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LETTERS

In silico docking studies of *Yucca gloriosa* L. phytoconstituents with TNF-α, IL-6 and IL-13 receptor against Asthma

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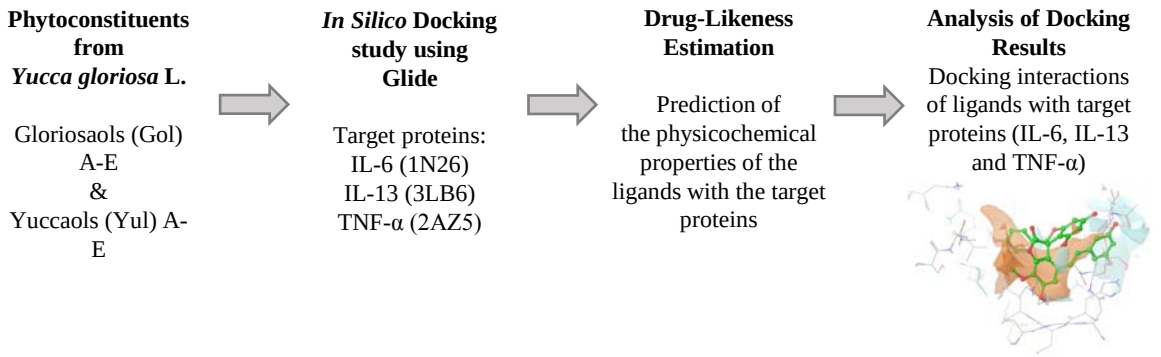
Article

ABSTRACT



Yucca gloriosa L. has been comprehensively assessed *in vitro* and *in vivo* for its action against asthma. *Y. gloriosa* L. is a rich source of phenolic compounds such as gloriosaols A-E and yuccaols A-E, which exhibit potent antioxidant activity. Gloriosaols A-E and yuccaols A-E are structurally related to corticosteroids. The current study describes the *in silico* docking of some important anti-asthmatic phytoconstituents from the plant *Y. gloriosa* L. with molecular targets of asthma. Toward the recognition of the binding methods of these pharmacologically dynamic components, molecular modelling studies were carried out with target proteins, i.e., interleukin (IL)-6 (1N26), IL-13 (3LB6) and TNF-α (2AZ5), using *in silico* molecular docking. The components demonstrated encouraging binding interactions with the amino acid residues at the active sites of these proteins, authenticating their verified efficiency as anti-asthmatic agents. The current research, in addition, provides insight into the possible herbal drug-receptor interaction and synthetic drug montelukast sodium receptor interaction, for the possible management of asthma.

Keywords: Yucca gloriosa, Asthma, TNF-α, Interleukins, Yuccaols, Gloriosaols, In silico study.

INTRODUCTION

Asthma is a common long-term, physiologically and clinically heterogeneous respiratory disorder characterized by an explicit prototype of chronic inflammation and obstacle in airways in respiration. Identification of discrete subsections of the pathophysiology of asthma has led to the concept of asthma as a compilation of endotypes.[1-2] The recognition of definite asthma endotypes united with the mounting acquaintance of airway inflammation, epithelial, and immune-resistant responses to viral and allergens infections, have offered new hopes for the application and expansion of endotype-specific treatment for the management of asthma. These advances allocated for an additional enlightening approach to classifying asthma that goes ahead of symptoms, lung function and response to medications and could permit the accurately customized treatment designed for an individual's distinctive pathophysiology.[3] As per the World Health Organization (WHO), over 262 million individuals experienced asthma and 4,61,000 died in 2019 throughout the world.[4-5] As per the global asthma report 2018, asthma affects 339 million people worldwide. In India, around 6% of children and 2% of adults are suffering from asthma out of the 1.35 billion population. Asthma was considered one of the main reasons for mortality and morbidity in rural and suburban India.[6-8] It is a chronic inflammatory disorder of the airways associated with

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hyper-responsiveness airway, frequent and persistent wheezing episodes, coughing, breathlessness and chest tightness due to reversible broncho-constriction consequential from augmented sensitivity of trachea bronchial tree to different stimuli.[9] This causes airway wall inflammation by increasing the number of inflammatory markers like eosinophils, basophils, mast cell macrophages, and certain types of lymphocytes.[10-11] The characteristic feature of asthma is the occurrence and activation of inflammatory cells in the airways.[11] Cytokines such as interleukins (ILs) and tumour necrosis factor (TNF)-α are involved in the enlistment, foundation, establishment and continuance of inflammatory cells in the airways and encourage the discharge of growth factors and chemokines from structure cells like epithelium.[12-13] Various cytokines and proteins have been considered as potential targets if inhibited, leading to the control over asthma. Allergic asthma, represented as the most common asthma endotype, is illustrated by the incidence of IgE-mediated sensitization reactions from environmental allergens. The cascades of Th2 cytokines together with IL-4, IL-5 and IL-13 among others, are essential to instigate and disseminate inflammation coupled with allergic reactions. Th2 cytokines are requisite to stimulate the class switching of B-cells to fabricate allergen-specific immunoglobulin E (meditated by IL-4 and IL-13), engage mast cells (IL-9) and eosinophils (IL-5) to positions of allergic inflammation along with persuade goblet cell metaplasia (IL-4 and IL-13).[14] *Yucca gloriosa* is generally known as a Spanish dagger belonging to the family Agavaceae.[15] *Y. gloriosa* usually grow in India, California and Mexico. In India, it generally exists in the Himalayas, Andhra Pradesh and Tamil Nadu. Since ancient times, entire plant parts of *Y. gloriosa* L. are used for bronchitis, asthma, dysentery, phthisis, menstrual disorders, haemorrhagic, septicaemia, anti-inflammatory, arthritis, cancer, cerebral ischemia, etc.[16-20] The fruits of *Y. gloriosa* L. have been employed as a purgative, blood purifier and cholagogue. The literature reports revealed that phytochemical composition of leaves consists of saponins like sapogenins, tigogenins, 12-β-hydroxysmilagenin, smilagenin, β-sitosterol, gitogenin 3-O-α-L-rhannopyranosyl-β-lycotetraosid, gitogenin 3-O-β-D-xylopyranosyl-β-lycotetra-oside, tigogenin 3-O-β-D-xylopyranosyl-β-lycotetraoside, stigmasterol, sitosterol, campesterol and cholesterol.[15-16,21-22] Roots and barks of *Y. gloriosa* L. are a prosperous resource of phenolic compounds like yuccaols A-E (Yul A-E) and gloriosaols A-E (Gol A-E) (Figure 1),[23-24] which showed strong antioxidant potential related to corticosteroids.[25-26]

