International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 3, 2016

Original Article

IN SILICO INVESTIGATION OF PHYTOCONSTITUENTS FROM VARIOUS PLANTS AGAINST NEUROINFLAMMATORY MARKERS AS POTENT THERAPEUTIC TARGETS

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Received: 26 Nov 2015 Revised and Accepted: 03 Feb 2016

ABSTRACT

Objective: Neuroinflammation is the inflammation of brain and brain tissue. Activation of glial cells (Microgila and astrocytes) takes place during neuroinflammation due to which a number of inflammatory mediators are released in brain. Thus the objective of the current study is to evaluate the potentialanti-neuroinflammatory activity of various phytoconstituents through virtual binding interactions against inflammatory mediators.

Methods: The preliminary screening of phytoconstituents was done by Lipinski's rule of five. Inflammatory mediators; Cycooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), Tumor necrosis factor-α (TNF-α), Interleukin 1-β (IL-1β), inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) protein sequence was retrieved from STRING database and molecular modeling was performed through SWISS-MODEL. And ligands ID was retrieved from ZINC database, and their MOL2 format was downloaded for further processing. Docking study of phytoconstituents with ligands was performed by iGEMDOCK. By using ADMET; absorption, distribution, metabolism, excretion and toxicity properties were predicted.

Results: Sissotrin out of the various phytoconstituents is the most active component having high binding affinity and inhibitor of neuroinflammatory activity.

Conclusion: Sissotrin may be a good inhibitor for neuroinflammatory disorders and act as anti-neuro inflammatory agent.

Keywords: COX-1, COX-2, iNOS, nNOS, TNF-α, IL-1β, iGEMDOCK, ADMET

INTRODUCTION

Inflammation is a protective reaction to various tissue injuries, in which debris or damaged tissue is removed and in turn, healing the affected part. When the inflammatory process becomes worse and tissue damage enhanced and more widespread, it is called chronic inflammation. In brain inflammation, there is excessive production of Reactive oxygen species (ROS) by mitochondria and NADPH oxidase (NOX), which leads to tissue injury, brain inflammation and neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD). In addition, there are various inflammatory mediators involved in it, such as COX-2, cytosolic phospholipase A_2 ($cPLA_2$), iNOS and cytokines. Glial cells, which include microglia and astrocytes, play a key role in the neuroinflammatory process. Activation of glial cells leads to neuroinflammation [1-4].

Need to screen natural inhibitors

Phytoconstituents are natural plant-derived products that have been part of traditional medicine, since ancient time and have contributed towards drug discovery or development. However, with time, it has also become more advanced and technically complicated. Number of advanced approaches is available for drug development, and bioinformatics is one of the important aspect of drug development. It is helpful in biotechnology for searching lead compounds as plant derived phytoconstituents are the major source of drugs used in the treatment of various diseases [4, 5]. Advancement in the tools of bioinformatics has made possible to conduct *in-silico* studies leading to drug development and discovery, thus saving significant time and resources. Therefore, the aim of present study is to reveal the therapeutic potential of various phytoconstituents to demonstrate their anti-neuro inflammatory activity.

Synthetic anti-neuro inflammatory drugs effectively suppress the diseases or any type of disorders in a short time, but the synthetic drugs are costly and result in side effects which are relatively safer in plant-derived natural drugs. Natural compounds also have some side effects; therefore, to overcome this limitation, computer aided drug design approach is a valuable method to investigate the targets and the effect of natural products [6, 7].

MATERIALS AND METHODS

A. Target protein identification

The protein sequence of target genes was retrieved from string database and modeling of it through SWISS-MODEL and taken for docking. The models were validated through procheck program.

B. Ligands preparation

Ligand ID was retrieved from ZINC database, and its MOL2 format was downloaded for docking.

Fig. 1: Experimental approach for putative drug discovery

Molecular docking

The molecular docking of 14 phytoconstituents was carried out using iGEMDOCK software with all the target proteins (COX-1, COX-2, IL-1β, iNOS, nNOS and TNF-α).

The binding site of the target protein was outfitted and compounds were imported for docking. The ligand molecule shows lowest binding affinity with the target protein is the best inhibitor to be chosen as a future drug [8, 9].

