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In silico Investigation of the Bioactive Component of *Zingiber Officinale* (GINGER) as a Potential Inhibitor of Angotensin-Converting Enzyme (ACE) in Hypertension

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Hypertension is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. Hypertension is a primary risk factor for a number of chronic health conditions and the major cause of premature death worldwide. Several new target and diseases pathway are emerging one of such is the Angiotensin Converting Enzymes (ACE), which is a central component of the renin–angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict. This study explored the anti-hypertensive potential of the bioactive compounds found in *Zingiber Officinale***.** In the study, 122 natural compounds obtained from literature were used for molecular

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docking against the ACE receptor target using the Python Prescription (PyRx) 0.8 software. An arbitrary score ≤ -7.3 kcal/mol was chosen as a cut-off value. 21 compounds were obtained after cutoffs which were further screened using Lipinkis, Ghose, and Verber rule regarding Rotatable bond (RB), TPSA, Saturation, Molar Refractivity (MR), and PAIN alert, resulting in 15 compounds. Pharmacokinetic screening (ADMET and bioactivity) was carried out on the compounds, and it was discovered that 5 compounds (Zenimbone, Delta Cadinene, Beta-Eudesmol, and Alpha Eudesmol and Ledol) are good drug candidates and have an effect on the protein (ACE) and have high potency to reduce hypertension**.**

Keywords: Hypertension; Angiotensin Converting Enzymes (ACE); Zingiber officinale; Renin–Angiotensin System (RAS); In-silico.

1. INTRODUCTION

"High blood pressure, clinically known as hypertension, affects more than 75 million Americans, an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries and is a serious, life threatening health condition" [1]. "It is a long-term medical condition in which the blood pressure in the arteries is persistently elevated" Court, [2]. "High blood pressure usually does not cause symptoms. High blood pressure, however, is a major risk factor for stroke, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia" Lackland and Weber [3]; Lau et al. [4]. "Hypertension is a major cause of premature death worldwide" [1].

"Angiotensin-converting enzyme or ACE is a central component of the renin–angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict. ACE inhibitors are widely used as pharmaceutical drugs for treatment of cardiovascular diseases" [5]. "Other lesser known functions of ACE are degradati on of bradykinin, substance P and amyloid beta-protein" [6]. **"**ACE hydrolyzes peptides by the removal of a dipeptide from the C-terminus. Likewise it converts the inactive decapeptide angiotensin I to the octapeptide angiotensin II by removing the dipeptide His-Leu" [7]."Angiotensin II is a potent vasoconstrictor in a substrate concentration-dependent manner" Zhang, et al. [8]. Angiotensin II binds to the type 1 angiotensin II receptor (AT1), which sets off a number of actions that result in vasoconstriction and therefore increased blood pressure. ACE is also part of the kinin-kallikrein system where it degrades bradykinin, a potent vasodilator, and other vasoactive peptides.

"Angiotensin-converting-enzyme inhibitors (ACE inhibitors) are a class of medication used primarily for the treatment of high blood pressure and heart failure" [5]. "These inhibitors work by causing relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart. ACE inhibitors inhibit the activity of angiotensin-converting enzyme, an important component of the renin–angiotensin system which converts angiotensin I to angiotensin II, and hydrolyses bradykinin. Therefore, ACE inhibitors decrease the formation of angiotensin II, a vasoconstrictor, and increase the level of bradykinin, a peptide vasodilator. As a result of inhibiting the ACE enzyme in the bradykinin system, the ACE inhibitor drugs allow for increased levels of bradykinin which would normally be degraded" Byrd et al. [9].

There are varieties of folk remedies used to manage hypertension and recently there has been a rise in the use of some of these alternative and complementary therapies for hypertension Yeh et al. [10]. Some herbal, animal and mineral products have been reported to be beneficial in management of hypertension such as *Allium sativum* (garlic), *Camellia sinensis* (green tea), *Terminalia arjuna* (arjuna)*, Zingiber officinale* (ginger)*, Withania somnifera* (Indian ginseng)*, Commiphora mukul/wightii* (guggul)*, Panax ginseng* and *Ginkgo biloba* Sanghal et al. [11]. "Zingiber Officinale, commonly known as ginger, has been widely used traditionally in the daily diet and a variety of medicinal purposes. In traditional Chinese medicine, ginger is classified as a warming remedy releasing exterior conditions. Fresh ginger is used for abdominal distension, coughing, vomiting, and for promoting sweating and reducing the poisonous effect of

