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STITCH, Physicochemical, ADMET, and In Silico Analysis of Selected *Mikania* Constituents as Anti-Inflammatory Agents

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Abstract: The *Mikania* genus has been known to possess numerous pharmacological activities. In the present study, we aimed to evaluate the interaction of 26 selected constituents of *Mikania* species with (i) cyclooxygenase 2 (COX 2), (ii) human neutrophil elastase (HNE), (iii) lipoxygenase (LOX), matrix metalloproteinase ((iv) MMP 2 and (v) MMP 9), and (vi) microsomal prostaglandin E synthase 2 (mPGES 2) inhibitors using an in silico approach. The 26 selected constituents of *Mikania* species, namely mikamicranolide, kaurenoic acid, stigmasterol, grandifloric acid, kaurenol, spathulenol, caryophyllene oxide, syringaldehyde, dihydrocoumarin, o-coumaric acid, taraxerol, melilotoside, patuletin, methyl-3,5-di-*O*-caffeoyl quinate, 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone, psoralen, curcumene, herniarin, 2,6-dimethoxy quinone, bicyclogermacrene, α-bisabolol, γ-elemene, provincialin, dehydrocostus lactone, mikanin-3-*O*-sulfate, and nepetin, were assessed based on the docking action with COX 2, HNE, LOX, MMP 2, MMP 9, and mPGES 2 using Discovery Studio (in the case of LOX, the Autodock method was utilized). Moreover, STITCH (Search Tool for Interacting Chemicals), physicochemical, drug-likeness, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analyses were conducted utilizing the STITCH web server, the Mol-inspiration web server, and Discovery Studio, respectively. In the present study, STITCH analysis revealed only six ligands (dihydrocoumarin, patuletin, kaurenol, psoralen, curcumene, and nepetin) that showed interactions with human proteins. Physicochemical analysis showed that seventeen ligands complied well with Lipinski's rule. ADMET analysis showed eleven ligands to possess hepatotoxic effects. Significantly, the binding free energy estimation displayed that the ligand methyl-3, 5-di-*O*-caffeoyl quinate revealed the highest binding energy for all the target enzymes, excluding LOX, suggesting that this may have efficacy as a non-steroidal anti-inflammatory drug (NSAID). The current study presents a better understanding of how *Mikania* is used as a traditional medicinal plant. Specifically, the 26 ligands of the *Mikania* plant are potential inhibitor against COX 2, HNE, LOX, MMP 2, MMP 9, and mPGES 2 for treatments for acute and/or chronic inflammatory diseases.

Keywords: STITCH; ADMET; docking; *Mikania*; methyl-3,5-di-*O*-caffeoyl quinate; cyclooxygenase; human neutrophil elastase; lipoxygenase

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1. Introduction

The *Mikania* genus belongs to the Asteraceae (Daisy) family and it is reported to have around 450 subspecies in the Central America and Asia–Pacific regions [1]. Traditionally, the decoction of *M. micrantha* leaves has been used indigenously to treat tumors by the

ethnic people of Assam, India [2,3]. Moreover, the Mizoram tribes in India have traditionally used *M. micrantha* juice to treat cuts and open wounds [4]. *M. cordata* has been used indigenously in Bangladesh to treat various ailments, such as bronchitis, cough, diabetes, fever, influenza, jaundice, muscle spasms, septic sores, and snake bites [5]. Da Silva et al. [6] have reviewed the pharmacological properties of the *Mikania* genus and reported that it possesses antibacterial, antidiarrheal, antifungal, anti-inflammatory, antinociceptive, antiophidian, antiparasitic, antiprotozoal, antispasmodic, antiulcerogenic, antiviral, bronchodilating, cytotoxic, mutagenic, and vasodilating properties. Recently, Radhakrishnan et al. [7] have reported the mosquitocidal activity of *M. scandens*.

Our research team identified 26 ligands of the phytoconstituents of *Mikania* species during the development of mosquito repellents [7]. The present study focuses on *Mikania* species to demonstrate the relationships among their pharmacological actions and the phytochemicals. Recently, species of *Mikania* have attracted the interest of researchers due to their numerous pharmacological actions [6]. In this work, therefore, we conducted a docking study with the phytoconstituents of *Mikania* species, viz., mikamicranolide (sesquiterpene dilactone), kaurenoic acid (diterpenoid), stigmasterol (phytosterol), grandifloric acid (diterpenoid), kaurenol (diterpenoid), spathulenol (sesquiterpenoid), caryophyllene oxide (sesquiterpenoid oxide), syringaldehyde (hydroxybenzaldehyde), dihydrocoumarin (benzopyrone), o-coumaric acid (hydroxycinnamic acid), taraxerol (triterpenoid), melilotoside (phenylpropanoid), patuletin (flavonol), methyl-3,5-di-*O*-caffeoyl quinate (cyclitol derivative), 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone (flavonol), psoralen (furanocoumarin), curcumene (sesquiterpenoid), herniarin (coumarin), 2,6-dimethoxyquinone (quinone derivative), bicyclogermacrene (sesquiterpenoid), α-bisabolol (monocyclic sesquiterpene), γ-elemene (triterpenoid), provincialin (sesquiterpene lactone), dehydrocostus lactone (sesquiterpene lactone), mikanin-3-*O*-sulfate (flavonoid sulfate), and nepetin (flavonoid). The above-mentioned phytoconstituents of *Mikania* species were investigated for docking with (i) cyclooxygenase 2 (COX 2), (ii) human neutrophil elastase (HNE), (iii) lipoxygenase (LOX), matrix metalloproteinase ((iv) MMP 2 and (v) MMP 9), and (vi) microsomal prostaglandin E synthase 2 (mPGES 2), with an examination of the enzymes' apparent binding sites using Discovery Studio (in the case of LOX, the Autodock method was applied). Furthermore, STITCH (Search Tool for Interacting Chemicals), physicochemical, drug-likeness, and ADMET analyses were conducted utilizing the STITCH web server, the Mol-inspiration web server, and Discovery Studio, respectively.

2. Results and Discussion

Computational approaches have been emerging as a new tool for evaluating the therapeutic potential of medicinal plants. In particular, molecular docking is used to select protein (enzymes/biomarkers) targets of interest and to identify the docking behavior of particular phytoconstituents on these targets [8]. Computational approaches have great potential for drug repositioning, target identification, ligand profiling, and receptor deorphanization [9].

