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In Silico Evaluation of *Sesamum indicum* Bioactive Compounds Targeting Angiotensin-Converting Enzyme and Phosphodiesterase 1A: A Preliminary Insights into Male Fertility Therapy

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ABSTRACT

Sesamum indicum L. is rich in sesamin and sesamol and possesses antioxidant properties. Its bioactive compounds may inhibit enzymes associated with sperm quality. This study investigated the bioactive compounds in the hexane extract of *Sesamum indicum* seeds (SIS) to evaluate their inhibitory potential against angiotensin-converting enzyme (ACE) and phosphodiesterase 1A (PDE1A), and their potential as therapeutic candidates for male infertility. Bioactive compounds were identified using gas chromatography–mass spectrometry (GC–MS) and screened with SwissADME for drug-likeness. Compounds with favorable oral drug-like properties were subjected to molecular docking using BIOVIA Discovery Studio Visualizer and AutoDock Vina. GC–MS analysis identified 5-hydroxy-4-methyl-3-heptanone as the most abundant compound, while octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl was the least abundant. Fourteen compounds exhibited favorable drug-like properties. Molecular docking revealed that 4-

thiazolidinone, 3-ethyl-5-[(phenylamino)methylene]-2-thioxo (4TET) showed the strongest binding affinity towards ACE (–6.9 kcal/mol), while glyceric acid (GA) exhibited the strongest binding affinity towards PDE1A (–6.2 kcal/mol), comparable to lisinopril and pentoxifylline respectively. Both compounds complied with Lipinski's rule of five, suggesting good drug-likeness. These findings highlight 4TET and GA as promising candidates for further investigation in the development of therapies for male infertility and provide insight into the mechanism by which SIS may enhance sperm quality and fertility

Keywords: Male infertility, *Sesamum indicum* seeds, Phosphodiesterase 1A, molecular docking, ADME screening, GCMS profiling.

INTRODUCTION

A disease of the reproductive system that affects both men and women is called infertility. According to Telefo et al [1], it is a global issue that affects 10% of people who are of reproductive age on average. One in six couples experience male infertility, which hinders spermatogenesis and lowers sperm quality and quantity [2]. It usually happens as a result of oxidative stress and lipid peroxidation. Given that these disorders have been shown to have detrimental effects on spermatogenesis, the majority of men who experience infertility may be suffering from ailments such as diabetes mellitus, chronic liver disease, chronic alcoholism, coronary heart disease, and deficiencies in antioxidants and vitamins [3].

In vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and hormone therapy with testosterone are three distinct approaches required to address the issue of infertility [4]. Regrettably, many of these fertility therapies are very expensive, particularly for underdeveloped and impoverished nations. As a result, a number of these individuals have sought the advice of conventional doctors, who mostly rely on the usage of potent botanicals to treat this problem and other related medical challenges [5]. Spermatozoa are prone to oxidative degradation by environmental or chemical toxicants because of the high content of polyunsaturated fatty acids (PUFAs) in the plasma membrane [6] and hence may be responsible for infertility in humans and animals. Also, the testicular tissues are crucial male reproductive organs that are very sensitive to toxic chemicals that might disrupt the blood-testis barrier, producing cell toxicity hence testicular

failure. According to Hampl et al. [7], these disruptions caused by chemicals or environmental factors can affect the quantity and quality of sperm cells by interfering with their growth and production. They can also have a dominant effect on the mechanism that impedes the essential cellular process that regulates the production of androgen binding protein and testosterone in leydig cells.

The rennin-angiotensin system (RAS) impacts reproductive function in human [8] Angiotensin-converting enzyme has been demonstrated to impact spermatogenesis by converting angiotensin 1 to angiotensin 11. Angiotensin 11 reduces leydig cell function, decreases testosterone synthesis [9] and induces the conversion of bradykinin of the associated kallikrein-kinin system to inactive peptides, consequently, suppression of ACE may promote spermatogenesis. Also, Phosphodiesterase 1 found in the testis and sperm is responsible for the degradation of sperm cyclic adenosine monophosphate (cAMP) which regulates sperm flagella and it is known that intracellular cAMP concentration plays a central role in sperm motility [10]. PDE1A inhibitors block cAMP breakdown and boost acrosomal exocytosis, sperm must undergo acrosomal exocytosis in an ordered manner to breach the zona pellucida hence, promote sperm motility. ACE and PDE1A inhibitors displayed a defense role against free radical damage, slowed oxidative metabolism and preserve antioxidant enzyme activity [11, 12].

However, due of the antioxidant features of medicinal plants such as *Sesamum indicum* seeds, they can serve as an alternative therapy for infertility in people or animals. Due to the adverse effects demonstrated by the modern-day synthetic and chemical pharmaceuticals, they are often taken with hesitation [13], prompting traditional herbals to attract great interests as they are more natural, environment-friendly and devoid of negative effects [14].

Medicinal plants are a good source of antioxidants, making them a viable alternative for treating infertility-related disorders including sexual dysfunction [15]. High flavonoid and phenol components in plants have been found in past studies to be able to scavenge free radicals, chelating pro-oxidants, inhibit certain enzymes and lower oxidative stress [16]. Beniseeds, or *Sesamum indicum* seeds, are an annual herbaceous plant that are part of the Pedaliaceae family. They are grown primarily for their edible seeds, oil, and flavorful qualities [17]. Because of its great level of resistance to oxidation and rancidity, it is frequently referred to as the "Queen of Oilseeds".

According to Sirato-Yasumoto et al [18], sesame oil improves the ability of the liver to detoxify toxins, lowers the frequency of chemically induced breast tumors, and guards against oxidative stress. Lignans, sesamin, and sesamolin, are constituents of sesame seeds which have been demonstrated to have antioxidant qualities and to have a significant impact on health [19]. Additionally, it has been reported that the administration of SIS to male wistar albino rats enhances spermatogenesis [20].

Therefore, because of the properties of *Sesamum indicum seeds* with a focus on fertility enhancement and also claims of its sperm quality improvement by some people of North Central Nigeria, there is a need to scientifically validate its possible mechanism of action by investigating the bioactive compounds of hexane extracts of sesame seeds as potent inhibitors of angiotensin converting enzymes and phosphodiesterase 1A receptors and thus may provide a drug candidate for male infertility therapy.

MATERIALS AND METHODS

Collection and Identification of Plant

Sesamum indicum seeds were obtained at Engenma Ward 3 of Ankpa Local Government Area, Kogi State. Authentication of the plant was conducted at the Department of Forestry and Environmental Management, Michael Okpara University of Agriculture, Umudike. A voucher specimen was stored in the Herbarium unit of the Department of Physiology and Pharmacology, College of Veterinary Medicine, MOUAU, with voucher number MOUAU/CVM/VPP/2021/1.

Preparation of Crude Extracts

Sesamum indicum seeds (Figure 1) were carefully cleaned and air-dried at room temperature. The dry seeds were pulverized using a miller. A crushed sample of *Sesamum indicum* seed was placed in the extraction chamber of a Soxhlet extractor, and extraction was performed using n-hexane at a temperature of 60 °C. After the extraction, the extract was concentrated to dryness in a water bath kept at 40 °C before being subjected to GCMS profiling.

