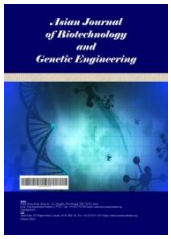

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Identification of Novel Bioactive Compounds from Banana Fruit (*Musa sapientum*) as Antidepressant in Pregnant Women: Molecular Docking, Physiochemical and ADMET Evaluation

K. R. Sharmili Banu[1*], I. Mohana Priya[2] and A. S. Azar Zochedh[3]

[1]Department of Gynaecology, Leonard Hospital, Batlagundu, Tamilnadu, India.
[2]Department of Bioinformatics, School of Distance Education, Bharathiar University, Coimbatore, Tamilnadu, India.
[3]Department of Biotechnology, Kalasalingam Academy of Research and Education, Krishnankoil, Tamilnadu, India.

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

Mood disorder in women during pregnancy is a critical public issue. Generally, pregnancy and childbirth has major impact in the development of mental depression in women. There are many factors in which depression occur, such as post pregnancy depression after past deliveries, event of depression in the family, limited or lack of support by the partner and environment, unplanned pregnancy, pregnancy during young age, previous miscarriage, low level or lack of education and unemployment. Depression may occur due to the influence of estrogen and progesterone in the neurotransmitter system of serotonin, dopamine and norepinephrine. Banana plant (*Musa sapientum*) is known to be utilized in Indian folklore medication and Ayurveda for the treatment of various diseases. Various parts of banana plant consist of many bioactive compounds. In this current investigation, eighteen bioactive compounds were retrieved from banana fruit and docked against ER and PR using PyRx tool. From the eighteen bioactive compounds five bioactive

**Corresponding author: E-mail: sharmilibanukr@gmail.com;*

compounds were chosen for further study based on the binding affinity. The predicted the physiochemical and ADMET properties were used to assess drug-likeness. According to the results campesterol, folic acid, quercetin, rutin and stigmasterol shown good molecular docking scores (> -8 Kcal/mol) and these compounds may be used a lead compounds to regulate ER and PR in the neurotransmitter system against depression in pregnant women.

Keywords: Depression; pregnancy; banana fruit; docking; drug-likeness.

1. INTRODUCTION

According to World Health Organization (WHO) definition, depression is a psychological disorder that comprises a significant social issue [1]. Globally over 350 million people suffer from depression as per WHO report [2]. The lifetime predominance of mental depression in women (20-25%) is around double that of men (7-12%) [3,4]. The justification behind the difference in the rate of depression between genders is not exactly known [5]. As indicated by psychiatrists, this might be because of women and men performing different roles in the society [6]. Higher incidence of mental depression in women is primarily seen during pubescence, before menstruation, during pregnancy, after delivery and also observed in at premenopausal age [7]. Mood disorder in pregnancy is a critical public health issue; pregnancy and childbirth play a vital role in the development of mental depression in women [8].

The occurrence of depression during pregnancy differs relying upon the present trimester [9]. Bennett et al. [10] based on previous report has estimated that in first trimester the depression happens in 7.4% (2.2-12.6%) of women, 12.8% (10.7-14.8%) depression in second trimester and during third trimester 12.0% (7.4-16.7%) of pregnant women undergo depression. According to various reports, the incidence of depression in pregnant women varies from 6-25% [11-19]. The diagnosing of depression is yet an imperfect framework. This is connected with the likeness of symptoms of depression to somatic problems happening during pregnancy [20]. For making the right diagnosis the accompanying symptoms, among others, are being utilized: lack of interest toward pregnancy, anhedonia and suicidal thoughts [21]. Depression may occur depending on many factors like post pregnancy depression after past deliveries, the event of depression in the family, limited or lack of support of the partner and environment, unplanned pregnancy, pregnancy during young age, previous miscarriage, low level or lack of education, unemployment and substance abuse [22]. At the first trimester, a fast change of the hormonal framework happens (an increase the quantity in estrogen and progesterone receptors) [23]. In the second trimester there is generally a stabilization of feelings and emotions. The final trimester is described by a renewed increase in the degree of anxiety and vulnerability because of the oncoming delivery. Because of changes in outer appearance the actual confidence of women diminishes, which likewise impacts the improvement of depression. Emotional disorders may occur due to the influence of estrogen and progesterone in the neurotransmitter system of serotonin, dopamine and norepinephrine [24].

Pregnancy effectively affects hormones that could impact state of mood. Many literatures based on this study have focused on hormonal changes that happen spontaneously before or after parturition, and how these physiological reactions may connect with post-partum depression. A very few research has stated the relationship between pregnancy related endocrine changes and risk standard mind states. Enormous expansions in estrogen and progesterone happen during pregnancy, and these are the two female sex steroids that are most commonly referenced according to mood disturbances at the time of pregnancy. There is solid proof that estrogen and progesterone can impact neural structures known to be significant in managing mood. Both estrogen and progesterone is lipid solvent and hence promptly enter the brain. High concentration of estrogen and progesterone receptors are found in the limbic system and related structures, including the hypothalamus, hippocampus, amygdale and entorhinal cortex [25,26]. Multiple and complex impacts have been shown by estradiol and progesterone on the serotonin, norepinephrine (noradrenaline) and dopamine neurotransmitter system [27,28], each of which has been involved in mood disorders. Regardless of the conceivable neuroanatomical reason for pregnancy-related changes in female sex steroids to impact mood during pregnancy, there is a restricted amount of empirical proof showing a connection between mood during pregnancy and female sex steroid levels. The available proof is conflicting. From a sample of 27

pregnant women, a weak connection between antenatal irritability and plasma estrogen levels was reported by Nott et al. [29]. In a sample of 120 pregnant women Harris et al. [30] reported that higher antenatal progesterone was related with postnatal maternity. In a pilot study, Parry et al. [31] reported that estradiol and progesterone were lower in depressed pregnant women.