Da Silva et al. [6] have demonstrated the anti-inflammatory activity of the *Mikania* genus and they further reported that *Mikania scandens* (leaf extract) possesses stronger anti-inflammatory activity than *M. scandens* (stem extract). Suyenaga et al. [10] have shown the anti-inflammatory activity of *Mikania laevigata* (leaf decoction) under an in vivo (animal model) approach. Perez-Amador et al. [11] have described the anti-inflammatory activity of *Mikania micrantha* ethyl acetate (EA) extract in a TPA (12-O-tetradecanoylphorbol-13-acetate)-induced animal model in an in vivo experiment. Della Pasqua et al. [12] have demonstrated that *M. laevigata* (leaf aqueous extract) possesses superior anti-inflammatory activity compared to *M. glomerata* (leaf aqueous extract). Thus, the above-summarized anti-inflammatory studies were evaluated to perform the present study.

The search tool for interacting chemicals (STITCH) free web server provides comprehensive particulars regarding: (i) metabolic pathways of interactions, (ii) crystal structure information, (iii) binding investigations, and (iv) target–drug correlations [13]. In the present

study, the STITCH analysis revealed that only six ligands, namely (a) dihydrocoumarin, (b) patuletin, (c) kaurenol, (d) psoralen, (e) curcumene, and (f) nepetin (eupafolin), showed interactions with human proteins (Figure 1). Interestingly, patuletin interacted with the human lipooxygenase (LOX, inflammatory) protein, as presented in Figure 1b.

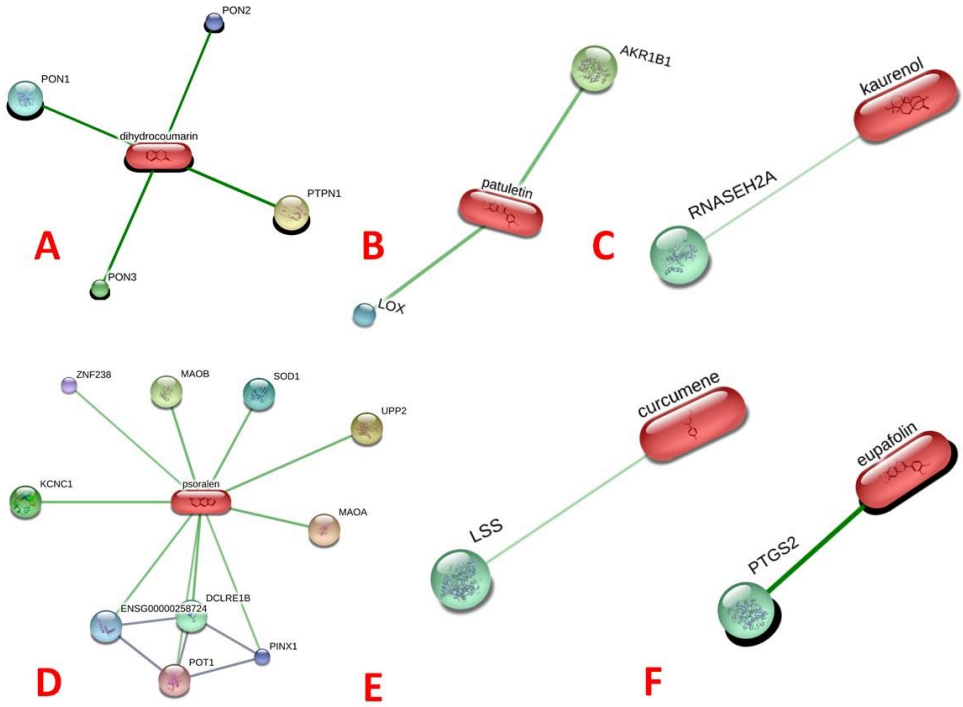

Figure 1. Representation of the protein network analysis (selected ligands of *Mikania* with human enzymes). (**A**) Dihydrocoumarin, (**B**) patuletin, (**C**) kaurenol, (**D**) psoralen, (**E**) curcumene, and (**F**) nepetin (eupafolin).

Prior to the docking experiments, it is vital to understand the (i) physicochemical, (ii) drug- likeness/bioactivity score, (iii) ADME, and finally, (iv) the toxicity of the 26 chosen phytoconstituents of the *Mikania* species. These analyses have been shown to help in the computer-aided drug development (CADD) process [14]. Regarding the physicochemical properties, six ligands (stigmasterol, taraxerol, curcumene, bicyclogermacrene, γ-elemene, and provincialin) showed one violation, while only one ligand (3,5-methyl-di-O-caffeoyl quinate) displayed three violations for the rule of five (Table 1). Similarly, with reference to supporting the drug-likeness or the score of the bioactivity analysis, only one ligand (mikamicranolide) revealed a bioactivity score of >0 towards the six descriptors; on the other hand, the other ligands showed a bioactivity score range of active to moderate. Moreover, the other 26 selected ligands showed an inactive score (<−5.0) (Table 2).

Table 1. The physicochemical analysis of 26 (*Mikania*) ligands using the Mol-inspiration free web server.

Ligand	Log A ◊	Natoms ■	MW ■	noN ●●	nOH NH ◊◊	Nviolations *	Nrotb **
Mikamicranolide	−2.14	22	308.3	7	1	0	0
Kaurenoic acid	4.67	22	302.5	2	1	0	1
Stigmasterol	7.87	30	412.7	1	1	1	5
Grandifloric acid	3.75	23	318.5	3	2	0	1
Kaurenol	4.79	21	288.5	1	1	0	1
Spathulenol	3.91	16	220.4	1	1	0	0
Caryophyllene oxide	4.14	16	220.4	1	0	0	0
Syringaldehyde	1.08	13	182.2	4	1	0	3
Dihydrocoumarin	1.79	11	148.2	2	0	0	0

Table 1. *Cont.*

Ligand	Log A ◊	Natoms ■	MW ■	noN ••	nOH NH ◊◊	Nviolations *	Nrotb **
o-Coumaric acid	1.67	12	164.2	3	2	0	2
Taraxerol	8.02	31	426.7	1	1	1	0
Melilotoside	−0.58	23	326.3	8	5	0	5
Patuletin	1.70	24	332.3	8	5	0	2
Methyl-3,5-di-*O*-caffeoyl quinate	2.04	38	530.5	12	6	3	10
3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone	2.31	26	360.3	8	3	0	4
Psoralen	2.29	14	186.2	3	0	0	0
Curcumene	5.82	15	202.3	0	0	1	4
Herniarin	2.05	13	176.2	3	0	0	1
2,6-Dimethoxyquinone	0.53	12	168.2	4	0	0	2
Bicyclogermacrene	5.29	15	204.4	0	0	1	0
α-Bisabolol	4.68	16	222.4	1	1	0	4
γ-Elemene	5.42	15	204.4	0	0	1	2
Provincialin	1.91	37	518.6	10	2	1	11
Dehydrocostus lactone	2.29	17	230.3	2	0	0	0
Mikanin-3-*O*-sulfate	0.36	29	424.4	10	2	0	6
Nepetin	1.99	23	316.3	7	4	0	2

Note: ◊-Octanol–Water (O/W) partition coefficient; ■-molecular weight; ■-number of non-hydrogen atoms; ◊◊- number of hydrogen bond donors [OH and NH groups]; •• number of hydrogen bond acceptors [O and N atoms]; *- no. of rule of five violations, and ** no. of rotatable bonds (Nrotb).