Figure 1: *Sesamum indicum* seeds

Identification of Bioactive Compounds with Gas Chromatography-Mass Spectrophotometer

Extraction of Bioactive Compounds

A known amount of extract (0.5 g) was weighed and put to a test tube, along with 25 ml of ethanol. The test tube was allowed to react on a hotplate at 600 ℃. Following the reaction time, the reaction product in the test tube was transferred to a separatory funnel. The tube was successfully cleansed with 20 ml ethanol, 10 ml cold water, 10 ml hot water, and 3 ml hexane, all of which were passed to the funnel. The extracts were mixed and rinsed three times with 10 ml of a 10% ethanol aqueous solution. The solution was dried using anhydrous sodium sulfate, and the solvent was evaporated. The sample was solubilized in 1000 µl of pyridine, with 200 µl transferred to an autosampler vial for analysis [21].

Quantification and Identification of Chemical Constituents with GC-MS

Using a BUCK M910 Gas Chromatography system with an HP-5MS column (30 m in length, 250 µm in diameter, and 0.25 µm film thickness), the phytochemical analysis was carried out. High energy electrons (70 eV) were used in an electron ionization system for spectroscopic detection to

300 °C at a rate by GC-MS. The carrier gas, which had a flow rate of one milliliter per minute, was pure helium gas (99.995%). The temperature was held for approximately 10 minutes after it was initially set at 50 °C and increased at a rate of 3 °C per minute. At last, the temperature was raised of 10 °C per minute. One microliter of the prepared 1% of the extracts diluted with acetonitrile was injected in a splitless mode. Based on the peak area created in the chromatogram, the relative amount of each extract's chemical components were expressed as a percentage [22]. Bioactive compounds extracted from different extracts were identified based on GC retention time on HP-5MS column and matching of the spectra with computer software data of standards (Replib and Mainlab data of GC–MS systems).

In Silico Pharmacokinetic Study of the Identified Compounds using SwissADME

Twenty-one compounds found by GC-MS analysis were evaluated for pharmacokinetics features using an integrative in silico model termed SwissADME [23]. The canonical Simplified Molecular Input Line Entry System (SMILE) of the phytocompounds was copied from Pubchem (https://pubchem.ncbi.nlm.nih.gov/) and inserted in the SMILE option of SwissADME for running and data retrieval.

The compounds that were orally bioactive with high GIT were employed for molecular docking. The drug-like properties of the best docked compounds were also analyzed using SwissADME according to Diana et al. [23] The canonical smile of the two best docked compounds from GCMS profiling of hexane extract of SIS were prepared and inputted into the software to compute drug-likeness metrics (molecular weight, hydrogen bond donors, hydrogen bond acceptors, lipophilicity and molecular refractivity).

In silico Molecular Docking

Data Preparation

Thirteen compounds that were orally bioactive with high Gastrointestinal Tract (GIT) after ADME screening namely -5-Hydroxy-4-methyl-3-heptanone (PubChem CID: 12712024), Butoxyacetic acid (PubChem CID: 41958) , Ether 6-methylheptyl vinyl (PubChem CID: 296393), 3-Deoxy-d-mannoic lactone (PubChem CID: 5411561), Oxazole, 5-hexyl-2,4-dimethyl- (PubChem CID: 573438), Hexadecanoic acid, methyl ester (PubChem CID: 8181), 1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester (PubChem CID: 6818), 1-Octenylsuccinic anhydride (PubChem CID:

536272), cis-Vaccenic acid (PubChem CID: 5282761), Oleic Acid (PubChem CID: 445639), 6-Octadecenoic acid (PubChem CID: 5282754),4-Thiazolidinone,3-ethyl-5-[(phenylamino)methylene]-2-thioxo- (PubChem CID: 170221) and Glyceric acid (ISP-TFA) (PubChem CID: 91691573), were selected as ligands. Lisinopril (PubChem CID: 5362119) and pentoxylline (Pubchem CID: 4740), were used as standard ligands. 3D molecular structures of these ligands were retrieved from the chemical database, PubChem. The retrieved files were converted to .pdb file format using BIOVIA Discovery Studio Visualizer (DSV) version 16.1.0.15350 (Accelrys Software Inc., San Diego, CA).

The crystal structures of desired target enzymes angiotensin converting enzyme (PDB ID: 2XY9) and phosphodiesterase 1A (ALPHAFOLD ID: AF-P54750-F1) were retrieved from RSCB Protein Data Bank (PDB) and Alphafold Protein Structure Database, respectively. Using DSV and AutoDock Tools (ADT) version 4.2, polar hydrogen atoms and Gasteiger charges were added respectively to the 3D structures. The macromolecule file was written as .pdbqt file format for further analysis.

Docking Procedure

Docking calculations were performed using AutoDock Vina. The intermolecular interactions of -5-Hydroxy-4-methyl-3-heptanone, butoxyacetic acid, Ether 6-methylheptyl vinyl, 3-Deoxy-d-mannoic lactone , Oxazole, 5-hexyl-2,4-dimethyl- , Hexadecanoic acid, methyl ester, 1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester, 1-Octenylsuccinic anhydride , cis-Vaccenic acid, oleic acid, 6-Octadecenoic acid, 4-Thiazolidinone,3-ethyl-5-[(phenylamino)methylene]-2-thioxo-, Glyceric acid (ISP-TFA) and the standard ligands (lisinopril and pentoxyfylline) with target enzymes (ACE and PD41A) were studied and then visualized using DSV (Swain *et al.*, 2017b). In this study, the active sites of the crystal structures of the target proteins were determined from PDB site records. The grid size xyz attributes were set to 11.925691 ×-0.112840 ×-17.910302 centered on ACE and -10.787316 ×12.803137× -8.543414 centered on PDE1A. Nine docking runs were simulated for each ligand and the best pose was selected based on the binding energy.

Protein-Ligand Complex Analysis

The protein-ligand complexes were investigated and characterized with Auto Dock Vina by a method termed gradient optimization algorithm. This was utilized to find the optimal binding

conformation and the binding energy. BIOVIA Discovery Studio Visualizer (DSV) was utilized to generate and visualize the 2D and 3D illustrations of these interactions. The program was used to determine the polar and hydrophobic interactions as well as other types of connections between the ligand and proteins (33).

