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MOLECULAR DOCKING STUDIES OF BIOACTIVE COMPOUNDS FROM THE ALCOHOLIC AND CHLOROFORM FRACTIONS OF *CALLISTEMON CITRINUS* AGAINST SEROTONIN TRANSPORTER PROTEIN

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ABSTRACT

Depression is a psychological disorder that has been classified and treated in a variety of ways. Though there are a number of synthetic drugs being used for the treatment of clinically depressed patient, their adverse effects and drug-food interactions compromise the therapeutic outcome. In the traditional systems of medicine, many plants and formulations are used to treat depression for thousands of years. *Callistemon citrinus* is one such plant which has been claimed in traditional literature to be valuable plant against a wide variety of diseases. In our research on the antidepressant activity of *C. citrinus* revealed that the alcoholic and chloroform fractions showed significant antidepressant activity by reducing the immobility time in forced swim test and tail suspension test. Therefore the aim of the present study was identification of bioactive compounds from the alcoholic and chloroform fractions of *Callistemon citrinus* by Gas chromatography and Mass spectroscopy (GC-MS) analysis, followed by *in-silico* docking to validate the activity of the compounds against active site of Serotonin transporter (SERT). GCMS analysis was done by standard protocol using the equipment JEOL GC MATE II. The identification of components was based on NIST (National Institute of Standards and Technology) Version-11 library as well as comparison of their retention indices. The molecular docking studies were done using Schrodinger software.

KEYWORDS: Callistemon citrinus, GC-MS Analysis, Docking, Serotonin transporter, anti-depressant.

INTRODUCTION

Depression refers to a wide range of mental health problems characterized by the absence of positive effect (loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioral symptoms.[1] Prevalence rate of mental disorders in India was observed to be 65.4/1000, out of which prevalence rate for affective disorders is 31.2/1000.[2] The pathophysiology of depression involves different hypothesis, among which involvement of monoamines is considered as major mechanism, via decrease in monoamine neurotransmitter turnover viz. noradrenaline, dopamine and serotonin.[3] An increase in the monoamine neurotransmitter turnover results in antidepressant activity.[4] Medicinal plants play a fundamental role in the world health, since they are sources of several pharmacologically active compounds.

Callistemon citrinus (Family: Myrtaceae) commonly known as bottle brush tree grows in Australia and cultivated throughout India, Malaysia and tropical countries. *Callistemon citrinus* has been claimed in traditional literature to be valuable against a wide variety of diseases.[5,6] The plant has been used by tribal communities for the treatment of gastrointestinal disorders and the leaves are used for their anthelmintic, anti-inflammatory, antipyretic, antitussive properties.[7] The Phytoconstituents reported from *C. citrinus* are flavonoids: pelargonidin-3,5-diglucoside, cyanidin-3,5-diglucoside and kaempferol; monoterpenoids: β-pinene and 1,8-cineole; The leaves contain Flavonoids: 3’4’7-trihydroxy flavonol, 3’4’7-trihydroxy flavone, 3’4’7-trihydroxy flavonol-3-glucoside, 3’4’7-trihydroxy flavone-7-galactoside.[8-14] The Pharmacological activities reported for *Callistemon citrinus* are, antiasthmatic, anti microbial, calcium channel blocking, cytotoxicity and anthelmentic effects.[15]

The combination of an ideal separation technique gas chromatography (GC) with the best identification technique mass spectroscopy (MS) made GC-MS an ideal technique for qualitative and quantitative analysis for phyto-constituents. It combines two analytical techniques to a single method for analyzing mixtures of chemical compounds. Gas chromatography separates the components of the mixture and mass spectroscopy analyzes each of the components separately.[16] Now-a-days, increased research has been carried out on flavanoids and the results obtained show that they possess significant antidepressant

