

Antipyretic Potential of Tamarixetin from *Ipomoea marginata* (Desr.) Verdcourt and its Validation by Computational Studies

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Ipomoea marginata (Desr.) Verdcourt is traditionally used in hypertension, diabetes and fever therapies. This research aims to determine the potential antipyretic function of *Ipomoea marginata* methanolic crude extract (MEIM) and its fractions in order to facilitate its usage as folk medicine, and to detect the phytochemical components responsible for it by in vivo & in silico studies. MEIM & its fractions were subsequently examined through GC-MS analysis. In vivo experiments were performed in Wistar albino mice by yeast-induced pyrexia test. In vivo antipyretic experiments demonstrated a substantial decrease of the rectal temperature of about 0.5°C in all doses for yeast-induced rat pyrexia. The molecular docking of certain significant compounds in MEIM to Cyclo-oxygenase-1, Cyclo-oxygenase-2 & Microsomal-Prostaglandin E Synthase-1 demonstrated noteworthy associations of these target proteins with the retained amino acid residue. Tamarixetin is the compound which attained best docking score. These findings suggest that Tamarixetin, isolated from *Ipomoea marginata* has a potential therapeutic efficacy for treating fever.

Keywords: ADMET; Antipyretic; In silico; *Ipomoea marginata*; Isolation.

Over the years many diseases have been treated successfully using synthetic chemicals.¹ Traditional herbal compounds often play an important role as medicine since ancient history, particularly in rural areas, where availability of modern medicine is limited.^{2,3} Phytochemicals (bioactive compounds) that serve as defensive mechanisms to fight different diseases have been shown to be found in plants.^{4,5} Many experiments have shown effectiveness in validating medicinal

plants for multiple diseases.⁶⁻¹⁶ *Ipomoea marginata* (Convolvulaceae) is a perennial herb that grows to a height of 2-5 meter, the herb is widely spread in West Africa.¹⁷ Its plant juice is used as diuretic, antihypertensive, anti-diabetic, antidote and uterine tonic.¹⁸ The plant has been documented to produce various compounds that can be used to cure diseases with medicinal ingredients.^{19,20} The therapeutic properties of this plant was due to the availability of chemical compounds that aid healing

processes. In light of these several effectiveness trials of *I. marginata* knowledge is scarce against a broad range of factors on specific disease of pyrexia.²¹

Pyrexia is a specific typical symptom defined outside the normal range by the rise in body temperature. The body offers an ideal habitat in which former natural protection mechanisms facilitate repair or render inviolable infectious agents. Increased hypothalamic prostaglandin E2 (PGE2) synthesis induces an uptick in body temperature through the release of tainted or impaired tissues.²² Almost, all existing antipyretic drugs hinder PGE2 production by the application of COX-2 inhibition. A few of these agents inhibit COX-2 through irreversible binding. Therefore, these synthetic agents may also exert toxic effects on the brain cortex, cardiac muscle, liver cells, and renal glomeruli. In contrast, natural COX-2 inhibitors are reported to be associated with comparatively fewer adverse outcomes.²³

Therefore, in the present report, an attempt was done to examine antipyretic role of methanol extract of *Ipomoea marginata* (MEIM) & of different sub fractions petroleum ether (PEFIM), chloroform (CFIM)) with an effort to explain their native usage as febrifuge. To explore the findings of MEIM and phytoconstituents chosen to treat pyrexia, studies on anti-pyretic actions using an in vivo and in silico approach was conducted.

MATERIALS AND METHODS

Plant Material Collection

New specimens of *I. marginata* were taken at Gudlavalleru, Andhra Pradesh. (16° 20' 53.52"N and also 81° 3' 5.5332"E). Identification of plant material was carried out, & corresponding voucher specimen was preserved in herbarium at V. V. Institute of Pharmaceutical Sciences. It was authenticated by S V University, Tirupati, Andhra Pradesh.

Preparation of Samples

The shade-dried plant matter was milled by means of milling apparatus into coarse powder. Approximately 1000 g of this powder underwent Soxhlet extraction using methanol to obtain the methanolic extract (MEIM). The resulting extract was subsequently partitioned by sequential extraction with petroleum ether

(PEFIM), chloroform (CFIM), and diethyl ether (DEFIM). Each fraction was then filtered, concentrated through rotary evaporation under reduced pressure, and preserved under refrigerated conditions until analysis.

GC-MS Analysis of MEIM

The gas chromatography analysis was performed on an Agilent 6890 Series instrument fitted with Agilent 5973 mass selective detector, operated through the Agilent Chemstation software and equipped with an HP-5MS capillary column. Ultra-high purity helium served as the carrier gas at constant flow rate of 1.0 mL/min with constant speed of 37 cm/s. Injector temperature was held at 250!. Oven program was initiated at 60! and stepped up to 280! in steps of 10! per minute with 4 min. each & Velectron multiplier voltage. The compounds were identified by direct comparing point. 2 iL injections are made with 20:1 split ratio, operated in 70 eV electron ionization rendered processing times with spectral information and separation patterns were cross-checked with the NIST library.²⁴

Molecular Docking Study

AutoDock 4.0 was used in order to perform molecular docking studies & Discovery Studio Biovia 2020 to evaluate the interactions among ligands & their target proteins. Compounds selected for analysis included ferulic, vanillic, gentisic acid, proanthocyanidins, p-hydroxybenzoic acid, quercetin, and 32 ,42 -dimethoxy derivatives (Figure 1). To this end, the three-dimensional crystal structures of COX-I (PDB ID: 3N8V), COX-II (PDB ID: 5KIR) and mPGES-1 (PDB ID: 3DWW) (Figure 2) were retrieved in Protein Data Bank.

