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In-Vitro and *In-Silico* Study: The Anti-Inflammatory Activity of Ethanol Extract from Cogon Grass Roots (*Imperata cylindrica* L.)

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Abstract

Background: *Inflammation is a protective reaction triggered by harmful substances, microbes, or physical trauma. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat inflammation, though they have certain drawbacks, such as the potential for chronic kidney failure and unfavorable gastrointestinal side effects. Therefore, alternative treatments are needed. Cogon grass (Imperata cylindrica L.) roots contain secondary metabolites that may offer potential for inflammation treatment.* ***Objective:*** *This study aims to investigate the potential of secondary metabolites from cogon grass roots as anti-inflammatory agents, both in vitro using protein denaturation inhibition techniques and in silico against the COX-1 and COX-2 enzyme receptors.* ***Methods:*** *Molecular docking of COX-1 (PDB ID 6Y3C) and COX-2 (PDB ID 1PXX) using AutoDock Tool 1.5.6 was used to test the anti-inflammatory activity. In parallel, the in vitro technique involved spectrophotometric denaturation inhibition of the BSA (bovine serum albumin) protein.* ***Results:*** *The in silico results showed that the cyclovalone ligand exhibited the highest interaction and stability, with Gibbs free energies of -9.3 kcal/mol against COX-1 and -9.8 kcal/mol against COX-2, compared to the control ligand diclofenac, which had Gibbs free energies of -6.5 kcal/mol against COX-1 and -8.5 kcal/mol against COX-2. The 30% ethanol extract of cogon grass roots demonstrated anti-inflammatory activity in the in vitro analysis, with an IC50 value of 71.79 µg/mL.* ***Conclusions:*** *These preliminary findings suggest that the ethanol extract of cogon grass roots contains cyclovalone compounds with potential as anti-inflammatory agents.*

Keywords: *anti-inflammatory, cyclooxygenase enzyme, cogon grass, ethanol extract, Imperata cylindrica L.*

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INTRODUCTION

Inflammation is a natural bodily response to combat illnesses, infections, and injuries. It can be triggered by various factors such as immune disorders, cancer, infections, and exposure to harmful chemicals (Mangkulion et al., 2023). Health research conducted by the Indonesian Ministry of Health in 2021 revealed a high incidence of diseases involving inflammation, including diabetes mellitus (2.0%), asthma (2.4%), dermatitis (6.8%), acute respiratory infections (4.4%), pneumonia (2.0%), joint diseases (7.3%), tumors/cancer (1.8%), and hepatitis (0.4%) (Kemenkes, 2021). Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to manage inflammation and provide pain relief. These medications, including aspirin, ibuprofen, and naproxen, work by inhibiting the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby reducing the production of inflammatory molecules like prostaglandins and thromboxanes (Ugwu et al., 2018).

While NSAIDs offer effective relief, their use comes with significant drawbacks. Blocking COX-1, which plays a role in maintaining the protective lining of the gastrointestinal tract, can lead to side effects such as gastrointestinal bleeding, kidney damage, and central nervous system disturbances. On the other hand, selective inhibition of COX-2 offers anti-inflammatory and analgesic benefits without many of these harmful effects. However, long-term use of NSAIDs can still cause complications, including chronic kidney failure, ulcers, and impaired healing of tendons, ligaments, and cartilage (Fischbach, 2019). As a result, there is an urgent need for alternative anti-inflammatory treatments that are both effective and less harmful.

Cogon grass (*Imperata cylindrica* L.), a plant native to tropical and subtropical regions, has emerged as a promising natural anti-inflammatory remedy. Numerous bioactive compounds have been isolated from *Imperata cylindrica*, including saponins, glycosides, coumarins, flavonoids, and phenols. These compounds have been shown to exhibit a wide range of biological activities, such as anti-inflammatory, antibacterial, and anticancer properties (Jung & Shin, 2021). Notably, *Imperata cylindrica* has demonstrated potent anti-inflammatory effects. Studies by Park et al. (2015) revealed that isogeunin, a compound derived from the roots of cogon grass, can reduce inflammation by inhibiting nitric oxide production and downregulating the expression of pro-inflammatory markers such as iNOS, COX-2, and cytokines like TNF-α, IL-6, and IL-1β. Furthermore, research has shown that extracts from the roots of *Imperata cylindrica* can protect against kidney inflammation in animal models (Chen et al., 2015), and its ethanol extract has been found to reduce nitric oxide secretion in fibroblast cells (Mangkulion et al., 2023). Additionally, Putri et al. (2020) found that the ethanol extract from cogon grass roots can effectively reduce sepsis scores, a condition characterized by inflammation.

Despite promising evidence of the anti-inflammatory potential of *Imperata cylindrica*, limited *in vitro* and *in silico* research exists on its ability to modulate COX-1 and COX-2 activity. This study aims to fill this gap by investigating the anti-inflammatory properties of ethanol extracts from the roots of *Imperata cylindrica in vitro*. Through protein denaturation assays, we will explore the anti-inflammatory effects of these extracts and examine their interactions with COX-1 and COX-2 receptors *in silico*.