effects. Therefore the main objectives of the present study are to analyze and determine the presence of bioactive compounds in alcoholic and chloroform fractions of *Callistemon citrinus* using GC-MS analysis, followed by molecular docking of the compounds against serotonin transporter protein (SERT) to elucidate the mechanism of their anti-depressant activity. The serotonin transporter (SERT) located in the membrane of presynaptic neurons plays an important role in the termination of serotonergic neurotransmission by transporting 5-Hydroxy tryptamine (5-HT) from the synaptic cleft into the presynaptic neuron.[17] SERT protein is one of the main targets for antidepressant drugs like the selective serotonin reuptake inhibitors (SSRIs). Although several synthetic SSRIS have emerged as antidepressant drugs, safe herbal antidepressant with proficient in surpassing the adverse effects and improve a better sustainability is the need of hour

MATERIALS AND METHODS

2.1 Collection and Identification of Plant Material

The aerial parts of *Callistemon citrinus* (CC) was collected at Guntur, Andhra pradesh, India. The plant was authentified by the Department of Botany, Acharya Nagarjuna University, Guntur and voucher specimen was preserved. The leaves and stems were separated, dried, powdered and then extracted with alcohol as solvent using soxhelation for 4 cycles. Then the extracted drug was further evaporated using simple distillation apparatus to obtain the concentrate. To this extract aliquots of water were added and then fractionated successively using petroleum ether and chloroform by mother liquor method.[18] To the extract 250ml of water was added and shaken thoroughly and then to this 100 ml of petroleum ether was added to separate the non polar constituents. This procedure was repeated until the appearance of colourless pet ether layer. All the fractions of pet ether layer were collected and evaporated to a concentrated residue. After separation of pet ether fraction, 100 ml of chloroform was added to the hydro-alcoholic extract and this procedure is repeated until the chloroform layer becomes colorless. All the fractions of chloroform layer were collected and evaporated to a concentrated residue. The left over portion is considered as hydro-alcoholic fraction.

GC-MS analysis was performed using the equipment JEOL GC MATE II. The equipment has a DB 35 – MS Capillary Standard non-polar column with dimensions of 30 mm×0.25 mm ID×0.25 µm. The carrier gas used was Helium with at rate of 1.0 ml/min. The injector was operated at 250°C and the oven temperature was programmed as follows: 110°C hold for 3.50 min, up to 200°C at the rate of 10°C/min-No hold, up to 280°C at the rate of 5°C / min-

12 min hold and total GC running time is 40min. The identification of components was based on NIST (National Institute of Standards and Technology) Version-11 library as well as comparison of their retention indices.[19]

2.2 Docking Studies

The compounds identified in GC-MS were docked to SERT from Homo sapiens. The structure of SERT (PDB ID: 1GOS), was obtained from PDB database. Unnecessary chains and hetero atoms were removed using SPDBV software, hydrogens were added to the protein and used for active site identification.

2.2.1 Active site Identification

The active site (binding pocket) and functional residues of SERT were identified and characterized by site-map module from Schrodinger package. Site Map calculation begins with an initial search step that identifies or characterizes- through the use of grid points- one or more regions on the protein surface that may be suitable for binding ligands to the receptor. Contour maps were then generated, hydrophobic, hydrophilic maps, hydrogen binding possibilities guide the protein-ligand docking analysis.

2.2.2 Ligand preparation

Totally 28 bioactive compounds are present in GC-MS analysis (Table 1 & 2). All the bioactive compounds and fluoxetine, most widely used SSRI for treatment of depression were subjected molecular docking studies. These ligands were prepared using the software Lig prep 2.4. The structure of each ligand was optimized by means of the OPLS 2005 force field using a default setting. All docking analysis was performed by using the standard precision (SP) which is Standard mode of Glide 5.6 (Grid-based Ligand Docking with Energetic) module from Schrodinger package. All the bioactive compounds and fluoxetine were docked into the binding site of SERT using GLIDE. Grid was prepared with the bounding box set on 20Aº. The co-ordinates of this enclosing box with the help of the active site residues were set as default. The force field is used for the docking protocol is OPLS 2005.

