



***Ficus subincisa* Buch.-Ham. Ex Sm (Chanchari): A Potential Source of Anti-Inflammatory Activities from Uttarakhand of the Indian Himalayan Region.**

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Abstracts: This study explores the *in vitro* anti-inflammatory and antioxidant activities, as well as the polyphenolic profile, of fruit extracts from *Ficus subincisa* Buch.-Ham. Ex Sm., a lesser-known species traditionally used as an herbal remedy in the Indian Himalayan regions. The fruit's 80% acetone extract was tested for anti-inflammatory effects using Human Red Blood Cell (HRBC) membrane-stabilization and protease-inhibition assays. Its antioxidant capacity was measured with DPPH and ABTS free radical scavenging tests. Polyphenolic profiling was done via High Resolution-Liquid chromatography-Mass Spectroscopy (HR-LC-MS) analysis. The total phenolics were 68.83 ± 12.50 mg GAE/100 g FW, and flavonoids totaled 178.37 ± 9.00 mg CE/100 g FW. The extract showed significant anti-inflammatory activity, with 151.3 ± 8.68 mg diclofenac equivalent (DE) per 100 g FW in HRBC stabilization and 41.53 ± 1.15 mg catechin equivalent (CE) per 100 g FW in protease inhibition. DPPH and ABTS assays revealed scavenging activities of 312.31 ± 11.50 mg ascorbic acid equivalents/100 g FW and 93.70 ± 8.13 mg butylated hydroxyanisole equivalent (BHA/E)/100 g FW, respectively. HR-LC-MS detected seven major bioactive compounds—bergenin, lomatolide, epigallocatechin, diosmin, dihydrorobinetin, peucenin, and rutin—known for their antioxidant and anti-inflammatory properties. The presence of these phenolics and flavonoids likely explains the bioactivity observed. This research offers scientific validation for the traditional use of *F. subincisa* and highlights its potential as a natural anti-inflammatory agent.

Keywords: *Ficus subincisa* • HR-LC-MS • Anti-inflammatory • Phenolics • Flavonoids • Himalayan medicinal plant

Introduction

Inflammation is a fundamental physiological defense mechanism activated by the human body in response to injury, infection, or harmful environmental stimuli (Ahmed 2011). While acute inflammation is vital for pathogen elimination and tissue repair, its persistence or dysregulation can result in chronic inflammation, which contributes to the onset and progression of numerous debilitating disorders such as arthritis, diabetes, cardiovascular diseases, cancer, and neurodegenerative conditions (Kiss 2022). Chronic inflammation is marked by excessive reactive oxygen species (ROS) generation and sustained activation of key inflammatory mediators, including cyclooxygenase (COX),

nitric oxide synthase (iNOS), and nuclear factor kappa B (NF- κ B). These pathways stimulate the release of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6), ultimately driving oxidative stress, cellular imbalance, and tissue degeneration (Kiss 2022).

Conventional anti-inflammatory therapies, particularly corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), are widely used to control inflammation. However, their long-term application is constrained by the risk of adverse effects, including gastrointestinal discomfort, kidney damage, and cardiovascular complications (Karinchai et al 2024). Consequently, there is increasing



scientific interest in identifying safer therapeutic alternatives from natural sources. Plant-derived bioactive compounds—especially flavonoids and phenolic acids—exert significant anti-inflammatory activity by scavenging free radicals, modulating inflammatory enzymes, and suppressing pro-inflammatory mediator synthesis (Yahfoufi et al 2018).

