

Anti-inflammatory ability of licorice (*Glycyrrhiza glabra*) root extract in cyclooxygenase-2 enzyme inhibition: In silico study

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Abstract

Background: Inflammation represents the body's natural response to injury, which can be induced by chemical, physical, or biological agents. Current approaches to managing inflammatory conditions involve addressing the primary etiological factors and administering anti-inflammatory medications like Nonsteroid Anti Inflammatory Drugs (NSAIDs) in inhibiting cyclooxygenase 2 (COX-2). However, data from 2021 reveals that 78.8% of patients experience gastritis as a side effect of such treatment. Licorice root extract (LRE)-an ayurvedic plants emerges as a promising alternative due to its potent anti-inflammatory properties attributed to the presence of glycyrrhizin, constituting between 2% to 25% of its dry weight.

Objectives: To find out and determine the molecular inhibition of compound in LRE against COX-2 enzyme.

Method: The process involves isolating the active constituents of LRE using pubchem and BioVia application, isolation active site of COX-2 by exploring RCSB PDB and isolate it using PyMol and engaging in molecular docking simulations using PyRx.

Results and discussions: Cyclooxygenase-2 (COX-2) emerges as a pivotal enzymatic orchestrator intricately woven into the fabric of the inflammatory cascade. Licorice root extract stands at the forefront of prospective candidates in the realm of anti-inflammatory drug development, buoyed by its remarkable anti-inflammatory attributes. Regarding to ΔG_{bind} value, molecular docking tests show LRE compounds inhibit COX-2 better than arachidonic acid and mefenamic acid. Six LRE compounds outperform reference compounds, indicating potential anti-inflammatory capabilities. Other compounds show anti-inflammatory activity, and RMSD values affirm the accuracy of in silico predictions.

Conclusion: LRE had potential as oral topical anti-inflammatory drugs through COX-2 inhibition with the best anti-inflammation ability is 18 β -glycyrrhetic acid.

Keywords: Licorice root extract; Anti-inflammation; Molecular docking; Cyclooxygenase enzyme; Drug discovery; Medicine

1. Introduction

Inflammation represents the body's natural response to injury or perceived foreign substances [1,2]. Oral inflammatory conditions commonly exhibit the five cardinal signs, including calor, tumor, dolor, rubor, and loss of function [3]. The

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inflammatory process is orchestrated by potent mediators such as prostaglandin E2 (PGE2), a product of arachidonic acid (AA) conversion facilitated by the COX-2 enzyme [4–6]. Excessive PGE2 production leads to the continuous recruitment of immune cells, intensifying tissue-destructive responses and contributing to the progression of chronic inflammation. Considering the pivotal role of PGE2 in inflammation, therapeutic interventions often involve anti-inflammatory medications targeting COX-2 to inhibit the conversion of AA to PGE2, such as Nonsteroid Anti-Inflammatory Drugs (NSAIDs) [7–9]. However, NSAIDs may induce gastritis as a side effect in patients. Findings from a 2021 study reported a 78.8% prevalence of gastritis in individuals due to the side effects of NSAID consumption. This occurrence is attributed to the oral consumption (tablets, pills, and capsules) of NSAIDs' active compounds, which inhibit COX enzymes in the stomach. The reduced production of PGE2 in the stomach eliminates its gastroprotective function, leading to stomach irritation (gastritis). Moreover, the use of oral formulations for drug delivery can diminish a drug's bioavailability, subsequently reducing the amount absorbed by the body [10]. In response to this challenge, researchers are exploring effective pharmaceutical formulations and active compound such as licorice-an ayurvedic plant[11].