RESULTS AND DISCUSSION

GC–MS chromatogram obtained from the chloroform and alcoholic extracts of *C. citrinus* isolated twenty-eight different compounds illustrated with twenty intense peaks indicating the presence of these phytochemicals in a high quantity (Figure 1 & 2). The constituents were

detected and catalogued in parallel to the NIST library (Table 1 & 2). Among them, the most prevailing compounds are 4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(2-methoxy phenyl), Oleic acid and Androst-5-en-17-one, 3-hydroxy-16-[1-methylethyldiene]-3a', with a retention time of 18.83, 19.43 and 21.73 min respectively. 4',5,7-trihydroxyisoflavone, 2,2,4-Trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl)-cyclohexanol, Oxirane, 2,2-dimethyl-3-(3,7,11,15,19-heneicosapentaneyl)-[all E] pursue the former compounds with retention time of 17.1, 30.35 and 32. 87 minutes respectively. The foremost compound 4H-1-Benzopyran-4-one, 5, 7-dihydroxy-2-(2-methoxy phenyl), is categorized as flavanoids and commonly called as 2-methoxy Chrysin. Reports unveil that flavanoids have neuroprotective properties and increased intake of flavanoids reduced depressive symptoms.[20] Furthermore, oleic acid is one another indigenous compound which has an antioxidant property and acts as a 5-alpha reductase inhibitor.[21] A diverse range of flavonoids occur in traditional medicines that exert sedation and carry out anxiolytic effects. Hence the analysis of GC–MS further extends a need of study to assay the antidepressant and neuroprotective aspect of the major compounds extricated from the chloroform and alcoholic extracts of *C. citrinus*. An *in silico* assay was done to determine the best compound by docking against SERT a major target for the evaluation of antidepressant activity. Alterations in monoaminergic transmission are reported to be related with the instigation of neurodegenerative diseases such as Parkinson's, Alzheimer's diseases and psychiatric disorders such as depression and anxiety. In the present study, the constituents obtained from the chloroform and alcoholic extracts of *C. citrinus* were docked computationally into the active site of the SERT and were investigated to endorse their inhibitory potency. The phytocompounds had the potential to dock with the target proteins and their interaction details are listed in Table 3 and illustrated in Fig. 3. The target protein SERT was counteracted with the standard SSRI drug, fluoxetine exhibited with a least score of -7.11 kcal/mol. The major compounds 4H-1-Benzopyran-4-one, 5, 7-dihydroxy-2-(2-methoxy phenyl), and 4',5,7-trihydroxyisoflavone, obtained from the gas chromatogram assay with a high concentration exhibited a minimum binding affinity energy values of -6.826 and -6.07 kcal/mol against SERT, which are comparable to fluoxetine.