Within this context, the genus *Ficus* (family Moraceae), comprising more than 1000 species distributed across tropical and subtropical regions, has gained attention for its nutritional and pharmacological importance (Christenhusz & Byng 2016; Shi et al 2018). Many *Ficus* species have been used traditionally for food and medicine, supported by phytochemical studies highlighting the presence of phenolic acids, flavonoids, tannins, sterols, and terpenoids (Saini et al 2012; dos Anjos Cruz 2022; Mir et al 2022; Walia et al 2022; Shukla & Kansal 2024). These bioactive constituents contribute to diverse biological activities, including antioxidant, antimicrobial, antidiabetic, and anti-inflammatory effects. Extracts of species such as *Ficus carica*, *F. auriculata*, *F. palmata*, *F. racemosa*, *F. infectoria*, *F. benghalensis*, and *F. lindsayana* have demonstrated significant inhibition of COX-2 and iNOS, along with enhancement of antioxidant defense pathways (Saini et al 2012; Mir et al 2022; dos Anjos Cruz 2022; Walia et al 2022; Karinchai et al 2024).

Ficus subincisa (Buch.-Ham. ex Sm.) is a comparatively underexplored species native to the Indian Himalayas, occurring between 500–2000 meters, typically along rocky slopes and ravines (Gaur 1999). Its edible fruits are small, oval to globular, with a rough surface and pale-yellow color when ripe. Ethnobotanical records indicate its traditional application among rural and tribal populations for managing inflammation, digestive ailments, and diabetes (Pramanick 2016; Bhardwaj et al 2019). Preliminary studies further suggest notable antioxidant, antidiabetic, and potential

anti-inflammatory effects linked to its flavonoid and phenolic composition (Singh et al 2015; Shukla et al 2021).

Despite the rich medicinal potential of *Ficus* species, scientific exploration of their anti-inflammatory activity and detailed polyphenolic profiling remains limited. Therefore, the present study aimed to evaluate the total phenolic and flavonoid contents of *Ficus subincisa* fruits; investigate their anti-inflammatory potential using Human Red Blood Cell (HRBC) membrane stabilization and protease inhibition assays; assess free radical scavenging activity through DPPH and ABTS assays; and identify phenolic and flavonoid constituents using High-Resolution Liquid Chromatography–Mass Spectroscopy (HR-LC-MS).

Materials and Methods

All chemicals used were of analytical grade and had a purity of over 99% pure. 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) were obtained from Sigma-Aldrich (St. Louis, MO, USA) and Calbiochem (Merck Pvt Ltd, Darmstadt, Germany), respectively. Other reagents were purchased from HiMedia Pvt. Ltd. (Mumbai, India).

Collection and Identification of Plant Material

Fresh, mature *Ficus subincisa* Buch.-Ham. Ex Sm. fruits were collected in May 2025 from the foothills of Agrakhal village, Tehri district, Uttarakhand, India. The fruits were transported to the laboratory, washed under running tap water, and preserved at - 20 °C for up to a month before use. Herbarium specimens were submitted to the Botanical Survey of India in Dehradun for confirmation of identification.

Preparation of Extracts

Extraction followed the method of Saini et al (2012), with modifications to improve phenolic recovery. The frozen fruit pulp (25 g) was homogenized and extracted with 80% acetone. For every 5 g of fruit slurry, three extractions were performed using 25 mL of



solvent, stirred continuously for 30 minutes at $25 \pm 2^\circ\text{C}$. After filtering through Whatman No. 1 and centrifuging at 4000 rpm for 10 minutes, the clarified extracts were stored at -20°C for up to one month before use.

Estimation of Total Phenolic Contents (TPC) and Total Flavonoid Contents (TFC)

TPCs were determined using the Folin-Ciocalteu method (Singleton *et al* 1999). Specifically, 1 mL of fruit extract was mixed with 2.5 mL of Folin-Ciocalteu reagent (0.2 mol/L) and left at room temperature for 5 minutes. Next, 2 mL of sodium carbonate solution (75 g/L in water) was added, and the mixture was incubated for an additional 2 hours. The absorbance was measured at 760 nm using a UV-Visible spectrophotometer (Systronics, India, Model No. 119), with water as a control. A gallic acid calibration curve (0.2 mg/mL) was used, and TPC values were expressed as milligrams gallic acid equivalent (GAE)/100 g of fruit weight (FW). The TFCs of the fruit extracts were measured following the method of Chang *et al* (2002). A diluted extract (0.6 mL) was incubated with 0.3 mL of 5% sodium nitrite for 5 minutes at room temperature. Then, 0.6 mL of 10% aluminum trichloride solution was added, and the mixture was incubated for another 5 minutes at room temperature. Absorbance was measured at 510 nm using water as a reference blank, and TFC was expressed as milligrams of catechin equivalent (CE) per 100 g FW, with catechin (0.5 mg/mL) as the standard.