Ayurveda, a traditional Indian system of medicine focused on balancing the mind, body, and soul to maintain health and prevent diseases [12]. utilizes various herbal plants to protect against a range of ailments, including digestive and mental health issues. Among these plants is licorice root (*Glycyrrhiza glabra*), a well-known component of Ayurvedic medicine. Licorice has a rich history in traditional medicine, valued not only for its flavorsome properties but also for its diverse medicinal benefits. The root of the licorice plant is particularly recognized for its adaptogenic properties, aiding the body in adapting to stress and promoting equilibrium. Licorice has played a significant role in various traditional medicinal practices, including Ayurveda, owing to its diverse health advantages. Licorice encompasses key constituents such as sugars, starch, bitters, resins, essential oils, tannins, inorganic salts, and limited levels of nitrogenous constituents like proteins, individual amino acids, and nucleic acids. Widely used as a natural sweetener and food flavoring agent, licorice is a common ingredient in commercial chewing gums, candies, beverages, as well as pharmaceutical drugs and lozenges. Licorice root extracts (LRE) find frequent application in cough syrups and herbal formulations, offering relief for conditions such as asthma, excessive coughing, common cold, sore throat, sinusitis, allergic rhinitis, and respiratory tract infections [13–16].



Figure 1 Licorice (*Glycyrrhiza glabra*) root (left) and flower (right).

Glycyrrhizin, a key active compound in licorice, is a triterpenoid saponin known for its extraordinary sweetness, approximately 50 times sweeter than sucrose. Comprising around 10% of the dry weight of licorice root, glycyrrhizin is a complex of potassium, calcium, and magnesium salts of glycyrrhizic acid, with concentrations ranging from 2% to 25%. The yellow hue of licorice is attributed to its flavonoid content, encompassing flavanones, flavones, flavanonols, chalcones, isoflavans, isoflavenes, isoflavons, and isoflavanones. Prominent flavonoids include glycosides of liquiritigenin and isoliquiritigenin, such as liquiritin, isoliquiritin, liquiritin apioside, and licuraside [16]. Traditionally valued for its appealing taste and diverse medicinal properties, licorice has gained attention in scientific studies. Recent research suggests that the extract from *Glycyrrhiza glabra* may serve as a potential treatment for anti-inflammatory drugs, with its efficacy attributed to compounds like 18 β -glycyrrhetic and glycyrrhizic acids. Licorice root extract has been extensively studied for its anti-inflammatory properties. Yu 2015 found that licorice extract and its active compounds, glycyrrhizic acid, liquiritin, and liquiritigenin, can inhibit the expression of pro-inflammatory mediators. Kim 2006 further supported this, demonstrating that roasted licorice extract can reduce the production of nitric oxide, prostaglandin E2, and pro-inflammatory cytokines. Yang 2016 summarized the anti-inflammatory properties of licorice and its compounds, which are attributed to their ability to decrease TNF, MMPs, PGE2, and free radicals. Tanaka 2008 also highlighted the antioxidant and anti-inflammatory activities of licorice root extract. These

studies collectively provide strong evidence for the anti-inflammatory potential of licorice root extract [13]. Reviewing the problems arising from the use of anti-inflammatory drugs NSAIDs orally and considering the potential of the licorice root extract. This study aim is to analyzing the potential of licorice root extract as an anti-inflammatory. Researches found the gap that previous study still questionable about spesific inhibition of active compound in licorice root extract against cyclooxygenase enzyme. Looking from that gap, the researcher conducting this research which is focusing on discovering the inhibition mechanism of licorice root extract against COX-2 that play key rols in inflammatory conditions. This research is expected to be able to provide specific descriptions and predictions regarding the inhibition ability of the licorice root extract against COX-2 [17–19].

2. Material and methods

2.1. Material

2.1.1. Licorice root extract compound and protein target materials

This study used the active compound of LRE which was downloaded and prepared in 2 dimensions from the PubChem website (<https://pubchem.ncbi.nlm.nih.gov/>). The active compounds used in the PPE are the highest levels compound including liquiritin (CID 503737), isoliquiritin (CID 5318591), liquiritigenin (CID 114829), isoliquiritigenin (CID 638278), glycyrrhetic acid (CID 10114), liquiritin apioside (CID 10076238), 18 β -glycyrrhetic acid (CID 5702287), licochalcone A (CID 5318998), and glabridin (CID 124052). As a comparison, the researchers used 2 comparator golden standar drugs mefenamic acid (CID 444899) and arachidonic acid (CID 4044). The target of this study is active conformation of protein COX-2 (PDB ID 5IKR) which was downloaded and prepared for its 3-dimensional structure from the RCSB Protein Data Bank web page (<https://www.rcsb.org/>). Selection of COX-2 is based on enzyme sources isolated from humans, has a resolution of more than 2Å, and has the most favorable region value of 90% in the Ramachandran range which is effective for protein docking targets [19,20].

