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ANTI-INFLAMMATORY STUDIES OF *TERMINALIA CATAPA* USING *IN-VITRO* METHODS AND MOLECULAR DOCKING AGAINST CYCLOOXYGENASE-II ENZYME

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Keywords:

Terminalia catappa, Bioactives, molecular docking, COX- 2, Ligplot

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ABSTRACT: In the present investigation, sequentially extracted plant samples from *T. catappa* in water, methanol, ethanol and hexane were evaluated for COX-2 inhibitory activity. The *in-vitro* anti-inflammatory activity of selected samples showing promising COX-2 inhibition assessed using thermally induced protein denaturation assay. A total of nineteen compounds belonging to various phytochemical classes from *T. catappa* were selected (as initial hits) and screened against COX-2 enzyme using docking and drug-likeness/ADMET studies. From our studies, sixteen phytochemicals were identified as notable antiinflammatory agents (best hit molecules) with promising inhibitory effects effective against COX-2 enzyme. These compounds are namely, arjunolic acid, betulinic acid, ellagic acid, oleanolic acid, kaempferol, quercitin, leucocyanidin, gallic acid, arachidic acid, palmitic and stearic acid.On the basis of drug likeliness and binding studies of protein-ligand intercations. oleanolic acid, betulinic acid, ellagic acid, quercetin and ursolic acid were found to be the most potent (*in-silico*) COX-2 inhibitors. A validated rapid HPLC method was employed for the identification and quantification of phenols and flavonoid in plant sample. The present investigation can be directed towards further experimental studies in order to, confirm the anti-inflammatory efficacy along with toxicities of identified phytomolecules.

INTRODUCTION: Plants have been widely recognized as a important source of novel therapeutic compounds since ancient times for the treatment of various diseases and were reported in traditional medicine system such as the Siddha and Ayurveda. Inflammation is a normal protective reaction to tissue damage caused by physical injury and harmful chemicals.

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The most commonly used drugs for the management of inflammatory conditions is the non-steroidal anti-inflammatory drugs (NSAIDs), which have various adverse effects, especially gastric irritation, leading to the formation of gastric ulcers. *T. catappa* is one of the most common plants used in Ayurveda; hence, it is considered as "King of Medicines" [1].

According to Ayurveda and Siddha, *T. catappa* is useful in the treatment of inflammation diseases, wound healing, allergies, skin related problems, asthma, ulcer, cardiovascular diseases, diarrhea etc. It is also said to be helpful in restoring the power of senses. It is a member of the Combretaceae family, which comprises approximately 600 species [2-4].

They are most commonly found on tropical and subtropical beaches [5]. In India, it is known as Malabar almond, Indian almond and tropical almond. It possess several medicinal properties, it is very rich in phytochemicals and a good source of natural antioxidants [5-6]. Parts of the tree, such as the leaves and fruit are astringent. The red leaves act as a vermifuge, while the sap of young leaves, cooked with oil from the kernel is used to treat leprosy. The bark and roots are useful for treating bilious fever, diarrhea and as a remedy for sores and abscesses. The kernel of the fruit mixed with beeswax stops putrid exudation and bloody faeces. It is recommended as a mild laxative and a galactagogue for women, but too frequent use causes diarrhea. The young leaves are used to cure headaches and colic [10].

Numerous pharmacological investigations have confirmed this plant's ability to exhibit antimicrobial, anticancer, wound healing, antioxidant activities and antidiabetic property usually seen in fruits [5-6]. Anti-inflammatory, hepatoprotective activity, aphrodisiac, antioxidant and anticancer properties were also reported [6]. *Terminalia catappa* species have been used since the Vedic period for the treatment of various diseases. Many preparations from *T. catappa* species are used in traditional medicine as a cardiac tonic and diuretic. *T. catappa* species represents a rich source of phenolic acids, tannins, cyclic triterpenoids and flavonoids. Their exact chemical classes and levels vary in different Terminalia species. Hence, in the present paper we report the development of an optimized, validated and simple HPLC method for the estimation of flavonoids and phenolics from *T. catappa* [7].