other herbs. The steamed and dried rhizome is used to treat abdominal pain, lumbago and diarrhoea, and also for the treatment of cholera, haemorrhage, rheumatism and toothache" (Mills, 2002). "*Zingiber officinale* (*ZO*) contains numerous components such as beta-carotene, gingerdiol, gingerol, gingerdione, caffeic acid, capsaicin and curcumin. The literature survey confirmed that ginger has multiple biological activities, counting blood pressure-lowering, antioxidant, cholesterol-lowering, anti-inflammatory, antimicrobial, anticancer, antiplatelet aggregation, hypoglycemic, cardiovascular protective, neuroprotective, respiratory protective, antidiabetic, chemopreventive, antiobesity, antiemetic, antinausea" Mao et al. [12]. The health profits of ginger are mainly credited to the presence of phenolic compounds like shogaol and gingerols.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Protein target

Angiotensin-converting enzyme (PDB ID: 1O86).

2.1.2 Ligand

Literature guided and ligand download from Pubchem

2.1.3 Stand-alone offline softwares

Pyrex, Pymol

2.1.4 Database

PubChem, Protein data base, Pubmed, Swiss ADME, pkCSM and Molinspiration.

2.2 Methods

2.2.1 Preparation, analysis and validation of the protein target

The Angiotensin-converting enzyme (ACE) target, identified with the PDB ID: 1O86, was retrieved from the Protein Data Bank. Subsequently, employing Pymol software, the native ligands and water molecules bound to the protein were eliminated to enhance the protein's readiness for molecular docking. Further refinements for the molecular docking procedure were conducted using the pdb fixer tool available on the Bioinformatics Galaxy Europe web server.

2.2.2 Ligand preparation

21 compounds obtained from literature on ginger were downloaded from PubChem. All the natural compounds on the collection were screened with the Lipinski's rule of five and the Veber rule i.e., molecular weight ≤500, hydrogen bond donor(HBD) ≤5, hydrogen bond acceptor(HBA) ≤ 10 logP≤ 5, polar surface area (PSA) ≤140, and rotatable bond ≤ 10. The 3D structure and the reference ligand compound (PubChem CID 10614) were downloaded from PubChem in Structure Data File (SDF) format.

2.2.3 *In silico* and adme and drug-likeness prediction

The *in silico* ADME screening and drug-likeness evaluation were performed using the free web tool SwissADME, which is developed by the Swiss Institute of Bioinformatics and freely available at www.swissadme.ch Daina et al. [13]. The compounds with high-ranking binding energy scores were subjected to this part of the screening process. Simple physicochemical properties such as molecular weight (MW), molecular refractivity (MR), atom counts, and polar surface area (PSA) were computed. Drug-likeness candidature was implemented by Lipinski [14]; Ghose [15]; Veber [16]; Egan [17]; Muegge [18] rules of 5 (RO5) screening. The Abbot Bioavailability scores were computed to predict the probability of a compound to have at least 10% oral bioavailability by relying on total charge, TPSA, and violation of the Lipinski's filter.

2.2.4 Molecular docking and virtual screening

The 122, Lipinski's and verbal rule complement compounds and the reference compound were uploaded to the virtual screening software, PyRx (python prescription) 0.8 using the open barrel plug-in tool. The ligands were subjected to energy minimization and transformed from sdf to protein data bank, partial charge and atom type (PDBQT) format to prep for molecular docking. All ligand was docked against the target protein angiotensin-converting enzyme using the AutodockVina plug-in tool in PYRX. The parameters for docking with the target protein were set as centre X=79.7763 Y=79.8336 Z=79.8336 and dimension (angstrom) x= 89.9405 y= 65.6233 z= 77.6795 for stable conformation. The universal force field and the conjugate gradient descent were used as energy minimization parameters and optimization algorithms, respectively.

The docking results were moved in Comma-separated value (csv) format to Excel for filtering. Only ligands with lower binding affinity than the reference compound Angiotensin Converting protein were selected due to the prediction of pharmacokinetic properties, molecular refractivity, and bioactivity of all the ligands were performed using PKCSM, Swiss ADME, and Molinspiration, respectively Daina et al. [13]; Pires et al. [19]; Molinspiration [20].

2.2.5 Analysis of the binding site

All the first front-runner compounds were superimposed with the target protein using the PYMOL software. The resultant structure was evaluated using the protein-ligand interaction profiler webserver. All the angiotensin converting enzyme protein bind pockets were analyzed with FPOCKET online server. The three-dimensional depictions of the best-docked complexes were analyzed using hydrogen bonds, salt bridges and another protein-ligand interaction.