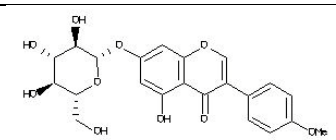
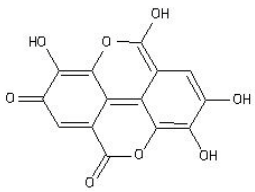
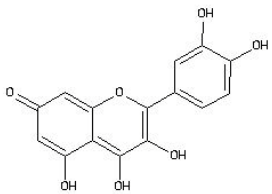
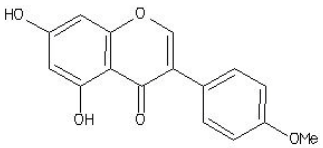
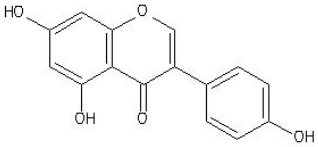
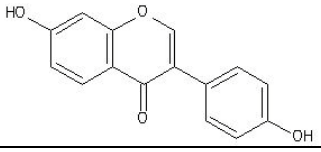
Drug likeliness

The ADMET parameters were determined by Admet SAR (Admet structure-activity relationship). These properties are valuable for a drug to be eligible for drug likeliness. Admet SAR supports the most recent data for various compounds allied with known ADMET profiles. The database has 22 qualitative categorization and 5 quantitative waning models with high analysis for estimation of mammalian ADMET properties of novel compounds [9].

Table 1: Bioactive components of various plants obtained from data mining (1-14)

S. No.	Zn file	Compound name
1.	Zinc_04096693	Sissotrin
2.	Zinc_03872446	Ellagic Acid
3.	Zinc_03869685	Quercitin
4.	Zinc_18847037	Biochanin A
5.	Zinc_18825330	Genistein
6.	Zinc_18847034	Daidzein
7.	zinc_8681784	Beta-sitosterol
8.	Zinc_00001504	Gallic acid
9.	Zinc-03802189	Linolenic acid
10.	Zinc_00153654	Sinapic acid
11.	Zinc_00021790	Ethyl gallate
12.	Zinc_14438802	Ascorbic acid
13.	Zinc_00083315	Tryptophan
14.	Zinc_02557133	Sulforaphane

Table 2: Bioactive components with their structure (1-14)

S. No.	Zn file	Compound name	Structure
1.	Zinc_04096693	Sissotrin	
2.	Zinc_03872446	Ellagic Acid	
3.	Zinc_03869685	Quercitin	
4.	Zinc_18847037	Biochanin A	
5.	Zinc_18825330	Genistein	
6.	Zinc_18847034	Daidzein	

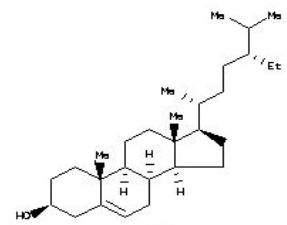
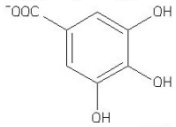
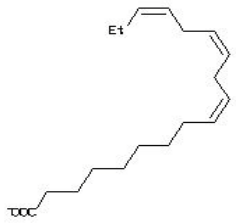
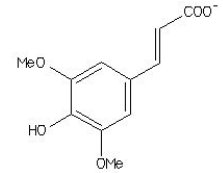
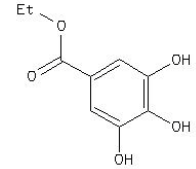
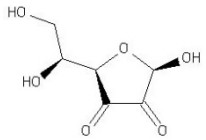
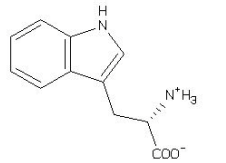
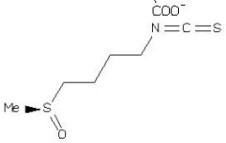
7.	Zinc_8681784	Beta-sitosterol	
8.	Zinc_00001504	Gallic acid	
9.	Zinc-03802189	Linolenic acid	
10.	Zinc_00153654	Sinapic acid	
11.	Zinc_00021790	Ethyl gallate	
12.	Zinc_14438802	Ascorbic acid	
13.	Zinc_00083315	Tryptophan	
14.	Zinc_02557133	Sulforaphane	