Molecular docking is a method that uses chemometrics to visualize molecular and intermolecular forces to identify and predict receptor- ligand complexes [7]. Molecular docking has shown great promise as a new tool for discovering novel small molecule drugs with high protein targeting potential. *In-silico* drug design interactions can predict the ligand-target protein interaction mechanism and the bond energy that occurs. The rich bioactives of *T. catappa*, represents a novel compounds with significant anti-inflammatory activity. However, most of these plant resources have not yet undergone chemical, pharmacological and toxicological studies to investigate their bioactive compounds. The objective of the present research is preliminary evaluation of the antiinflammatory activity of different fractions of *T. catappa* using *in-vitro* and *in-silico* experiments.

MATERIALS AND METHODS:

Collection of Plant Material and Preparation of Extract: The fresh leaves stem, bark and seeds of *T. catappa* were collected from Lal Bagh Botanical Garden, Bangalore. This plant authentication number was AUT/PUS/070 dated 17/12/2014. Thus collected plant was rinsed with tap water and then the various parts of plant were dried under shade at room temperature for 2 weeks.

The dried parts were powdered using an electric grinder. 10 grams of each extracted powder was dissolved in 200 ml of different solvents acetone, chloroform, methanol and pet ether and kept in the shaker for overnight using Whatman filter paper, the content was filtered twice and the filtrate was evaporated to obtain the crude extract for qualitative and quantitative analysis of phytochemicals.

Preliminary Phytochemical Screening: It involves testing of plant powder for the presence of different classes of compounds and to determine their chemical profile. The methods used for detection of various phytochemicals were done as per standard protocol.

Estimation of Total Phenols: The total phenolic content of the extract was estimated according to a modified procedure [7]. Briefly, deionised water (0.5 ml) and 125 µl of Folin-Colcalteu reagent were added to 125 µl of MEA dissolved in distilled water. The mixture was allowed to stand for 6 min before adding 1.25 ml of 7% (w/v) Na_2CO_3 solution. The reaction mixture was then allowed to stand for additional 90 min before taking the absorbance at 760 nm against the blank. The tannic acid standard curve was prepared by adding 125 µl of tannic acid dissolved in distilled water (2, 4, 8 and 10 µg/ml final concentrations) in lieu of extract. The amount of total phenolics was expressed as tannic acid equivalents (TAE, mg tannic acid/g sample) through the calibration curve of tannic acid [7].

Estimation Total Flavonoid: Flavonoid content was estimated using the aluminum chloride colorimetric method [6]. The plant extract in methanol (1 g/ml) was mixed with 0.1 ml of 10% aluminum chloride (w/v), 0.1 ml of 1M potassium acetate and 2.8 ml distilled water. The mixture was allowed to stand at room temperature for 30 min. The absorbance of the reaction mixture was read at 415 nm. Results were expressed as mg/g quercetin equivalent (QE) [7].

HPLC Sample Preparation: The analysis was made on C_{18} column (symmetry, 4·6mm×250mm) in an isocratic mode. A 10 µL aliquot of the extract was injected into a C18 reverse-phase column (Phenomenex Luna 5µ C18(2) 100A analytical column, 250 × 4.60 mm, 5 µm), with a guard column of the same material. The mobile phase contain 0.1% phosphoric acid (A) and acetonitrile (B). The gradient profile was as follows: 95:5 (A/B) for 10 min, 85:15 for 5 min, 85:15 to 80:20 (A/B) in 20 min, 80:20 to 45:55 (A/B) in 10 min 45:55 to 35:65 (A/B) in 10 min, 35:65 to 5:95 (A/B) in 5 min, hold for 8 min and 95:5 (A/B) for 5 min. The flow rate was 1.0 mL/min at room temperature and the wavelength was 270 nm. Gallic acid, chebulagic acid, rutin, and eugenol were used as markers. The peak area of each compound was used for the quantitative HPLC analysis [8].

Anti-denaturation Activity: A solution of 0.2% w/v of BSA was prepared in a tris buffer saline and pH was adjusted to 6.8 using glacial acetic acid stock solutions of 10,000µg/ml. From these stock solutions, 4 different concentrations of 1, 100, 200, and 500µg/ml were prepared by using ethanol as a solvent. 50µl (0.5ml) of each extract was transferred to eppendorf tubes using 1ml micropipette. 5ml of 0.2% w/v BSA was added to the entire above eppendorf tubes. The control consists of 5ml of 0.2% w/v BSA solution with 50µl ethanol. The standard consists of 100µg/ml of ibuprofen in ethanol with 5ml 0.2% w/v BSA solution. The test tubes were heated at 72^0C for 18 min and cooled for 10 min. The absorbance of these solutions was determined by using a UV-VIS double beam spectrophotometer (ELICO SL 244) at a wavelength of 660 nm. Each experiment was carried out in triplicate and mean absorbance was recorded. The percentage of inhibition of precipitation was determined on a percentage basis relative to control using the formula [9].