RESULTS AND DISCUSSION

GCMS Analysis of Hexane Extract of *Sesamum indicum* Seeds

The list of bioactive compounds identified in hexane extract of *Sesamum indicum* seeds and the chromatogram of the identified compound were presented in Table 1 and figure 2 respectively. Bioactive compounds (21) were found in the extract with different peak area percentage and retention time. The compounds are 5-Hydroxy-4-methyl-3-heptanone, 3 methyl Decanoic acid, Butoxyacetic acid, Ether, 6-methylheptyl vinyl, Docosyl octyl ether, 3-Deoxy-d-mannoic lactone, Oxazole, 5-hexyl-2,4-dimethyl-, Hexadecanoic acid, methyl ester, 1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester, n-Hexadecanoic acid, 1-Octenylsuccinic anhydride, 13-Octadecenoic acid cis, methyl ester, 1H-Cycloprop[e]azulene, decahydro-1,1,4,7-tetramethyl-, cis-Vaccenic acid, Oleic Acid, 7-Pentadecyne, 2-Propenoic acid, 2-methyl-, 3-[tris(2-methoxyethoxy)silyl]propyl ester, 6-Octadecenoic acid, 4-Thiazolidinone, 3-ethyl-5-[(phenylamino)methylene]-2-thioxo, glyceric acid (ISP-TFA and Octasiloxane, 1,1,3,3,5,5,7,7,9,9, 11,11,13,13,15,15-hexadecamethyl. 5-Hydroxy-4-methyl-3-heptanone was identified as the most abundant compound with peak area% of 17.87 and Octasiloxane, 1,1,3,3,5,5,7,7,9,9, 11,11,13,13,15,15-hexadecamethyl was identified as the least abundant compound with the concentration of 0.95 peak area% (Table 1)

Table 1: List of compounds identified in GCMS analysis of hexane extract of *Sesamum indicum* seeds

S/N	Compounds	Retention Time(min)	Peak Area %)
1	5-Hydroxy-4-methyl-3-heptanone	11.877	17.87
2	3 methyl Decanoic acid	12.460	7.45
3	Butoxyacetic acid	12.699	1.96
4	Ether, 6-methylheptyl vinyl	14.435	7.31
5	Docosyl octyl ether	14.527	2.70
6	3-Deoxy-d-mannoic lactone	14.703	3.49
7	Oxazole, 5-hexyl-2,4-dimethyl-	15.474	1.39
8	Hexadecanoic acid, methyl ester	16.982	2.94
9	1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester	17.486	2.17
10	n-Hexadecanoic acid	17.621	11.12
11	1-Octenylsuccinic anhydride	18.208	1.66
12	13-Octadecenoic acid cis, methyl ester	18.800	6.41
13	1H-Cycloprop[e]azulene, decahydro-1,1,4,7-tetramethyl-	19.102	5.18
14	cis-Vaccenic acid	19.425	12.69
15	Oleic Acid	19.604	5.64
16	7-Pentadecyne	20.268	2.33
17	2-Propenoic acid, 2-methyl-, 3-[tris(2-methoxyethoxy)silyl]propyl ester	20.564	2.33
18	6-Octadecenoic acid	23.602	2.82
19	4-Thiazolidinone, 3-ethyl-5-[(phenylamino)methylene]-2-thioxo-	23.931	1.58
20	Glyceric acid (ISP-TFA)	26.110	1.22
21	Octasiloxane, 1,1,3,3,5,5,7,7,9,9, 11,11,13,13,15,15-hexadecamethyl	29.714	0.95

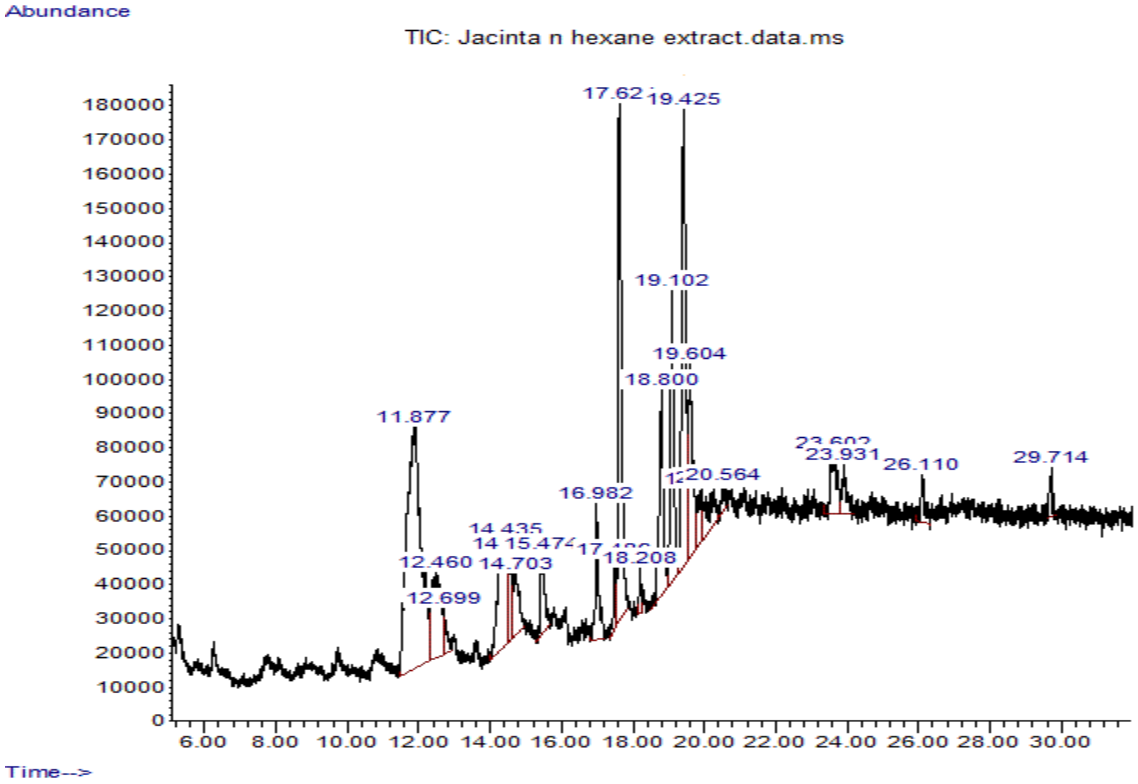

Figure 2: Chromatogram of GCMS Analysis of Hexane Extract of *Sesamum indicum* Seeds

Pharmacokinetics Prediction of the Compounds Using Swissadme

The fourteen compounds were found to have high GIT bioavailability and some were able to pass through the blood brain barrier (BBB) while the remaining seven compounds have low GIT bioavailability. The fourteen compounds are -5-Hydroxy-4-methyl-3-heptanone, Butoxyacetic acid, Ether, 6-methylheptyl vinyl, 3-Deoxy-d-mannoic lactone, Oxazole, 5-hexyl-2,4-dimethyl, Hexadecanoic acid, methyl ester, 1,2-benzenedicarboxylic acid, butyl 2-ethylhexyl ester, N-hexadecanoic acid, 1-Octenylsuccinic anhydride, cis-Vaccenic acid, Oleic Acid, 6-Octadecenoic acid, 4-Thiazolidinone,3-ethyl-5-[(phenylamino)methylene]-2-thioxon and glyceric acid (ISP-TFA). The pubchem CID, molecular formular, canonical smile, soluble IT class, gastrointestinal tract (GIT) and blood brain barrier (BBB) results of the fourteen compounds were reported; 7 compounds were soluble, 4 compounds were moderately soluble and 3 compounds were poorly soluble. The entire compounds can pass through the GIT and only 9 compounds can cross blood brain barrier (Table 2).