In Vitro Anti-Inflammatory Assays

Two assays were conducted to assess the anti-inflammatory potential:

HRBC Membrane Stabilization Assay

The HRBC assay was carried out as described by Mir *et al* (2022). Fresh human blood mixed with Alsever's solution was centrifuged (3000 rpm, 10 min), washed thrice with isotonic saline, and reconstituted as a 10% RBC suspension. The reaction mixture (4.5 mL) contained 1 mL phosphate buffer, 2 mL

hypotonic saline, 0.5 mL HRBC suspension, and 1 mL of extract (0.5–7.5 mg FW/mL). After incubation (37°C , 30 min) and centrifugation, absorbance was recorded at 560 nm. Diclofenac sodium served as a standard.

$$A_c - A_s \text{ Stabilization (\%)} = \frac{\text{-----}}{A_c} \times 100$$

A calibration curve of % HRBC stabilization against diclofenac concentration (0.05–2 mg/mL) was prepared, and the % HRBC stabilization activity of fruit extracts was expressed as mg diclofenac equivalent HRBC membrane stabilization activity (DE)/100 g FW.

Proteinase Inhibition Assay

The assay followed the method of Kumar *et al* (2013). Reaction mixture (2.0 mL) contained 0.06 mg trypsin, 1 mL Tris-HCl buffer (20 mM, pH 7.4), and 1 mL extract (100–500 µg/mL). After incubation at 37°C for 5 minutes, 1 mL of 0.8% casein was added, followed by a 20-minute incubation. The reaction was stopped by adding 2 mL of 70% perchloric acid, centrifuged (3000 rpm for 10 min), and the absorbance was measured at 210 nm.

$$\text{Inhibition (\%)} = \frac{A_c - A_s}{A_c} \times 100$$

A calibration curve of the % protease inhibition activity was plotted against the catechin concentration (0.05–0.5 mg/mL), and the protease inhibition activity of fruit extracts was presented as mg catechin equivalent (CE) protease inhibition activity /100 g FW.

Antioxidant activities

The antioxidant activities of fruit extracts were assessed using DPPH radical scavenging activity (DPPH[•]SA) and ABTS^{•+} radical scavenging activity (ABTS^{•+}SA), as described by Saini *et al* (2012).

HR-LC-MS Analysis of Phenolic and Flavonoid Compounds

The HR-LC-MS analysis of *Ficus subincisa* fruit extracts was conducted using the method described by Singh *et al* (2017). A 10 mg



sample of dried extract was dissolved in 5 mL of 80% acetone, filtered through a 0.2 μ m syringe filter, and analyzed at IIT Mumbai's SAIF facility. The system included an Agilent 1290 Infinity UHPLC coupled with a 6550 i-Funnel QTOF mass spectrometer. Separation was performed using a Zorbax SB-C18 Rapid Resolution HD column (2.1 $\times$ 100 mm, 1.8 μ m). The mobile phase consisted of 0.1% formic acid in water (solvent A) and acetonitrile (solvent B), with a flow rate of 0.3 mL/min over 30 minutes, using a linear gradient. Nebulizer pressure was set at 35 psi; nitrogen flow at 13 mL/min; sheath gas at 11 mL/min; drying gas at 25°C; and sheath gas at 30°C. The capillary voltage was 3500 V, the nozzle voltage 1000 V, and the fragmentation energy 175 V. Data were collected in both positive and negative ESI modes using Agilent Mass Hunter Data Acquisition (Version B.05.00) and analyzed with Agilent Mass Hunter Qualitative Analysis Software (Version B.06.00). Phenolic and flavonoid compounds were identified by comparing their mass

spectra and fragmentation patterns to authentic standards and databases provided by Agilent Technologies.