Percentage of inhibition of denaturation = Absorbance of control – absorbance of extract × 100 Absorbance of control

Pharmacokinetic Profile: Swiss ADME (http://www.swissadme.ch/index.php) was used to determine the pharmacokinetic profile of the tested compounds by entering the simplified molecular input line entry system (SMILES) formula for each active substance. SMILES data were retrieved from the Pub Chem database. Lipinski's Rule of Five analysis was conducted to determine the compounds pharmacokinetic properties [10-12].

Obtaining the Crystal Structure of the Target COX-2: To prepare the COX-2 structure, the crystal structure was taken from the Protein Data Bank (PDB_ID: 5KIR). Heteroatoms were eliminated from the active site and the A chain was chosen for docking studies. Hydrogen atoms have been added to the enzyme. Docking experiments were performed using the COX-2 binding site [11-13].

Ligand Preparation: In our present research, chosen 16 natural phytochemicals from *T. catappa* were obtained from the pubchem database in SDF format and translated into a PDB file format using the Online Smile Translator. Energy minimization of ligands was completed using ChemBio 3D Ultra 12.0, based on the method stated. Energy reduced ligand structures have been transferred to PyRx 0.8 docking tool [14].

Molecular Docking Analysis: The ligands and the protein were converted into.pdbqt format using PyRx 0.8 docking tool with a built in Vina wizard. The protein and ligands were docked with a grid box size of 108, 111, 135 Å. The atomic interactions and electrostatic maps of the ligands were calculated using the autogrid module. Molecular graphics laboratory (MGL) tools, were used to analyse the results from Vina Wizard and the best conformation with lowest binding energy was exported for 2D plot generation using Ligplot+ [15-16].

RESULTS AND DISCUSSION: Phytochemical screening revealed the presence of saponins, tannins, flavonoids and terpenoids. In the present study, aqueous *Terminalia catappa* extracts of

leaves was screened for HPLC analysis. Leaves of *T. catappa* showed flavanoid at RT is 1.503 peak area **Fig. 1A** is 100, Rutin as standard RT time showed 1.873 **Fig. 1B** phenols shown the RT as1.510 **Fig.1C** peak area and standard gallic acid is 1.507 **Fig. 1D** showed the amount of 152.34 mg/sample, flavanoid is one of the bioactive compound beneficial to health by strengthening and protecting blood vessels and numerous pharmacological activities **Table 1**.

