. M. Ikezu[1] and **Sylvester N. Ugariogu**[2,*]

[1] Chemistry Department, Imo State University, Owerri, Nigeria

[2] Chemistry Department, Federal University of Technology, Owerri, Nigeria

*E-mail address: mastersylvester@yahoo.com

ABSTRACT

Medicinal plants have been acclaimed and documented over the years to play vital role in promoting human health. The study evaluated the activities of the compounds extracted from the *Ricinodendron heudelotii* seed against carbonic anhydrase enzyme which is responsible for inflammation and oxidation in the body. In this study, phytocompounds from the seed were extracted and characterized using gas chromatography coupled to a mass selective detector to identify the component phytochemicals responsible for its anti-oxidation and inflammatory activity. Site directed multi-ligand docking of the identified compounds was performance on Crystal structure of human Carbonic anhydrase I in complex with polmacoxib as the cocrystalline ligand with (PDB ID:5gmm). The compounds identified from GCMS results were compared with some standard anti-inflammatory and antioxidant drugs like Diclofenac, Indomethacin, Celecoxib, Naproxen and the cocrystaline ligand Polmacoxib. The docking result showed that the cocrystallized ligand have the best binding affinity of -8.5 kcal/mol followed by Naproxen (drug) -7.6 kcal/mol, phytocompound 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide and a commercial drug Celecoxib has the same affinity -7.5 kcal/mol, better than Diclofenac -7.0 kcal/mol, Indomethacin (drug) -6.7 kcal/mol, other phytocompounds like Phenol, 2-methoxy-4-(2-propenyl)-, acetate -6.4 kcal/mol, 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester -6.1 kcal/mol also showed good binding affinities with the protein showing that most of the compounds may have good anti-inflammatory and antioxidant properties there by validating the ethnomedical claims of the plant use as having anti-inflammatory potentials. The interactions of the phytocompounds with better binding affinity were visualized and their results proved that the dockings were done in the active sites with strong bonds. ADMET properties of the drugs, cocrystalline ligand and compounds with good binding affinities were carried out to check

(Received 15 May 2024; Accepted 16 June 2024; Date of Publication 18 June 2024)

for their adsorption, distribution, metabolism, excretion and toxicity properties. The result showed that the compounds and drugs have good absorption, distribution, metabolism with the human body and are not toxic to the body. The research justifies the local claims on the use of the plant and strengthens the relevance of these compounds as promising lead candidates for the treatment of anti-inflammatory diseases.

***Keywords*:** *Ricinodendron heudelotii*, carbonic anhydrase, Insilico studies, anti-inflammatory and antioxidant

1. INTRODUCTION

Medicinal plants have been reported to contain diverse groups of phytochemicals which gives them the therapeutic and physiological effects making them suitable for use in treating different diseases [1]. The major importance of using medicinal plants and their derivatives is due to their availability and affordability while still offering profound therapeutic benefits. The usage is also based on the belief that herbs might be more effective in treating certain diseases [2]. The therapeutic potential of these plants are linked to one or more compounds they contain which are termed phytochemicals [3].*Ricinodendron heudelotii* from the family *Euphorbiaceae*, genus *Ricinodendron*, commonly called the African oil-nut tree in English,"*Okwe*"in Igbo and "*Erimado*" in Yoruba, Nigeria while the Cameroonians call it "*Njansang"*was studied to determine the bioactive compounds responsible for its therapeutic properties Different parts of the tree have been used for treatments with the bark being the most efficaciously and most frequently used. The bark extract is used to cure cough and as antidote to poison [4].The bark decoction is used to relieve inflammations and it is equally employed as aphrodisiac. The bark is also used to ease sexual, fertility, menstrual, childbirth pain [5].It helps cure malaria, yellow fever, and dysentery and equally has diuretic functions [6].*Ricinodendron heudelotii* roots have been used as laxative and in treatment of stomach pain in Ghana and Nigeria [5].

The leaves and latex are used to extract guinea worm and as a purgative. It is commonly used in rural areas of Cameroon to prevent abortion. Recently, the antimicrobial effect of *R. heudelotii* extract [7] and the cytotoxic effect of isolated compounds from the leaf extract [8] were reported. It was also reported that the leaf extract exhibited regulatory role on the toxicity of artemisinin when co-administered with artemisinin[9].Antioxidants are molecules that fight free radical in the body, these free radical are compounds that can cause harm if their levels become too high. Reactive oxygen species are the upper most free radical in cells and are generated as a result of oxidative processes in the body[10]. Some of them include hydroxyl and hydrogen peroxide. Oxidative processes are unavoidable as they are important in energy metabolism and utilization of nutrients [11].

Antioxidants help to scavenge free radicals and eliminate them from the body system. Studies have shown a retroverted relationship between disease progression and disease genesis and intake of antioxidant rich foods [13]. Although synthetic antioxidants are available, they are out of reach of many due to high cost, reduced distribution and side effects [12]. Natural antioxidants are however very much available with minimal cost and showing little or no side effects. Compounds high in antioxidant ability are flavonoids and phenols. Trace elements such as copper, manganese and magnesium also act as antioxidants [13]. In small concentrations, ROS are important in the human system as they help in gene expression, regulation of signal

transduction and other biological processes [1]. In high concentrations however, ROS can have deleterious effects on biomolecules such as proteins, lipids and other biomolecules and eventually cause cell death. An excess of ROS is also implicated in the genesis of many diseases such as cancer and other age-related diseases including inflammation [15]. Inflammation which is the body's immune response to foreign substances as well as response to processes such as degeneration and cell death has been implicated in the genesis or progression of most diseases and medicinal plants have recently been used as potent anti-inflammatory therapy [16]. it is one of the innate immune responses of the body [18]. Many diseases have been related to the mechanism of oxidative stress and inflammation. It is therefore important to explore the anti-inflammatory and antioxidant abilities of *Ricinodendron heudelotii* which could further add to existing knowledge on the mode of action of the herbal plant.

Cyclooxgenase (COX) and Anhydrase (CA)

Cyclooxygenase-2 (COX-2) is up-regulated in stromal and inflammatory cells. The inducible COX-2 isoform is expressed during inflammation, in some cancers, and in brain tissue after global and focal ischemia. Tissue acidosis is a dominant factor in inflammation, and contributes to pain and hyperalgesia. Recently, compelling epidemiological and clinical evidence has documented the COX-independent effects of some COX-2 inhibitors (i.e., celecoxib, valdecoxib, and rofecoxib); among these effects are carbonic anhydrase (CA) inhibition.

Plate 1. Picture of the seed and fruit of seed of *Ricinodendron heudelotii*

Carbonic anhydrases are zinc metalloenzymes expressed in various cell types, including those of the kidney, where they act as general acid-base catalysts. The kidneys are also known

to express the highest concentration of COX-2 messenger ribonucleic acid. Celecoxib, like the prototypic CA inhibitor acetazolamide, is structurally characterized by an unsubstituted sulfonamide moiety. In the present study, we report that celecoxib exhibits the characteristics of a potent CA inhibitor, showing inhibitory human carbonic anhydrase II (hCAII) activity in the nanomolar range. [18].Among the class of nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors or "coxibs" selectively inhibit the activity of the inducible isoform of cyclooxygenase. Moreover, there is emerging evidence that the sulfonamide-type coxibs, but not the methylsulfones, display an inhibitory activity also against several isoforms of human carbonic anhydrase (CA, EC).The multiple pharmacological effects of the sulfonamide anti-inflammatory agents could be ascribed to the dual inhibition of CA and COX enzymes, supporting the evidence that inflammation and hypoxia pathways are involved in cancer onset and progression and suggesting that the antiinflammation activity of these compounds should be further explored for their possible use in the polypharmacology of cancer prevention and therapy [20]

2. MATERIAL AND METHOD

All the materials for the analysis were of analytical grade. Discovery Studio 2020 was used to prepare the protein and view the interaction. Pyrx was used for the docking. The protein used for the docking was a Crystal structure of human Carbonic anhydrase I in complex with polmacoxib as the cocrystalline ligand with (PDB ID:5gmm). Polmacoxib is not only a selective COX-2 inhibitor but also a potent inhibitor of carbonic anhydrases (CAs). Both CA I and CA II are highly expressed in the GI tract and kidneys, organs that are also thought to be the sites at which selective COX-2 inhibitors show their side effects. COX is a known inflammatory protein. The compounds from the seed extracts was docked on the protein to know there binding affinity and compared with that of the cocrystalline ligand and known anti-inflammatory drugs to determine the one with better binding affinity against the binding site of the disease protein.

