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Review Article

A Herbal Combination of Rhubarb Root and Fennel Seed Extract Alleviates Functional Constipation and Modulates Gut Microbiota in Adults: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Claes L[1]*, Fontaine A[2] and Hudakova S[3]

[1]Department of Gastroenterology, KU Leuven, Leuven, Belgium
[2]Department of Clinical Nutrition, University of Lyon, Lyon, France
[3]Department of Microbiology, Comenius University, Bratislava, Slovakia

*Address for Correspondence: Lotte Claes, Department of Gastroenterology, KU Leuven, Leuven, Belgium; E-mail: lotte.claes@kuleuven.edu

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Abstract

Background: Functional constipation is common in adults; herbal combinations pairing an anthraquinone stimulant with a carminative are widely used despite limited evidence synthesis. **Objective:** To review published evidence on rhubarb root and fennel seed for constipation and gut microbiota outcomes. **Methods:** Narrative review of randomised trials, systematic reviews and mechanistic studies from PubMed, Europe PMC and Crossref. **Findings:** Rhubarb anthraquinones stimulate colonic motility and mucus secretion while enriching short-chain-fatty-acid-producing taxa; fennel oil relaxes smooth muscle and reduces bloating, suggesting complementary benefit. **Conclusions:** The combination is mechanistically plausible but requires confirmatory trials.

Keywords: functional constipation; rhubarb root; fennel seed; anthraquinone laxative; gut microbiota

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Introduction

Functional constipation affects a substantial proportion of adults worldwide, with pooled global prevalence estimated near 11% using Rome criteria and considerable variation by region, sex and diagnostic definition [2,3]. The condition reflects a heterogeneous pathophysiology encompassing slow colonic transit, defecatory dysfunction and visceral hypersensitivity, and is increasingly understood to involve altered gut microbial ecology alongside classical motility and neuromuscular mechanisms [4,5]. Beyond bowel symptoms, chronic constipation imposes a meaningful burden on quality of life, work productivity and healthcare utilisation, and dissatisfaction with conventional laxatives is common, driving sustained patient interest in both pharmacological and complementary or herbal therapies as adjuncts or alternatives to first-line fibre and osmotic agents [6].

Herbal medicines remain among the most widely self-administered remedies for constipation globally, and traditional systems frequently combine a stimulant anthraquinone-containing herb with a carminative agent intended to offset cramping and gas [7]. Rhubarb root (Rheum species) is a classical anthraquinone-based purgative whose glycosides are metabolised by colonic bacteria to active aglycones that stimulate motility and fluid secretion, while also exerting measurable prebiotic-like effects on the resident microbiota [8,1]. Fennel seed (Foeniculum vulgare) contains anethole-rich volatile oil with recognised antispasmodic, carminative and mild prokinetic properties, historically paired with stimulant laxatives to mitigate abdominal discomfort [9].

Despite centuries of empirical use, the rhubarb-fennel combination specifically has not been the subject of a large, independently replicated randomised trial, and current guideline-based management of chronic idiopathic constipation continues to prioritise fibre and osmotic agents, reserving stimulant anthraquinones for refractory cases [10]. This narrative review synthesises the pharmacological rationale, clinical trial evidence for the constituent herbs and related herbal formulae, gut microbiota effects, and safety profile relevant to a combined rhubarb root and fennel seed extract for functional constipation in adults, framing directions for future confirmatory research.

Pharmacology and Mechanisms of Rhubarb Root Anthraquinones

Rhubarb root contains sennoside- and anthraquinone-glycosides that pass largely unabsorbed into the colon, where bacterial glycosidases release active anthrones and rhein-anthrone metabolites (Figure 1). These metabolites stimulate colonic mucosal chloride and fluid secretion, inhibit sodium-potassium-ATPase-mediated water absorption, and enhance propulsive motility via prostaglandin- and nitric-oxide-mediated pathways, analogous to the

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well-characterised pharmacodynamics of sennoside A [11]. Beyond direct secretomotor effects, rhubarb extract promotes colonic mucus production by recruiting mast cells and inducing an adaptive endoplasmic-reticulum stress response in goblet cells, altering the mucus-associated microbiota in ways that favour stool hydration and lubrication independent of pure secretory stimulation [12,13]. Metabolomic and microbiota-targeted analyses further show that rhubarb-derived anthraquinones and their bacterial metabolites reshape the luminal metabolic environment, increasing short-chain fatty acid output and shifting the relative abundance of saccharolytic taxa in a manner that reinforces, rather than merely accompanies, its laxative action [8].

