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Exploring the Anti-Inflammatory Activity of Purified *Ficus septica* Extracts: Insights from In Vitro and In Silico Studies

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ABSTRACT: *Ficus septica* is a plant that has demonstrated significant potential as an anti-inflammatory agent. This study evaluates the anti-inflammatory activity and molecular mechanisms of compounds from *Ficus septica*, focusing on their interactions with Bovine Serum Albumin (BSA) and Cyclooxygenase-2 (COX-2). The results show that the purified extracts from Kadia and Batalaiworu exhibited better anti-inflammatory activity, with IC_{50} values of 32.04 µg/mL and 32.06 µg/mL, respectively, compared to the crude extracts, which had IC_{50} values of 42.07 µg/mL and 42.44 µg/mL. Diclofenac Sodium demonstrated a notably low IC_{50} value of 7.99 µg/mL. Computational analyses identified Genistein as having the strongest binding affinity to BSA, with a binding energy of -7.52 kcal/mol, closely matching that of Diclofenac (-7.51 kcal/mol). Additionally, Ficuseptine B and Septicine exhibited robust interactions with COX-2, with binding energies of -9.51 kcal/mol and -9.45 kcal/mol, respectively, surpassing the binding energy of Diclofenac (-8.49 kcal/mol). These results highlight the potential of *Ficus septica*-derived compounds, particularly Genistein, Ficuseptine B, and Septicine, as promising anti-inflammatory agents due to their strong binding affinities with BSA and COX-2.

Keywords: **anti-inflammatory activity; binding energy; *Ficus septica*; molecular interaction.**

Introduction

Inflammation is a vital biological process that helps maintain tissue homeostasis and facilitates the body's response to injury or infection [1]. Acute inflammation is crucial for healing, but when dysregulated or persistent, it can drive the progression of numerous diseases, such as autoimmune disorders, cardiovascular conditions, diabetes, neurodegenerative diseases, and certain cancers [2,3]. Although widely used, conventional anti-inflammatory treatments like non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids often cause adverse effects, including gastrointestinal irritation, kidney dysfunction, and increased infection risk [4,5]. These limitations underscore the need for safer, alternative anti-inflammatory agents, particularly those derived from natural sources.

Medicinal plants have historically been a rich source of drug discovery due to their diverse chemical profiles and bioactive properties [6]. One notable example is *Ficus septica*, a member of the Moraceae family, which has been traditionally used in Southeast Asia to treat inflammation-related ailments, including wounds, infections, and fever [7,8]. Phytochemical studies reveal that *Ficus septica* contains secondary metabolites, such as flavonoids, terpenoids, alkaloids, and phenolic compounds, known for their anti-inflammatory and antioxidant activities [9]. However, comprehensive studies investigating its bioactive properties and molecular mechanisms remain scarce.

This research aims to bridge the gap between traditional knowledge and scientific evidence regarding the therapeutic potential of *Ficus septica*. Specifically, the study explores its anti-inflammatory effects by focusing on its interactions with key inflammation-related proteins. The stabilization of bovine serum albumin (BSA) under stress-induced conditions is widely utilized as a model to assess anti-inflammatory activity [10]. This method leverages the principle that BSA denaturation reflects protein destabilization commonly associated with inflammatory processes [11]. Compounds with the ability to stabilize BSA have demonstrated significant potential in mitigating inflammation by modulating protein-protein interactions and preserving cellular homeostasis [12].

Furthermore, cyclooxygenase-2 (COX-2), a pivotal enzyme in the inflammatory response, serves as a key target for evaluating the anti-inflammatory

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potential of the *Ficus septica*. This enzyme plays a central role in mediating the production of prostaglandins, which are responsible for pain, swelling, and fever during inflammation [13]. The development of selective COX-2 inhibitors has offered an effective approach to reducing inflammation while minimizing the gastrointestinal side effects commonly associated with traditional NSAIDs [14]. This study evaluates the anti-inflammatory properties of *Ficus septica* through its crude and purified extracts by examining their ability to stabilize BSA and interact with COX-2. Molecular docking and binding analyses further clarify the mechanisms underlying these interactions. These findings aim to provide insights into the plant's potential to modulate inflammatory pathways and support the development of safer, plant-based anti-inflammatory agents.