MATERIALS AND METHODS

Materials

The resources utilized in this investigation included *Cogon Grass Roots* roots, aquadest, ethanol (Smart Lab), glacial acetic acid (Merck), H_2SO_4 (Merck), NaOH (Merck), reagents (Liebermann-Bouchard, Dragendorff, Mayer), BSA standard (Sigma Aldrich), $FeCl_3$ (Merck), Tris buffer (Sigma Aldrich), sodium chloride (Merck), sodium diclofenac, formic acid (Merck), and acetonitrile (Merck).

Tools

The tools used in this research include: Analytical balance (Ohaus), Glassware (Pyrex Iwaki), Water bath (Memmert), Blender (Miyako), Oven (Memmert), Rotary evaporator (Buchi), Mortar, Whatman filter paper No. 1, Vortex (Labnet), UV-Vis spectrophotometer (Shimadzu), LC-MS/MS system (Thermo Scientific). Hardware used includes a Dell laptop with Intel Core i5-1135G7 processor, 12.00 GB RAM, and Windows 11 (64-bit). Software used includes: ChemDraw Professional 15.0, SwissADME: www.swissadme.ch, AutoDock Tool 1.5.6, BIOVIA Discovery Studio Visualizer, and ProTox Online Tool: tox-new.charite.de/protox_II.

Methods

Sample collection

The roots of *Imperata cylindrica* were collected in February 2024 from Ciherang District, Bogor Regency, West Java, Indonesia. The voucher specimen was identified at the National Research and Innovation Agency. The roots were cleaned to remove dirt and contaminants, washed with running water, and drained

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to eliminate excess water. The cleaned roots were dried in an oven set at 40-50°C. After drying, the roots were cleaned again to remove any remaining impurities. The powdered dried roots were sieved using a 40-mesh sieve (Sahidin et al., 2023).

Preparation of extract

A total of 100 grams of *Imperata cylindrica* roots were macerated at a 1:10 (w/v) ratio in a 30% ethanol (E30) solution for three days. The solvent was changed daily, and Whatman filter paper No. 1 was used for filtration. After filtration, the solvent was removed using a rotary evaporator at 40°C under reduced pressure. The same procedure was followed for maceration using 70% ethanol (E70) and 96% ethanol (E96) solutions at the same ratio (1:10, w/v) (Dahlan et al., 2020).

Phytochemical screening

The extracts obtained from E30, E70, and E96 were screened for secondary metabolites using standard colorimetric phytochemical screening methods. Following Harborne's methods, the presence of flavonoids, phenols, tannins, terpenoids, steroids, and alkaloids was tested (Sahidin et al., 2023).

Bovine serum albumin assay

To assess the anti-inflammatory properties of *Imperata cylindrica* extracts, a modified version of the BSA assay (Bailey-Shaw et al., 2017) was used. A 0.2% w/v BSA solution was prepared using Tris Buffered Saline (TBS), where one TBS tablet was dissolved in 15 mL of deionized water to form a 0.15M NaCl and 0.05M tris solution with a pH of 7.6. The pH was adjusted to 6.4 using glacial acetic acid. A negative control was prepared with 50 µL of solvent added to the BSA solution, bringing the total volume to 5 mL. For the positive control, a stock solution of sodium diclofenac (4000 ppm) was prepared by dissolving 100 mg of the drug in ethanol, and serial dilutions were made to achieve concentrations of 130, 250, 500, 1000, 2000, and 4000 ppm. A stock solution of *Imperata cylindrica* root extract (20,000 ppm) was prepared by dissolving 500 mg of extract in ethanol and making serial dilutions for testing concentrations of 100, 500, 1000, and 5000 ppm. The test solutions were incubated at 72°C for 5 minutes, followed by cooling at room temperature. Absorbance was measured at 660 nm using a UV-Vis spectrophotometer.

Identification of secondary metabolite compounds using LC-MS/MS

A total of 1.4 mg of *Imperata cylindrica* root extract was obtained by dissolving it in 100 mL of methanol. The solution was subsequently inserted through the UPLC system following filtration via a 0.2 m GHP filter. LC-MS/MS analysis was conducted using a Xevo-ToF-1 system (Thermo Scientific) with a C-18 column (1.8 µm, 2.1 × 100 mm). The elution system consisted of 0.1% formic acid in distilled water (A) and 0.1% formic acid in acetonitrile (B), with a gradient run for 20 minutes at 100°C (Warnasih et al., 2024).

Data were processed using the MassLynx 4.1 application and subsequently compared with online spectral databases, including ChemSpider (chemspider.com), MassBank (massbank.eu/massbank.jp), the Human Metabolome Database (hmdb.ca), and PubChem (pubchem.org). The acceptance criteria is a mass error of less than 5 ppm.