Extraction of Phytochemicls

Ricinodendron heudelotii seeds were bought from a local market in Imo State washed with water and then dried for 2 weeks at room temperature. The seed following dryness was powdered with new mechanical grinder. The powdered seed was weighed (1.2 kg) and stored in amber coloured Winchester bottle. The powdered *Ricinodendron heudelotii* seed (500 g) were percolated with 1000 ml of redistilled ethanol (99 %) for 72 hours. The extracts were filtered and concentrated in a water bath at 55 °C and sent for GC-MS analysis [21].

GC-MS analysis

The crude sample was analyzed using Gas chromatography-Mass Spectrometer (GC-MS) instrument (Model: 7890 GC and 5977B MSD, Agilent Technologies USA). An HP-5 MS capillary standard non-polar column, L*I.D, 30 m, *0.25 mm, film thinkness: 0.25 µm, was used. The flow rate mobile phase (carrier gas: He) was set at 1.0 mL/min. In the gas chromatography part, the temperature programme (oven temperature) was set at 40 °C and raised to 250 °C at 50 °C / Min and injection volume 1 µl. The crude extract sample was dissolved in methanol (≥ 99.8 %, Sigma Aldrich, Darmstadt, Germany) and fully scanned at a

range of 40-650 m/z, and the results were compared and interpreted using National Institute of Standards and Technology (NIST). Mass spectral library database search programme [22].

Identification and preparation of ligands

The 3D structure-data files (SDF) of the compounds in the crude extract sample and some anti-inflammatory drugs were identified and downloaded from the PubChem database. They were minimized in PyRx virtual screening tool, using Universal Force Field at 200 steps. They were then converted to AutoDock ligands (pdbqt) and used for the docking analysis. Identification and preparation of molecular targets Crystal structure of human carbonic anhydrase I in complex with polmacoxib with protein ID: 5gmm was done and downloaded from the Protein Data Bank (PDB). The interfering crystallographic water molecules and cocrystallized ligand were removed, and minimization of the energy of the protein was then done using BioviaDiscovery studies 2020. [23]

Docking procedure and analysis of results

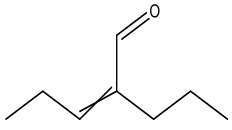
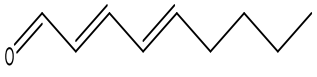
The screening of the phytochemical compounds from the seed extract was performed by docking them on selected binding pockets of proteins of Crystal structure of human carbonic anhydrase I in complex with polmacoxib and ranked based on their binding affinities. The multiple docking of the ligands and proteins were done with Autodock Vina in PyRx software. A rigid-flexible docking was performed after setting a grid box surrounding the binding sites of the receptors at exhaustiveness = 8, center x = 0.05, center y = 5.54, center z = -54.28, size x = 23.40, size y = 21.18, size z = 21.32.[22]. The molecular docking results were organized on an Excel spreadsheet, and the Heat Map of the data and the interaction was viewed using the Biovia discovery studio.

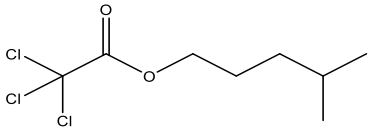
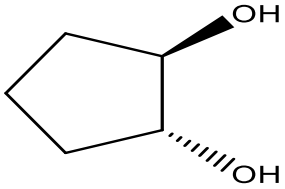
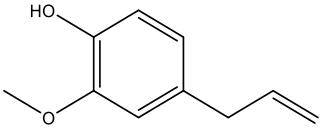
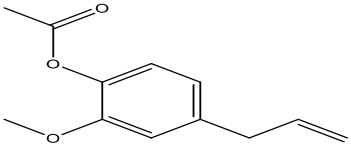
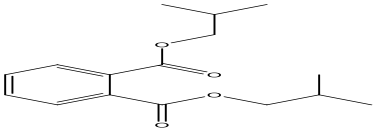
3. RESULT AND DISSCUSSION

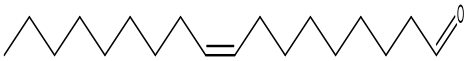
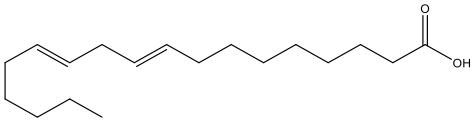
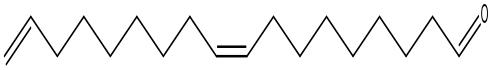
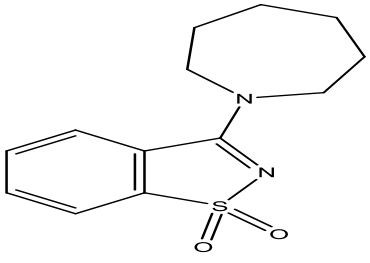
Result

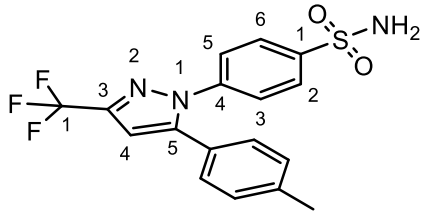
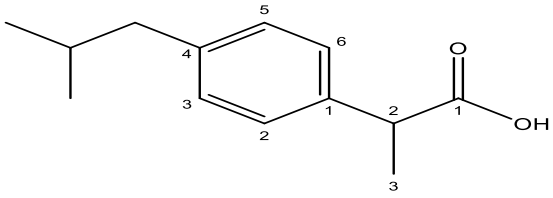
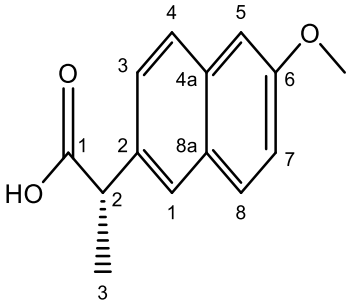
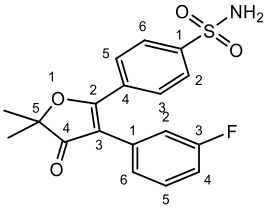
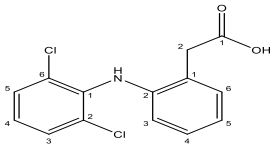
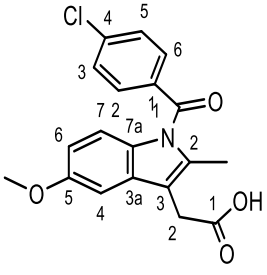
The GC–MS analysis of *Jansa* seed extract gave 26 peaks for the compounds detected, their percentage composition, retention time and structures are shown in the table below (Table 1).

Table 1. Result of Chemical compositon of the seed extract of *Jansa*

Area Pct	Library/ID	Pub ID	Structure
0.57	2-Heptenal, 2-propyl-	6386353	
1.85	2,4-Nonadienal, (E,E)-	5283339	

0.32	Trichloroacetic acid, 4-methylpentyl ester	537749	
0.32	1,2-Cyclopentanediol, trans-	225711	
1.32	Eugenol	3314	
0.49	Dodecanoic acid, methyl ester	8139	
1.43	Phenol, 2-methoxy-4-(2-propenyl)-, acetate	7136	
0.14	Hexadecanoic acid, methyl ester	8181	
0.21	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	6782	
5.90	n-Hexadecanoic acid	985	
11.4	cis-Vaccenic acid	5282761	
25.40	Oleic Acid	445639	
0.95	Heptadecyl acetate	69967	
1.45	Z-10-Tetradecen-1-ol acetate	5363221	

1.41	Decyl oleate	5363234	
18.09	2-Methyl-Z,Z-3,13-octadecadienol	5364412	
1.40	trans-13-Octadecenoic acid	6161490	
0.91	9-Octadecenal, (Z)-	5364492	
1.46	trans-13-Octadecenoic acid, methyl ester	5364506	
5.93	Linoelaidic acid	5282457	
4.04	9,12-Octadecadienoic acid (Z,Z)-	3931	
2.58	12-Methyl-E,E-2,13-octadecadien-1-ol	90107969	
0.27	9,17-Octadecadienal, (Z)-	5365667	
4.12	E-11-Hexadecenal	5283376	
4.42	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	535203	
4.01	cis-7,cis-11-Hexadecadien-1-yl acetate	5363265	

Celecoxib	2662	
Ibuprofen	3672	
naproxen.	156391	
Polmacoxib (Cocryst Main)	9841854	
Diclofenac	3033	
Indomethacin (drug)	3715	

The phytochemical components present were arranged in the order of highest to lowest percentage. Oleic Acid (25.40) >2-Methyl-Z,Z-3,13-octadecadienol (18.09)>cis-Vaccenic acid (11.4)>Linoelaidic acid (5.93) >n-Hexadecanoic acid (5.90) >1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide (4.42) >E-11-Hexadecenal (4.12)>9,12-Octadecadienoic acid (Z,Z)- (4.04)>cis-7,cis-11-Hexadecadien-1-yl acetate (4.01)>12-Methyl-

E,E-2,13-octadecadien-1-ol (2.58) >2,4-Nonadienal, (E,E)- (1.85) >trans-13-Octadecenoic acid, methyl ester (1.46) >Z-10-Tetradecen-1-ol acetate (1.45)>Phenol, 2-methoxy-4-(2-propenyl)-, acetate (1.43) >Decyl oleate (1.41) >trans-13-Octadecenoic acid (1.40) >Eugenol (1.32) the other compounds have percentage composition of less than 1.00 percent though they may also have significant medicinal contributions. From the result ethanol extract of the seed contains some alkanes, alkenes, fatty acids and phytochemicals like eugenol present at different concentrations which has been reported to have physiological and medicinal application.Some details of the compounds present are reported below.