Statistical Analysis

To maintain consistency, three independent extractions were conducted, each analyzed at least three times for each parameter. The results are shown as the averages of three replicates ($n = 3$), with the standard error (SE). Data analysis was performed using Microsoft Excel and Prism 3 (GraphPad Software, Redmond, CA, USA).

Result and Discussion

TPC and TFC

The TPC was calculated using gallic acid as the standard ($R^2 = 0.984$), yielding a value of 68.83 ± 12.50 mg GAE/100 g FW in acetone extracts. TFC was measured with catechin as the standard ($R^2 = 0.999$), showing a significantly higher amount of 198.37 ± 9.00 mg CE/100 g FW compared to the TPC in the extracts (see Table 1).

Table 1: TPC and TFC of *F. subincisa* fruit extracts

Extracts	TPC mg GAE/100 g FW	TFC mg CE/100 g FW
80% acetone extracts	68.83 ± 12.50	198.37 ± 9.00

TPC mg GAE/100 g FW: Total phenol contents mg Gallic acid equivalents/ 100 g Fruit weight; TFC mg CE/100 g FW: Total flavonoid contents mg catechin equivalent /100 g of fruit weight. Each value was expressed as mean $\pm$ SE ($n = 3$).

In Vitro Anti-inflammatory Activities

HRBC Membrane Stabilization Assay

The % HRBC membrane stabilization activity of *F. subincisa* fruit was plotted against fruit extract concentrations (Fig.1). The graph illustrates a dose-dependent increase in HRBC membrane stabilization. The extract's protective effect steadily increased with increasing concentration, from 0 to 7 mg FW/ml. At lower concentrations (1–2 mg

FW/ml), stabilization was minimal, ranging from 5% to 20%. A sharp rise occurred between 2 and 5 mg FW/ml, reaching about 40–50%. At the highest concentration tested (7 mg FW/ml), the extract showed a maximum stabilization activity of approximately $62 \pm 3\%$. The HRBC membrane stabilization activity of the fruit extracts was further determined using Diclofenac ($R^2=0.965$) as a standard and represented as mg diclofenac equivalent (DE) HRBC stabilization activity/100g FW. The extract exhibited notable HRBC membrane stabilization activity of 151.3 ± 8.68 mg diclofenac equivalent (DE)/100 g FW (Table 3).

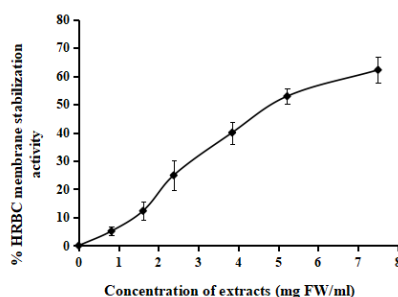


Fig. 1: % HRBC Membrane Stabilization Activity Against Extract Concentration

Proteinase Inhibition Assay

Proteinase inhibition was used to evaluate the ability of *F. subincisa* fruit extract to suppress the proteinases involved in inflammation (Fig. 2). The data showed a concentration-dependent increase in the inhibition of proteinase (trypsin) activity by the 80% acetone extract. At lower concentrations (1–2 mg FW/ml), the inhibition was less than 10%, but it gradually increased with higher extract levels. At 5 mg FW/ml, the extract inhibited

around 25–30% of the proteinase activity; this inhibition rose to about 50% at 9 mg FW/ml and reached approximately $65 \pm 3\%$ at 10 mg FW/ml. The proteinase-inhibitory activity of the extracts was further evaluated using catechin as a standard ($R^2 = 0.854$) with trypsin as the proteinase. The study revealed potent proteinase-inhibitory activity (41.53 ± 1.15 mg catechin equivalent/100 g FW) in the extracts.