Molecular docking, lipinski's rule, and toxicity test

Molecular docking is a crucial method in drug discovery to predict the binding affinities and interactions between ligands (small molecules) and receptors (proteins). In this study, molecular docking was used to evaluate the binding efficiency of compounds derived from the root of Cogon Grass Roots. AutoDock Vina (version 4.2) and AutoDock Tools 1.5.6 were employed for the docking simulations (Trott & Olson, 2010). The crystal structures of Cyclooxygenase-1 (COX-1) (PDB ID 6Y3C) and Cyclooxygenase-2 (COX-2) (PDB ID 1PXX) were obtained from the RCSB Protein Data Bank (Muthukrishnan et al., 2024; Ibrahim et al., 2018). To ensure accurate protein representation, polar hydrogen atoms were added, and the heteroatoms were replaced. The proteins were assigned partial atomic charges and solvation parameters, and the data was converted to the PDBQT format.

The structures of the compounds identified by LC-MS/MS analysis were sourced from the PubChem database in three-dimensional format. Hydrogen atoms were added, and the Gasteiger charges for each structure were calculated. The preparation process for each molecule was carried out using AutoDock Tools 1.5.6. Docking simulations were performed with AutoDock v.4.2 using a population size of 100, employing the Lamarckian genetic algorithm to study protein-ligand interactions and affinity. The docking validation was conducted by redocking diclofenac to COX-2, and the RMSD criterion was set at < 2 Å. The compounds were docked using the appropriate grid coordinates (for COX-1: x = -36.654; y = -49.843; z = 0.492, with a spacing of 1 Å; for COX-2: x = 26.655; y = 27.965; z = 10.933, with a spacing of 1 Å). Protein-ligand interactions were visualized using Discovery Studio Visualizer, and the sum of affinity energies was calculated. Bioavailability of the compounds was

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assessed using Lipinski's Rule of Five, and the toxicity of the compounds was predicted using the Protox-II tool.

Statistical analysis

Data were analyzed using IBM SPSS 20.0 for Windows. Results are presented as means ± standard deviation (X ± SD). One-way ANOVA and Duncan's test were employed to analyze group differences. A p-value < 0.05 was considered statistically significant. IC50 values, representing the concentrations required to achieve 50% of the maximum inhibitory effect, were determined using dose-response curves.

RESULTS AND DISCUSSION

Phytochemical screening

The extraction and phytochemical screening results for E30, E70, and E76 of cogon grass roots are displayed in Table 1. The findings revealed that E30, E70, and E76 samples of cogon grass roots included terpenoids, saponins, tannins/polyphenols, flavonoids, and alkaloids. Multiple investigations found that cogon grass roots include polyphenols, flavonoids, saponins, terpenoids, tannins, and alkaloids (Jung & Shin, 2021; Indriyanti et al., 2022; Nayim et al., 2023; Nayim et al., 2021).

***In-vitro* anti-inflammatory activities**

A heat-induced albumin denaturation assay was used to assess the anti-inflammatory properties of cogon grass root extract. The advantages of this method include its simplicity, the use of small sample sizes, and a relatively short duration. This assay measures the ability of anti-inflammatory substances to inhibit protein denaturation induced by high heat, which is the basis for assessing anti-inflammatory activity (Kaur et al., 2018). Sodium diclofenac, a common non-steroidal anti-inflammatory drug (NSAID), was used as a positive control. Diclofenac inhibits protein denaturation by preventing conformational changes in heat-treated proteins at physiological pH (Aidoo et al., 2021). It also competes with arachidonic acid for binding to cyclooxygenase (COX)-1 and COX-2 enzymes, blocking the inflammatory pathway (Rowlinson et al., 2003).

At a concentration of 200 µg/mL, the 30% ethanol extract (E30) of cogon grass roots exhibited the most promising anti-inflammatory activity, with an inhibition percentage of 88.09 ± 0.07%. The percentage of inhibition for each concentration was determined based on absorbance values, and the IC50 value was calculated using a linear regression equation. The IC50 is the concentration required to inhibit 50% of inflammation (Gaffar et al., 2018). According to Ghasemian et al. (2016), strong anti-inflammatory activity is defined by an IC50 value below 50 µg/mL, weak activity by an IC50 between 50 and 100 µg/mL, and very weak activity by an IC50 between 101 and 250 µg/mL.

In this study, the IC50 value for sodium diclofenac (positive control) was 15.56±0.09 µg/mL, indicating high anti-inflammatory activity. Sodium diclofenac, a synthetic drug that has undergone clinical testing and proven effective in treating inflammation (Suciu et al., 2019), exhibits high effectiveness. The 30% ethanol extract (E30) showed the best activity, with an IC50 value of 71.79±0.45 µg/mL. In contrast, the 70% ethanol extract (E70) exhibited lower anti-inflammatory activity, with an IC50 of 96.94±0.92 µg/mL, while the 96% ethanol extract (E96) showed even weaker activity, with an IC50 value of 141.84±10.35 µg/mL. Based on these values, the anti-inflammatory activity of the 30% and 70% ethanol extracts is considered weak, while the 96% ethanol extract is classified as very weak (Table 2, Figure 1).