Drug likeliness and ADMET Analysis

In this study, DruLiTo was engaged to evaluate drug-likeness of selected compounds.²⁵ Assessment of pharmacokinetic parameters was carried out to establish their behavior within body. ADMET properties were examined using admetSAR approach, while acute toxicity predictions were generated with the Test Estimation Software Tool (T.E.S.T).²⁶⁻²⁸

PASS Analysis

This software-based platform is designed to predict the possible physiological activities of compounds. For each substance, the outcomes are expressed as Pa & Pi (range 0.000 to 1.000). In

present analysis, only activities where Pa exceeded Pi were observed.^{29,30}

Isolation of 4'-Methoxy Quercetin

Column chromatography with the silica gel G as stationary phase was applied to the MEIM & eluted with gradient manner from 100% petroleum ether to 100% methanol. At a particular concentration from 40% ethyl acetate: 60% methanol got a fraction enriched with rich in flavonoids. Then that fraction was subjected to recolumn by sephadex LH-20 with an eluent 100% methanol, which results in production of light yellow powder. Purity of isolated compound melting point test done and structure elucidation using IR, NMR and mass spectroscopy.

Experimental animals

The experiments included Albino Wistar rats (120-150 g) obtained from Mahaveer's animal resource firm, Hyderabad. The animals have been kept in sanitised polypropylene cages attain sterile

paddy husk as bedding under normal environmental conditions. Seven days before analysis, animals were acclimatised. The animals were assigned to study and control groups and the food was withheld 12 hours prior to the study hours. All experimental protocols met with the IAEC and CPCSEA guidelines (Protocol No. P16/IAEC/VVIPS/PH/Rats-24).

Acute toxicity tests

Acute oral toxicity was assessed following the guidelines outlined in OECD Test No. 423.³¹ In the toxicity analysis, entirety of five animals inward single oral dose of 2000 millig/kilog bw of MEIM. Food was supplied for 3 or 4 hours after dosing. During the first 30 min after dosing, each animal was watched closely, regularly for the first 24 hours, and again for 3 days to record latent sensitivity. In order to measure the appropriate therapeutic dose, median fatal dose ($LD_{50} > 2.0$ g / kg) was identified according to Zaoui *et al.*³²