TABLE 1: HPLC DATA OF AQUEOUS FRACTION OF *T. CATAPPA* LEAVES

Sample	Amount (µg /mg of sample)	
Leaves	152.34	phenols
	78.73	Flavonoids

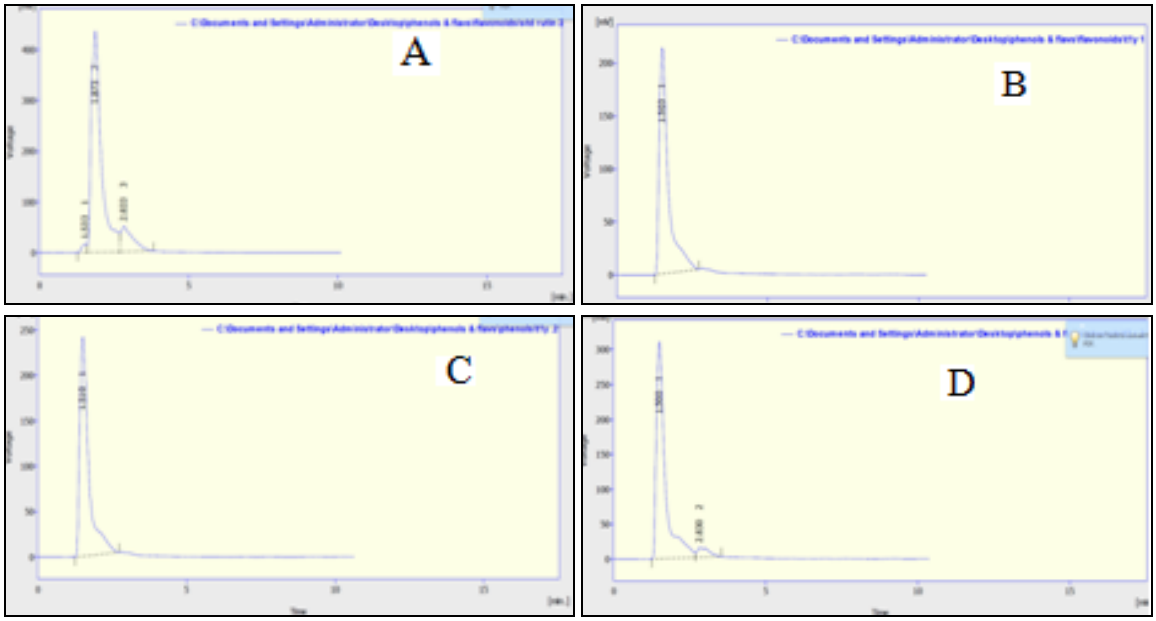

FIG. 1: CHROMATOGRAM FROM HPLC ANALYSIS OF THE AQUEOUS FRACTION OF LEAVES OF *T. CATAPPA*. A-RUTIN, B-FLAVONOIDS, C- PHENOL AND D-GALLIC ACID

The developed HPLC method is simple, precise, time saving economic and accurate. This method is suitable for quantitative analysis as well as quality control of extracts and herb formulations. Phenolic compounds are not found in animals, they are majorly synthesized by plants and are secondary metabolites derived from the shikimate-phenylpropanoids flavonoids pathways. Anti-inflammatory activity is studied using albumin denaturation method. Inflammation is mainly caused by protein denaturation. Anti-inflammatory activity was performed for three different solvent extracts of *T. catappa* to determine its ability to inhibit protein denaturation. Ibuprofen, a standard anti-inflammatory drug showed the inihibition 22.06% at the concentration of 100µg/ml. Maximum percentage of inhibition 68.59% is observed for methanol extract of leaves **Table 2**. The data of our studies suggests that *Terminalia catappa* extract showed significant anti-inflammatory activity. The ligands obtained from PubChem was Arjunolic-acid (CID: 73641), arachidonic acid (CID:), Kaempferol (CID:), gentisic acid (CID:), Beta-sitosterol (CID: 222284), gallic acid (CID: 370), quercitin (CID: 5280343), linolenic acid (CID: 10494), Leucocyanidin (CID: 71629), oxalic acid (CID: 971), Stearic acid (Palmitoleic acid (CID:), Palmitic acid (CID:), oleic acid (CID:), oleanolic acid (CID:), ellagic acid (CID: 5281855), betullinic acid(CID: 64971) with a molecular weight as shown in **Table 3**.

TABLE 2: ANTI-DENATURATION OF BSA IN PRESENCE OF *TERMINALIA CATAPPA* METHANOLIC EXTRACTS

Sl. no.	Sample	Inhibition (%)
1	Ibuprofen	22.06
2	Leaves	68.59
3	Seed	57.54
4	Mesocarp	38.05
5	Bark	33.50

The target proteins were identified in the PDB database with protein data bank code 5KIR. A sample was aligned in the laboratory using the X-ray method. COX-2 receptor structure had a resolution of 3Å. Meanwhile, the protein resolution