Results of GC-MS Analysis of *Callistemon citrinus*

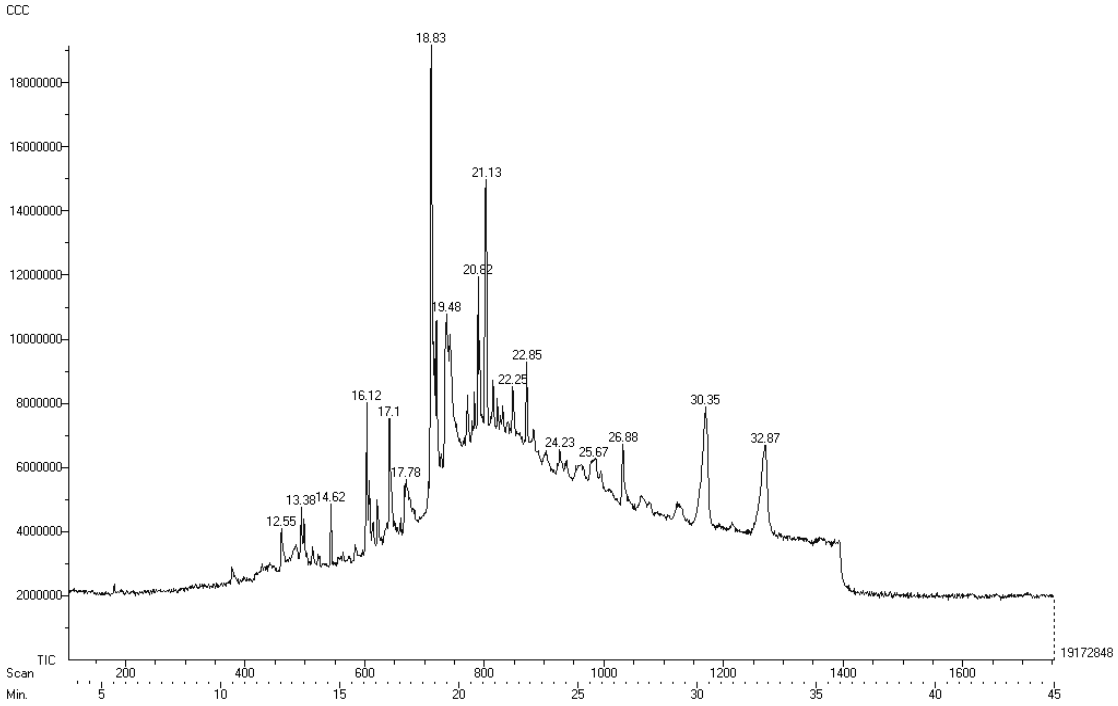

Figure 1: Gas chromatogram of chloroform fraction of *Callistemon citrinus.*

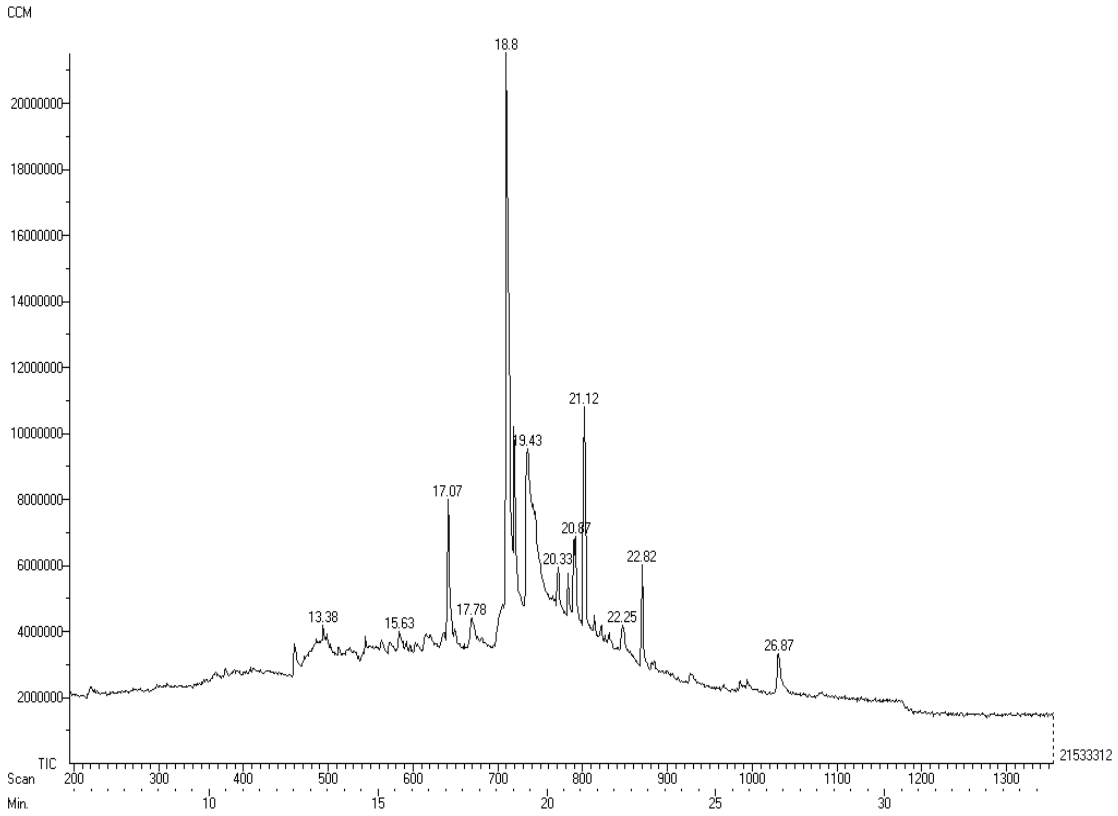

Figure 2: Gas chromatogram of hydroalcoholic fraction of *Callistemon citrinus.*

Table 1: Results of GC-MS of chloroform fraction of *Callistemon citrinus.*

S.No.	Retention time	IUPAC name of the compound	Molecular formula	Molecular weight
1	12.55	3-Buten-2-one, 3-methyl-4-(2,6,6, trimethyl-1-cyclohexen-1-yl)	$C_{13}H_{20}O$	192.2
2	13.38	Globulol	$C_{15}H_{26}O$	222.3
3	14.62	9-undecanoic acid, 2,6,10-trimethyl	$C_{14}H_{26}O_2$	226.3
4	16.12	3-Eicosyne	$C_{20}H_{38}$	278.5
5	17.1	4',5,7-trihydroxyisoflavone	$C_{15}H_{10}O_5$	270.2
6	17.78	Estra-1,3,5-(10, trien-17a'-ol)	$C_{18}H_{24}O$	256.3
7	18.83	4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(2-methoxy phenyl)	$C_{16}H_{12}O_5$	284.2
8	19.48	Oleic acid	$C_{18}H_{34}O_2$	282.4
9	20.82	11-keto progesterone	$C_{21}H_{28}O_3$	328.4
10	21.13	Androst-5-en-17-one, 3-hydroxy-16-[1-methylethyldiene]-3a'	$C_{22}H_{32}O_2$	328
11	22.25	2,6,9,12,16-Pentamethyl hepta deca-2,6,11,15-tetraene-9- carboxylic acid		346
12	22.85	Docosanoic acid methyl ester	$C_{23}H_{46}O_2$	354.6
13	24.23	Corynan-17-ol,18,19-didehydro-10-methoxy acetate	$C_{22}H_{28}N_2O_3$	368.4