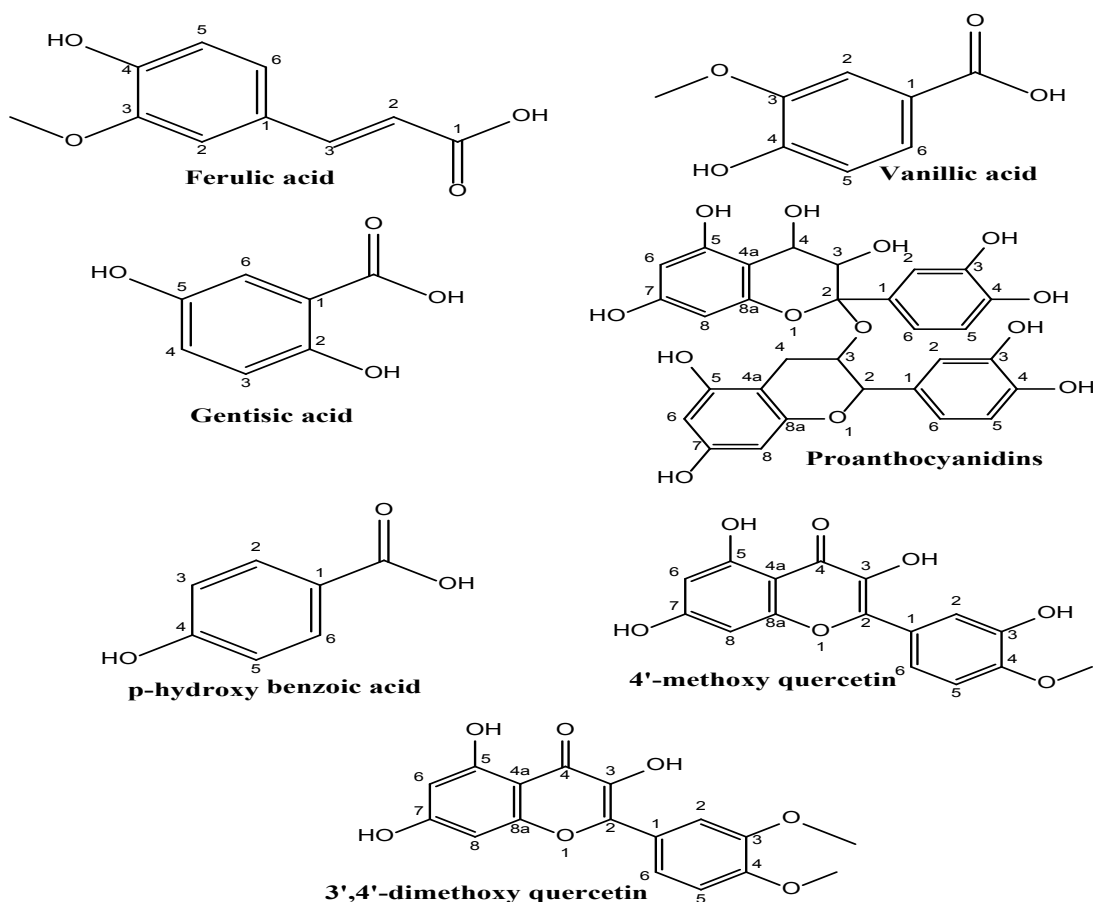


Fig. 1. The two-dimensional structures of *in silico* active ligands from *Ipomoea marginata*

Antipyretic testing

Anti-pyretic function of MEIM & its different sub-fractions has been measured by pyrexia with the administration of Brewer's yeast suspension in Swiss mouse albinos of both sexes. The animals were classified into nine classes of five mice each. Using an automated thermometer, natural body temperature was registered and subsequently pyrexia was caused by administering a Brewer's aqueous yeast suspension of 20% (10 ml/kg, sc). Every group fasted overnight, but permitted with free use of drinking water, and every mouse had a rectal temperature reported after 18 hours. Pyrexia induction was verified

by temperature changes above 0.5°C.³³ Negative control (group I), standard drug (group II), tamarixetin (20 millig/kilog), and the rest of the groups (IV-IX) were fed MEIM, CFIM, PEFIM, at 200 millig/kilog level, or 400 millig/kilog level respectively. After administering control, normal & test samples, rectal temperature was reported one hour, two hours, three hours & four hours after the administration.

Statistical analysis

Data have been represented as the mean±SEM of five animals. For regression research, ANOVA was accompanied by a multiple comparison post hoc Dunnett test. The findings were found important at level $p < 0.05$.

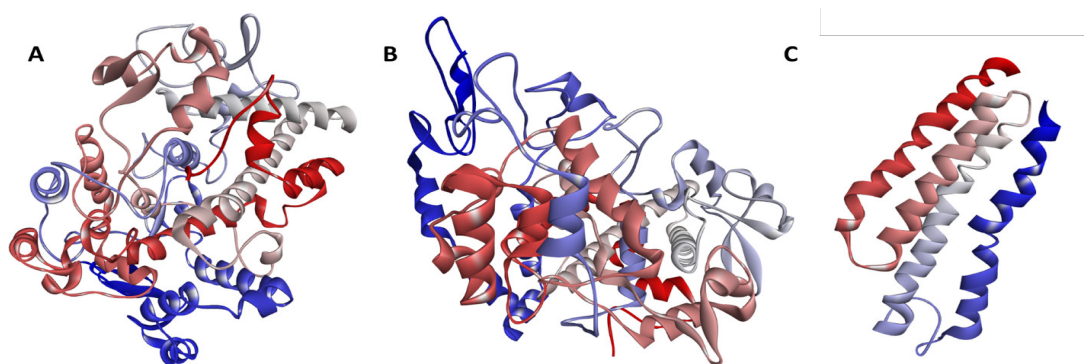


Fig. 2. Three-dimensional structures of the molecular targets in their unbound (free) forms include: (A) Cyclooxygenase-1 (PDB ID: 3NRV), (B) Cyclooxygenase-2 (PDB ID: 5KIR), and (C) Human microsomal prostaglandin E synthase-1 (PDB ID: 3DWW)

Table 1. Biological active compounds obtained from *Ipomoea marginata*

S. No	Retention Time	Compound name	Canonical Smiles	Area (%)	Mol. formula	Mol. weight
1	6.252	4-Hydroxybenzoic acid	<chem>OC(c(cc1ccc1O)=O</chem>	8.68	$C_7H_6O_3$	138.12
2	6.647	Gentisic acid	<chem>OC(c(cc1O)c1O)=O</chem>	5.22	$C_7H_6O_4$	154.12
3	8.292	Vanillic acid	<chem>COc(c c(cc1)C(O)=O)c1O</chem>	10.98	$C_8H_8O_4$	168.15
4	8.917	Ferulic acid	<chem>COc(cc(/C=C/C(O)=O)cc1)c1O</chem>	5.53	$C_{10}H_{10}O_4$	194.18
5	11.334	Tamarixetin	<chem>COc(ccc(C(Oc(cc1O) O) c1C1=O)=C1O)c1c1O</chem>	48.23	$C_{16}H_{12}O_7$	316.26
6	13.324	Proanthocyanidins	<chem>O[C@H]([C@H]1O)[C@](c(cc2cc(O)c2O)(O)[C@@H](C2)[C@@H](c(cc3)cc(O)c3O)Oc3c2c(O)cc(O)c3)Oc2c1c(O)cc(O)c2</chem>	10.14	$C_{30}H_{26}O_{13}$	594.5
7	14.985	Cinnamic acid	<chem>C1=CC=C(C=C1)C=CC(=O)O</chem>	6.28	$C_9H_8O_2$	148.16

RESULTS

GC-MS Analysis

Variety of compounds were identified in methanolic extract of *Ipomoea marginata* through GC-MS analysis. These compounds have been detected in the course of mass spectrometry linked to GC. The different biological active components of the whole herb of *I. Marginata* found by GC-MS were tabulated in Table 1.