The investigation of biologically active natural products has played a significant part in observing new compound elements which has fundamentally added to the improvement of various traditional frameworks of medication for the treatment of different diseases. This has reached out to the revelation of various medicinal plants to track down the scientific premise of their traditional uses [32]. Despite the fact that, difficulties and open doors in drug disclosure from plants still need to be settled, various parts of the banana plant are generally utilized as food and medication in numerous Asian nations [33]. Banana plant is known to be utilized in Indian folklore medication and Ayurveda for the treatment of skin illnesses, kidney stones, gout, ulcers, etc. [34]. Various parts of banana plant like fruit, rhizome, flower, pseudo stem, etc. has been reported for its pharmacological activities such as anti-ulcerogenic [35], hypolipidemic [36], anti-microbial [37], anti-hypertensive, injury healing, diuretic, antacid and anti-estrogenic [38]. The pharmacological activity of mixed bioactive compounds is always greater than that of an individual compound [39-41]. In the current investigation, in-silico approach helps to analyse the effective bioactive compounds in banana fruit as an antidepressant in women during pregnancy. The docking scores were identified for all the bioactive compounds from the banana fruit and the best scores were selected to analyse the interaction between the compounds and target ER and PR proteins. The predicted ADMET (absorption, distribution, metabolism, excretion, and toxicity) and drug-likeness characteristics of the selected bioactive compounds from banana fruits were also investigated.

2. METHODOLOGY

2.1 Phytochemicals Retrieval

The phytochemicals present in the banana fruit (*Musa sapientum*) were retrieved using the online tool Dr. Duke's Phytochemical and Ethnobotanical Databases (http://phytochem.nal.usda.gov/). From the retrieved results the bioactive compounds were selected. A total of eighteen bioactive compounds were selected in the banana fruit.

2.2 Protein Selection

The 3D structures of target proteins ER and PR (PDB ID: 2J6M and 4OAR) were retrieved in ".pdb" format from online database called RCSB Protein Data Bank (PDB) (https://www.rcsb.org/).

2.3 Protein Processing

BIOVIA Discovery studio software was used to process the downloaded protein structures. The processed was done by removing all the water molecules and hetatms. The hydrogen bond structure optimization was done by adding atoms in the missing loops or side chains. The final processed protein structure was saved in ".pdb" format.

2.4 Ligand Selection and Preparation

The 3D structures of selected eighteen bioactive compounds of banana fruit were downloaded from PubChem in ".sdf" format (https://pubchem.ncbi.nlm.nih.gov/).

2.5 Molecular Docking

PyRx, a freely available tool was used to perform molecular docking of selected bioactive compounds and target proteins. In the PyRx the ligand molecules were first imported. Then, all the ligands were minimized and converted in ".pdbqt" format. Then the target proteins were loaded and made as macromolecules. Then in the Vina wizard window the ligands were selected and the grid box was made for the active site of target proteins. Finally, the docking was performed and results were analyzed.

2.6 Construction of Protein-Ligand Complex

The construction of protein-ligand complex structure was built by using PyMol 2.4 tool. The complex structure was built for five ligand molecules that shows best docking score (>-8 Kcal/mol). In the workspace, the target protein was first loaded and then ligand was imported. Then the complex structure was exported as a single molecule file in ".pdb" format.

2.7 Visualization of Protein-ligand Interaction

BIOVIA discovery studio tool was used to visualize the interaction of protein-ligand complex.

The constructed complex molecule was imported on the graphical window. Then the ligand was defined and ligand interaction was made. Then the interacting amino acid residues and type of bond and bond distances were analysed. Then the interaction of protein and ligand molecule was saved in ".jpeg" format.

2.8 Physiochemical and ADMET Studies

The "SMILES" file of ligands with best docking score was retrieved from PubChem. Then the retrieved SMILES files were uploaded in pkCSM online tool to analyze the physiochemical and ADMET properties (http://biosig.unimelb.edu.au/pkcsm/prediction). Finally, the analyzed physiochemical and ADMET properties were used to assess the drug-likeness property.

3. RESULTS AND DISCUSSION

3.1 Molecular Docking

The molecular docking was performed for eighteen bioactive compounds of banana fruit against the target proteins ER and PR using PyRx tool. The ligand molecules were docked at the binding pockets of target proteins. The docking scores of the eighteen bioactive compounds were tabulated in Table 1 along with their PubChem ID. PyRx results showed that among the eighteen bioactive compounds only five bioactive compounds were selected based on good binding score (i.e., >-8 Kcal/mol). The compounds campesterol, folic acid, quercetin, rutin and stigmasterol (PubChem CID: 173183, 135398658, 5280343, 5280805 and 5280794) showed strong interactions at the active sites of target proteins ER with binding scores of -8.4 Kcal/mol, -8.3 Kcal/mol, -8.4 Kcal/mol, -8.9 Kcal/mol and -8.8 Kcal/mol and PR with binding scores of -9.8 Kcal/mol, -8.9 Kcal/mol, -8.0 Kcal/mol, -8.4 Kcal/mol and -9.0 Kcal/mol respectively. These five ligand molecules were further visualized to analyze the interactions.

3.2 Visualization of Protein-ligand Interaction

The complex structure was constructed for ligands with best docking score (PubChem CID: 173183, 135398658, 5280343, 5280805 and 5280794) with the target proteins ER and PR using the software PyMol. Then the interactions of the ligands with target proteins were analyzed using BIOVIA discovery studio tool. The Amino acid, residues and the type of bond interaction of the ligand molecules with target proteins were tabulated in Table 2 and the complex structure and the 3D interaction of the ligands with target proteins were shown in Figs. 1-10.