Table 2: ADME properties of compounds (identified by GCMS) predicted by swissADME

Compounds	Pubchem CID	Formular	Canonical Smile	Solicos IT Class	GIT	BBB
-5-Hydroxy-4-methyl-3-heptanone	12712024	C8H16O2	CCC(C(C)C(=O)CC)O	Soluble	High	Yes
Butoxyacetic acid	41958	C6H12O3	CCCCOCC(=O)O	soluble	High	Yes
Ether, 6-methylheptyl vinyl	296393	C10H20O	CC(C)CCCCCOC=C	soluble	High	Yes
3-Deoxy-d-mannoic lactone	5411561	C6H10O5	C1C(C(OC(=O)C1O)CO)O	soluble	High	No
Oxazole, 5-hexyl-2,4-dimethyl	573438	C11H19NO	CCCCCCC1=C(N=C(O1)C)C	Moderately soluble	High	Yes
Hexadecanoic acid, methyl ester	8181	C17H34O2	CCCCCCCCCCCCCCCC(=O)OC	Poorly soluble	High	Yes
1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester	6818	C20H30O4	CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCCCC	Poorly soluble	High	Yes
N-hexadecanoic acid	985	C16H32O2	CCCCCCCCCCCCCCCC(=O)O	Moderately soluble	High	Yes
1-Octenylsuccinic anhydride	5362721	C12H18O3	CCCCCCC=CC1CC(=O)OC1=O	soluble	High	Yes
cis-Vaccenic acid	5282761	C18H34O2	CCCCCCC=CCCCCCCCCC(=O)O	Moderately Soluble	High	No
Oleic Acid	445639	C20H39NO2	CCCCCCCC/C=C\CCCCCCCC(=O)NCCO	Poorly soluble	High	Yes
6-Octadecenoic acid	5282754	C18H34O2	CCCCCCCCCCCC=CCCCCC(=O)O	Moderately soluble	High	No
4-Thiazolidinone,3-ethyl-5-[(phenylamino)methylene]-thioxo	170221	C10H10F6O6	CCN1C(=C(SC1=S)C=NC2=CC=CC=C2)O	Soluble	High	No
Glyceric acid (ISP-TFA	91691573	C16H48O7Si8	CC(C)OC(=O)C(COC(=O)C(F)(F)F)OC(=O)C(F)(F)F	Soluble	High	No

BBB-Blood brain barrier, GIT- Gastrointestinal tract

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In silico molecular docking score of the identified compounds (with high GIT) and standard ligands against proteins or enzymes associated with sperm count and motility.

The potency of bioactive compounds present in hexane extract of *Sesamum indicum* seeds were examined in the form of docking score (kcal/mol) or binding affinity. The 14 compounds with high GIT and standard ligands (Lisinopril and Pentoxyfylline) were docked against two target enzymes; angiotensin converting enzymes and phosphodiesterase 1A. Based on the docking scores, 4-Thiazolidinone, 3-ethyl-5-[(phenylamino)myethlene]-2-thioxo exhibited a favorable docking score or binding affinity of -6.9 Kcal/mol against ACE when compared with other 13 compounds but the lisinopril (LIS) exhibited a better score of -9.3 Kcal/mol when compared with TET {ACE: -6.9 (Kcal/mol) (TET) vs -9.3(Kcal/mol) (LIS)} with different boding interactions. Also, glyceric acid (GA) exhibited a favorable docking score or binding affinity of -6.2 Kcal/mol when compared with other 13 compounds while pentoxyfylline exhibited a docking score or binding affinity of -6.3 Kcal/mol which was almost similar with the score of PEN {PDE1A: -6.2(Kcal/mol) (GA) vs -6.3(Kcal/mol) (PEN)} with different boding interactions (Table 3).

Table 3: Molecular Docking Score and Ligand Efficacy of the Identified Compounds (with high GIT) and Standard Drugs against Proteins (ACE and PDE1A) associated with Sperm Count and Motility.

	ACE (PDB ID: 2XY9)	PDE1A (APSD: AF-P54750-F1)
LIGANDS	Binding energy (Kcal/mol)	Binding energy (Kcal/mol)
5-Hydroxy-4-methyl-3-heptanone	-5	-4.5
Butoxyacetic acid	-4.5	-4.1
Ether,6-methylheptyl vinyl	-5	-4.5
3-Deoxy-d-mannoic lactone	-5.4	-4.9
Oxazole,5-hexyl-2,4-dimethyl	-6	-5.2
Hexadecanoic acid, methyl ester	-5.4	-5.4
1,2-Benzenedicarboxylic acid, butyl 2-ethylhexyl ester	-6.7	-6
N-hexadecanoic acid	-4.7	-5.3
1-Octenylsuccinic anhydride	-6.4	-5.9
cis-Vaccenic acid	-5.5	-5.9
Oleic Acid	-5.9	-5.3
6-Octadecenoic acid	-5.7	-5.6

ACE: Angiotensis converting enzyme, PDE1A: Phosphodiesterase 1A, PDB: Protein data bank, APSD: Alphafold Protein Structure Database

Molecular Interaction of 4-Thiazolidinone, 3-ethyl-5-[(phenylamino) methylene]-2-thioxo, glyceric acid against ACE and PDE1A

4-Thiazolidinone, 3-ethyl-5-[(phenylamino) methylene]-2-thioxo and glyceric acid exhibited the highest binding energy against the target enzymes; ACE and PDE1A respectively when compared to other bioactive compounds, with 4-Thiazolidinone, 3-ethyl-5-[(phenylamino) methylene]-2-thioxo showing a binding energy of -6.9kcal/mol against ACE and glyceric acid with a binding energy of -6.3kcal/mol against PDE1A. 4-Thiazolidinone,3-ethyl-5-[(phenylamino)methylene]-2-thioxo formed different bond interactions with 3 amino acids residue of ACE; **HIS387**, HIS353 and TYR523. Lisinopril formed different bond interaction with different amino acid residue of ACE; **HIS 387**, ARG532, PHE391, ALA356, GLY 404, ALA 63, TYR 360, and TRP59. Glyceric acid formed different bond interaction with 5 amino acids of PDE1A. GLN337 and **ARG94,** LEU81, **ILE84,** ARG94 and SER333. Pentoxyfyllne formed different bond interaction with different amino acids residue of PDE1A; LYS340, **ILE84, ARG94**, PHE336, ARG103, LEU94, ALA98 (Figure 3, Figure 4, Table 4).

