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Phytochemical Profiling and Comparative In Vitro Anti-inflammatory Evaluation of *Senna italica* Mill. and *Phyllanthus reticulatus* Poir.

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ABSTRACT

Ethnopharmacological relevance

Senna italica and *Phyllanthus reticulatus* are widely used in traditional medicine for treating inflammation-related disorders. Their documented uses in Ayurveda and folk systems justify scientific validation.

Aim of the study:

To compare the phytochemical composition and the *in vitro* anti-inflammatory activity of ethanol extracts from *S. italica* and *P. reticulatus* using LC-MS and enzyme inhibition assays.

Materials and methods:

Ethanol extracts were prepared using cold maceration and sonication techniques. LC–MS profiling was conducted to identify major phytoconstituents. In vitro assays for cyclooxygenase (COX) and lipoxygenase (LOX) enzyme inhibition were performed using LPS-stimulated RAW 264.7 macrophage cells. Diclofenac served as the standard.

Results:

LC–MS analysis revealed the presence of flavonoids, tannins, anthraquinones, and phenolic acids. *S. italica* exhibited higher COX (50.02%) and LOX (47.61%) inhibition than *P. reticulatus* (42.88% and 42.41%, respectively) at 100 µL. IC_{50} values for both extracts were greater than 100 µL, while Diclofenac showed IC_{50} values of 52.19 and 60.22 µg/mL, respectively. The activities correlated with the presence of emodin, quercetin, kaempferol, and ellagic acid.

Conclusions:

Both extracts demonstrated promising anti-inflammatory activity. S. italica showed greater efficacy. These findings support the ethnomedicinal use of both plants and justify their inclusion in polyherbal anti-inflammatory formulations.

Highlights:
- LC–MS revealed key anti-inflammatory phytochemicals in *Senna italica* and *Phyllanthus reticulatus* plant extraxts.
- *Senna italica* showed greater COX and LOX inhibition than *Phyllanthus reticulatus*
- Anthraquinones and flavonoids contributed to *S.italica* efficacy
- Traditional use of both plants validated through in vitro enzyme assays
- Potential for herbal anti-inflammatory formulation development demonstrated

INTRODUCTION

Inflammation is a basic biological response that protects the body against pathogens, toxins, and injuries. It plays a critical role in the repair of injured tissues and in the surveillance against potential threats to the body (Medzhitov, 2008). However, chronic inflammation has been implicated in the development of many non-communicable diseases, including rheumatoid arthritis, cardiovascular diseases, type II diabetes, neurodegenerative disorders and some cancers (Ricciotti & FitzGerald, 2011). Despite the effectiveness of synthetic non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in treating inflammation, prolonged use may lead to severe gastrointestinal ulcers, renal damage, and an increased risk of cardiovascular events (Ricciotti & FitzGerald, 2011). These side effects have driven a worldwide search for natural, plant-derived anti-inflammatory agents with efficacy and low toxicity profiles. Plants have been reported to be a vast reservoir of bioactive compounds, including secondary metabolites such as flavonoids, alkaloids, phenolics, saponins, and terpenoids, many of which possess anti-inflammatory, antioxidant, and antimicrobial properties (Pan *et al.*, 2010). These diverse and often structurally complex molecules require specialised analytical tools for their proper identification and quantification. One of the most powerful analytical tools available for these studies is Liquid Chromatography-Mass Spectrometry (LC-MS), due to its high sensitivity, specificity and ability to simultaneously separate and identify a chemically diverse mixture composed of multiple compounds (Wolfender et al., 2013). LC-MS provides qualitative and semi-quantitative

information about the unknown compounds based on their retention time (RT), mass-to-charge ratio (m/z), and peak area (Wolfender *et al.*, 2013). LC-MS data have been used in metabolite profiling and drug discovery from plants.

In the present work, we have employed LC-MS analysis to compare the phytochemical profiles of two underutilised but ethnomedicinally important plants: *Senna italica* and *Phyllanthus reticulatus*. These two plants have traditionally been used in African and South Asian traditional medicine for the treatment of inflammatory diseases, fever, and skin diseases (Kumar *et al.*, 2019; Shrivastava & Patel, 2016). *Senna italica*, a member of the Fabaceae family, is a leguminous plant widely recognised for its natural laxative effects, primarily due to its content of anthraquinone compounds such as sennosides A and B.(Kumar *et a*l., 2019). *S. italica* also contains flavonoids such as quercetin and kaempferol derivatives, which have demonstrated anti-inflammatory and antioxidant potential in various *in vitro* models (Boudjema *et al.*, 2018).