The current study discloses the association among the structure and activity of the medicinally significant components of the plant *Y. gloriosa* L. to the receptor site. To recognize the binding methods of aforesaid dynamic components, molecular modelling studies have been carried out with IL-6, IL-13 and TNF-α using *in silico* docking studies.

RESULTS AND DISCUSSION

Docking of the phytoconstituents of the plant *Y. gloriosa* L. showed excellent H-bond interactions at the receptor sites of the target proteins, i.e., IL-13 (PDB ID: 3LB6), IL-6 (PDB ID: 1N26)

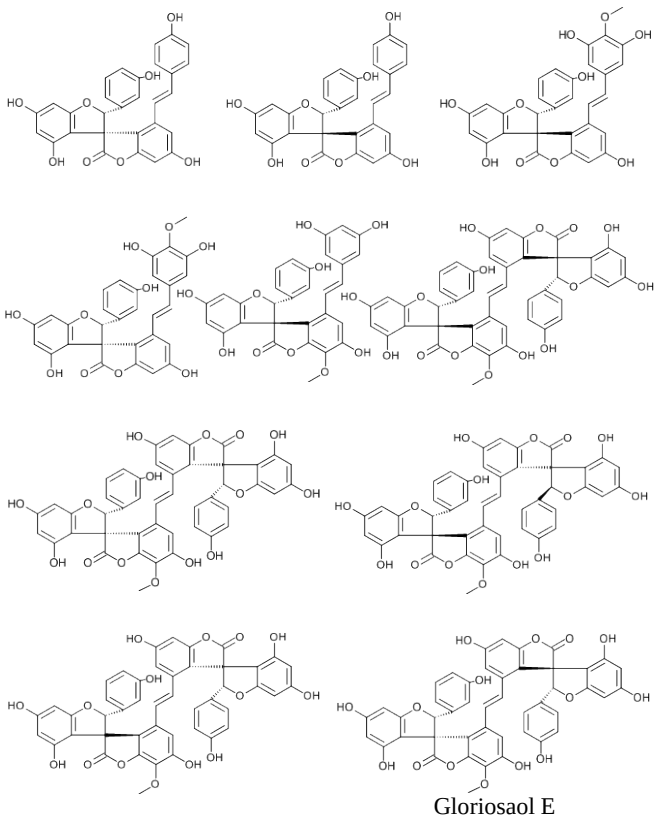

Figure 1. Chemical structures and ligand codes of the phenolic compounds, yuccaols (A-E) and gloriosaols (A-E) of the plant *Y. gloriosa* L.

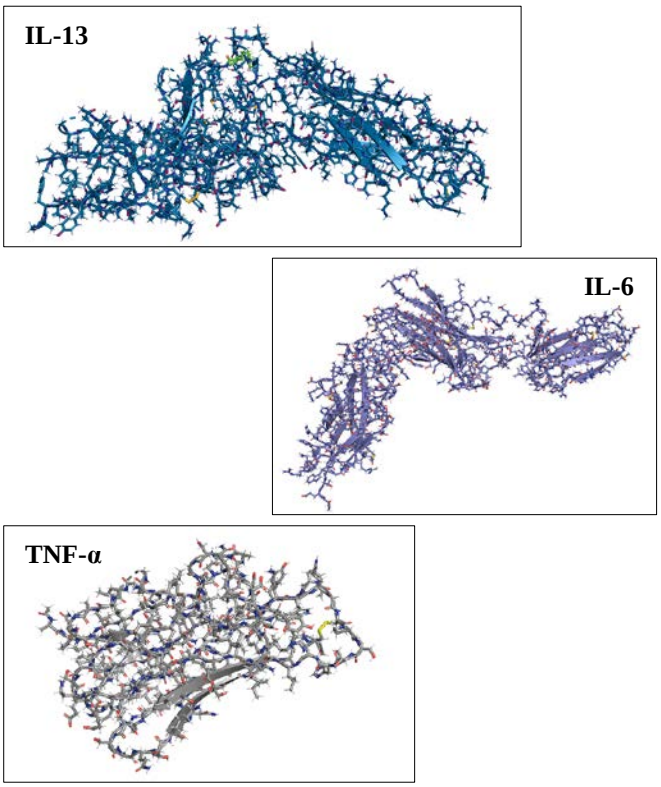

Figure 2. Prepared 3D structures of docking ready proteins (IL-13, IL-6 and TNF-α).

and TNF-α (PDB ID: 2AZ5). The 3-dimensional structure of the prepared docking ready target proteins (IL-13, IL-6 and TNF-α) are presented in Figure 2.