3. RESULTS AND DISCUSSION

3.1 Results

Table 1 lists the potential hypertensive compound of *Zingiber Officinale* identified from literatures that were used for this study. The result of molecular docking of Angiotensin-Converting Enzyme (ACE) against the bioactive components shows that the screened compounds at binding affinity of less than -7.3kcal/mol and RMSD equal to zero(0).

The result of fifteen (15) compounds that were further screened based on their physio-chemical properties using the Lipinski's rule of 5, Veber Rule and Ghose rule are presented in Table 2. Eight (8) compounds that did not meet the demand of the rules were screened out leaving seven (7) compounds.

The result of seven (7) compounds after undergoing pharmacokinetic studies (ADMET) is shown in Table 3. Pharmacokinetic study is based on Absorption, Distribution, Metabolism, Excretion and Toxicity. The compounds that were not in line with these rules were cut-off.

Table 4 shows result of the Bioactivity assessment of the seven lead compounds. This result shows the bioactive compound, GCPR ligands, ion channel modulators, kinase inhibitors, protease inhibitors, nuclear receptor ligands, and enzyme inhibitors of the componds.

Table 1. The docking scores/interaction for the identified compounds

S/N	Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1	Nicotiflorin	-9.8	0	0
2	Beta-Sitosterol	-9.5	0	0
3	Kaempferol 3-Glucuronide	-9.3	0	0
4	Quercetin	-8.7	0	0
5	(+)-Catechin	-8.3	0	0
6	Gingerenone A	-8.1	0	0
7	P-Hydroxy-5,6-Dehydrokawain	-7.9	0	0
8	(-)-Alpha-Gurjunene	-7.8	0	0
9	Zerumbone	-7.8	0	0
10	Hexahydrocurcumin	-7.7	0	0
11	Viridifloro	-7.6	0	0
12	Delta Cadinene	-7.6	0	0
13	Gamma-Cadinene	-7.5	0	0
14	Epiglobulol	-7.4	0	0
15	Calarene	-7.4	0	0
16	Germacrene B	-7.4	0	0
17	Beta-Eudesmol	-7.4	0	0
18	Alpha-Eudesmol	-7.4	0	0
19	Ledol	-7.4	0	0
20	(-)-Germacrene D	-7.3	0	0
21	Yakuchinone-A	-7.3	0	0

Table 2. Basic physicochemical properties and computational descriptors of the screened compounds

S/N	Compounds	Binding Affinity	MW	log p	HBD	HBA	RTB	MR	TPSA (A)	SAT	PROM (PAIN alert)
1	Gamma-Cadinene	-7.5	204.35	4.3	0	1	1	69.04	0	1	0
2	Viridiflorol	-7.6	222.37	3.7	1	1	0	68.82	20.23	1	0
3	Epiglobulol	-7.4	222.37	3.7	1	1	0	68.82	20.23	1	0
4	Ledol	-7.4	222.37	3.7	1	1	0	68.82	20.23	1	0
5	Calarene	-7.4	204.35	4.7	0	0	0	66.88	0	0.87	0
6	Alpha-Gurjunene	-7.8	204.35	4.1	0	0	0	67.14	0	0.87	0
7	Alpha-Eudesmol	-7.4	222.37	3.5	1	1	1	70.46	20.23	0.87	0
8	Beta-Eudesmol	-7.4	222.37	3.7	1	1	1	70.46	20.23	0.87	0
9	Delta cadinene	-7.6	222.37	3.3	1	1	1	70.72	20.23	0.87	0
10	Germacrene B	-7.4	204.35	4.1	0	0	0	70.68	0	0.6	0
11	Germacrene D	-7.3	204.35	4.7	0	0	1	70.86	0	0.6	0
12	Zerumbone	-7.8	218.33	3.9	0	1	0	70.62	17.07	0.53	0
13	Hexahydrocurcumin	-7.7	374.4	2.7	3	6	10	103.13	96.22	0.38	0
14	Yakuchinone-A	-7.3	312.4	3.6	1	3	9	93.45	46.53	0.35	0
15	Gingerenone A	-8.1	356.4	3.7	2	5	9	101.49	75.99	0.29	0

