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In-silico study on biomolecules derived from *Cissus quadrangularis* towards anti-inflammation

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ABSTRACT

Objective: CD 163 protein is a macrophage-specific protein and hemoglobin scavenger receptor. Elevated expression of CD 163 protein in macrophages is an important feature indicating that tissues are subjected to inflammation. It can be an effective diagnostic biomarker for inflammatory diseases like gingivitis and periodontitis. Cissus quadrangularis is used as a potent alternative medicine to control inflammation and heal fractured bones. It has high osteogenic potential by increasing osteoblast mineralization. Being a natural product with a wide range of benefits can lead to drug development for its high anti-inflammatory and anti-osteoporotic properties. Studies have shown that Cissus quadrangularis has significant anti-inflammatory potential and can be used as a potential target for therapeutic agents. The objective of the study is to explore the interaction of the phytonutrients derived from Cissus quadrangularis with CD 163 protein to establish the anti-inflammatory activity by in silico approach.

Materials and methods: The biomolecules derived from the plant Cissus quadrangularis namely β-Sitosterol, luteolin, piceatannol, quadrangualrin, resveratrol, and tannins were subjected to molecular docking using Autodock of 4.0 PyRx software.

Results: The study results showed drug-likeness and binding affinity between biologically active Cissus quadrangularis molecules against inflammation associated with CD 163 protein.

Conclusion: It can be concluded that the biomolecules derived from Cissus quadrangularis exhibited anti-inflammatory potential and thus it can be further explored by invitro analysis in developing a new drug.

1. Introduction

Plants are utilized in phytotherapy, also known as phytomedicine, which employs medicinal plants to promote bodily health and well-being. This practice serves as the foundation of traditional medicine. The utilization of medicinal plants dates back approximately 60,000 years.[1] Traditional Indian medicine, known as Ayurveda, alleviates patient symptoms, enhances health conditions, and improves overall quality of life. In the Indian subcontinent, nearly 10,000 plants are employed for medicinal purposes, of which only 1,200 to 1,500 are incorporated into Ayurvedic formulations. [2,3].

Cissus quadrangularis Linn is a perennial grapevine known for its medicinal properties and is often regarded as an underappreciated asset in the dental sector. Few studies have been conducted, all highlighting its effectiveness in bone regeneration and fracture healing through the enhancement of ALP activity and the proliferation of osteoblasts.[4–8] This succulent plant is native to tropical regions. It has been utilized for centuries in Indian Ayurvedic medicine to treat fractures, diarrhea, gout, ulcers, hemorrhage, allergies, and syphilis. It is emerging as a promising dental biomaterial due to its remarkable anti-inflammatory, antioxidant, and regenerative properties. [9–13].

Herbal medicine may be a viable alternative to contemporary pharmaceuticals as an adjuvant to periodontal treatment. [14–19] Cissus quadrangularis is a good source of vitamins and minerals that help in the bone healing process and bone regeneration. [20–24] Cissus quadrangularis contains ketosteroids- β sitosterol, luteolin, tannins, resveratrol, piceatannol, and quadragulurin A are bioactive constituents. It possesses antibacterial properties and aids in fracture healing, serving to manage

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pain and metabolic disorders. It has been utilized in the treatment of periodontal osseous defects for the regeneration of alveolar bone, either independently or in conjunction with growth factors. Cissus quadrangularis contains numerous pharmacologically active compounds. More than 70 active metabolites have been identified in Cissus quadrangularis, with stilbenes, flavonoids, phytosterols, and quercetin derivatives being the most prevalent.

The CD163 protein functions as a hemoglobin scavenger receptor or a protein associated with monocytes/macrophages, demonstrating significant anti-inflammatory properties. Phagocytes that express the CD-163 protein act as therapeutic agents in the modulation of the inflammatory response by downregulating inflammatory mediators such as interleukin-10 and interferon-gamma.[25] Elevated levels of soluble CD163 have been observed in both acute and chronic inflammation, exhibiting a cytokine-like anti-inflammatory role. Targeting CD163+ is proposed as a potential marker for drug delivery and for the treatment of inflammatory diseases. [26] An increased expression of CD163 in tissues signifies that these tissues are actively responding to inflammation. Cissus quadrangularis shows remarkable anti-inflammatory effects by disrupting prostaglandin synthesis [27] and inhibiting the activity of cyclooxygenase (COX-1), cyclooxygenase (COX-2), and 5-lipoxygenase (5-LOX) enzymes. [28].

