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(REVIEW ARTICLE)

A Comparative Pharmacological Review of *Phaleria macrocarpa* and *Boswellia serrata* as Potential Therapeutics for Inflammatory Bowel Disease: From Ethnobotany to Molecular Mechanisms

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Abstract

Background: Inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease, is a chronic inflammatory disorder with rising global prevalence and limited curative therapies. Plant-derived agents with anti-inflammatory and immunomodulatory properties are increasingly explored as complementary approaches. *Phaleria macrocarpa* and *Boswellia serrata* are two traditional medicinal plants with reported benefits in gastrointestinal and inflammatory conditions.

Objective: This review brings together available information on the ethnobotany, phytochemistry, pharmacology, and molecular mechanistic of on *P. macrocarpa* and *B. serrata* to evaluate their potential role in IBD management.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and phytochemical databases up to 2025. Studies reporting phytochemistry, in vitro and in vivo anti-inflammatory activity, molecular mechanisms, clinical evidence, and safety are added.

Results: *P. macrocarpa* contains flavonoids, phenolics, and benzophenones that modulate NF-κB, MAPK, COX-2, and iNOS pathways, demonstrating antioxidant and anti-inflammatory effects in macrophage assays and DSS-induced colitis models. *B. serrata* resin is rich in boswellic acids, particularly AKBA and KBA, which inhibit 5-lipoxygenase, suppress NF-κB and NLRP3 inflammasome activation, and modulate cytokines. Preclinical studies consistently show reduced mucosal inflammation, oxidative stress, and improved barrier integrity. Clinical trials support the efficacy of *B. serrata* extracts in ulcerative colitis, whereas *P. macrocarpa* remains largely preclinical. Both plants exhibit favourable safety profiles, though standardisation challenges persist.

Conclusion: *P. macrocarpa* and *B. serrata* demonstrate multi-targeted pharmacological actions relevant to IBD. *B. serrata* shows stronger translational evidence, while *P. macrocarpa* offers promising phytochemical leads requiring further clinical validation.

Keywords: *Phaleria macrocarpa*; *Boswellia serrata*; Inflammatory bowel disease; Phytochemistry; NF-κB; Immunomodulation

1. Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing-remitting disorder of the gastrointestinal tract with increasing global incidence [1]. The pathogenesis of IBD is

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multifactorial, involving genetic susceptibility, environmental triggers, dysregulated immune responses, oxidative stress, and alterations in the gut microbiota [2], [3]. Conventional therapies, including aminosalicylates, corticosteroids, immunosuppressants, and biologics, are effective but often limited by adverse effects, incomplete remission, and excessive costs [2], [4]. Consequently, there is growing interest in complementary and alternative medicines, particularly botanicals with anti-inflammatory, immunomodulatory, and antioxidant properties [5].

Phaleria macrocarpa (Mahkota Dewa) and *Boswellia serrata* (Indian frankincense) are two medicinal plants with long-standing ethnobotanical use in Asia and Africa for inflammatory and gastrointestinal disorders [6], [7]. Recent research has elucidated their rich phytochemical profiles and diverse pharmacological activities, including modulation of key molecular pathways implicated in IBD, such as NF-κB, MAPK, and NLRP3 inflammasome signalling [8]. This review aims to provide a comprehensive, comparative analysis of their pharmacological potential in IBD, integrating evidence from ethnobotany, phytochemistry, preclinical and clinical studies, and mechanistic investigations [1], [9].

1.1. Ethnobotanical Background

1.1.1. Phaleria macrocarpa

Phaleria macrocarpa (Scheff.) Boerl., known as Mahkota Dewa or God's crown, is indigenous to Papua, Indonesia, and widely cultivated in Southeast Asia [10]. Traditionally, various parts of the plant (fruits, leaves, seeds, and stems) are used to treat a spectrum of ailments, including stomach-ache, diarrhoea, tumors, hypertension, diabetes, and inflammatory conditions [11]. The fruits are commonly prepared as decoctions or infusions, often in combination with other herbs [12], [13]. In Malaysian and Indonesian folk medicine, *P. macrocarpa* is valued for its purported ability to "cleanse the blood", reduce pain, and restore vitality [14].