Table 3. Predicted pharmacokinetics (adme) parameters of the screened compounds

ADMET Parameters	Viridiflorol	Epiglobulol	Ledol	Alpha-Eudesmol	Beta-Eudesmol	Delta cadinene	Zerumbone
Water solubility	-3.83	-3.83	-3.83	-4.422	-4.9	-4.073	-4.837
Caco2 permeability	1.479	1.479	1.479	1.501	1.508	1.479	1.418
Intestinal absorption (human)	93.323	93.323	93.479	93.022	94.296	94.296	95.07
Skin Permeability	-2.174	-2.174	-1.479	-1.874	-1.967	-1.923	-1.739
P-glycoprotein substrate	No	No	-2.174	No	No	No	Yes
P-glycoprotein I inhibitor	No	No	No	No	No	NO	No
P-glycoprotein I inhibitor	No	No	No	No	No	NO	No
VDss (human)	0.546	0.546	0.546	0.486	0.459	0.42	0.475
Fraction unbound (human)	0.327	0.327	0.327	0.276	0.164	0.28	0.374
BBB permeability	0.627	0.627	0.627	0.594	0.634	0.596	0.677
CNS permeability	-2.297	-2.297	-2.297	-0.309	-1.858	-2.151	-2.509
CYP2D6 substrate	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	No	Yes	No	No
CYP1A2 substrate	NO	NO	NO	NO	NO	NO	NO
CYP2C19 inhibitior	No	No	No	Yes	No	No	No
CYP2C9 inhibitior	NO	NO	NO	NO	NO	NO	NO
CYP2D6 inhibitior	NO	NO	NO	NO	NO	NO	NO
CYP3A4 inhibitior	NO	NO	NO	NO	NO	NO	NO
Total Clearance	0.798	0.798	0.798	1.03	1.032	1.085	1.279
Renal OCT2 substrate	NO	NO	NO	NO	NO	NO	NO
AMES toxicity	NO	NO	NO	NO	NO	NO	NO
Max. tolerated dose (human)	-0.032	-0.032	-0.032	0.131	-0.22	0.343	0.606
hERG I inhibitor	NO	N0	NO	NO	NO	NO	NO
hERG II inhibitor	NO	N0	NO	NO	NO	NO	NO
Oral Rat Acute Toxicity (LD50)	1.6	1.6	1.6	1.68	1.727	1.918	1.779
Oral Rat Chronic Toxicity (LOAEL)	1.223	1.223	1.223	1.231	1.304	1.475	1.361
Hepatotoxicity	NO	NO	NO	NO	NO	NO	NO
Skin Sensitisation	YES	YES	YES	YES	YES	YES	YES
T.Pyriformis toxicity	1.133	1.133	1.133	I.522	1.805	1.49	1.323
Minnow toxicity	1.256	1.256	1.256	0.819	0.412	0.743	0.833

Table 4. Bioactivity scores of the screened compounds

COMPOUNDS	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Viridiflorol	-0.5	-0.29	-0.82	-0.22	-0.48	-0.13
Epiglobulol	-0.5	-0.29	-0.82	-0.22	-0.48	-0.13
Ledol	-0.5	-0.29	-0.82	-0.22	-0.48	0.14
Alpha-Eudesmol	0.03	0.37	-0.63	0.55	0.11	0.5
Beta-Eudesmol	-0.02	0.43	-0.62	0.6	-0.1	0.48
Delta cadinene	-0.09	0.05	-0.87	0.39	-0.63	0.4
Zerumbone	-0.28	-0.08	-1.07	0.22	-0.52	0.24

3.2 Discussion

Table 1 shows the result of 21 bioactive compounds of *Zingiber Officinale* obtained from literature were docked against the protein target Angiotensin-Converting Enzymes ACE with various binding affinities with their best conformation at 0 RSMD. “For screening, a uniform docking score of -7.3 kcal/mol was chosen as a cut-off value compared to the standard (ledol -7.4 kcal/mol) as this depicts strong protein-ligand binding. A lower docking score would increase the amount of data to be handled and affect potency” [21]. The binding affinity values reveal the strength of ligand-protein interaction. Of the 122 ligands docked against the target, 21 compounds had binding affinities less than the -7.3 kcal/mol cut-off.

