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IN-SILICO ANALYSIS OF PHYTOCHEMICALS FROM *GINKGO BILOBA* AND *AEGLE MARMELOS* AGAINST ALLERGIC CONJUNCTIVITIS

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ABSTRACT: Allergic conjunctivitis (AC) is a prevalent ocular condition characterized by inflammation of the conjunctiva due to allergen exposure, resulting in itching, redness, and discomfort. Traditional medicinal plants such as *Ginkgo biloba* and *Aegle marmelos* have been recognized for their potential anti-inflammatory and anti-allergic properties. In this study, we conducted an *in-silico* analysis to explore the therapeutic potential of phytochemicals derived from *Ginkgo biloba* and *Aegle marmelos* against AC. First, we compiled a list of phytochemicals in *Ginkgo biloba* and *Aegle marmelos*, focusing on compounds known for their anti-inflammatory and immunomodulatory activities. Molecular docking studies were performed to investigate the binding interactions between these phytochemicals and key proteins implicated in the pathogenesis of AC, including histamine receptors, inflammatory cytokines, and enzymes involved in the allergic response. Virtual screening techniques were employed to identify potential lead compounds with high binding affinities and favorable pharmacokinetic properties. Additionally, ADME/T properties were predicted to assess the bioavailability, metabolic stability, and potential toxicity of the selected phytochemicals. *In-silico* findings suggest that certain phytochemicals from *Ginkgo biloba* and *Aegle marmelos* exhibit promising anti-allergic and anti-inflammatory activities, making them attractive candidates for further experimental validation and development as potential therapeutic agents for the management of allergic conjunctivitis. These computational insights contribute to the rational design and discovery of novel phytochemical-based treatments for AC, offering new avenues for drug development in ocular allergy management.

INTRODUCTION: Allergic conjunctivitis (AC) represents a prevalent ocular disorder characterized by inflammation of the conjunctiva due to hypersensitivity reactions to environmental allergens. It is a common condition affecting individuals of all ages worldwide, leading to significant morbidity and impairing quality of life.

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The hallmark symptoms of AC include itching, redness, tearing, and swelling of the conjunctiva, often accompanied by discomfort and visual disturbances. Despite its non-life-threatening nature, AC can have a substantial impact on daily activities, productivity, and overall well-being, underscoring the need for effective therapeutic interventions [4, 5, 20, 21, 25].

AC management typically involves using antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunomodulatory agents to alleviate symptoms and suppress the inflammatory response.

However, these conventional treatments are associated with limitations such as potential adverse effects, incomplete efficacy, and the risk of rebound inflammation upon discontinuation. Therefore, there is a growing interest in exploring alternative approaches, including natural products derived from medicinal plants, as potential adjunctive or standalone therapies for AC [26, 19, 3, 7, 16, 24].

Medicinal plants have long been recognized as valuable sources of bioactive compounds with diverse pharmacological properties, including anti-inflammatory, antioxidant, and immunomodulatory activities. Among the numerous botanicals studied for their therapeutic potential, *Ginkgo biloba* and *Aegle marmelos* have garnered attention for their reputed medicinal properties and traditional uses in various healing systems [18]. *Ginkgo biloba*, commonly known as the maidenhair tree, is one of the oldest living tree species native to China. Extracts from *Ginkgo biloba* leaves have been extensively studied for their pharmacological effects, attributed primarily to the presence of flavonoids, terpenoids, and other bioactive constituents. *Ginkgo biloba* extract (GBE) is widely marketed as a dietary supplement and herbal remedy for various health conditions, including cognitive impairment, cardiovascular disorders, and inflammatory diseases [6].

Aegle marmelos, also known as bael or Bengal quince, is a medicinal plant native to the Indian subcontinent and Southeast Asia. Different parts of the *Aegle marmelos* tree, including the leaves, fruits, and bark, have been used in traditional medicine for the treatment of gastrointestinal disorders, respiratory ailments, and skin conditions [8]. Phytochemical analysis of *Aegle marmelos* has revealed the presence of alkaloids, flavonoids, tannins, and essential oils, among other constituents, which contribute to its therapeutic properties [1].

Given the rich chemical diversity and pharmacological potential of *Ginkgo biloba* and *Aegle marmelos*, there is growing interest in exploring their efficacy in the management of ocular disorders, including allergic conjunctivitis. Phytochemicals derived from these botanical sources have been reported to possess anti-inflammatory, anti-allergic, and antioxidant activities, which are pertinent to the pathophysiology of AC. AC involves the activation of various receptors that contribute to the inflammatory response in the conjunctiva. Glucocorticoid receptors (GRs) play a major role in immune response regulation as well as inflammation regulation, both of which are important aspects of allergic conjunctivitis.

GRs can suppress allergy mediators, lower eosinophilic activity, control immune cell activity, and modify inflammatory mediators. They are frequently used to reduce symptoms and manage inflammation in allergic conjunctivitis. They are normally prescribed for brief periods or in small doses, but their usage is restricted because of possible adverse effects. Additionally, GRs control gene transcription, which suppresses pro-inflammatory genes and increases anti-inflammatory genes, both of which reduce inflammation and ease allergy symptoms. Targeting GRs pharmacologically represents a potential therapeutic strategy for managing allergic conjunctivitis [17]. In recent years, computational approaches, collectively referred to as *in-silico* analysis [9], have emerged as valuable tools for drug discovery and development. *In-silico* methods encompass a range of computational techniques and algorithms that enable the prediction, modeling, and analysis of biological interactions at the molecular level [10].