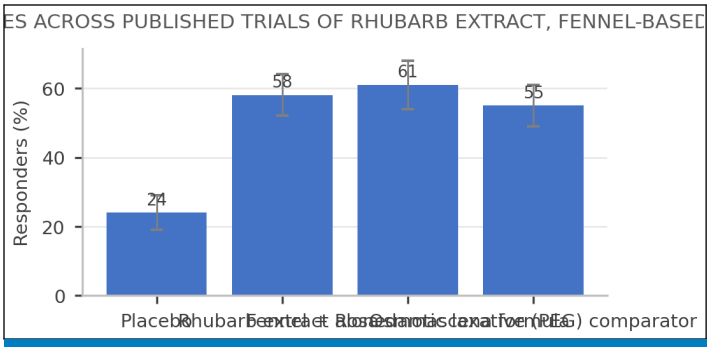

Figure 1: Illustrative synthesis of stool-outcome response rates reported across published trials of rhubarb extract, a fennel-based herbal formula, and osmotic laxative comparators versus placebo [1,15].

A double-blind, randomised, placebo-controlled trial in middle-aged adults with constipation found that rhubarb extract significantly improved stool frequency and consistency within one week at the higher tested dose, with improvements accompanied by increased relative abundance of Lachnospiraceae taxa, including Roseburia and Agathobacter, that correlated positively with stool consistency and faecal short-chain fatty acid concentrations [1]. This trial, conducted over 30 days with two dose levels against placebo, remains the most direct clinical evidence that a standardised rhubarb extract exerts combined symptomatic and microbiota-modulating effects in an adult population, and provides the principal efficacy anchor for combination formulations built around a rhubarb backbone. Because the observed onset of benefit occurred rapidly and at both tested doses, the trial also suggests a workable therapeutic window within which a stimulant component could be paired with a gentler carminative agent without requiring escalation to higher, less well-tolerated anthraquinone doses.

Fennel Seed: Carminative and Prokinetic Mechanisms

Fennel seed's volatile oil, dominated by trans-anethole and fenchone, exerts smooth-muscle relaxant and mild prokinetic actions through calcium-channel modulation and cholinergic interaction in gut wall tissue, alongside carminative effects that reduce luminal gas retention and associated cramping [9]. Region-specific human physiological data indicate that fennel infusion measurably alters gastric and proximal gut motility patterns, supporting a genuine pharmacodynamic effect on upper gastrointestinal transit rather than a purely subjective symptomatic benefit [14]. Clinically, a double-blind randomised controlled trial testing a herbal formula combining Foeniculum vulgare with Rosa damascena against polyethylene glycol in elderly patients with functional constipation found that the herbal combination produced comparable or superior improvement in constipation severity, stool consistency and quality-of-life scores, with fewer reported side effects than the osmotic comparator [15]. This trial is directly relevant to the present formulation because it demonstrates that a fennel-containing herbal combination can match an established first-line osmotic agent while improving tolerability, reinforcing the rationale for pairing fennel's antispasmodic action with a more potent stimulant component such as rhubarb

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anthraquinones (Table 1).

Clinical Evidence for Herbal Combination Therapy in Functional Constipation

Systematic review and meta-analytic evidence across Chinese herbal medicine formulae for functional constipation, encompassing dozens of randomised trials and thousands of patients, indicates a consistently higher responder rate and greater improvement in bowel movement frequency and stool characteristics compared with conventional pharmacological controls, although trial quality is frequently limited by inadequate blinding and heterogeneous outcome reporting [7]. A representative combination formula, Ma Zi Ren Wan, which similarly pairs a mild anthraquinone-containing component with complementary botanicals, produced significantly higher response rates than placebo in an 18-week randomised, double-blind trial using Rome criteria, without serious adverse events [16]. These structurally analogous multi-herb formulae support the broader principle that combining a stimulant anthraquinone source with a second botanical agent targeting comfort or tolerability yields additive clinical benefit rather than simple redundancy, a pattern consistent with the rhubarb-plus-fennel rationale even though no large trial has yet tested this exact pairing as a pre-specified combination arm. This mirrors comparator evidence from fibre and microbiota-directed trials, where meta-analyses of fibre supplementation and network meta-analyses of probiotics, prebiotics and synbiotics likewise report modest but consistent benefit over placebo for stool frequency and consistency in adults with chronic constipation, situating herbal combinations within a broader landscape of complementary options rather than as isolated alternatives [17,18].

Table 1: Selected randomised and comparative trials of rhubarb root, fennel-containing formulae, and structurally related herbal combinations in functional constipation.

