INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com Volume-4, Issue-1, Jan-Mar-2013 Coden : IJABPT Copyrights@2013

ISSN : 0976-4550

Received: 12th Jan-2013 *Revised: 20th Jan-2013* *Accepted: 21st Jan-2013*

Research article

PHYTOCHEMICAL SCREENING AND INSILICO APPROACH FOR THE IDENTIFICATION OF ANTI STRESS COMPOUNDS FROM MEDICINAL PLANTS

D.Jayasimha Rayalu[1], D.Muralidhararao[2] and D.S.Rao[3]

[1]Department of Biotechnology, JNTUA, Anantapur, Andhra Pradesh. INDIA
[2]Department of Biotechnology, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh. INDIA
[3]Department of Chemical Engineering, JNTUA, Anantapur, Andhra Pradesh. INDIA.

ABSTRACT: In India, many forms of alternative medicines are available for those who cannot be helped by conventional medicine. Ayurvedha and Herbal medicine are two important forms of alternative medicine that is widely available in India. This work was mainly concerned with the identification of the therapeutic properties of Indian medicinal plant extracts. Everyone knows that medicinal plants have disease curing properties and this is due to the compounds presents in the extracts used for the treatment. So we identified the compounds of different medicinal plants like Celastrus paniculatus, Withania somnifera, Convolvulus pluricaulis, Rauvoifia Serpentina etc which are used as medicine for Stress in Ayurvedha from previous literature. After identification using chemsketch software these compounds were designed and screened for antistress property. The proteins responsible for stress in *Homo sapiens* were collected using Protein databank (PDB). Active sites were identified and used for docking with the compounds. Then the compounds were docked to the Calcium channel in order find better inhibitor. Among 33 compounds 10 compounds showed best docking results for each protein. ADMET studies were performed using Molinspiration and OSIRIS server.

Key words: Anti stress, Docking, ADME studies, Calcium Channels,

INTRODUCTION

Stress and its concepts were explained as a stimulus-response manner like how a psycho biological sensory system operates. Stress is the one of the reason for a variety of diseases that includes psychiatric disorders such as endocrine disorders including diabetes mellitus, male impotence, cognitive dysfunction, peptide ulcer, depression and anxiety, immunosuppression, hypertension and ulcerative colitis. The nervous system plays a crucial role in the body's stress-related mechanisms. Mainly brain plays a critical role in the body's perception of and response to stress. Stress is the body's mechanism to any stimuli that disturb its equilibrium. When the equilibrium of various hormones is changed the effect of these changes can alter the immune system (Khansari, D et al 1990, Boenisch ED et al 2004). All drugs have side effects, and these side effects are increased in the case of an overdose. Most of the anti-stress medications available are comprised of benzodiazepines, antidepressants and antipsychotic drugs. These drugs make feel stress less for as long as one is taking the drug, but gets addicted to these drugs, and this holds true for non-prescription over-the counter analgesics, too. Antistress compounds from different plants was reported earlier to produce Non-specifically increased resistance in animal models of stress (Bhargava KP et al 1981; Bhattacharya A et al 2000; Bhattacharya SK et al 1994; Brekhman and Dordymov 1969; Bhargava and Singh 1985; Jyoti S et al 2007; Maity TK et al 2000; Mishra LC et al 2000; Roy S et al 1996; Singh, 1986; Singh et al., 1978). A calcium channel blocker (CCB) is a compund that disrupts the movement of calcium (Ca^{2+}) through calcium channels. CCB drugs devised to target neurons are used as antiepileptics. However, the most widespread clinical usage of calcium channel blockers is to decrease blood pressure in patients with hypertension (Nelson M, 2010). In this work we identified some compounds in the antistress plants from the previous literature and identified the action of these drugs on calcium channels through docking studies.

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METHODOLOGY

Selection of Stress expressed proteins, from NCBI and Swiss prot and searched for structures using BLAST. The best model was selected from Protein data Bank. The selected protein, calcium channel was modified by removing unnecessary chains. Then the required chain was selected for SPDBV software.

Active site Identification

Active site of Calcium channel was identified using CASTp server. A new program, CASTp, for automatically locating and measuring protein pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory. CASTp identifies and measures pockets and pocket mouth openings, as well as cavities. The program specifies the atoms lining pockets, pocket openings, and buried cavities; the volume and area of pockets and cavities; and the area and circumference of mouth openings.