By leveraging *in-silico* approaches, researchers can expedite the identification of lead compounds, elucidate their mechanisms of action, and optimize their pharmacological properties before experimental validation. In this context, the present study aims to conduct an *in-silico* analysis of phytochemicals derived from *Ginkgo biloba* and *Aegle marmelos* against allergic conjunctivitis.

Through a systematic computational investigation, we seek to identify potential lead compounds with therapeutic relevance, elucidate their molecular interactions with key targets implicated in AC pathogenesis, and evaluate their pharmacokinetic properties and safety profiles. By integrating computational modeling, molecular docking, and virtual screening, we aim to provide valuable insights into the pharmacological potential of

Ginkgo biloba and *Aegle marmelos* phytochemicals as novel therapeutic agents for allergic conjunctivitis. This *in-silico* analysis represents a crucial step towards the rational design and development of effective and safe botanical-based interventions for the management of ocular allergies, addressing the unmet clinical needs in this field.

MATERIALS AND METHODS:

Ligand Retrieval and Preparation: A total of 39 bioactive substances were chosen as ligands from the phytoconstituents of the *Aegle marmelos* and *Ginkgo biloba* plants. A library of bioactive chemicals was created, and their PDB 3D structures were retrieved from the IMPAAT database (https://cb.imsc.res.in/imppat/). The PyRx software comes with Open Babel installed by default, which was used to construct the ligand structures. 3D structures of the standard drug Levofloxacin were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in .sdf format.

Protein Retrieval and Preparation: Research Collaboratory for Structural Bioinformatics (RCSB) maintains the Protein Data Bank (PDB) database, from which the target proteins, namely the glucocorticoid receptor (PDB ID: 4MDD), were obtained. The X-ray crystallographic structure, lower resolution (< 2.40 Å), and percentile scores in global validation measures, which suggest superior structure quality, are the reasons this PDB ID was taken into consideration. Pre-processing of the protein structures was done using Discovery Studio Visualizer 2022. Through the removal of other heteroatoms, such as water molecules, and natural inhibitors, the protein models were cleaned and optimized. To protonate proteins to improve docking efficiency [22].

Physicochemical, Pharmacokinetic, and Drug Likeness Properties of *Aegle marmelos*, *Ginkgo biloba* Phytoconstituents: Using Lipinski's rule of five (RO5), the SwissADME database (http://www.swissadme.ch/) and Molsoft (https://molsoft.com/mprop/) were utilized to predict the pharmacological and pharmacokinetic features of certain lead compounds. For every lead molecule, canonical simplified molecular-input line-entry system (SMILES) structures were obtained from the IMPAAT database. To anticipate the drug-likeness of lead compounds, these servers require these SMILES as an entry method **Table 1** [11].

Molecular Docking and Interaction Studies: Using PyRx. Ink software and molecular docking were used to investigate every orientation, conformation, and binding affinity that ligands could have with the glucocorticoid receptor. Selected phytoconstituents and standard drugs were subjected to molecular docking analysis with the protein target **Fig. 1**.

Using Open Babel software, all ligands were translated to PDBQT format so that AutoDock Vina could acceptably dock them. To apply blind docking, the entire protein was entrapped within the grid box. The docking data were molecularly visualized, and BIOVIA Discovery Studio Client 2022 was utilized to examine bonding interactions between the docked protein-ligand complexes and the docking pose. As the lead compound, the conformation with the lowest docking score (in kcal/mol) was chosen [12, 23, 13].

RESULTS AND DISCUSSION: The major component analysis of the respective ligands on the structure of the glucocorticoid receptor is schematically represented in **Fig. 1.**