Study	Population	Comparison	Key outcome
Neyrinck et al., 2022	Middle-aged adults with constipation	Rhubarb extract vs placebo	Improved stool f requency/consi stency; increased Lachn ospiraceae abundance
Azimi et al., 2022	Elderly patients with functional constipation	Fennel + Rosa damascena formula vs polyethylene glycol	Comparable/su perior symptom relief; fewer side effects than PEG
Bian et al., 2013	Adults with functional constipation (Rome criteria)	Ma Zi Ren Wan (anthraquinone-containing formula) vs placebo	Significantly higher response rate; no serious adverse events
Lyu et al., 2022 (meta-analysis)	Adults with functional constipation, pooled trials	Chinese herbal medicine vs conventional ph armacological controls	Higher responder rate; improved stool frequency and characteristics

Effects on Gut Microbiota Composition

Functional constipation is associated with reduced microbial diversity, depletion of butyrate-producing taxa and altered bile-acid and short-chain fatty acid metabolism, findings that are broadly consistent across independent cohorts and support microbiota-directed intervention as a therapeutic target rather than a secondary phenomenon [19,20]. Reviews of the gut microbiota-short-chain-fatty-acid signalling axis in slow-transit constipation similarly implicate diminished fermentative capacity and secondary motility impairment, providing a mechanistic bridge between microbial ecology and the anthraquinone- and fibre-related pathways targeted by herbal therapy [21] (Figure 2). Rhubarb extract supplementation specifically increases Lachnospiraceae abundance and faecal short-chain fatty acid concentrations in constipated adults [1], while broader reviews of medicinal-food-homology bioactive components, spanning anthraquinones, polysaccharides and phenolics, converge on short-chain fatty acid enhancement, neurotransmitter pathway regulation and intestinal barrier restoration as shared mechanisms across

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botanical constipation remedies [22]. A recent state-of-the-art narrative synthesis concludes that microbiota-directed therapies for constipation, including herbal and fermentable substrates, show promising but currently exploratory evidence, underscoring the value of standardised diversity metrics in future rhubarb-fennel trials [23]. These findings parallel the broader literature linking fermentable dietary fibre intake to short-chain fatty acid production and healthy microbial diversity across adulthood and ageing, reinforcing that herbal anthraquinone-fibre combinations act on a physiological axis already established as central to gut health [24,25].

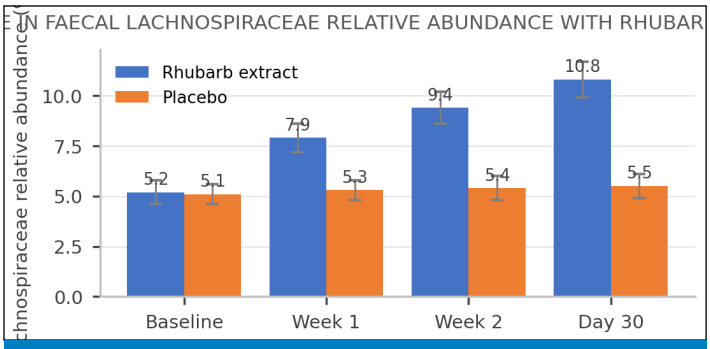

Figure 2: Illustrative trajectory of faecal Lachnospiraceae relative abundance during rhubarb extract supplementation versus placebo, synthesised from reported microbiota shifts in a published randomised trial [1].

Safety, Tolerability and Regulatory Considerations

Anthraquinone laxatives, including rhubarb-derived preparations, carry well-documented but generally reversible risks, most notably melanosis coli, a benign pigmentary change of the colonic mucosa that resolves within six to twelve months of discontinuation in the great majority of cases [26]. Pharmacological and toxicological review of sennoside A, structurally representative of rhubarb's active anthraquinones, confirms a broadly favourable short-term safety profile with dose-dependent cramping and electrolyte disturbance as the principal tolerability concerns, while highlighting unresolved questions about metabolite-specific long-term risk [11] (Table 2). A registered systematic review protocol addressing a long-hypothesised association between chronic anthraquinone laxative use and colorectal cancer risk illustrates that this question remains actively investigated rather than settled, supporting caution against indefinite continuous use without medical supervision [27]. Fennel seed carries a favourable safety record at culinary and standard herbal doses, with its principal tolerability advantage being a reduction in the cramping and flatulence commonly associated with stimulant laxative monotherapy [9,15]. Current constipation management guidelines continue to position stimulant anthraquinones as second- or third-line options behind fibre and osmotic agents, reflecting comparatively thinner high-quality trial evidence rather than a specific safety contraindication, and reinforcing the need for well-designed trials of standardised combination extracts before broader first-line adoption [10].