Table 2. The drug-likeness or bioactivity analysis of 26 (*Mikania*) ligands utilized the Mol-inspiration free web server.

Ligand	GPCR ■ Ligand	Ion-Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Mikamicranolide	0.28	0.03	0.01	0.66	0.07	0.56
Kaurenoic acid	0.29	0.15	−0.39	0.75	0.06	0.46
Stigmasterol	0.12	−0.08	−0.49	0.74	−0.02	0.53
Grandifloric acid	0.21	0.12	−0.47	0.78	0.10	0.43
Kaurenol	0.21	0.10	−0.21	0.67	−0.02	0.44
Spathulenol	−0.42	−0.28	−0.68	0.28	−0.36	0.05
Caryophyllene oxide	−0.08	0.14	−0.86	0.62	0.00	0.57
Syringaldehyde	−0.95	−0.36	−0.80	−0.69	−1.27	−0.39
Dihydrocoumarin	−0.90	−0.48	−1.25	−0.75	−1.13	−0.47
o-Coumaric acid	−0.64	−0.37	−0.98	−0.25	−0.90	−0.21
Taraxerol	0.21	0.02	−0.20	0.54	0.00	0.49
Melilotoside	0.17	−0.03	−0.13	0.27	0.04	0.40
Patuletin	−0.14	−0.34	0.22	0.13	−0.35	0.17
3,5-Methyl-di-*O*-caffeoyl quinate	0.11	−0.07	−0.06	0.34	0.07	0.25
3,3′,5-Trihydroxy−4′,6,7-trimethoxyflavone	−0.14	−0.33	0.20	0.09	−0.34	0.14
Psoralen	−0.89	−0.38	−1.11	−1.13	−1.19	−0.37
Curcumene	−0.47	−0.12	−0.80	−0.24	−0.72	−0.14
Herniarin	−1.23	−0.84	−1.28	−1.06	−1.28	−0.47
2,6-Dimethoxyquinone	−1.48	−0.69	−0.78	−1.50	−1.36	−0.42
Bicyclogermacrene	−0.75	−0.69	−1.11	−0.65	−0.88	−0.16
α-Bisabolol	−0.06	0.26	−0.78	0.37	−0.38	0.43
γ-Elemene	−0.46	0.02	−1.01	0.51	−0.71	0.24
Provincialin	0.32	0.23	−0.15	0.95	0.07	0.82
Dehydrocostus lactone	−0.04	−0.02	−0.56	1.00	−0.22	0.66
Mikanin-3-*O*-sulfate	0.08	−0.30	0.02	0.01	0.06	0.45
Nepetin	−0.08	−0.23	0.22	0.17	−0.31	0.16

Note: ■- G Protein-coupled receptors (GPCR).

Before docking, it is vital to know a compound's/ligand's properties, such as (i) physicochemical, (ii) drug-likeness or score of bioactivity, and (iii) ADMET, along with its (iv) toxicity. Moreover, standardized rule (Lipinski's rule of five) and ADMET are available for determining such properties [15]. Concerning ADMET analysis, eleven ligands (mikamicranolide, spathulenol, caryophyllene oxide, patuletin, 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone, psoralen, herniarin, 2,6-dimethoxyquinone, dehydrocostus lactone, mikanin-3-*O*-sulfate, and nepetin) have hepatotoxic properties, as displayed in Table 3.

Table 3. ADMET analysis of 26 (*Mikania*) ligands using Discovery Studio.

Ligand	HIA ◊	AS ■	BBB [a]	PPB **	CYP2D6 ◊◊	HT [b]
	L *	L **	L ***	Predication		
Mikamicranolide	0	4	3	F	F	T
Kaurenoic acid	0	2	0	T	F	F
Stigmasterol	3	1	4	T	F	F
Grandifloric acid	0	2	1	T	F	F
Kaurenol	0	2	0	T	F	F
Spathulenol	0	3	1	T	F	T
Caryophyllene oxide	0	2	0	T	F	T
Syringaldehyde	0	4	3	T	F	F
Dihydrocoumarin	0	3	1	T	F	F
o-Coumaric acid	0	4	3	F	F	F
Taraxerol	3#	0	4	T	F	F
Melilotoside	1#	4	4	F	F	F
Patuletin	1	3	4	F	F	T
3,5-Methyl-di-*O*-caffeoyl quinate	3#	3	4	F	F	F
3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone	0	3	4	T	F	T
Psoralen	0	3	2	F	F	T
Curcumene	1	2	0	T	F	F
Herniarin	0	3	2	T	F	T
2,6-Dimethoxyquinone	0	4	3	F	F	T
Bicyclogermacrene	1	2	0	T	F	F
α-Bisabolol	0	2	0	T	F	F
γ-Elemene	1	2	0	T	F	F
Provincialin	2	3	4	F	F	F
Dehydrocostus lactone	0	2	1	T	F	T
Mikanin-3-*O*-sulfate	1	3	4	T	F	T
Nepetin	0	3	4	T	T	T

Note: (■-AS—Aqueous solubility; ◊-HIA—Human intestinal absorption; ** PPB—Plasma protein binding; [a]-BBB—Blood–brain barrier; [b] HT—Hepatotoxicity; ◊◊ CYP2D6—Cytochrome P450 2D6; T—True, F—False, and L—Level). * [0—Strong. 1—Medium. 2—Weak, and 3—Very weak]; ** [0—Extremely weak, 1—Very weak, 2—Weak, 3—Strong, 4—Optimal, 5—Soluble, and 6—Warning]; *** [0—Very strong penetration, 1—Strong, 2—Moderate, 3—Low, and 4—Undefined].

Regarding the toxicological screening of 26 ligands, as illustrated in Table 4, 5 ligands (dihydrocoumarin, patuletin, 3,3′,5-trihydroxy-4′,6, 7-trimethoxyflavone, 3-*O*-mikanin-sulfate along with nepetin) are non-degradable in terms of aerobic biodegradability nature. Two ligands (patuletin and 3, 3′, 5-trihydroxy-4′, 6, 7-trimethoxyflavone) are predicated as mutagens.

