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Study the molecular docking for established phytochemicals of *Cissus quadrangularis* against tumor necrosis factor alpha (TNF-α) for the prevention of inflammation of arthritis as a major risk of urinary incontinence

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Abstract
Cissus quadrangularis is a medicinal plant. It has been used for the treatment of inflammation related diseases. The local name of *Cissus quadrangularis* is harbhanga. This plant are used in all over the countries medicinally due to their potent anti-inflammatory and free radical scavenging properties. Tumor necrosis factor or TNF-α is a pro inflammatory cytokine protein, which increases during inflammation and causes pain related diseases. Different non-steroidal anti-inflammatory drugs that has been used for pain relief but this drugs have adverse side effects. For this reason researchers are showing interest for medicinal plants or Phytomedicine without any adverse side effects. The main aim of this work was to know the inhibitory activity by observing binding affinity and energy value of TNF-α towards different phytochemicals present in *Cissus quadrangularis* through the molecular docking study.

Keywords: Molecular docking, *Cissus quadrangularis*, phytomedicine, TNF-α

1. Introduction
The 'phyto' meaning plant is derived from Greck word. These chemicals are referred to as 'secondary metabolites'. Phytochemicals are naturally occuring compound with bioactive potentials. These are several classes of compounds like alkaloids, flavonoids, polysaccharides, phenols, tannins and terpenoids [1, 2]. These phytochemicals are produced by external stimuli such as infection, nutritional or climatic changes and they may be accumulated or gathered in only certain parts of the plant [3]. These phytochemicals act as a natural defense system for host against infection due to their therapeutic potentials such as anti oxidants, memory enhancing and anti-inflammatory activity. Urinary incontinence is a highly prevalent condition affecting nearly 50% of middle-aged and older women [4]. Urinary incontinence is a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable [5] by the International Continence Society Standardization Committee.
Cissus quadrangularis, locally name harbhanga belonging to family vitaceae [6]. *Cissus quadrangularis* is used as a herbal medicine due to their different medicinal properties such as anti-inflammatory and free radical scavenging properties [7].
Tumor necrosis factor (TNF-α) is a proinflammatory cytokine protein that increases during inflammation and causes different diseases such as arthritis [8] risk of urinary incontinence [9]. Non steroidal anti inflammatory drugs (NSAIDs) or steroidal medicines that are used for pain relief by inhibition of TNF-α receptor antagonists [10]. But this drug (NSAIDs) have potent side effects when used for the inhibition of proinflammatory cytokines such as TNF-α etc. [11]. For this reason researchers are interested to show their interest by the use of phytomedicine without any adverse side effects [12].
In the study of molecular docking and interaction, proteins (receptors) are the main molecular targets to detect the action of drug. Several compounds (ligands) that are phytochemicals bind to the protein targets to show their allosteric or inhibitory effects. This allosteric effects help in new drug design as a lead molecule. These drug like compounds which are commercially available are revealed in the molecular docking and interaction study and computationally screened against targets of recognized structure in an experiment [13, 14].
The main objective of this study work was to know the inhibitory activity by observing binding affinity and energy value of TNF-α towards different phytochemicals present in *Cissus quadrangularis* through the molecular docking study for the prevention of inflammation of arthritis risk of urinary incontinence.

2. Materials and Methods

2.1 Compounds of *Cissus quadrangularis*

Compounds of Cissus quadrangularis that were selected for this study were i. Asarone ii. Leteolin iii. Quercetin iv. Resveratrol v. Piceatannrl vi. Kaempferol vii. Stigmasterol viii. Lupeol ix. Freidalin x. Phytol xi. Eugenol.

2.2 Protein or receptor selection

The X-ray diffraction crystallographic structure of the protein TNF-α (2.1 A resolution) was obtained from the website of protein data bank in Europe. (http:// www.ebi.ac.uk/pdb.e) [15].

The X-ray diffraction crystallographic structure of the TNF-α was deposited by the experiment and covered from amino acid 10-157 [15]. After visualizing in Auto Dock Tool [16] the 3-D ribbon structure was exhibited in Fig 1. An inhibitory molecule [6,7-Dimethyl-3-[(Methyl{2-[Methyl ({1-[3-(Trifluoromethyl) Phenyl]-1H-Indol-3-YL}Methyl) Amino] Ethyl}amino)Methyl]-4H-Chromen-4-One] attached in chain A and C (307) which are exhibited in Fig 2 and 3 after obtaining two-dimensional view in Ligand Environment Viewer (Le View version 1.0) tool developed by Caboche [17].