Table 4: Ligands and amino acids they interacted with in ACE

LIGANDS	TARGET ENZYMES	INTERATING AMINO ACIDS
4-Thiazolidinone	ACE	TYR 523, HIS 353, **HIS 387**
Lisinopril	ACE	**HIS 387**, ARG 532, PHE 391, ALA 356, GLY 404, ALA 63, TYR 360, TRP 59
Glyceric acid	PDE1A	**ARG 94**, SER 333, GLN 337, **ILE 84**, LEU 81
Pentoxifylline	PDE1A	LYS 340, **ILE 84**, **ARG 94**, PHE 336, ARG 103, LEU 94, ALA 98

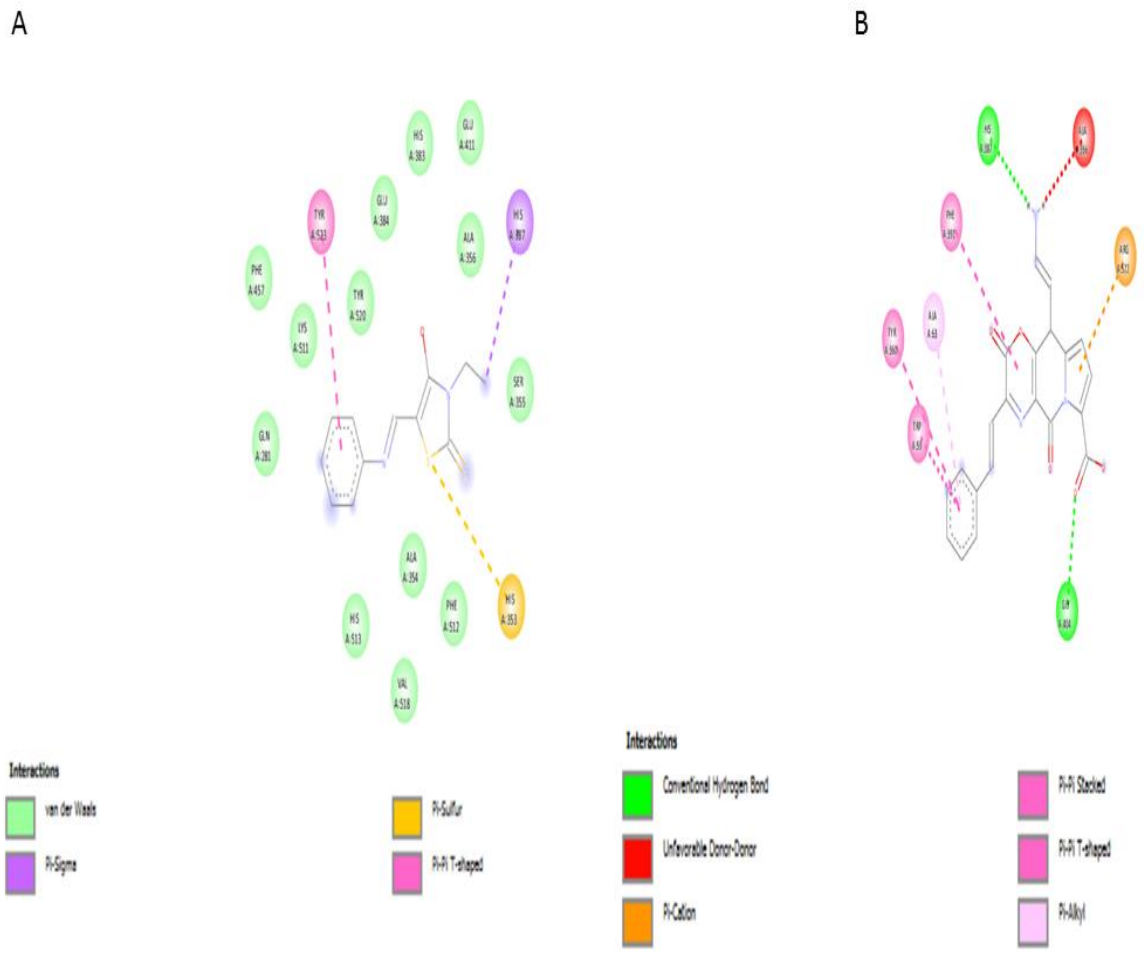

Figure 3: 2D Illustration of Molecular interaction of (A)4-Thiazolidinone, 3-ethyl-5-[(phenylamino) methylene]-2-thioxo and (B) lisinopril against Angiotensin converting enzyme

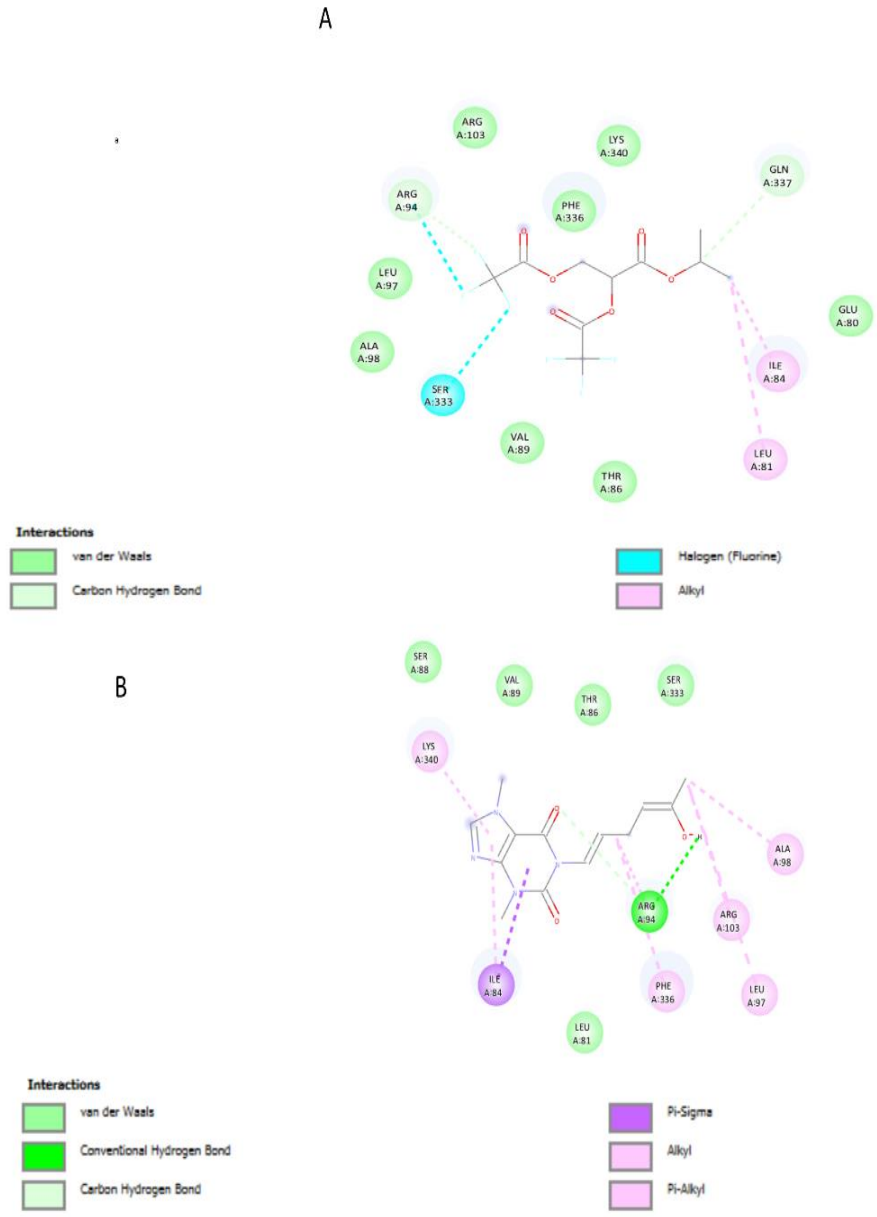

Figure 4: 2D Illustration of Molecular interaction of (A)Glyceric acid and (b)Pentoxyfylline against Phosphosdiesterase 1A

Drug-likeness analysis of two best docked compounds of hexane extract of SIS after SwissADME screening.