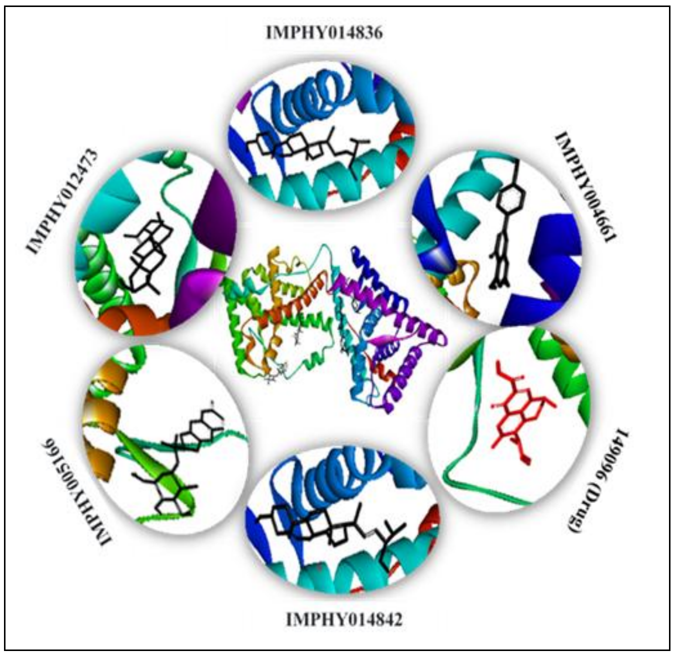
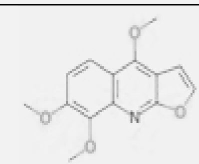
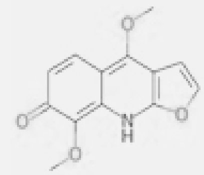
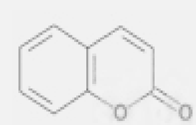
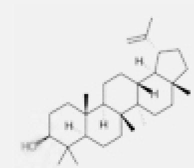
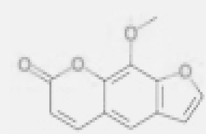
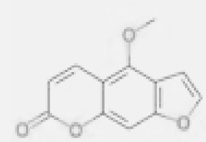
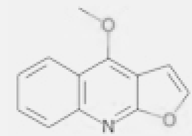
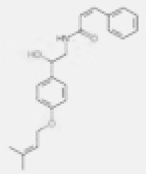
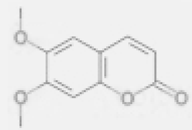
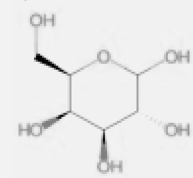
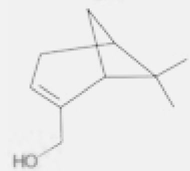
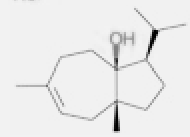
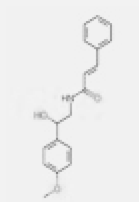
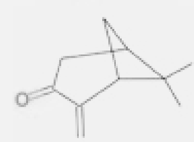
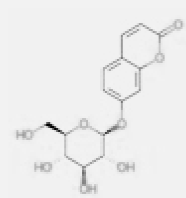
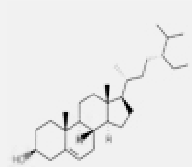
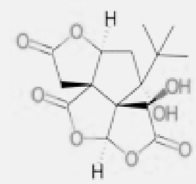
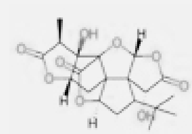
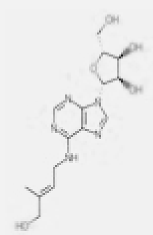
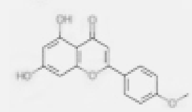
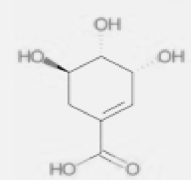
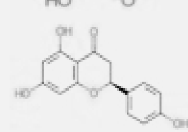
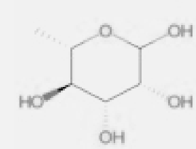
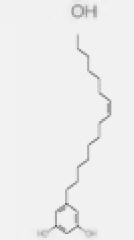


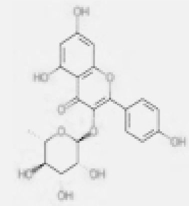
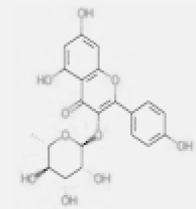
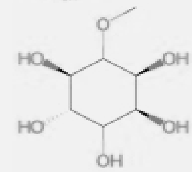
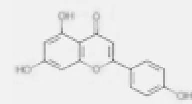
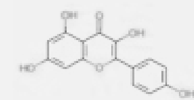
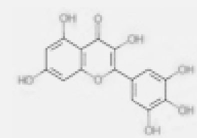
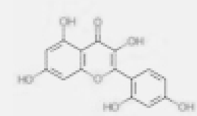
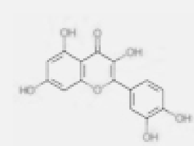
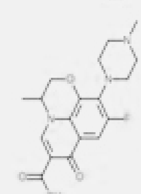
FIG. 1: SCHEMATIC REPRESENTATIONS OF MAIN COMPONENT ANALYSIS OF THEIR RESPECTIVE LIGANDS ON THE STRUCTURE OF GLUCOCORTICOID RECEPTOR

TABLE 1: PHYTOCONSTITUENT FROM *AEGLE MARMELOS*, *GINKGO BILOBA* AND THEIR CLASSIFICATION, IMPAAT ID, CANONICAL SMILE, 3D STRUCTURE, AND LIPINSKI'S RULE OF 5 INCLUDING STANDARD DRUG LEVOFLOXACIN

S. no.	Plant name	Phytochemical name	Part of Plant	NP Classifier Biosynthetic pathway	IMPAAT Phytochemical identifier	Smile Id	Lipinski's rule of 5	3D structure
1	*Aegle marmelos*	Skimmianine	Aerial part	Alkaloids	IMPHY007265	COc1ccc2c(c1OC)nc1c(c2OC) cco1	0	
2	*Aegle marmelos*	Haplopine	Aerial part	Alkaloids	IMPHY008279	COc1c(=O)ccc2c1[nH]c1occc1c2OC	0	
3	*Aegle marmelos*	Auraptene	Bark	Shikimates	IMPHY001552	C/C(=CCOc1ccc2c(c1)oc(=O)cc2)/CCC=C(C)C	0	
4	*Aegle marmelos*	Coumarin	Bark	Shikimates	IMPHY003490	O=c1ccc2c(o1)cccc2	0	
5	*Aegle marmelos*	Ammijin	Whole plant	Shikimates	IMPHY005166	OC[C@H]1O[C@@H](OC([C@H]2Oc3c(C2)cc2c(c3)oc(=O)cc2)(C)C)[C@@H]([C@H]([C@@H]1O)O)O	0	
6	*Aegle marmelos*	Marmesin	Bark	Shikimates	IMPHY011661	O=c1ccc2c(o1)cc1c(c2)C[C@H](O1)C(O)(C)C	0	
7	*Aegle marmelos*	Lupeol	Bark	Terpenoids	IMPHY012473	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]1CC[C@H]3[C@@]([C@]1(C)CC2)(C)CC[C@@H]1[C@]3(C)CC[C@@H](C1(C)C)O)C	1	
8	*Aegle marmelos*	Methoxsalen	Fruit	Shikimates	IMPHY003037	COc1c2oc(=O)ccc2cc2c1occ2	0	
9	*Aegle marmelos*	Bergapten	Fruit	Shikimates	IMPHY005428	COc1c2ccc(=O)oc2cc2c1cco2	0	