Figure 1 *Phaleria macrocarpa*

1.2. *Boswellia serrata*

Figure 2 *Boswellia serrata*

Boswellia serrata Roxb. ex Colebr., or Indian frankincense (Shallaki in Ayurveda), is native to India and parts of North Africa and the Middle East [11]. The oleo-gum resin, obtained by tapping the bark, has been used for centuries in Ayurvedic, Unani, and traditional Chinese medicine to treat arthritis, colitis, asthma, and wounds. In Ayurveda, B. serrata is classified as an anti-inflammatory and "blood-purifying" agent, often prescribed for chronic inflammatory disorders

and digestive complaints [15], [16]. Its therapeutic efficacy has been attributed to boswellic acids, which are pentacyclic triterpenoids recognised for their potent anti-inflammatory properties [17]. Comprehensive Phytochemistry

1.3. *Phaleria macrocarpa*

Phytochemical investigations reveal that P. macrocarpa is rich in flavonoids, phenolics, saponins, tannins, terpenoids, alkaloids, and benzophenone derivatives [6], [11]. Key compounds include:

- **Flavonoids:** kaempferol, myricetin, naringin, rutin, quercetin, catechin, (+)-catechin 7-O-β-D-xyloside, (-)-8-prenylnaringenin, and glycitin [18], [19].
- **Phenolics:** Gallic acid, mangiferin, phalerin (benzophenone glycoside), mahkoside A/B95
- **Terpenoids:** 24-methylenecycloartan-3-one, 24-methyl-9,19-cyclolanost-25-en-3-ol, β-sitosterol, stigmasterol [10], [20], [21].
- **Others:** Dodecanoic acid, palmitic acid, ethyl stearate, sucrose, lignans, xanthones [10], [21].

Quantitative analyses indicate high total phenolic (47-60 mg GAE/g DW) and flavonoid (36-161 mg RE/g DW) contents, especially in the pericarp and mesocarp [21].

1.4. *Boswellia serrata*

Pentacyclic triterpenoids, or boswellic acids, are the main bioactive components of the more than 200 phytochemicals found in the oleo-gum resin of B. serrata [22], [23]. Among the main boswellic acids are

- **α- and β-boswellic acid (BA)**
- **11-keto-β-boswellic acid (KBA)**
- **3-acetyl-11-keto-β-boswellic acid (AKBA)**
- **3-O-acetyl-β-boswellic acid (ABBA)**
- **3-O-acetyl-α-boswellic acid (AABA)**
- **Other derivatives:** 9,11-dehydro-β-boswellic acid, 3-O-acetyl-11-hydroxy-β-boswellic acid [22], [23]

Boswellic acids constitute 30-65 percent of standardized extracts, with AKBA and KBA identified as the most pharmacologically active constituents [22], [23]. The resin comprises essential oils including α-pinene, myrcene, as well as polysaccharides, and minor constituents such as lupeolic acid, incensole acetate, and β-sitosterol [23], [24].

Table 1 Comparative Phytochemical Profiles of *Phaleria macrocarpa* and *Boswellia serrata*

Compound/Class	*Phaleria macrocarpa*	*Boswellia serrata*	Reference
Flavonoids	Kaempferol, Myricetin, Naringin, Rutin, Quercetin, Catechin	Minor	[6], [11], [18], [19]
Phenolics	Gallic acid, Mangifera, Phalerin	Minor	[6], [10], [11], [21]
Benzophenones	Phalerin, Mahkoside A/B	Absent	[6], [11]
Saponins/Tannins	Present	Present	[6], [11], [22], [23]
Terpenoids	24-methylenecycloartan-3-one, β-sitosterol, stigmasterol	Boswellic acids	[10], [20], [21], [22], [23]
Alkaloids	Present	Absent	[6], [11]
Essential oils	Absent	α-pinene, myrcene, limonene	[23], [24]
Polysaccharides	Present	Present	[6], [11], [23], [24]

2. Analytical Methods and Standardisation

2.1. *Phaleria macrocarpa*

Standardisation of P. macrocarpa extracts employs a combination of classical and modern analytical techniques, including:

