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Rheum Emodi in Chronic Inflammatory Disorders: Potential and Pitfalls

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Abstract

Rheum emodi, commonly known as Himalayan or Indian Rhubarb, is a medicinal plant with notable anti-inflammatory, antioxidant, and immunomodulatory properties, traditionally valued in Ayurveda for managing inflammation-related disorders. Modern preclinical studies confirm its efficacy in autoimmune conditions, arthritis, and chronic ulcers, mainly due to bioactive constituents such as anthraquinones (emodin, rhein, aloe-emodin), flavonoids, and polyphenols. These compounds suppress pro-inflammatory cytokines, block NF-κB and MAPK signaling, and mitigate oxidative stress, showing comparable activity to drugs like ibuprofen.

Green extraction techniques including ultrasound-assisted, supercritical fluid, and microwave-assisted methods optimize enrichment and stability of these phytochemicals, while bioassay-guided fractionation enables enhanced purification. In vivo studies reveal dose-dependent reductions in acute and chronic inflammation with fewer side effects than conventional agents. Despite promising pharmacological evidence, clinical validation, safety assessment in at-risk populations, and standardized extraction protocols remain crucial for the therapeutic development of Rheum emodi against chronic inflammatory diseases.

Graphical abstract: Rheum emodi in chronic inflammatory disorders.

Keywords: Rheum emodi; anthraquinones; antibacterial; anti-inflammatory; green extraction; immunomodulatory; NkB; MAPK

Introduction

Traditional and Modern Perspectives

Traditionally, Rheum emodi has been used to treat conditions such as ulcers and other inflammation-related ailments in Ayurveda and other traditional medicine systems [2,3]. Modern pharmacological studies reinforce its reputation as a natural remedy, supporting its utility in disorders characterized by chronic inflammation, including autoimmune conditions, chronic ulcers, and other related diseases [2,4].

Poly-pharmacology of Rheum Compounds

Anti-Inflammatory Effects

Rheum emodi extracts, particularly from its rhizome, exhibit dose-dependent inhibition of inflammation in experimental models. The anti-inflammatory activity has been shown to be comparable to standard drugs like Ibuprofen in animal studies [1,4]. Mechanistically, the plant's active constituents—primarily anthraquinones such as emodin—modulates the release of pro-inflammatory cytokines including TNF-α and IL-12, and anti-inflammatory cytokine IL-10, thus shifting immune responses toward inflammation resolution [1,5]. This property is considered crucial for the treatment of chronic inflammatory conditions.

Antioxidant and Cytoprotective Activities

The phenolic and flavonoid compounds in Rheum emodi are potent antioxidants, scavenging free radicals and protecting tissues from oxidative stress, which often accompanies chronic inflammation [2,3,6]. This antioxidant property is protective against oxidative stress-related injuries and supports the idea that these nutraceuticals can play a supportive role in chronic inflammatory diseases where oxidative stress contributes to tissue damage [2,3].

Immunomodulatory Action

The immune-enhancing effects of Rheum emodi have been reported in cell line studies, showing increased regulation of nitric oxide and pro-inflammatory cytokines, suggesting a role in immune system modulation [1,5]. This modulation of immune responses supports its potential application for immune-mediated chronic inflammatory diseases.

Safety and Considerations

Despite its promising effects, caution is advised regarding dosage and prolonged use due to possible side effects and contraindications in specific populations, such as those with chronic diarrhea, gout, or kidney disorders [7].

In summary, Rheum emodi demonstrates notable therapeutic potential for chronic inflammatory disorders through its anti-inflammatory, antioxidant, and immunomodulatory actions, but careful clinical validation and safety monitoring are essential for its broader application in chronic conditions [1-3,5,8-13].

Active Compounds in Rheum Emodi Targeting Inflammatory Pathways

The main active compounds in Rheum emodi that target inflammatory pathways are anthraquinones (especially emodin, aloe-emodin, chrysophanol, rhein, and physcion), as well as flavonoids and polyphenols [14-16,21,22].