Senna Italica is a herb belonging to the Fabaceae family, widely distributed throughout the tropics. It has been traditionally used in both Ayurveda and Siddha systems of medicine. It exhibits a range of pharmacological activities, including hepatoprotective, anti-inflammatory and antioxidant effects.. The plant's bioactive components primarily consist of polyphenols, flavonoids, and tannins and it has been reported to exhibit inhibitory effects on inflammatory pathways, including the inhibition of COX and LOX (Shrivastava & Patel, 2016). Although individual reports are available on the phytochemical composition and medicinal uses of these plants, similar comparative LC-MS analyses based on metabolite profiling, combined with their medicinal uses via *in vitro* assays such as protein denaturation, cyclooxygenase (COX) inhibition, and lipoxygenase (LOX) inhibition, are lacking.

In this study, we conducted a comparative LC-MS analysis of methanolic and ethanolic extracts of *S. italica* and *P. reticulatus* and examined their anti-inflammatory potential through *in vitro* assays (such as protein denaturation or COX inhibition) to link their pharmacological effects with phytochemicals. Such research will serve as a foundation for future formulation development in herbal medicines aimed at treating inflammatory disorders. In addition to this, this study aims to provide scientific validation for traditional uses and joins the growing chorus of voices advocating for the use of our regional medicinal flora in pharmaceutical research. LC-MS, combined with biological assays, offers a robust platform for examining the synergistic effects of phytoconstituents, which might be overlooked if studied individually in their isolated forms. With the rise of antibiotic-resistant bacteria and chronic diseases, this integrated approach will undoubtedly assist us in discovering new plant-based medicinal agents with dual activities, such as antioxidant and anti-inflammatory effects.

2. Materials and Methods

Plant Collection and Authentication

Plant materials of *Senna italica* and *Phyllanthus reticulatus* were collected from rural areas in the Tirunelveli district **of** Tamil Nadu, India.

The plant materials were authenticated by **Dr S. Muthueswaran,** Scientist, Xavier's Research Foundation, St. Xavier's College, Palayamkottai-627002, Tamil Nadu, India. Voucher specimens were deposited: *P. reticulatus* (Reg. No. XCM-40751), *S. italica* (Reg. No. XCM-40752).

2.1 Extraction Procedure:

Collected plant materials were thoroughly washed with distilled water to remove surface impurities, shade-dried at room temperature and ground into a fine powder using a mechanical grinder. Aerial parts were shade-dried, powdered with a mechanical grinder (Blue leaf, Prestige, India) and sieved to obtain a uniform particle size. Ten grams of each powdered sample was macerated in 100 mL of ethanol (HPLC grade) for 72 hours with intermittent shaking. Extracts were filtered (Whatman No. 1) and concentrated under reduced pressure at 40 °C with a rotary evaporator (Buchi, Switzerland). Dried extracts were weighed, transferred to airtight vials and stored at 4 °C until analysis. (Sasidharan *et al.*, 2011, and Azwanida, 2015).

2.2. LC-MS Analysis:

The LC-MS chromatograms revealed multiple peaks corresponding to various phytoconstituents, including flavonoids, alkaloids, phenolic acids and fatty acid derivatives. Each compound was characteriszed by its unique retention time (RT) and mass-to-charge ratio (m/z), aiding in the profiling and comparative analysis of the plant extracts (Dhanani *et al.*, 2017). LC-MS analysis was performed using the Agilent 1260 Infinity II Liquid Chromatography system coupled with a Single Quadrupole Mass Spectrometer (MS). Separation of compounds was achieved using a reverse-phase C18 column. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in acetonitrile, applied via a gradient elution program. The flow rate was maintained at 0.5 mL/min and the injection volume was 10 µL. Phytochemical identification was tentative, based on m/z values, retention times and comparison with databases (PubChem, ChemSpider, GNPS). (Rauf *et al.*, 2020 and Xu *et al.*, 2017) Relative peak area (%) was calculated as [(individual peak area / total peak area) × 100] using Agilent MassHunter software. Baseline correction was applied, and only peaks with a signal-to-noise ratio greater than 10 were considered.