4-Thiazolidinone,3-ethyl-5-[(phenylamino) methylene]-2-thioxo showed molecular weight of 264.37g/mol, HB acceptor of of 2, HB donor of 1, lipophilicity of 3.05, Molecular Refractivity of 74.93 and Lipinski violation of 0 and Glyceric acid (ISP-TFA) showed molecular weight of 340.17g/mol, HB acceptor of of 9, HB donor of 0, lipophilicity of 2.75, Molecular Refractivity of 54.42 and Lipinski violation of 0 (Table 5)

Table 5: Drug-likeness analysis of two best docked compounds of hexane extract of SIS after SwissADME screening.

Bioactive Compounds	Molecular weight (g/mol)[1]	HB Acceptor[2]	HB Donor[3]	Lipophilicity[4]	Molecular Refractivity[5]	Lipinski violation
4-Thiazolidinone, 3-ethyl-5-[(phenylamino) methylene]-2-thioxo	264.37	2	1	3.05	74.93	0
Glyceric acid (ISP-TFA)	340.17	9	0	2.72	54.42	0

Molecular weight (acceptable range: ≤ 500), HB, Hydrogen bond acceptor (acceptable range:≤ 10), HB, Hydrogen bond donor (acceptable range:≤ 5), Lipophilicity (Log Po/w, acceptable bounds <5), Molar refractivity, acceptable bounds 40-130, Lipinski violations (ideal range: 0–4).

Herbal medicines are generally derived from crude plant extracts containing diverse bioactive compounds, and their therapeutic potential is often evaluated for disease treatment applications [24]. In this study, GC–MS analysis of the hexane extract of *Sesamum indicum* seeds revealed 21 phytochemicals with varying retention times and peak areas, which may contribute to the plant's therapeutic properties [25]. The most abundant compound was 5-hydroxy-4-methyl-3-heptanone, while octasiloxane derivatives were least abundant. Importantly, 4-thiazolidinone has been reported to possess anti-inflammatory and anti-ulcer activities, while glyceric acid exhibits antioxidant and anticomplement properties [26]. The detection of n-hexadecanoic acid and oleic acid in our extract is consistent with earlier findings by Okoronkwo et al. [27] and Yusuf et al. [28].

Pharmacokinetic evaluation using SwissADME showed that 13 compounds demonstrated high gastrointestinal absorption, suggesting potential oral bioavailability. This is significant because ADME properties are critical determinants of pharmacokinetics [29], and compounds with high GI absorption are considered suitable for drug development [30]. Guan et al. [31] emphasized that effective drug candidates must combine therapeutic efficacy with favorable ADMET characteristics. In line with this, 4-thiazolidinone and glyceric acid (GA) satisfied Lipinski's rule of five, indicating strong drug-likeness and reduced risk of attrition during clinical trials [23,45].

Molecular docking analysis provided mechanistic insights into fertility enhancement. Docking scores are expressed in negative kcal/mol, with more negative values indicating stronger binding [37]. In this study, 4TET exhibited a binding energy of –6.9 kcal/mol against ACE, forming interactions with HIS387, HIS353, and TYR523. Although lisinopril bound more strongly (–9.3 kcal/mol), the comparable affinity of 4TET suggests potential ACE inhibition. ACE suppression prevents the conversion of angiotensin I to angiotensin II, thereby improving Leydig cell function and testosterone synthesis [9,12]. Similarly, GA showed a binding energy of –6.2 kcal/mol against PDE1A, nearly identical to pentoxifylline (–6.3 kcal/mol). GA interacted with GLN337, ARG94, LEU81, ILE84, and SER333, indicating effective PDE1A inhibition. PDE1A inhibition prevents cAMP degradation, enhances acrosomal exocytosis, and promotes sperm motility [10,11].

Thiazole derivatives, such as 4TET, are widely recognized for their pharmacological potential due to their structural diversity and biological activities [38–40]. They have been reported to exhibit antidiabetic [43], anti-inflammatory, analgesic, and anti-ulcer properties [44]. Similarly, glyceric acid has been associated with antioxidant and anticomplement activity [26]. However, no prior studies have reported their fertility-enhancing potential, making this investigation novel. It is plausible that inhibition of ACE and PDE1A by 4TET and GA of Sesamum indicum seeds contributes to increased Leydig cell activity, enhanced testosterone synthesis, and improved spermatogenesis, as suggested by earlier reports [41,42].

Overall, the dual inhibition mechanism is significant because ACE suppression enhances spermatogenesis through testosterone regulation, while PDE1A inhibition preserves intracellular cAMP, thereby promoting sperm motility. Together, these pathways suggest a synergistic role in

fertility enhancement. Importantly, the binding affinities of 4TET and GA were comparable to standard drugs lisinopril and pentoxifylline highlighting their therapeutic potential. While previous studies have highlighted the antioxidant and spermatogenic effects of *Sesamum indicum* [18, 20], few have identified specific compounds with dual enzyme inhibitory activity. Therefore, the findings of this study provide novel pharmacological insights and support the exploration of these compounds as affordable, natural alternatives for male infertility therapy.

CONCLUSION

This study provides preliminary evidence that bioactive compounds from *Sesamum indicum* seeds, particularly 4-thiazolidinone (4TET) and glyceric acid (GA), possess drug-like properties and exhibit inhibitory activity against ACE and PDE1A. GC–MS profiling identified 21 phytochemicals, several of which demonstrated favorable pharmacokinetic features in SwissADME screening. Docking analysis revealed that 4TET and GA achieved binding affinities comparable to standard drugs lisinopril and pentoxifylline, interacting with key amino acid residues of ACE and PDE1A respectively. These findings suggest that *Sesamum indicum* phytochemicals may enhance male fertility through dual inhibition of ACE, which supports testosterone synthesis and spermatogenesis and PDE1A, which preserves cAMP levels critical for sperm motility and this provides basis for their traditional use in fertility enhancement and highlight their potential as lead compounds for the development of novel therapies in male infertility. However, as this study is limited to *in silico* analysis, further *in vitro* and *in vivo* validation of 4TET and GA is essential to confirm biological efficacy, safety, and therapeutic relevance.Also, it was deduced that the abundance of a compound in a plant does not show that the effect of the plant or extract depends on that compo