Table 3: Interaction profiles of phytoconstituents with COX-1

S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissotrin	-143.2	-118.54	-24.68	0
2.	Zinc_03872446	Ellagic Acid	-111.6	-82.69	-28.9	0
3.	Zinc_03869685	Quercitin	-111.94	-82.29	-29.65	0
4.	Zinc_18847037	Biochanin A	-113.1	-102.18	-10.89	0
5.	Zinc_18825330	Genistein	-120.7	-103.92	-16.75	0
6.	Zinc_18847034	Daidzein	-112.1	-98.74	-13.4	0
7.	zinc_8681784	Beta-sitosterol	-100.4	-93.4	-7	0
8.	Zinc_27643987	Indomethacine(Control)	-119	-109.95	-9.01	0
9.	Zinc_00001504	Gallic acid	-76.2	-62.02	-14.23	0
10.	Zinc-03802189	Linolenic acid	-118.8	-102.98	-12.23	-3.62
11.	Zinc_00153654	Sinapic acid	-91.9	-80.77	-9.99	-1.09
12.	Zinc_00021790	Ethyl gallate	-91.9	-59.32	-32.58	0
13.	Zinc_14438802	Ascorbic acid	-80.5	-37.2	-43.33	0
14.	Zinc_00083315	Tryptophan	-88.9	-69.29	-19.5	-0.1
15.	Zinc_02557133	Sulforaphane	-67.6	-58.67	-8.9	0

RESULTS AND DISCUSSION

Molecular docking simulation

Docking of 14 phytoconstituents with COX-1

The binding energy of sissotrin out of all 14 compounds is lowest i.e.-143.2, and it is also lower than the control drug, Indomethacin (-119). The interaction profile of other compounds also has lower energy than control drug, as shown in table 3. It shows that sissotrin is a good inhibitor of COX-1 as compared to control drug.

Docking of 14 phytoconstituents with COX-2

The binding energy of sissotrin out of all 14 compounds, is lowest i.e.-129.4, while Meloxicam has-96.7, which is a controlled drug.

The interaction profile shows other compounds also have lower energy than the control drug, as shown in table 4. Lower energy than the drug control shows along with other compounds sissotrin could be putative inhibitors of COX-2.

Docking of 14 phytoconstituents with IL-1β

The binding energy of sissotrin out of all 14 compounds is lowest i.e.-109, and control drug Lidocaine shows binding energy of-69.8. The interaction profile and energies of other compounds also have lower energy than control drug, as shown in table 5. Interacting properties of the compounds shows that sissotrin is a potent inhibitor of IL-1β, along with other compounds that shows lower energies compared to Meloxicam.

Table 4: Interaction profiles of phytoconstituents with COX-2

S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissortin	-129.4	-105.09	-24.29	0
2.	Zinc_03872446	Ellagic Acid	-118.5	-78.67	-39.87	0
3.	Zinc_03869685	Quercitin	-117.7	-92.76	-24.97	0
4.	Zinc_18847037	Biochanin A	-108.5	-93.25	-39.58	0
5.	Zinc_18825330	Genistein	-107	-89.98	-17.04	0
6.	Zinc_18847034	Daidzein	-103.6	-91.51	-12.06	0
7.	zinc_8681784	Beta-sitosterol	-100.1	-100.14	0	0
8.	Zinc_13129998	Meloxicam(Control)	-96.7	-78.92	-17.82	0
9.	Zinc_00001504	Gallic acid	-92.7	-65.73	-26.98	0
10.	Zinc-0302189	Linolenic acid	-88.8	-76.72	-12.06	0
11.	Zinc_00153654	Sinapic acid	-88	-73.2	-9.91	-4.95
12.	Zinc_00021790	Ethyl gallate	-84.6	-54.01	-30.57	0
13.	Zinc_14438802	Ascorbic acid	-83.06	-43.48	-39.58	0
14.	Zinc_00083315	Tryptophan	-81.7	-71.41	-10.28	0
15.	Zinc_02557133	Sulforaphane	-68.4	-58.75	-9.61	0