in-silico represents the clarity of the atomic distance between amino acid residues when presented in the software; the higher the value, the more described the molecular visualization. The compound XX5 (ChemID 395128) was used as a control ligand and download as sdf file. Drug-likeness parameters for top 16 dock scored compounds are displayed in **Table 3**. All drug-likeness data were found to be within the considerable range indicating the good drug-likeness behavior of the screened phytochemicals. LogP, MW and molecular PSA indicate good membrane permeability, intestinal absorption and oral bioavailability. Some compounds showed relatively higher lipophilicity which could be accounted for better biological activity due to the increased absorption of biological membranes. Whereas other parameters such as nHBDs, and nRotb bonfacilitate drug metabolism and pharmacokinetics (DMPK). The predicted ADMET data of top 16 compounds exhibited good aqueous solubility and gastrointestinal absorption, which could help compounds attain increased concentration in blood for optimal biological action. These compounds also exhibited poor blood brain barrier (BBB) penetration indicating less probability of producing CNS toxicity. Molecular docking is frequently used to understand how a small-molecule recognize and interact with macromolecule, which is important in pharmaceutical research and drug discovery by placing a ligand (molecule) into a preferred specific region of receptor (DNA/protein) to form a stable complex of potential efficacy and specificity. PyRx software was used to estimate binding energy, prediction of binding energy is accomplished by calculating the physical-chemical properties of the ligand-receptor complex using mathematical equations; a low (negative) energy indicates a stable complex and a high probability of forming a binding interaction. Our natural compounds have binding energies ranging from -6.0 to -9.6 kcal/mol, with the top five candidates having the lowest score when compared to the control ligand, indicating the highest binding affinity: quercitin (-9.6 kcal/mol), oleanolic acid oleanolic acid, betulinic acid, ellagic acid and ursolic acid (-9.2 kcal/mol) as shown in **Fig. 3**. Due to oleanolic acid, betulinic acid, ellagic acid and ursolic acid low binding energy, it will have a strong interaction with the COX-2 receptor. Active chemical interaction takes place between the COX-2 protein and the selected phytochemicals by Van der Waals forces, electrostatic and hydrogen bonding. The findings showed that all the investigative molecules had higher energy values on the COX-2 receptor, which means that these phytochemicals have greater affinity and steric compatibility with COX-2 **Table 4.** The findings of this study can be used as a baseline for future research as a potential therapeutic candidate.

TABLE 3: DRUG-LIKENESS PROPERTIES OF TOP 16 DOCK SCORED COMPOUNDS

Compound	Molecular Formula	Molc.wt(g/mol)	nHB	nHBD	Mol. PSA Å^2	Lipinski drug likeliness	Synthetic accesabiliy	(Log *Po*/w)	Pubchem ID
Arjunolic-acid	C30H48O5	488.70	5	4	90.99	4.52	0	7.45	73641
Beta-sitosterol	C29H50O	414.71	1	1	22.23	6.24	1	7.30	222284
Betulinic-acid	C30H48O3	456.70	3	2	60.53	7.14	1	6.63	64971
Gallic acid	C7H6O5	170.12	5	4	99.99	0.25	0	2.22	370
Ellagic acid	C14H6O8	302.19	8	4	150.5	1.00	0	4.17	5281855
Oleanolic acid	C30H48O3	456.70	3	2	59.33	7.07	1	5.08	10494
Oxalic acid	C2H2O4	90.03	4	2	78.60	-0.70	0	1.00	971
Leucocyanidin	C15H14O7	306.27	7	6	132.31	0.08	1	3.66	71629
Kaempferol	C15H10O6	286.24	6	4	115.15	1.60	0	3.20	5380863
Gentisic acid	C7H6O4	154.12	4	3	80.76	0.75	0	1.10	3469
Quercetin	C15H10O7	302.24	7	5	135.36	1.43	0	3.23	5280343
Arachidic acid	C20H40O2	312.53	2	1	47.30	1.0	2.77	6.62	10467
Linoleic acid	C18H32O2	280.45	2	1	47.30	0.0	0	4.12	5280450
Oleic acid	C18H34O2	282.46	2	1	47.30	2.0	3.07	6.65	445639
Palmitic acid	C16H32O2	256.42	2	1	47.30	0.0	3.31	5.20	985
Stearic acid	C18H36O2	254.41	2	1	47.30	2.0	3.54	5.93	5281

LogP: log of n-octanol/water partition coefficient; Mol. wt: molecular weight; nHBA: number of hydrogen bond acceptor(s); nHBD: number of hydrogen bond donor(s); nRotB: number of rotable bond(s); Mol. PSA- molecula polar surface area.

Against COX-2. A more detailed explanation about the phytochemicals including their phytochemical nature of structural skeleton is given in **Fig. 2.**