2,4-Heptadienal

2,4-Heptadienal is a natural product found in *Vaccinium macrocarpon*, *Vaccinium vitisidaea*, and other organisms with data available. It is a food additives and flavoring agents. (E, E)-hepta-2, 4-dienal is a heptadienal in which the two double bonds are located at positions 2 and 4 (the E, E-geoisomer). It has a role as a flavouring agent. [23]

Eugenol

Eugenol is a volatile phenolic constituent of clove essential oil obtained from *Eugenia caryophyllata* buds and leaves. It is a functional ingredient of numerous products which have been used in the pharmaceutical, food and cosmetic industry in restricted concentrations. Its derivatives have been used in medicine as a local antiseptic and anesthetic. The wide range of eugenol activities includes antimicrobial, anti-inflammatory, analgesic and antioxidant. Eugenol, a phenylpropanoid, is pale yellow oil with a spicy aroma. This molecule is a weak acid which is soluble in organic solvents and specially extracted from clove oil, nutmeg, cinnamon, basil and bay leaf. Eugenol is useful for treatment of skin infections, skin lesions and inflammatory disorders [24].

Octadecanoic acid

Stearic acid, another name for octadecanoic acid is one of the most common fatty acids. It exists as a glycerol ester in most animal and plant fats (Beare-Rogers*et al*). Stearic acid is more abundant in animal fat (up to 30%) than vegetable fat (typically <5%). The important exceptions are cocoa butter and shea butter, in which the stearic acid content (as a triglyceride) is 28–45%. Unlike the other long-chain saturated fatty acids, stearic acid has no effect on lipoprotein cholesterol concentrations in men or women (Yu, Derr, *et al*). Results from the study by Kelly *et al.* indicate that stearic acid (19 g/day) in the diet has favorable effects on thrombogenic and atherogenic risk factors in males, the authors recommend that the food industry consider enriching foods with stearic acid instead of palmitic acid and trans fatty acids. Thus, stearic acid is nontoxic and biocompatible with the human body. With a polar head group that can bind with metal cations and a nonpolar chain that confers solubility in organic solvents, stearic acid is commonly used in the production of detergents, soaps, and cosmetics, such as shampoos and shaving cream products. [25]

Oleic acid

Evidences in the last years have showed the effects of oleic acid (OA) in human health and disease. Olive oil, rich in oleic acid, is supposed to present modulatory effects in a wide physiological function, while some studies also suggest a beneficial effect on cancer,

autoimmune and inflammatory diseases, besides its ability to facilitate wound healing. Administration of olive oil containing diets may improve the immune response associated to a more successful elimination of pathogens such as bacteria and fungi, by interfering in many components of this system such as macrophages, lymphocytes and neutrophiles. Then, novel putative therapies for inflammatory and infectious diseases could be developed based on the characteristics presented by unsaturated fatty acids like Oleic Acid [26]

Vaccinic acid

Vaccinic acid is a naturally occurring trans fatty acid and an omega-7 fatty acid. It is the predominant kind of trans-fatty acid found in human milk, in the fat o ruminants, and in dairy products such as milk, butter, and yogurt. *cis-Vaccenicacid* is *used* as *therapeutic* agent against cardiovascular diseases, it has anticarcinogenic properties, and also helps in reduction of total cholesterol, LDL cholesterol and triglyceride level [27]

Linolenic acid

Alpha Linolenic Acid (ALA) is an 18-carbon polyunsaturated fatty acid with three double bonds. It is also called an omega-3 fatty acid, and is essential for all mammals. Alpha-linolenic acid (or omega 3 fatty acid) intake can decrease the risk of cardiovascular diseases in the following ways by preventing arrhythmias that can lead to sudden cardiac death, decreasing the risk of thrombosis (blood clot formation) that can lead to heart attack or stroke, decreasing serum triglyceride levels, slowing the growth of atherosclerotic plaque, improving vascular endothelial function, lowering blood pressure slightly, and decreasing inflammation. ALA deficiencies can lead to visual problems and sensory neuropathy. Scaly and hemorrhagic skin or scalp inflammations may also develop [28].All these compounds showed medicinal properties therefore supported the ethnomedical claim of the plant as a medicinal plant.

Table 2. Result of Molecular Docking of the compounds from Jansa seed against an inflammatory and Antioxidant disease protein

Area Pct	Library/ID	Pub ID	Binding Affinity
0.57	2-Heptenal, 2-propyl-	6386353	-5.2
1.85	2,4-Nonadienal, (E,E)-	5283339	-5.1
0.32	Trichloroacetic acid, 4-methylpentyl ester	537749	-5.3
0.32	1,2-Cyclopentanediol, trans-	225711	-4.4
1.32	Eugenol	3314	-5.8
0.49	Dodecanoic acid, methyl ester	8139	
1.43	Phenol, 2-methoxy-4-(2-propenyl)-, acetate	7136	-6.4
0.14	Hexadecanoic acid, methyl ester	8181	-5.1
0.21	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	6782	-6.1
5.90	n-Hexadecanoic acid	985	-5.4
11.4	cis-Vaccenic acid	5282761	-5.7

25.40	Oleic Acid	445639	-5.6
0.95	Heptadecyl acetate	69967	-5.1
1.45	Z-10-Tetradecen-1-ol acetate	5363221	-5.1
1.41	Decyl oleate	5363234	-5.1
18.09	2-Methyl-Z,Z-3,13-octadecadienol	5364412	-5.2
1.40	trans-13-Octadecenoic acid	6161490	-5.7
0.91	9-Octadecenal, (Z)-	5364492	-5.3
1.46	trans-13-Octadecenoic acid, methyl ester	5364506	-5.9
5.93	Linoelaidic acid	5282457	-5.2
4.04	9,12-Octadecadienoic acid (Z,Z)-	3931	-5.7
2.58	12-Methyl-E,E-2,13-octadecadien-1-ol	90107969	-5.6
0.27	9,17-Octadecadienal, (Z)-	5365667	-5.1
4.12	E-11-Hexadecenal	5283376	-5.4
4.42	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	535203	-7.5
4.01	cis-7,cis-11-Hexadecadien-1-yl acetate	5363265	-5.1
	Celecoxib	2662	-7.5
	Ibuprofen	3672	
	naproxen.	156391	-7.6
	Polmacoxib (Cocrystallized ligand)	9841854	-8.5
	Diclofenac	3033	-7.0
	Indomethacin (drug)	3715	-6.7

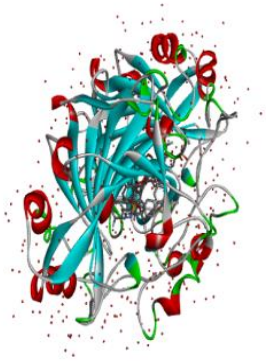


Fig. 1. Diagram of 5gmm raw protein

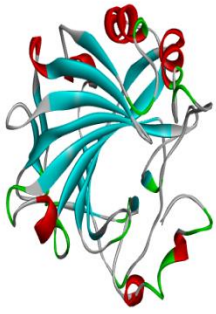


Fig. 2. Diagram of prepared protein

The protein used for the docking was a Crystal structure of human Carbonic anhydrase I in complex with polmacoxib as the cocrystalline ligand with (PDB ID:5gmm). Polmacoxib is not only a selective COX-2 inhibitor but also a potent inhibitor of carbonic anhydrases (CAs). Both CA I and CA II are highly expressed in the GI tract and kidneys, organs that are also thought to be the sites at which selective COX-2 inhibitors show their side effects. COX is a known inflammatory protein. The compounds from the seed extracts were docked on the protein to determine their binding affinity and compared with the binding of the cocrystalline ligand, some known anti-inflammatory drugs to determine the one with better binding affinity against the binding site of the disease protein.The docking result showed that the cocrystallized ligand have the best binding affinity of -8.5 kcal/mol followed by Naproxen (drug) -7.6 kcal/mol. Phytocompound 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide -7.5 kcal/mol and drug Celecoxib have affinities-7.5 kcal/mol, better than drug Diclofenac -7.0 kcal/mol andIndomethacin -6.7 kcal/mol, Phenol, 2-methoxy-4-(2-propenyl)-, acetate -6.4kcal/mol, 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester -6.1 kcal/mol and other phytocompounds also showed good binding affinities with the disease protein showing that most of the extracted compounds may have good anti-inflammatory properties there by validating the ethno medical claims of the used of the plant as having anti-inflammatory potentials. This research agrees with the reports of previous researchers that the plant has inflammatory activities. The interactions of the best binding compound were checked to confirm that the docking was done at the active site and pocket which denoted a good docking.