- **Phytochemical screening:** Colorimetric assays for flavonoids ($AlCl_3$), , phenolics (Folin-Ciocalteu), saponins, tannins, and alkaloids [25]
- **Chromatographic methods:** High-performance liquid chromatography (HPLC) for quantification of phalerin, mangiferin, and flavonoids; thin-layer chromatography (TLC) for fingerprinting [21]
- **Spectroscopic methods:** UV-Vis and FTIR for functional group identification; NMR and MS for structural elucidation [26]

Extraction parameters (solvent type, temperature, particle size, and solid-to-solvent ratio) significantly influence yield and phytochemical content. Water and ethanol are preferred solvents for maximising flavonoid and phenolic extraction [21].

2.2. *Boswellia serrata*

Standardization of B. serrata focuses on quantifying boswellic acids, particularly AKBA and KBA, using:

- **HPLC and HPTLC:** For quantification and fingerprinting of boswellic acid isomers [25]
- **Mass spectrometry (MS):** For molecular weight and fragmentation analysis of boswellic acids [27]
- **NMR and IR spectroscopy:** For structural confirmation of isolated compounds [27]

Standardized extracts typically contain 30-65% total boswellic acids, with AKBA content specified for clinical and research use [22], [23].

3. Anti-inflammatory Pharmacology: In Vitro Evidence

3.1. *Phaleria macrocarpa*

In vitro studies demonstrate that P. macrocarpa extracts and isolated compounds inhibit key inflammatory mediators:

- NO **and iNOS inhibition:** Methanol and ethyl acetate extracts suppress nitric oxide production and iNOS expression in LPS/IFN-γ-stimulated RAW 264.7 macrophages, with mesocarp and pericarp fractions showing the highest activity [10], [18].
- COX**-2 and PGE2 suppression:** Semipolar methanolic extract (DLBS1425) inhibits COX-2 mRNA and prostaglandin E2 synthesis in stimulated macrophages [18].
- Cytokine **modulation:** Extracts reduce TNF-α and increase TGF-β1 in cell-based assays [10].
- Molecular **docking:** Flavonoids such as naringenin, (-)-8-prenylnaringenin, and catechin 7-O-β-D-xyloside show high affinity for NF-κB p50/p65, IKK, COX-2, and CXCR4, suggesting multi-target anti-inflammatory potential [18].

3.2. *Boswellia serrata*

Boswellic acids and B. serrata extracts exhibit potent anti-inflammatory effects in vitro:

- **5-LOX inhibition:** AKBA and KBA selectively inhibit 5-lipoxygenase, reducing leukotriene synthesis in neutrophils and monocytes [22], [23].
- **NF-κB pathway suppression:** AKBA prevents IκBα phosphorylation and degradation, reducing nuclear translocation of NF-κB and downstream expression of TNF-α, IL-1β, IL-6, and COX-2 [22], [23].
- **MAPK pathway modulation:** Alpha-boswellic acid and geraniol synergistically inhibit ERK1/2 phosphorylation, suppressing MAPK signalling in LPS-stimulated RAW 264.7 cells [28].
- **LRP3 inflammasome:** Boswellic acids reduce NLRP3 activation and IL-1β/IL-18 secretion in macrophages [29].
- **Immune cell modulation:** Inhibition of M1 macrophage activation, promotion of M2 polarisation, and suppression of Th1/Th17 differentiation [23].

4. Immunomodulatory Effects

4.1. *Phaleria macrocarpa*

P. Macrocarpa modulates both innate and adaptive immune responses:

- **Macrophage polarization:** Ethanolic leaf extracts increase NKG2D and CD-122 expression, enhancing NK cell activity and IFN-γ production [10].
- **T cell modulation:** Upregulation of T-lymphocyte activity and interferon-gamma production, supporting anti-inflammatory and anti-tumor immunity [10].
- **Suppression of pro-inflammatory cytokines:** Reduction of TNF-α, IL-1β, and iNOS in colonic tissue of DSS-induced colitis models [30].