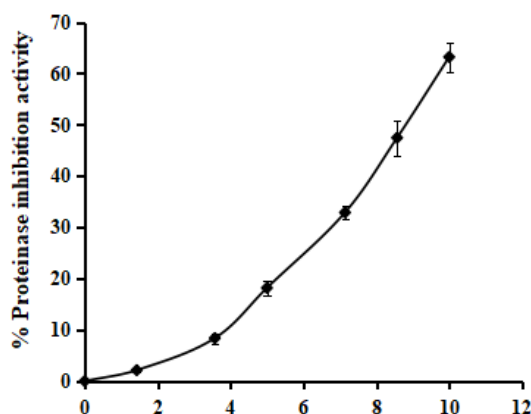


Fig. 2: % Proteinase Inhibition Activity Against Fruit Extracts

Human Red Blood Cell (HRBC) membrane stabilization activity was represented as mg diclofenac equivalent (DE) /100 g FW;

Proteinase inhibition activity represented as mg Catechin equivalent (CE)/100 g FW; Each value was represented as mean $\pm$ SE (n = 3).

Table 2: *In vitro* Anti-inflammatory Activities of Wild Edible Fruit Extracts

Extracts	HRBC Membrane stabilization activity (mg DE/100 g FW)	Proteinase inhibition activity (mg CE/100 g FW)
80% acetone extracts	151.3 $\pm$ 8.68	41.53 $\pm$ 1.15

Antioxidant activity

The antioxidant activity of *F. subincisa* fruit extracts were assessed by testing their capacity to neutralize free radicals, specifically DPPH and ABTS⁺. As shown in Table 3, DPPH RSA was assessed with ascorbic acid as a standard

($R^2 = 0.949$). The results showed significant DPPH RSA levels in the extracts, with a value of 312.31 ± 11.50 mg AAE/100 g FW. ABTSRSA was calculated using BHA as a standard ($R^2 = 0.981$), yielding a value of 93.70 ± 8.13 mg BHAE/100 g FW.



Table 3: DPPH (DPPHRS) and ABTS Radical Scavenging Activities (ABTSRSA) of *Ficus subincisa* Fruit Extracts

Extracts	DPPHRS (mg AAE/100 g FW)	ABTSRSA mg (BHA) /100 g FW
80% acetone extracts	312.31 ± 11.50	93.70 ± 8.13

Polyphenolic Profiling of *F. subincisa* Fruit Extracts by HR-LC-MS Analysis

Polyphenols in 80% aqueous acetone extracts of *F. subincisa* fruit were analyzed qualitatively using HR-LC-MS analysis. Compounds were identified by comparing their mass spectra and fragmentation patterns with the polyphenol database from Agilent Technologies, utilizing Agilent Masshunter Qualitative Software (Version B.06.00). As shown in Table 4 and Fig. 3, the polyphenolic

profile of the 80% acetone extract of *Ficus subincisa* fruit features seven main compounds: Bergenin, Lomatin, Epigallocatechin, Diosmin, Dihydrorobinetin, Peucenin, and Rutin, with retention times ranging from 0.901 to 58.19 minutes. Their molecular ions (m/z) and molecular formulas verified that these compounds are naturally occurring phenolic acids, flavonoids, and coumarin derivatives.

Table 4: Polyphenolic Composition of the Acetone Fruit Extracts of *F. subincisa*

SN	Compounds	Retention time (min)	MS (m/z)	Mass	Formula
1	Bergenin (C-glycoside of 4-O-methyl gallic acid)	0.901	351.0651	328.0758	C ₁₄ H ₁₆ O ₉
2	Lomatin,	9.496	247.0948	246.087	C ₁₄ H ₁₄ O ₄
3	Epigallocatechin	9.609	311.0525	306.0737	C ₁₅ H ₁₄ O ₇
4	Diosmin	11.27	608.1915	608.1683	C ₂₈ H ₃₂ O ₁₅
5	Dihydrorobinetin (3,3',4',5',7-, pentahydroxyflavanone),	11.996	287.0524	304.0557	C ₁₅ H ₁₂ O ₇
6	Peucenin	20.869	243.0995	260.1027	C ₁₅ H ₁₆ O ₄
7	Rutin	58.19	610.1775	610.1519	C ₂₇ H ₃₀ O ₁₆