14	25.67	4-Piperidine acetic acid, 1-acetyl-5-ethyl-2-[3-(2-hydroxy ethyl)-1H-indol-2yl]-acid methyl-methylester	$C_{23}H_{32}N_2O_4$	400
15	26.88	5-a-Cholest-3-ene-2a'-methyl	$C_{28}H_{46}O$	398.6
16	30.35	2,2,4-Trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl) cyclohexanol	$C_{30}H_{52}O$	428.7
17	32.87	Oxirane,2,2-dimethyl-3-(3,7,11,15,19-heneicosapentaneyl)-[all E]	$C_{30}H_{50}O$	426.7

Table 2: Results of GC-MS of hydroalcoholic fraction of *Callistemon citrinus.*

S.No.	Retention time	IUPAC name of the compound	Molecular formula	Molecular weight
1	13.38	Spiro [4,5] decan-7-one, 1,8-dimethyl-8,9-epoxy 4-isopropyl	$C_{15}H_{24}O_2$	236.3
2	15.63	Perhydrocyclopropa[e]azulene-4,5,6-triol,1,1,4,6-tetramethyl	$C_{15}H_{26}O_3$	254.3
3	17.07	Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270.4
4	17.78	Estra-1,3,5-(10, trien-17a'-ol)	$C_{18}H_{24}O$	256.3
5	18.8	Phytol	$C_{20}H_{40}O$	296.5
6	19.43	Oleic acid	$C_{18}H_{34}O_2$	282.4
7	20.33	9-Octadecenamide	$C_{18}H_{35}NO$	281.4
8	20.87	Hexadecanoic acid, 15 methyl, methyl ester	$C_{17}H_{34}O_2$	270.4
9	21.12	Androst-5-en-17-one, 3-hydroxy-16-[1-methylethyldiene]-3a'	$C_{22}H_{32}O_2$	328
10	22.5	9-Octadecenoic acid ethyl ester	$C_{20}H_{38}O_2$	310.5
11	26.87	1,2, bis [p-(trans-styryl)-phenyl]-cis-ethylene	$C_{30}H_{24}$	384.5