Methods

Plant Material

The leaves of *Ficus septica* were collected from two locations: Kadia District (3°58'49.0"S, 122°31'27.5"E) in Kendari City and Batalaiworu District (4°47'57.4"S, 122°42'46.4"E) in Muna Regency, Southeast Sulawesi, Indonesia. The plant used in this study was taxonomically identified at the Biology Education Program, Faculty of Teacher Training and Education, Universitas Halu Oleo, with identification number 9/BIO/PB/VI/2024. The plant sample was identified using the following key: 11a-2b-4b-5a-6a-7a-8b-9a-10b-11b-12b-13b-14b-15b, corresponding to *Ficus septica*. The collected samples were air-dried under controlled conditions at temperatures below 45°C for four days. Finally, the dried simplicia was ground into a fine powder and stored in a sealed, dry container to maintain its quality.

Extraction and Purification

The dried simplicia of *Ficus septica* were macerated individually in methanol (Merck) for 72 hours. The resulting filtrates were concentrated using a vacuum rotary evaporator (Stuart RE300, USA) at 50°C with a rotation speed of 85 rpm. The concentrated extracts were subsequently purified using n-hexane. Finally, the purified extracts were evaporated using a water bath at 50°C (Merck).

Inhibition of Protein Denaturation

The anti-inflammatory activity of *Ficus septica* leaf extract and its purified form was assessed using a modified BSA assay based on the method described in previous study [15]. A 0.2% (w/v) bovine serum albumin (BSA, HIMEDIA®) solution was prepared in Tris-buffered saline (HIMEDIA®). The buffer was prepared by dissolving 4.35 g of sodium chloride (Merck) and 0.6 g of Tris base (HIMEDIA®) in distilled water, adjusting the pH to 6.5 (pathological pH) with glacial acetic acid (Merck), and diluting the solution to a final volume of 500 mL.

Stock solutions of the extracts were prepared at a concentration of 100 mg/L in methanol (Merck). Aliquots of 10 µL, 20 µL, 30 µL, 40 µL, and 50 µL, corresponding to final concentrations of 1 mg/L, 2 mg/L, 3 mg/L, 4 mg/L, and 5 mg/L, respectively, were added to test tubes containing 1 mL of the 0.2% BSA solution. Methanol (Merck) was used as the negative control, and diclofenac sodium (Sigma-Aldrich) served as the positive control.

The mixtures were incubated at 72°C for 20 minutes and then allowed to cool at room temperature for 30 minutes. The turbidity of each sample was measured at 660 nm using a UV-Vis spectrophotometer. All experiments were conducted in duplicate, and the average absorbance values were recorded. The percentage inhibition of turbidity was calculated using the following formula:

Inhibition (%) = (Absorbance of Control-Absorbance of Sample)/(Absorbance of Control) x 100

Molecular Docking Study

The potential of *Ficus septica* to stabilize bovine serum albumin (BSA) was evaluated as an indicator of its anti-inflammatory activity. The three-dimensional structure of BSA (PDB ID: 4OR0) [16] dan COX-2 (1PXX) [17] were retrieved from the Protein Data Bank, while the structures of 26 metabolites from *Ficus septica* were obtained from the KnapSacK-3D (http://knapsack3d.sakura.ne.jp/). KNApSAcK-3D provides three-dimensional (3D) structural data for all metabolic compounds in the KNApSAcK database. The 3D structures were optimized using the Merck Molecular Force Field (MMFF94) and a multi-objective genetic algorithm to extensively explore conformations and identify the global energy minimum. Consequently, these optimized structures serve as reliable molecular models for docking simulations in structure-based drug discovery [18]. Both protein and ligand structures were prepared using AutoDockTools v1.5.6, following standard protocols [19]. Protein preparation involved removing water molecules and bound ligands, protonation, and the addition of Kollman charges to ensure accurate electrostatic properties [20]. Meanwhile, the preparation of the standard and test ligand involved optimizing rotatable bonds to ensure flexible

Table 1. The yield of *Ficus septica* leaf extracts and purified extracts.

Samples	Weigh of Simplicia (g)	Extract Methanol (g)	Purified Extract (g)
Kadia District	500	303.7	157.1
Batalaiworu District	500	302	155.9

conformational sampling and assigning Gasteiger charges to accurately represent the ligand's electrostatic properties for molecular docking simulations .

Molecular docking simulations were performed using AutoDock Vina [21], targeting the active site of BSA with coordinates (x = 9.746, y = 18.079, z = 122.303) and COX-2 with coordinates (x = 27.131, y = 24.348, z = 14.747). The interactions between the protein and ligands were analyzed and visualized using Discovery Studio Visualizer to identify key binding residues and molecular interactions.