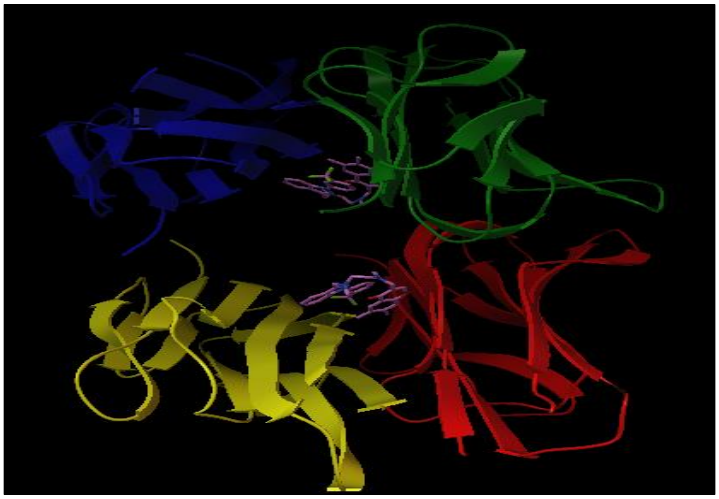

Fig 1: Three-dimensional (3D) ribbon structure of tumor necrosis factor-α (PDB ID: 2az5) [Chain A = yellow; Chain B = red; Chain C = blue and Chain D = green]

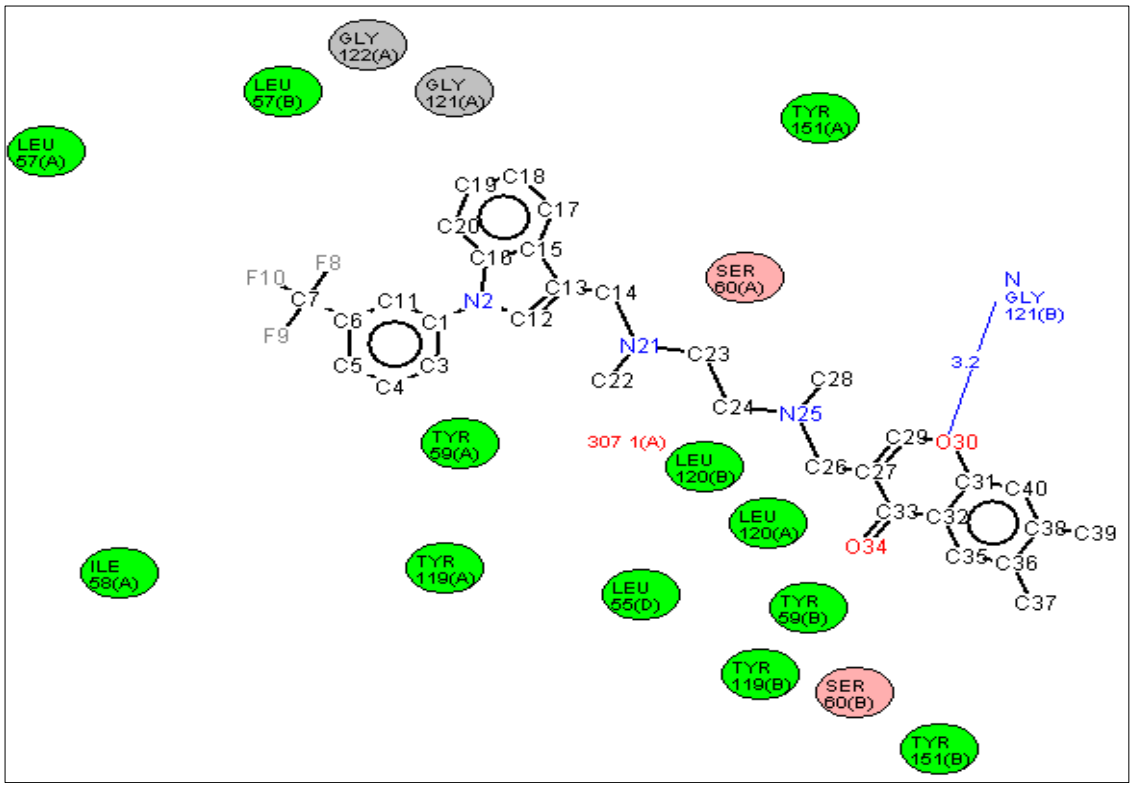

Fig 2: TNF-α attached with inhibitory ligand in Chain A (307)