Table 1. Docking scores of 18 bioactive compounds of Banana fruit with ER and PR protein

S. No	PubChem CID	Phytochemicals	Binding Affinity (Kcal/mol)	
			ER (PDB ID: 2J6M)	PR (PDB ID: 4OAR)
1	54670067	Ascorbic-Acid	-6.4	-6.3
2	222284	Beta-Sitosterol	-5.8	-6.2
3	173183	Campesterol	-8.4	-9.8
4	681	Dopamine	-5.5	-6.1
5	135398658	Folic Acid	-8.3	-8.9
6	938	Niacin	-5.1	-5.5
7	445639	Oleic-Acid	-5.2	-5.4
8	985	Palmitic-Acid	-4.7	-4.9
9	5280343	Quercetin	-8.4	-8.0
10	493570	Riboflavin	-7.3	-7.7
11	5280805	Rutin	-8.9	-8.4
12	5202	Serotonin	-6.0	-5.9
13	5280794	Stigmasterol	-8.8	-9.0
14	1130	Thiamin	-5.6	-6.1
15	6057	Tyrosine	-5.6	-6.4
16	6305	Tryptophan	-6.4	-7.3
17	8468	Vanillic-Acid	-5.7	-6.3
18	135191	Xylose	-5.6	-5.6

Table 2. List of amino acid interactions between selected bioactive compounds with ER and PR protein

Compounds	ER (PDB ID: 2J6M)			PR (PDB ID: 4OAR)		
	Residues	Amino Acid	Bond Category	Residues	Amino Acid	Bond Category
Campesterol	718	LEU	Hydrophobic	794	PHE	Hydrophobic
	718	LEU	Hydrophobic	718	LEU	Hydrophobic
	726	VAL	Hydrophobic	759	MET	Hydrophobic
	726	VAL	Hydrophobic	797	LEU	Hydrophobic
	743	ALA	Hydrophobic	801	MET	Hydrophobic
	743	ALA	Hydrophobic	887	LEU	Hydrophobic
	844	LEU	Hydrophobic	891	CYS	Hydrophobic
	844	LEU	Hydrophobic	756	MET	Hydrophobic
	718	LEU	Hydrophobic	718	LEU	Hydrophobic
	726	VAL	Hydrophobic	759	MET	Hydrophobic
	745	LYS	Hydrophobic	891	CYS	Hydrophobic
	766	MET	Hydrophobic	715	LEU	Hydrophobic
	766	MET	Hydrophobic	718	LEU	Hydrophobic
	788	LEU	Hydrophobic	797	LEU	Hydrophobic
	726	VAL	Hydrophobic	715	LEU	Hydrophobic
	745	LYS	Hydrophobic	797	LEU	Hydrophobic
				778	PHE	Hydrophobic
				794	PHE	Hydrophobic
				794	PHE	Hydrophobic
				890	TYR	Hydrophobic
Folic acid	855	ASP	Hydrogen Bond	766	ARG	Hydrogen Bond
	718	LEU	Hydrophobic	815	GLN	Hydrogen Bond
	726	VAL	Hydrophobic	822	LYS	Hydrogen Bond
	743	ALA	Hydrophobic	822	LYS	Hydrogen Bond
				692	MET	Hydrogen Bond
				692	MET	Hydrogen Bond
				759	MET	Hydrogen Bond
				728	SER	Hydrogen Bond
				762	GLY	Hydrogen Bond
				762	GLY	Hydrogen Bond
				766	ARG	Hydrogen Bond
				766	ARG	Electrostatic
				695	GLU	Electrostatic
				695	GLU	Electrostatic
				695	GLU	Electrostatic
				696	PRO	Hydrophobic
				766	ARG	Hydrophobic
Quercetin	793	MET	Hydrogen Bond	728	SER	Hydrogen Bond
	762	GLU	Hydrogen Bond	766	ARG	Hydrogen Bond
	793	MET	Hydrogen Bond	699	ILE	Hydrogen Bond
	718	LEU	Hydrophobic	778	PHE	Hydrogen Bond
	718	LEU	Hydrophobic	699	ILE	Hydrogen Bond
	726	VAL	Hydrophobic	758	LEU	Hydrogen Bond
	726	VAL	Hydrophobic	766	ARG	Electrostatic
	743	ALA	Hydrophobic	822	LYS	Electrostatic
	844	LEU	Hydrophobic	699	ILE	Hydrogen Bond
	726	VAL	Hydrophobic	696	PRO	Hydrophobic
	743	ALA	Hydrophobic	696	PRO	Hydrophobic
	745	LYS	Hydrophobic	699	ILE	Hydrophobic
Rutin	794	PRO	Hydrogen Bond	719	ASN	Hydrogen Bond
	804	GLU	Hydrogen Bond	759	MET	Sulfur-X

Compounds	ER (PDB ID: 2J6M)			PR (PDB ID: 4OAR)		
	Residues	Amino Acid	Bond Category	Residues	Amino Acid	Bond Category
	855	ASP	Hydrogen Bond	794	PHE	Hydrogen Bond
	795	PHE	Hydrophobic	718	LEU	Hydrophobic
	796	GLY	Hydrophobic	718	LEU	Hydrophobic
	743	ALA	Hydrophobic	759	MET	Hydrophobic
	726	VAL	Hydrophobic			
	745	LYS	Hydrophobic			
	797	CYS	Hydrophobic			
Stigmasterol	718	LEU	Hydrophobic	759	MET	Hydrogen Bond
	718	LEU	Hydrophobic	794	PHE	Hydrophobic
	718	LEU	Hydrophobic	759	MET	Hydrophobic
	743	ALA	Hydrophobic	891	CYS	Hydrophobic
	743	ALA	Hydrophobic	718	LEU	Hydrophobic
	844	LEU	Hydrophobic	801	MET	Hydrophobic
	844	LEU	Hydrophobic	718	LEU	Hydrophobic
	718	LEU	Hydrophobic	715	LEU	Hydrophobic
	726	VAL	Hydrophobic	797	LEU	Hydrophobic
	766	MET	Hydrophobic	718	LEU	Hydrophobic
	745	LYS	Hydrophobic	797	LEU	Hydrophobic
	745	LYS	Hydrophobic	778	PHE	Hydrophobic
	788	LEU	Hydrophobic	778	PHE	Hydrophobic
				794	PHE	Hydrophobic
				794	PHE	Hydrophobic
				890	TYR	Hydrophobic