10	*Aegle marmelos*	Dictamnine	Fruit	Alkaloids	IMPHY007199	COc1c2ccccc2nc2c1cco2	0	
11	*Aegle marmelos*	Marmeline	Fruit	Phenylpropanoids	IMPHY009589	OC(c1ccc(cc1)OCC=C(C)C)CNC(=O)/C=Cc1ccccc1	0	
12	*Aegle marmelos*	Scoparone	Fruit	Phenylpropanoids	IMPHY011395	COc1cc2oc(=O)ccc2cc1OC	0	
13	*Aegle marmelos*	D-Galactose	Fruit	Phenylpropanoids	IMPHY012050	OC[C@H]1OC(O)[C@@H]([C@H]([C@H]1O)O)O	0	
14	*Aegle marmelos*	Myrtenol	Leaf	Terpenoids	IMPHY000099	OCC1=CCC2CC1C2(C)C	0	
15	*Aegle marmelos*	Carotol	Leaf	Terpenoids	IMPHY001050	CC1=CC[C@@]2([C@@](CC1)(O)[C@H](CC2)C(C)C)C	0	
16	*Aegle marmelos*	Aegeline	Leaf	Phenylpropanoids	IMPHY002030	COc1ccc(cc1)C(CNC(=O)/C=C/c1ccccc1)O	o	
17	*Aegle marmelos*	Pinocarvone	Leaf	Terpenoids	IMPHY002072	C=C1C(=O)CC2CC1C2(C)C	0	
18	*Aegle marmelos*	Marmin	Root	Phenylpropanoids	IMPHY006258	C/C(=CCOc1ccc2c(c1)oc(=O)cc2)/CC[C@H](C(O)(C)C)O	0	
19	*Aegle marmelos*	Skimmin	Root	Phenylpropanoids	IMPHY007363	OC[C@H]1O[C@@H](Oc2ccc3c(c2)oc(=O)cc3)[C@@H]([C@H]([C@@H]1O)O)O	0	
20	*Aegle marmelos*	beta-Sitosterol	Seed	Terpenoids	IMPHY014836	CC[C@@H](C(C)C)CC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[	1	

						C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C		
21	*Ginkgo biloba*	Ginkgolic acid	Stem	Aromatic polyketides	IMPHY005538	CCCCCC/C=CCCCCCCCCc1cccc(c1C(=O)O)O	1	
22	*Ginkgo biloba*	Bilobalide	Stem	Terpenoids	IMPHY010150	O=C1O[C@@H]2[C@@]3(C1)C(=O)O[C@H]1[C@]3([C@](C2)(O)C(C)(C)C)[C@@H](O)C(=O)O1	0	
23	*Ginkgo biloba*	Ginkgolide A	Root	Terpenoids	IMPHY006729	O=C1O[C@@H]2[C@@]([C@@H]1C)(O)C13C4(C2)[C@H](OC3=O)CC(C24[C@H](O1)OC(=O)[C@@H]2O)C(C)(C)C	0	
24	*Ginkgo biloba*	Zeatin riboside	Leaf	Alkaloids	IMPHY003593	OC/C(=C/CNc1ncnc2c1ncn2[C@@H]1O[C@@H]([C@H]([C@H]1O)O)CO)/C	0	
25	*Ginkgo biloba*	Acacetin	Leaf	Phenylpropanoids	IMPHY004611	COc1ccc(cc1)c1cc(=O)c2c(o1)cc(cc2O)O	0	
26	*Ginkgo biloba*	Shikimic acid	Leaf	Shikimates	IMPHY006945	O[C@@H]1CC(=C[C@H]([C@H]1O)O)C(=O)O	0	
27	*Ginkgo biloba*	Naringetol	Leaf	Shikimates	IMPHY010550	Oc1ccc(cc1)[C@@H]1CC(=O)c2c(O1)cc(cc2O)O	0	
28	*Ginkgo biloba*	L-Rhamnose	Fruit	Carbohydrates	IMPHY015056	O[C@H]1[C@H](C)OC([C@@H]([C@@H]1O)O)O	0	
29	*Ginkgo biloba*	Bilobol	Fruit	Polyketides	IMPHY005536	CCCCCC/C=CCCCCCCCCc1cc(O)cc(c1)O	1	