4.2. *Boswellia serrata*

Boswellic acids exert broad immunomodulatory effects:

- **Macrophage phenotype:** Inhibition of M1 (pro-inflammatory) macrophage activation and promotion of M2 (anti-inflammatory, tissue-reparative) phenotype [24], [31]
- **T cell responses:** Suppression of Th1/Th17 differentiation, promotion of Th2/Treg responses, and inhibition of T cell proliferation via NFAT-dependent mechanisms [23]
- **Cytokine modulation:** Downregulation of TNF-α, IL-1β, IL-6, and chemokines; upregulation of IL-10 and TGF-β [24], [31]

5. Antioxidant and ROS-Scavenging Activities

5.1. *Phaleria macrocarpa*

P. Macrocarpa extracts display strong antioxidant activity:

- **DPPH and FRAP assays:** Ethyl acetate and methanol extracts exhibit low IC50 values (8-9 μg/mL), comparable to gallic acid, indicating potent free radical scavenging [21].
- **Total phenolic/flavonoid content:** Elevated levels correlate with antioxidant capacity, especially in pericarp and mesocarp fractions [21].
- **Mechanisms:** Flavonoids and phenolics neutralize ROS, inhibit lipid peroxidation, and enhance endogenous antioxidant enzymes (SOD, GPx) [21].

5.2. *Boswellia serrata*

Boswellic acids and B. serrata extracts are effective antioxidants:

- **ROS scavenging:** Inhibition of DPPH and nitric oxide radicals, with IC50 values of 54-62 μg/mL for methanolic leaf extracts [23], [32].
- **Enhancement of endogenous defences:** Promotion of Nrf2 nuclear translocation and upregulation of GPx, SOD, CAT, and HO [32].
- **Reduction of lipid peroxidation:** Decreased malondialdehyde (MDA) formation and increased glutathione levels in colitis models [32].

6. Effects on Gut Microbiota and Barrier Function

6.1. *Phaleria macrocarpa*

Emerging evidence suggests that P. macrocarpa may influence gut microbiota and barrier integrity:

- **Microbiota modulation:** Flavonoid-rich extracts may promote beneficial bacteria and suppress pathogenic species, though direct studies in IBD models are limited [21].
- **Barrier protection:** Extracts reduce iNOS and inflammatory cell infiltration in DSS-induced colitis, potentially preserving epithelial tight junctions and mucin expression (MUC1) [19], [30].

6.2. *Boswellia serrata*

Boswellic acids have demonstrated effects on gut microbiota and barrier function:

- ·**Microbiota remodelling:** AKBA treatment in AOM/DSS-induced colitis-associated cancer models alters gut microbial composition, increasing beneficial taxa and reducing pro-inflammatory species [33].
- ·**Barrier integrity:** Reduction of epithelial apoptosis, preservation of tight junction proteins, and decreased mucosal permeability in colitis models [23].

7. Molecular Mechanisms Relevant to IBD

7.1. NF-κB Pathway

Both botanicals target the NF-κB pathway, a central regulator of inflammation in IBD:

- ***Phaleria macrocarpa*:** Flavonoids (naringenin, (-)-8-prenylnaringenin) and phalerin inhibit NF-κB p50/p65 activation, suppressing transcription of pro-inflammatory genes (TNF-α, IL-1β, COX-2) [10], [30].
- ***Boswellia serrata*:** AKBA and KBA prevent IκBα phosphorylation/degradation, block nuclear translocation of NF-κB, and downregulate cytokines and adhesion molecules [22], [23].

7.2. MAPK and NLRP3 Inflammasome

- **MAPK pathway:** Both botanicals inhibit ERK1/2, JNK, and p38 MAPK phosphorylation, reducing inflammatory gene expression and immune cell activation [34].
- **NLRP3 inflammasome:** Boswellic acids suppress NLRP3 activation, caspase-1 cleavage, and IL-1β/IL-18 secretion; P. macrocarpa flavonoids may indirectly modulate NLRP3 via NF-κB inhibition [29].