2.1.2. Research tools

This research employs a bioinformatics approach (in silico), utilizing database pages and supporting applications running Python programs. The in silico test methodology involves distinct stages, employing various database pages and applications. The preparation of test materials and visualization of docking results is facilitated by applications like Biovia and PyMol. The Way2Drug page (<http://www.way2drug.com/PASSOnline>) is utilized for PASS prediction, the Lipinski Rule of Five page (<http://www.scbio-iitd.res.in/>) for physicochemical tests, and the pkCSM website (<https://biosig.lab.uq.edu.au>) for predicting ADME and toxicity. To identify active research target sites, the Uniprot website (<https://www.uniprot.org/>) is referenced, and molecular docking tests are conducted using PyRx applications. This comprehensive integration of various tools and platforms enhances the efficiency and accuracy of the in silico analysis [19,21].

2.2. Methods

2.2.1. Preparation of ligand molecular structure and protein structure

The initiation of test material preparation involves acquiring the test compound and targets from the PubChem and RCSB PDB databases. Following the download, the test and target compounds are assigned names corresponding to the compound name, as the downloaded forms are initially in CID numbers. Subsequently, the identification of the active site of COX-2 (PDB ID 5IKR) is crucial for its role in cyclooxygenase activity, achieved through the Uniprot site. By inputting the PDB ID code, the peptide chain sequence is obtained, requiring isolation before the docking process. Utilizing the Biovia application, the target protein is prepared by eliminating water molecules and native ligands, also retrieved from the database. Following preparation, the isolation of the peptide chain, serving as the active site of COX-2 at the 371st peptide chain, is performed using the PyMol application. This meticulous preparation ensures the accuracy and reliability of subsequent molecular docking tests [22].

2.2.2. Molecular docking test

The molecular docking assessment commenced with the input of the test compound, reference compound, and target protein into the PyRx application. Subsequent to the upload, the PyRx program was executed to determine binding affinity results in kcal/mol units, mode, RMSD lower bound, and upper bound. A compound exhibits a propensity for binding to the target protein when it possesses a low binding affinity value. The lower the binding affinity value, the less energy required for bond formation, indicating a higher tendency for bond creation with the target protein. The mode parameter delineates the diversity of formed bonds. The RMSD parameter gauges the accuracy and precision of the

predictions, with compounds ideally having low binding affinity values and optimal RMSD in the lower bound and zero in the upper bound modes.

3. Results

3.1. Molecular docking test result

Table 1 Molecular docking test result of LRE active compound with comparative compound of arachidonic acid and mefenamic acid

Compound	Binding Affinity (kcal/mol)	Mode	RMSD	
			Lower Bound	Upper Bound
Arachidonic acid	-3.7	0	0	0
Mefenamic acid	-5.0	0	0	0
Liquiritin	-5.3 ^{^*}	0	0	0
Isoliquiritin	-5.0 ^{^*}	0	0	0
Liquiritigenin	-4.5 [^]	0	0	0
Isoliquiritigenin	-4.7 [^]	0	0	0
Glycyrrhetic acid	-5.5 ^{^*}	0	0	0
Liquiritin apioside	-5.5 ^{^*}	0	0	0
18 β -Glycyrrhetic acid	-5.6 ^{^*}	0	0	0
Licochalcone A	-4.8 [^]	0	0	0
Glabridin	-5.1 ^{^*}	0	0	0

[^]value lower/equal than arachidonic acid, ^{^*}value lower/equal than mefenamic acid

The results of the molecular docking test determine the ability and anti-inflammatory potential of licorice root extract compounds reviewed through their ability to inhibit COX-2 compared to comparison compounds. On the same mode value, RMSD lower bound, and upper bound value of 0, several substances of LRE has lower binding affinity than arachidonic acid and mefenamic acid are liquiritin, isoliquiritin, glycyrrhetic acid, liquiritin apioside, 18 β -Glycyrrhetic acid, and glabridin.