30	*Ginkgo biloba*	Docosanol	Flower	Fatty acids	IMPHY009358	CCCCCCCCCCCCCCCCCCCCCCO	1	
31	*Ginkgo biloba*	Afzelin	Flower	Shikimates	IMPHY011919	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O[C@@H]1O[C@@H](C)[C@@H]([C@H]([C@H]1O)O)O)O	1	
32	*Ginkgo biloba*	D-Pinitol	Flower	Carbohydrates	IMPHY015039	COC1[C@H](O)[C@@H](O)C([C@@H]([C@@H]1O)O)O	0	
33	*Ginkgo biloba*	Apigenin	Leaf	Shikimates	IMPHY004661	Oc1ccc(cc1)c1cc(=O)c2c(o1)cc(cc2O)O	0	
34	*Ginkgo biloba*	Kaempferol	Leaf	Shikimates	IMPHY004388	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	0	
35	*Ginkgo biloba*	Myricetin	Leaf	Shikimates	IMPHY005471	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1cc(O)c(c(c1)O)O	1	
36	*Ginkgo biloba*	Stigmasterol	Flower	Terpenoids	IMPHY014842	CC[C@@H](C(C)C)/C=C/[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C	1	
37	*Ginkgo biloba*	Morin	Leaf	Shikimates	IMPHY005463	Oc1ccc(c(c1)O)c1oc2cc(O)cc(c2c(=O)c1O)O	0	
38	*Ginkgo biloba*	Benzoic acid	Root	Shikimates	IMPHY013890	CCCCCCCCCCCCCCc1cc(O)cc(c1C(=O)O)O	1	
39	*Ginkgo biloba*	Quercetin	Leaf	Shikimates	IMPHY004619	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	0	
40	Drug	Levofloxacin	NA	NA	NA	CC1COC2=C3N1C=C(C(=O)C3=CC(=C2N4CCN(CC4)C)F)C(=O)O	0	

Physicochemical, Pharmacokinetic, and Drug Likeness Properties of *Aegle marmelos*, *Ginkgo biloba* Phytoconstituents: A good orally active drug candidate should not have more than one violation of Lipinski's criteria otherwise it might compromise its bioavailability (Namachivayam *et al.,* 2014). The selected phytoconstituents were screened and selected based on Lipinski's rule for their drug-like properties **Table 2.**

None of the selected phytoconstituents exhibited any Lipinski's violation. A high MW favours digestion and slower absorption from the GI tract thereby decreasing the plasma concentration and bioavailability of drug molecules.

In the present study, the MWs of all selected phytoconstituents including reference drug Levofloxacin were found to be less than 500, thus favoring rapid GI absorption.

The Num. rotatable bonds of all selected phytoconstituents including reference drug Levofloxacin were found to be less than 10, thus favoring rapid Num. rotatable bonds. Num. H-bond donors of all selected phytoconstituents including reference drug Levofloxacin were found to be less than 10 and all the phytoconstituents have less than 5 Num. H-bond acceptors except for Ammijin and standard drug Levofloxacin.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF *AEGLE MARMELOS, GINKGO BILOBA* PHYTOCONSTITUENTS

S. no.	Compounds name	Molecular weight (g/mol)	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	% Absorption	TPSA (Å²)	Lipinski's rule of 5
1	Lupeol	426.72	1	1	1	102.02	20.23	Passed
2	Stigmasterol	412.69	5	1	1	102.02	20.23	Passed
3	Ammijin	408.40	4	9	4	61.10	138.82	Passed
4	Acacetin	284.26	2	5	2	81.43	79.90	Passed
5	beta-Sitosterol	414.71	6	1	1	102.02	20.23	Passed
6	Levofloxacin (Standard drug)	361.37	2	6	1	83.12	75.01	Passed

Where %ABS=109-0.345×TPSA

It is evident from **Table 3** that all phytoconstituents were found to be incapable of crossing the BBB versus other phytoconstituents and CQ which showed a high BBB permeability. Skin permeability (Kp) is related to the molecular size and lipophilicity of drug-like compounds and negative values of Kp correspond to decreased skin permeability of all the compounds. Standard drug Levofloxacin was found not to behave as P-gp substrates and hence, unlikely to be pumped out of the cell by the glycoprotein, thus lessening the probability of cells developing resistance towards them. Acacetin was predicted to behave as CYP1A2 inhibitors and thus, were less likely to be metabolized and rendered inactive by the enzyme. On the other hand, none of the compounds and drugs was found to behave as CYP2C19 inhibitors while a high level of GI absorption with Acacetin and Standard Drug Levofloxacin and Lupeol, Stigmasterol, Ammijin, and beta-Sitosterol have a low level of GI absorption.

TABLE 3: PHARMACOKINETIC STUDIES OF *AEGLE MARMELOS, GINKGO BILOBA* PHYTOCONSTITUENTS

S. no.	Compounds name	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	Log Kp (skin permeation) (cm/s)
1	Lupeol	Low	No	No	No	No	-1.90
2	Stigmasterol	Low	No	No	No	No	-2.74
3	Ammijin	Low	No	No	No	No	-8.56
4	Acacetin	High	No	No	Yes	No	-5.66
5	beta-Sitosterol	Low	No	No	No	No	-2.20
6	Levofloxacin (Standard drug)	High	No	Yes	No	No	-8.78

Further evaluation of drug-likeness was done using SwissADME software with additional filters viz. Ghose, Veber, Egan, Muegge and lead likeness filters. As is evident from **Table 4**, Lupeol and

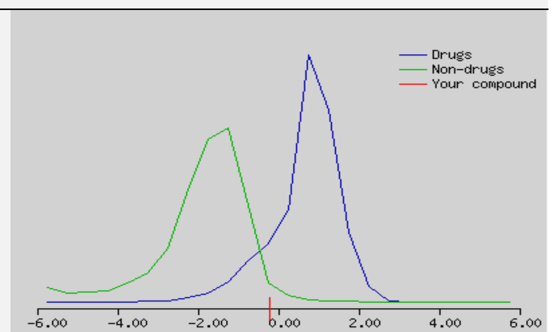
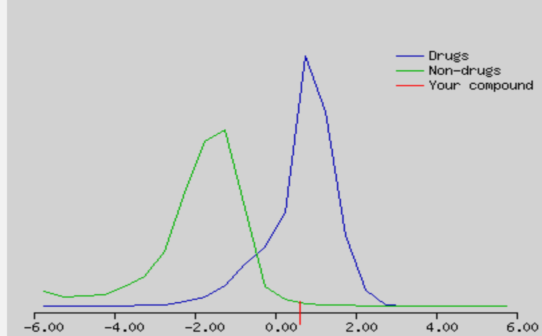
Stigmasterol follow Lipinski and Veber while Ammijin follows Lipinski, Ghose, Veber, and Muegge rules while except Ghose rule beta-Sitosterol follow all rules, and Acacetin and Standard Drug Levofloxacin follow all drug-likeness property respectively.