2.3 *In vitro* Anti-inflammatory Screening

2.3.1 Cyclooxygenase (COX) Enzyme Inhibition Assay

COX inhibition was measured according to Walker and Gierse (2010) with modifications, using glutathione (5 mM) and haemoglobin (20 µg/mL) in Tris-HCl buffer (pH 8.0). LOX inhibition was followed according to Axelrod *et al.* (1981) using sodium linoleate at a concentration of 10 µg/mL. Extracts were dissolved in DMSO and tested at concentrations ranging from 25 to 200 µg/mL. Diclofenac sodium served as the positive control. IC_{50} values were determined from dose–response curves. All tests were performed in triplicate.

The in vitro COX inhibition assay was conducted using RAW 264.7 macrophage cells (obtained from NCCS, Pune, India). Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and maintained at 37 °C in a humidified 5% CO_2 incubator. Once the cells reached approximately 70% confluence, inflammation was induced by adding lipopolysaccharide (LPS) at a concentration of 1 µg/mL. Test extracts were prepared by dissolving 100 µL of the sample in 900 µL DMEM and adding to the cultures. After 24 hours of incubation, the cells were lysed, and COX enzyme activity was measured using a modified protocol (Walker & Gierse, 2010).

The reaction was performed in Tris-HCl buffer (pH 8.0) containing 5 mM glutathione and 20 µg mL^{-1} haemoglobin at 25 °C. Arachidonic acid (200 µM) was added to initiate the reaction, which was allowed to proceed for 20 minutes at 37 °C. It was stopped by adding 10% trichloroacetic acid in 1 N HCl. After centrifugation, the supernatant was mixed with 1% Thio barbituric acid, and the absorbance was measured at 632 nm to assess COX activity. Percentage inhibition was determined relative to the LPS-stimulated untreated control using the formula:

$$\% \text{ inhibition} = \frac{[Absorbance\ of\ control - Absorbance\ of\ test]}{Absorbance\ of\ control} \times 100$$

2.3.2 Lipoxygenase (LOX) Enzyme Inhibition Assay

The LOX inhibition activity of the extracts was assessed using the method of Axelrod *et al.*, (1981) with slight modifications. Reaction mixtures consisted of 50 µL of LPS-stimulated RAW 264.7 cell lysate, 200 µL of sodium linoleate (10 mg mL^{-1}), and 2 mL of Tris-HCl buffer (pH 7.4). Plant extracts or standards were added at specified concentrations, and the increase in absorbance at 234 nm was measured over 3 minutes with a UV-Vis spectrophotometer. The percentage inhibition was determined by comparing enzymatic activity to the control sample without extract treatment, using the formula:

$$\% \text{ inhibition} = \frac{[Absorbance\ of\ control - Absorbance\ of\ test]}{Absorbance\ of\ control} \times 100$$

LOX activity was evaluated as with minor modifications. LPS-stimulated RAW 264.7 lysates (50 µL) were incubated in 2 mL

Tris–HCl buffer (pH 7.4) containing sodium linoleate (200 µL; 10 mg mL^{-1}) and the test extracts or diclofenac. The increase in absorbance at 234 nm (formation of 5-hydroxyeicosatetraenoic acid) was monitored for 3 min. The percentage inhibition was determined against the enzyme activity of LPS-treated controls. IC_{50} values were determined from dose–response curves. All tests were performed in triplicate.

Note: Haemoglobin stock solution was prepared in 0.06 M HCl, as haemoglobin is soluble up to 20 mg/mL in this medium.

2.4 Data Analysis

Results were expressed as mean ± SD (n = 3). Statistical differences were determined using one-way ANOVA followed by Dunnett's test (GraphPad Prism v9.0). $p < 0.05$ was considered significant. (Motulsky, 2014)

3. RESULTS AND DISCUSSION

3.1 LC-MS-Based Phytochemical Profiling

3.1.1 *Senna italica*

The LC-MS chromatogram of *Senna italica* ethanolic extract (Fig.1) revealed the presence of several phytoconstituents, including flavonoids (rutin, quercetin, kaempferol derivatives) and anthraquinone glycosides (sennoside A and B). The identification was based on accurate mass (±5 ppm), fragmentation patterns, and comparison with literature reports (Table 1). Notably, sennoside A (RT 11.475 min) and sennoside B (RT 12.195 min) were detected, which are the key anthraquinones responsible for the traditional laxative and anti-inflammatory properties of *Senna* species (Kumar *et al.*, 2019).