IL-13 in complex with IL-13Rα2 (3LB6)

The development of reactions of T helper cell type 2 (Th2) demonstrated a vital function in allergic reactions and asthma, fashioned by an important cytokine interleukin-13. IL-13 canonical Jak/STAT indicating functions inhibited by the IL-13 receptor α-2 (IL-13Rα2) receptor. The biophysical and mutational investigation of the IL-13/IL-13Rα2 complex besides with a crystal structure, while preserving an analogous mode of IL-13 binding to its associated signaling receptor, IL-13Rα1, IL-13Rα2 employs peripheral receptor residues unexploited within the IL-13/IL-13Rα-1 compound to engender a bigger along with added balancing and harmonizing interface for IL-13.[27] Compared to IL-13Rα1 this results in amplification in magnitude affinity by four orders, to the femtomolar level. A number of widespread "hotspot" residues disclose that alanine scanning mutagenesis of the IL-13 interface is essential for attaching to both receptors, but in addition, recognize an outstanding IL-13Rα2-specific contact. These outcomes present a skeleton for the expansion of receptor subtype-selective IL-13 antagonists and point out a decoy function for IL-13Rα2. With variable dissimilar approaches to antagonize IL-13 in addition to targeting IL-13Rα2 in remedial improvement, essential to recognize the molecular foundation for mutual cytokine identification by the IL-13 receptor family. Molecular research studies will too significant to facilitate recognizing whether IL-13Rα2 is exclusively a decoy receptor or has an application as a signaling receptor via homo/hetero-dimerization as well. The reason that anti-IL-4 did not authenticate efficiency in atopic asthma in massive components was probably due to the biological idleness afforded by IL-13. The IL-13 and IL-4 are enormously homologous to each other, are articulated by an assortment of identical immune cell types and contribute to several signaling pathways. There are two identified heterodimer receptors for IL-4. The IL-4 type 1 receptor is encompassing the universal gamma chain (γC) and the IL-4Rα chain, while the IL-4 type 2 receptor is consisting of the IL-13Rα1 and IL-4Rα chain intervened the signaling equally with IL-13 and IL-4. Also, there is a subsequent IL-13 receptor, known as IL-13Rα2, which binds IL-13 (not with IL-4) and possibly will perform like an inhibitory receptor.[28] IL-13Rα2 has also fascinated increasing importance for its probable function in malignant cells. IL-13Rα2 is upregulated in a numeral of human tumors, including ovarian and glioblastomas and cancers.[29-31]

The docking study of yuccaols and gloriosaols at the binding site of chain A of 3LB6 specified that these compounds interact through one or more than one bond, every one of the potential sites S2, S1 and S1α compartment of the enzyme (Tables 1 and 2). Those components confirmed H-bond interactions at the imperative amino acids of the site namely Gly216, Ser217, Ile130, Trp129, Tyr128, Ser131, Pro132, Ile223, Arg224, Gln133, Tyr227, Ser225, Ace222, Ile223, Gln133, Pro132,

Table 1. Physicochemical properties of yuccaols and gloriosals on IL-13 (PDB ID: 3LB6).

Ligand code	Glide score	Lipophilic EvdW	H-bond	Electro	Exposure penalty	Rotational penalty
Yul D	-5.95	-1.82	-4.29	-0.86	0.93	0.09
Gol C	-5.56	-3.28	-2.07	-0.61	0.34	0.06
Yul C	-4.77	-2.12	-2.26	-0.97	0.48	0.09
Yul E	-4.60	-2.66	-1.92	-0.81	0.70	0.09
Yul B	-4.38	-2.31	-1.89	-0.74	0.45	0.11
Gol B	-4.04	-1.93	-1.83	-0.79	0.45	0.06
Yul A	-3.71	-2.60	-1.48	-0.64	0.89	0.11
Gol A	-3.39	-2.19	-1.29	-0.46	0.49	0.06
Gol E	-3.31	-3.10	-1.58	-0.73	1.04	0.06
Gol D	-3.18	-1.83	-1.53	-0.45	0.57	0.06
Mlt	-1.47	-4.98	-1.06	-0.36	1.20	0.24

Table 2. Docking parameters of examined molecules on IL-13 (PBD ID: 3LB6).

Ligand code	Glide energy (Kcal/mol)	Hydrogen bond		
		H-bond acceptor	H-bond donor	Bond length (Å)
Mlt	-47.296	C=O (Mlt), OH (Mlt), OH (Mlt)	Amide NH (Gln133), Phenolic OH (Tyr227), OH -7 (Nag501)	1.867, 2.084, 2.462
Gol C	-47.830	C=O (Gol C), 5a- OH (Gol C), Ether- O (Nag 501), 7a- OH (Gol C), Amide C=O (Gly216 & Ser217)	Phenolic OH (Tyr227), OH-7 (Nag501), OH-5a (Gol C), OH (Ser225), OH-6’ (Gol C)	2.086, 2.167, 2.233, 2.134, 2.324
Yul C	-39.727	4’’’-OCH_3 (Yul C), Amide C=O (Nag501), Amide C=O (Ile223 & Arg224), 5’’’-OH (Yul C), C=O (Asp42), Amide C=O (Ile130 & Trp129)	Amide NH (Ace222 & Ile223), OH-3’’’ (Yul C), OH-5’’’ (Yul C), Amide NH (Gln133 & Pro132), OH-5’’ (Yul C), OH-4’ (Yul C)	2.430, 1.861, 2.252, 2.379, 1.634, 2.498
Yul D	-35.518	3’’’-OH (Yul D), Amide C=O (Ser131 & Pro132), Amide C=O (Nag501), 5’’’-OH (Yul D), Phenolic OH (Tyr128), 4’-OH (Yul D)	Amide NH (Pro132 & Gln133), OH-3’’’ (Yul D), OH -5’’’ (Yul D), Amide NH (Nag501 & Asn215), OH-5’’ (Yul D), Phenolic OH (Tyr227)	2.200, 2.116, 1.933, 2.199, 2.105, 2.119
Yul E	-45.830	Ether- O (Nag501), 3’’’-OH (Yul E), Amide C=O (Ile223 & Arg224)	OH-5 (Yul E), Amide NH (Asn215 & Gly216), OH-3’’’ (Yul E)	1.746, 2.400 1.973