Campesterol with the target protein ER formed sixteen (16) Alkyl hydrophobic interactions with the amino residues tabulated in Table 2 with the bond distances 4.9193 Å, 4.04215 Å, 4.83552 Å, 4.9427 Å, 4.18288 Å, 4.15779 Å, 4.95414 Å, 4.1092 Å, 3.86339 Å, 3.65515 Å, 3.95468 Å, 5.19713 Å, 4.84339 Å, 3.77058 Å, 5.1274 Å and 4.03322 Å. Campesterol with PR formed one (1) Pi-Sigma hydrophobic interaction with Phe794 at distance 3.69725 Å, fifteen (15) Alkyl hydrophobic interactions with amino residues Leu718, Met759, Leu797, Met801, Leu887, Cys891, Met756, Leu718, Met759, Cys891, Leu715, Leu718, Leu797, Leu715, Leu797 at 5.12932 Å, 5.41424 Å, 4.73234 Å, 5.49339 Å, 5.04013 Å, 5.46186 Å, 5.46051 Å, 4.5678 Å, 4.04702 Å, 3.885 Å, 4.93621 Å, 5.01558 Å, 5.18852 Å, 4.71978 Å, 4.17424 Å bond distances and four (4) Pi-Alkyl hydrophobic interaction with Phe778, Phe794 (2) and Tyr890 at distances 4.72607 Å, 4.7905 Å, 5.35554 Å and 4.88385 Å. Folic acid with ER formed one (1) donor conventional hydrogen bond interaction with Asp855 at 2.65788 Å and three (3) Pi-Alkyl hydrophobic interactions with amino residues Leu718, Val726 and Ala743 at bond distances 4.9751 Å, 5.26681 Å and 5.12365 Å respectively. Folic acid with protein of target PR formed eight (8) conventional hydrogen bonds with four donor with amino acids Arg766, Gln815, Lys822(2) and four acceptor Met692(2), Met759 and Ser728 at distances 2.28849 Å, 2.16064 Å, 2.5104 Å, 2.89892 Å, 3.09556 Å, 2.64959 Å, 2.21761 Å and 2.45197 Å, two (2) carbon hydrogen bond with Gly762(2) at 3.98635 Å and 3.32461 Å, one (1) Pi-Cation and three (3) Pi-Anion electrostatic interaction with Arg766 and Glu695(3) at 3.98635 Å, 4.84535 Å, 4.9708 Å, 3.63762 Å and two (2) Pi-Alkyl hydrophobic interactions with residues Pro696 and Arg766 at bond distances 5.23432 Å and 5.20371 Å respectively. Quercetin with ER protein formed four (4) conventional hydrogen bond interaction with one donor Met793 and three acceptors with Glu762, Met793 and Leu718 at distances 2.19186 Å, 2.25678 Å, 2.15468 Å and 2.66188 Å respectively. Other interactions include eight (8) Pi-Alkyl hydrophobic interactions with amino residues Leu718, Val726(3), Ala743(2), Leu844 and Lys745 at 4.62517 Å, 5.02864 Å, 5.24186 Å, 5.40774 Å, 4.08461 Å, 4.97498 Å, 4.98994 Å and 4.84101 Å distances. Quercetin with PR formed six (6) conventional hydrogen bonds with two donors Ser728 and Arg766 and four acceptors Ile699(2), Phe778 and Leu758 at distances 2.11624 Å, 2.64316 Å, 2.30466 Å, 2.35525 Å, 2.95297 Å and 2.151 Å, one (1) Pi-Donor hydrogen bond with Ile699 at 3.07691 Å, two (2) electrostatic interaction with amino residues Arg766 and Lys822 at 3.6634 Å and 2.97909 Å and three (3)

Pi-Alkyl hydrophobic interactions with Pro696(2) and Ile699 at 5.20882 Å, 4.16223 Å and 4.63923 Å bond distances. Rutin with ER formed three (3) acceptor conventional hydrogen bond interactions with Pro794, Glu804 and Asp855 at distances 2.64504 Å, 2.66759 Å and 2.64177 Å respectively. Other interactions include two (2) Amide-Pi stacked, three (3) Alkyl and one (1) Pi-Alkyl hydrophobic interactions with amino residues Phe795, Gly796, Ala743, Val726, Lys745 and Cys797 at 4.60524 Å, 3.94993 Å, 4.02148 Å, 4.84175 Å, 3.91978 Å and 5.37322 Å bond distances. Target protein PR with rutin formed one (1) donor conventional hydrogen bond with Asn719 at 2.13176 Å, one (1) Pi-Donor hydrogen bond with Phe794 at 2.79826 Å, one (1) Sulfur-X interaction with Met759 at 3.09674 Å and three (3) Pi-Alkyl hydrophobic interactions with Leu718(2) and Met759 at 5.25419 Å, 5.34202 Å and 5.35684 Å bond distances. Stigmasterol with ER formed thirteen (13) Alkyl hydrophobic interactions with amino residues shown in Table 2 at the bond distances 5.0588 Å, 3.292545 Å, 3.91387 Å, 4.60447 Å, 4.41611 Å, 5.38091 Å, 4.50065 Å, 4.32809 Å, 3.74198 Å, 4.71081 Å, 4.25043 Å, 4.1548 Å and 4.91917 Å respectively and Stigmasterol with PR formed one (1) acceptor conventional hydrogen bond with Met759 at 2.6578 Å, one (1) Pi-Sigma hydrophobic interaction with Phe794 at 3.84897 Å, nine (9) Alkyl hydrophobic interactions with Met759, Cys891, Leu718, Met801, Leu718, Leu715 and Leu797 at 4.66221 Å, 4.52749 Å, 4.72662 Å, 5.15437 Å, 3.8183 Å, 4.85583 Å, 4.2238 Å, 4.5427 Å and 4.90179 Å distances and five (5) Pi-Alkyl hydrophobic interactions with Phe778(2), Phe794(2) and Tyr890 at bond distances 5.3395 Å, 4.60453 Å, 4.59076 Å, 5.23563 Å and 4.8542 Å respectively. Most of the previous reports have stated that hydrogen bond interaction, hydrophobic interaction, distance of the interacting bond and the binding affinity of the ligand with the target proteins have great impact on influencing the molecular interaction between the drug compound and the protein of target [42]. The interaction of our bioactive compounds (PubChem CID: 173183, 135398658, 5280343, 5280805 and 5280794) showed strong binding affinity at the active sites of the protein of targets ER and PR. This could be easily interpreted that based on our docking scores of our compounds with target proteins makes them potent antidepressant drugs foe women during pregnancy.