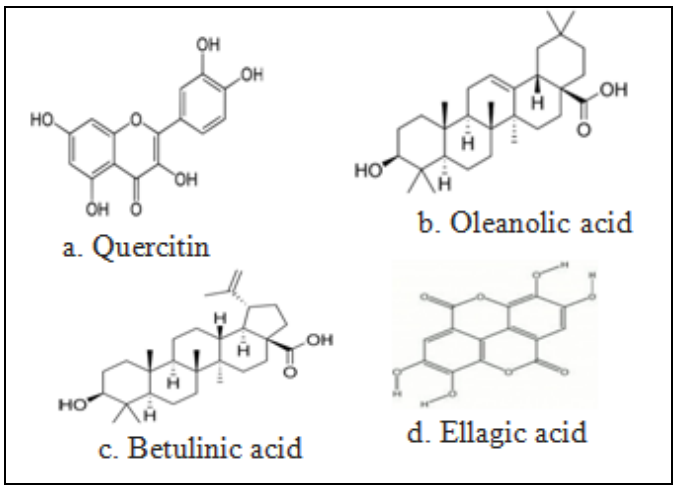

FIG. 2: STRUCTURE OF PHYTOCHEMICALS IDENTIFIED AS POTENTIAL COX-2 INHIBITORS

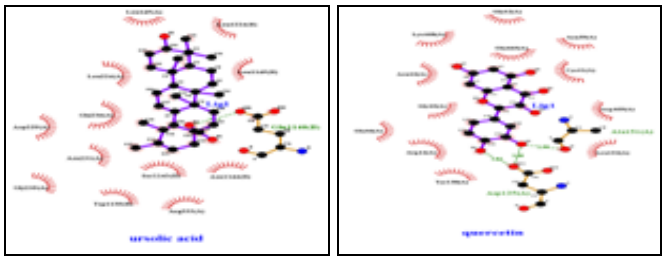

FIG. 3: MOLECULAR INTERACTION OF BEST TWO COMPOUNDS TARGET COX-2 WITH (A) OLEANOIC ACID AND (B) URSOLIC ACID

The phytochemical analysis of seed, bark, mesocarp, fruit and leaves of *Terminalia catappa* revealed the presence of secondary metabolites. Drug likeliness properties of the ligand based on Swiss ADME analysis include their chemical properties like, molecular weight being < 500 Daltons, with < 5 hydrogen bond donors, < 10 hydrogen bond acceptors and QPlogPo/w < 5. The n octanol/water partition coefficient (log P o/w) is a key physicochemical parameter for drug discovery depicts lipophilicity indices of the ligand as within the range. The parameters measured for the ligand's solubility in water identifies the ligand to be an ideal drug. The most favorable phytochemicals as anti-inflammatory agents were selected via ADMET profiling and molecular docking with specific protein of the COX-2 enzyme. Molecular docking was performed between the target protein COX-2 and ligands using PyRx software. The findings indicate that Ser 530, Arg 120, Tyr 355, Arg 513, Leu 503, Val 523, Val 434, Tyr 385 serve as binding residues in the COX-2 protein. The main objective of the molecular docking analysis of phytochemicals from *T.Catappa* is to find a molecule that displays a strong binding affinity to the target protein COX-2 and also to build a stable complex From the results obtained, the findings in oleanolic acid indicates that Arg1061, Lys1083 and in quercetin Ala151(A) serve as binding residues in the COX- 2 active pocket. Oleanolic acid from the bark and quercetin from the leaves of *T. catappa* has the highest binding energy (least energy) of ΔG 9.6 kcal/mol, the investigative molecules in bark had higher energy values on COX-2. A validated rapid HPLC method was analyzed for the identification and quantification of phenols and flavonoid in the leaves of *T. catappa*. Denaturation of protein is well documented cause of inflammation. The *in-vitro* anti-inflammatory activity of selected samples showed promising COX-2 inhibition, which is assessed using thermally induced protein denaturation assay. This study also provide the supporting evidence to demonstrate the anti-inflammatory effects, which may be due to the potentiality of the identified compounds to reduce various inflammatory mediators. The results obtained may be useful in strengthening the standardization of the selected botanicals. Moreover the screened bioactive of *T.catappa* can be considered as a resource for searching novel anti-inflammatory agents possessing COX-2 inhibition.

TABLE 4: BINDING ENERGIES OF TOP SIX DOCK SCORED COMPOUNDS

Ursolic acid	-9.5
Leucocyanidin	-9.0
Gallic acid	-7.2
Arachidic acid	-6.5
Palmitic acid	-6.2
Stearic acid	-7.2

CONCLUSION: The present study validates the anti-inflammatory activity of *T. catappa*. Methanolic extracts from *T. catappa* showed the presence of important metabolites like flavonoids, phenols and triterpenoids. The presence of these chemical constituents in this plant is an indication that the plant, if properly screened, could yield drugs of pharmaceutical significance. A validated rapid HPLC method was analyzed for the identification and quantification of phenols and

flavonoids. Protein denaturation is a well documented cause of inflammation. The present investigation can be directed towards further experimental studies in order to confirm the anti-inflammatory efficacy along with toxicities of identified phytomolecule.

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