Pro132, Gln133, Asn215, Tyr227, Asn215 & Gly216 with Glide score (docking score) ranging between -4.60 & -5.95 and Glide energy (free binding energy, Kcal/mol) ranging -35.518 & -47.830. Whereas the standard drug montelukast sodium showed a Glide score of -1.47 and Glide energy of -47.296. With these interactions, it can be concluded that the components of *Y. gloriosa* may be good inhibitors of 3LB6 enzyme. Yuccaols and gloriosaols showed excellent hydrogen bonding interactions at the active site of DPP-3LB6 enzyme. The docked pose represents the important interactions of yuccaol C, yuccaol D, yuccaol E and gloriosaol C at the active site of IL-13 protein (Figure 3). It can be concluded that yuccaols and gloriosaols could be active components of *Y. gloriosa* inhibiting the enzyme IL-13 (PDB ID: 3LB6). This *in silico* study concluded that specifically blocking of binding of IL-13 to the IL4Rα1, in spite of the IL13Rα1, possibly will be proficient in avoiding sensitivity reactions subsequent to the allergen attack.

IL-6 subunit alpha interaction on 1N26

Deregulated manufacture of IL-6 along with their receptors (IL-6R) is concerned in the pathogenesis of autoimmune diseases, prostate tumor and multiple myeloma. The two molecules encompass by IL-6R complex either IL-6 or IL-6R along with gp130, a signaling molecule. The N-terminal strand of the Ig domains, where D1 is disulfide linkage with domain D2, and disulphide bond linkage between domains D2 and D3, the cytokine-binding domain, are structurally identical to recognized cytokine-linking domains. The human IL-6 subunit alpha protein comprises of 325 amino acids with an expected molecular weight 36.41 kDa.[32] As of clinical perspective, it is significant that IL-6 be actives upon hepatocytes towards stimulation of acute-phase reactants, together with decrease serum albumin levels with other proteins such as serum amyloid A, C-reactive as well as fibrinogen too. In very recent times, it has been found that these cytokine augments the synthesis of hepcidin, a peptide in the hepatic cells which involves in the regulations of iron recycling, leads to anemia as a result of hypoferremia. Moreover, it has been revealed that IL-6 is accountable for an assortment of clinical indications, such as anemia, anorexia, fatigue, fever, increase in the erythrocyte sedimentation rate, together with the appearance of autoantibodies, and all aforesaid symptoms are built up in patients with a number of chronic autoimmune inflammatory ailments. IL-6 endorse the improvement of a newer form of T-helper cells, Th17 cells so as to affect the autoimmune diseases pathogenesis in the mice.[33] IL-6 is a pleiomorphic cytokine, whose development factor characteristics exhibit significant role in the evolution and amelioration of numerous varieties of tumors. IL-6 is formed during reply to an assortment of stimulus which is essential for the progression of T and B lymphocytes to effector cells. In multiple myeloma, IL-6 is formed and essential for endurance by tumor cells itself while into another form of neoplasias, IL-6 may possibly draw as of the cancer neighboring tissues. Therefore, the therapeutic approaches intended towards hampering the formation, action or elucidation of IL-6 would be fairly favorable during management of tumor. Moreover, IL-6 is a pathophysiological feature in a number of hyperproliferative diseases and the paraneoplastic syndromes which usually be an adjunct to cancer, including osteoporosis and cachexia; furthermore, IL-6 inhibitory treatment would be helpful in treating these entities simultaneously.[34]