Table 5: Interaction profiles of phytoconstituents with IL-1β

S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissortin	-109	-74.71	-34.32	0
2.	Zinc_03869685	Quercitin	-100.3	-79.97	-20.32	0
3.	Zinc_03872446	Ellagic Acid	-99.7	-74.16	-25.51	0
4.	Zinc_18825330	Genistein	-90.9	-68.37	-22.52	0
5.	Zinc_00083315	Tryptophan	-89.4	-62.78	-25.93	-0.72
6.	Zinc_18847034	Daidzein	-87.8	-75.75	-12.04	0
7.	Zinc-03802189	Linolenic acid	-82.8	-75.93	-6.9	0
8.	Zinc_8681784	Beta-sitosterol	-80	-75.46	-4.57	0
9.	Zinc_14438802	Ascorbic acid	-78.5	-42.66	-35.82	0
10.	Zinc_18847037	Biochanin A	-78.1	-66.17	-11.97	0
11.	Zinc_00021790	Ethyl gallate	-76.9	-56.94	-20	0
12.	Zinc_00153654	Sinapic acid	-72.8	-58.69	-14.08	0
13.	Zinc_00001504	Gallic acid	-71.9	-56.52	-15.41	0
14.	Zinc_00020237	Lidocaine(Control)	-69.8	-66.29	-3.5	0
15.	Zinc_02557133	Sulforaphane	-62.2	-49.27	-12.97	0

Table 6: Interaction profiles of phytoconstituents with iNOS

S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissortin	-133.16	-110.74	-22.42	0
2.	Zinc_18847037	Biochanin A	-123.1	-109.9	-13.15	0
3.	Zinc_18847034	Daidzein	-109.1	-100.09	-9.02	0
4.	Zinc_03872446	Ellagic Acid	-103.2	-93.58	-9.59	0
5.	Zinc_03869685	Quercitin	-100.6	-87.6	-13.03	0
6.	Zinc_18825330	Genistein	-98.4	-71.26	-27.15	0
7.	Zinc_00021790	Ethyl gallate	-93.3	-60.21	-33.08	0
8.	Zinc_08143636	Tomatidine(Control)	-90.4	-80.65	-9.73	0
9.	Zinc_00001504	Gallic acid	-90.2	-52.16	-35.33	-2.69
10.	Zinc_8681784	Beta-sitosterol	-89.7	-87.94	-1.76	0
11.	Zinc-03802189	Linolenic acid	-88.9	-68.98	-20.52	-0.57
12.	Zinc_00153654	Sinapic acid	-88.8	-84.4	-4.42	0
13.	Zinc_00083315	Tryptophan	-86.7	-86.7	0	0
14.	Zinc_14438802	Ascorbic acid	-85.4	-46.07	-39.29	0
15.	Zinc_02557133	Sulforaphane	-63.4	-50.86	-12.5	0

Docking of 14 phytoconstituents with iNOS

The binding energy of sissotrin out of all 14 compounds is lowest i.e.-133.16, and drug control tomatidine shows binding energy of-90.4. The interaction profile of other compounds also has lower energy than the control drug, as shown in table 6, demonstrating that sissotrin is the best candidate among the putative inhibitors.

Docking of 14 phytoconstituents with nNOS

The binding energy of sissotrin out of all 14 compounds is lowest i.e.-120.1, and drug control L-NAME shows binding energy of-96. The interaction profile of the phytol compounds (table 7) demonstrates that sissotrin is a best putative inhibitor of nNOS among all the listed compounds.

Docking of 14 phytoconstituents with TNF-α

The binding energy of sissotrin out of all 14 compounds is lowest i.e.-100.8, and control drug Apremilast shows binding energy of-91.1. The interaction profile of other compounds also has lower energy than the control drug (table 8). Profile of the phyto-compounds shows that sissotrin is a preferably good inhibitor of TNF-α as compared to the control drug.