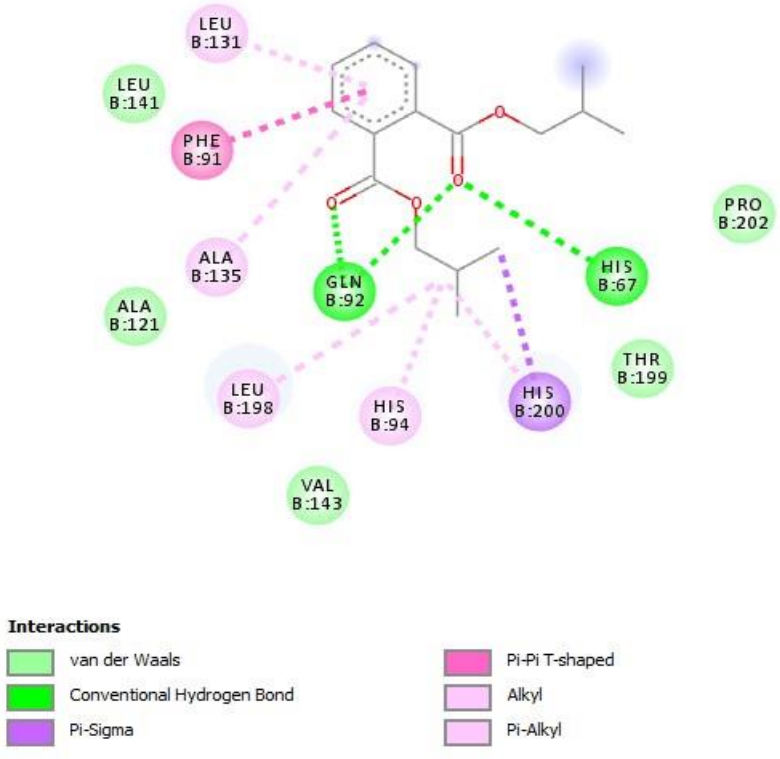


Fig. 3. Interaction ofthe protein with 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester

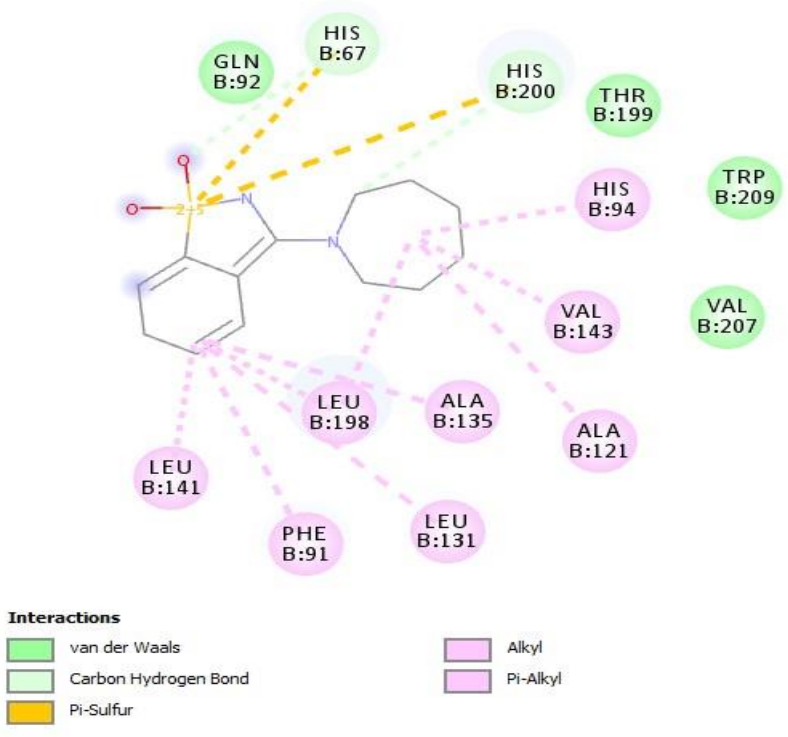


Fig. 4. Interaction of protein with 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide

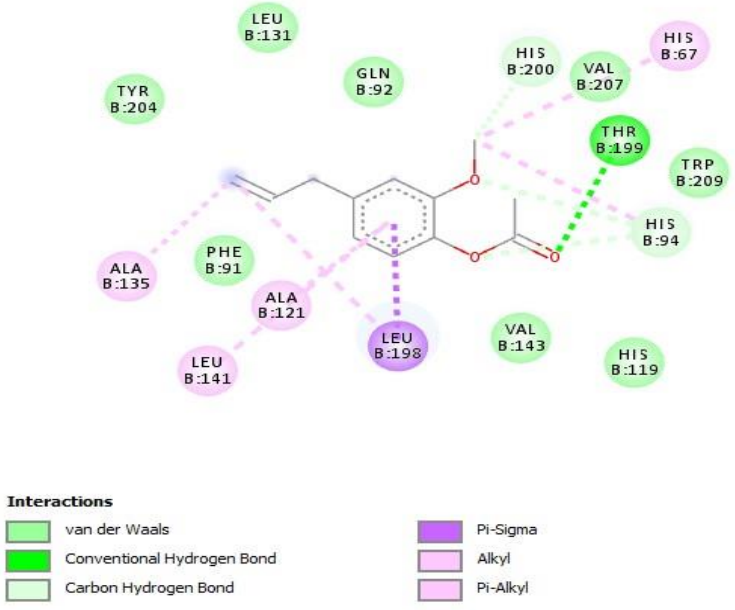


Fig. 5. Interaction of protein with Phenol, 2-methoxy-4-(2-propenyl)-, acetate

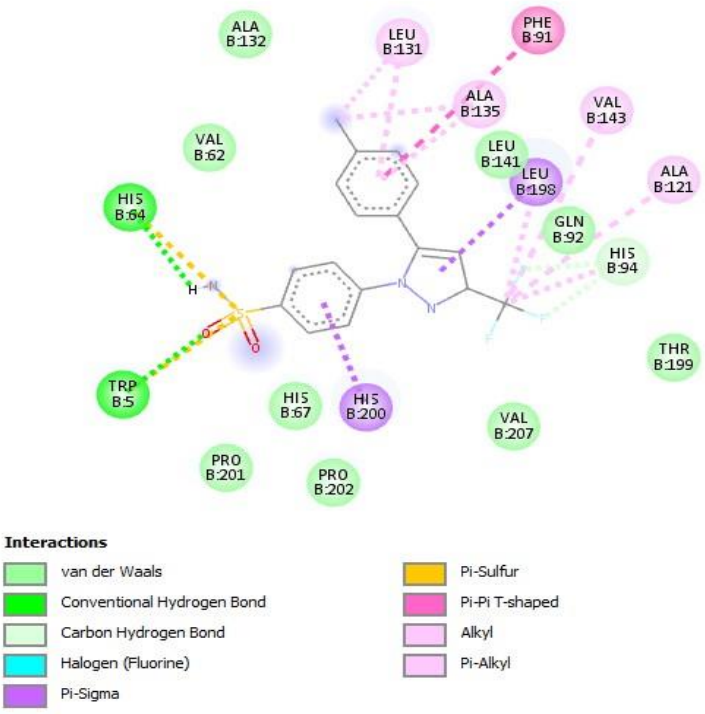


Fig. 6. Interaction of protein with Celecoxib

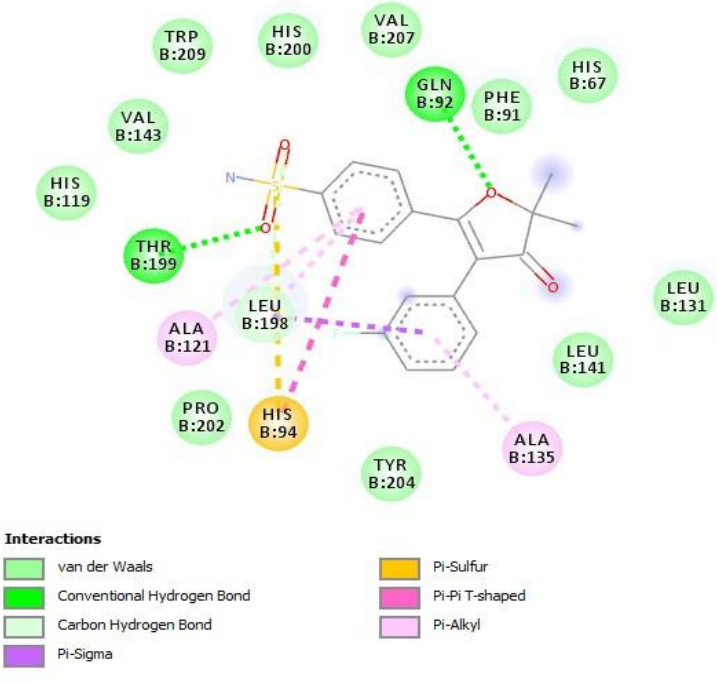


Fig. 7. Interaction of protein with Cocrystalline polmacoxib

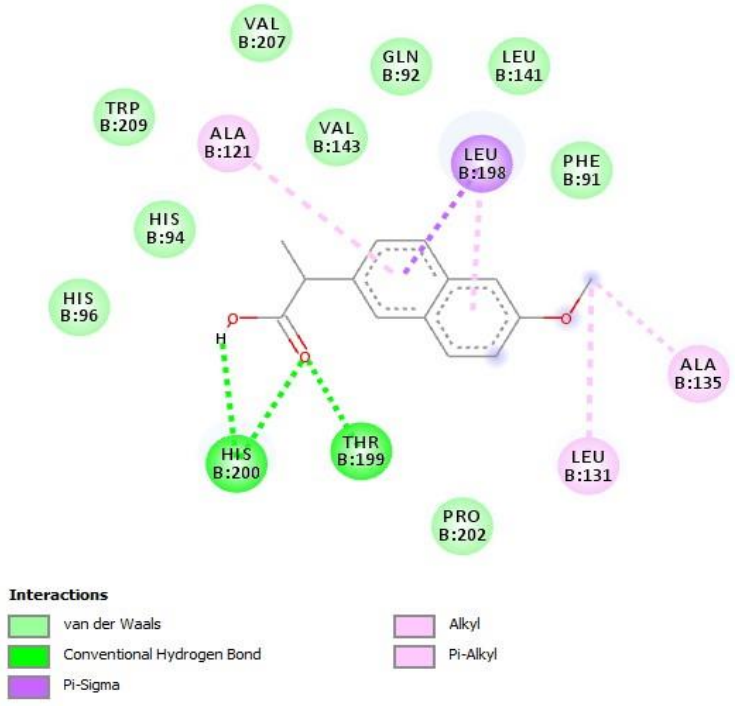


Fig. 8. Interaction of protein with drug Naprofex

From the interaction it was observed that docking was at the binding site and pocket. The result portray a strong interaction with a strong bonds like conventional hydrogen bond, pi-sigma, carbon hydrogen bond,pi-pi t shaped etc indicating a good bond with same Amino acids. The result of the interaction, binding affinities and amino acids involved were recorded in table below

Table 3. Results of interaction and amino acids involved

Compound	Binding affinity	Type of interaction	Amino acids
1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	-6.1	Van der waals	ALA 121, LEU 141, VAL 143 PRO 202, THR 199.
		Conventional hydrogen bond	HIS 67, GLN 92
		Pi-Sigma	HIS 200
		Pi-Pi Tshape	PHE 91
		Alkyl	LEU 131, ALA 135

		Pi-Alkyl	HIS 94, LEU 198
1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	-7.5	Van der waals Carbon hydrogen bond and Pi-sulfur Alkyl and Pi-Alkyl	GLN 92, THUR 199, VAL 207, TRP 209, HIS 67, HIS 200 PHE 91, HIS 94, ALA 121, LEU 131, ALA 135, LEU 141, VAL 143, LEU 198,
Phenol, 2-methoxy-4-(2-propenyl)-, acetate	-6.4	Van der waals Conventional hydrogen bond Carbon hydrogen bond Pi-Sigma Alkyl and Pi-Alkyl	PHE 91, GLN 92, HIS 119, LEU 131, VAL 143, TYR 204, VAL 207, TRP 209. THR 199 HIS 94, HIS 200 LEU 198 HIS 67, ALA 121, ALA 135, LEU 141
Celecoxib	-7.5	Van der waals Conventional hydrogen bond Carbon hydrogen bond Pi-Sigma Pi-Pi T shape Alkyl and Pi-Alkyl	VAL 62, HIS 67, GLN 92, ALA 132, LEU 141,THR 199, PRO 201, PRO 202, VAL 207. TRP 5, HIS 64 HIS 94 LEU 198, HIS 200 PHE 91 ALA 121, LEU 131, ALA 135, VAL 143,
Cocrystallineligand polmacoxib	-8.5	Van der waals Conventional hydrogen bond Carbon hydrogen bond Pi-Sulfur and Pi-Pi T shape	HIS 67, PHE 91, HIS 119, LEU 131, LEU 141, VAL 143, TRP 209, HIS 200, PRO 202, TYP 204, VAL 207, GLN 92, THR 199 LEU 198 HIS 94

		Pi-Alkyl	ALA 121, ALA 135
Naproxen	-7.6	Van der waals Conventional hydrogen bond Pi-Sigma Alkyl and Pi-Alkyl	PHE 91, GLN 92, HIS 94, HIS 96, LEU 141, VAL 143, PRO 202. VAL 207, TRP 209, THR 199, HIS 200. LEU 198 ALA 121, LEU 131, ALA 135.

.

The interaction results above showed that some of the identified compounds have significant potentials to block the active site of the enzyme. Out of the 26 identified compounds, 3 compounds with binding affinities close to the reference drugs , the cocrystalline ligand,and the reference drugs were used to study their interaction with the disease protein, the cocrystalline ligand polmacoxib has the best value of the binding affinity -8.5kal/moland strongest interaction. It interacted with the CA enzyme through two conventional hydrogen bond GLN 92 and THR 199, Pi sulfur bond with HIS 94, carbon-hydrogen bond LEU 198, it also has pi alkyl bond with ALA 121 and ALA 135 and a hydrophilic Vander waals bond with HIS 67, PHE 91, HIS 119, LEU 131, LEU 141, VAL 143, TRP 209, HIS 200, PRO 202, TYP 204 and VAL 207,

Naproxen a commercial drug with affinity -7.6 kcal/mol displayed a strongest interaction with the diseased protein, Naproxen constructed a conventional hydrogen bond with THR 199 and HIS 200. Pi sigma bond with LEU 198, Pi Alkyl and Alkyl with ALA 121, LEU 131 and ALA 135. and a hydrophobic vander waal bond with PHE 91, GLN 92, HIS 94, HIS 96, LEU 141, VAL 143, PRO 202. VAL 207 and TRP 209. 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide a compound from the seed showed a strong carbon hydrogen bond and pi-sulphur bond with HIS 67, HIS 200, pi alkyl and alkyl bond with PHE 91, HIS 94, ALA 121, LEU 131, ALA 135, LEU 141, VAL 143, LEU 198, and vander waal interaction with GLN 92, THUR 199, VAL 207, TRP 209.

Celecoxib showed strong bonding with Carbon hydrogen bond LEU 198, and HIS 200, convectional hydrogen bond with HIS 94, Pi sigma with PHE 91, Pi-Pi T shape with ALA 121, LEU 131, ALA 135, VAL 143, and van der waal. Compounds 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester and Phenol, 2-methoxy-4-(2-propenyl)-, acetate have very good bonding like the drugs as they have carbon-hydrogen and conventional hydrogen bonding. The high binding affinity may be due to its strong binding with other residue at the active site. Phenol although having a binding affinities of -6.4 kcal/mol showed a similar type of bond with the cocrystalline ligand and the standard drug celecoxib having both carbon-hydrogen bond, conventional hydrogen and pi-sigma bond.

These compounds serve as leads in treating inflammatory diseases. From the table it can be deduced that all extracted compounds are and drugs have stable bonding with the protein binding site due to the presence of the conventional hydrogen bonding except for the 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide which have only Van der waals Carbon hydrogen bond, Pi-sulfur, Alkyl and Pi-Alkyl.

The ADMET properties of the 3 best binding compounds from the plant material, the standard drugs and cocrystaline ligand were done using ADMETSAR. The results are reported below.

An ADMET study is the assessment of pharmacokinetics of a drug which stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the fate of a drug and the effects caused by a drug inside the body, such as how much drug is absorbed if administered orally and how much is absorbed in the gastrointestinal tract, is an indispensable part of drug discovery. In a similar way, if the absorption is poor, its distribution and metabolism would be affected, which can lead to causing neurotoxicity and nephrotoxicity. Ultimately, the study is to understand the disposition of compounds within an organism. Thus, ADMET study is one of the most essential parts of computational drug design. The computed ADMET properties of the compounds from the seed and the standard drug with the cocrystalline are below in Table 4.