Pharmacokinetic and Toxicity Prediction

The pharmacokinetic profile and safety of the top-ranked compound from the docking study were predicted using a computational approach, encompassing absorption, distribution, metabolism, excretion, and toxicity (ADMET) aspects through pkCSM [22]. This web server utilizes graph-based signatures to represent small-molecule chemistry and topology for predicting the pharmacokinetic and toxicological outcomes of a molecule [22].

Result and Discussion

The extraction process yielded *Ficus septica* leaf extracts with a content of 60.74% from Kadia District and 60.40% from Batalaiworu District (Table 1). Furthermore, the purified extracts demonstrated yields of 51.72% and 51.62% for Kadia and Batalaiworu Districts, respectively.

The purified extracts from both locations (Kadia and Batalaiworu) exhibited enhanced anti-inflammatory activity compared to the crude extracts. At the Kadia location, the crude extract exhibited an IC_{50} value of 42.07 µg/mL, while the purified extract demonstrated an improved IC_{50} value of 32.04 µg/mL (Figure 1). A comparable trend was observed in the Batalaiworu sample, with the crude extract showing an IC_{50} value of 42.44 µg/mL and the purified extract achieving a lower IC_{50} value of 32.06 µg/mL. For comparison, Diclofenac Sodium displayed a markedly superior anti-inflammatory potential with an IC_{50} value of 7.99 µg/mL.

The purification of *Ficus septica* leaf extract using n-hexane enhanced the concentration of bioactive compounds responsible for its anti-inflammatory properties. Bioactive molecules such as flavonoids, alkaloids, and triterpenoids, which are well-known for their anti-inflammatory effects, are likely enriched during the purification process [23,24]. While the anti-inflammatory activity of the purified extracts is still lower than that of Diclofenac Sodium, the findings highlight

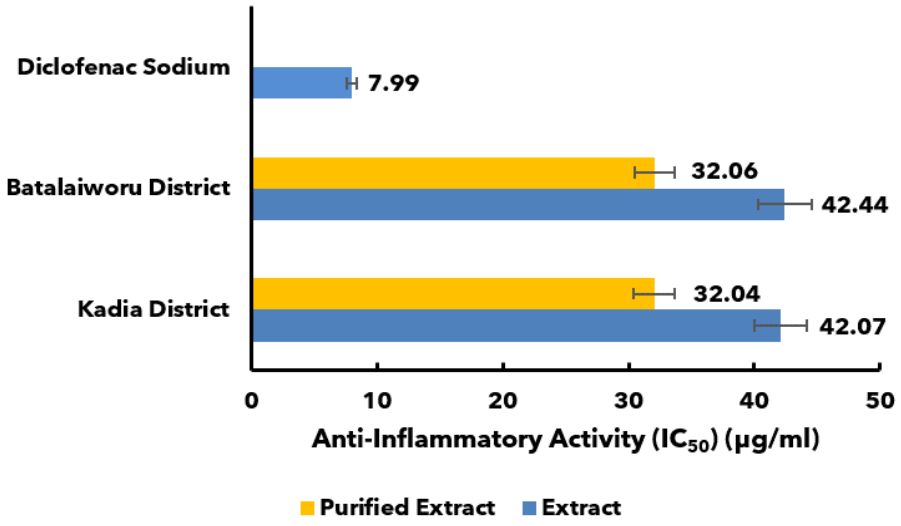

Figure 1. The anti-inflammatory activity of *Ficus septica* leaf extracts and purified extracts.

the potential of *Ficus septica* as a natural source of anti-inflammatory compounds. The observed differences in IC_{50} values between the Kadia and Batalaiworu samples may be influenced by environmental factors such as soil composition, climate conditions, and nutrient availability, which can affect the production and concentration of secondary metabolites [25].

The docking results revealed three potential compounds from *Ficus septica* that contribute to the stabilization of the Bovine Serum Albumin (BSA) and the inhibition of the COX-2 enzyme, namely Genistein, Ficuseptine B, and Septicine. The structures of these three compounds are shown in Figure 2. This computational study exhibited the binding capacity of Genistein with BSA, with a binding energy of -7.52 kcal/mol, comparable to Diclofenac (-7.51 kcal/mol). However, Naproxen, as the native ligand, exhibited a more negative binding energy of -9.20 kcal/mol (Table 2). The docking results highlight distinct interaction profiles among the evaluated compounds, reflecting their varying capacities to stabilize BSA. Genistein, a flavonoid compound, formed four hydrogen bonds with residues Tyr410, Cys437, Thr448, and Ser488, complemented by hydrophobic interactions with residues Arg409, Val432, Thr448, and Leu452 (Figure 3A). With a balanced combination of hydrogen bonding and hydrophobic interactions, Genistein demonstrates a promising interaction profile as a natural compound, though its hydrophobic contacts are less extensive

Table 2. Binding energy values of compounds from the *Ficus septica* against BSA protein and the COX-2 enzyme.