Table 1. Phytochemical screening of E30, E70, and E96 of *Imperata cylindrica* L. roots

Sample	Yield (%)	Phenolic	Flavonoid	Saponin	Terpenoid/ steroid	Tannin	Alkaloid
E30	22.87	++	+++	++	+	+	++
E70	19.98	++	++	++	+	+	++
E96	19.42	++	++	++	+	+	++

+++ = Strong presence, ++ = Moderate presence, and + = Weak presence

Table 2. Inhibition percentage of cogon grass root extracts

Samples	Concentration (µg/mL)				
	1	5	10	50	200
30% Ethanol (E30)	21.01±0.51	22.92±0.43	32.32±0.79	44.34±0.13	88.20±0.17
70% Ethanol (E70)	30.85±0.26	32.99±0.62	38.52±0.17	51.71±0.23	63.36±0.60
96% Ethanol (E96)	13.83±0.26	25.97±1.01	26.61±0.39	39.57±0.90	59.56±4.20

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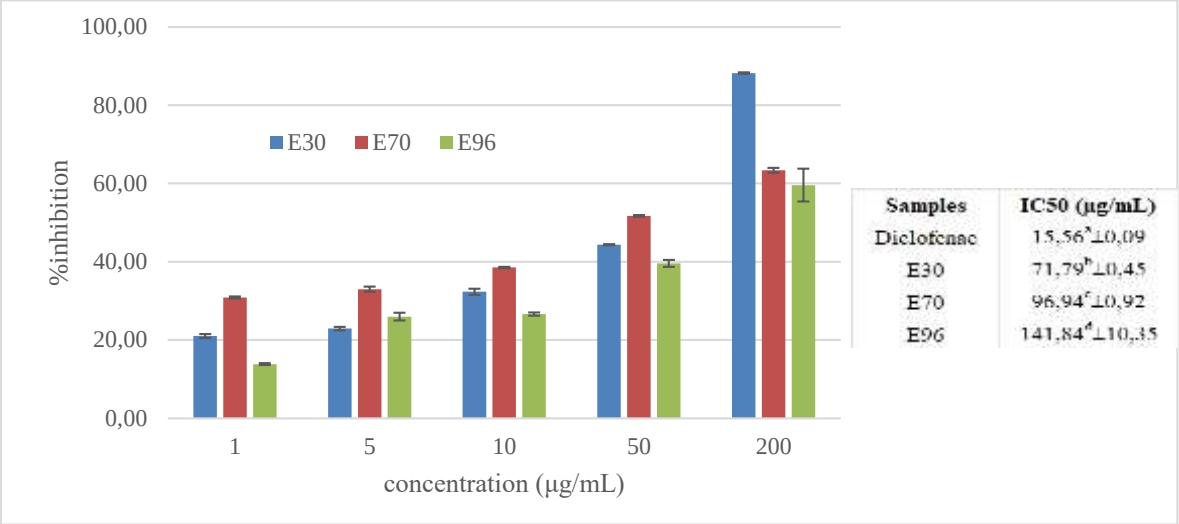

Figure 1. In vitro anti-inflammatory assessment of cogon grass roots extracts via albumin denaturation. Each value is represented as mean ± SD (n = 3). Means with different superscript (a–d) letters in the column are significantly ($p < 0.05$) different from one another

The differences in anti-inflammatory activity among the extracts are likely due to the polarity effects of the solvents used. The 30% ethanol extract (E30), being more polar, may have extracted more active compounds, while the less polar 70% and 96% ethanol extracts possibly extracted fewer bioactive compounds or compounds with lower anti-inflammatory potential. This difference in extract activity can be attributed to the varying solubilities of different phytochemicals in solvents of different polarities, which can influence the biological activity of the extracts (Karta et al., 2024). One compound that acts as an anti-inflammatory is flavonoids. Previous research has shown that the presence of phytochemical compounds such as phenolics, especially flavonoids, plays a role in anti-inflammatory activity (Razafindrakoto et al., 2021). This is also proven based on the results of phytochemical screening (Table 1) in flavonoid testing showing that 30% ethanol extract produces a more concentrated color, which indicates that the flavonoid content in 30% ethanol extract is higher than that in 70% and 96% ethanol extracts, so that the anti-inflammatory activity of 30% ethanol extract is also better than other extracts.

The anti-inflammatory properties of cogon grass roots have been explored in various studies. For example, Razafindrakoto et al. (2021) demonstrated that methanol extracts of the aerial parts of cogon grass roots reduced inflammation significantly through the inhibition of chemical mediator release at doses of 50, 100, and 200 mg/kg. Helma et al. (2024) found that both methanol and ethanol extracts from the leaves of cogon grass roots possess anti-inflammatory compounds, although their activities were relatively weak, with IC50 values of 194.15 µg/mL for methanol extract and 209.36 µg/mL for ethanol extract.

Although this study suggests that the ethanol extract of cogon grass roots demonstrates weak anti-inflammatory activity, further research is needed. It is recommended to conduct fractionation of active compounds and determine the total flavonoid and phenolic content in the extracts, which may provide insights into the active components contributing to the observed anti-inflammatory effects.