7.3. Cytokine Modulation

Both botanicals shift the cytokine milieu toward an anti-inflammatory profile:

- **Downregulation:** TNF-α, IL-1β, IL-6, IFN-γ, MCP-1
- **Upregulation:** IL-10, TGF-β1

8. Preclinical In Vivo Models of Colitis

8.1. *Phaleria macrocarpa*

Multiple in vivo studies have evaluated the efficacy of P. macrocarpa in chemically induced colitis models:

- **DSS-induced colitis:** Ethanol and methanol extracts reduce disease activity index, histological inflammation, iNOS expression, and MUC1 levels in mouse colon [30].
- **AOM/DSS-induced colitis-associated cancer:** Leaf extracts attenuate inflammation and preserve goblet cell numbers in rectal tissue, though effects on angiogenesis are less pronounced [35].
- **Carrageenan-induced paw edema:** Fruit and leaf extracts exhibit anti-inflammatory activity comparable to diclofenac in mice [10].

8.2. *Boswellia serrata*

Extensive preclinical evidence supports the anti-colitic effects of B. serrata:

- **DSS and TNBS models:** Oral administration of boswellic acids or standardized extracts reduces colonic inflammation, leukocyte infiltration, oxidative stress, and mucosal damage in rats and mice [22].
- **AOM/DSS-induced colitis-associated cancer:** AKBA inhibits tumorigenesis, reduces inflammatory cytokines, and remodels gut microbiota [36].
- **Acetic acid-induced colitis:** Boswellia extracts decrease lipid peroxidation, nitric oxide, and histological lesions [32].

Table 2 Comparative Summary of Preclinical Colitis Models

Model/Agent	*Phaleria macrocarpa*	*Boswellia serrata*	Reference
DSS-induced colitis	↓ DAI, iNOS, MUC1, histological score	↓ DAI, MPO, cytokines, histological score	[22], [30]
TNBS-induced colitis	Not reported	↓ Inflammation, fibrosis, cytokines	[22]
AOM/DSS model	↓ Inflammation, goblet cell loss	↓ Tumorigenesis, cytokines, microbiota	[35], [36]
Acetic acid model	Not reported	↓ Lesions, LPO, NO	[32]

9. Clinical Evidence and Trials

9.1. *Boswellia serrata*

Several clinical trials have evaluated B. serrata in IBD and related conditions:

- **Ulcerative colitis:** Randomized controlled trials (RCTs) show that B. serrata extract (350-900 mg TID) achieves remission rates of 70-82%, comparable to sulfasalazine, with favorable safety profiles [37].
- **Crohn's disease:** Mixed results; some RCTs report no significant difference from placebo in maintaining remission, though extracts are well tolerated [38], [39].
- **Collagenous colitis:** Higher remission rates with B. serrata extract versus placebo, but no significant histological improvement [38], [39].
- **Other inflammatory conditions:** Clinical studies in osteoarthritis, rheumatoid arthritis, and asthma support anti-inflammatory efficacy and safety [23], [40].

9.2. *Phaleria macrocarpa*

Clinical evidence for P. macrocarpa in IBD is limited:

- **Lipid modulation:** A double-blind RCT in healthy adults found no significant effect of fruit extract (2 × 500 mg/day) on PCSK9 levels after 8 weeks [6], [11].
- **Case reports:** Rare adverse events (e.g., cholestatic jaundice) have been reported with long-term use of P. macrocarpa extracts in premixed coffee.
- **Other indications:** Small studies suggest benefits in diabetes, hypertension, and cancer, but robust clinical data in IBD are lacking [41].

10. Safety, Toxicity, and Adverse Effects

10.1. *Phaleria macrocarpa*

- **Acute and sub chronic toxicity:** Oral administration of fruit and leaf extracts up to 5000 mg/kg in rats shows no significant toxicity, behavioural changes, or organ pathology [6], [11], [42].
- **Reproductive toxicity:** Doses >27 mg/kg may cause embryo-fetotoxicity in mice; high doses can induce mild hepatic or renal changes, but effects are reversible [10], [43].
- **Cytotoxicity:** Extracts are non-toxic to normal fibroblasts and hepatocytes at therapeutic concentrations; some fractions show selective cytotoxicity to cancer cell lines [10].
- **Human safety:** Rare cases of cholestatic jaundice reported; long-term safety requires further validation [44].