In Table 2, compounds were screened based on their physio-chemical properties using Lipinski rule, Ghose rule and Verber Rule. According to Lipinski et al. [14], oral drugs should not have a molecular weight of more than 500g/mol. The significance of this is, molecules larger than 500g/mol. The octanol/water partition coefficient determines the Hydrophobicity (Water hating) or Hydroliphicity (Water loving) of a substance [22]. It is a direct measure of the transport abilities of a compound across biological membranes. Drug molecules should have enough solubility to transverse the membrane, but not too soluble as to get trapped in it Hansch et al. [23]. Hydrogen Bond donors are determined by the number of OH and NH bonds in each molecule, while the Hydrogen Bond Acceptors are determined by summing up the nitrogen and oxygen atoms in each molecule (Lipinski et al. [14]. They are a critical aspect to the drug-likeness of a molecule Chen et al. [24].The 15 compounds were screened using the following rules; hydrogen bond acceptors should be ≤ 10, hydrogen bond donors should be ≤5; Log P should be ≤5, molecular weight should be ≤ 500g/mol.

“Also using Verber and Ghose Rules, Verber and Ghose rule states that molecular complexity which is measured by the carbon bond saturation (fraction of sp^3 carbons - fsp^3) plays a vital role in drug discovery. Saturation directly correlates with solubility and saturated hydrocarbons have stability of the chemical bonds which make them unreactive. All compounds with values less than 0.25 are unsaturated and therefore eliminated” Putra et al. [25]; Ghose et al. [15]. “Also, molar refractivity is the measure of the total polarizability of a mole of a ligand and is dependent on the temperature, the index of refraction and pressure. The ideal molar refractivity should range from 40 to 130” Ghose et al. [15].

Rotatable bonds are the measure of molecular flexibility of a compound Veber et al. [16]. TPSA-This is the sum of the contributions to the molecular (usually Van der Waals) surface area of polar atoms such as oxygen, nitrogen and their attached hydrogens (Prasanna & Doerksen, 2009). In terms of the Veber's rule, compounds with a TPSA of ≤140Å and a Rotatable Bond count of ≤10 have a high probability of positive oral bioavailabilty for drug like candidates Medjahed et al. [26].

The Pan Assay Interference compounds (PAINS) also known as promiscuous compounds are bioactive substances that are difficult to detect in data due to interactions with unintended biological targets. None of the compounds including the standard Lenol, violated the Molecular weight, hydrogen bond donor and hydrogen bond acceptors, the Molar refractivity

range of 40 to 130, the PAINS alert of >0, the Fraction Csp3 value of ≥0.25, the Log P value of ≤ 5.

Table 3 shows the result of pharmacokinetic study of the four lead compounds using ADMET parameters. While screening using the physiochemical properties above speed up the drug development process, studies have shown that these rules have limitations and on their own are insufficient to establish the exact drug-likeness of a substance. Ghose et al. [15]; [27].

“ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is a crucial component of the drug discovery process. It is used to 'fine-tune' results obtained from drug-likeness screening. A high quality drug candidate should not only possess sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at therapeutic doses” Guan et al. [28]. The ADMET screening was carried out using the manual by Pires et al. [19]. The goal is for a molecule to have as little violations as possible, but a complete non-violation is rare.

A key physiochemical factor in drug research and development is water solubility, which affects pharmacokinetic properties and formulations Cui et al. [29]. Viridiflorol and Epiglobulol appears to be the most soluble of the chemicals based on the findings as compare to the standard Lenol. Beta-Eudesmol is the least soluble in the group with a water solubility value of less than -4.0 log mol/L Pires et al. [19].

Since oral administration is still the most common form of administration, in vitro permeability studies can be used to predict bioavailability as a drug is being developed. The $CaCO_2$ cell monolayers are used as a model of human intestinal absorption because they closely resemble the human intestinal epithelium in many aspects and establish tight connections between cells (Peng *et al*, 2014). As observed in Table 3, Alpha-Eudesmol and Beta-Eudesmol showed the highest caco-2 permeability, while Zerumbone showed the lowest of all the lead compounds. The standard also showed a high $CaCO_2$ value being higher than 0.9 Pires et al. [19]. The measurement of human intestinal absorption (HIA), similar to caco-2 permeability, is a crucial step in the development of new pharmaceutical substances (Hou *et al.,* [30]). Zerumbone gets the highest value despite the fact that all the lead compounds have high HIA. The standard also showed a high HIA value Pires et al. [19]. Drug penetration through the skin must be evaluated in order to create a transdermal medication delivery system for use on people [31]. Most of the lead compounds have a permeability more than -2.5, exhibited a good skin permeability (LogKp) except for Viridiflorol and Epiglobulol that have values less than -2.5 suggesting low skin permeability.