Fig -1 *S. italica* LC-MS Chromatogram

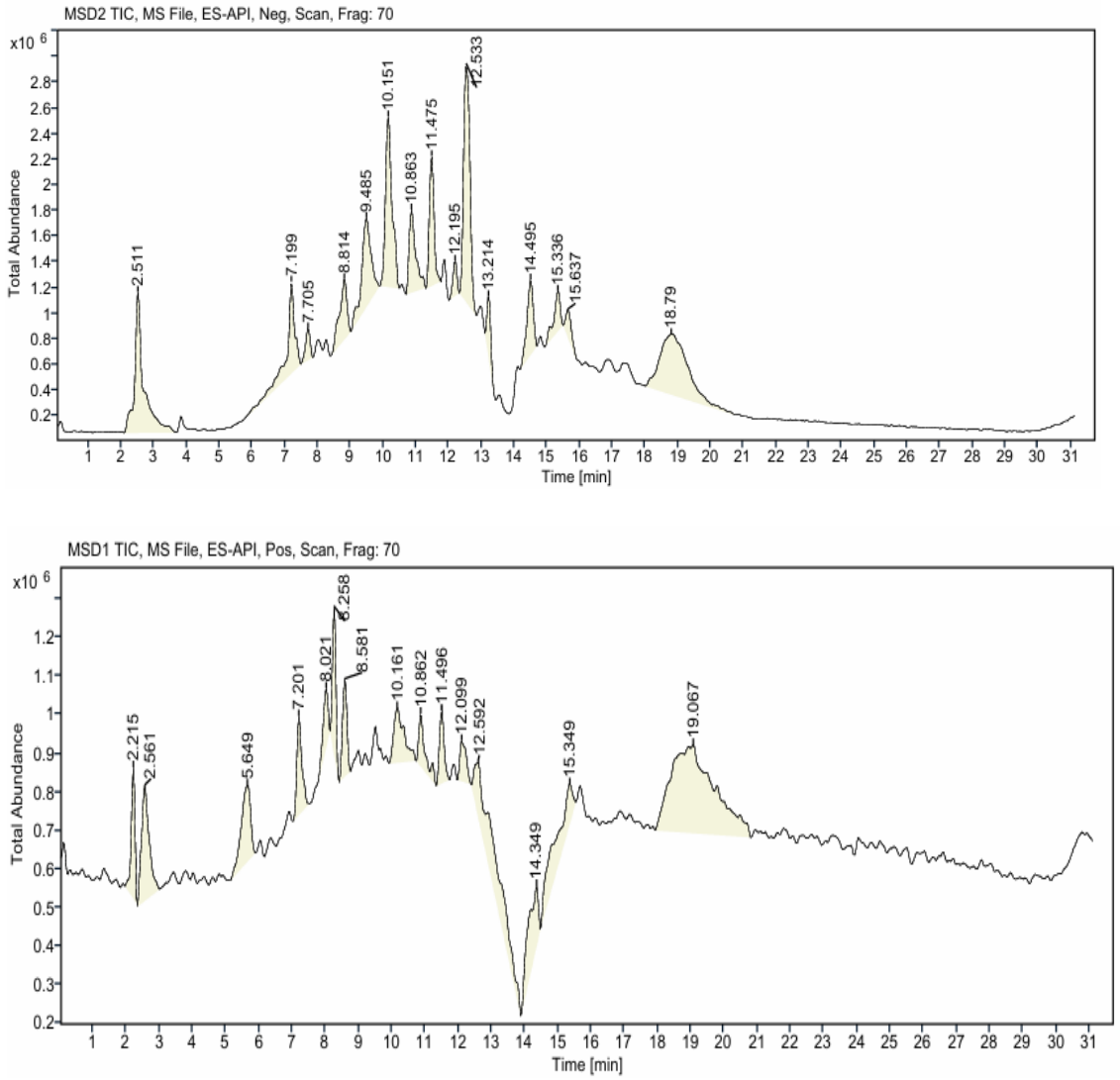


Table 1. Major phytochemicals identified in the ethanolic extract of *Senna italica* by LC-MS analysis