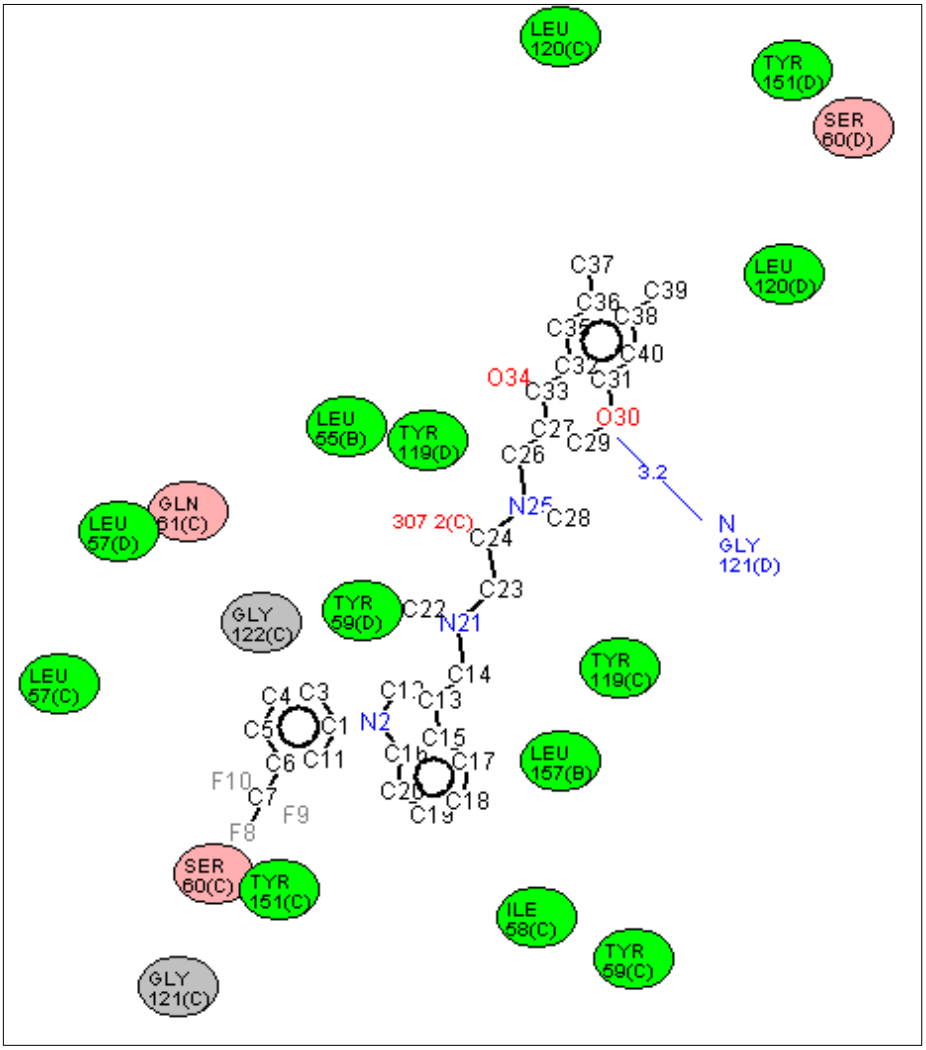

Fig 3: TNF-α attached with inhibitory ligand in Chain C (307)

2.3 Selection of phytochemicals (ligands)

The phtochemicals or ligand selection of *Cissus quadrangularis* were done from the literatures [18-20]. In the present study, 10 phytochemicals were established and taken. There CAS no and Canonical SMILES were obtained from the pubchem database (www.ncbi.nlm.nih. Gov/pubchem) and tabulated in Table 1. The three dimensional (3-D) structure and. pdb file of each phytochemicals was obtained from CORINA online server after inserting SMILESs ring in appropriate place. Some 3-D structure of ligands are depicted in Fig 4.

Table 1: Phytochemicals of *Cissus quadrangularis* and their inhibitory ligand

S. No.	Phytochemicals	CAS No.*	Canonical SMILES*
1.	Asarone	5273-86-9	CC=CC1=CC(=C(C=C1OC)OC)OC
2.	Luteolin	491-70-3	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O
3.	Quercetin	117-39-5	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
4.	Resveratrol	501-36-0	C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O
5.	Piceatannol	4339-71-3	C1=CC(=C(C=C1C=CC2=CC(=CC(=C2)O)O)O)O
6.	Kaempferol	520-18-3	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
7.	Stigmasterol	83-48-7	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
8.	Lupeol	545-47-1	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C
9.	Freidalin	559-74-0	CC1C(=O)CCC2C1(CCC3C2(CCC4(C3(CCC5(C4CC(CC5)(C)C)C)C)C)C)C
10.	Phytol	150-86-7	CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C
11.	Eugenol	97-53-0	COC1=C(C=CC(=C1)CC=C)O