The C-docking study and free energy binding analysis (Table 5) showed that 3,5-methyl-di-O-caffeoyl quinate possesses the maximum energy interaction (−42.51 kcal/mol) with the COX 2 enzyme (as presented in Figure 2a). In contrast, psoralen revealed the least interaction energy (−15.57 kcal/mol). Moreover, eight ligands (grandifloric acid, kaurenol, o-coumaric acid, melilotoside, patuletin, 3,5-methyl-di-*O*-caffeoylquinate, mikanin-3-*O*-sulfate, and nepetin) showed interaction with the Glu539 residues of the COX 2 enzyme, as displayed in Table 5. The present results were in good conformity with our previous findings where 4-hydroxyisoleucine (4-HIL) and phytic acid (PA) showed interaction with

(i) Glu539; (ii) Glu350; (iii) Asn546; and (iv) Trp531 amino acid (AA) residues of the COX 2 enzyme [16].

Table 4. The toxicological screening of 26 (*Mikania*) ligands using Discovery Studio.

Ligands	AB ■	AM ◊	OI •	SI ◊◊	Oral Toxicity *
Mikamicranolide	D	NM	I	I	1.02
Kaurenoic acid	D	NM	I	I	1.53
Stigmasterol	D	NM	I	I	1.18
Grandifloric acid	D	NM	I	I	1.44
Kaurenol	D	NM	I	I	1.85
Spathulenol	D	NM	I	I	0.75
Caryophyllene oxide	D	NM	I	I	1.13
Syringaldehyde	D	NM	I	I	1.26
Dihydrocoumarin	ND	NM	I	I	0.74
o-Coumaric acid	D	NM	I	NI	1.59
Taraxerol	D	NM	I	I	0.93
Melilotoside	D	NM	I	NI	1.32
Patuletin	ND	M	I	NI	1.08
Methyl-3,5-di-*O*-caffeoyl quinate	D	NM	I	NI	2.37
3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone	ND	M	I	NI	0.93
Psoralen	D	NM	I	I	0.30
Curcumene	D	NM	NI	I	2.47
Herniarin	D	NM	NI	I	0.68
2,6-Dimethoxyquinone	D	NM	I	I	0.63
Bicyclogermacrene	D	NM	I	I	0.48
α-Bisabolol	D	NM	I	I	1.65
γ-Elemene	D	NM	I	I	2.00
Provincialin	D	NM	I	I	3.11
Dehydrocostus lactone	D	NM	I	I	1.45
Mikanin-3-*O*-sulfate	ND	NM	I	NI	NA **
Nepetin	ND	NM	I	NI	0.68

Note: (AM ◊—Ames mutagenicity, AB ■—Aerobic biodegradability, SI ◊◊—Skin irritancy, I •—Ocular irritancy, and Oral toxicity *—Oral toxicity in rat [LD_{50} in g/Kg]; D—Degradable, ND—Non-degradable, M—Mutagen, NM—Non-mutagen, I—Irritant, NI—Non-irritant, and NA **—Not analyzed).

Stigmasterol has been described to inhibit thromboxane B_2 (TXB_2) production, which afterwards leads to inhibition of cyclooxygenase 1 (COX 1) activity [17]. However, no reports are available for stigmasterol's cyclooxygenase 2 (COX 2) inhibition activity. Additionally, caryophyllene has been reported to exhibit cyclooxygenase-2 (COX-2) inhibition activity in THP-1 (human monocytic) cells [18]. Psoralen, spathulenol, syringaldehyde, and taraxerol acetate have been found to exhibit cyclooxygenase-2 (COX-2) inhibition activity [19–23]. All the above findings were in agreement with our results on cyclooxygenase 2 (COX 2) inhibition activity.

The HNE is an additional targeted enzyme whose docking analysis and free energy binding analysis showed that 3,5-methyl-di-*O*-caffeoyl quinate displayed the maximum energy of interactions (−54.66 kcal/mol), as presented in Figure 2b. Thirteen ligands (kaurenol, syringaldehyde, o-coumaric acid, melilotoside, patuletin, 3,5-methyl-di-O-caffeoyl quinate, trihydroxy-3,3′,5-trimethoxy-4′,6,7-flavone, psoralen, herniarin, 2,6-dimethoxyquinone, provincialin, mikanin-3-*O*-sulfate, and nepetin) exhibited interaction with Ser195 amino acid residue of HNE, as shown in Table 6. The present finding was in good agreement with our previous study, where phytic acid (PA) and 4-hydroxyisoleucine (4-HIL) demonstrated interaction with (i) Ser195; (ii) Arg147; (iii) Cys191; (iv) Phe192; (v) Gly193; (vi) Asp194; and (vii) Ser214 amino acid (AA) residues of the HNE enzyme [16].

Five sesquiterpene lactones, namely (15- (3′-Hydroxy)-methacryloyloxy-micrantholide, isobutyryloxy-15-(2′,3′-Epoxy) -micrantholide, isobutyryloxy-15-(2′-Hydroxy)-micrantholide, 4α hydroxy-1β-Acetoxy-15- eudesma-isobutyryloxy-12-8β-olide11-13-en from *M. cordifolia*, and Scandenolide from *M. micrantha* have been reported to exhibit human neutrophil

elastase (HNE) inhibition activity [24]. Similarly, *p*-coumaric acid and di-*O*-caffeoyl-3,5-quinic acid, two phytochemicals, were described as possessing human neutrophil elastase (HNE) inhibition activity [25]. Both reports were in close agreement with the present findings on the human neutrophil elastase (HNE) inhibition activity.

Table 5. Energy interaction analysis of twenty-six (*Mikania*) ligands along with cyclooxygenase 2 (COX 2) utilizing Discovery Studio.

Ligands	c-Docker Energy Interaction (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	22.37	Asn546	1.1
Kaurenoic acid	F *	-	-
Stigmasterol	34.51	Lys346	2.5
		Asp348	1.2
Grandifloric acid	24.17	Glu539	0.91
		Asn546	1.5 and 1.7
Kaurenol	21.75	Glu539	0.55
Spathulenol	18.08	No interaction	-
Caryophyllene oxide	17.20	No interaction	-
Syringaldehyde	21.57	Asn546	1.5
Dihydrocoumarin	16.97	No interaction	-
o-Coumaric acid	18.23	Glu539	2.0
		Asn546	1.5
		Lys543 ♦	6.5
Taraxerol	29.03	Glu350	0.96
		Lys346	2.2
		Asp348	1.9
Melilotoside	32.06	Glu539	1.7
		Asn546	1.7
		Lys328 ♦	6.3
		Asp348	0.53
Patuletin	28.65	Glu350	2.2
		Trp531	1.4
		Glu539	2.3
		Lys346	2.4
		Asp348	0.96
Methyl-3,5-di-*O*-caffeoyl quinate	42.51	Glu350	1.8
		Glu539	2.4
		Asn546	2.2 and 2.3
3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone	28.20	Asn546	2.4
Psoralen	15.57	Asn546	0.8 and 2.2
		Lys543 ♦	5.1 and 5.8
Curcumene	19.47	No interaction	-
Herniarin	17.10	Asn546	2.4
2,6-Dimethoxyquinone	18.20	Asn546	1.3
Bicyclogermacrene	17.12	No interaction	-
α-Bisabolol	23.26	Asn546	2.2
γ-Elemene	17.41	No interaction	-
Provincialin	37.74	Lys346	1.8
Dehydrocostus lactone	19.95	No interaction	-
Mikanin-3-*O*-sulfate	29.99	Glu539	2.1
		Asn546	2.2 and 2.5
		Lys328 ♦	6.6
		Asp348	0.31
Nepetin	32.50	Glu350	2.2
		Trp531	1.7
		Glu539	2.1