Table 4. Combine result of the ADMET properties of the compounds with best binding affinities, the drugs and the cocrystalline ligand.

Absorption						
Blood brain barrier	BBB+	BBB+	BBB+	BBB+	BBB+	BBB+
Human intestinal absorption	HIA+	HIA+	HIA+	HIA+	HIA+	HIA+
Caco-2 permeability	CaCo2+	CaCo2+	CaCo2+	CaCo2+	CaCo2+	CaCo2+
p-glycoprotein substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
p-glycoprotein inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Inhibitor	Inhibitor	Non-inhibitor
Renal organic cation transport	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
Distribution						
Subcellular localization	mitochondria	Mitochondria	mitochondria	lysosome	lysosome	Lysosome
Metabolism						
CYP450 2C9 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 2D6 substrate	Non-substrate	Substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 3A4 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 1A2 inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	inhibitor	inhibitor	Non-inhibitor
CYP450 2C9 inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	inhibitor	Non-inhibitor	Inhibitor
CYP450 2D6 inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor

CYP450 2C19 inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	inhibitor	Non-inhibitor	Inhibitor
CYP450 3A4 inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP inhibitory promiscuity	Low CYP inhibitor promiscuity	High CYP inhibitor promiscuity	High CYP inhibitor promiscuity	Low CYP inhibitor promiscuity	Low CYP inhibitor	High CYP inhibitor promiscuity
Excretion/ Toxicity						
Human ether-ago-go-related gene inhibition	Weak inhibitor, Non-inhibitor	Weak inhibitor, Non-inhibitor	Weak inhibitor, Non-inhibitor	Weak inhibitor, Non-inhibitor	Weak inhibitor, Non-inhibitor	Weak inhibitor, Non-inhibitor
AMES Toxicity	Non Ames toxic	Non Ames toxic	Non Ames toxic	Non Ames toxic	Ames toxic	Non Ames toxic
Carcinogens	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non-carcinogen
Fish toxicity	High FHMT	High FHMT	High FHMT	High FHMT	High FHMT	High FHMT
Tetrahymena pyriformis toxicity	High TPT	High TPT	High TPT	High TPT	High TPT	High TPT
Honey bee toxicity	High HBT	Low HBT	High HBT	Low HBT	High HBT	Low HBT
Biodegredation	Ready biodegradable	Not ready biodegradable	Ready biodegradable	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable
Acute oral toxicity	IV	III	IV	III	II	III
Carcinogenicity (Three-class)	Non-required	Non-required	Non-required	Non-required	Non-required	Non-required
ADMET predicted profile-Regression						
Aqueous solubility	-4.5973	-3.1816	-2.6394	-3.3478	-4.0976	-3.6959
CaCo-2 permeability	1.2521	1.0149	1.2587	0.3818	1.2775	0.7922
Rat acute toxicity	1.2291	2.3719	2.0606	2.5023	2.4579	2.5972
Fish toxicity	0.3153	1.5816	0.7363	1.8314	0.8696	1.1932
Tetrahymena pyriformis toxicity	1.0247	0.5421	0.5977	0.5549	1.3533	0.4376

From the result of the ADMET properties it shows that all the compounds from the plant, the cocrystalline ligand and the control drug are non carcinogenic substances, all the compounds can be absorbed by the body because they have good human intestinal absorption and their permeability is good. 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide and Naproxen are inhibitors of glycoprotein inhibitor while the rest are not. Only Celecoxib is the

substrate of CYP450 2D6 substrate the rest are not substrate. Naproxen is the only one with Ames toxicity others are not. 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester and Phenol, 2-methoxy-4-(2-propenyl)-, acetate are ready biodegradable the rest are not ready degradable.

The Caco-2 cell monolayer is commonly employed as an in vitro model of the human intestinal mucosa to predict medication absorption when given orally. A compound is considered to have a high Caco-2 permeability if it has a Papp $>8\times10^{-6}$ cm/s. Thus, high Caco-2 permeability would translate in predicted values >0.90, presenting the compounds values much higher at above 0.9 except for 1,2- benzisothiazole (0.38) and Polmacoxib (0.79). The Intestine is normally the primary site for absorption of a drug from an orally administered solution and the Intestinal Absorption (IA)parameter predicts the percentage of a drug absorbed through the human intestine. An absorbance of less than 30% is considered poor. From the table all the compounds will be absorbed as their absorbance are more than 30%. P-glycoprotein functions as a biological barrier by extruding toxins and xenobiotics out of cells. The model predicts whether a given compound is likely to be a substrate of Pgp or not.

The prediction is in the negative as all the compounds and drugs are non p-glycoprotein substrate. Modification of P-glycoprotein- mediated transport has significant pharmacokinetic consequences for Pgp substrates, which might be employed for specific therapeutic benefits or create contraindications. Thus, this study predicts that all compounds and drugs considered in this study will not act as P-glycoprotein inhibitors except 1,2 – benzisothiazole which are inhibitors. The degree to which a medicine binds proteins in the blood can impair its efficacy, as the more bound it is, the less efficiently it can pass cellular membranes or diffuse. The Fraction Unbound predicts the fraction that will be unbound in plasma resulting in the values shown in Table 2.The ability of a medicine to pass the blood-brain barrier is an important feature to examine to avoid side effects and toxicities. The logarithmic ratio of brain to plasma drug concentrations is used to calculate permeability. A logBB>- 0.3indicates that a substance can easily penetrate the blood-brain barrier, whereas molecules with a logBB>-1 are poorly distributed to the brain all the compounds and drugs have logBB greater than -0.3 hence they can easily penetrate the blood brain. Another measurement is the bloodbrainpermeability-surface area product (logPS) or CNS Permeability. It is predicted that the compounds and drugswill be able to penetrate the CNS. Because it oxidizes xenobiotics to promote excretion.
Cytochrome P450 is a key detoxification enzyme in the body,primarily found in the liver. Many medicines are destroyed, and some are activated by the cytochrome P450 iso- forms. As a result, determining a compound's capacity to inhibit cytochromeP450 is critical. If the concentration required to achieve50% inhibition for each isoform is less than 10 μM, the substance is termed a cytochrome P450 inhibitor. As can be seen from Table 4-9, all the drugs and compounds were non inhibitor and inhibitor of different number of p450 cytochrome are predicted as not being P450 inhibitors for any isoform. It is all important to know if a given compound is likely to be a cytochrome P450substrate. The prediction indicate that all the compounds and drugs were non substrate for all the different numbers of P450 cytochrome except for celecoxib which was a substrate for CYP450 2D6

The AMES test is a widely used bacteria-based method for determining a compound's mutagenic potential. A positive test indicates that the substance is mutagenic and so could cause cancer. All of the compounds under investigation have favorable predictions as they are not AMES toxic except for the standard drug Naproxen which is AMES toxic. The aqueous solubility of all the compounds and drugs are in the range as they are all soluble.

4. CONCLUSIONS

The result obtained from the GC-MS showed that *Ricinodendron heudelotii* seed contain 26 bio-active compounds with known medicinal, biological and therapeutic properties with their percentage composition as follows: Oleic Acid (25.40), 2-Methyl-Z,Z-3,13-octadecadienol (18.09) and cis-Vaccenic acid (11.4)were the most abundant compounds in the extract. Oleic acid and 2-Methyl-Z,Z-3,13-octadecadienol both amounting to 43.49% of the total percentage of compound found in the extract. Oleic acid has been reported to present modulatory effects in a wide physiological function, while some studies recorded its beneficial effect on cancer, autoimmune and inflammatory diseases, besides its ability to facilitate wound healing. Administration of olive oil containing diets may improve the immune response associated to a more successful elimination of pathogens such as bacteria and fungi, by interfering in many components of this system such as macrophages, lymphocytes and neutrophiles. Then, novel putative therapies for inflammatory and infectious diseases could be developed based on the characteristics presented by unsaturated fatty acids.2-Methyl-Z,Z-3,13-octadecadienol present favorable effects on thrombogenic and atherogenic risk factors in males, thereby positively validating the claims made that *Ricinodendron heudelotii* can cure inflammatory diseases [25]. Inflammation has been an underlying factor in most health condition like diabetes, arthritis, heart disease and cancer. The dried seed of *Ricinodendron heudelotii*is reported to have been used medically to reduce inflammation. This can be attributed to the presence of oleic acid,2-Methyl-Z,Z-3,13-octadecadienol, eugenol, 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide,Phenol, 2-methoxy-4-(2-propenyl)-, acetate 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester and other compounds found in the seed. *Ricinodendron heudelotii*seed contains antimicrobial, antioxidant and larvividal compounds such as Eugenol, and oleic acid (anticancer). The research revealed that the efficacy of *Ricinodendron heudelotii*seed medicinally is due to its phytocompounds.