Docking method

Docking with GOLD 3.0.1

GOLD (Genetic Optimization of Ligand Docking) a genetic algorithm (GA) based software, mainly utilizes an evolutionary strategy involving 3 genetic operators; cross overs, mutations and migrations. GOLD imports the partial flexibility to proteins and full flexibility to inhibitors. The compounds are docked into the active site of Calcium channel and the interaction of these ligands with the active site residues are thoroughly studied using calculations of molecular mechanics. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size. Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0A° (dH-X) for hydrogen bonds and 6.0A° for vanderwaals were employed. The default algorithm speed was selected and the inhibitor binding site in Calcium channel was defined within a 10A° radius with the centroid as HH atom of TYR51, HIS13, GLN8 respectively. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of inhibitors were within 1.5A° RMSD. After docking, the individual binding poses of each inhibitor were observed and their interactions with the protein was studied. The best and most energetically favorable conformation of each inhibitor was selected.

GOLD Score fitness function

The four components vig, Protein-ligand hydrogen bond energy (external H-bond); Protein-ligand vanderwaals energy (external vdw); Ligand internal vanderwaals energy (internal vdw); and Ligand intramolecular hydrogen bond energy (internal- H- bond) were considered for calculating the fitness function of GOLD score. The protein-ligand hydrophobic contact was encouraged by making an empirical correction by multiplying external vdw score with 1.375. The fitness function has been optimized for the prediction of ligand binding positions.

Gold Score = S (hb_ext) + S (vdw_ext) + S (hb_int) + S (vdw_int)

Where S (hb_ext) is the protein-ligand hydrogen bond score, S (vdw_ext) is the protein-ligand vanderwaals score, S (hb_int) is the score from intramolecular hydrogen bond in the ligand and S (vdw_int) is the score from intramolecular strain in the ligand.

RESULTS AND DISCUSSION

COMPOUND STRUCTURES

The anti stress compounds were identified from different medicinal plants like Celastrus paniculatus, Withania somnifera, Convolvulus pluricaulis, Rauvoifia Serpentina. These compounds were collected using pubchem and designed using chemsketch software. Totally 25 compounds were selected for screening. The structures are of the compounds are listed below and the properties were tabulated in Table 1.

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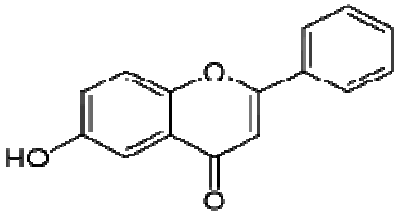
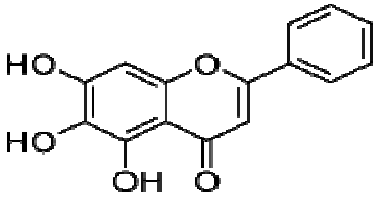
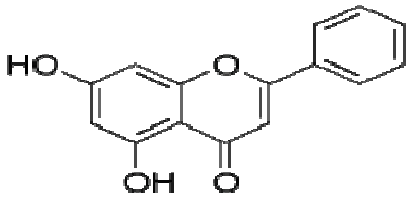
HYDROXYFLAVONE