Molecular Docking Studies

All compounds identified through GC-MS were subjected to docking analysis against the target proteins COX-I (PDB ID: 3N8V), COX-II (PDB ID: 5KIR), and human microsomal prostaglandin E synthase-1 (PDB ID: 3DWW), and their performance was ranked based on docking scores. From this screening, seven molecules were shortlisted owing to their favorable binding

affinities & interactions within active sites of 3N8V, 5KIR, and 3DWW (Figures 3–5). Among these, Tamarixetin demonstrated strong binding, with docking energies of -8.1 , -9.5 , & -7.8 kcal/mol against COX-I, COX-II, and mPGES-1, respectively (Tables 2–4).

Drug likeliness

Lipinski's rule of 5 is commonly applied to predict oral bioavailability of drug-like molecules in humans.^{3t} The physicochemical parameters of ten compounds selected from the docking study were evaluated using the DataWarrior software, & results are summarized in Table 5. With exception of proanthocyanidins, which deviated in molecular weight and hydrogen bond acceptor count, all molecules complied with the rule. The distribution plots indicated that most compounds were located within 'Lipinski compliant' region (MW < 500, logP < 5, HBA < 10, HBD < 5).

Table 2. Interactions of COX-I (3N8V) amino acid residues with ligands at receptor sites

Ligands	Binding Affinity, ΔG (Kilocal/mol)	Amino acids involved & Distance ($\text{\AA}$)		
		Hydrogen Binding Inter-actions	Hydrophobic Interactions	Electrostatic Inter-actions
Tamarixetin	-8.1	ALA A:199 (3.67), TYR A:385 (3.57), ASN A:382 (3.22)	PHE A:210 (6.46), HIS A:386 (4.68)	MET A:391 (6.41)
4-hydroxy benzoic acid	-5.9	-	LEU A:352 (5.63), GLY A:526 (4.84), ALA A:527 (4.27)	-
Cinnamic acid	-6.3	TYR A: 355 (6.04)	ALA A:527 (4.69), GLY A:526 (3.85), LEU A:352 (5.75), ILE A:523 (6.00)	-
Ferulic acid	-6.3	TYR A:355 (5.94)	ALA A:527 (4.56), ILE A:523 (6.47), GLY A:526 (4.78), LEU A:352 (5.31, 5.42), TYR A:348 (5.52), VAL A:349 (5.49)	-
Gentisic acid	-6.3	SER A:530 (4.17)	LEU A:352 (5.51), ILE A:523 (4.06), ALA A:527 (4.16), GLY A:526 (4.87)	-
Proanthocyanidins	-8.4	PHE A:210 (6.02), ASN A:382 (3.99, 4.41), HIS A:386 (4.96), TRP A:387 (5.12)	VAL A:447 (5.67), HIS A:388 (6.38)	-
Vanillic acid	-6	HIS A:388 (4.08)	HIS A:207 (5.49), MET A:391 (4.53), HIS A:388 (4.50, 4.95), HIS A:386 (3.49)	-
Paracetamol	-6.1	HIS A:386 (3.82)	ALA S:202 (5.22)	

Pass Analysis

Biological activity spectra of the ligands were predicted using PASS online, and the outcomes are summarized in Table 6. Compounds with Pa values greater than 0.7 were considered highly likely to demonstrate the predicted activity in experimental conditions, whereas those with Pa values below 0.5 were regarded as unlikely to exhibit such activity.³⁵

ADMET Analysis

ADMET characteristics of ligands were assessed with the aid of the admetSAR platform, & results are provided in Table 7. All compounds demonstrated excellent HIA and strong BBB permeability. High HIA values indicate the potential for effective oral absorption. In addition, all ligands tested negative in the AMES assay, suggesting a non-mutagenic profile. Toxicity evaluation revealed that compounds with lower

LD... € values exhibited higher toxicity compared to those with higher LD... € values.³

Acute toxicity studies

No mortality was observed with the extracts and fractions of *I. marginata* at doses up to 2000 mg/kg. Therefore, 1/10th & 1/5th of this dose (200 and 400 mg/kg) were selected for subsequent experiments.