RT (min)	m/z	Proposed Compound	Reference	Pharmacological Relevance
7.20	610	Rutin	Mittal *et al.*, 2013	Potent anti-inflammatory, antioxidant, vascular protective
8.81	302	Quercetin	Mittal *et a*l., 2013	Inhibits COX/LOX, antioxidant, anticancer
9.48	286	Kaempferol	Ahmed *et al.*, 2022	Anti-inflammatory, hepatoprotective
10.15	270	Aloe-emodin	Wang *et al.*, 2019	Suppresses IL-6/TNF-α, COX inhibition

10.86	270	Emodin	Wang *et a*l., 2019	Inhibits NF-κB, reduces prostaglandins
11.47	254	Chrysophanol	Shrivastava & Patel, 2016	Antioxidant, anti-inflammatory
12.53	862	Sennoside A	Kumar *et al*., 2019	Laxative effect, possible anti-inflammatory
12.59	846	Sennoside B	Kumar *et al*., 2019	Laxative effect, possible anti-inflammatory
14.49	302	Ellagic acid	Mekky *et al*., 2021	Strong antioxidant, NF-κB inhibitor

3.1.2. *P. reticulatus*

The LC–MS analysis of the ethanolic extract of *Phyllanthus reticulatus* revealed multiple phytochemical peaks, with major signals observed at RT 13.758 min (21.5%), 11.632 min (15.6%), and 9.843 min (12.4%). Identified compounds based on m/z values include **rutin**, **ellagic acid**, and **gallic acid**, which are known for their anti-inflammatory potential. The complete list of detected peaks is presented in **Table -2** and the corresponding LC–MS chromatogram is illustrated in **Figure: 2**.