P-glycoprotein (Pgp), a member of the ATP-binding cassette (ABC) superfamily of transporter proteins, is expressed in the cells of several organs and affects the ADMET properties of drugs. The PgP is a unidirectional efflux pump that extrudes its substrate from inside to outside of cells, including toxins, drugs, and other xenobiotics (Prachayasittikul *et al.,* 2016). From the results only Zerumbone is not a P-gP substrates. This implies that while the bioavailabilities of the P-gp substrates would be reduced by P-glycoprotein that of Zerumbone will not.

The volume of distribution steady state (VDSS) is the theoretical volume required to maintain the whole dose of a drug delivered at the same blood plasma concentration. Important pharmacokinetic characteristics that control a drug's half-life and frequency of dose (Smith, 2015). Of all the compounds, Viridiflorol and Epiglobulol has the highest VDSS value (0.546/kg) as compare to the standard Lenol (0.546/kg) while Delta cadinene the lowest requiring only 0.42l/kg to maintain uniform distribution to give the same concentration in plasma.

A drug's effectiveness is influenced by how strongly it binds to plasma proteins. With less binding, the drug can enter cellular membranes more effectively. The percentage unbound (human) readings for the Beta-Eudesmol indicate that it is the least available for biological activity while the most widely accessible is Zerumbone.

Most drugs cannot cross the blood-brain barrier (BBB), which is anatomically and physiologically unique. But some medications with particular chemical characteristics can pass through the BBB via lipid-mediated free diffusion [32]. According to the findings, all lead compounds have log BBB values more than -1.0, indicating that they are all mildly to moderately distributed in the brain. The best predicted brain distribution is for the Zerumbone, while the worst is for Alpha-Eudesmol and Delta cadinene.

The majority of drugs used in clinical settings are biotransformed by cytochrome P450 (CYP), which is also the main driver of drug

pharmacokinetic variability. The liver's major CYPs are 3A4, 2C9, and 1A2, while 2D6 and 2C19 are less common [33]. Remarkably, Viridiflorol, Epiglobulol and Beta-Eudesmol were predicted to be an inhibitors of CYP3A4 molecules. A drug's total clearance from the blood is the sum of its clearance through the kidneys, the liver, and all other tissues (Horde and Gupta, [34). The total clearance ranges from 0 to 1.0 depending on the functionality of the implicated organs and a number of other variables. The findings indicate that Alpha-Eudesmol, Beta-Eudesmol, Delta cadinene and Zerumbone has a total clearance value above 1.0, indicating that they will be eliminated from the plasma at a very rapid rate.

The proximal epithelial cells' basolateral membrane contains the renal organic cation transporter 2 (ROCT2) protein, which is involved in the uptake and secretion of cationic drugs. None of the lead compounds will be carried from the plasma into the cells of the proximal convoluted by the ROCT2. The human ether-a-go-go related gene (hERG) expresses a potassium channel protein that is crucial for cardiac repolarization and arrhythmias induced by long QT waves (Babcock *et al.,* 2013). The research also revealed that none of the lead compounds were predicted to be hERG I protein inhibitors, demonstrating no possible cardiotoxic effect Pires et al. [19]. The maximum tolerated dosage (MTD) of a drug is the largest dose that does not cause overt toxicity or unfavourable side effects within a specific amount of time, as determined through early human clinical trials Stampfer et al. [35]. “In the present study, only Zerumbone have high MTD being higher than 0.477 (log mg/kg/day). The oral acute toxicity or LD50 is a measurement of how much of a drug is necessary to kill 50% of rats in a test, whereas the oral rat chronic toxicity is the lowest dose of a substance that results in an observed unfavourable effect over time” Pires et al. [19]. “In terms of acute toxicity and chronic toxicity, Viridiflorol and Epiglobulol are the safest of all the compounds. Similarly, for toxicity to *Tetrahymena pyriformis*, Viridiflorol and Epiglobulol are the safest while for Minnows, Beta-Eudesmol is the safest. Despite the fact that the liver is the most common target organ for drug candidates in animal toxicity tests, hepatotoxicity seldom causes drug development to be halted during the preclinical stage. When a drug has great therapeutic promise, hepatotoxicity in humans may be tolerable due to the fact that it is frequently reversible and dose dependent” [36]. At this stage of virtual screening based on ADMET properties, none of the lead compounds were eliminated because they do not inhibit P-gp I, P-gp II, and CYPs 2C19, 2C9, and 3A4 completely.

Table 4 shows the result of the bioactivity assay of the standard and the 6 lead compounds. The lead compounds should have a pharmacological effect in addition to ligand binding to the proper target. GCPR ligands, ion channel modulators, kinase inhibitors, protease inhibitors, nuclear receptor ligands, and enzyme inhibitors are some of the drug candidates that are categorized depending on their bioactivity [20].