Table 3. Physiochemical and ADMET property of selected bioactive compounds

ADMET Properties	Campesterol	Folic acid	Quercetin	Rutin	Stigmasterol
Molecular weight (Da)	400.691	441.404	302.238	610.521	412.702
LogP	7.6347	-0.0448	1.988	-1.6871	7.8008
Surface area (Å)	180.674	179.278	122.108	240.901	186.349
Hydrogen bond acceptor	1	9	7	16	1
Hydrogen bond donor	1	6	5	10	1
Rotatable bonds	5	9	1	6	5
Human Intestinal Absorption (HIA) %	94.5	1.108	77.207	23.446	94.97
Caco2 Permeability	1.223	-0.877	-0.229	-0.949	1.213
Skin Permeability	-2.86	-2.735	-2.735	-2.735	-2.783
Blood Brain Barrier (BBB) Permeability	0.774	-1.615	-1.098	-1.899	0.771
CNS Permeability	-1.758	-4.262	-3.065	-5.178	-1.652
P450 Inhibitor	No	No	Yes	No	No
Total clearance	0.572	0.527	0.407	-0.369	0.618
Hepatotoxicity	No	No	No	No	No
Skin Sensitization	No	No	No	No	No
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.08	2.67	2.471	2.491	2.54

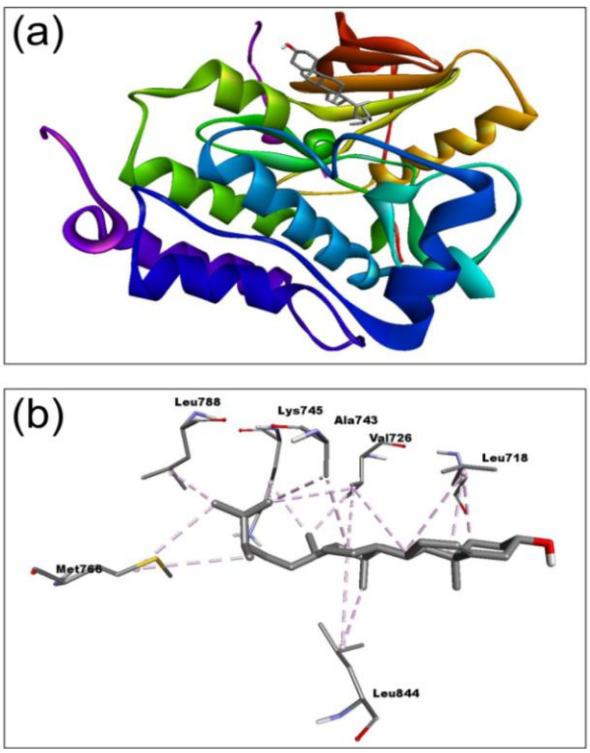

Fig. 1. a) Complex structure of Campesterol with ER. b) 3D structure of Campesterol and ER interaction

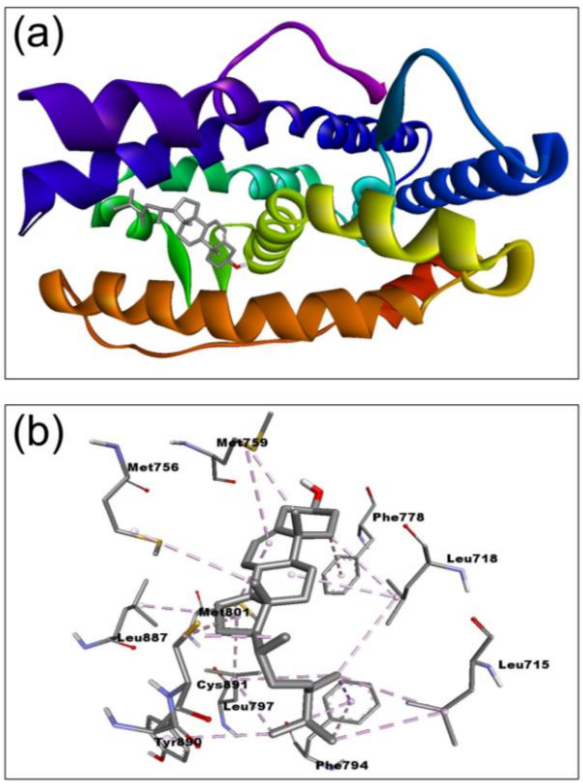

Fig. 2. a) Complex structure of Campesterol with PR. b) 3D structure of Campesterol and PR interaction