Note: [F *—Failed to dock; ♦—+-π interaction].

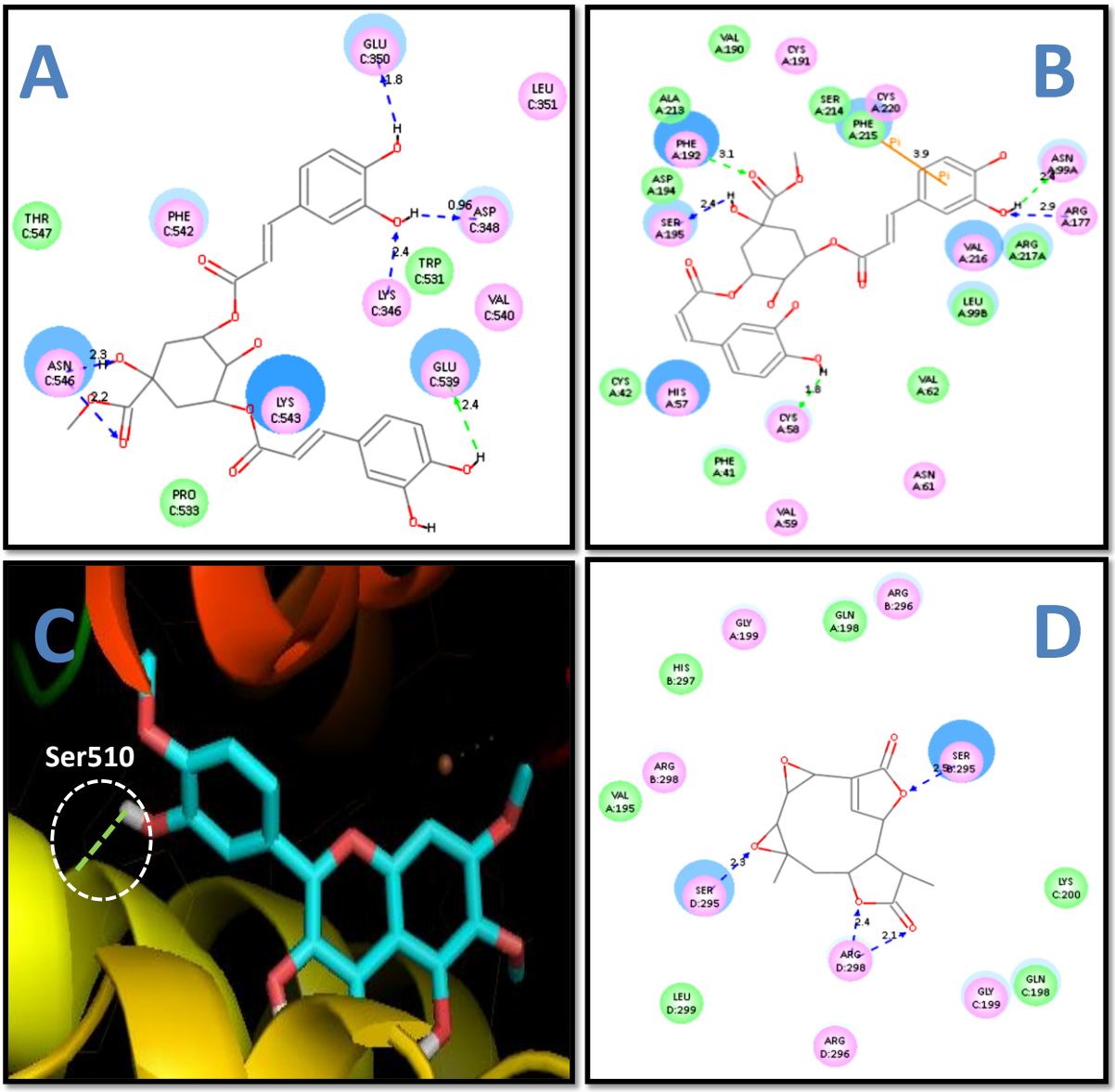

Figure 2. The two-dimensional (2D) structure of methyl-3,5-di-*O*-caffeoyl quinate with (**A**) COX 2 and (**B**) HNE; hydrogen atoms have been excluded in two-dimensional (2D) images for good explanation and bond distances are expressed in (Å) angstroms; (**C**) three-dimensional (3D) structure of 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone with LOX (docked using Autodock and analyzed using pyMOL method) and (**D**) two-dimensional (2D) structure of provincialin with mPGES 2.

The docking study and free binding energy analysis showed that 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone (Figure 2c) had the least binding energy (−9.71 kcal/mol) (Table 7). Moreover, five ligands (mikamicranolide, syringaldehyde, patuletin, 2,6-dimethoxyquinone, and mikanin-3-*O*-sulfate) exhibited interactions with the His518 amino acid residue of LOX. The current finding was in good accord with our previous study, where the compound-3e (Geranylacetophenone derivative) showed interaction with His518 amino acid residue of the LOX enzyme [26]. Similarly, our earlier study also displayed that 4-hydroxyisoleucine (4-HIL) showed interaction with (i) Ser510; (ii) His513; and (iii) Gln716 amino acid (AA) residues of the LOX enzyme [16].

Table 6. Energy interaction analysis of 26 ligands (*Mikania*) along with HNE using Discovery Studio.