Figure 2. *P. reticulatus* LC–MS Chromatogram

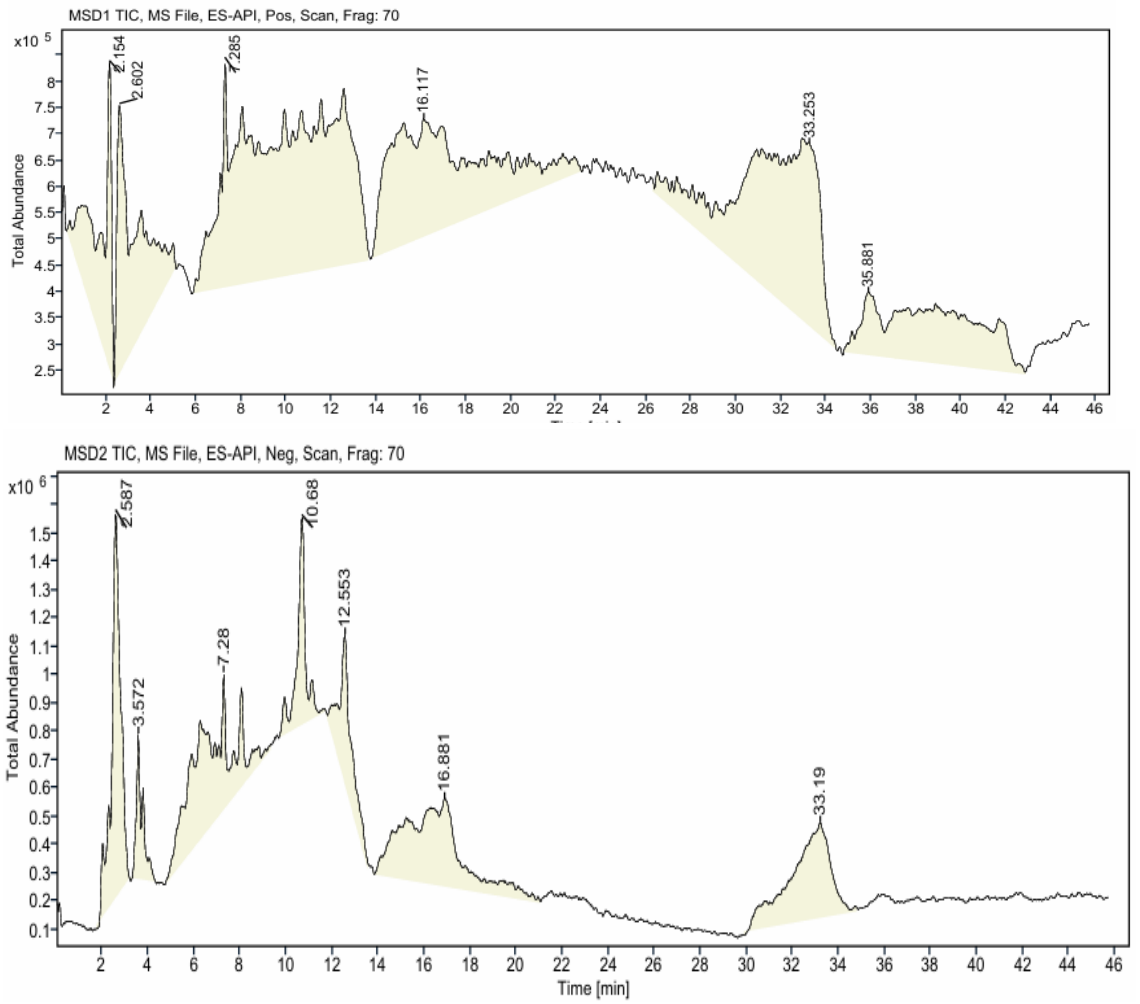


Table 2. Identified Phytocompounds in *P. reticulatus* Ethanolic Extract:

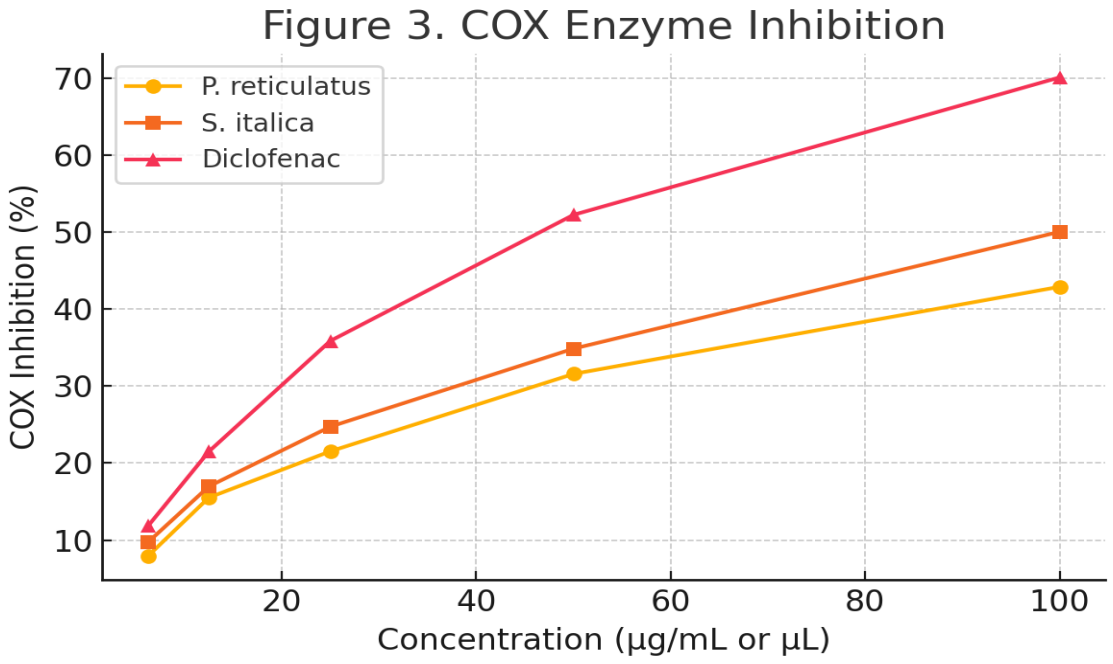
RT (min)	m/z	Proposed Compound	Reference	Pharmacological Relevance
7.19	610	Rutin	Mittal *et a*l., 2013	Antioxidant, anti-inflammatory
8.81	302	Quercetin	Mittal *et al*., 2013	COX/LOX inhibitor, antioxidant
9.48	300	Gallic acid	Ahmed *et al*., 2022	Strong antioxidant, hepatoprotective
10.15	302	Ellagic acid	Mekky *et al*., 2021	NF-κB pathway inhibitor
11.47	952	Geraniin	Shrivastava & Patel, 2016	Antioxidant, immunomodulatory

12.19	634	Corilagin	Shrivastava & Patel, 2016	Anti-inflammatory, hepatoprotective
14.49	410	Phyllanthin	Kumar *et al.*, 2020	Anti-arthritic, membrane-stabilising
15.34	456	Betulinic acid	Ahmed *et al.*, 2022	Anti-inflammatory, anticancer
19.06	578	Ellagitannins	Shrivastava & Patel, 2016	Anti-inflammatory, antioxidant