Characterization of Tamarixetin

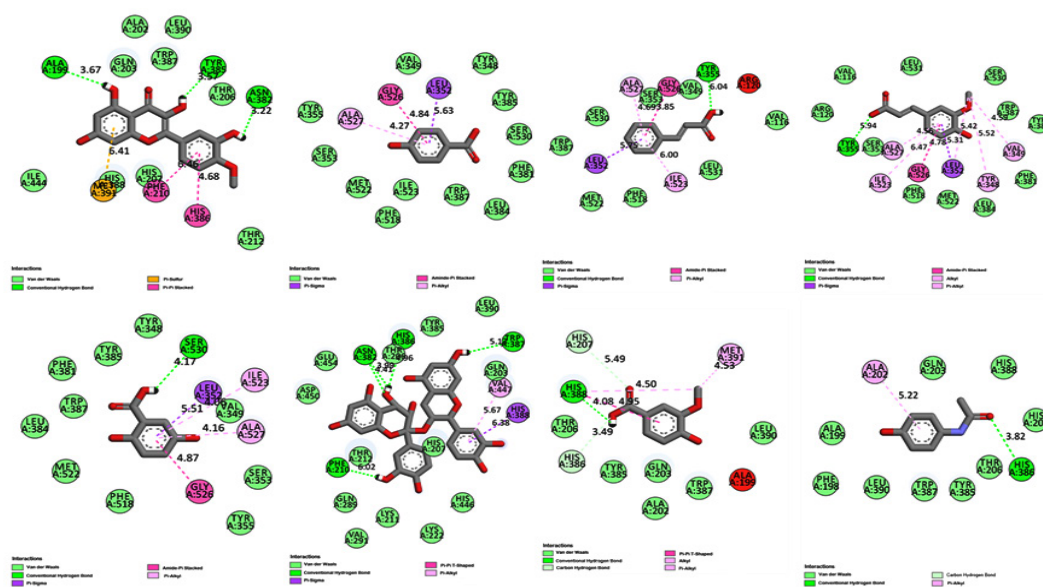
The compound isolated from methanolic extract of *Ipomoea marginata* was characterized as Tamarixetin. It exhibited a melting point of 195–197 °C. UV (MeOH) absorption maxima were recorded at 257 and 357 nm. The ¹H NMR spectrum (400 MHz, CDCl₃) displayed signals at δ 7.77 (1H, dd, J = 9.0, 1.8 Hz), 7.37 (1H, d, J = 9.0 Hz), 7.33 (1H, d, J = 1.9 Hz), 7.26 (1H, s), 6.54 (1H, d, J = 2.0 Hz), 6.43 (1H, d, J = 1.8 Hz), and 4.05 (2H, s). The ¹³C NMR spectrum (400

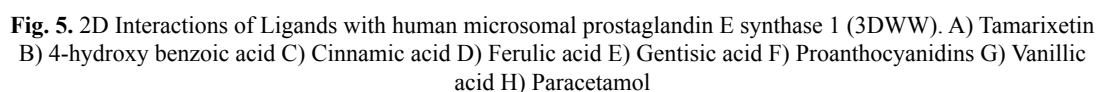
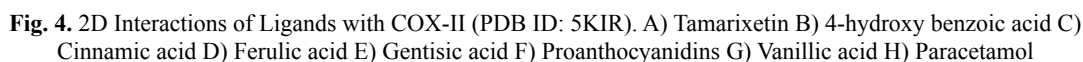
Table 3. Interactions of COX-II (5IKR) amino acid residues with ligands at receptor sites

Ligands	Binding Affinity, ΔG (Kcal/mol)	Amino acids involved & Distance (Å°)		
		Hydrogen Binding Inter-actions	Hydrophobic Inter-actions	Electrostatic Inter-actions
Tamarixetin	-9.5	SER A: 353 (4.35),	TYR A:385 (6.64), VAL A:344 (5.82), TYR A:348 (5.37), VAL A:349 (5.35, 4.88), LEU A:352 (4.30, 4.38), VAL A:523 (4.21, 4.86)	-
4-hydroxy benzoic acid	-6.1	THR A:206 (3.28)	ALA A:202 (4.19)	-
Cinnamic acid	-6.7	TYR A:355 (5.10)	VAL A:523 (5.30), LEU A:352 (5.78), ALA A:527 (3.93)	-
Ferulic acid	-7.3	-	LEU A:352 (5.56), VAL A:523 (4.45), TRP A:387 (6.50), PHE A:518 (5.93), VAL A:349 (6.56, 4.85)	-
Gentisic acid	-6.2	THR A:206 (3.45), TRP A:387 (6.17)	ALA A:202 (4.18), HIS A:388 (6.73)	
Proanthocyanidins	-7.4	GLN A:289 (5.54), THR A:212 (4.69), GLN A:454 (5.09)	VAL A:291 (5.75), HIS A:214 (6.31), HIS A:386 (5.85, 7.93), LEU A:294 (6.17)	
Vanillic acid	-6.2	TRP A:387 (5.53)	HIS A:207 (6.72), HIS A:388 (5.25), TYR A:385 (6.43), HIS A:386 (3.82), ALA A:202 (6.09)	
Paracetamol	-6.1	ALA A:199 (3.68), THR A:206 (3.94)	ALA A:202 (5.64), HIS A:386 (3.53)	

Table 4. Interactions of human microsomal prostaglandin E synthase 1 (PDB ID: 3DWW) amino acid residues with ligands at receptor sites