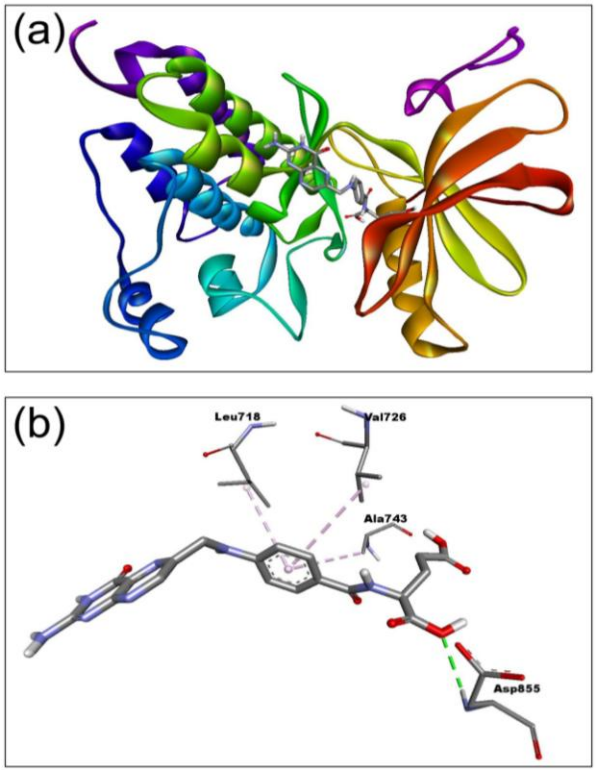

Fig. 3. a) Complex structure of Folic acid with ER. b) 3D structure of Folic acid and ER interaction

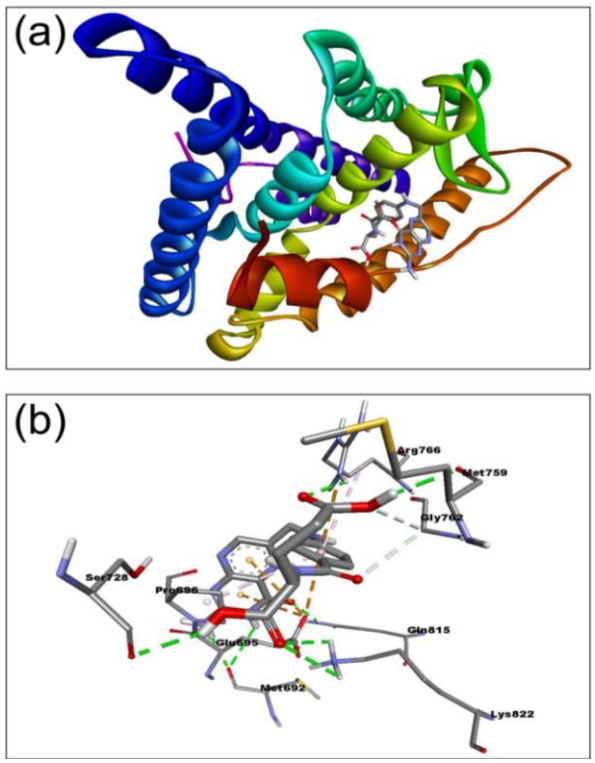

Fig. 4. a) Complex structure of Folic acid with PR. b) 3D structure of Folic acid and PR interaction

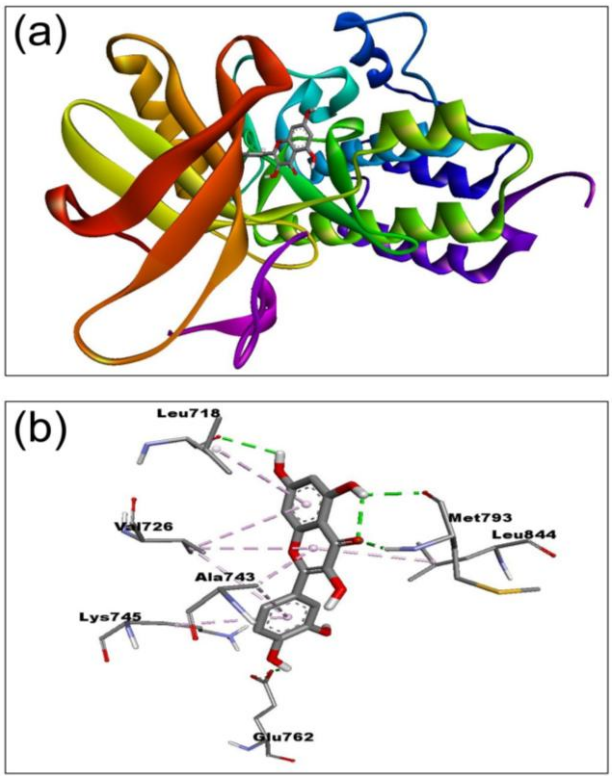

Fig. 5. a) Complex structure of Quercetin with ER. b) 3D structure of Quercetin and ER interaction

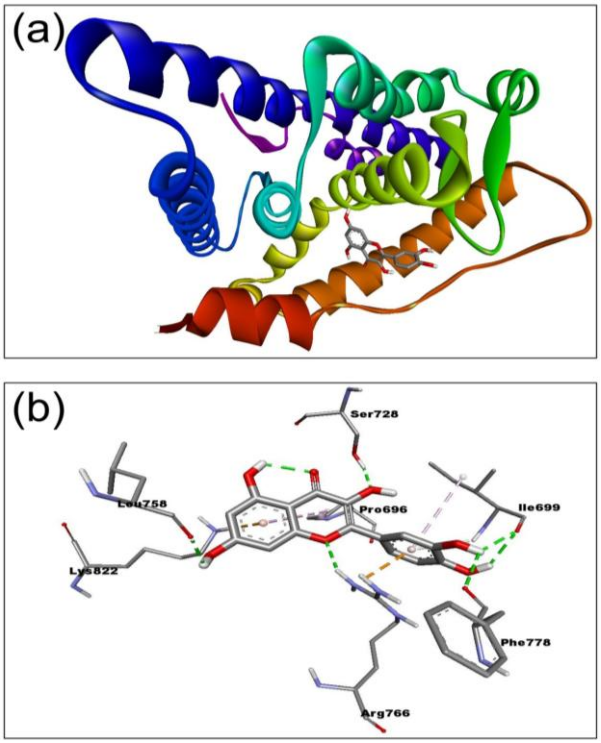

Fig. 6. a) Complex structure of Quercetin with PR. b) 3D structure of Quercetin and ER interaction