In this in silico study, the drug-likeness and the binding energy of the drug Cissus quadrangularis with selected biomolecules were studied with the CD 163 protein to show its ability as a drug to treat inflammatory diseases.

2. Materials and methods

2.1. Structure retrieval of macromolecules and molecular visualisation

According to Jumper et al 2021, the AlphaFold algorithm's deep neural network has proven to be incredibly accurate at predicting the three-dimensional structure of proteins with previously unidentified folds by combining features acquired from homologous templates and multiple sequence alignment. From the Uniprot database, the CD163 alpha fold structure was obtained. Fig. 1 depicts the Scavenger receptor cysteine-rich type 1 protein in three dimensions (CD 163). BIOVAVA Discovery studio visualizer software was utilised to visualise the 3-D structure of a protein.

An insilico study was performed in a DELL Inspiron 14 with Intel Core i3 processor, 4 GB RAM, and a 500 GB hard disk capacity. The software used for docking was Autodock 4.0 PyRx. Visual inspection for the binding pattern was done using PYMOL.

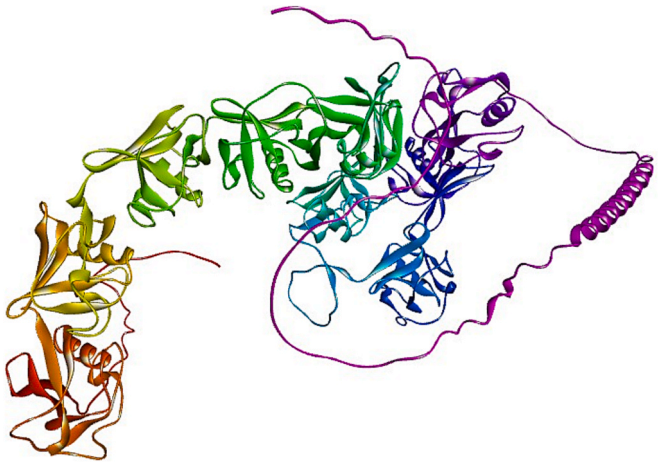

Fig. 1.

3. Docking study

3.1. Ligand preparation

Chemical structures and biological details on chemical substances are both included in the PubChem database. Using this, beta-sitosterol, luteolin, piceatannol, quadrangularin, resveratrol, and tannins #39; SDF structures were downloaded. Then, using the Python Prescription Virtual Screening Tool, the chemicals were put into Open Babel and subjected to energy minimization (PyRx). The Universal Force Field minimized energy using the conjugate gradient method (UFF). The number of update steps was set to one, making the total number of steps 200. Additionally, the reduction was set up to stop when the energy difference fell below 0.1 kcal/mol. The following compounds beta-sitosterol, luteolin, piceatannol, quadrangularin, resveratrol, and tannins are selected for the study. The binding ability of each compound and drug-likeness were detected and scored.

3.2. Docking using Autodock version 4.0 of Pyrx software

Using Autodock version 4.0 of the Pyrx software, the process of docking ligands with receptors has been carried out (Trott and Olson, 2010). Docking is the technique of predicting the most efficiently binding ligand(s) from a library of chemicals by utilising several scoring algorithms. Docking is the virtual screening of a database of compounds. All of the ligands were placed in a PyRx Autodock (Autodock vina) folder to build the ligand library [Morris et al., 2009]. The library preparation helps to facilitate easier ligand comparison research by carrying out simultaneous docking of many ligands against the receptor. Additionally, grid batch docking was done. Each docked molecule receives a final minimum score (Dock score interaction/Docking energy of receptor-ligand) that is used to express the results.