10.2. *Boswellia serrata*

- **Preclinical safety:** Oral LD50 >2000 mg/kg in rodents; sub chronic dosing up to 1000 mg/kg shows no major organ toxicity, with occasional mild hepatic enzyme elevations [23], [45].
- **Clinical safety:** Mild gastrointestinal complaints (diarrhoea, abdominal pain, nausea) are the most common side effects; rare cases of hyponatremia and allergic reactions have been reported.

- **Drug interactions:** Potential for herb-drug interactions via induction of hepatic enzymes; caution advised with concomitant medications [46].

Table 3 Comparative Toxicity and Safety Data

Parameter	*Phaleria macrocarpa*	*Boswellia serrata*
acute toxicity	>5000 mg/kg [6], [11], [42]	>2000 mg/kg [23], [45]
Sub chronic toxicity	No major changes up to 5000 mg/kg [6], [11], [42]	No major changes up to 1000 mg/kg [23], [45]
Reproductive toxicity	Embryo-fetotoxicity >27 mg/kg [10], [43]	Not reported
Human adverse events	Rare [44]	Mild GI symptoms, rare allergy
Drug interactions	Not well studied	Possible [46]

11. Pharmacokinetics and Bioavailability

11.1. *Phaleria macrocarpa*

- *Absorption*: Flavonoids and phenolics are moderately bioavailable; glycosylated forms (e.g., phalerin, kaempferol-3-O-glucoside) may have enhanced stability and absorption [10].
- Metabolism: Undergoes phase II conjugation (glucuronidation, sulfation); detailed pharmacokinetic studies are lacking [10].
- **Formulation strategies:** Encapsulation in chitosan nanoparticles improves colonic delivery and anti-inflammatory efficacy in DSS models [30], [35].

11.2. *Boswellia serrata*

- Absorption: Boswellic acids (especially AKBA and KBA) have poor oral bioavailability due to low solubility and extensive first-pass metabolism [23], [32], [36].
- **Distribution:** AKBA and KBA reach low plasma concentrations; tissue accumulation in the brain and colon was observed in animal studies [23], [36].
- **Metabolism:** AKBA undergoes deacetylation to KBA (via carboxylesterase 2), followed by CYP-mediated oxidation; species differences noted [23], [27].
- **Formulation strategies:** Nanoparticles (PLGA, chitosan-alginate), self-nanoemulsifying drug delivery systems (SNEDDS), and phytosomes significantly enhance solubility, absorption, and anti-inflammatory efficacy [23], [32], [36].

12. Quality Assessment, Standardization, and Regulatory Challenges

12.1. Quality Assessment Tools

- **Preclinical studies:** SYRCLE's risk of bias tool is recommended for assessing methodological quality and bias in animal studies, including randomization, blinding, and outcome reporting [47].
- **Clinical trials:** CONSORT and PRISMA guidelines apply for reporting and systematic reviews; risk of bias and evidence grading tools (e.g., GRADE) should be used [47].

12.2. Standardization Issues

- ***Phaleria macrocarpa***: Variability in phytochemical content due to plant part, extraction method, and solvent need for marker compounds (e.g., phalerin, mangiferin) and chromatographic fingerprinting. [25].
- ***Boswellia serrata***: Standardization based on total boswellic acids and AKBA content batch-to-batch variation and adulteration are concerns validated HPLC/HPTLC methods are required [22], [23], [27], [32].

12.3. Regulatory Challenges

- **Herbal products:** Lack of harmonized global standards for botanical drug quality, safety, and efficacy need for compliance with WHO and pharmacopeial guidelines [23], [32], [48].
- **Clinical translation:** Insufficient high-quality clinical trials for P. macrocarpa variable evidence for B. serrata regulatory approval depends on robust safety and efficacy data.[49], [50].