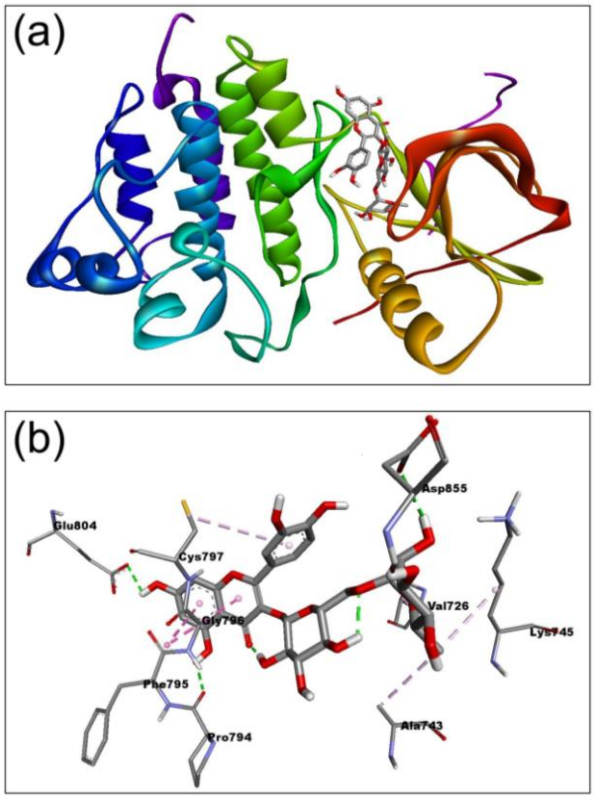

Fig. 7. a) Complex structure of Rutin with ER. b) 3D structure of Rutin and ER interaction

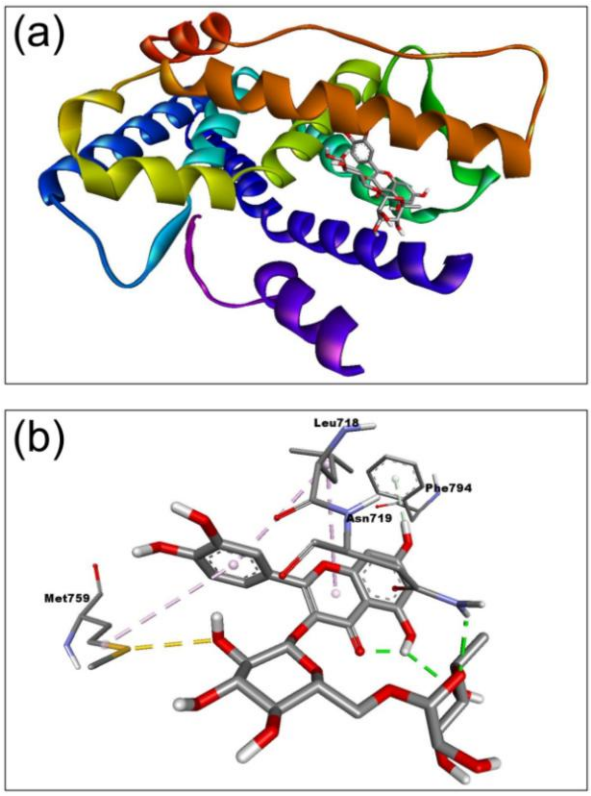

Fig. 8. a) Complex structure of Rutin with PR. b) 3D structure of Rutin and PR interaction

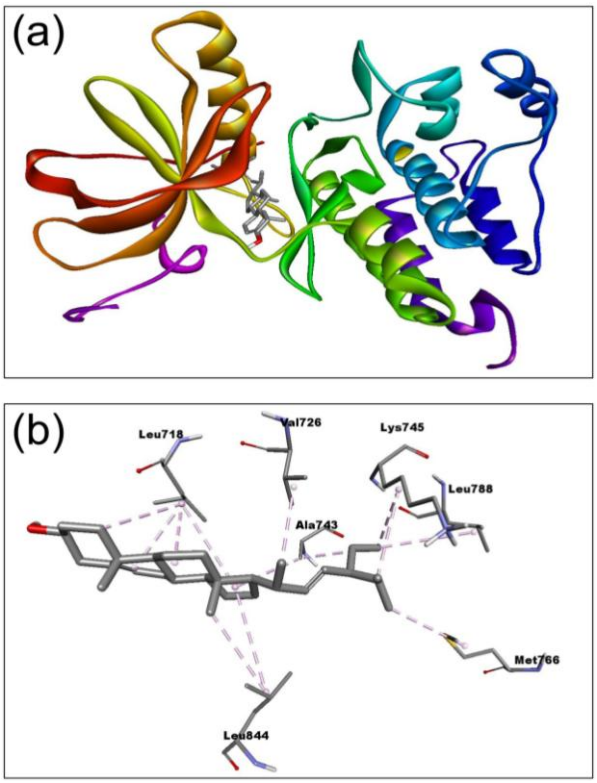

Fig. 9. a) Complex structure of Stigmasterol with ER. b) 3D structure of Stigmasterol and ER interaction