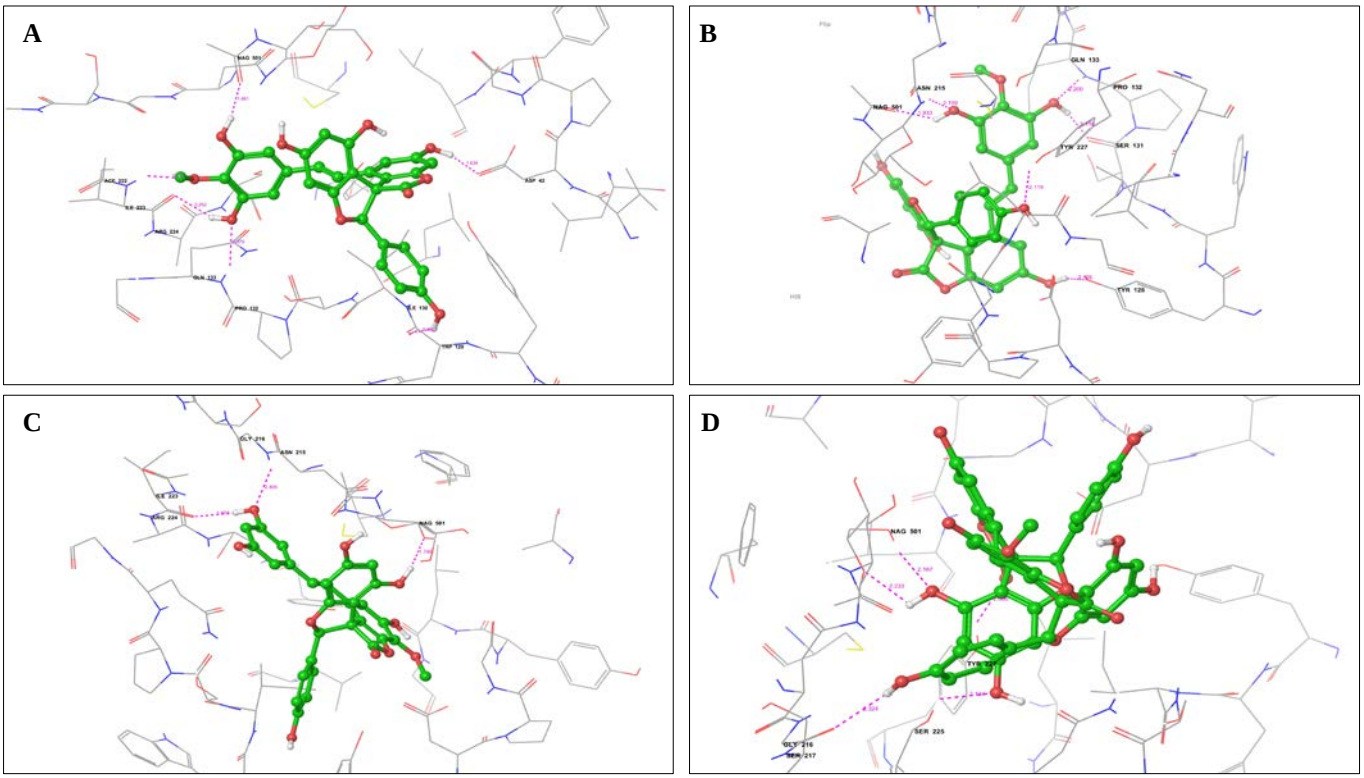

Figure 3: The docking interaction of yuccaol C (A), yuccaol D (B), yuccaol E (C) and gloriosaol C (D) with IL-13 (PDB ID: 3LB6).

Therefore, to evaluate the potential of *Y. gloriosa* L., the in-silico screening of its components was performed at the catalytic site of the chain A of 1N26. The experimental outcomes were analogous to the establish IL-6α 1N26 inhibitors, suggested that yuccaols as well as gloriosaols act mutually with every one of the recognized amino acids, Val91, Asp92, Glu10, Arg13, Gly14, Gly73, Nag611, Nag612, Leu89 and Val11 by hydrogen bonding at the protein's active site. Tables 3 and 4 and Figure 4 represent the docking score and docking pose showing hydrogen bond interactions of gloriosaol E, yuccaol C, yuccaol E, yuccaol D and montelukast sodium respectively at the active site of IL-6. Hence, it can be concluded that *Y. gloriosa* may also be acting as anti-asthmatic due to its synergistic property as a potential IL6α inhibitor.

Tumor necrosis factor alpha (TNF-α) 2AZ5

The human TNF-α protein has been comprised of 233 number of amino acids having expected molecular weight 25.6 kDa. initially TNF-α is formed in a membrane associated structure, further subjected to N-terminal 76 amino acids removal through enzymatic reaction of a TNF-α converting enzyme TACE/ ADAM17, to forms homotrimer that engender the dispersible 17kDa TNF-α molecule. TNF-α is the earliest identified prototypic component within the TNF superfamily, which currently composed of 19 well differentiated components. Several other associates, for instance TNFSF19, TNFSF21, and TNFSF22 have not been finely differentiated.[35-39] Even though each solitary member possesses receptor preference, have a common functional characteristic, like NF-kB activation and initiation of apoptosis, has been pragmatic amongst the majority of such members. As pointed out in the phylogenetic representation in Figure 5, each one of these components demonstrate a progressional preservation with their amino acid, several of which demonstrate uniqueness of type II membrane proteins. The TNF superfamily characteristics propose that, the members of the family may derive from the identical ancestral gene. While some members constitute C-terminal preserved domain, known as TNF-homology domain which shares sequence identity up to 20-30%. TNFSF3 (lymphotoxin b) and TNFSF1 (lymphotoxin a) are capable to form either homotrimer or hetero-trimer, whereas homo-trimer is the active form of other members in this family.[40-41]

Macrophages and monocytes are the main profuse cellular source to secrete TNF-α, that can stimulate necrotic or apoptotic cell death of numerous tumor cell lines, in response to inflammatory stimulation.[42] Furthermore, TNF-α is also a competent of stir up cell proliferation and discrimination in numerous categories of cells under definite conditions. TNF-α can act as a pyrogen, causes fever either by direct action or by invigoration of interleukin 1 secretion. Persistent production of TNF-α can be reason for cachexia-like syndrome in an assortment of human diseases, particularly in malignancy and in severe infections. The amplified expression of TNF-α in adipose tissue been believed to be liable for the progress of obesity and/or diabetes due to the initiation of insulin resistance. Despite the fact that functional attributes of TNF-α are accomplished solitary through definite members of the TNF receptor superfamily, soluble TNF-α principally stimulates TNF-R1 only, whereas memTNF predominantly associate with TNF-R2 receptors. The signaling pathways, most prominently, the IKK (IkB kinase) and aforementioned receptors trigger a number of intracellular

Table 3. Physicochemical properties of yuccaols and gloriosals on IL-6 (PBD ID: 1N26).

Ligand code	Glide score	Lipophilic EvdW	H-bond	Electro	Exposure penalty	Rotational penalty
Yul C	-7.75	-4.96	-1.95	-0.97	0.06	0.09
Yul E	-6.95	-5.05	-1.33	-0.9	0.24	0.09
Yul D	-6.74	-4.96	-1.73	-0.29	0.15	0.09
Mlt	-6.73	-6.42	-0.84	-0.46	0.75	0.24
Gol E	-6.15	-3.15	-2.81	-0.71	0.58	0.06
Gol D	-6.1	-3.81	-2.03	-0.59	0.33	0.06
Yul A	-5.49	-5.02	-0.96	-0.21	0.59	0.11
Yul B	-5.02	-4.47	-0.7	-0.52	0.55	0.11
Gol B	-4.21	-2.45	-0.92	-0.49	0.62	0.18
Gol C	-4.05	-2.18	-0.81	-0.63	0.74	0.18
Gol A	-3.68	-1.57	-0.74	-0.38	0.77	0.29

Table 4. Docking parameters of examined molecules on IL-6 (PBD ID: 1N26).