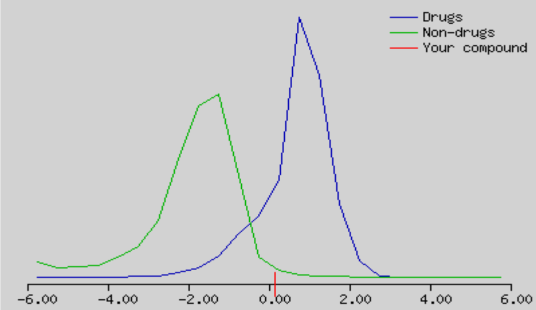
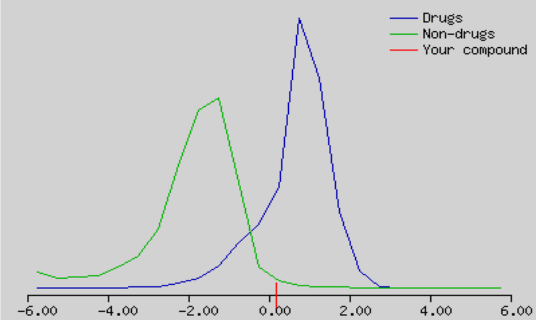
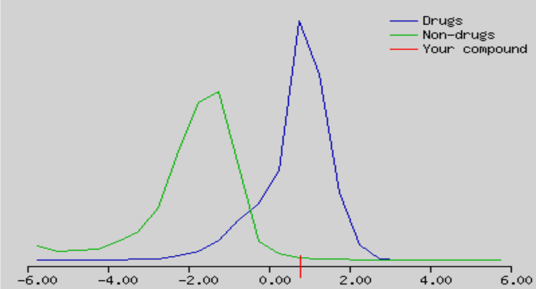
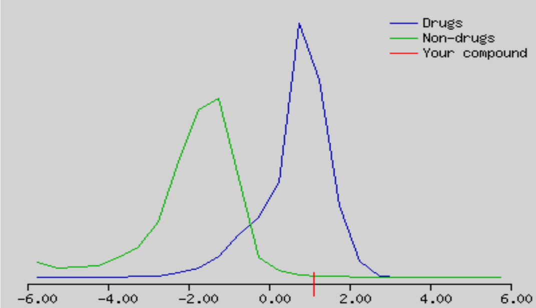
TABLE 4: DRUG LIKENESS PROPERTY OF *AEGLE MARMELOS*, *GINKGO BILOBA* PHYTOCONSTITUENTS

S. no.	Compounds name	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
1	Lupeol	Yes	No	Yes	No	No	0.55
2	Stigmasterol	Yes	No	Yes	No	No	0.55
3	Ammijin	Yes	Yes	Yes	No	Yes	0.55
4	Acacetin	Yes	Yes	Yes	Yes	Yes	0.55
5	beta-Sitosterol	Yes	No	Yes	No	No	0.55
6	Levofloxacin (Standard drug)	Yes	Yes	Yes	Yes	Yes	0.55

In the fields of structure prediction, structural proteomics, cheminformatics, bioinformatics, molecular visualization and animation, and rational drug design, Molsoft is a leading supplier of tools, databases, and consulting services. By developing novel technologies for structure prediction, MolSoft is advancing our knowledge of the spatial arrangement of biological molecules and how they interact with biological substrates, other molecules, and drug-like substances at the atomic level. The molecular properties of the selected compounds were calculated using the Molsoft database tool and the values are given in **Table 5.** The magnitude of drug-likeness score of compounds ranges from -0.22 to 1.12 of synthesized molecules based on the MolSoft database tool.

TABLE 5: DRUG-LIKENESS PROPERTIES AND PHYSICOCHEMICAL PROPERTIES OF *AEGLE MARMELOS*, *GINKGO BILOBA* PHYTOCONSTITUENTS CALCULATIONS USING MOLSOFT DATABASE TOOL

S. No.	Compounds name	Mol LogP (> 5)	Mol LogS (in Log(moles/L))/ (in mg/L)	Mol PSA (A^2)	Mol Vol (A^3)	pKa of most Basic /Acidic group	Number of stereo centers	Drug-likeness model score	Drug-likeness model
1	Lupeol	8.35	-6.31/ 0.21	16.09	563.87	<0. / 17.28	10	-0.22	
2	Stigmasterol	7.74	-6.24/ 0.24	16.28	529.89	<0. / 16.77	9	0.62	