Table 3: Docking scores of the all compounds obtained from GC-MS on SERT.

S.No.	Ligand	Docking score on SERT
1.	4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(2-methoxy phenyl)	-6.826
2.	4-Piperidine acetic acid, 1-acetyl-5-ethyl-2-[3-(2-hydroxy ethyl)-1H-indol-2yl]-acid methyl-methylester	-6.4
3.	4',-5,7-trihydroxy isoflavone	-6.067
4.	Globulol	-5.772
5.	Corynan-17-ol,18,19-didehydro-10-methoxy acetate	-5.753
6.	Spiro [4,5] decan-7-one, 1,8-dimethyl-8,9-epoxy 4-isopropyl	-5.743
7.	Estra-1,3,5-(10, trien-17a'-ol)	-5.376
8.	11-keto progesterone	-5.29
9.	Perhydrocyclopropa[e]azulene-4,5,6-triol,1,1,4,6-tetramethyl	-5.268
10.	1,2, bis [p-(trans-styryl)-phenyl]-cis-ethylene	-5.193
11.	Oxirane,2,2-dimethyl-3-(3,7,11,15,19-heneicosapentaneyl)-[all E]	-5.075
12.	Androst-5-en-17-one,3-hydroxy-16-[1-methylethyldiene]-3a'	-4.906
13.	2,2,4-Trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl) cyclohexanol	-4.494
14.	5-a-Cholest-3-ene-2a'-methyl	-4.381
15.	3-Buten-2-one, 3-methyl-4-(2,6,6, trimethyl-1-cyclohexen-1-yl)	-4.334
16.	9-Octadecenoic acid ethyl ester	-2.401
17.	9-undecanoic acid, 2,6,10-trimethyl	-2.392
18.	Docosanoic acid methylester 871	-2.2
19.	Phytol	-1.827
20.	9-Octadecenamide	-0.878
21.	Oleic acid	-0.606
22.	Hexadecanoic acid, 15 methyl, methyl ester	-0.422
23.	Hexadecanoic acid, methyl ester	-0.422
24.	3-Eicosyne	1.315

Table 4: Docking scores and interactions at active site of compounds with least binding scores.

S. NO	Compound Code	Glide Score	Glide e model	Interactions at active site	
	Fluoxetine	-7.313	-56.293	Pi-Cation Hydrogen bonding	ARG 30 ASP 401
1.	4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(2-methoxy phenyl)	-6.844	-52.348	Hydrogen bonding Pi-Pi Stacking	GLU 37 ARG 30
2.	4-Piperidine acetic acid, 1-acetyl-5-ethyl-2-[3-(2-hydroxy ethyl)-1H-indol-2yl]-acid methyl-methylester	-6.400	-48.344	Hydrogen bonding Pi-Pi Stacking	ALA 319 PHE 253
3.	Globulol	-5.772	-24.755	Hydrogen bonding	ARG 30
4.	Corynan-17-ol,18,19-didehydro-10-methoxy acetate	-5.771	-53.420	Pi-Cation Hydrogen bonding	ARG 30 ARG 30
5.	Spiro [4,5] decan-7-one, 1,8-dimethyl-8,9-epoxy 4-isopropyl	-5.410	-22.675	Hydrogen bonding	ARG 30
6.	Estra-1,3,5-(10, trien-17a'-ol)	-5.376	-39.315	Pi-Pi Stacking Hydrogen bonding	PHE 320 GLU 37
7.	Perhydrocyclopropa[e]azulene -4,5,6-triol,1,1,4,6-tetramethyl	-5.268	-41.572	Hydrogen bonding	ASP 404
8.	1,2, bis [p-(trans-styryl)-phenyl]-cis-ethylene	-5.193	-53.201	Pi-Pi Stacking Pi-Cation	PHE 253 LYS 398