ADMET profile

AdmetSAR predicts that phytoconstituents have drug-like properties. All phytoconstituents showed ADMET properties in the acceptable range (table 9.1, 9.2, 9.3)

Table 7: Interaction profiles of phytoconstituents with nNOS

S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissortin	-120.1	-92.29	-27.78	0
2.	Zinc_03869685	Quercitin	-102.4	-78.41	-23.94	0
3.	Zinc_03872446	Ellagic Acid	-101.5	-75.41	-26.06	0
4.	Zinc_15987659	L-Name(Control)	-96	-61.02	-34.97	-0.05
5.	Zinc_18825330	Genistein	-93.6	-75.93	-17.68	0
6.	Zinc_18847037	Biochanin A	-93.5	-67.63	-25.86	0
7.	Zinc_8681784	Beta-sitosterol	-93.1	-85.96	-7.11	0
8.	Zinc_00153654	Sinapic acid	-92.4	-68.35	-19.54	-4.54
9.	Zinc_00021790	Ethyl gallate	-88	-52.4	-35.58	0
10.	Zinc_00083315	Tryptophan	-87.3	-68.34	-16.25	-2.73
11.	Zinc_18847034	Daidzein	-86.7	-74.48	-12.19	0
12.	Zinc_00001504	Gallic acid	-86.7	-59.07	-24.64	-3
13.	Zinc-03802189	Linolenic acid	-82.7	-70.23	-11.68	0.79
14.	Zinc_14438802	Ascorbic acid	-76.6	-55.34	-21.25	0
15.	Zinc_02557133	Sulforaphane	-61.8	-54.96	-6.87	0

Table 8: Interaction profiles of phytoconstituents with TNF-α

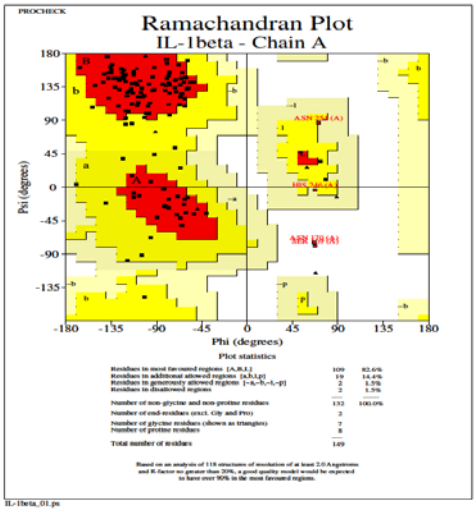
S. No.	Zn file	Compound name	Energy(kcal/mol)	VDW	H-Bond	Elec
1.	Zinc_04096693	Sissortin	-100.8	-73.02	-27.82	0
2.	Zinc_03869685	Quercitin	-95.8	-68.57	-27.2	0
3.	Zinc_03872446	Ellagic Acid	-92.1	-58.44	-33.65	0
4.	Zinc_30691736	Apremilast(Control)	-91.1	-81.72	-9.38	0
5.	Zinc-03802189	Linolenic acid	-90.8	-80.56	-10.64	0.41
6.	Zinc_18847037	Biochanin A	-85.8	-70.71	-15.12	0
7.	Zinc_00083315	Tryptophan	-85.7	-64.8	-16.99	-3.93
8.	Zinc_18825330	Genistein	-85.6	-72.61	-12.98	0
9.	Zinc_00021790	Ethyl gallate	-84.5	-45.8	-38.72	0
10.	Zinc_18847034	Daidzein	-80.6	-58.94	-21.68	0
11.	Zinc_14438802	Ascorbic acid	-78.6	-48.98	-29.67	0
12.	Zinc_8681784	Beta-sitosterol	-78	-78.01	0	0
13.	Zinc_00001504	Gallic acid	-77	-52.27	-24.74	0
14.	Zinc_00153654	Sinapic acid	-73.9	-54.07	-19.82	0
15.	Zinc_02557133	Sulforaphane	-62.1	-55.25	-6.82	0

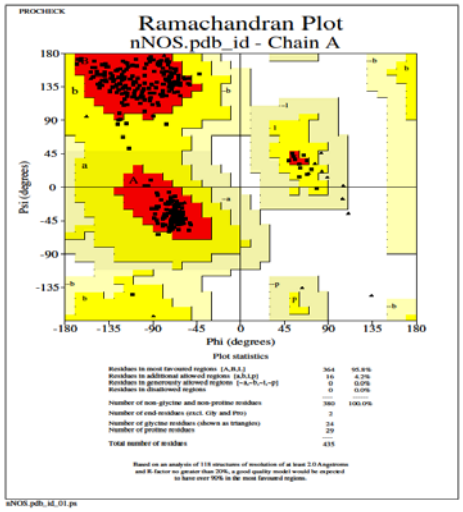
Table 9.1: ADMET predicted profile for active component-absorption (1-14)