Ligands	Binding Affinity, ΔG (Kcal/mol)	Hydrogen Binding Inter-actions	Amino acids involved & Distance (Å°)	
			Hydrophobic Inter-actions	Electrostatic Inter-actions
Tamarixetin	-7.8	ARG A:38 (4.27), ala a:43 (4.20), ARG A:60 (6.26), CYS A:59 (3.69), ARG A:67 (4.85)	ILE A:33 (5.02), VAL A:37 (5.62), ARG A: 38 (6.55)	LYS A:41 (4.61), ASP A:64 (4.41, 4.75), ARG A:67 (4.94)
4-hydroxy benzoic acid	-4.9	ALA A:43 (3.89)	ARG A:38 (4.67), LYS A:41 (4.12)	ASP A:64 (5.09)
Cinnamic acid	-5.4	ASP A:67 (3.97), ASP A:64 (2.66)	ARG A:38 (6.18), LYS A:41 (4.95)	ASP A:64 (5.75)
Ferulic acid	-6.2	CYS A:68 (4.61), CYS A:59 (4.14), ARG A:60 (6.32)	LYS A:41 (5.03), LYS A:42 (4.18), PHE A:44 (5.30), ARG A:38 (4.53)	ASP A:64 (5.03)
Gentisic acid	-5.4	LYS A:41 (5.73)	ARG A:38 (6.42)	ASP A:64 (4.46), LYS A:41 (4.77)
Proanthocyanidins	-7.6	ARG A:67 (6.16)	ALA A:43 (6.68), ARG A:38 (5.62), VAL A:37 (6.19), PRO A:63 (4.74)	ASP A:64 (4.87), LYS A:41 (6.82), ARG A:67 (5.16)
Vanillic acid	-5.5	ASP A:64 (4.34)	ARG A:38 (5.80), LYS A:41 (4.46), PHE A:44 (4.99), ALA A:43 (3.96), ARG A:60 (5.00)	ASP A:64 (5.23)
Paracetamol	-4.7	ARG A:110 (5.65), ARG A:126 (6.25)	ALA A:133 (4.52)	-

**Fig. 3.** 2D Interactions of Ligands with COX-I (PDB ID: 3N8V). A) Tamarixetin B) 4-hydroxy benzoic acid C) Cinnamic acid D) Ferulic acid E) Gentisic acid F) Proanthocyanidins G) Vanillic acid H) Paracetamol



MHz, CDCl₃) showed signals at δ 177.67, 165.13, 160.84, 157.69, 150.26, 147.33, 146.63, 136.33, 123.05, 120.17, 114.62, 112.77, 103.23, 99.58, 94.40, and 56.21 (Figure 6).

Antipyretic test

Statistical research indicates the methanol extracts as well as subfractions of *I. marginata* demonstrated strong antipyretic impact. MEIM and their subfractions showed significant effects at intervals of 2, 3 and 4 hours. Tamarixetin on the other side, with the 20 mg/kg dosage, had highly significant effects at all stages. The influence on the rectal temperature of the extract and fractions in mice are as seen in Table 8 and Figure 7.

DISCUSSION

In this study, antipyretic effects of MEIM; their subfractions and Tamarixetin have been seen. Subcutaneous Brewer yeast injection improves the development of prostaglandins that induce pyrexia. Pyrexia brewer is a yeast-induced technique known as a convenient test for antipyretic effects of plant and synthetic products.^{37,38} Antipyretic activity may

be done by inhibiting prostaglandin production, which can be accomplished by blocking the cyclooxygenase (COX) enzyme function. Many mediators, like TNF- α , IL-1, IL-6, engage in a rise in temperatures and may be responsible for antipyretic reactions by decreasing their involvement.³⁹ Subcutaneous administration of *S. cerevisiae*, the components of cell walls serve as exogenous pyrogens that trigger immune cells in rodents including lymphocytes and macrophages. The release of endogenous pyrogens is cytokines that get access to hypothalamus via circulation and result in changes in body temperature of the handled mice.⁴⁰ MEIM and its subfractions also lowered temperature of rectal of handled mice significantly. Decrease in temp. can be induced by existence of Tamarixetin in *I. marginata*, a pharmacologically active portion that interact with prostaglandin synthesis. However, during the biosynthesis of prostaglandins, numerous biological events occur and more study is required to establish exactly the degree to which Tamarixetin exercises its antipyretic effects.

This analysis was mainly based on the discovery of useful natural products from *Ipomoea marginata* herbal plant with sufficient pharmacological performance and minimal toxicity against pyresis. The seven phytoconstituents from *I. marginata* picked from this result is selected for further analysis explicitly.

The computer-aided drug design (CADD) software PASS has been used to speed up effective natural product study in order to forecast biological behaviour. The prediction method was to use 20,000 primary substances.⁴¹ Prediction findings were displayed as Pa & Pi ratio. This experiment demonstrated the highest Pa benefit for all antipyretic actions in vanillic

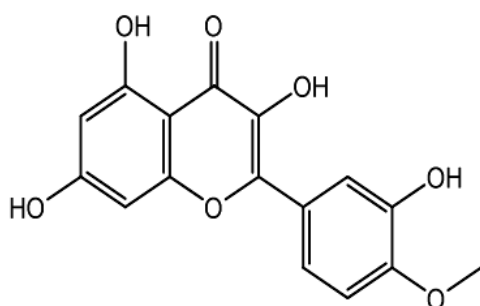


Fig. 6. Structure of the isolated compound from *Ipomoea marginata* (Tamarixetin)

Table 5. Physicochemical characteristics of active substances & compliance with principles of drug-likeness