Chemical screening using LC-MS/MS

The identification of secondary metabolites in the 30% ethanol extract of cogon grass roots (E30) was carried out using LC–MS/MS. The crude extract chromatogram (Figure 2) displayed multiple peaks, reflecting the presence of various compounds since the sample had not undergone purification. Data were processed using the MassLynx 4.1 application and subsequently compared with online spectral databases, including ChemSpider (chemspider.com), MassBank (massbank.eu/massbank.jp), the Human Metabolome Database (hmdb.ca), and PubChem (pubchem.org). In positive ionization mode (ESI+), most compounds were detected as protonated ions $[M+H]^+$, whereas in negative ionization mode (ESI–), they appeared as deprotonated ions $[M–H]^-$. Therefore, the calculation of the neutral molecular mass was adjusted by considering the protonation or deprotonation process during ionization. Based on data interpretation, a total of 26 metabolites were putatively identified (MSI Level 2), among which six compounds are known to possess anti-inflammatory potential (Table 3).

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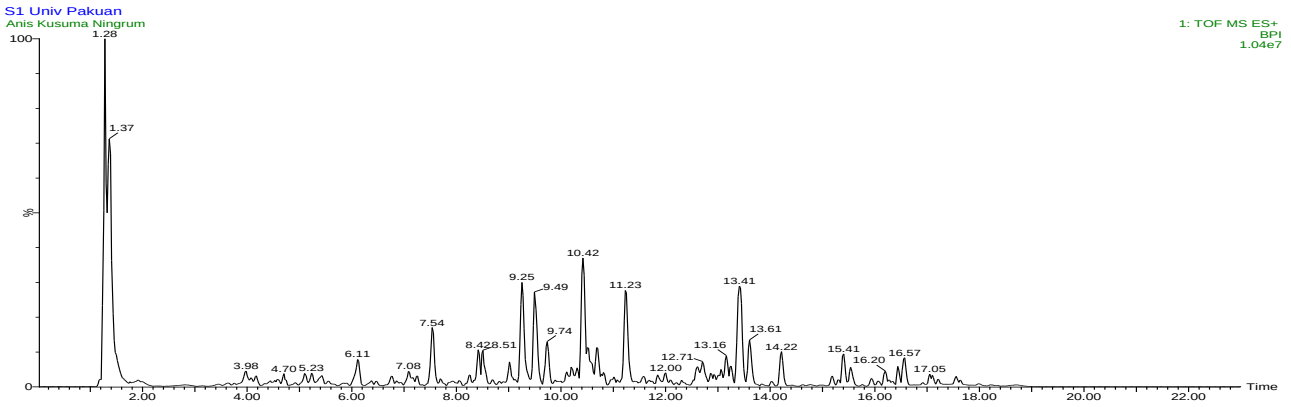


Figure 2. Chromatogram of ethanol extract of cogon grass roots (E30)

The findings indicate that the flavonoid, alkaloid, acetogenin, and phenolic groups are present in the cogon grass root ethanol extract. An investigation by Xiao et al. (2011), the chemical quercetin was discovered to impair COX-2 expression by blocking the transactivator NF-kB and limiting the recruitment of coactivator p300, which functions as a promoter for COX-2. According to Rahmawati et al. (2020), 1.57µM cyclovalone inhibited protein denaturation due to heat by 19.64%. Cyclovalone, a monocarbonyl analog of curcumin, exhibits anti-inflammatory properties. *In vitro* experiments by González et al. (2007) revealed showed the chemical umbelliferone may suppress serotonin and histamine production at the site of inflammation. Additionally, it appears to block the synthesis of prostaglandins from arachidonic acid by inhibiting cyclooxygenase (COX) activity. In vivo, isorhamnetin demonstrates anti-inflammatory properties. A study by Xu et al. (2022) states that isorhamnetin significantly reduces the inflammatory response in COPD-induced rats exposed to cigarette smoke (CS), particularly by affecting the Nrf2/Keap1 pathway. Strychnine and brucine are closely related to alkaloids. The main chemical substances present in the plant's seeds, leaves, roots, and bark are brucine and strychnine. According to pharmacological testing, brucine has analgesic, anti-inflammatory, and antitumor properties (Lu et al., 2020). Annohexocin, an acetogenin discovered in plants of the Annonaceae family, has prospective as an anti-inflammatory compound (Enema et al., 2024).

***In-silico* docking results**

Cogon grass roots contain 6 phytochemical compounds. Based on several studies, these compounds have the potential to be anti-inflammatory. The main mediators of the production of prostaglandins causing inflammation have been identified as cyclooxygenases (COX-1 and COX-2). COX-1, an enzyme that maintains homeostasis, can be found in all tissues, while COX-2 is highly sensitive to cytokines and pro-inflammatory stimuli (Deepika et al., 2023).