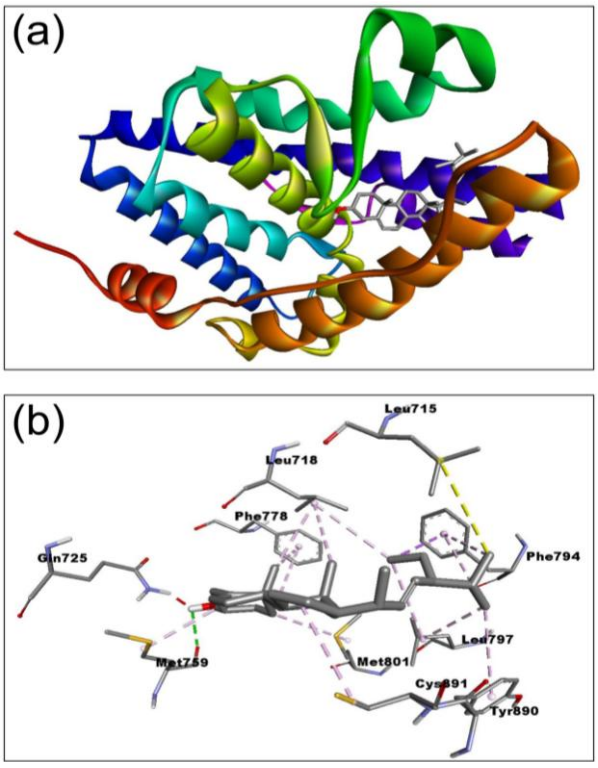

Fig. 10. a) Complex structure of Stigmasterol with PR. b) 3D structure of Stigmasterol and PR interaction

3.3 Physiochemical and ADMET Properties Evaluation

According to the Lipinski's Rule of Five, the molecular weight of drug should not exceed 500 Dalton, partition co-efficient (LogP) should be less than 5 (< 5), hydrogen bond acceptors should be less than 10 (< 10), hydrogen bond donors should be less than 5 (< 5) and the violation of rule should not exceed more than 1 rule [43].

The absorption and bioavailability of drug molecule was affected based on the physiochemical properties such as molecular weight (MW), polar surface area, lipophilicity (clogP) and aqueous solubility (logS). The molecular weight of our compounds campesterol, folic acid, quercetin and stigmasterol has molecular weight less than 500Da. The surface area plays a vital role in investigating the drug distribution attributes based on the sum of polar atoms like oxygen, nitrogen and attached hydrogen value. The number of rotatable bonds indicates the good bioavailability of drug compounds. The number of rotatable bonds of compounds CID: 173183, 135398658, 5280343, 5280805 and 5280794 were 5, 9, 1, 6 and 5. The hydrogen bond donors in campesterol, quercetin and stigmasterol was less than and equal to five whereas hydrogen bond acceptors where less than ten for four compounds except rutin. The surface area values indicate good oral bioavailability of our bioactive compounds and rotatable polar atomic bond increase flexibility and efficiency of our compounds to interact at the active site of target proteins ER and PR [44]. The Human Intestinal Absorption (HIA) values of campesterol and stigmasterol were greater than 90% and quercetin was greater than 75% and rutin and folic acid were less than 25%. A drug molecule is consider as highly Caco2 permeable when its Caco2 value is greater than 0.90 and our compounds campesterol and stigmasterol shows high Caco2 permeability with values greater than 0.90 and other three compounds were consider as poor Caco2 permeability. Skin permeability of a drug compound is consider as low skin permeable when its permeability value is higher than -2.5, whereas the skin permeability rate of our compounds is less than -2.5 that shows that our compounds were slightly higher skin permeable. Blood Brain Barrier was generally used to protect the brain from exogenous compounds to reduce the side-effects, toxicity and efficacy of drugs within the brain. Generally, compounds with the Blood-Brain permeability greater than 0.3 can rapidly cross Blood Brain Barrier and compounds with Blood-Brain permeability less than -1 will be poorly distributed to the brain. According to the BBB values of our compounds, they can rapidly distribute to the brain. The compounds with permeability rate greater than -2 are able to penetrate Central Nervous System (CNS) and compounds with lesser than -3 will not be able to penetrate through CNS. Therefore our campesterol and stigmasterol can penetrate through CNS and other three compounds were not able to penetrate as the CNS permeability values were lesser than -3. Cytochrome P450 is an enzyme, which is involved in the process of detoxification. The drug compounds can be activated or deactivated by the enzyme cytochrome P450. A drug is consider as cytochrome P450 inhibitor, if less than 10µm of the drug concentration required for 50% inhibition. The drug clearance is generally measured by the proportionality constant and the total clearance range of our drug compounds were 0.572, 0.527, 0.407, -0.369 and 0.618 ml/min/kg. Hepatotoxicity is a damage or injury of liver caused by drugs and skin sensitization is the identification of allergic response caused by drugs. Our drug compounds show no hepatotoxicity and skin sensitization. The LD50 is the amount of drug given all at once, that cause 50% of death in rats. The oral lethal dose 50% (LD50) in rats of our compounds were 2.08, 2.67, 2.471, 2.491 and 2.54 mol/kg. More over our drugs have satisfied most of the physiochemical and ADMET parameters, even though our drugs has not satisfied Lipinski's rule of five, they can be given in the form of injection as our drugs shows no toxicity and have good efficacy against the target proteins.

4. CONCLUSION

The current study looked at the antidepressant properties of bioactive compounds present in the banana fruit against the target proteins ER and PR induced depression in women during pregnancy. Through a detailed computer aided investigation using the molecular docking tools, eighteen bioactive compounds against ER and PR, the antidepressant potential of banana fruit has been proven in this current work. In silico docking studies found that the five lead phytochemicals (Campesterol, Folic acid, Quercetin, Rutin and Stigmasterol) may regulate the Estrogen and Progesterone in the neurotransmitter system of serotonin, dopamine and norepinephrine. In addition, Physiochemical

and ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) analysis gives a safety profile and drug-likeness properties of five bioactive compounds in banana fruit. In order to determine the antidepressant effectiveness of banana fruit, further *in vivo* and *in vitro* investigation will be necessary.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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