Compound	MW	logp	Alogp	HBA	HBD	TPSA	AMR	nRB
Ferulic acid	184	0.78	0.267	4	0	26.3	55.45	3
Vanillic acid	160	0.51	-0.09	4	0	26.3	45.2	2
Gentisic acid	148	0.62	-0.16	4	0	17.07	40.17	1
Proanthocyanidins	567.9	1.5	-2.07	13	0	27.69	161.2	4
4-Hydroxybenzoic acid	132	0.27	0.405	3	0	17.07	38.56	1
Tamarixetin	304	1.73	-1.18	7	0	35.53	88.48	2

acid, gentisic acid, and tamarixetin. Tamarixetin had a higher antipyretic activity rate of 0.735 Pa. The docking studies indicate that tamarixetin is the powerful compound of these seven compounds, although more *in vivo* studies had also studied its mechanism. The findings are also compatible with the literature as tamarixetin had antipyretic properties in a previous study.⁴²

With respect to the COX-I enzyme, the least binding capacity of proanthocyanidins -8.4 Kcal/mol and found to make 3 hydrogen bonds, i.e.

PHE A:210, ASN A:382, HIS A:386, TRP A:387; the development of hydrophobic associations requires two amino acids VAL A:447, HIS A:388. Tamarixetin established hydrogen bonding with ALA A:199, TYR A:385, ASN A:382 hydrophobic interactions with PHE A:210, HIS A:386 and electrostatic interactions with MET A:391.

In the enzyme pocket of COX-II, tamarixetin was better observed to be stabilised by the presence of a hydrogen bond with SER A: 353 and hydrophobic interactions with TYR

Table 6. PASS analysis of different compounds from *Ipomoea marginata*

Compound	Antiviral (Picornavirus)		Antiviral (Influenza)		Antiviral (Adenovirus)		Antiviral (Rhinovirus)		Antiviral (CMV)		Antiviral (Herpes)	
	P _a	P _i	P _a	P _i	P _a	P _i	P _a	P _i	P _a	P _i	P _a	P _i
Ferulic acid	0.62	0.02	0.58	0.01	0.54	0	0.54	0	0.37	0.01	0.38	0.04
Vanillic acid	0.5	0.05	0.56	0.02	0.45	0.01	0.46	0.04	0.33	0.02	0.36	0.06
Gentisic acid	0.63	0.01	0.53	0.04	0.47	0.01	0.41	0.08	0.36	0.01	0.35	0.06
Proanthocyanidins	-	-	0.44	0.04	-	-	0.55	0.01	-	-	0.44	0.02
4-Hydroxy benzoic acid	0.62	0.02	0.58	0.01	0.54	0	0.49	0.03	0.37	0.01	0.38	0.04
Tamarixetin	-	-	0.37	0.06	-	-	-	-	-	-	0.47	0.01

Table 7. ADMET Properties of different compounds from *Ipomoea marginata*

Compound	HIA	BBB	AMES Toxicity	Carcinogenicity	LD ₅₀ in rat (mol/kg)
Ferulic acid	0.9614	0.5305	Non-toxic	Non-carcinogenic	1.4314
Vanillic acid	0.9231	0.5146	Non-toxic	Non-carcinogenic	1.8710
Gentisic acid	0.9223	0.6660	Non-toxic	Non-carcinogenic	2.1788
Proanthocyanidins	0.6772	0.5112	Non-toxic	Non-carcinogenic	2.2049
4-Hydroxybenzoic acid	0.9872	0.5320	Non-toxic	Non-carcinogenic	1.3983
Tamarixetin	0.9783	0.6382	Non-toxic	Non-carcinogenic	2.7192
Paracetamol	0.9544	0.9921	Non-toxic	Non-carcinogenic	1.8596

Table 8. Antipyretic activity of extract & fractions of *Ipomoea marginata* by Brewer's yeast-induced pyrexia method

Groups	Initial rectal Temperature before yeast injection (°C)	Rectal temperature at yeast injection & after the administration of sample (°C)				
		0 hr	1st hour	2nd hour	3rd hour	4th hour
Control	37.47±0.15	38.02±0.67	38.12±0.21	38.04±0.09	38±0.10	38.04±0.12
Paracetamol	37.07±0.32	38.18±0.17	37.87±0.37 ^s	37.43±0.13 ^s	37.24±0.09 ^s	36.94±0.14 ^s
Tamarixetin (20 mg/kg)	37.23±0.56	38.11±0.22	37.95±0.36 ^s	37.73±0.11 ^s	37.54±0.12 ^s	37.26±0.41 ^s
MEIP (200 mg/kg)	37.42±0.11	38.06±0.18	38.05±0.15 [*]	37.8±0.12 [*]	37.72±0.67 [*]	37.61±0.18 [*]
MEIP (400 mg/kg)	37.79±0.32	37.78±0.63	37.51±0.62	37.28±0.06 ^s	37.15±0.17 ^s	37.1±0.20 ^s
PEFIP (200 mg/kg)	37.56±0.18	38.28±0.42	38.23±0.41	37.91±0.23 [*]	37.78±0.12 [*]	37.75±0.89 [*]
PEFIP (400 mg/kg)	37.18±0.26	38.26±0.52	37.64±0.11	37.37±0.20 [%]	37.26±0.67 [%]	37.25±0.19 [%]
CFIM (200 mg/kg)	37.21±0.52	37.91±0.47	37.88±0.26 [%]	37.47±0.09 [%]	37.37±0.12 [*]	37.21±0.67 [*]
CFIM (400 mg/kg)	37.1±0.25	38.05±0.13	37.6±0.15 ^s	37.22±0.05 ^s	37.08±0.20 ^s	36.97±0.33 ^s

Values are expressed as mean±SEM or percentage (n = 5). The data were analyzed by one-way ANOVA followed by Dunnett's test. *p < 0.05, %, p < .01, and ^s, p < .001 compared with control.