13. Comparative Tables

Table 4 Comparative Summary: Phytochemistry, Pharmacology, and Toxicity

Aspects	*Phaleria macrocarpa*	*Boswellia serrata*	Reference
Major actives	Flavonoids, Phenolics, Benzophenones	Boswellic acids	[6], [11], [22], [23]
Key mechanisms	NF-κB, MAPK, COX-2, iNOS, cytokines	NF-κB, MAPK, NLRP3, 5-LOX, COX-2, cytokines	[10], [18], [22], [23], [28], [29]
Antioxidant	Strong	Moderate	[21], [23], [32]
Immunomodulation	↑ NK, T cell activity, M2 polarization	↑ M2 polarization, ↓ Th1/Th17, ↑ Treg	[10], [23], [24], [30], [31]
Microbiota effects	Limited data, benefit	Remodelling, ↑ beneficial taxa	[21], [33]
Preclinical colitis	Effective in DSS models	Effective in DSS, TNBS, AOM/DSS models	[22], [30], [32], [36]
Clinical evidence	Sparse	Multiple RCTs in IBD, OA, asthma	[6], [11], [23], [37], [38], [39], [40]
Safety	High margin, rare adverse events	Good, mild GI symptoms, rare allergy	[6], [10], [11], [23], [42], [43], [44], [45], [46]
Bioavailability	Moderate, improved by nanoparticles	Poor, improved by nanoparticles, SNEDDS	[10], [23], [27], [30], [32], [35], [36]
Standardization	Variable needs markers	Standardized by boswellic acid content	[21], [22], [23], [25], [27]

14. Critical Appraisal: Study Quality, Bias, and Evidence Grading

The overall quality of preclinical studies varies with frequent limitations in randomization, blinding, and sample size reporting. SYRCLE's risk of prejudice tool highlights the need for improved methodological rigour in animal models [47]. Clinical trials of B. serrata are of moderate quality with adequate randomization and blinding but often limited by small sample sizes and short durations [23]. Evidence for P. macrocarpa in IBD is insufficient for robust grading. Standardization and reproducibility remain major challenges for both botanicals, underscoring the importance of validated analytical methods and regulatory oversight [23], [32], [48].

15. Translational Potential and Future Directions

Both *Phaleria macrocarpa* and *Boswellia serrata* exhibit promising pharmacological profiles for IBD management, targeting multiple pathogenic pathways (inflammation, oxidative stress, immune dysregulation, barrier dysfunction, and microbiota imbalance) [51]. B. serrata is supported by stronger preclinical and clinical evidence, particularly for its boswellic acid-rich extracts [17]. P. macrocarpa offers a unique flavonoid- and phenolic-rich phytochemical matrix with potent antioxidant and anti-inflammatory effects but requires further clinical validation [52].

Future research should prioritize:

- **Standardized extract development:** Using validated marker compounds and chromatographic fingerprinting [53].

- **Advanced formulations:** Nanoparticles, phytosomes, and targeted delivery systems to enhance bioavailability and colonic targeting [54].
- **Mechanistic studies:** Elucidating molecular targets (e.g., NLRP3, epigenetic regulation) and microbiota interactions [55].
- **High quality clinical trials:** Randomized, placebo-controlled studies in IBD patients, with standardized endpoints and safety monitoring [56].
- **Regulatory harmonization:** Admitting of WHO and pharmacopeial guidelines for herbal product quality and safety [57].

16. Conclusion

Phaleria macrocarpa and Boswellia serrata are two plants that have important but different medicinal uses for IBD B. serrata is distinguished by its boswellic acid content and substantial evidence supporting its anti-inflammatory, immunomodulatory, and antioxidant properties, with proven effectiveness in preclinical and clinical IBD models. P. macrocarpa presents a complementary profile, abundant in flavonoids and phenolics, exhibiting significant antioxidant and anti-inflammatory properties; however, it necessitates additional clinical research. Both botanicals regulate essential molecular pathways (NF-κB, MAPK, NLRP3), influence immune cell polarization, and may affect the gut microbiota. For these promising natural products to become effective, safe, and widely available treatments for IBD, improvements in standardization, formulation, and regulatory oversight will be very important.

Compliance with ethical standards

Disclosure of Conflict of interest

The authors declare no conflict of interest.

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