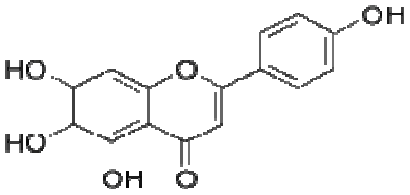
BAICALEIN



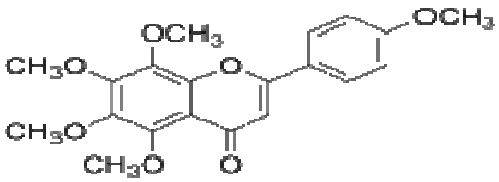
CHRYSIN



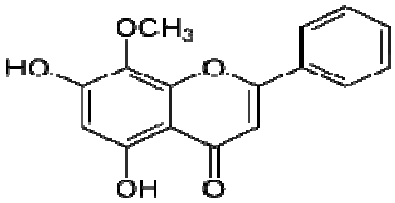
SCUTELLAREIN



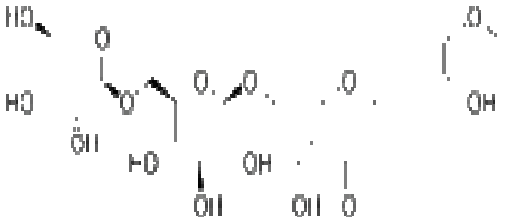
TANGERITIN



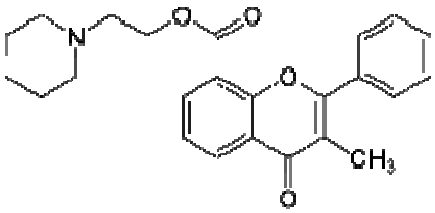
WOGONIN



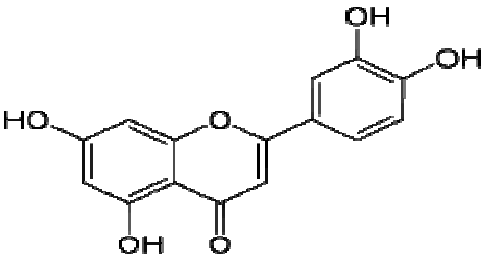
DIOSMIN



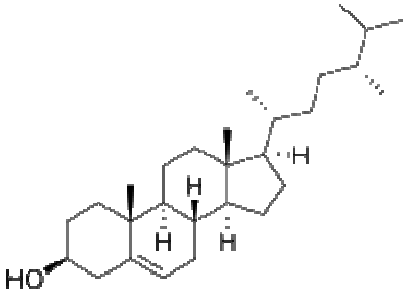
FLAVOXATE



LUTEOLIN



CAMPESTROL



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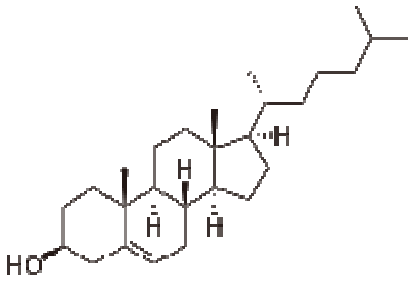
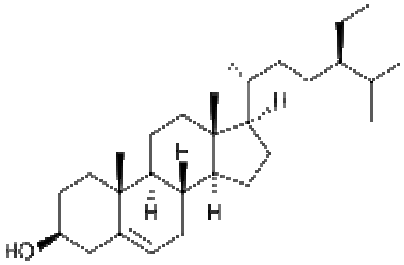
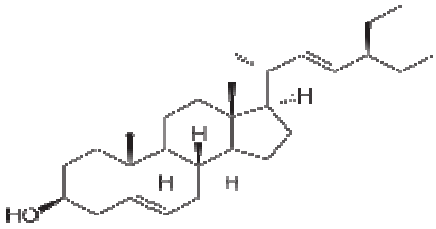
CHOLESTEROL