Authors' Contribution

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REFERENCES

1. Telefo, P. B., Lienoua, L. L., Yemelea, M. D., Lemfacka, M. C., Mouokeua, C. & Gokaa, C. S. (2011). Ethnopharmacological survey of plants used for the treatment of female infertility in Baham, Cameroon. *Journal of Ethnopharmacology, 136*(1), 178–187. https://doi.org/10.1016/j.jep.2011.04.036
2. Deka, J. & Kalita, J. C. (2013). Ethnobotanical important medicinal plants of Kamrup district, Assam, India used in fertility treatment. *International Research Journal of Pharmacy, 4*(4), 1–4. https://doi.org/10.7897/2230-8407.04349
3. Nath, S. & Deb, B. (2015). Survey on the effect of plant extract on reproductive parameters of mammals. *International Journal of Pure & Applied Bioscience, 3*(3), 216–223.
4. Ashamu, E., Salawu, E., Oyewo, O., Alhassan, A., Alamu, O. & Adegoke, A. (2010). Efficacy of vitamin C and ethanolic extract of *Sesamum indicum* in promoting fertility in male Wistar rats. *Journal of Human Reproductive Sciences, 3*(1), 11–14. https://doi.org/10.4103/0974-1208.63115
5. Oyedemi, S. O., Oyedemi, B. O., Ijeh, I. I., Ohanyerem, P. E., Coopoosamy, R. M. & Aiyegoro, O. A. (2017). Alpha-amylase inhibition and antioxidative capacity of some antidiabetic plants used by traditional healers in Southeastern Nigeria. *The Scientific World Journal, 2017*, 1–11. https://doi.org/10.1155/2017/3592491
6. Ommati, M. M., Zamiri, M. J., Akhlaghi, A., Atashi, H., Jafarzadeh, M. R., Rezvani, M. R. & Saemi, F. (2013). Seminal characteristics, sperm fatty acids, and blood biochemical attributes in breeder roosters orally administered with sage (*Salvia officinalis*) extract. *Animal Production Science, 53*(6), 548–554. https://doi.org/10.1071/AN12257
7. Hampl, R., Kubatova, J. & Starka, L. (2016). Steroids and endocrine disruptors—History, recent state of the art and open questions. *Journal of Steroid Biochemistry and Molecular Biology, 155*, 217–223. https://doi.org/10.1016/j.jsbmb.2014.04.013

8. Köhn, F. M., Müller, C., Drescher, D., Neukamm, C., Mulla, K. E., Henkel, R. & Schill, W. B. (1998). Effect of angiotensin converting enzyme (ACE) and angiotensins on human sperm functions. *Andrologia*, *30*(4–5), 207–215. https://doi.org/10.1111/j.1439-0272.1998.tb01162.x
9. Leung, P. S. & Sernia, C. (2003). The renin-angiotensin system and male reproduction: New functions for old hormones. *Journal of Molecular Endocrinology, 30*(3), 263–270. https://doi.org/10.1677/jme.0.0300263
10. Fisch, J. D., Behr, B. & Conti, M. (1998). Enhancement of motility and acrosome reaction in human spermatozoa: Differential activation by type-specific phosphodiesterase inhibitors. *Human Reproduction, 13*(5), 1248–1254. https://doi.org/10.1093/humrep/13.5.1248
11. Wong, W. Y., Merkus, H. M., Thomas, C. M., Menkveld, R., Zielhuis, G. A. & Steegers-Theunissen, R. P. (2002). Effects of folic acid and zinc sulfate on male factor subfertility: A double-blind, randomized, placebo-controlled trial. *Fertility and Sterility, 77*(3), 491–498. https://doi.org/10.1016/S0015-0282(01)03229-0
12. Asaad, G. F., Hassan, A. & Mostafa, R. E. (2021). Anti-oxidant impact of lisinopril and enalapril against acute kidney injury induced by doxorubicin in male Wistar rats. *Heliyon, 7*(1), e05985. https://doi.org/10.1016/j.heliyon.2021.e05985
13. Philomena, G. (2011). Concerns regarding the safety and toxicity of medicinal plants—An overview. *Journal of Applied Pharmaceutical Science, 1*, 40–44.
14. Sahoo, N. & Manchikant, P. (2012). Herbal drug regulation and commercialization: An Indian industry perspective. *Journal of Alternative and Complementary Medicine, 19*, 957–963. https://doi.org/10.1089/acm.2012.0275
15. Nwonuma, C. O., Nwatu, V. C. & Mostafa-Hedeab, G. (2022). Experimental validation and molecular docking to explore the active components of cannabis in testicular function and sperm quality modulations in rats. *BMC Complementary Medicine and Therapies*, *22*, 227. https://doi.org/10.1186/s12906-022-03704-z.
16. Silva, B. M., Andrade, P. B., Valentão, P., Ferreres, F., Seabra, R. M. & Ferreira, M. A. (2004). Quince (*Cydonia oblonga* Miller) fruit (pulp, peel, and seed) and jam: Antioxidant activity. *Journal of Agricultural and Food Chemistry*, *52*(15), 4705–4712. https://doi.org/10.1021/jf040057v

17. Bedigian, D. (2015). Systematics and evolution in *Sesamum* L. (Pedaliaceae), Part 1: Evidence regarding the origin of sesame and its closest relatives. *Webbia, 70*(1), 1–42. https://doi.org/10.1080/00837792.2014.968457
18. Sirato-Yasumoto, S., Katsuta, M., Okuyama, Y., Takahashi, Y. & Ide, T. (2001). Effect of sesame seeds rich in sesamin and sesamolin on fatty acid oxidation in rat liver. *Journal of Agricultural and Food Chemistry, 49*(5), 2647–2651. https://doi.org/10.1021/jf001362t
19. Schwertner, H. A. & Rios, D. C. (2012). Analysis of sesamin, asarinin, and sesamolin by HPLC with photodiode and fluorescent detection and by GC/MS: Application to sesame oil and serum samples. *Journal of the American Oil Chemists' Society, 89*, 1943–1950. https://doi.org/10.1007/s11746-012-2098-7
20. Ukpabi-Ugo, J. C., Anosike, C. A. & Chukwuma, E. W. (2023). Chemical composition and *in vitro* antioxidant properties of hexane and methanol extract of *Sesamum indicum* seeds obtained from Kogi State, Nigeria. *African Scientist, 24*(2), 205–214.
21. Buss, A. D. & Butler, M. S. (2010). *Natural product chemistry for drug discovery*. The Royal Society of Chemistry.
22. Kelly, D. A. & Nelson, R. (2014). Characterization and quantification by gas chromatography of flavonoids. *Journal of the Brazilian Chemical Society, 25*, 35–46. https://doi.org/10.5935/0103-5053.20130288
23. Daina, A., Michielin, O. & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports, 7*, 42717. https://doi.org/10.1038/srep42717
24. Anand, U., Jacobo-Herrera, N., Altemimi, A. & Lakhssassi, N. (2019). A comprehensive review on medicinal plants as antimicrobial therapeutics: Potential avenues of biocompatible drug discovery. *Metabolites, 9*(11), 258. https://doi.org/10.3390/metabo9110258
25. Kabra, A., Sharma, R., Hano, C., Kabra, R., Martins, N. & Baghel, U. S. (2019). Phytochemical composition, antioxidant, and antimicrobial attributes of different solvent extracts from *Myrica esculenta* leaves. *Biomolecules, 9*(8), 357. https://doi.org/10.3390/biom9080357.