4. Discussion

COX-2, a crucial enzyme in inflammation, facilitates prostaglandin synthesis, which modulates inflammation. Inhibition of COX-2 is vital for anti-inflammatory drugs, like mefenamic acid, to reduce prostaglandin production at the inflammation site, providing relief from symptoms like pain, swelling, and fever. Mefenamic acid's precision in targeting COX-2 is essential in drug development, sparing constitutive COX-1 responsible for gastric integrity and platelet regulation. In the complex field of anti-inflammatory drug development, COX-2 inhibition, exemplified by mefenamic acid, plays a pivotal role in managing inflammatory conditions [23–25]. Licorice root extract, with over 300 compounds, is a promising anti-inflammatory candidate, primarily due to glycyrrhizin. Research supports its potential for managing inflammatory diseases [14,15]. Studies reveal licorice root extract's ability to reduce pro-inflammatory cytokines and inhibit COX-2, a key enzyme in inflammation. COX-2 inhibition, exemplified by mefenamic acid, curbs prostaglandin production, alleviating symptoms. This is pivotal in anti-inflammatory drug development [23,24]. Apart from its anti-inflammatory properties, licorice root extract also possesses antioxidant and antimicrobial attributes, enhancing its status as a versatile anti-inflammatory agent. Recent pharmacological studies have highlighted its diverse effects, including anti-inflammatory, antiviral, antibacterial, and immunomodulatory actions. These findings underscore licorice root extract's potential as a natural and effective remedy for inflammatory conditions [13]. Molecular docking results highlight the crucial role of the COX-2 enzyme in inflammation. COX-2 catalyzes the production of PGE₂, triggering immune cell recruitment, edema, and pro-inflammatory cytokine synthesis. Licorice root extract (LRE) shows strong inhibitory potential against COX-2, with 6 of its compounds exhibiting superior binding affinity compared to reference compounds (arachidonic acid and mefenamic acid). Notable among these are liquiritin, glycyrrhetic acid,

liquiritin apioside, 18 β -glycyrrhetic acid, and glabridin. These findings suggest that LRE compounds can inhibit COX-2 more efficiently. Other LRE compounds, while less potent than mefenamic acid, still demonstrate anti-inflammatory capabilities, surpassing arachidonic acid's control [26]. Among the 9 predominant compounds in LRE, 6 show superior COX-2 inhibitory potential with binding affinity values ranging from -4.5 to -5.6 kcal/mol. These values indicate their strong ability to form bonds with COX-2's active site, surpassing arachidonic acid and mefenamic acid. Other LRE compounds like liquiritigenin, isoliquiritigenin, and licochalcone A, while not as potent as mefenamic acid, still inhibit COX-2 effectively. RMSD values confirm the accuracy of in silico predictions, with all compounds, including mefenamic acid and arachidonic acid, showing high accuracy in docking predictions that align closely with laboratory outcomes [17,20,27–30].

5. Conclusion

Derived from the findings and preceding discourse, the primary bioactive constituents within LRE are envisaged to exhibit notable anti-inflammatory prowess against COX-2 enzymes, with 18 β -Glycyrrhetic acid compounds emerging as the most potent in terms of anti-inflammatory efficacy. Furthermore, these investigations suggest the potential for topical application of the compound onto the mucosal surface of the oral cavity. In the subsequent phases of research, it is envisaged that this study can be further expanded, encompassing comprehensive in vitro and in vivo assessments, alongside a systematic literature review, thereby bolstering the foundation for the success of this innovative concept.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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