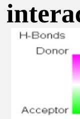
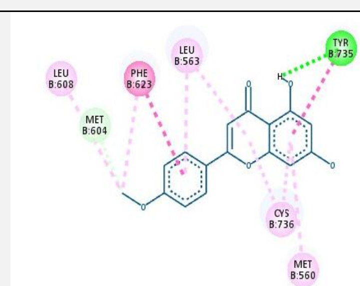
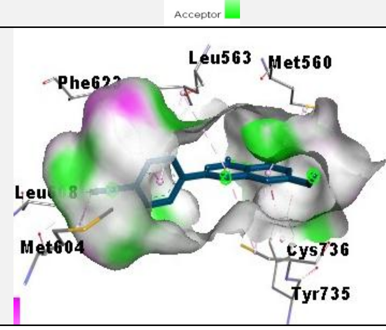
3	Ammijin	0.28	-1.27/ 21708.58	107.06	394.31	<0. / 13.01	6	0.16	
4	Acacetin	3.74	-3.78 / 46.61	63.49	281.44	<0. / 6.70	0	0.20	
5	beta-Sitosterol	8.45	-6.34 / 0.19	16.28	519.36	<0. / 16.77	9	0.78	
6	Levofloxacin (Standard drug)	0.23	-1.41/ 14020.71	59.39	365.21	7.52 / 5.52	1	1.12	

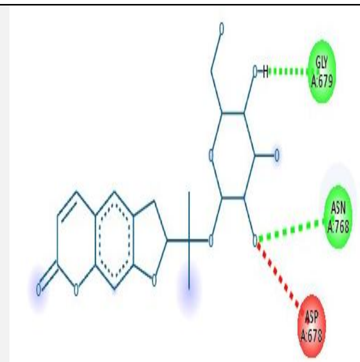
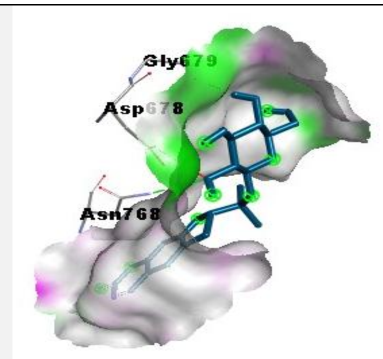
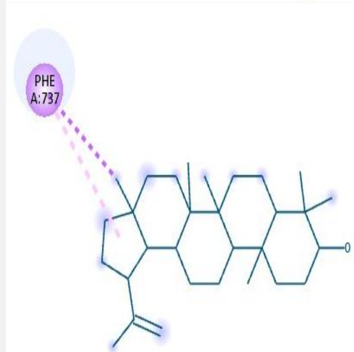
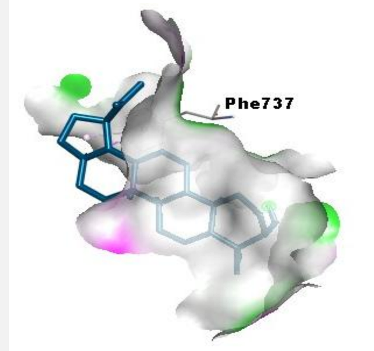
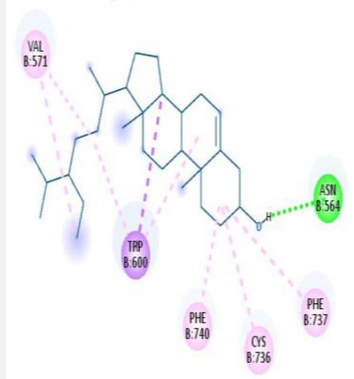
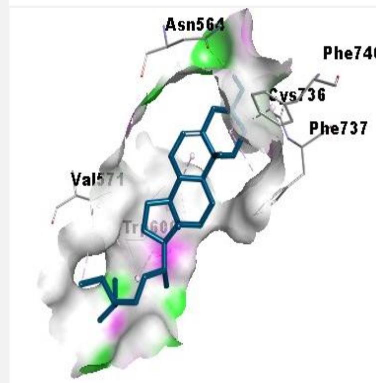
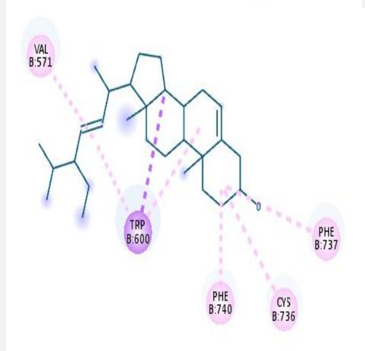
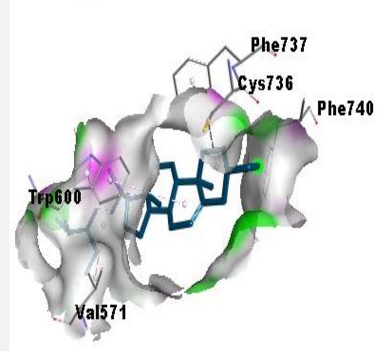
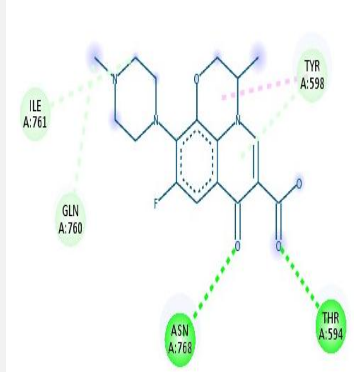
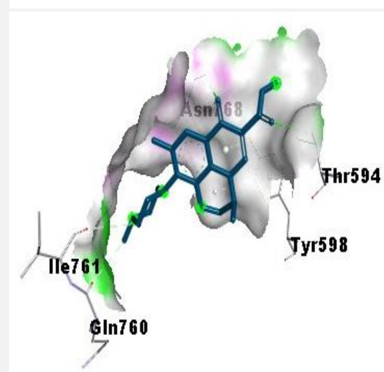
Molecular Docking and Interaction Studies of *Ginkgo biloba* and *Aegle marmelos* Plant Phytoconstituents with Standard Drug: In docking results, the binding affinity (Docking Free energy) and amino acid interactions of the compounds; with selected drugs are shown in **Tables 6** and **7**. A highest docked score of − 9.1 kcal/mol was shown by Lupeol against the Glucocorticoid receptor and the lowest docked score of − 4.4 kcal/mol against the Docosanol. The docked structure was imaged to illustrate the ligand Lupeol interactions with significant amino acids such as LEU608, LEU563, CYS736, PHE623, MET604, MET604, and TYR735 through Alkyl, and Pi-alkyl as well as hydrogen bonding. Ligand Stigmasterol interacts with significant amino acids such as GLY679, ASN768, and ASP678 through hydrogen bonding. Ligand Ammijin interacts with significant amino acids such as PHE737 and Ligand Acacetin with VAL571, TRP600, PHE740, CYS736, PHE737, ASN564 through Alkyl, Pi-alkyl as well as hydrogen bonding. And rest of the compound's docking score and interacting amino acid are shown in **Tables 6** and **7.**