Key Compounds and Their Actions

- Emodin: Significantly inhibits pro-inflammatory cytokines, such as TNF-α, and suppresses inflammatory signaling pathways, including NF-κB and MAPK, thereby reducing inflammation [14,18].
- Aloe-emodin, Rhein, Chrysophanol, Physcion: These anthraquinones also exhibit anti-inflammatory effects, although emodin is most prominent. They modulate immune responses and decrease the production of pro-inflammatory mediators [14,16].
- Flavonoids (like myricetin and myricitrin): These compounds show strong antioxidant actions and possess significant anti-inflammatory, antifibrotic, and immune-modulating properties [16,18].
- Other Polyphenols: Contribute to the reduction of oxidative stress and modulation of inflammation by scavenging free radicals and inhibiting key inflammatory pathways [14,16].

Targeted Pathways of major anthraquinones

The bioactive molecules in Rheum emodi primarily (fig.1):

- Inhibit cytokines involved in inflammation (e.g., TNF-α, IL-6) [14,18].
- Block NF-κB and MAPK signaling, key regulators of immune and inflammatory responses [18].
- Neutralize oxidative stress, which is closely linked to chronic inflammation [14,17].

In summary, anthraquinones (especially emodin), flavonoids, and polyphenols are the principal compounds in Rheum emodi that directly target and suppress inflammatory pathways [14-18,20-26].

Optimal Extraction Methods to Enrich Anti-Inflammatory Compounds

Optimal extraction methods (fig.2) to enrich anti-inflammatory compounds—such as anthraquinones, flavonoids, and polyphenols—in medicinal plants like Rheum emodi typically involve modern techniques that improve yield and selectivity while preserving compound integrity [28,29,32].

Recommended Extraction Methods

Ultrasound-Assisted Extraction (UAE): Uses ultrasonic waves to enhance solvent penetration and compound release, maximizing yield in a short time and at lower temperatures—ideal for thermo-sensitive compounds. Ethanol (around 70-95%) is commonly used, and an extraction at 50–60°C for 30–60 minutes with a solvent-to-material ratio of approximately 5:1 (ml/g) is considered optimal. Combining with a centrifugation step improves purity [27,32].

Supercritical Fluid Extraction (SFE): Utilizes supercritical CO_2 (sometimes modified with ethanol) to target non-polar and moderately polar anti-inflammatory compounds, producing extracts free of solvent residue and preserving compound structure. This method is sustainable, efficient, and suitable for sensitive phytochemicals [28,29].

Microwave-Assisted Extraction (MAE): Accelerates extraction by heating plant matrices

quickly, resulting in higher yields and rapid processing, well-suited for polyphenols and anthraquinones while using less solvent [28,32].

Traditional Methods

Maceration/ Percolation: While simpler, methods like maceration and percolation are less efficient, requiring longer times and more solvent, but may be appropriate for certain heat-sensitive compounds if modern equipment is unavailable [29].

Fractionation and Purification Steps

Bioassay-Guided Fractionation: Successive fractionation (using techniques like Reverse phase-high performance liquid chromatography (RP-HPLC) helps enrich the most potent anti-inflammatory fractions by focusing on biological activity during compound selection [29].

Solvent Optimization: Ethanol–water mixtures often extract a broad spectrum of anti-inflammatory phytochemicals; pure ethanol or aqueous ethanol (70–90%) is particularly effective for anthraquinones and flavonoids [27,29,32].

In summary, ultrasound-assisted, microwave-assisted, and supercritical fluid extraction are optimal modern methods, especially when paired with bioassay-guided purification and solvent optimization, to selectively enrich anti-inflammatory compounds from botanical extracts [27-29,32].

Preclinical studies have provided substantial evidence supporting the use of Rheum emodi in chronic inflammatory diseases, showing its efficacy in animal models of inflammation and exploring its molecular mechanisms of action.

Animal Model Evidence of Extracts of Rheum emodi

Extracts (specifically from rhizome and root) have demonstrated significant anti-inflammatory effects in models such as carrageenan-induced paw edema and formalin-induced inflammation in rodents. These studies show that administration of plant extracts reduces paw swelling and inflammatory cell infiltration at doses similar in effect to standard anti-inflammatory drugs [33].

Rheum emodi extract has also been evaluated in models of chronic inflammatory diseases, such as Arthritis- a chronic debilitating age-related condition. Administration resulted in decreased joint inflammation, reduced levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6), and improved histopathological outcomes in affected tissues [33].