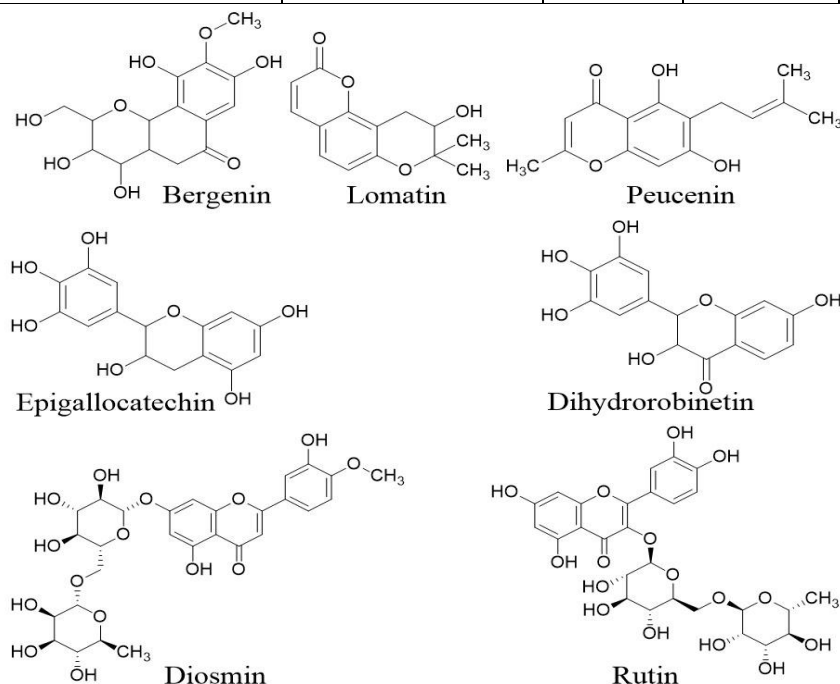


Fig. 3: Phenolic and Flavonoid Compounds in *F. subincisa* Fruit Extract

This study provides the first comprehensive evidence that *Ficus subincisa* fruit is a rich



source of polyphenolic compounds exhibiting strong anti-inflammatory and moderate antioxidant activities. Based on prior optimization work, 80% aqueous acetone was selected as the extraction solvent, as it has been reported to yield high levels of phenolics and related bioactivities in fruits (Saini *et al* 2012; Saini *et al* 2013; Saini *et al* 2014). The total phenolic (68.83 ± 12.50 mg GAE/100 g FW) and total flavonoid (198.37 ± 9.00 mg CE/100 g FW) contents obtained in this study are somewhat higher than those previously reported for *F. subincisa* fruit, supporting the efficiency of acetone as an extraction medium for polyphenols and flavonoids (Singh *et al*. 2015). These values are also comparable with those documented for other *Ficus* species, where total phenolic contents range between 2.5–131 mg GAE/g extract and total flavonoid contents between 2.1–204 mg/g, depending on solvent polarity and extraction method (Walia *et al* 2022; dos Anjos Cruz *et al* 2022).

The moderate antioxidant activity of the *F. subincisa* fruit extract against DPPH and ABTS radicals confirms the presence of efficient radical scavengers and agrees with previous reports on *Ficus* fruits exhibiting similar patterns of activity (Walia *et al* 2022; dos Anjos Cruz *et al* 2022). Notably, the fruit extract demonstrated significant anti-inflammatory activity by stabilizing human red blood cell membranes and inhibiting proteinase activity, slightly surpassing earlier findings (Singh *et al* 2015; Shukla *et al* 2021). The results clearly establish that *F. subincisa* possesses substantial anti-inflammatory activity, consistent with the broad pharmacological potential reported in other *Ficus* species, including antioxidant, anti-inflammatory, antimicrobial, and antidiabetic properties (Walia *et al* 2022).