Ligands	Energy Interaction of c-Docker (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	31.32	No interaction	-
Kaurenoic acid	F *	-	-
Stigmasterol	34.31	No interaction	-
Grandifloric acid	26.95	Gly219	2.8
Kaurenol	28.05	Ser195	2.3
Spathulenol	23.55	No interaction	-
Caryophyllene oxide	23.54	No interaction	-
Syringaldehyde	30.11	Cys191	1.8
		Gly193	2.6
		Asp194	2.8
		Ser195	2.8
		Val216	3.1
Dihydrocoumarin	20.95	Arg147	2.2
		Phe192	2.8
o-Coumaric acid	22.74	Cys191	2.0
		Gly193	2.8
		Asp194	3.1
		Ser195	1.9, 2.6 and 2.9
		Ser214	2.1
Taraxerol	28.96	No interaction	-
Melilotoside	37.79	Arg147	2.4
		Phe192	1.9 and 2.9
		Gly193	3.0
		Ser195	3.1
		Gly219	2.5
Patuletin	35.32	Cys191	2.0
		Gly193	2.8
		Asp194	3.1
		Ser195	2.8
		Ser214	2.1
		Gly218	3.0
		Gly219	2.8
3,5-Methyl-di-O-caffeoyl quinate	54.66	Cys58	1.8
		Asn99A	2.4
		Arg177	2.9
		Phe192	3.1
		Ser195	2.4
		Phe215◊	3.9
4′,6,7-trimethoxy-3,3′,5-Trihydroxyflavone	34.66	Gly193	3.0
		Ser195	3.1 and 3.1
		Gly219	2.9
Psoralen	19.74	Phe192	3.2
		Ser195	2.1
Curcumene	24.66	No interaction	-
Herniarin	24.89	Arg147	2.9
		Phe192	2.8
		Ser195	2.1
2,6-Dimethoxyquinone	22.60	Gly193	2.7
		Ser195	2.9 and 3.0
Bicyclogermacrene	23.35	No interaction	-
α-Bisabolol	25.75	No interaction	-
γ-Elemene	18.53	No interaction	-
Provincialin	49.20	Gly193	2.9
		Ser195	2.7 and 3.1
		Gly219	2.6
		Val216	3.1
Dehydrocostus lactone	25.02	No interaction	-

Table 6. *Cont.*

Ligands	Energy Interaction of c-Docker (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikanin-3-*O*-sulfate	40.31	Cys191	1.8
		Phe192	2.6
		Gly193	3.0
		Ser195	2.8 and 3.1
		Ser214	3.2
		Val216	1.7 and 2.7
Nepetin	31.90	Cys191	2.1
		Gly193	2.9
		Ser195	3.0
		Gly218	2.8
		Gly219	2.6

Note: [F *—Failed to dock].

Table 7. Energy interaction analysis of twenty-six (*Mikania*) ligands along with LOX utilizing Autodock.

Ligands	Minimal Binding Energy (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	8.21	His518	2.2
		Trp519	3.2
Kaurenoic acid	6.50	His513	3.3
		Gln716	2.0 and 3.2
Stigmasterol	7.03	Ile557	2.6
Grandifloric acid	4.82	No interaction	-
Kaurenol	8.37	No interaction	-
Spathulenol	7.43	No interaction	-
Caryophyllene oxide	8.00	No interaction	-
Syringaldehyde	5.33	Gln514	2.0
		His518	2.7
Dihydrocoumarin	5.74	His523	3.6
		Ile557	3.2
o-Coumaric acid	4.44	Ser510	2.1
		Gln514	2.1
Taraxerol	+11.79	ND *	ND *
Melilotoside	6.79	Ser510	1.8 and 3.4
		Gln514	2.3
Patuletin	9.32	His513	1.9 and 3.4
		Gln514	2.7
		His518	3.2
		Arg726	2.1
3,5-Methyl-di-*O*-caffeoyl quinate	+30.23	ND *	ND *
4′,6,7-3,3′,5-Trihydroxy-trimethoxyflavone	9.71	Ser510	2.1
Psoralen	6.51	No interaction	-
Curcumene	7.73	No interaction	-
Herniarin	5.79	No interaction	-
2,6-Dimethoxyquinone	4.93	His518	3.1
Bicyclogermacrene	7.94	No interaction	-
α-Bisabolol	8.11	Gln716	1.9 and 3.2
γ-Elemene	7.54	No interaction	-
Provincialin	+46.86	ND *	ND *
Dehydrocostus lactone	8.26	His523	2.7
		Ser510	1.7
Mikanin-3-*O*-sulfate	4.88	His513	3.2
		Gln514	1.8 and 2.4
Nepetin	9.21	His518	3.5
		Arg726	2.1 and 3.4

Note: [+—Positive sign represents the (weak) binding energy, which may be due to an improper binding feature as demonstrated by Castro et al. [27]; ND *—Not determined].

Mikania micrantha (leaves and stems—ethyl acetate extract) [11], *Mikania lindleyana* (aerial parts of the plant—methanolic extract), and *Mikania cordata* (root—methanolic extract) have been described to have anti-inflammatory properties [28,29], whereas three

other *Mikania* species (*M. glomerata*, *M. hirsutissima*, and *M. laevigata*) have been reported to inhibit 5- lipoxygenase (5-LOX) activity in a dose-dependent manner [30,31]. Jyothi Lakshmi [32] reported the cyclooxygenase (COX), lipoxygenase (LOX), and nitric oxide synthase (iNOS) inhibition activities of *Mikania micrantha* (leaf and flower extract). Similarly, (i) 6,7-dihydroxy coumarin, (ii) β- caryophyllene, and (iii) β- caryophyllene oxide have been reported to inhibit 5- lipoxygenase (5-LOX) activity [33], whereas stigmasterol has been described to inhibit 15- lipoxygenase (15-LOX) activity [34]. Kaurenoic acid has been reported to have weak lipoxygenase (LOX) inhibition activity [35]. All the above-mentioned studies are in good correlation with the current results on lipoxygenase (LOX) inhibition activity.

The docking study and binding free energy analysis with MMP 2 showed that 3,5-methyl-di-*O*-caffeoylquinate possessed the maximum interaction energy (−83.34 kcal/mol), and five ligands (syringaldehyde, o-coumaric acid, 3,5-methyl-di-*O*-caffeoylquinate, 3-*O*-mikanin-sulfate, and nepetin) showed interaction with the MMP2 amino acid residue Glu-202 (Table 8). This observation was in agreement with previous findings, where 4-hydroxyisoleucine (4-HIL) has shown interaction with the (i) Glu202; (ii) Ala165; and (iii) His201 amino acid (AA) residues of the MMP 2 enzyme [16].

Table 8. Energy interaction analysis of twenty-six ligands of (*Mikania*) MMP 2 utilizing Discovery Studio.