Molecular and Cellular Mechanisms

Preclinical assays have confirmed that major anthraquinones (like emodin and aloe-emodin) modulate immune signaling pathways (e.g., NF-κB, MAPK), which regulate cytokine production and inflammatory responses.

Suppression of these pathways leads to lowered production of TNF-α and other pro-inflammatory mediators in vivo and in vitro [33].

Antioxidant actions of Rheum emodi contribute to inhibition of oxidative stress in chronically inflamed tissues, further supporting its preclinical efficacy in models where reactive oxygen

species exacerbate inflammation.

Comparative Effectiveness:
In animal studies, the anti-inflammatory activity of Rheum emodi extracts has been reported to be dose-dependent, with higher doses sometimes producing effects comparable to non-steroidal anti-inflammatory drugs (NSAIDs), but with a potentially lower risk of adverse effects on gastrointestinal and renal systems.

In summary, robust preclinical evidence in both animal models and cell-based assays substantiates the use of Rheum emodi in chronic inflammatory diseases due to its combined anti-inflammatory, immunomodulatory, and antioxidant mechanisms, with effects seen at both cellular and whole-animal levels [32-34].

A green and efficient protocol to enrich emodin and rhein from Rheum emodi involves using advanced environmentally friendly extraction techniques such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and natural deep eutectic solvents (DES) or supercritical fluid extraction (SFE).

Green Considerations
Use water, ethanol, or natural DES (not toxic organics). Limit energy usage via UAE/MAE, which are faster and less energy-intensive than conventional methods. No toxic solvent residues, supporting both safe consumption and environmental sustainability.

Recommended Protocols and Green Extraction Methods
Sample Preparation: Dry and powder the Rheum emodi rhizome/root to increase surface area.

Ultrasound-Assisted Extraction (UAE):
Use a mixture of eco-friendly solvents (often ethanol–water, typically 70–80% ethanol).

Recommended ratio: 1:10 (w/v, plant:solvent).
Extract at 50°C for 30–40 minutes with ultrasonic power around 120–200 W.
Filter and collect the extract.

Microwave-Assisted Extraction (MAE):
Natural DES (e.g., choline chloride–citric acid, 1:3 molar ratio) can increase yield vs. ethanol alone.

Extraction parameters: 400 W microwave, 60–80°C, 10–15 minutes, solvent/solid 10:1 (v/w). Cool, filter, and collect the extract.

Supercritical Fluid Extraction (SFE):
Use supercritical CO_2 with ethanol as a modifier.

- Parameters: 40–60°C, 200–300 bar for 30–60 minutes.SFE yields high emodin and rhein content without harmful solvents.
- Ethanol Reflux Extraction (as an alternative): Use 70–80% ethanol at 60–80°C with stirring for 1–2 hours.

- Filtration and evaporation concentrate the anthraquinones.

Purification (Optional):
Employ column chromatography (silica gel) using toluene:ethyl acetate:acetic acid (e.g., 6:3.5:0.5, v/v/v) for rhein and emodin separation and further concentration. Use HPTLC or HPLC for quantification and assessment of extract purity.

This methodology ensures high yield and purity of emodin and rhein from Rheum emodi with a minimal environmental footprint.

Conclusion

We present in this review, importance of green extraction, and purification protocols in furthering non-toxic, affordable botanical-dietary supplements, from Rheum emodi derived biologic molecules, as an example that can help manage with proven efficacy; chronic inflammatory diseases of most debilitating and lifestyle related disorders.

Tables with captions

Table 1: Comparative MIC and IC_{50} values of anthraquinones based on antimicrobial and antioxidant activities

Compound	MIC (µg/mL)	Test Organism / Assay	IC_{50} (µg/mL)	Bioassay Type	Reference
Emodin	2-4	Antibacterial (various)	18.2	Antioxidant (DPPH)	PMC8778091; MDPI 27(4):1204
Emodin	50	Aeromonas hohydrophila	-	Antibacterial	ResearchGate 225137321
Rhein	2-4	Antibacterial (various)	16.7	Antioxidant (DPPH)	PMC8778091; MDPI 27(4):1204
Physcion	-	-	20.5	Antioxidant (DPPH)	MDPI 27(4):1204
Chrysophanol	2-4	Antibacterial (various)	15.8	Antioxidant (DPPH)	PMC8778091; MDPI 27(4):1204
Chrysophanol	200	Aeromonas hohydrophila	-	Antibacterial	ResearchGate 225137321
Chrysophanol	-	Antifungal / other anthraquinone activity	15.8	IC_{50} (plaque assay)	MDPI 27(4):1204
Aloe-emodin	-	Antifungal / other anthraquinone activity	17.4	IC_{50} (plaque assay)	MDPI 27(4):1204