Table 3. Secondary metabolite compounds of ethanol extract of cogon grass roots

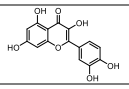
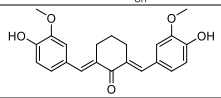
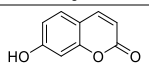
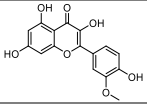
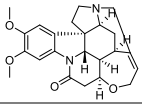
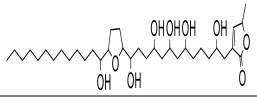
No	RT (Min.)	Observed $[M+H]^+$ m/z	MS^n Fragmentation	Structure	Compound Name	Group
1	2.730	303.0512 $C_{15}H_{10}O_7$	153.0213 97.0295		Quercetin	Flavonoid
2	3.546	367.1508 $C_{22}H_{22}O_5$	277.1200 205.0979 163.0403		Cyclovalone	Phenolic
3	3.981	163.0405 $C_9H_6O_3$	151.0766 89.0392		Umbelliferone	Phenolic
4	7.383	317.2121 $C_{16}H_{12}O_7$	189.0918 105.0705		Isorhamnetin	Flavonoid
5	9.739	395.1857 $C_{23}H_{26}N_2O_4$	377.1754 283.0977 257.1186		Brucine	Alkaloid
6	17.627	617.4416 $C_{35}H_{64}O_9$	469.4251 379.1909 338.3419		Annohexocin	Acetogenin

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Table 4. Docking scores (ΔG Values) for COX-1 and COX-2 binding of ligands

Compound	COX-1 ΔG (kcal/mol)	COX-2 ΔG (kcal/mol)
Diclofenac	-6.5	-8.5
Quercetin	-9.0	-9.0
Umbelliferone	-6.9	-7.6
Brucine	-8.7	-8.2
Annohexocin	-7.0	-7.2
Isorhamnetin	-8.6	-8.9
Cyclovalone	-9.3	-9.8

Table 5. Physicochemical Properties, Lipinski's Rule, and Toxicity Classification of Ligands

Compound	Molecular Weight (Da)	Log P	Hydrogen Bond Donors	Hydrogen Bond Acceptors	Refractivity Molar	Lipinski's Violation	LD50 (mg/kg)	Toxicity Class
Diclofenac	318.13	3.1	1	2	75.61	0	53	3
Quercetin	310.13	1.99	5	6	78.04	0	159	3
Umbelliferone	163.04	1.5	1	2	44.51	0	10,000	6
Brucine	395.18	2.11	0	6	114.04	0	150	3
Annohexocin	617.441*	5	6*	9	175	2	400	4
Isorhamnetin	317.212	0,24	7*	11*	114,63	2	5,000	5
Cyclovalone	367.15	4.34	2	5	105.3	0	5,000	5

Note: *Not by Lipinski's Rule of Five

Docking analyses were performed to identify the binding ability of potential ligands for COX-1 and COX-2 proteins (Table 4). These studies compared the ligand's binding affinity to that of the reference drug, diclofenac. The docking results, including the Gibbs free energy (ΔG) values, were analyzed to assess the strength of the binding interactions. The docking simulations demonstrated that cyclovalone exhibited the strongest binding affinity toward both COX-1 and COX-2, with docking scores of –9.3 and –9.8 kcal/mol, respectively. These values were lower than those of the reference drug diclofenac (–6.5 and –8.5 kcal/mol), indicating that cyclovalone may form more stable interactions with both enzymes. Quercetin and isorhamnetin also showed high affinities, though not as strong as cyclovalone. Importantly, cyclovalone's stronger binding to COX-2 suggests potential selectivity, which is associated with reduced gastrointestinal adverse effects compared to non-selective NSAIDs such as diclofenac (El-Malah et al., 2022).

Based on the molecular docking results, the conformation with the lowest Gibbs free energy was identified. The ability of the drug to bind to the receptor is quantified by its Gibbs free energy value; a lower value indicates a stronger potential for compound interaction with the test protein (Trott & Olson, 2010). This shows that secondary metabolites from cogon grass roots have good stability and ability to bind to receptors, as some compounds have lower binding energy to receptors than diclofenac controls. Referring to the ΔG value, the most stable compounds are cyclovalone, quercetin, and isorhamnetin. In this test, diclofenac was used as a comparison because this compound is commonly used in anti-inflammatory drugs (Savitri et al., 2023).

Lipinski's rule and toxicity

A key criterion for assessing a compound's suitability as a drug candidate and determining its capacity to cross biological membranes during bodily reactions is Lipinski's Rule of Five. According to this rule, the compound must have a molar refractivity value between 40 and 130, a molecular weight of no more than 500 Daltons, a log (P) (lipophilicity) of no more than 5, no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. Based on the physicochemical analysis of the ligands (Table 5), annohexocin and isorhamnetin fail to meet Lipinski's Rule due to violations.