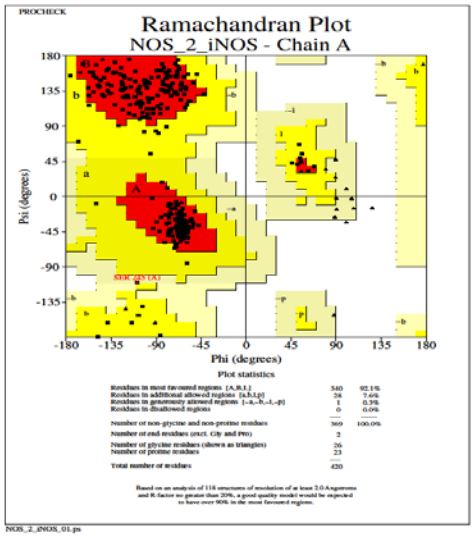
Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
BBB	+	+	-	+	+	-	-	+	+	-	+	-	+	+
Human Intestinal Absorption	-	+	+	+	+	+	-	+	+	+	+	+	+	+
Caco-2 Permeability	-	+	+	+	-	-	-	+	+	-	+	-	+	-
P-glycoprotein substrate	NS	NS	NS	NS	S	S	NS	S	NS	S	NS	S	NS	NS
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	I	NI

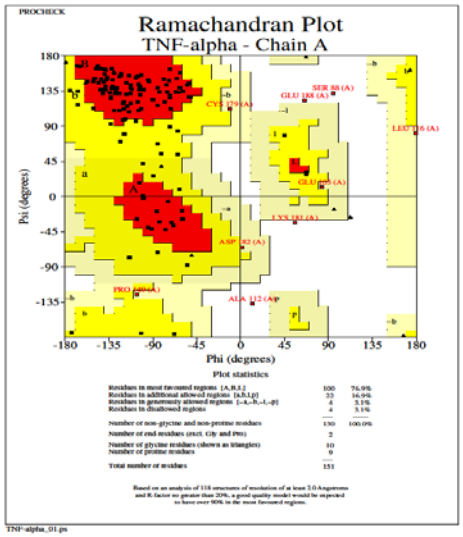
Active components: 1-Ascorbic acid, 2-Beta Sitosterol, 3-BiochaninA, 4-Daidzein,5-Ellagic acid, 6-Ethyl gallate, 7-Gallic acid, 8-Genistein, 9-Linolenic acid, 10-Quercitin, 11-Sinapic acid, 12-Sissotrin, 13-Sulforaphane, 14-Tryptophan.

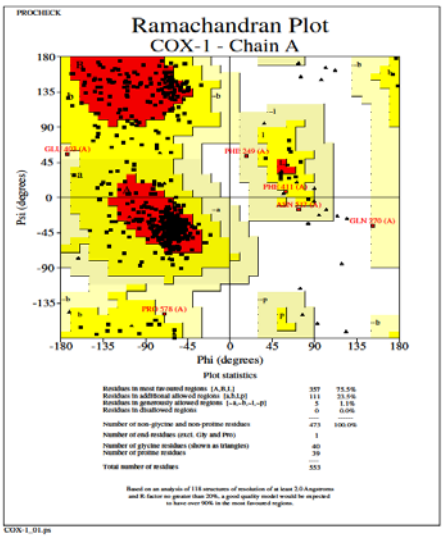
+: Positive,-: Negative, NS: Nonsubstrate, S: Substrate, NI: Noninhibitor,I: Inhibitor, BBB: Blood-brain barrier, ADMET: Absorption, Distribution, Metabolism, and Excretion and Toxicity.