No.	Compounds	Binding Energy (kcal/mol)	
		BSA	COX-2
1.	Naproxen	-9.20	-8.34
2.	Genistein	-7.52	-9.19
3.	Diclofenac	-7.51	-8.49
4.	Ficuseptamine C	-7.50	-7.17
5.	Ficusin A	-7.44	-7.22
6.	Esculin	-7.22	-8.61
7.	Ficuseptine C	-7.15	-9.27
8.	Pungenin	-6.97	-8.00
9.	10S,13aR-antofine N-oxide	-6.78	-7.98
10.	Genistoside	-6.70	-8.52
11.	2-Demethoxytylophorine	-6.70	-8.40
12.	Ficuseptine B	-6.65	-9.51
13.	Antofine	-6.65	-8.42
14.	Ficuseptine D	-6.64	-8.46
15.	beta-Stigmasterol	-6.62	-7.27
16.	10S,13aR-Isotylocrebrine N-oxide	-6.50	-8.48
17.	Kaempferitrin	-6.49	-8.29
18.	Daucosterol	-6.48	-7.84
19.	10S,13aR-Tylocrebrine N-oxide	-6.40	-7.39
20.	Isotylocrebrine	-6.40	-6.52
21.	Septicine	-6.34	-9.45
22.	Ficuseptamine A	-6.34	-6.95
23.	10R,13aR-Tylophorine N-oxide	-6.29	-7.84
24.	Dehydrotylophorine	-6.18	-7.19
25.	Tylocrebrine	-6.13	-8.41
26.	Tylophorine	-6.11	-7.23
27.	beta-Sitosterol	-6.03	-7.21
28.	Ficuseptamine B	-5.98	-7.12

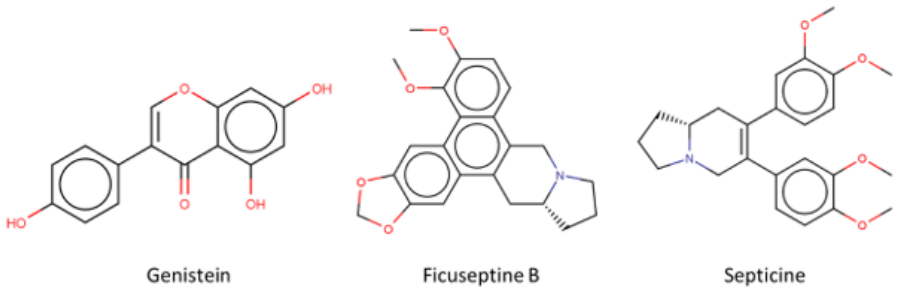

Figure 2. Molecular structures of compounds with potential anti-inflammatory activity from *Ficus septica*.

compared to the reference drugs.

In contrast, Naproxen and Diclofenac demonstrate stronger interaction profiles, primarily due to their more extensive hydrophobic interactions, which play a critical role in enhancing binding affinity and complex stability. Naproxen, a well-established reference drug, formed three hydrogen bonds with residues Arg409, Val432, and Thr488, in addition to hydrophobic interactions with Leu406, Lys413, Leu429, Leu452, and Arg484 (Figure 3C). These hydrophobic interactions surpass those observed for Genistein, suggesting a stronger binding affinity and greater stability for the Naproxen-BSA complex. The predominance of hydrophobic contacts underscores Naproxen's ability to stabilize proteins by shielding key residues from solvent exposure, aligning with its clinical efficacy.

Meanwhile, Diclofenac exhibited a unique interaction pattern, forming two hydrogen bonds with residues Tyr410 and Lys413, and establishing an extensive hydrophobic network involving residues Leu386, Phe402, Leu406, Leu429, Val432, Leu462, Leu456, and Arg484 (Figure 3B). This comprehensive hydrophobic interaction profile further supports Diclofenac's high binding affinity and stable complex formation with BSA.