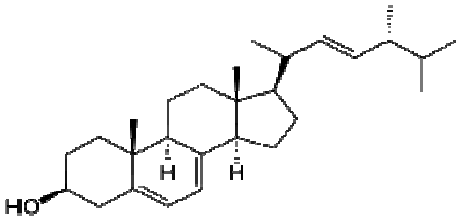
SITOSTEROL



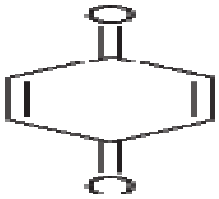
STIGMASTERIN



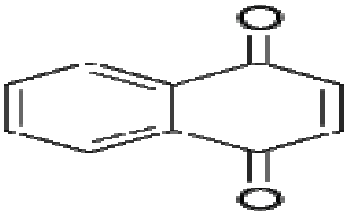
ERGOSTEROL



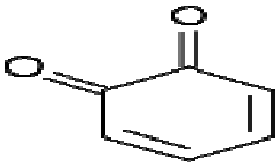
P BENZOQUINONE



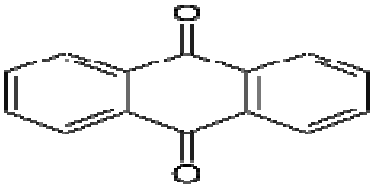
NAPHTHOQUINONE



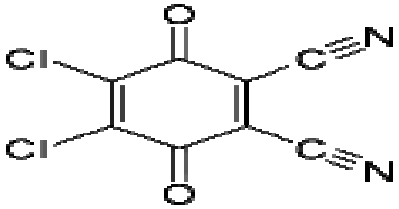
ORTHOBENZOQUINONE



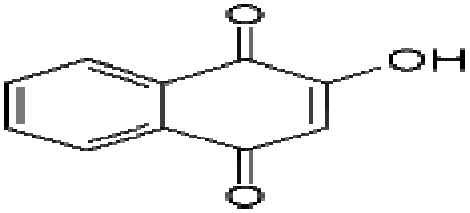
ANTHRAQUINONE



DICHLORODICYANOBENZOQUIONE



HNQ



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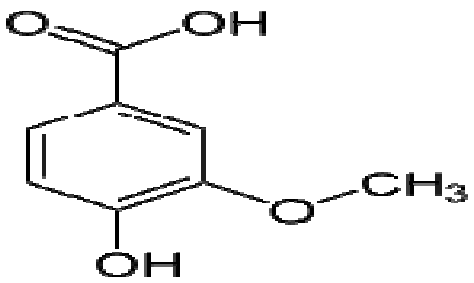
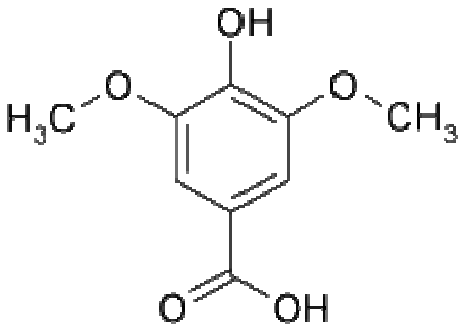
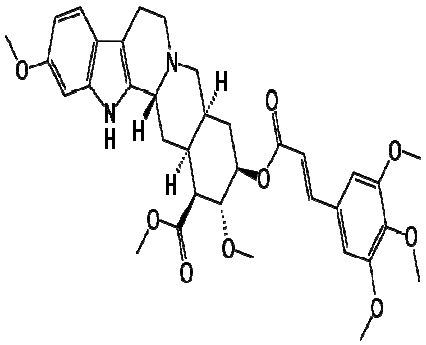
Vanillin



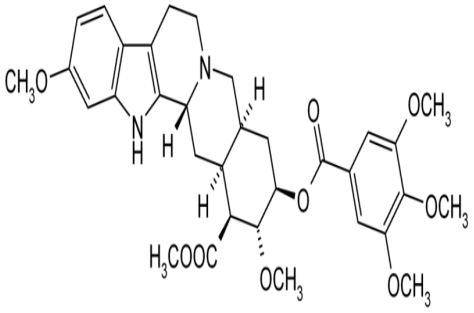
Syringic acid



Rescinnamine



Reserpine



P hydroxy benzoic

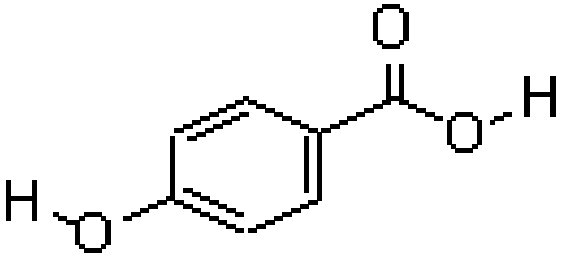


Figure 1(1A-33A): Structures of the compounds identified from medicinal plants

CALCIUM CHANNEL

Docking results

The concept of docking is important to determine the properties associated with protein-ligand interactions such as binding energy, electron distribution, hydrogen bond donor acceptor properties and hydrophobicity. In the present study, CASTp server was used to found the possible binding site of Calcium Channel (Figure 2). From the binding site analysis it was observed that binding pockets are identified and the largest binding pocket was selected for the docking studies. The anti stress compounds were docked into calcium channel using GOLD 3.0.1 and all docking solutions for calcium Channels were ranked according to the GOLD fitness function. The docking results showed that all the Anti stress compounds are active Calcium Channel inhibitors.

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Table 1: Properties of the molecules