Ligands	Minimal Binding Energy (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	F *	-	-
Kaurenoic acid	F *	-	-
Stigmasterol	F *	-	-
Grandifloric acid	F *	-	-
Kaurenol	F *	-	-
Spathulenol	F *	-	-
Caryophyllene oxide	F *	-	-
Syringaldehyde	33.92	Ala167	2.5
		Glu202	2.0
Dihydrocoumarin	31.67	No interaction	-
o-Coumaric acid	38.99	Glu202	1.7
Taraxerol	F *	-	-
Melilotoside	F *	-	-
Patuletin	47.85	Gly162	2.5
		Leu164	2.0
		Ala167	1.2 and 1.7
		Zn501 ♦	3.6
		His201 ◊	4.7
3,5-Methyl-di-*O*-caffeoylquinate	83.34	Glu202	1.3
		Glu210	1.9
		His166	2.0
4′,6,7-trimethoxyflavone-3,3′,5-Trihydroxy	48.36	Ala167	2.3
		Pro221	2.4
Psoralen	34.40	No interaction	-
Curcumene	34.54	Zn501 ♦	3.4
Herniarin	36.51	No interaction	-
2,6-Dimethoxyquinone	33.27	Leu164	2.0
		Ala165	1.6
Bicyclogermacrene	19.70	No interaction	-
α-Bisabolol	39.85	His201	2.5
γ-Elemene	F *	-	-
Provincialin	F *	-	-
Dehydrocostus lactone	F *	-	-
Mikanin-3-*O*-sulfate	52.36	Leu163 ■	2.2
		His166	2.3
		Ala167	1.7
		Glu202	1.9
		Pro221	1.8
Nepetin	46.27	Gly162	2.4
		Ala167	2.1
		Glu202	1.5

Note: [F *—Failed to dock; ♦ —+–π interaction; ◊— π–π interaction; ■—Sigma–π interaction].

Similarly, in the C-docking study and binding energy analysis with MMP 9, 3,5-methyl-di-*O*-caffeoyl quinate exhibited the maximum binding energy (−81.65 kcal/mol), and three ligands (3,5-methyl-di-O-caffeoylquinate, curcumene, and 2,6-dimethoxyquinone) displayed an interaction with His226 amino acid (AA) residue of MMP 9 (Table 9). The current result was in good correlation with our preceding study, where 3-phenyllactic acid (3-PLA) showed interaction with His226 amino acid (AA) residues of the MMP 9 enzyme [36]. Stigmasterol has been reported to reduce matrix metalloproteinase 3 (MMP 3) mRNA expression in humans and mouses, MMP 3 protein in mice, and matrix metalloproteinase 13 (MMP 13) mRNA expression in humans and mice [37]. However, in the present study, stigmasterol failed to dock with both enzymes (MMP 2 and 9).

Table 9. Energy interaction analyzes of twenty-six ligands (*Mikania*) MMP 9 utilizing Discovery Studio.

Ligands	Energy Interaction of c-Docker (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	F *	-	-
Kaurenoic acid	F *	-	-
Stigmasterol	F *	-	-
Grandifloric acid	F *	-	-
Kaurenol	F *	-	-
Spathulenol	F *	-	-
Caryophyllene oxide	F *	-	-
Syringaldehyde	36.26	Tyr248	3.2 and 3.2
Dihydrocoumarin	33.03	No interaction	-
o-Coumaric acid	40.73	Ala189	2.0
Taraxerol	F *	-	-
Melilotoside	F *	-	-
Patuletin	43.96	Leu188	2.3
Methyl-3,5-di-*O*-caffeoyl quinate	81.65	His226 ■ Gln227	5.1 1.7
3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone	45.60	Pro180 His190	2.4 2.7
Psoralen	33.72	No interaction	-
Curcumene	32.74	His226 ■	3.7
Herniarin	35.71	Tyr248	2.8
2,6-Dimethoxyquinone	31.79	Leu188 Ala189 His226	2.9 2.7 3.2
Bicyclogermacrene	F *	-	-
α-Bisabolol	42.26	No interaction	-
γ-Elemene	F *	-	-
Provincialin	F *	-	-
Dehydrocostus lactone	F *	-	-
Mikanin-3-*O*-sulfate	48.76	Gln227	3.0
Nepetin	44.73	Pro180 His190	2.3 and 2.5 2.7

Note: [F *—Failed to dock, ■—π–π interaction].

Docking and energy binding analysis (Table 10) shows that the provincialin had maximum energy binding (−54.18 kcal/ mol) with the mPGES 2 enzyme (as illustrated in Figure 2d) and twelve ligands (syringaldehyde, o-coumaric acid, melilotoside, patuletin, 3,5-methyl-di-*O*-caffeoylquinate, 4′,6,7-trimethoxyflavone-3,3′,5-trihydroxy, psoralen, herniarin, provincialin, dehydrocostus lactone, mikanin-3-*O*-sulfate, and nepetin) had interaction with Arg298 amino acid (AA) residue of mPGES 2. Interestingly, in the present study, all 25 ligands (except for 2,6-dimethoxyquinone) showed docking and binding affinities with microsomal prostaglandin E synthase 2 (mPGES 2). Maione et al. [38] have reported that the amino acids (i) Cys110, (ii) His241, (iii) His244, (iv) Ser247, (v) Arg292,

and (vi) Arg296 are the key binding residues for mPGES 2. However, there are no reports on their mPGES 2 inhibition activity.

Table 10. Energy interaction analyzes of twenty-six ligands (*Mikania*) of mPGES 2 utilizing Discovery Studio.

Ligands	Energy Interaction of c-Docker (-kcal/mol)	Amino Acid Interaction Residue (AA)	Bond Distance (Å)
Mikamicranolide	26.05	SerB295	2.3 and 2.5
		SerD295	1.9
		ArgD292	2.1
Kaurenoic acid	22.92	SerD295	1.9
		ArgD296	2.3
Stigmasterol	32.09	Lys200	2.0
Grandifloric acid	23.59	SerD295	1.9
Kaurenol	22.25	No interaction	-
Spathulenol	24.46	SerD295	1.3 and 1.4
Caryophyllene oxide	19.57	No interaction	-
Syringaldehyde	28.24	SerD295	1.8, 1.8 and 2.4
		ArgD298	1.7
Dihydrocoumarin	23.83	No interaction	-
o-Coumaric acid	26.40	SerD295	1.5
		ArgB298	1.7
Taraxerol	29.16	SerB295	1.7 and 2.3
		GlnA198	1.6 and 2.2
Melilotoside	42.13	SerB295	1.3 and 2.2
		ArgB298	1.7
		GlnA198	1.6
		GlyA199	0.96
Patuletin	39.66	GlyC199	1.6
		ArgB298	1.7 and 1.8
		ArgD298	1.7
		GlnA198	1.8
		GlnC198	1.9
		GlyC199	2.3
3,5-Methyl-di-*O*-caffeoyl quinate	52.22	SerB295	1.9, 2.4 and 2.5
		ArgD296	1.5 and 1.8
		ArgD296 ■	2.8
		ArgD298	1.8
		GlyA199	1.3
6,7-Trimethoxyflavone-3,3′,5-Trihydroxy-4′	39.70	GlyC199	1.8
		ArgB298	2.0 and 2.5
		ArgD298	1.3
Psoralen	26.93	ArgB298	1.5 and 1.9
Curcumene	26.84	No interaction	-
Herniarin	25.62	SerD295	2.3
		ArgD298	1.8
2,6-Dimethoxyquinone	F *	-	-
Bicyclogermacrene	22.19	No interaction	-
α-Bisabolol	28.37	SerB295	1.1 and 2.7
γ-Elemene	20.98	No interaction	-
Provincialin	54.18	ArgB292	2.2
		ArgD292	2.3
		SerB295	2.0 and 2.4
		ArgB296	2.4
		ArgB298	1.6
		ArgD298	1.7
Dehydrocostus lactone	21.58	SerB295	1.8
		ArgD298	2.2
Mikanin-3-*O*-sulfate	42.38	SerD295	2.5
		ArgB298	1.5
		GlyA199	1.4
Nepetin	39.41	GlyC199	1.9
		SerD295	1.4
		ArgB298	1.4 and 1.7