Ligand code	Glide energy (Kcal/mol)	Hydrogen bond		
		H-bond acceptor	H-bond donor	Bond length (Å)
Mlt	-56.077	Amide C=O (Val91 & Asp92), C=O (Mlt)	OH (Mlt), Amide NH (Nag611)	2.219, 1.876
Gol E	-42.951	6-OH (Nag611), 4'-OH (Gol E), Ether-O (Nag612), 5a'-OH (Gol E)	OH -4' (Gol E), Amide NH (Nag612), OH- 7a (Gol E), Amide NH (Val11 & Ala12)	1.987, 1.793, 2.301, 1.883
Yul C	-52.057	7-OH (Yul C), Amide C=O (Arg13 & Gly14), C=O (Leu89)	Amide NH (Nag612), OH- 3''' (Yul C), OH-4'' (Yul C)	1.834, 1.606, 2.244
Yul D	-46.238	4''' -OCH_3 (Yul D), C=O (Gly73), 7''-O (Yul D)	Amide NH (Glu10 & Val11), OH-4'' (Yul D), Amide NH (Nag611)	2.366, 2.030, 2.021
Yul E	-42.699	7-OH (Yul E), Amide C=O (Arg13 & Gly14), C=O (Leu89)	Amide NH (Nag612), OH-3''' (Yul E), OH-4'' (Yul E)	1.746, 1.794, 2.297

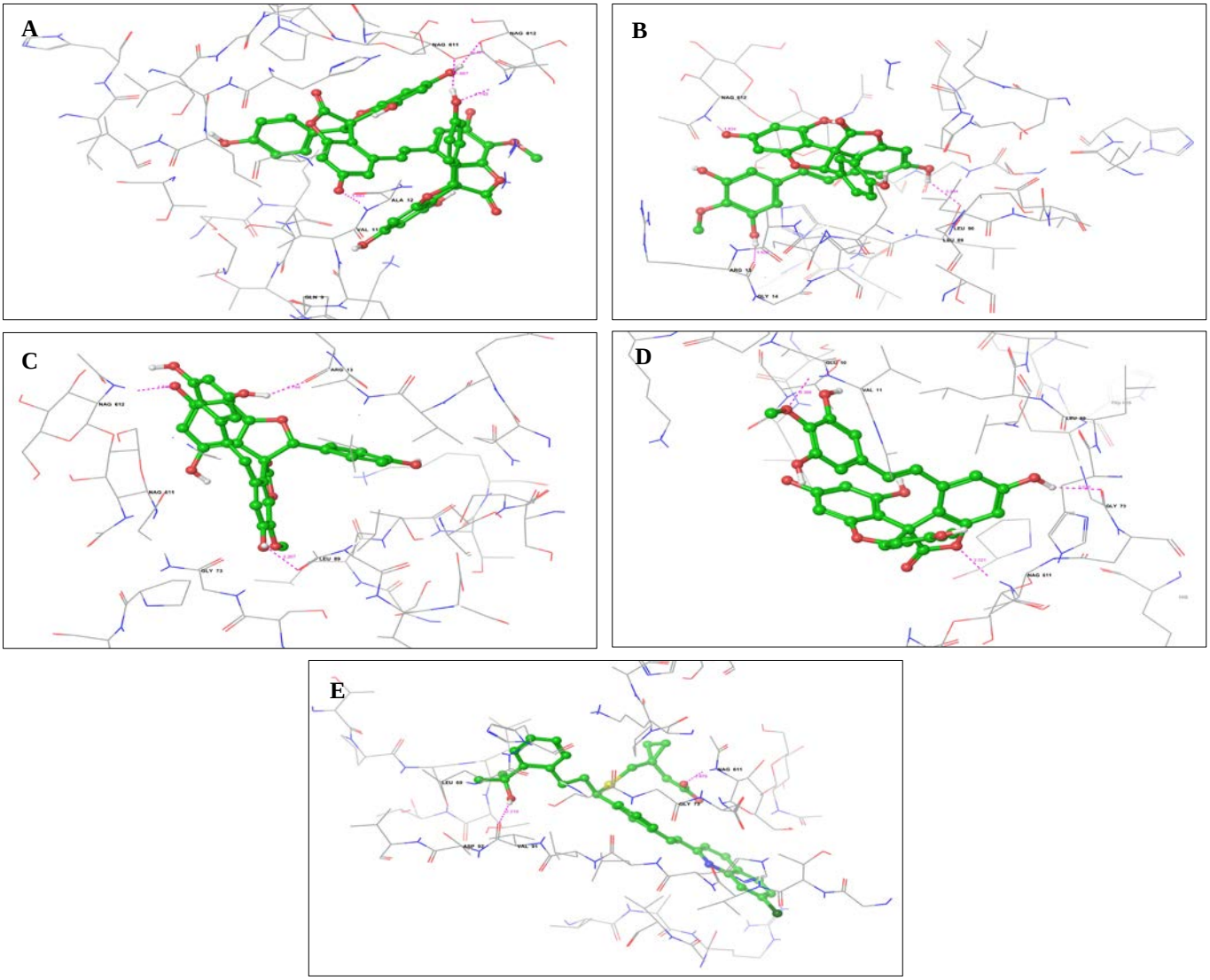

Figure 4: The docking interaction of yuccaol C (A), yuccaol D (B), yuccaol E (C) and gloriosaol C (D) with IL-13 (PDB ID: 3LB6).

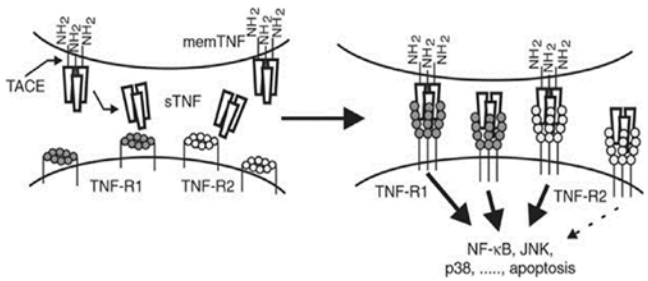

Figure 5: Phylogenetic tree which demonstrate an evolutionary conservation in amino acid sequences of TNF-α.