Molecule	Molecular Formula	Formula Weight	Molar Refractivity cm^3	Index of Refraction cm^3	Density g/cm^3	Polarizability
1	$C_{15}H_{10}O_3$	238.23	*166.08 ± 0.3*	1.666 ± 0.02	1.340 ± 0.06	$26.19 \pm 0.5x10^{-24}$
2	$C_{15}H_{10}O_5$	270.23	*69.85 ± 0.3*	1.732 ± 0.02	1.548 ± 0.06	$27.69 \pm 0.5x10^{-24}$
3	$C_{15}H_{10}O_4$	254.23	*67.97 ± 0.3*	1.698 ± 0.02	1.443 ± 0.06	$26.94 \pm 0.5x10^{-24}$
4	$C_{15}H_{10}O_6$	286.23	*111.73 ± 0.3*	1.767 ± 0.02	1.654 ± 0.06	$28.43 \pm 0.5x10^{-24}$
5	$C_{25}H_{20}O_7$	432.42	114.34 ± 0.3	1.594 ±0.02	1.283 ± 0.06	$45.33 \pm 0.5x10^{-24}$
6	$C_{17}H_{12}O_5$	296.27	77.99 ± 0.3	1.674 ±0.02	1.426 ± 0.06	$30.92 \pm 0.5x10^{-24}$
7	$C_{28}H_{32}O_{15}$	608.54	141.70 ± 0.4	1.711 ±0.03	1.68 ±0.1	$56.17 \pm 0.5x10^{-24}$
8	$C_{24}H_{25}NO_4$	391.45	109.95 ± 0.3	1.591 ±0.02	1.203 ± 0.06	$43.58 \pm 0.5x10^{-24}$
9	$C_{15}H_{10}O_6$	286.23	71.73 ± 0.3	1.767 ±0.02	1.654 ± 0.06	$28.43 \pm 0.5x10^{-24}$
10	$C_{28}H_{48}O$	400.68	124.58 ± 0.4	1.522 ±0.03	0.98 ± 0.1	$49.38 \pm 0.5x10^{-24}$
11	$C_{27}H_{46}O$	386.65	119.97 ± 0.4	1.525 ±0.03	0.98 ± 0.1	$47.56 \pm 0.5x10^{-24}$
12	$C_{29}H_{50}O$	414.70	129.21 ± 0.4	1.521 ± 0.03	0.97 ± 0.1	$51.22 \pm 0.5x10^{-24}$
13	$C_{29}H_{48}O$	412.69	129.12 ± 0.4	1.530 ± 0.03	0.98 ±0.1	$51.18 \pm 0.5x10^{-24}$
14	$C_{28}H_{44}O$	396.64	124.19 ± 0.4	1.542 ± 0.03	1.00 ±0.1	$49.23 \pm 0.5x10^{-24}$
15	$C_6H_4O_2$	108.09	27.13 ± 0.3	1.543 ±0.02	1.256 ± 0.06	$10.75 \pm 0.5x10^{-24}$
16	$C_{10}H_6O_2$	158.15	42.90 ± 0.3	1.617 ±0.02	1.290 ± 0.06	$17.00 \pm 0.5x10^{-24}$
17	$C_6H_4O_2$	108.09	27.13 ± 0.3	1.543 ±0.02	1.256 ± 0.06	$10.75 \pm 0.5x10^{-24}$
18	$C_{14}H_8O_2$	208.21	58.66 ± 0.3	1.659 ±0.02	1.308 ±0.06	$23.25 \pm 0.5x10^{-24}$
19	$C_8Cl_2N_2O_2$	227.00	45.73 ± 0.4	1.601 ±0.03	1.70 ± 0.1	$18.13 \pm 0.5x10^{-24}$
20	$C_{10}H_6O_3$	174.15	44.49 ± 0.3	1.681 ±0.02	1.481 ±0.06	$17.63 \pm 0.5x10^{-24}$
21	$C_8H_8O_4$	168.14	41.74 ± 0.3	1.585 ±0.02	1.351 ±0.06	$16.54 \pm 0.5x10^{-24}$
22	$C_9H_{10}O_5$	198.17	48.42 ± 0.3	1.566 ± 0.02	1.335 ±0.06	$19.19 \pm 0.5x10^{-24}$
23	$C_{36}H_{46}N_2O_9$	650.75	174.13 ± 0.4	1.601 ± 0.03	1.28 ±0.1	$69.03 \pm 0.5x10^{-24}$
24	$C_{16}H_{21}NO_4$	291.34	77.88 ± 0.4	1.560 ± 0.03	1.21 ± 0.1	$30.87 \pm 0.5x10^{-24}$
25	$C_7H_6O_3$	138.12	35.06 ± 0.3	1.615 ±0.02	1.375 ±0.06	$13.90 \pm 0.5x10^{-24}$