Comparative table summarizing available MIC and IC_{50} values for the anthraquinones- emodin, rhein, physcion, and chrysophanol based on antimicrobial and antioxidant activities reported in the literature [1,8]:

Notes:
*MIC values for bacterial growth inhibition typically range from 1–3 μM for emodin and rhein, with physcion and chrysophanol showing higher MICs.
*IC50 antioxidant and cytotoxic values vary by assay but emodin generally shows lower IC_{50} indicating stronger activity.
*These ranges are approximate, depending on assay type, microorganism, or cell model used. This table highlights emodin as the most bioactive anthraquinone followed by rhein in Rheum emodi, with physcion and chrysophanol showing lower potency in most bioassays [4-10].

Figure 1: Targeted Pathways of Major Anthraquinones from Rheum Emodi.

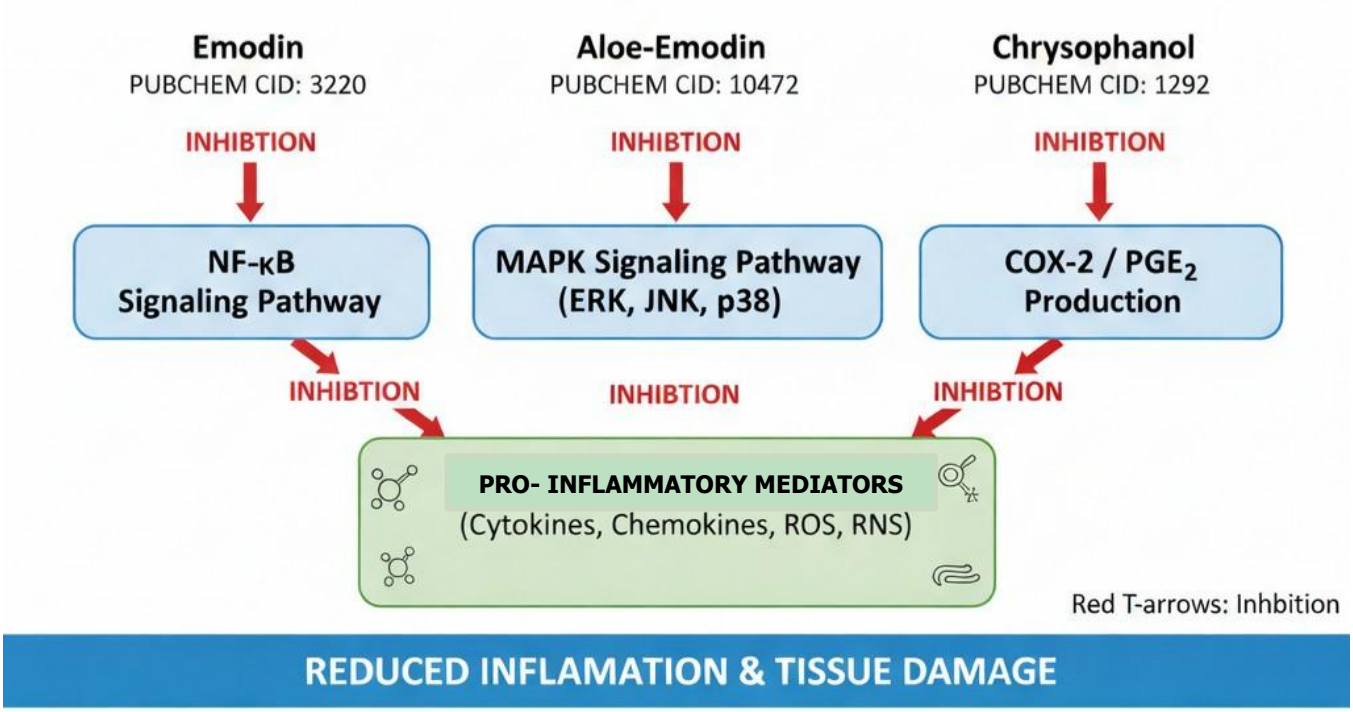
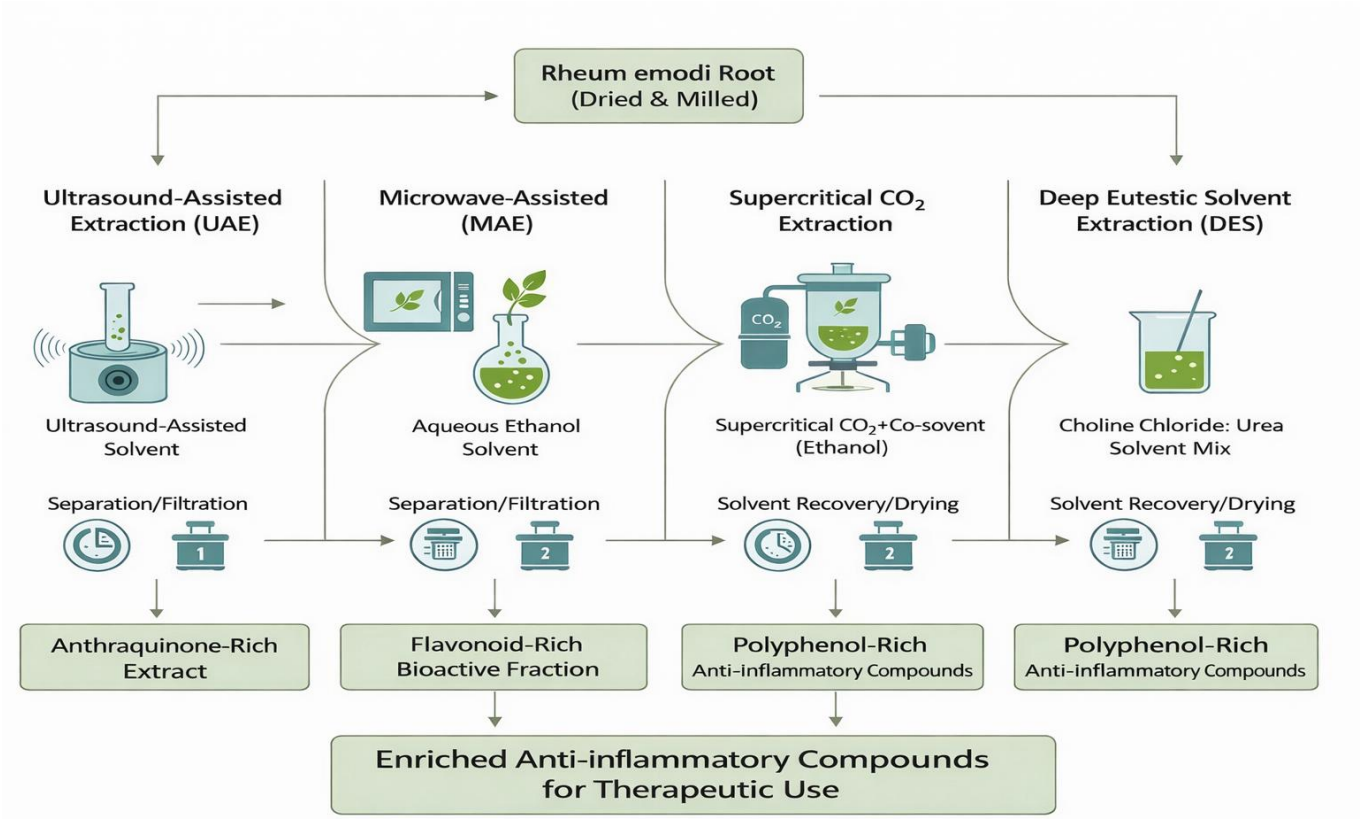


Figure 2:



Author Contributions:

AGB: Conceptualized the study; Wrote the first draft of the article, planned and supervised the structure and contents, reviewed and edited the article, while providing scientific writing training to the graduate student.

VMS: Performed literature review, performed dry lab (computational) molecular analysis, assimilated tables and illustrations, reviewed and edited the final manuscript, on principal authors instructions. Both the authors have read the article and agree to its submission for publication.

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