MAPK (mitogen-activated protein kinase) cascades, which regulates gene expression through NF-kB and AP-1 transcription factors, respectively.[43-45] Therefore, to evaluate the potential of Y. gloriosa we also performed the *in silico* screening of its components at the catalytic site of the chain B of TNF-α (PDB ID: 2AZ5). The experimental outcomes were analogous to the proved TNF-α (2AZ5) inhibitors furthermore, recommended that yuccaols and gloriosaols mutually interacts amid all the recognized amino acids, Ser95, Ala9, Leu94, Ser95, Leu120, Gly121, Ile118, Tyr119, Tyr151, Gln61 and Ser60 at the protein's catalytic site by H-bond interactions, having Glide score (ranging from -4.61 to -5.32) and Glide energy (between -27.728 to -43.681 Kcal/mol). Tables 6 and 7 represent the docking score with H-bonding at the active site of TNF-α. Figure 6 represent the docked pose showing hydrogen bonding interactions of gloriosaol D, gloriosaol E, yuccaol B, yuccaol D and montelukast sodium respectively at the active site of the TNF-α protein. Hence, it can be concluded that Y. gloriosa plant may be acting as anti-asthmatic due to its synergistic property as a potential TNF-α inhibitor.

EXPERIMENTAL

Ligands preparation

The 2-D chemical structures of ligands (Figure 1) were drawn using ChemDraw Professional in the CDX format. Further, Optimization of ligand was done by using the small-molecule topology generator Dundee PRODRG 2 server, a device utilized

Table 5. Physicochemical properties of yuccaols and gloriosals on TNF-α protein (PDB ID: 2AZ5).

Ligand code	Glide score	Lipophilic EvdW	H-bond	Electro	Exposure penalty	Rotational penalty
Gol E	-5.32	-3.16	-1.90	-0.70	0.40	0.06
Gol D	-5.02	-2.2	-2.11	-0.87	0.14	0.06
Yul D	-4.99	-2.21	-2.34	-0.83	0.47	0.09
Mlt	-4.83	-4.7	-1.58	-0.62	1.82	0.24
Yul B	-4.61	-3.32	-1.33	-0.49	0.42	0.11
Yul A	-4.60	-3.23	-1.33	-0.5	0.36	0.11
Yul C	-4.40	-2.83	-1.62	-0.46	0.47	0.09
Gol B	-4.01	-1.93	-1.92	-0.53	0.44	0.06
Gol C	-3.35	-1.83	-1.79	-0.37	0.59	0.06
Gol A	-3.21	-2.19	-0.87	-0.35	0.23	0.06
Yul E	-3.04	-1.58	-1.30	-0.41	0.16	0.09

Table 6. Docking parameters and H-bonding of examined molecules on TNF-α protein (PDB ID: 2AZ5).

Ligand code	Glide energy (Kcal/mol)	Hydrogen bond		
		H-bond acceptor	H-bond donor	Bond length (Å)
Mlt	-43.681	O-Na (Mlt), OH (Mlt), Amide C=O (Ser95 & Ala96)	NH (Lys98), Amide NH (Leu94 & Ser95), OH (Mlt)	1.808, 2.473, 2.131
Gol D	-37.522	5-OH (Gol D), 7-OH (Gol D), 5”-OH (Gol D), Amide C=O (Leu120 & Gly121)	Amide NH (Ile118 & Tyr119), NH (Lys98), Amide NH (Leu120 & Gly121), OH -7a (Gol D)	2.435, 1.781, 2.208, 1.840
Gol E	-43.645	5-OH (Gol E), 7-OH (Gol E), 5’’-OH (Gol E)	Amide NH (Ile118 & Tyr119), NH (Lys98), Amide NH (Leu120 & Gly121)	2.472, 1.671, 2.091
Yul B	-27.728	Amide C=O (Leu120 & Gly121), Phenolic-OH (Tyr151)	OH -5 (Yul B), OH -7 (Yul B)	2.028, 1.862
Yul D	-28.788	3’’’ -OH (Yul D), C=O (Gln61), Phenolic-OH (Tyr151), C=O (Ser60 & Gln61)	OH- Phenolic (Tyr151), OH -3’’’ (Yul D), OH -7 (Yul D), OH -5 (Yul D)	2.292, 1.913, 1.782, 2.205

ligands were prepared using the LigPrep of Maestro for protein-ligand complexes high-throughput crystallography, which receives input from numerous 2-D coordinates or existing formats and involuntarily produces molecular topologies coordinates which are appropriate for protein-ligand complexes X-ray refinement. The physicochemical properties of the ligands were calculated by using ChemOffice (Cambridge, USA). If the ligand molecules have implicit hydrogen atoms their valances have been satisfied by adding up the hydrogen atoms. Furthermore, the bond orders were specified. To study the efficacy of individual stereotypes of each ligand, the most probable stereoisomers and all potential tautomers were generated. At the concluding phase of LigPrep, the OPLS-2005 force field was used to minimize the energy of compounds (test as well as standard compounds).

Preparation of protein structures

The X-ray crystal structures of TNF-α, IL-6 and IL-13 (PDB IDs: 2AZ5, 1N26 and 3LB6, respectively) were attained from the RCSB protein data bank (http://www.rcsb.org/) after assessing numerous entries (based on the resolution of ligand bound complex). The protein preparation module of Schrodinger was used to prepare the protein files. The proteins were processed independently by removing the substrate cofactor, optimizing H-bonds and addition/deletion of side chain residues to the protein. The charge assignment, protonation state and energy minimization of 0.3 Å was carried out by OPLS 2005 force field with RMSD (root mean square deviation). The grid was generated on the selected proteins by means of the default value of the protein atom inside a cubic box; centred on the centroid of the X-ray ligand pose.