Meanwhile, the anti-inflammatory potential of *Ficus septica* was also confirmed through simulations against the COX-2 enzyme. The compounds Ficuseptine B and Septicine showed binding energies of -9.51 kcal/mol and -9.45 kcal/mol, respectively, which are more favorable compared to Naproxen and Diclofenac, with binding energies of -8.34 kcal/mol and -8.49 kcal/mol (Table 2). Ficuseptine B, a bioactive compound derived from *Ficus septica*, demonstrated a strong binding affinity to COX-2, forming a hydrogen bond with Ser353 and engaging

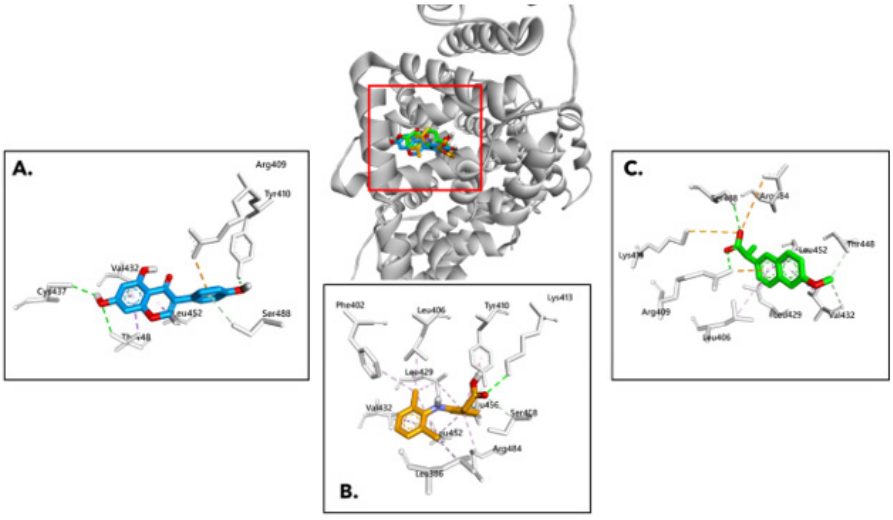

Figure 3. Molecular interactions of (A) Genistein, (B) Diclofenac, and (C) Naproxen with Bovine Serum Albumin (BSA).

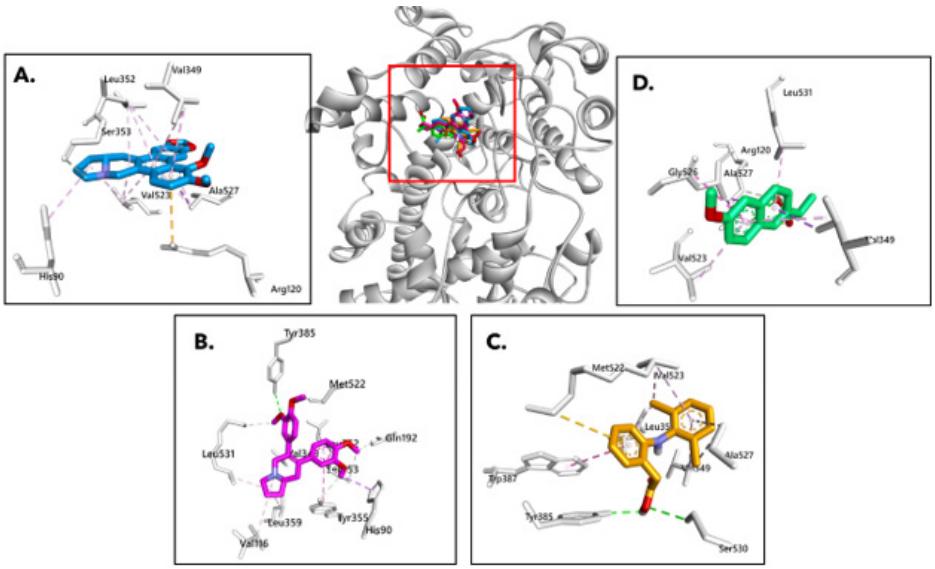

Figure 4. Molecular interactions of (A) Ficuseptine B, (B) Septicine, (C) Diclofenac, and (D) Naproxen with the COX-2 enzyme.