Toxicity prediction was carried out using ProTox-II, a program that classifies toxicity into six stages. Substances classified as class 1 have a lethal dose 50 (LD50) of 5 mg/kg or less, making them extremely dangerous to swallow. Class 2 drugs have LD50s ranging from 5 mg/kg to 50 mg/kg, making them lethal if consumed. The LD50 of class 3 substances ranges

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from 50 mg/kg to 300 mg/kg, making them toxic if swallowed. The LD50 of class 4 substances is between 300 and 2000 mg/kg, making them dangerous if swallowed. A class 5 substance's LD50 ranges from 2000 mg/kg to 5000 mg/kg, making it potentially hazardous. A chemical with an LD50 of 5000 mg/kg or higher is considered non-toxic.

The toxicity analysis results for the 6 ligands showed that 1 ligand is non-toxic, 2 ligands are possibly harmful, 1 ligand is harmful if swallowed, and 2 ligands are toxic if swallowed. This indicates that the compounds contained in cogon grass roots include relatively safe compounds, such as umbelliferone. Cyclovalone complies with Lipinski's rule of five (MW = 367 Da, logP = 4.34, H-bond donors = 2, acceptors = 5), implying favorable oral bioavailability (Chahal et al., 2023). Its LD50 value of 5000 mg/kg points to relatively low acute toxicity, offering a notable safety advantage over diclofenac. This aligns with ongoing research emphasizing scaffold optimization to balance efficacy and safety (Elewa et al., 2024).

Amino acid residues interaction

To evaluate the binding affinity between the active compounds and the target enzymes, COX-1 and COX-2, we identify the amino acid residues that interact with each ligand. An active compound is estimated to have a strong bond with the target enzyme if it can form strong hydrogen bonds with the same amino acid residues, compared to the control drug, diclofenac. The hydrogen bond interactions between the ligands and amino acids at the COX-1 receptor's active site suggest that only the ligands quercetin and brucine exhibit similar interactions with the control diclofenac. This is because these ligands form hydrogen bonds with the amino acid residue Gln44. Meanwhile, binding to the COX-2 receptor does not show a ligand that binds to the same amino acid as the diclofenac control. The similarity of these residues suggests that the active compounds in the ethanol extract of cogon grass roots resemble the comparison compound, making them potential candidates for anti-inflammatory agents. These chemicals are thought to have the capacity to prevent the overexpression of the proteins COX-1 and COX-2, which are the principal causes of inflammation.

Cyclovalone formed hydrogen bonds with key residues of COX-1 (Glu465, Cys47, Asn34) and COX-2 (Ala156, Asn43; Table 6; Figure 3), which likely contributes to its binding stability and enhanced COX-2 affinity. Diclofenac, in contrast, formed three hydrogen bonds with COX-1 (Tyr130, Arg469, and Gln44) and two hydrogen bonds with COX-2 (Asn104 and Arg109). Although diclofenac engages multiple residues in COX-1, its overall docking score was weaker than cyclovalone, suggesting that binding affinity depends not only on the number of hydrogen bonds but also on their orientation, strength, and involvement with key catalytic residues. This aligns with structural insights highlighting how COX-2 selective inhibitors exploit unique binding pockets absent in COX-1 (Mohsin et al., 2022; Ju et al., 2022).

Taken together, these findings suggest that cyclovalone is a promising candidate as a COX-2 selective, low-toxicity anti-inflammatory agent, outperforming diclofenac in in silico affinity and safety metrics. However, limitations remain: docking cannot fully account for pharmacokinetics, metabolism, or chronic toxicity. Thus, further validation via ADMET modeling, in vitro enzymatic assays, and in vivo evaluations is essential. Additionally, rational design strategies, such as scaffold hybridization or linker modification to optimize selectivity and pharmacokinetic properties, could further enhance the therapeutic profile of cyclovalone (Chahal et al., 2023; Bokhtia et al., 2023).

Table 6. Hydrogen bond interactions between ligands and COX-1/COX-2 residues

Ligand	COX-1 Residue	COX-2 Residue	Hydrogen Bond Interaction with COX-1	Hydrogen Bond Interaction with COX-2
Diclofenac	Tyr130, Arg469, Gln44	Asn104, Arg109	Yes	Yes
Quercetin	Cys47, Gly45, Gln44, Cys41, Glu465, Gln461	Gln461	Yes	Yes
Cyclovalone	Glu465, Cys47, Asn34	Ala156, Asn43	Yes	Yes
Umbelliferone	-	Thr206	No	Yes
Isorhamnetin	Asn382	Pro154, Gly45, Cys47	Yes	Yes
Brucine	Gln44, Arg83	Asn43	Yes	Yes
Annohexocin	Arg79, Arg120	Tyr130, Asn39, Gln461, Gln42, Lys468	Yes	Yes