Protein structure

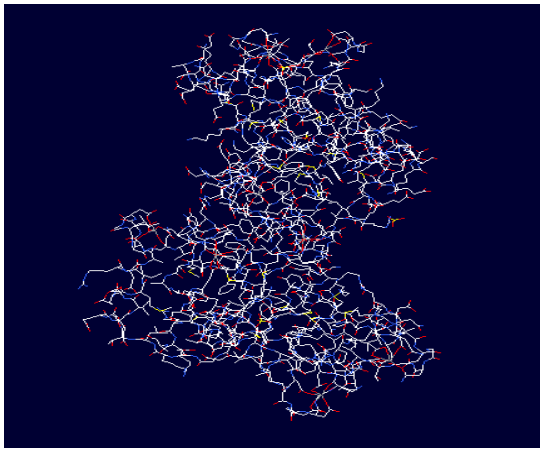

Figure 2: Calcium channel

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CAST P results

Active site Identification of calcium channel prediction by CASTp

After selecting receptor from PDB and isolated the A-chain in SPDBV, the possible binding sites of calcium channel receptor was searched based on the structural comparison of template and the model build and also with CASTp server and was shown in Figure 2 ,the residues are GLN8, GLU11, PHE12, MET72, LYS75, ASP78, THR79, SER81, GLU82, ILE85, ARG86, TYR138, VAL142.

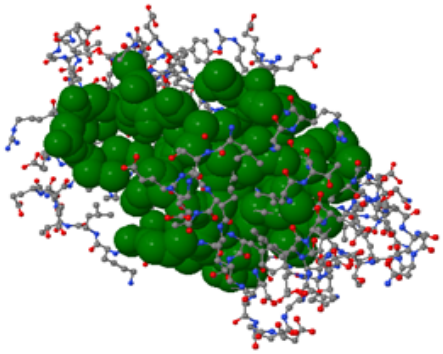

Figure 3: shows Representing active site Pockets of the CACIUM CHANNEL receptors shows highest area and volume.

Among the 25 compounds docked only Anthraquinone showed best docking results, indicating the inhibitory activity. The best inhibitors of Calcium Channels are given below and the docking energy values are tabulated in Table 2.

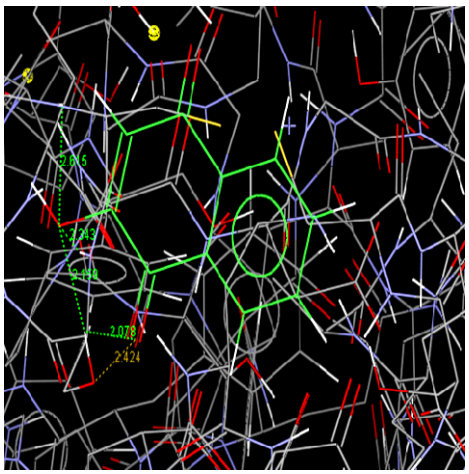

Fig 4: Docking results of best inhibitors of Calcium channel

ADME STUDIES

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the ADMET properties plays an important role in the drug design process because these properties account for the failure of about 60% of all drugs in the clinical phases. Where traditionally ADME tools were applied at the end of the drug development pipeline, nowadays ADME is applied at an early phase of the drug development process, in order to remove molecules with poor ADME properties from the drug development pipeline and leads to significant savings in research and development costs. These studies helped to identify a better antistress compound.

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Table 2: Calcium Channel Fitness

Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)	Ligand name
42.13	0.00	32.64	0.00	0.00	anthraquinone
40.16	0.00	23.54	0.00	-5.20	baicalin
-59.71	0.00	21.25	0.00	-88.93	campestrol
-28.64	0.00	23.07	0.00	-60.37	cholestrol
29.86	6.00	21.02	0.00	-5.05	chrysin
27.97	1.30	18.90	0.00	0.68	dichlorodicyano
31.68	2.66	35.70	0.00	-10.06	diosmin
-34.28	0.00	25.24	0.00	-68.99	ergosterol
34.41	0.00	30.92	0.00	-8.10	flavoxate
24.74	5.97	14.16	0.00	-0.71	HNQ
22.51	6.00	12.88	0.00	-1.20	hydroxy benzoic
28.92	0.00	23.67	0.00	-3.63	hydroxyflavone
30.68	6.00	22.26	0.00	-5.93	leuteolin
20.09	0.00	14.61	0.00	0.00	napthoquinone
16.25	0.00	11.82	0.00	0.00	orthobenzoquinone
15.82	0.00	11.51	0.00	0.00	benzoquinone
20.06	0.00	35.24	0.00	-28.40	rescinnamine
28.44	0.00	32.05	0.00	-15.62	reserpine
28.21	10.11	18.87	0.00	-7.84	scutellarien
-62.01	0.00	21.70	0.00	-91.85	sitosterol
-35.39	0.00	22.23	0.00	-65.96	stigmasterien
23.76	4.61	17.27	0.00	-4.61	syringic
16.34	0.00	26.82	0.00	-20.53	tangeritin
23.13	5.40	15.63	0.00	-3.75	vanellin
27.78	6.00	22.15	0.00	-8.67	wogonin

From the molinspiration the properties and bioactivity studies were identified and tabulated in Table 3.