The pronounced anti-inflammatory potential observed in this study can be linked to the secondary metabolites identified in *F. subincisa* fruit. For the first time, the polyphenolic profile of this species was characterized, revealing the presence of seven

key compounds—bergenin, lomatin, epigallocatechin, diosmin, dihydrorobinetin, peucenin, and rutin. Among these, epigallocatechin, dihydrorobinetin, and rutin have been previously detected in the fruits of *F. carica*, *F. sycomorus*, *F. vasta*, and *F. macrocarpa* (Walia *et al* 2022). However, the detection of bergenin, lomatin, diosmin, and peucenin in *F. subincisa* represents the first report of their occurrence in any *Ficus* species, thus significantly expanding the known phytochemical spectrum of the genus.

All seven phenolic compounds identified are well recognized for their antioxidant and anti-inflammatory properties (Kamel *et al* 2012; Hussain *et al* 2018; Tian *et al* 2019; Zeng *et al* 2019; Gasparrini *et al* 2020; Elmore & Singh 2022; Khan *et al* 2023; Li *et al* 2023; Singh & Roy 2023; Rahman *et al* 2024; Zhang *et al* 2024). Bergenin functions as a potent free radical scavenger and suppresses inflammation by inhibiting cytokine release and blocking STAT3 and NF- κ B signaling pathways (Li *et al* 2023; Singh & Roy 2023; Zhang *et al* 2024). Lomatin, a coumarin derivative, exhibits moderate antioxidant capacity and mitigates inflammation by disrupting the arachidonic acid metabolic pathway and inhibiting cyclooxygenase-mediated reactions (Zeng *et al* 2019). Epigallocatechin acts as an effective ROS scavenger and downregulates NF- κ B-dependent pathways involving iNOS and TNF- α , leading to reduced expression of pro-inflammatory cytokines (Gasparrini *et al* 2020; Khan *et al* 2023). Dihydrorobinetin protects against oxidative stress and inflammatory responses by inhibiting interleukin-6 and nitric oxide production in macrophages (Tian *et al* 2019). Diosmin contributes additional anti-inflammatory benefits by reducing lipid peroxidation, neutralizing reactive species, and downregulating COX-2, TNF- α , and IL-6 expression while improving endothelial integrity (Elmore & Singh 2022; Rahman *et al* 2024). Peucenin, another coumarin-derived compound, suppresses COX-2 and iNOS



activity by interfering with prostaglandin biosynthesis pathways (Hussain *et al* 2018), while rutin enhances superoxide dismutase and catalase activity, stabilizes cellular membranes, and prevents cytokine-driven inflammation through NF- κ B inhibition (Kamel *et al* 2012). Collectively, these phytoconstituents act synergistically to modulate oxidative and inflammatory pathways, thereby supporting the strong bioactivities observed in *F. subincisa* extracts. The presence of such a diverse range of polyphenols not only validates the traditional therapeutic use of *F. subincisa* in inflammatory disorders but also underscores its potential as a natural source of anti-inflammatory and antioxidant compounds. This study thus establishes a scientific foundation for further in vivo evaluations, isolation of active fractions, and development of functional formulations from *F. subincisa* fruits.

Conclusion: This study offers the first detailed evidence that *F. subincisa* fruit is rich in bioactive polyphenols, showing significant anti-inflammatory and moderate antioxidant effects. It highlights seven key phenolic compounds, including bergenin, lomatol, diosmin, and peucenin, which are reported here for the first time in any *Ficus* species, expanding the known phytochemical profile of the plant genus. The combined effects of these compounds likely explain the observed health benefits, supporting the plant's traditional use for inflammatory conditions. Overall, these results suggest that *F. subincisa* could serve as a valuable natural source for the development of functional foods and anti-inflammatory treatments.

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