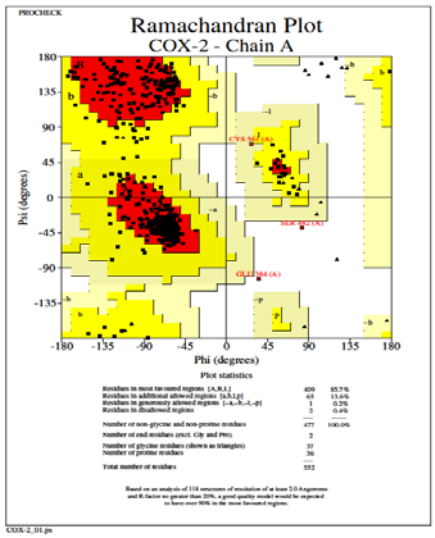


Fig. 2: Ramachandran plots of Genes (COX-1, COX-2, TNF-α, IL-1β, iNOS and nNOS)

Table 9.2: ADMET predicted profile for active component-Metabolism (1-14)

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
CYP450 2C9 Substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 Substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 Substrate	NS	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 1A2 Inhibitor	NI	NI	I	I	NI	NI	NI	I	I	NI	NI	NI	NI	NI
CYP450 2C9 Inhibitor	NI	NI	I	I	NI	NI	NI	I	NI	NI	NI	NI	NI	NI
CYP450 2D6 Inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2C19 Inhibitor	NI	NI	I	I	NI	NI	NI	I	NI	NI	NI	NI	NI	NI
CYP450 3A4 Inhibitor	NI	NI	I	NI	NI	NI	NI	I	NI	NI	NI	NI	NI	NI

NS: Non-substrate; NI: Non-Inhibitor; I: Inhibitors; S: Substrate, CYP450: Cytochrome P450

Table 9.3: ADMET predicted profile for active component-Toxicity (1-14)

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Human Ether-a-go-goRelated Gene Inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	SI	I
AMES Toxicity	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Carcinogens	NC	NC	NC	NC	NC	NC	NC	NC	C	NC	NC	NC	C	NC
Fish Toxicity Tetrahymena	LT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	LT	HT
Pyriformis Toxicity	LT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	LT	HT
Honey Bee Toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Biodegradation	RB	NRB	NRB	NRB	NRB	RB	RB	NRB	RB	NRB	RB	NRB	NRB	RB
Acute Oral Toxicity	IV	I	III	II	II	III	III	II	III	II	III	III	III	II

WI: Weak inhibition, NT: Non-Toxic, NC: Noncarcinogen, C: Carcinogen, HT: High toxic, RB: Readily biodegradable, NRB: Not readily biodegradable, SI: Strong inhibitor