26. Barbakadze, V. V., Kemertelidze, E. P., Mulkijanyan, K. G., Van den Berg, A. J. J., Beukelman, C. J., Van den Worm, E., Quarles van Ufford, H. C. & Usov, A. I. (2007). Antioxidant and anticomplement activity of poly[3-(3,4-dihydroxyphenyl)glyceric acid] from *Symphytum asperum* and *Symphytum caucasicum* plants. *Pharmaceutical Chemistry Journal, 41*(1), 14–17. https://doi.org/10.1007/s11094-007-0004-7
27. Okoronkwo, N. E., Osuji, E. Q. & Nwankwo, C. C. (2014). Assessment of potential values of *Sesamum indicum* seed. *International Journal of Arts & Sciences, 7*(3), 19–27.
28. Bankole, M. A., Shittu, L. A., Ahmed, T. A., Bankole, M. N., Shittu, R. K., Terkula, K. & Ashiru, O. A. (2007). Synergistic antimicrobial activities of phytoestrogens in crude extracts of two sesame species against some common pathogenic microorganisms. *African Journal of Traditional, Complementary and Alternative Medicines, 4*(4), 427–433. https://doi.org/10.4314/ajtcam.v4i4.31237
29. Jang, G. R., Harris, R. Z. & Lau, D. T. (2001). Pharmacokinetics and its role in small molecule drug discovery research. *Medical Research Reviews, 21*(5), 382–396. https://doi.org/10.1002/med.10155
30. Daina, A. & Zoete, V. (2016). A BOILED-Egg to predict gastrointestinal absorption and brain penetration of small molecules. *ChemMedChem, 11*(11), 1117–1121.
31. Guan, L., Yang, H., Cai, Y., Sun, L., Di, P., Li, W. & Tang, Y. (2019). ADMET-score: A comprehensive scoring function for evaluation of chemical drug-likeness. *MedChemComm, 10*(1), 148–157. https://doi.org/10.1039/C8MD00472B
32. Rollinger, J. M., Stuppner, H. & Langer, T. (2008). Virtual screening for the discovery of bioactive natural products. *Progress in Drug Research, 65*, 211–249. https://doi.org/10.1007/978-3-7643-8117-2_6.
33. Swain, S. S., Paidesetty, S. K. & Padhy, R. N. (2017). Development of antibacterial conjugates using sulfamethoxazole with monocyclic terpenes: A systematic medicinal chemistry-based computational approach. *Computer Methods and Programs in Biomedicine, 140*, 185–194. https://doi.org/10.1016/j.cmpb.2016.12.0133.

34. Gupta, M. K., Vemula, S., Donde, R., Gouda, G., Behera, L. & Vadde, R. (2021). *In silico* approaches to detect inhibitors of the human severe acute respiratory syndrome coronavirus envelope protein ion channel. *Journal of Biomolecular Structure and Dynamics, 39*(7), 2617–2627. https://doi.org/10.1080/07391102.2020.1751300
35. Sourav, D., Sarmah, S., Lyndem, S. & Singha, R. A. (2021). An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study. *Journal of Biomolecular Structure and Dynamics, 39*(9), 3347–3357. https://doi.org/10.1080/07391102.2020.1763201
36. Yang, J., Hocking, D. M. & Cheng, C. (2013). Disarming bacterial virulence through chemical inhibition of the DNA binding domain of an AraC-like transcriptional activator protein. *Journal of Biological Chemistry, 288*, 31115–31126. https://doi.org/10.1074/jbc.M113.503912
37. Swain, S. S., Paidesetty, S. K., Dehury, B., Das, M., Vedithi, S. C. & Padhy, R. N. (2020). Computer-aided synthesis of dapsone-phytochemical conjugates against dapsone-resistant *Mycobacterium leprae*. *Scientific Reports, 10*(1), 6839. https://doi.org/10.1038/s41598-020-63913-9
38. Bhardwaj, N., Pathania, A. & Kumar, P. (2021). Naturally available nitrogen-containing fused heterocyclics as prospective lead molecules in medicinal chemistry. *Current Traditional Medicine, 7*(1), 5–27. https://doi.org/10.2174/2215083805666190613125700
39. Slobbe, P., Ruijter, E. & Orru, R. V. A. (2012). Recent applications of multicomponent reactions in medicinal chemistry. *MedChemComm, 3*(10), 1189–1218. https://doi.org/10.1039/C2MD20089A
40. Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K. & Jonnalagadda, S. B. (2020). A review on recent advances in nitrogen-containing molecules and their biological applications. *Molecules, 25*(8), 1909. https://doi.org/10.3390/molecules25081909
41. Ukwenya, V., Oluyemi, K., Ashamu, E., Saalu, C., Oyewo, O. & Makanjuola, V. (2007). Profertility effects of alcoholic extract of sesame in male Sprague-Dawley rats. *Internet Journal of Nutrition and Wellness, 5*(2), 1–5.

42. Yusuf, M. K., Ibegbu, A. O., Alawa, J. N., Ilyas, M. O. & Evang, A. (2018). Effects of ethanolic extract of *Sesamum indicum* seeds on histology and sperm concentration in ketoconazole-induced testicular damage in male Wistar rats. *Clinical Research*, *4*(4), 1–5. http://dx.doi.org/10.16966/2469-6714.141
43. Kishore, A., Nampurath, G. K., Mathew, S. P., Zachariah, R. T., Potu, B. K., Rao, M. S. & Chamallamudi, M. R. (2009). Antidiabetic effect through islet cell protection in streptozotocin diabetes: A preliminary assessment of two thiazolidin-4-ones in Swiss albino mice. *Chemico-Biological Interactions*, *177*(3), 242–246. https://doi.org/10.1016/j.cbi.2008.10.032
44. Taranalli, A. D., Bhat, A. R., Srinivas, S. & Saravanan, E. (2008). Anti-inflammatory, analgesic and antipyretic activity of certain thiazolidinones. *Indian Journal of Pharmaceutical Sciences*, *70*(2), 159–164. https://doi.org/10.4103/0250-474X.41448
45. Nwankwo, C. I., Omeh, T. N., Omodamiro, O. D., Otuokere, I. E., Alaebo, P. O., Atasie, O. C. & Ekwuribe, G. A. (2022). Phenolics of *Abelmoschus esculentus* pods: HPLC identification and *in silico* studies to identify potential anti-inflammatory agents. *Tropical Journal of Natural Product Research*, *6*(8), 1311–1319. http://doi.org/10.26538/tjnpr/v1i4.5