References

[1] O.F Yakubu, A.B. Abiodun, H. Adebayo, A. Emeka, E.J. Iweala, A. Isaacson, B. Adelani, A. Temitope, A. Ishola, A.Ying-Jun Zhang, Anti-inflammatory and antioxidant activities of fractions and compound from Ricinodendron heudelotii (Baill.). *Heliyon* 5 (2019) e02779

[2] V.O. Taiwo, O.A. Olukunle, I.C. Ozor, A.T. Oyejobi, Consumption of aqueous extract of raw Aloe vera leaves: histopathological and biochemical studies in rat and tilapia, *African Journal of Biomedical Research*, Vol. 8 (2005); 169-178

[3] C. Leitzmann, Characteristics and health benefits of phytochemicals, *Forschende Komplement€armedizin* 23 (2016) 69–74.

[4] S.F. Kimbu, F. Keumedjio, L.B. Sondengam, J.D. Connolly, Two dinorditerpenoids from Ricinodendron heudelotii, *Phytochemistry* 30 (1991) 619–621.

I. Izundu, N.N. Nnacho, Nutritional and A-nutritional composition of Ricinodendron heudelotii, *J. Nat. Appl. Sci.* 12 (2011) 108–116.

[5] V.A. Oyono, C. Fokunang, Assam-Assam JP, Voundi S, Tsafack P, Mouafo ET. et al. Acute toxicity studies, antioxidant and in vitro antibacterial activities of extract from the barks of Ricinodendron heudoletti (Euphorbiaceae), *J. Pharmacogn. Phytotherapy* 6 (2014) 47–53.

[6] O.F. Yakubu, A.H. Adebayo, T.O. Famakinwa, O.S. Adegbite, T.A. Ishola, L.O. Imonikhe, et al., Antimicrobial and toxicological studies of Ricinodendron heudelotii (Baill.), *Asian J. Pharm. Clin. Res.* 11 (2018) 299–305.

[7] O.F. Yakubu, A.H. Adebayo, T.M. Dokunmu, Y.J. Zhang, E.E.J. Iweala, Cytotoxic effects of compounds isolated from Ricinodendron heudelotii (Baill.), *Molecules* 24 (2019) 145–151.

[8] O.F. Yakubu, A.H. Adebayo, E.S. Okechukwu, O.A. Adeyemi, E.E.J. Iweala, Y.J. Zhang, Co-administration of artemisinin and Ricinodendron heudelotii leaf extract—effects on selected antioxidants and liver parameters in male Wistar rats, *Comp. Clin. Pathol*. 27 (2018) 765–772.

[9] Atli Arnarson (2023) Antioxidants Explained in Simple Terms: https://www.healthline.com/nutrition/antioxidants-explained

[10] T.A. Ajith, K.K. Janardhanan, Indian medicinal mushrooms as a source of antioxidant and antitumor agent, *J. Clin. Biochem. Nutr.* 40 (2007) 157–162.

[11] K. Duduku, R. Sarbatly, R. Nithyanandam, A review of the antioxidant potential of medicinal plant species, *Food Bioprod. Process*. 89 (2011) 217–233

[12] A.S. Ravipati, L. Zhang, S.K. Rao, S.C. Jeong, N. Reddy, J. Bartlett, et al., Antioxidant and anti-inflammatory activities of selected Chinese medicinal plants and their relation with antioxidant content, *BMC Complement Altern. Med.* 12 (2012) 172–184.

[13] Z. Li, H.W. Lee, X. Liang, D. Liang, Q. Wang, D. Huang, et al., Profiling of Phenolic compounds and antioxidant activity activity of 12 cruciferous vegetables, *Molecules* 23 (2018) 1138–1144.

[14] L.A. Diaz, W. Richard, W. Jian, K.J. Isaac, J.H. Randolph, B. Jordan, et al., The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers, *Nature* 486 (2012) 537–540.

[15] P. Arulselvan, T.F. Masoumeh, S.T. Woan, G. Sivapragasam, F. Sharida, E.N. Mohd, et al., Role of antioxidants and natural products in inflammation, *Oxid. Med. Cell Longev.* (2016) 15. Article ID 5276130.

[16] L. Chen, D. Huidan, C. Hengmin, F. Jing, Z. Zhicai, D. Junliang, et al., Inflammatory responses and inflammation- associated diseases in organs, *Oncotarget* 9 (2018) 7204–7218

[17] Knudsen JF, Carlsson U, Hammarström P, Sokol GH, Cantilena LR. The cyclooxygenase-2 inhibitor celecoxib is a potent inhibitor of human carbonic anhydrase II. *Inflammation.* 2004 Oct ;28(5): 285-90

[18] De Monte C, Carradori S, Gentili A, Mollica A, Trisciuoglio D, Supuran CT. Dual Cyclooxygenase and Carbonic Anhydrase Inhibition by Nonsteroidal Anti-

Inflammatory Drugs for the Treatment of Cancer. *Curr Med Chem*. 2015; 22(24): 2812-8

[19] Ricinodendron botanical classification retrieved 6 February 2023 https://en.m.wikipedia.org/wikipedia/wiki/Ricinodendron

[20] Nortjie, E,. Basitere, M., Moyo, D. and Nyamukamba, P. (2022) Extraction Methods, Quantitative and Qualitative Phytochemical Screening of Medicinal Plants for Antimicrobial Textiles: A Review, *Plants* (Basel). 11(15): 2011.

[21] Duru, C.E., Duru I.A., and Adegboyega A.E (2021) In silico identification of compounds from Nigella sativa seed oil as potential inhibitors of SARS-CoV-2 targets Bull Natl Res Cent 45 (57): 1-13 https://doi.org/10.1186/s42269-021-00517-x

[22] Ugariogu, S.N and Duru, I.A. (2022) Anticolorectal Cancer Properties of Some Flavonoids and Terpenoids from African Propolis via Molecular Docking South Asian *Research Journal of Natural Products* 5(3): 209-221

[23] 2, 4- Heptadienal retrieved on the 6th of June 2023 https://pubchem.ncbi.nlm.nih.gov/compound/2_4-Heptadienal

[24] Mohammadi-Nejad, S., Özgüneş, H. and Başaran, N. (2017) Pharmacological and Toxicological Properties of Eugenol. *Turk J Pharm Sci*. 14(2): 201-206

[25] Lock, A.L, Corl, B.A, Barbano, D.M, and Bauman, D.E.,(2004). The anticarcinogenic effect of trans-11 18:1 is dependent on its conversion to cis-9, trans-11 CLA by delta9-desaturase in rats". *J Nutr*. 134 (10): 2698– 704

[26] Field, C.J., Blewett, H.H., Proctor, S. and Vine, D. (2009) Human health benefits of vaccenic acid. Appl Physiol Nutr Metab. 34(5):979-991. doi: 10.1139/H09-079. PMID: 19935865.

[27] Flores-Hplguin, N., Frau, J. and Glossman-mitrik, D (2021) computational pharmacokinetics report, ADMET study and conceptual DFT based estimation of the chemical reactivity properties of marine cyclopeptides. *Chemistry open* 10, 1142-1149.

Appendix

Appendix 1: ADMET result for the properties of 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.9308
Human Intestinal Absorption	HIA+	0.9745
Caco-2 Permeability	Caco2+	0.7151
P-glycoprotein Substrate	Non-substrate	0.6465
P-glycoprotein Inhibitor	Non-inhibitor	0.7684
	Non-inhibitor	0.8162
Renal Organic Cation Transporter	Non-inhibitor	0.8914
Distribution		
Subcellular localization	Mitochondria	0.8897
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.8206
CYP450 2D6 Substrate	Non-substrate	0.8820
CYP450 3A4 Substrate	Non-substrate	0.6097
CYP450 1A2 Inhibitor	Non-inhibitor	0.5666
CYP450 2C9 Inhibitor	Non-inhibitor	0.6604
CYP450 2D6 Inhibitor	Non-inhibitor	0.9218
CYP450 2C19 Inhibitor	Non-inhibitor	0.7906
CYP450 3A4 Inhibitor	Non-inhibitor	0.8983
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.7003

Excretion		
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9738
	Non-inhibitor	0.9621
AMES Toxicity	Non AMES toxic	0.9132
Carcinogens	Non-carcinogens	0.5391
Fish Toxicity	High FHMT	0.9862
Tetrahymena Pyriformis Toxicity	High TPT	0.9669
Honey Bee Toxicity	High HBT	0.6573
Biodegradation	Ready biodegradable	0.6348
Acute Oral Toxicity	IV	0.7836
Carcinogenicity (Three-class)	Non-required	0.5420