in hydrophobic interactions with key residues, including His90, Arg120, Val349, Leu352, Val523, and Ala527 (Figure 4A). Notably, the binding energy of Ficuseptine B was lower than that of the reference drugs Naproxen and Diclofenac, indicating a more stable complex with COX-2. This lower binding energy reflects its superior affinity and enhanced inhibitory potential. The combination of robust hydrophobic interactions and moderate hydrogen bonding provides a balanced mechanism for COX-2 inhibition, making Ficuseptine B a promising candidate for further study

Additionally, Septicine exhibited the most extensive interaction network among the tested compounds. It formed multiple hydrogen bonds with critical residues, including Gln192, Ser353, Tyr355, Tyr385, and Met522, alongside hydrophobic interactions with His90, Val116, Leu352, Leu359, Val349, Val523, Ala527, and Leu531 (Figure 4B). Despite its complex interaction profile, Septicine's binding energy was slightly higher than that of Ficuseptine B, though still significantly lower than the reference drugs. This suggests that Septicine is also a potent COX-2 inhibitor, capable of effectively stabilizing the enzyme's active site.

In comparison, Naproxen, a reference drug, showed limited interactions with COX-2, forming only one hydrogen bond with Arg120 and hydrophobic contacts with Val349, Val523, Gly526, Ala527, and Leu531 (Figure 4D). Similarly, Diclofenac, another reference compound,

Table 3. The pharmacokinetic and toxicity profile of the best compounds from *Ficus septica*.

Properties	Genistein	Ficuseptine B	Septicine
Caco-2 permeability (log Papp in 10^{-6} cm/s)	0.9	0.755	1.17
Intestinal absorption (human) (% Absorbed)	93.387	94.201	92.665
Volume of Distribution (log L/kg)	0.094	1.231	1.101
CYP2D6 substrate	No	No	No
CYP3A4 substrate	No	Yes	Yes
Total Clearance (log ml/min/kg)	0.151	1.12	0.937
AMES toxicity	No	Yes	No
Hepatotoxicity	No	Yes	No

formed two hydrogen bonds with Tyr385 and Ser530 while establishing hydrophobic interactions with Val349, Leu352, Trp387, Val523, Val527, and Met522 (Figure 4C). These findings underscore the promising inhibitory potential of natural products, such as Ficuseptine B and Septicine, in terms of binding affinity and stability compared to conventional COX-2 inhibitors .

The pharmacokinetic and toxicological profiles of the three lead compounds identified from molecular docking against BSA and COX-2 were predicted, as summarized in Table 3. Genistein and Septicine exhibited high Caco-2 permeability (log Papp > 0.9), suggesting efficient passive diffusion across the intestinal epithelium and favorable oral bioavailability. Additionally, all compounds demonstrated high intestinal absorption (>90%), indicating their potential for effective systemic uptake following oral administration. Ficuseptine B and Septicine exhibited higher tissue distribution (VDss > 0.45), suggesting a greater propensity for extravascular distribution compared to plasma retention [22].

None of the compounds were predicted to inhibit CYP2D6, implying a low risk of drug-drug interactions related to this metabolic pathway. However, Ficuseptine B and Septicine were identified as CYP3A4 substrates, indicating that they may undergo phase I metabolism via CYP-mediated oxidation, which could significantly impact their systemic clearance, bioavailability, and half-life [26]. Additionally, these two compounds exhibited higher total clearance values compared to Genistein, suggesting faster systemic elimination and potentially shorter duration of action. Finally, Genistein and Septicine were predicted to be non-mutagenic and non-hepatotoxic, indicating a favorable safety profile for further pharmacological evaluation .

Conclusion

The purified extracts from both the Kadia and Batalaiworu locations of *Ficus septica* demonstrated enhanced anti-inflammatory activity compared to the crude extracts, with IC_{50} values of 32.04 µg/mL and 32.06 µg/mL, respectively, in contrast to 42.07 µg/mL and 42.44 µg/mL for the crude extracts. Molecular interaction analysis conducted in this study further supports the therapeutic potential of *Ficus septica* compounds as anti-inflammatory agents. Genistein, in particular, exhibited strong binding affinity and stability in interactions with BSA, suggesting its potential to modulate protein stability and inhibit inflammatory pathways. Furthermore, Ficuseptine B and Septicine demonstrated promising anti-inflammatory potential by binding to and inhibiting the COX-2 enzyme. These findings emphasize the significant therapeutic promise of *Ficus septica* as a source of bioactive compounds for the development of alternative, plant-based anti-inflammatory agents. The ability of its constituents to rival established reference drugs in terms of binding affinity and interaction stability further underscores the value of *Ficus septica* as a natural resource for drug development.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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