Enzyme inhibitors are molecules that interact with enzymes (Temporarily or permanently) is some way and reduces the rate of an ezyme-catalysed reaction or prevent an enzyme from working in a certain way [37]. Since the target protein of this study is an enzyme, the results show that Viridiflorol and Epiglobulol are poor enzyme inhibitors, with a bioactivity score lower than zero. The standard and the four other lead compounds have bioactivity scores greater than zero Pires et al. [19]. Alpha-Eudesmol and Beta-Eudesmol are significantly better enzyme inhibitor than Zerumbone.

4. CONCLUSION

The need for assessable and inexpensive drugs for the management of hypertension is of utmost importance. Inactive and unhealthy lifestyles have given rise to the prevalence of hypertension in both developed and developing countries. While sensitization will go a long way in disease prevention, sustainable treatment options for the millions of sufferers is much needed. Thiazide therapy which has been the most widely used for disease management is expensive and saddled with side-effects like headaches, rash, hives, wheezing or trouble breathing, asthma attack and anaphylaxis etc.

Ginger (*Zingiber officinale*) is found in abundance in Nigeria and can be easily accessed. While studies have been carried out extensively on its ethnomedicinal and therapeutic use such as it counting blood pressure-lowering, antioxidant, cholesterol-lowering, anti-inflammatory, antimicrobial, anticancer, antiplatelet aggregation, hypoglycemic, cardiovascular protective,neuroprotective, respiratory protective, antidiabetic, chemopreventive, antiobesity, antiemetic, antinausea effects, the bioactive

compounds responsible have not been identified and explored. This study indicates that Alpha-Eudesmol and Beta-Eudesmol, can serve as alternative inhibitor of Angiotensin Converting Enzyme (ACE) which is supported by Sanghal et al. [11]; Mao et al. [12]. Therefore, Alpha-Eudesmol and Beta-Eudesmol, can be considered a potential drug candidate for in vivo analysis as a potential inhibitor of ACE.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO. Hypertension. World health organization; 2023.
   Available:https://www.who.int/news-room/fact-sheets/detail/hypertension
2. Naish J, Court DS. Medical sciences (2 ed.). 2014:562.
   ISBN 9780702052491.
3. Lackland DT, Weber MA. "Global burden of cardiovascular disease and stroke: hypertension at the core". The Canadian Journal of Cardiology. 2015;31(5):569–571.
4. Lau DH, Nattel S, Kalman JM, Sanders P. modifiable risk factors and atrial fibrillation. Circulation (Review). 2017;136(6).583-596.
   DOI:10.1161/CIRCULATIONAHA.116.023163
   PMID 28784826.
5. Kaplan's essentials of cardiac anesthesia. Mechanisms of action: ACE inhibitors act by inhibiting one of several proteases responsible for cleaving the decapeptide Ang I to form the octapeptide Ang II. Because ACE is also the enzyme that degrades bradykinin, ACE inhibitors increase circulating and tissue levels of bradykinin. Elsevier; 2018.
   DOI:10.1016/c2012-0-06151-0
   ISBN 978-0-323-49798-5.
6. Hemming ML, Selkoe DJ. Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. The Journal of Biological Chemistry. 2005;280(45):37644–37650.
   DOI: 10.1074/jbc.M508460200
   PMC 2409196. PMID 16154999.
7. Coates D. The angiotensin converting enzyme (ACE)". The International Journal of Biochemistry & Cell Biology. Renin–Angiotensin Systems: State of the Art. 2003;35(6):769–773.
   DOI: 10.1016/S1357-2725(02)00309-6
   PMID 12676162.
8. Zhang R, Xu X, Chen T, Li L, Rao P. An assay for angiotensin-converting enzyme using capillary zone electrophoresis. Analytical Biochemistry. 2000;280(2):286–290.
   DOI: 10.1006/abio.2000.4535
   PMID 10790312.
9. Byrd JB, Ram C, Venkata S, Lerma EV. Pharmacologic treatment of hypertension. Nephrology Secrets. Elsevier. ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II, thereby producing vasodilation and lowering BP. Because the hydrolysis of bradykinin is also inhibited by these drugs, cough (7% to 12%) can occur. 2019;477–482.
   DOI: 10.1016/b978-0-323-47871-7.00078-2.
   ISBN 978-0-323-47871-7.
10. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. Am J Cardiol. 2006;98(5):673–680.
11. Sanghal A, Pant KK, Natu SM, Nischal A, Khattri S, Nath R. An experimental study to evaluate the preventive effect of *Zingiber officinale* (ginger) on hypertension and hyperlipidaemia and its comparison with *Allium sativum* (garlic) in rats. Journal Medicinal Plants Res. 2012;6(25):4231–4238.
12. Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, Li HB. Foods. 2019;8:185–206.
    Available:https://doi.org/10.3390/foods8060185
13. Daina A, Michielin O, Zoete V. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017; 7:42717.
14. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.