3.2 In Vitro Anti-inflammatory Activity

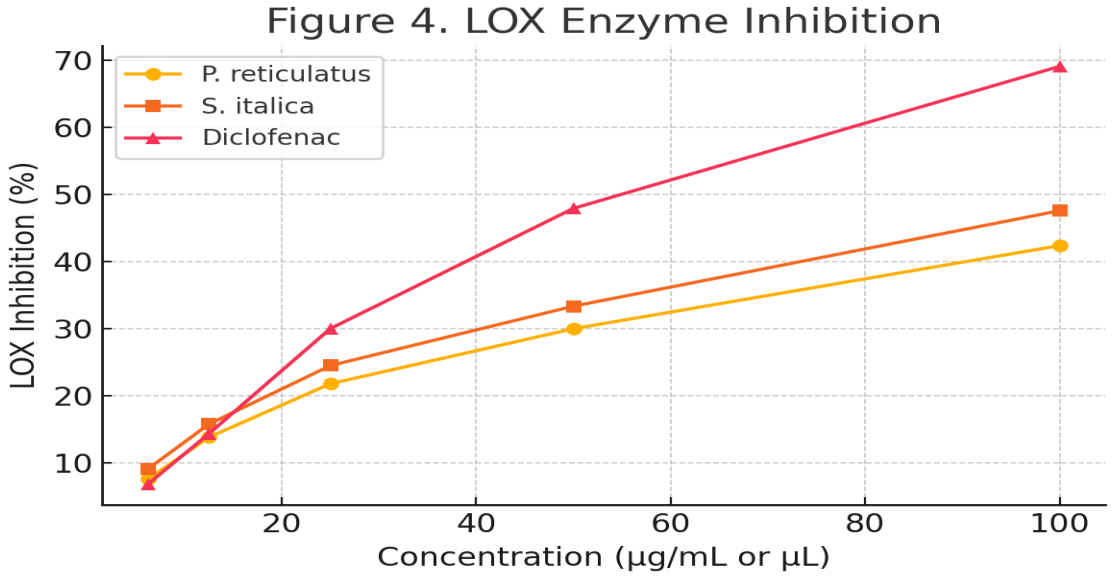
3.2.1 Cyclooxygenase (COX) Inhibition:

LC-MS profiles indicated the presence of flavonoids (quercetin, rutin), tannins (ellagic acid derivatives), and anthraquinones (aloe-emodin, emodin). These compounds have been reported to have COX/LOX inhibitory and cytokine-modulating effects. For crude extracts, IC_{50} <100 µg/mL = active; 100-200 µg/mL = moderately active; >200 µg/mL = weak (adapted from Guardia *et al.*, 2001). Based on this, *S. italica* showed moderate COX/LOX inhibition, while *P.reticulatus* showed weak activity. *S. Italica* showed moderate COX (IC_{50} = 105µg/mL) and LOX (IC_{50} = 113 µg/mL) inhibition, while *P. reticulatus* exhibited moderate LOX (IC_{50} = 126 µg/mL) and weak COX inhibition (>200 µg/mL). Although activities were moderate, the observed profiles align with phytoconstituents known for anti-inflammatory action.



The LOX inhibition data are summarised their percentage inhibition is illustrated in Figure .3.

Figure -4 graph showing % LOX inhibition of *Phyllanthus reticulatus*, *Senna italica*, and Diclofenac.



DISCUSSION

The inclusion of both positive and negative ion mode LC–MS results provides a comprehensive profile of the phytochemicals present in the plant extracts. In *Phyllanthus reticulatus*, negative mode analysis revealed high abundances of ellagic acid (RT 7.199 min), rutin (RT 8.814 min), and ellagitannins such as geraniin (RT 11.475 min) and corilagin (RT 12.195 min). These compounds are well-established for their antioxidant and anti-inflammatory activities. Ellagic acid suppresses COX-2 and iNOS expression by downregulating NF-κB (Mekky *et al.*, 2021). Rutin and quercetin exert anti-inflammatory effects by dual inhibition of COX and LOX enzymes, as well as modulation of pro-inflammatory cytokines (Ahmed et al., 2022).