Note: [F *—docking failed, ■—π–sigma interaction].

3. Materials and Methods

3.1. Ligand (Small Molecule of Interest) Preparation

The simplified molecular input line entry specification (SMILES) of the 26 selected ligands: (i) mikamicranolide (Chemspider ID 10189069); (ii) kaurenoic acid (CID 73062); (iii) stigmasterol (CID 5280794); (iv) grandifloric acid (CID 159930); (v) kaurenol (CID 443465); (vi) spathulenol (CID 522266); (vii) caryophyllene oxide (CID 14350); (viii) syringaldehyde (CID 8655); (ix) dihydrocoumarin (CID 660); (x) o-coumaric acid (Chemspider ID 553146); (xi) taraxerol (CID 92097); (xii) melilotoside (CID 5280759); (xiii) patuletin (CID 5281678); (xiv) methyl-3,5-di-*O*-caffeoyl quinate (ChEBI ID 66708); (xv) 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone (Chemspider ID 4476175); (xvi) psoralen (CID 6199); (xvii) curcumene (CID 92139); (xviii) herniarin (Chemspider ID 10295); (xix) 2,6-dimethoxyquinone; (xx) bicyclogermacrene (CID 5315347); (xxi) α-bisabolol (CID 442343); (xxii) γ-elemene (CID 6432312); (xxiii) provincialin (ChEBI ID 8599); (xxiv) dehydrocostus lactone (CID 73174); (xxv) mikanin-3-*O*-sulfate (CID 14630674); and (xxvi) nepetin (Chemspider ID 4476172) were obtained from (i) Chemspider, (ii) PubMed, and (iii) Chemical Entities of Biological Interest. A three-dimensional structure of 2, 6-dimethoxy quinone was generated using ChemBioDraw Ultra 12.0. All the 26 ligands [above-mentioned] were sketched using Ultra 12.0 ChemBioDraw software and further MM2—molecular mechanics ligand minimization—was performed using Ultra 12.0 ChemBio3D software. Thus, these minimized energy ligands [3D images] were engaged for Autodock and in the C-docker case, and the ligand in-build preparation procedure (Accelrys, San Diego, CA, USA) was applied [16].

3.2. Protein Network Interaction Analysis

The search tool for interacting chemicals [STITCH] free web server [39] was employed to identify the interaction between ligands (26 selected phyto-constituents of *Mikania* species) and human proteins.

3.3. Selection of Target Protein (Enzyme) and Preparation

The 3D enzymes of (i) COX 2 (3LN1), with a resolution of 2.40 Å; (ii) HNE (1H1B [PDB number], with a resolution of 2.00 Å; (iii) LOX (1JNQ [PDB number], with a resolution of 2.10 Å; (iv) MMP 2 (1QIB [PDB number], with 2.80 angstrom (Å) resolution; (v) MMP9 (4H1Q) with 1.59 Å resolution; and (vi) mPGES 2 (1Z9H), with 2.60 Å resolution. were retrieved from the RCSB Protein Data Bank. In COX2, the C chain was processed, and mPGES 2, all chains were processed individually by eliminating the B, C, and D ligands along with the crystallographically detected water (H_2O) particles. The enzymes mentioned above were primed using Chimera UCSF software for Autodocking and C-docker in-built protein preparation procedure (Accelrys, San Diego, CA, USA) was applied [16].

3.4. Physicochemical and Drug-Likeness or Bioactivity Score Analyses

The physicochemical and drug-likeness or biological activity score analyses were conducted for the selected twenty-six selected (*Mikania*) ligands utilizing the Mol-inspiration-free web server [16].

3.5. ADMET and TOPKAT Analyses

The ADMET and TOPKAT analyses were performed using Discovery Studio (Accelrys, San Diego, CA, USA) for the 26 selected (*Mikania*) ligands [16].

3.6. Docking Analysis

The docking analysis was performed for twenty-six screened compounds extracted from *Mikania* utilizing C-docker. The 3D structures of COX 2; MMP 2; HNE; MMP 9; and mPGES 2 were recovered from the Protein Data Bank and further processed with the C-docker procedure [40] along the protein–ligand interaction section using 3.1. Discovery Studio® (Accelrys, San Diego, CA, USA) was utilized. A model of Autodock 4.2 was used for LOX alone, where all rotatable bonds [rotb] along the twenty-six Mikania ligands were

withheld for the flexible docking approach. The grid size was fixed (60 × 60 × 60) with a space of 0.375 Å between the grid points. Lamarckian Genetic Algorithm (LGA) was used to choose the good conformers. Similarly, a genetic algorithm was used to produce 100 individual docking runs for each selected *Mikania* ligand. In summary, the standardized Autodock step-wise docking protocol was used for the current study [16].

4. Conclusions

The present study found that 3,5-methyl-di-*O*-caffeoylquinate was efficient in binding with five target enzymes, whereas kaurenoic acid did not bind with the selected four targeted proteins. These two phytochemicals showed good efficacy as potential anti-inflammatory drugs of non-steroid [NSAIDs] nature. Interestingly, all 26 selected ligands (except 2, 6-dimethoxy quinone) from *Mikania* species showed good docking and binding to mPGES 2. Thus, the findings of this study indicate that it is possible to suppress COX 2, HNE, LOX, MMP 2 and 9, and mPGES 2 in the treatment of acute and chronic inflammatory diseases using these ligands of *Mikania* species.

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