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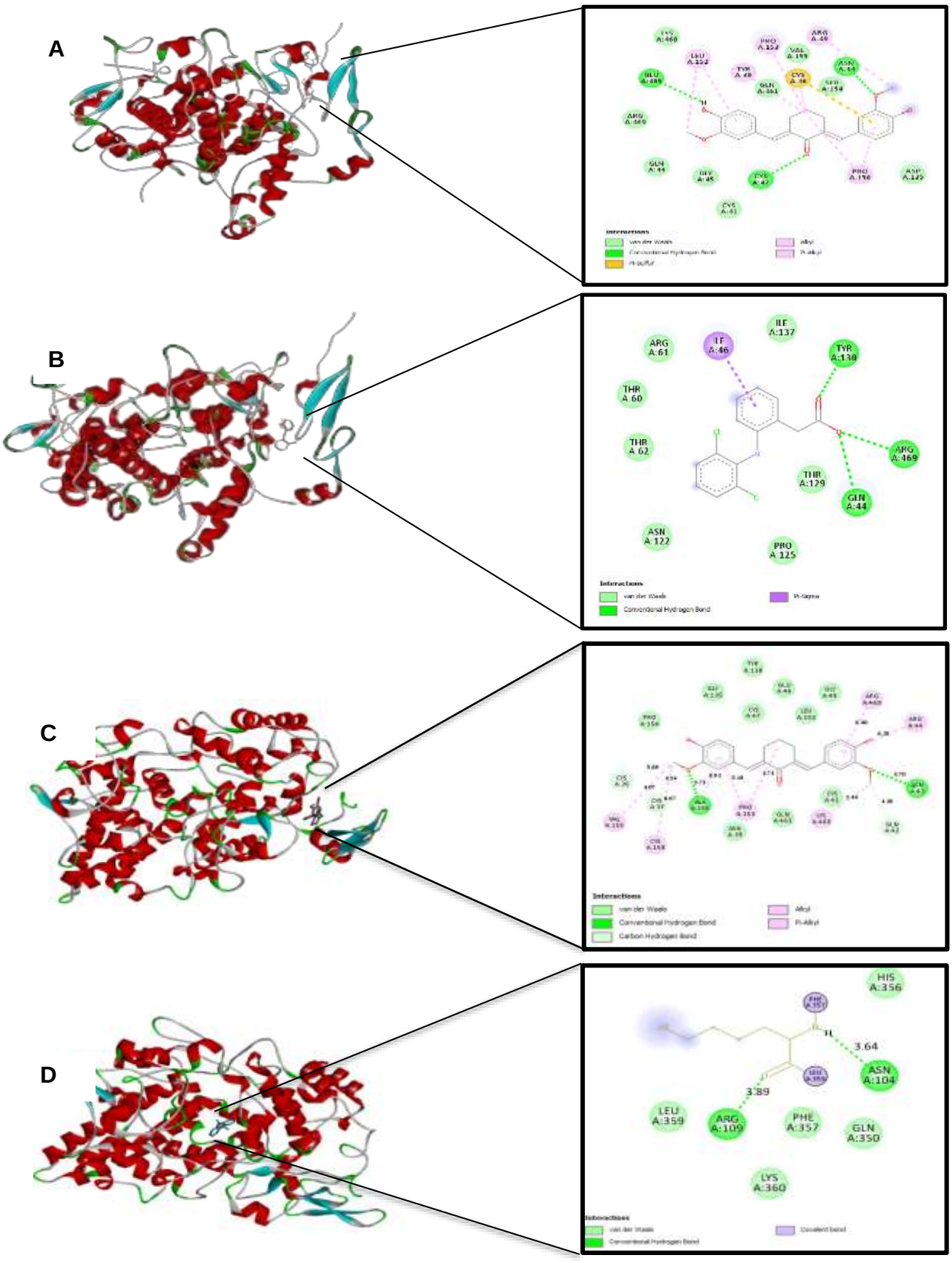

Figure 3. Docking of (A) cyclovalone to COX-1; (B) diclofenac to COX-1; (C) cyclovalone to COX-2; and (D) diclofenac to COX-2; and its hydrogen bond interactions are shown in green dotted lines

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CONCLUSION

The study's findings reveal that the ethanol extract from cogon grass roots includes cyclovalone, a promising ligand with anti-inflammatory properties. In-silico experiments have shown that cyclovalone interacts with COX-2 and exhibits a higher binding score compared to COX-1. Furthermore, a 30% ethanol extract of cogon grass roots exhibited anti-inflammatory activity with an IC50 value of 71.79 µg/mL, according to *in vitro* testing using the BSA protein denaturation method. Further research is required to confirm the potential of cogon grass roots as a promising anti-inflammatory candidate. This can be achieved through *in vitro* testing, utilizing the COX-2 enzyme inhibition method.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.W., U.H., S.J.S.; Methodology, S.J.S., D.W.; Software, S.W.; Validation, A.H.M., D.W., U.H.; Formal Analysis, U.H., A.H.M.; Investigation, D.W., S.W.; Resources, A.H.M., D.W.; Data Curation, S.W., A.H.M., S.J.S.; Writing - Original Draft, S.W., U.H., S.J.S., A.H.M., D.W.; Writing - Review & Editing, S.W., U.H., S.J.S.; Visualization, S.W., S.J.S.; Supervision, A.H.M., D.W.; Project Administration, U.H.; Funding Acquisition, S.W.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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