Table 3: Molinspiration Results

NAMES	MILogP	TPSA	N ATOM	MW	nON	nOHNH	N VIOLATIONS	nROTB	VOLUME
ANTHRAQUINONE	3.669	34.142	16	208.216	2	0	0	0	182.577
BAICALINE	2.682	90.895	20	270.24	5	3	0	1	224.049
BENZOQUINONE	2.98	340142	12	245.876	2	0	0	0	148.737
CAMPESTROL	8.305	20.228	29	400.691	1	1	1	5	439.715
CHOLESTEROL	7.62	20.228	28	386.664	1	1	1	5	423.128
CHRYSIN	2.943	70.667	19	254.241	4	2	0	1	216.031
DICHLORODICYANO BENZOQUINONE	1.134	81.726	14	227.006	4	0	0	0	155.384
DIOSMIN	-0.205	238.205	43	608.549	15	8	3	7	505.578
ERGOSTEROL	7.182	20.228	29	396.659	1	1	1	4	427.316
FLAVOXATE	4.836	59.754	29	391.467	5	0	0	6	364.079
HNQ	1.376	54.37	13	174.155	3	1	0	0	146.603
HYDROXYFLAVONE	3.234	50.439	18	238.242	3	1	0	1	208.013
LUTEOLIN	1.974	111.123	21	286.239	6	4	0	1	232.067
NAPHTHOQUINONE	1.667	34.142	12	158.156	2	0	0	0	138.586
ORTHOBENZO QUINONE	0.508	34.142	8	108.096	2	0	0	0	94.594
P HYDROXY BENZOIC	1.369	57.527	10	138.122	3	2	0	1	119.063
RESCINNAMINE	4.393	153.23	51	698.813	11	1	2	11	639.375
RESERPINE	5.142	114.045	47	65.769	11	1	3	11	599.996
SCUTELLAREIN	2.203	111.123	21	286.239	6	4	0	1	232.067
SITOSTEROL	8.62	20.228	30	414.718	1	1	1	6	456.517
SYRINGIC ACID	1.204	75.995	14	198.174	5	2	0	3	170.154
STIGMASTERIN	7.869	20.228	30	412.702	1	1	1	5	450.33
TANGERITIN	2.99	115.566	32	432.428	7	0	0	6	377.718
VANILLIN	1.187	66.761	12	168.148	4	2	0	2	144.608
WOGONIN	3.237	87.738	22	296.278	5	2	0	2	251.575

The Toxicity and muatagenic studies were performed using OSIRIS server and the results were tabulated in Table 4.

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Table 4: Osiris Results

NAME	MUTAGENIC	TUMORIGENIC	IRRITANT	REPRODUCTIVE EFFECT	cLOGP	SOLUBILITY	MOL WEIGHT	DRYLIKENESS	DRY SCORE
NAPHTHOQUINONE	+	+	-	+	2.01	-2.84	158	-2.44	0.11
ORTHOBENZOQUINONE	+	-	-	-	0.88	-1.0	108	-3.12	0.31
BENZOQUINONE	+	+	-	-	0.88	-1.0	108	-3.05	0.18
ANTHRAQUINONE	-	-	-	+	3.52	-4.73	208	-3.88	0.08
DICHLORODICYANO BENZOQUINONE	+	+	+	-	1.56	-2.92	226	-6.63	0.18
HNQ	+	-	+	-	1.42	-2.77	174	-1.89	0.25
VANILIN	+	-	-	-	1.1	-1.35	168	-1.31	0.35
HYDROXYFLAVONE	-	-	-	-	3.29	-3.45	238	1.35	0.74
BAICALEIN	+	-	-	-	2.7	-2.86	270	0.75	0.44
CAMPESTROL	-	-	-	-	7.78	-6.4	400	-8.19	0.14
CHRYSIN	+	+	-	+	2.90	-3.15	254	0.97	0.28
SCUTELLARIN	+	-	-	+	2.4	-2.58	286	0.99	0.28
TANGERITIN	-	-	-	-	3.07	-3.83	372	-1.78	0.43
WOGONIN	+	-	-	-	2.89	-3.17	284	0.87	0.43
DIOSMIN	+	-	-	-	-0.42	-2.97	608	3.85	0.34
FLVOXATE	-	-	-	-	4.77	-4.39	391	3.6	0.57
ERGOSTEROL	-	-	-	-	7.52	-5.91	396	-1.18	0.19
LUTEOLIN	+	+	-	+	2.4	-2.56	286	1.9	0.32
P HYDROXY BENZOIC	-	-	-	-	1.2	-1.33	138	-1.5	0.57
SITOSTEROL	-	-	-	+	7.97	-6.49	399	-4.48	0.11
CHOLESTROL	-	-	-	-	7.44	-6.24	386	-2.13	0.16
SYRINGIC ACID	+	-	-	-	0.99	-1.37	198	1.99	0.54
STIGMASTERIN	-	-	-	+	7.61	-6.26	397	1.22	0.21
RESCINNAMINE	-	-	-	-	3.73	-4.82	634	2.99	0.39
RESERPINE	-	-	-	-	3.61	-4.45	608	6.86	0.45