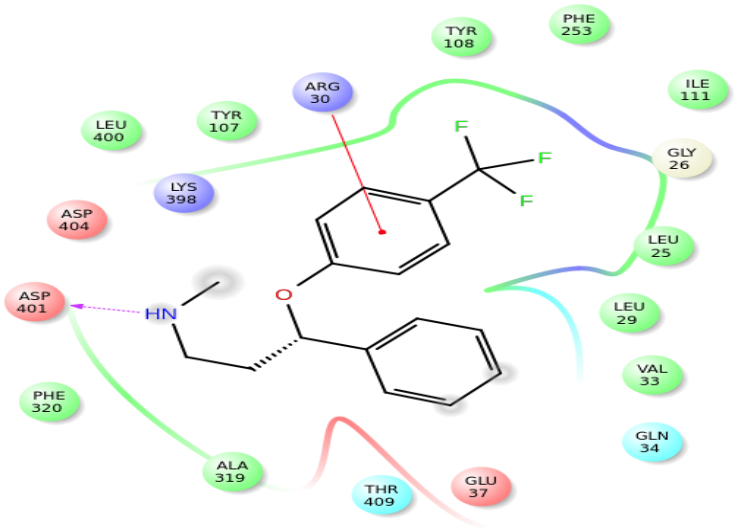

Figure 3: Binding of Flouxetine with SERT ligand.

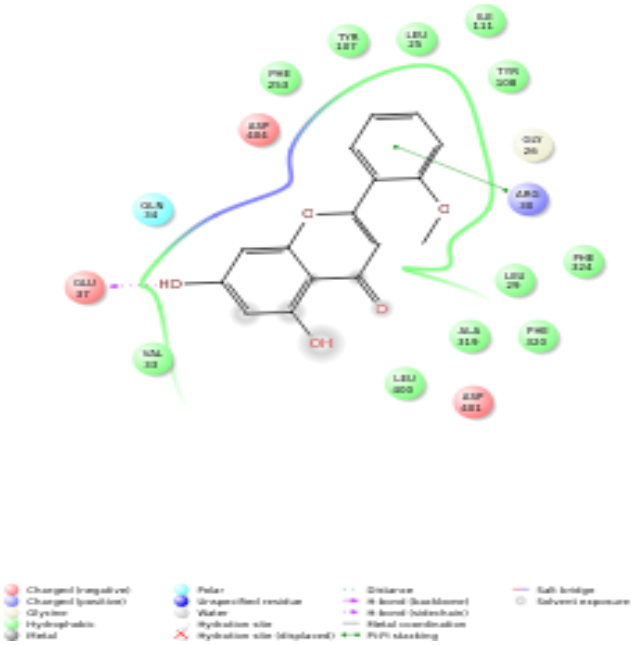

Figure 4: Binding of *4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(2-methoxy phenyl)* with SERT ligand.

CONCLUSION

The present study provides an evidence for the compounds isolated from the plant *C. citrinus* as new potent and selective serotonin reuptake inhibitor. The results hoists two compounds, 4H-1-Benzopyran-4-one, 5, 7-dihydroxy-2-(2-methoxy phenyl) and 4',5,7-trihydroxyisoflavone, as potential lead molecules for developing novel selective serotonin reuptake inhibitors which can confer better acceptability. The *in-silico* assay endorses the reference compound fluoxetine as an established anti depressant drug. The efficacy of these potent phytocompounds needs to be further confirmed with in vivo studies.

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