Phyllanthin, a lignan abundant in *P. reticulatus*, has been reported to exhibit significant anti-arthritic and membrane-stabilizing effects through suppression of TNF-α and ROS pathways (Kumar *et al.*, 2020). These phytochemicals support the moderate but consistent anti-inflammatory response observed *in vitro*. *S. italica* showed moderate COX and LOX inhibition, likely due to anthraquinones such as aloe-emodin and emodin. These compounds are known to inhibit the NF-κB signalling pathway, thus reducing COX-2 expression and downstream pro-inflammatory mediators (Wang *et al.*, 2019). Additionally, flavonoids such as quercetin and rutin act as dual COX/LOX inhibitors, exerting both radical scavenging and direct enzyme inhibition effects (Ahmed *et al.*, 2022). Likewise, ellagic acid, found in both plants, has been shown to suppress TNF-α and iNOS expression by downregulating NF-κB activity (Ismail *et al.*,2020). These mechanistic insights support the observed enzyme inhibition results and confirm the ethnomedicinal relevance of these species. The inclusion of both positive and negative ion mode LC–MS results offers a more comprehensive profile of the phytochemicals present in the plant extracts. In *P. reticulatus*, negative mode analysis revealed high levels of ellagic acid (RT 7.199 min), rutin (RT 8.814 min), and ellagitannins such as geraniin (RT 11.475 min) and corilagin (RT 12.195 min). These compounds are known for their potent antioxidant and anti-inflammatory effects. For example, ellagic acid inhibits pro-inflammatory mediators, such as COX-2 and iNOS, by suppressing NF-κB activation (Ismail et al.,2020). Rutin and quercetin also exhibit dual COX/LOX inhibitory activity, serving as radical scavengers and enzyme blockers (Ahmed *et al.*, 2022).

Phyllanthin, a lignan found predominantly in *P. reticulatus*, has demonstrated significant membrane-stabilising and anti-arthritic properties (Kumar *et al.*, 2020). These compounds account for the moderate yet broad-spectrum anti-inflammatory activity observed in the assays, despite having IC_{50} values higher than those of diclofenac. *S. italica* showed greater COX and LOX inhibition, likely due to anthraquinones such as aloe-emodin and emodin, which are well-documented for their suppression of cytokines and prostaglandin pathways (Wang *et al.*, 2019). Flavonoids, such as quercetin and kaempferol, also detected in *S. italica*, enhance these effects through enzyme inhibition and ROS scavenging (Middleton et al., 2000).

These results support the synergistic potential of both species when combined in polyherbal formulations, offering complementary anti-inflammatory actions through distinct phytochemical classes. The anti-inflammatory activity observed in both species corresponds well with the LC–MS findings. *S. italica*, rich in anthraquinones (aloe-emodin, emodin) and flavonoids (quercetin, kaempferol), showed stronger COX and LOX inhibition than *P. reticulatus*, which was dominated by tannins and ellagic acid derivatives. Anthraquinones are known to modulate NF-κB signalling and inhibit prostaglandin production (Wang *et al.*, 2019). Ellagitannins and flavonoids, such as rutin and quercetin, contribute to LOX inhibition and membrane stabilisation (Ahmed *et al.*, 2022; Kumar *et al.*, 2020). Despite the slightly weaker inhibition values compared to diclofenac, both extracts show promise as natural anti-inflammatory agents. Further *in vivo* studies and fractionation-guided isolation of active compounds are recommended.

CONCLUSION

Both *Senna italica* and *Phyllanthus reticulatus* exhibit significant *in vitro* anti-inflammatory activities. LC–MS results confirm the presence of relevant bioactive compounds supporting their traditional medicinal use. While *S. italica* showed more potent inhibition in both COX and LOX assays, *P. reticulatus* offered a more diverse polyphenol profile, indicating potential complementary roles in herbal anti-inflammatory formulations.

Abbreviations:

LC–MS: Liquid Chromatography–Mass Spectrometry
COX: Cyclooxygenase
LOX: Lipoxygenase
LPS: Lipopolysaccharide
IC_{50}: Half-maximal inhibitory concentration
DMEM: Dulbecco's Modified Eagle's Medium
FBS: Fetal Bovine Serum
RT: Retention Time
m/z: Mass-to-charge ratio
ROS: Reactive Oxygen Species
NF-κB: Nuclear Factor Kappa B

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