Bioactivity studies of the antistress compounds were tabulated in Table 5.

CONCLUSION

Stress is a term that is commonly used today but has become increasingly difficult to define. It shares, to some extent, common meanings in both the biological and psychological sciences. Some medicinal plants and compound herbal agents possessing anti-stress activity. The compounds from medicinal plants were screened for the Antistress activity. For this study the medicinal plants used are Celastrus paniculatus, Withania somnifera, Convolvulus pluricaulis, Rauvoifia Serpentina. Among many terpinoids, flavones and alkaloids we identified 25 compounds which have antistress property. These were screened and docked to the protein like Calcium Channel which is expressed in Stress. Docking results shows that out of 25 Compunds, Anthraquinone was shown best docking energy to the calcium channel protein, By this we can say that the above docked compounds may show the antistress activity.

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Table 5: Bioactivity Results

NAMES	GPCR LIGAND	ION CHANNEL MODULATO R	KINASE INHIBIT OR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
ANTHRAQUINONE	-0.40	-0.16	-0.30	-0.44	-0.51	-0.03
BENZOQUINONE	-0.94	-0.43	-0.91	-1.08	-1.03	-0.29
BAICALINE	-0.12	-0.18	0.19	0.17	-0.35	0.26
CAMPESTROL	0.11	0.01	-0.48	0.71	0.02	0.50
CHOLESTEROL	0.13	0.02	-0.51	0.75	0.04	0.54
CHRYSIN	-0.11	-0.08	0.15	0.30	-0.30	0.26
DICHLORODICYANO BENZOQUINONE	-0.62	-0.24	-0.44	-0.58	-0.68	-0.13
DIOSMIN	-0.05	-0.53	-0.13	-0.23	-0.06	0.09
ERGOSTEROL	0.14	-0.13	-0.34	0.74	-0.08	0.53
FLAVOXATE	0.02	-0.44	-0.15	-0.08	-0.35	-0.12
HNQ	-1.00	-0.37	-0.40	-0.92	-1.09	-0.07
HYDROXY FLAVONE	-0.16	-0.13	0.04	0.10	-0.43	0.15
LUTEOLIN	-0.02	-0.07	0.26	0.39	-0.22	0.28
NAPHTHOQUINONE	-0.94	-0.46	-0.77	-1.00	-1.10	-0.34
ORTHOBENZOQUINONE	-3.34	-3.02	-3.19	-3.56	-3.41	-2.64
P HYDROXY BENZOIC	-0.98	-0.39	-1.21	-0.62	-1.19	-0.41
RESCINNAMINE	-0.60	-1.59	-1.46	-1.24	-0.49	-1.08
RESERPINE	0.03	-0.79	-0.59	-0.45	-0.04	-0.41
SCUTELLARIN	-0.06	-0.16	0.24	0.28	-0.29	0.27
SITOSTEROL	0.14	0.05	-0.51	0.73	0.07	0.51
SYRINGIC ACID	-0.65	-0.28	-0.69	-0.44	-0.82	-0.15
STIGMASTERIN	0.12	-0.08	-0.49	0.74	-0.02	0.53
TANGERITIN	-0.15	0.33	-0.14	0.03	-0.27	0.00
VANILIN	-0.85	-0.42	-0.99	-0.62	-1.12	-0.35
WOGONIN	-0.03	-0.30	0.03	0.17	-0.30	0.15

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