4. Results and discussion

To find undiscovered targets, protein and drug interactions can be identified using molecular docking. There is evidence to support the use of plant-based medicines in the treatment of numerous ailments. In this work, the type 1 protein of the Scavenger receptor was chosen to interact with plant-derived ligands (CD 163). The potential of beta-sitosterol, luteolin, piceatannol, quadrangularin, resveratrol, and tannins were examined using in silico analysis. These ligands' binding energies can be used to study their inhibitory potential (B.E). The highest binding affinity with the target protein is indicated by higher negative energy. The study's findings demonstrated that all six compounds demonstrated strong binding to the target protein. These chemicals binding energy ranges are shown to be between −4.7 and −6.1 kcal/mol. The molecular interactions of the selected biomolecules against the target CD163 protein. In docking analysis, the highest negative scores indicate a better active compound. The results revealed that the β-sitosterol compound showed the highest binding affinity of −6.1 kcal/mol and binding pockets as shown in Fig. 2. Table 1 shows the docking outcomes and residues LEU404, LYS421, THR522, ASP661, ALA419, and others listed were predicted as active sites in target protein CD163. The hydrogen bonding interactions increase the ligand–protein interactions.

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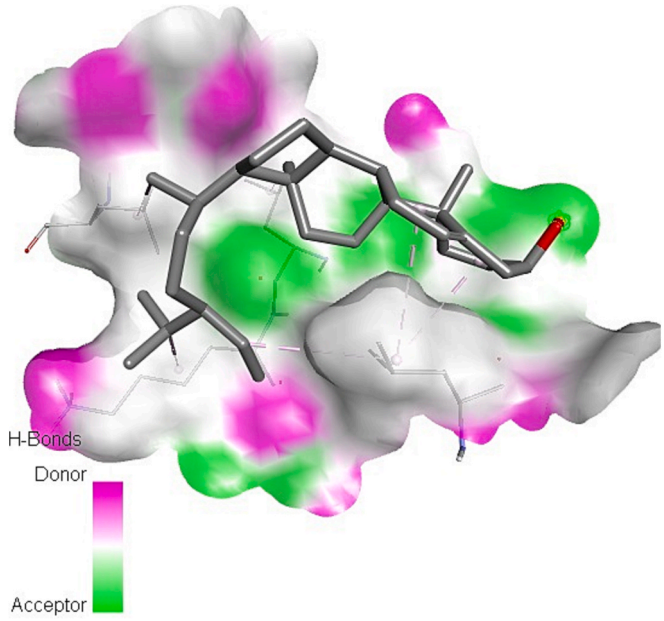

Fig. 2.

Table 1
Docking results showing binding energy and interacting amino acids.

S. No:	Biomolecules of Cissus quadrangularis	Binding Energy kcal/mol	Interacting residues Pi-alkyl
1	Beta-Sitosterol	−6.1	LEU-404 LEU-420 LYS-421 LEU-556
2	Luteolin	−4.9	THR-422 SER-552 LYS-421 LEU-556
3	Piceatannol	−4.8	ARG-579 THR-523 THR-665 ASP-661 GLY-947 GLN-866
4	Quadrangularin	−5.1	ALA-419 GLY-444
5	Resveratrol	−5.7	LYS-405 HIS-550 SER-552 LEU-556 LYS-421 LEU-404
6	Tannins	−4.7	SER-578 LEU-824 TRP-945 MET-822

5. Conclusion

Plant extracts, being an efficient ethnobiological alternative medicine, are safe, feasible, biocompatible, and effective in treating various ailments. Our research attempts to explore the anti-inflammatory properties of Cissus quadrangularis. Proteins have a crucial role in reducing inflammation. In this study drug likeness of the compound was evaluated and was found to comply with Lipinski's rule. Our study has shown that all six selected biomolecules of Cissus quadrangularis showed strong binding to the target CD-163 protein and exhibited anti-inflammatory potential. The outcome of the current study proved the anti-inflammatory potential. Henceforth, further confirmation necessitates more in vitro and in vivo studies for using Cissus quadrangularis as an alternative drug.

Ethical approval

Institutional review board approval is not required.

Declaration of patient consent

Patient consent is not required as it is a virtual clinical trial.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI) assisted technology for manuscript writing or editing and no manipulation of figures using AI.

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CRediT authorship contribution statement

H. Nilofer Farjana: Writing – original draft, Validation, Software, Methodology, Data curation, Conceptualization. **G. Mohan Valiathan:** Writing – review & editing. **S. Mohanasatheesh:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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