Advanced Drug Delivery Reviews. 2001;46(1-3):3-26

15. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. Journal of Combinatorial Chemistry. 1999;1:55-68
16. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry. 2002;45(12):2615-2623.
17. Egan WJ, Merz KM, Baldwin JJ. Prediction of drug absorption using multivariate statistics. The Journal of Medicinal Chemistry. 2000;43:3867–3877.
18. Muegge I, Heald SL, Brittelli D. Simple selection criteria for drug-like chemical matter. The Journal of Medicinal Chemistry. 2001;44:1841–1846.
19. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry. 2015;58(9):4066-72.
DOI: 10.1021/acs.jmedchem.5b00104.
20. Molinspiration cheminformatics. Calculation of molecular properties and bioactivity score; 2020.
Available:http://www.molinspiration.com/cgi-bin/properties Accessed 8th December 2020
21. Hopkins AL. Pharmacological space in the practice of medicinal chemistry. (4th ed.). USA: Elsevier. 2015;395-408.
22. Khanna V, Ranganathan S. Physiochemical property space distance among human metabolites, drugs and toxins. BMC Bioinformatics. 2009;10(15):S10.
23. Hansch C, Bjorkroth JP, Leo A. Hydrophobicity and the central nervous system agents: on the principle of minimal hydrophobicity in drug design. Journal of Pharmaceutical Sciences. 1987;76(9):663-687.
24. Chen X, Li H, Tian L. Analysis of the physio-chemical properties of acaricides based on Lipinski's Rule of 5. Journal of Computational Biology. 2020;27:1397-1406.
25. Putra PP, Abdullah SS, Rahmatunisa R. Structure, activity, and drug-likeness of pure compounds of Sumatran lichen (*Stereocaulon* halei) for the targetd ACE2 protein in COVID-19 disease. Pharmacina. 2020;10:135.
26. Medjahed S, Belaidi S, Djekheba S. Computational study of molecular electrostatic potential, drug-likeness screening and structure-activity/property relationships of thiazolidine-2,4-dione derivatives. Journal of Bionanoscience. 2016;10:118-126.
27. Oprea TI. Property distribution of drug-related chemical databases. Journal of Computer-Aided Molecular Design. 2000;14(3):251–264.
Available:https://doi.org/10.1023/a:1008130001697
28. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, Liu G, Tang Y. ADMET-Score- a comprehensive scoring function for evaluation of chemical drug-likeness. Comprehensive Medicinal Chemistry. 2019;10(1):148-157.
29. Cui Q, Lu S, Ni B, Zeng X, Tan Y, Chen YD, Zhao H. Improved prediction of aqueous solubility of novel compounds by going deeper with deep learning. Frontiers in oncology. 2020;10:121.
30. Hou T, Wang J, Li Y. ADME evaluation in drug discovery. 8. The prediction of human intestinal absorption by a support vector machine. Journal of chemical Information and Modelling. 2007;47(6): 2408-2415.
31. Supe S, Takudage P. Methods for evaluating penetration of drug into the skin: A review. Skin Research and Technology. 2021;27(3):299-308.
32. Pardridge WM. Drug transport across the blood–brain barrier. Journal of Cerebral Blood Flow & Metabolism. 2012; 32(11):1959-1972.
33. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & therapeutics. 2013; 138(1):103-141.
34. Horde GW, Gupta V. Drug clearance. Government medical college Amritsar. Study guide from statpearls publishing, Treasure Island (FL); 2020.
PMID: 32491690
35. Stampfer HG, Gabb GM, Dimmitt SB. Why maximum tolerated dose?. British Journal of Clinical Pharmacology. 2019;85(10): 2213-2217.

36. Ballet F. Hepatotoxicity in drug development: detection, significance and solutions. Journal of hepatology. 1997; 26:26-36.

37. Kuddus M. Introduction to food enzymes. Enzymes in Food Biotechnology. 2019: 1-18.

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