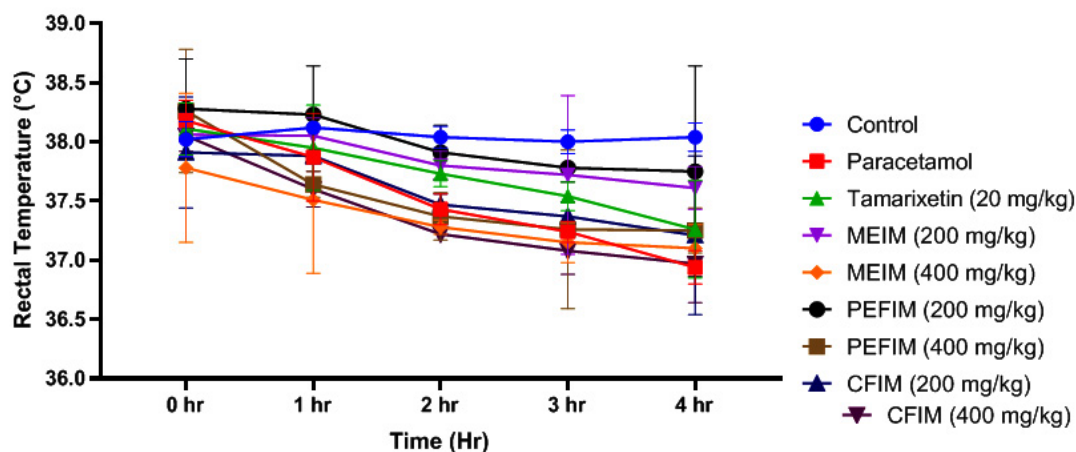


Fig. 7. Comparison between antipyretic effects of methanol extract of *Ipomoea marginata* with its fractions at dose level of 200 & 400 mgkg⁻¹ body weight on Brewer's yeast-induced pyrexia in rats

A:385, VAL A:344, TYR A:348, VAL A:349, LEU A:352, VAL A:523 with a docking score -9.5 Kcal/mol. Proanthocyanidins also attaches to the COX-II enzyme pocket by establishing a sequence of H-bonds with GLN A:289, THR A:212, GLN A:454, residues and hydrophobic interactions with VAL A:291, HIS A:214, HIS A:386, LEU A:294 (docking score: -7.4 Kcal/mol).

In the enzyme pocket of microsomal prostaglandin E synthase 1, tamarixetin was better observed to be stabilised by the presence of five hydrogen bonds with ARG A:38, ALAA:43, ARG A:60, CYS A:59, ARG A:67 and hydrophobic interactions with ILE A:33, VAL A:37, ARG A:38 with docking score of -7.8 Kcal/mol; followed by Proanthocyanidins with docking source of -7.6 Kcal/mol.

In all the *in silico* studies, two compounds had the least dock score against 3N8V, 5KIR, 3DWW i.e., tamarixetin and proanthocyanidins. Among these two compounds, tamarixetin had good HIA and BBB and as per PASS analysis also, Tamarixetin had good predictive antipyretic activity.⁴³

Lipinski's rule of 5 is a widely accepted guideline for evaluating drug-likeness, as it highlights key molecular features that influence pharmacokinetic processes such as ADME.⁴⁴ Although the three top-ranked compounds did not fully comply with Lipinski's criteria—mainly

due to deviations in hydrogen bond donors and acceptors associated with their natural origin—ADME profiling of seven selected compounds confirmed that all passed the screening parameters (Table 7). This initial *in-silico* evaluation provides a rapid approach for identifying potential candidates for antipyretic therapy.

CONCLUSION

It can be inferred beyond any uncertainty that tamarixetin has beneficial structural features that effectively associate and inhibit COX-I, COX-II and mPGES-1, based on the strongly supportive binding energy values obtained in our research into *In Silico* and *in vivo*. This suggests that tamarixetin is a safe antipyretic and a promising future lead compound for safe antipyretic medicines.

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Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not applicable

Author Contributions

Haritha Potluri: Conceptualization, Methodology, Writing – Original Draft; Lakshmana Rao Atmakuri: Data Collection, Analysis; Usha Rani Nannapaneni: Project Administration, Writing – Review & Editing; Chakrapani Challari: Funding Acquisition, Resources; Abdul Mathin Shaik: Supervision, Data Interpretation; Venkata Hari Prasad Potluri: Visualization, Final Draft Approval.

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