*Data retrieved from PubChem Database, CAS No. = Chemical Abstract Service Registry Number; SMILES = Simplified molecular-input line-entry system

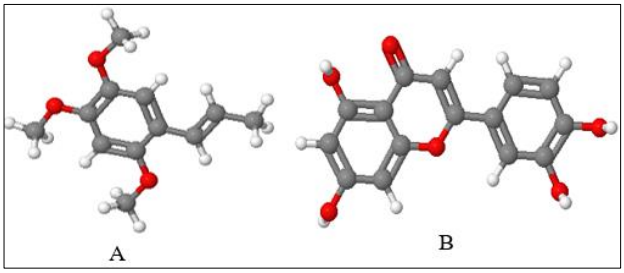

Fig 4: Three-dimensional structure of two phytochemicals Such as (A=Asarone; B=Luteolin)

2.4 Study of molecular docking and interaction

The docking was carried out by virtual screening method through PyRx software (version 0.8) [21]. The molecular docking was imagined the output. Pdbqt file by using AutoDock Vina software [16] and the results of three dimensional structure were depicted by using MGL Tools. The PyRx software is combination of Auto Dock Vina, Auto Dock 4.2, Mayavi open Babel and phyton tools. This software is also non-commercial, less time consuming docking program that describes receptor-ligand interactions along with energy value for each test compound. 11 phytochemicals was visualized for the docking of phytoconstituents (ligands) and the TNF-α (receptor) for identification of residues involved in the study of receptor-ligand interactions. The present tool describes docking result by obtaining energy value for each ligand. At least all the 11 ligands were visualized to detect the binding position and energy value.

3. Results

The results indicate the molecular docking and interaction of established phytochemicals of *Cissus quadrangularis* with the target protein Tumor necrosis factor (TNF-α) was tabulated in Table 2. In this table the energy values were obtained lowest for Lupeol and highest for Eugenol respectively. All 11 phytochemicals were also studied to check binding energy values, hydrogen bond contacts and hydrophobic bonds. All of these 11 phytochemicals Lupeol was observed suitable binding energy against TNF-α receptor which may act as an inhibitor.

Table 2: Receptor-ligand binding energy value and molecular interaction

S. No.	Name of Phytochemicals	Binding energy (Kcal/mol)	Hydrogen bond number and contact residues	Close contact residues
1.	Lupeol	-10.7	1 and Gln149	Tyr151, Tyr159, Ile155 and Leu57
2.	Freidalin	-9.9	---	Leu67 and Tyr59
3.	Stigmasterol	-9.7	1 and Tyr151	Leu57 and Val123
4.	Luteolin	-8.9	2 and Gln125	Gln125 and Arg82
5.	Quercetin	-8.7	2 and Gln125	Arg82 and Leu93
6.	Piceatannol	-7.9	1 and Gln125	Gln125, Arg82, Phe124, Leu93 and Arg82
7.	Kaempferol	-7.8	---	Arg82, Val91, Gln125 and Phe124
8.	Resveratrol	-7.7	1 and Gln125	Arg82 and phe124
9.	Phytol	-6.7	1 and Tyr151	Tyr59, Val123, Gly121, Val123 and Leu55
10.	Asarone	-6.0	---	Leu67 and Tyr69
11.	Eugenol	-5.9	---	Tyr59 and Leu57

4. Discussion

The study of Phyto ligands through the molecular docking and interactions is well known to detect receptor- ligand binding site. This molecular docking study has low cost, faster and no animal harm [22, 23]. The binding affinity between the receptor TNF-α and phytoligands had been carried out with bioactive compounds of several medicinal plants in new drug discovery [24, 25]. The herbal medicinal plant *Cissus quadrangularis* is used for the treatment of inflammatory diseases and pain etc [26, 20].

Among established 11 phytocompounds Lupeol phytocompound has highest binding energy value with one hydrogen bond contact against the TNF-α receptor through the computational screening study when compaired with other phytocompounds. So the phytocompound Lupeol of *Cissus quadrangularis* may be considered as potent anti-inflammatory drug for arthritis, risk of urinary incontinence due to their strong binding affinity as well as one hydrogen bond. Therefore overactivity of TNF-α may be inhibited by phytoligand Lupeol of *Cissus quadrangularis* and prevented inflammation in arthritis, risk of urinary incontinence.

5. Conclusion

The molecular docking is a computional screening method or tool of ligands for known receptor. The score values of Lupeol were predicted that Lupeol has good binding affinity towards TNF-α based on the present results compared to other phytoligands. So the phytoligand Lupeol may be expected as lead molecule to inhibit the activity of TNF-α and may prevent inflammation of arthritis, risk of urinary incontinence.

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