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-4.5973	LogS
Caco-2 Permeability	1.2521	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	1.2991	LD50, mol/kg
Fish Toxicity	0.3153	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	1.0247	pIGC50, ug/L

Appendix 2: ADMET result for the properties of Celecoxib

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.9713
Human Intestinal Absorption	HIA+	1.0000
Caco-2 Permeability	Caco2+	0.8866
P-glycoprotein Substrate	Non-substrate	0.9287
P-glycoprotein Inhibitor	Non-inhibitor	0.8619
	Non-inhibitor	0.7920
Renal Organic Cation Transporter	Non-inhibitor	0.8582
Distribution		
Subcellular localization	Mitochondria	0.4738
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.6237
CYP450 2D6 Substrate	Substrate	0.8919
CYP450 3A4 Substrate	Non-substrate	0.5751
CYP450 1A2 Inhibitor	Inhibitor	0.7805
CYP450 2C9 Inhibitor	Inhibitor	0.6172
CYP450 2D6 Inhibitor	Non-inhibitor	0.8594
CYP450 2C19 Inhibitor	Inhibitor	0.7169
CYP450 3A4 Inhibitor	Inhibitor	0.7959
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.7392
Excretion		
Toxicity		

Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9856
	Non-inhibitor	0.8419
AMES Toxicity	Non AMES toxic	0.7185
Carcinogens	Non-carcinogens	0.7905
Fish Toxicity	High FHMT	0.9891
Tetrahymena Pyriformis Toxicity	High TPT	0.7897
Honey Bee Toxicity	Low HBT	0.8783
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.6499
Carcinogenicity (Three-class)	Non-required	0.7022

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-3.1816	LogS
Caco-2 Permeability	1.0149	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.3719	LD50, mol/kg
Fish Toxicity	1.5816	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.5421	pIGC50, ug/L

Appendix 3: ADMET result for the properties Phenol, 2-methoxy-4-(2-propenyl)-, acetate

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.8760
Human Intestinal Absorption	HIA+	0.9890
Caco-2 Permeability	Caco2+	0.8518
P-glycoprotein Substrate	Non-substrate	0.6659
P-glycoprotein Inhibitor	Non-inhibitor	0.5791
	Non-inhibitor	0.7525
Renal Organic Cation Transporter	Non-inhibitor	0.8742
Distribution		
Subcellular localization	Mitochondria	0.8711
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.8126
CYP450 2D6 Substrate	Non-substrate	0.8400
CYP450 3A4 Substrate	Non-substrate	0.5851
CYP450 1A2 Inhibitor	Non-inhibitor	0.5728
CYP450 2C9 Inhibitor	Non-inhibitor	0.8912
CYP450 2D6 Inhibitor	Non-inhibitor	0.9379
CYP450 2C19 Inhibitor	Non-inhibitor	0.5839
CYP450 3A4 Inhibitor	Non-inhibitor	0.7406
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.5128
Excretion		
Toxicity		

Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9535
	Non-inhibitor	0.9606
AMES Toxicity	Non AMES toxic	0.7381
Carcinogens	Non-carcinogens	0.8445
Fish Toxicity	High FHMT	0.9897
Tetrahymena Pyriformis Toxicity	High TPT	0.9882
Honey Bee Toxicity	High HBT	0.8377
Biodegradation	Ready biodegradable	0.5000
Acute Oral Toxicity	III	0.8552
Carcinogenicity (Three-class)	Non-required	0.6079

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-2.6394	LogS
Caco-2 Permeability	1.2587	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.0606	LD50, mol/kg
Fish Toxicity	0.7363	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.5977	pIGC50, ug/L

Appendix 4: ADMET result for the properties 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.9791
Human Intestinal Absorption	HIA+	1.0000
Caco-2 Permeability	Caco2-	0.6064
P-glycoprotein Substrate	Non-substrate	0.5223
P-glycoprotein Inhibitor	Non-inhibitor	0.6125
	Inhibitor	0.6592
Renal Organic Cation Transporter	Non-inhibitor	0.5206
Distribution		
Subcellular localization	Lysosome	0.3531
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.5824
CYP450 2D6 Substrate	Non-substrate	0.7569
CYP450 3A4 Substrate	Non-substrate	0.5308
CYP450 1A2 Inhibitor	Inhibitor	0.5224
CYP450 2C9 Inhibitor	Inhibitor	0.5388
CYP450 2D6 Inhibitor	Non-inhibitor	0.8638
CYP450 2C19 Inhibitor	Inhibitor	0.5681
CYP450 3A4 Inhibitor	Non-inhibitor	0.7831
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.5692
Excretion		
Toxicity		

Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.7363
	Non-inhibitor	0.5728
AMES Toxicity	Non AMES toxic	0.5856
Carcinogens	Non-carcinogens	0.8436
Fish Toxicity	High FHMT	0.5624
Tetrahymena Pyriformis Toxicity	High TPT	0.7991
Honey Bee Toxicity	Low HBT	0.6669
Biodegradation	Not ready biodegradable	0.8469
Acute Oral Toxicity	III	0.6068
Carcinogenicity (Three-class)	Non-required	0.5952

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-3.3478	LogS
Caco-2 Permeability	0.3868	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.5023	LD50, mol/kg
Fish Toxicity	1.8314	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.5549	pIGC50, ug/L

Appendix 5: ADMET result for the properties Naproxen

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.6881
Human Intestinal Absorption	HIA+	0.9948
Caco-2 Permeability	Caco2+	0.9091
P-glycoprotein Substrate	Non-substrate	0.5860
P-glycoprotein Inhibitor	Non-inhibitor	0.8747
	Non-inhibitor	0.8396
Renal Organic Cation Transporter	Non-inhibitor	0.8615
Distribution		
Subcellular localization	Mitochondria	0.8334
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7548
CYP450 2D6 Substrate	Non-substrate	0.9116
CYP450 3A4 Substrate	Non-substrate	0.5715
CYP450 1A2 Inhibitor	Inhibitor	0.9107
CYP450 2C9 Inhibitor	Non-inhibitor	0.9070
CYP450 2D6 Inhibitor	Non-inhibitor	0.9521
CYP450 2C19 Inhibitor	Non-inhibitor	0.9447
CYP450 3A4 Inhibitor	Non-inhibitor	0.8905
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.8598
Excretion		
Toxicity		

Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9588
	Non-inhibitor	0.9144
AMES Toxicity	AMES toxic	0.5184
Carcinogens	Non-carcinogens	0.8685
Fish Toxicity	High FHMT	0.9211
Tetrahymena Pyriformis Toxicity	High TPT	0.9738
Honey Bee Toxicity	High HBT	0.8851
Biodegradation	Not ready biodegradable	0.7809
Acute Oral Toxicity	II	0.7756
Carcinogenicity (Three-class)	Non-required	0.4961

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-4.0976	LogS
Caco-2 Permeability	1.2775	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.4579	LD50, mol/kg
Fish Toxicity	0.8696	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	1.3533	pIGC50, ug/L

Appendix 6: ADMET result for the properties Polmacoxib

ADMET Predicted Profile --- Regression

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.7157
Human Intestinal Absorption	HIA+	1.0000
Caco-2 Permeability	Caco2-	0.5640
P-glycoprotein Substrate	Non-substrate	0.7180
P-glycoprotein Inhibitor	Inhibitor	0.5184
	Non-inhibitor	0.8785
Renal Organic Cation Transporter	Non-inhibitor	0.8915
Distribution		
Subcellular localization	Lysosome	0.5114
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7808
CYP450 2D6 Substrate	Non-substrate	0.7955
CYP450 3A4 Substrate	Non-substrate	0.5128
CYP450 1A2 Inhibitor	Non-inhibitor	0.5730
CYP450 2C9 Inhibitor	Inhibitor	0.5374
CYP450 2D6 Inhibitor	Non-inhibitor	0.8714
CYP450 2C19 Inhibitor	Inhibitor	0.5283
CYP450 3A4 Inhibitor	Non-inhibitor	0.6968
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.8658
Excretion		
Toxicity		

Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9864
	Non-inhibitor	0.8543
AMES Toxicity	Non AMES toxic	0.6183
Carcinogens	Non-carcinogens	0.6342
Fish Toxicity	High FHMT	0.9990
Tetrahymena Pyriformis Toxicity	High TPT	0.9143
Honey Bee Toxicity	Low HBT	0.5000
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.5626
Carcinogenicity (Three-class)	Non-required	0.5377

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-3.6959	LogS
Caco-2 Permeability	0.7922	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.5972	LD50, mol/kg
Fish Toxicity	1.1932	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.4376	pIGC50, ug/L