Docking methodology

Docking studies were performed for yuccaols A-E and gloriosaols A-E with target proteins on windows 10 workstation by Glide of Schrodinger suit. All the prepared proteins were undergone docking studies separately. All the prepared ligands were docked with the individual proteins using Glide, version 9.2, Schrodinger software in XP mode (extra precision) based minimization. A standard drug, montelukast sodium (Mlt) was also included in the study to evaluate its binding affinity and possible herb-drug interaction in silico between the plant extract and synthetic molecule if co-administered. The analysis was performed on the most excellent docked poses, having the lowest glide score value for understanding docking interactions and orientation in the active site.[46-47]

CONCLUSION

The anti-asthmatic potential of the plant *Y. gloriosa* is known worldwide since ancient times but the association between the structural interaction and activity of medicinally significant components of the plant with various targets involved in the pathophysiology of asthma has never been explored using *in silico* approaches. Molecular modelling studies were carried out to recognize the binding mechanisms of active constituents, with TNF-α, IL-6 and IL-13. The aforesaid components exhibit encouraging connections with the amino acid residues at the the established efficiency as anti-asthmatic agents. With the explored results we conclude that the *in vitro* and *in vivo* studies on yuccaols and gloriosaols must be performed to evaluate their active sites of the proteins that were explored, thereby validating

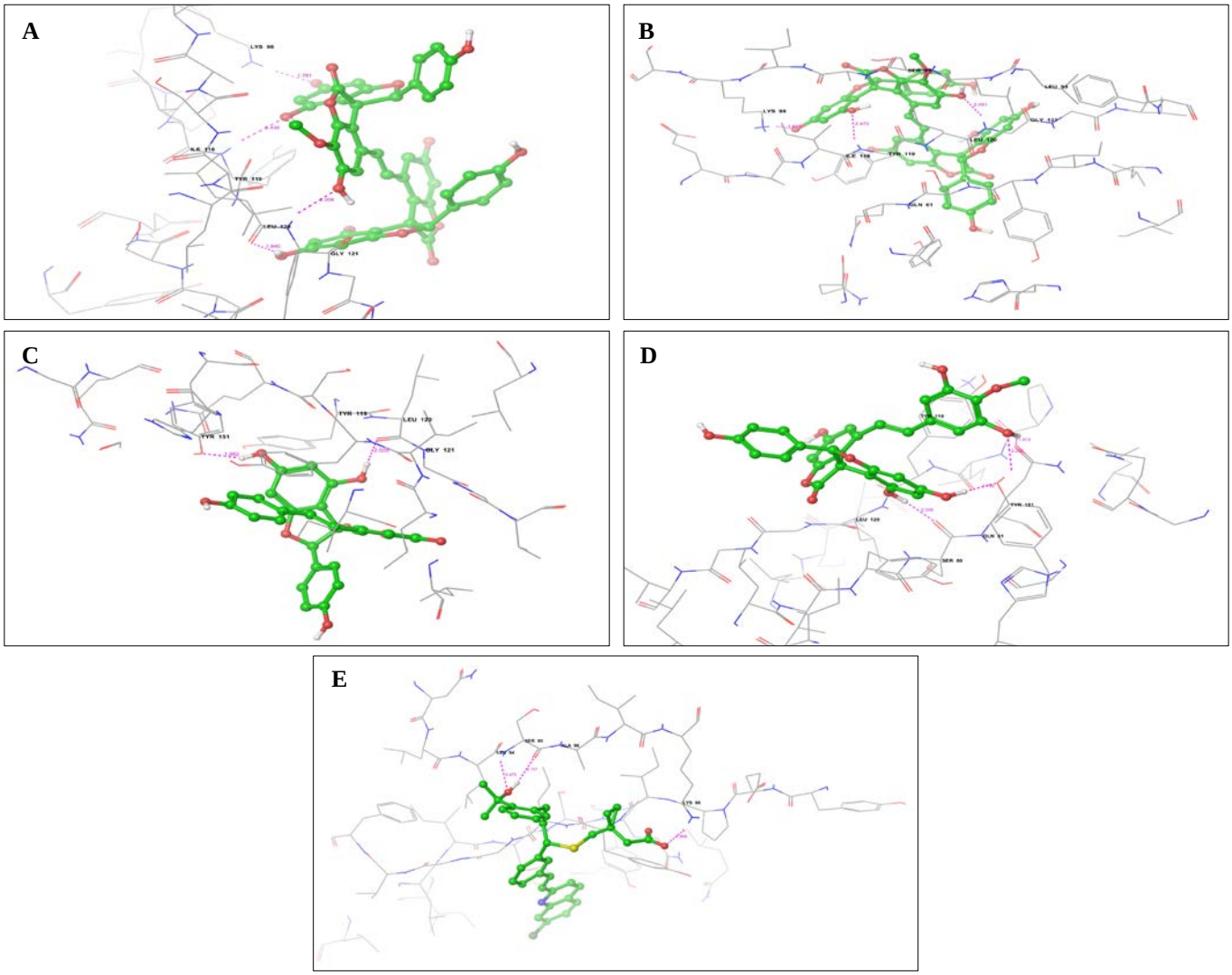

Figure 6: The docking interactions of gloriosaol D (A), gloriosaol E (B), yuccaol B (C), yuccaol D (D) and montelukast sodium (E) with active site residues of TNF-α protein (PDB ID: 2AZ5).

exact potential in the treatment of asthma. In addition, the current research gives an insight into the possible herb-drug interaction and rationale behind the contemporaneous administration of *Y. gloriosa* extract and synthetic drug molecule, montelukast sodium in the treatment of asthma. It may also alter the pharmacokinetic and pharmacodynamic profile of montelukast sodium. These observations motivated us to perform anti-asthmatic studies on the isolated yuccaols and gloriosaols and *in vivo* herb-drug interaction studies on the perspectives of pharmacokinetics.

Supplementary Information

Supplementary information contains the ligand-protein targets complex and other information related to this docking study (i.e., grid coordinates X, Y and Z, the RMSD and RMSF results of the docking study).

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Conflict of Interest

The authors declare there is no conflict of interest for publication of this work.

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