TABLE 6: MOLECULAR DOCKING STUDIES OF *GINKGO BILOBA* AND *AEGLE MARMELOS* PLANT PHYTOCONSTITUENTS WITH STANDARD DRUG

S. no.	IMPAAT Phytochemical identifier	Phytochemical name	Binding Affinity
1	IMPHY012473	Lupeol	-9.1
2	IMPHY014842	Stigmasterol	-8.7
3	IMPHY005166	Ammijin	-8.1
4	IMPHY004611	Acacetin	-8
5	IMPHY014836	beta-Sitosterol	-8
6	IMPHY004661	Apigenin	-7.9
7	IMPHY010550	Naringetol	-7.9
8	IMPHY004619	Quercetin	-7.8
9	IMPHY005463	Morin	-7.7
10	IMPHY005471	Myricetin	-7.7
11	IMPHY006729	Ginkgolide A	-7.7
12	IMPHY004388	Kaempferol	-7.5
13	IMPHY006258	Marmin	-7.3
14	IMPHY002030	Aegeline	-7.2
15	IMPHY003490	Coumarin	-7.2
16	IMPHY011919	Afzelin	-7.2
17	IMPHY005538	Ginkgolic acid	-7.1
18	IMPHY007363	Skimmin	-7
19	IMPHY001552	Auraptene	-6.9
20	IMPHY009589	Marmeline	-6.9
21	IMPHY008279	Haplopine	-6.8
22	IMPHY011661	Marmesin	-6.8
23	IMPHY003593	Zeatin riboside	-6.7
24	IMPHY005428	Bergapten	-6.7
25	IMPHY001050	Carotol	-6.6
26	IMPHY002072	Pinocarvone	-6.6
27	IMPHY013890	Benzoic acid	-6.6
28	IMPHY010150	Bilobalide	-6.5
29	IMPHY000099	Myrtenol	-6.3
30	IMPHY011395	Scoparone	-6.3
31	IMPHY007199	Dictamnine	-6.2
32	IMPHY006945	Shikimic acid	-6
33	IMPHY003037	Methoxsalen	-5.9
34	IMPHY005536	Bilobol	-5.9
35	IMPHY012050	D-Galactose	-5.8
36	IMPHY015039	D-Pinitol	-5.6
37	IMPHY007265	Skimmianine	-5.5
38	IMPHY015056	L-Rhamnose	-5.5
39	IMPHY009358	Docosanol	-4.4
40	149096 (Pubchem CID)	Levofloxacin (standard drug)	-6.6

TABLE 7: MOLECULAR DOCKING AND INTERACTION STUDIES OF *AEGLE MARMELOS*, *GINKGO BILOBA* PHYTOCONSTITUENTS WITH GLUCOCORTICOID RECEPTOR

S. no.	Compounds name	PyRx Binding energy (Kcal mol^{-1})	Amino acid involved in Interaction	2D Interaction	3D interaction 
1	Lupeol	-9.1	LEU608, LEU563, CYS736, PHE623, MET604, MET604, TYR735		

2	Stigmasterol	-8.7	GLY679, ASN768, ASP678		
3	Ammijin	-8.1	PHE737		
4	Acacetin	-8	VAL571, TRP600, PHE740, CYS736, PHE737, ASN564		
5	beta-Sitosterol	-8	VAL571, TRP600, PHE740, CYS736, PHE737		
6	Levofloxacin (Standard drug)	-6.6	ILE761, GLN760, TYR598, ASN768, THR595		

CONCLUSION: The study analyzed the therapeutic efficacy of phytochemicals from *Ginkgo biloba* and *Aegle marmelos* against allergic conjunctivitis using computational methods. The findings showed that these phytochemicals interact with key molecular targets involved in allergic response pathophysiology. Molecular docking studies revealed anti-inflammatory mechanisms, with some compounds inhibiting pro-inflammatory cytokine production and modulating mast cell degranulation and eosinophil activity. These phytochemicals could be potential alternatives to conventional treatments for allergic conjunctivitis. Further experimental validation and synergistic effects studies are needed to confirm their bioactivity. The study also underscores the importance of exploring traditional herbal remedies as novel anti-allergic agents.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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