Docking images

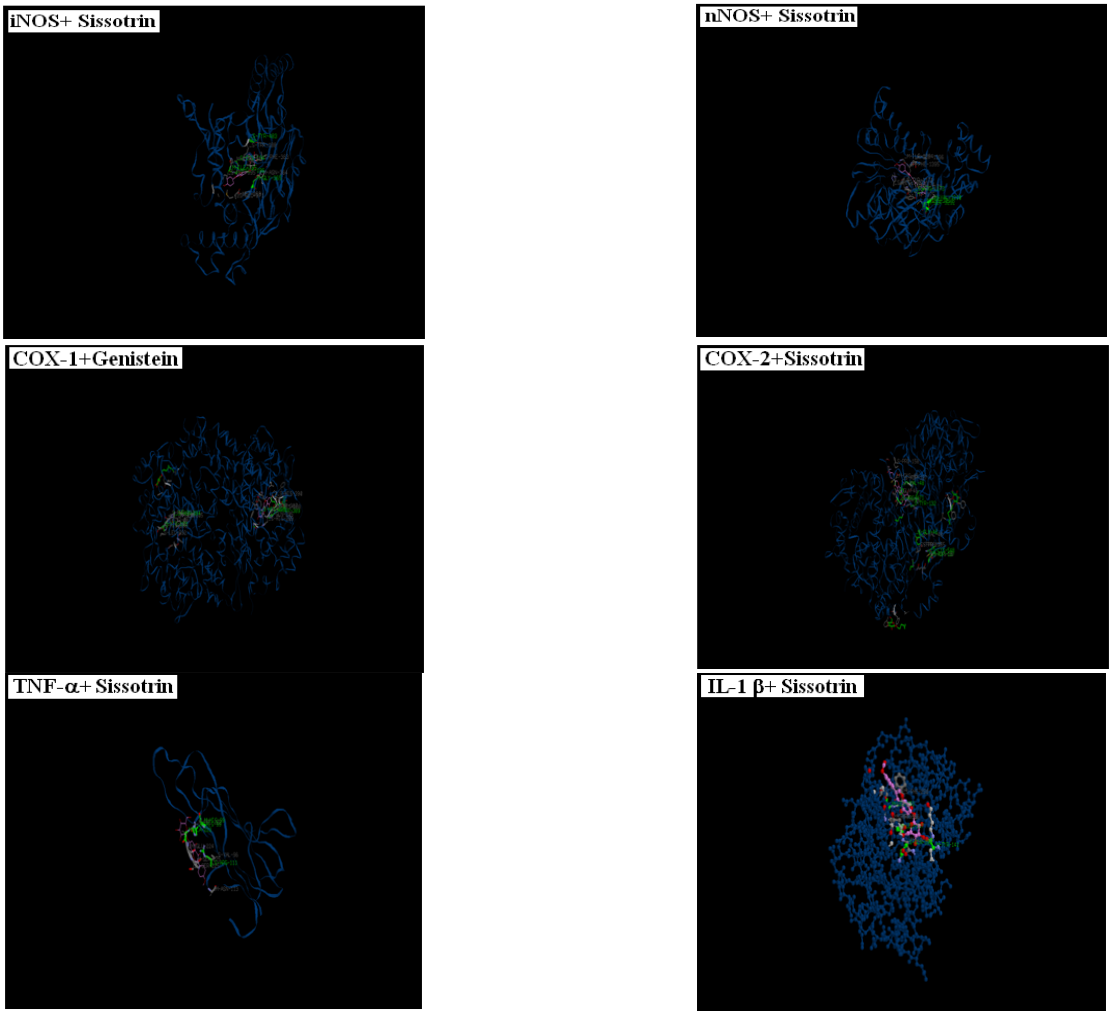


Fig. 3: Docking pattern of various phytoconstituents with different proinflammatory genes

In silico molecular docking is a useful approach in drug discovery and therapeutics employable to neuro inflammatory disorders/ diseases. Lipinski's rule of five and ADMET are useful tools in detecting the drug-likeness and toxicity of phytoconstituents or drugs. These tools predicted the drug-likeness and non-toxicity of these compounds making suitable drug candidates based on their pharmacokinetic nature.

The present study was undertaken to evaluate the antineuro-inflammatory activity of selected phytoconstituents. This is the first study in our knowledge to carry out *in silico* study on multiple neuroinflammatory mediators as therapeutic targets of phytoconstituents [10-12]. The molecular docking analysis of the 14 phytoconstituents mined from various plants-performed on different proinflammatory mediators such as TNF-α, IL-1β, COX-1, COX-2, nNOS and iNOS, using the iGEMDOCK. The phytoconstituent sissotrin has come out as the common best putative drug candidate against all the neuroinflammatory mediator proteins showing highest binding affinity. The phytoconstituents Genistein, quercitin, biochanin A, β-sitosterol, shows comparatively less binding affinity. The activity of these phytoconstituents can be further analyzed and assessed by *in vitro* and *in vivo* studies to validate the anti-neuro inflammatory nature.

CONCLUSION

The Present study indicates that all the 14 phytoconstituents following Lipinski's rule of fives and expected to be an active component as a drug. The results obtained from the docking studies showed that sissotrin has a highest binding affinity with all proinflammatory genes. Sissotrin can be utilized to treat various neuroinflammatory diseases like AD and PD. ADMET showed the molecular properties of the compound which support the fact that it becomes a lead drug. As proteins taken for docking are proinflammatory mediators involved in neuroinflammation. This *in silico* study is actually an additional advantage to screening the proinflammatory mediator's inhibition. Further research with the above compounds and *in vivo* studies are essential to developing a potent drug for the prevention and treatment of neuroinflammatory disorders. Therefore, *in silico* study reveals that sissotrin may act as a potent drug against neurological disorders.

ACKNOWLEDGEMENT

We wish to thank Graphic Era University for their constant support

CONFLICT OF INTERESTS

Declared none

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