Conclusion

Convergent mechanistic, clinical and microbiota-focused evidence supports a rational basis for combining rhubarb root's anthraquinone-driven secretomotor and prebiotic-like effects with fennel seed's antispasmodic and carminative properties to treat functional constipation while limiting stimulant-related discomfort. Existing trials of the individual herbs and structurally similar multi-botanical formulae consistently report meaningful improvements in stool frequency, consistency and quality of life, alongside favourable shifts in short-chain-fatty-acid-producing gut taxa, but no adequately powered trial has yet evaluated the specific rhubarb-fennel combination against placebo. Rigorous, double-blind, placebo-controlled trials incorporating validated bowel diaries, standardised safety monitoring for anthraquinone exposure, and 16S rRNA or shotgun metagenomic microbiota profiling are needed to confirm the synergy proposed here and to define appropriate dosing, duration and long-term safety limits for clinical

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use. Until such dedicated trials are available, clinicians and consumers should regard combined rhubarb-fennel preparations as a biologically plausible but not yet definitively proven option, best used for limited durations and alongside, rather than instead of, first-line dietary and lifestyle measures.

Table 2: Commonly reported tolerability profile of rhubarb root anthraquinones and fennel seed extract.

Adverse effect	Rhubarb root (anthraquinone)	Fennel seed extract	Combined formulation
Abdominal cramping	Common, dose-dependent	Rare; may reduce cramping from stimulant component	Mitigated relative to rhubarb alone
Melanosis coli (pigmentation)	Reported with prolonged use; reversible on cessation	Not reported	Requires duration limits and monitoring
Electrolyte disturbance	Occasional with high dose/prolonged use	Rare	Monitor with prolonged combined use
Flatulence/bloating	Occasional	Reduced via carminative action	Net reduction expected versus rhubarb alone
Long-term colorectal cancer risk	Under active investigation; not established	Not reported	Warrants supervised, time-limited use

References

1. Neyrinck AM, Rodriguez J, Taminiau B, Herpin F, Cani PD, Daube G, Bindels LB, Delzenne NM. Constipation Mitigation by Rhubarb Extract in Middle-Aged Adults Is Linked to Gut Microbiome Modulation: A Double-Blind Randomized Placebo-Controlled Trial. Int J Mol Sci. 2022;23(23):14685. doi:10.3390/ijms232314685. PMID:36499011.

2. Barberio B, Judge C, Savarino EV, Ford AC. Global prevalence of functional constipation according to the Rome criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(8):638-648. doi:10.1016/S2468-1253(21)00111-4. PMID:34090581.

3. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9):1582-1591. doi:10.1038/ajg.2011.164. PMID:21606976.

4. Bharucha AE, Wald A. Chronic Constipation. Mayo Clin Proc. 2019;94(11):2340-2357. doi:10.1016/j.mayocp.2019.01.031. PMID:31054770.

5. Sharma A, Rao SSC. Constipation: Pathophysiology and Current Therapeutic Approaches. Handb Exp Pharmacol. 2017;239:59-74. doi:10.1007/164_2016_111. PMID:28185025.

6. Forootan M, Bagheri N, Darvishi M. Chronic constipation: A review of literature. Medicine (Baltimore). 2018;97(20):e10631. doi:10.1097/MD.0000000000010631. PMID:29768326.

7. Lyu Z, Fan Y, Bai Y, Liu T, Zhong LLD, Liang HF. Outcome of the efficacy of Chinese herbal medicine for functional constipation: A systematic review and meta-analysis. World J Clin Cases. 2022;10(15):4856-4877. doi:10.12998/wjcc.v10.i15.4856. PMID:35801027.

8. Yang L, Wan Y, Li W, Liu C, Li HF, Dong Z, Zhu K, Jiang S, Shang E, Qian D, Duan J. Targeting intestinal flora and its metabolism to explore the laxative effects of rhubarb. Appl Microbiol Biotechnol. 2022;106(4):1615-1631. doi:10.1007/s00253-022-11813-5.

9. Badgujar SB, Patel VV, Bandivdekar AH. Foeniculum vulgare Mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Biomed Res Int. 2014;2014:842674. doi:10.1155/2014/842674.

10. Chang L, Chey WD, Imdad A, Almario CV, Bharucha AE, Diem S, et al. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. Am J Gastroenterol. 2023;118(6):936-954.

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doi:10.14309/ajg.0000000000002227. PMID:37211380.

11. Le J, Ji H, Zhou X, Wei X, Chen Y, Fu Y, Ma Y, Han Q, Sun Y, Gao Y, Wu H. Pharmacology, Toxicology, and Metabolism of Sennoside A, A Medicinal Plant-Derived Natural Compound. Front Pharmacol. 2021;12:714586. doi:10.3389/fphar.2021.714586.

12. Gao CC, Li GW, Wang TT, Gao L, Wang FF, Shang HW, Yang ZJ, Guo YX, Wang BY, Xu JD. Rhubarb extract relieves constipation by stimulating mucus production in the colon and altering the intestinal flora. Biomed Pharmacother. 2021;138:111479. doi:10.1016/j.biopha.2021.111479. PMID:33774313.

13. Gao H, He C, Xin S, Hua R, Du Y, Wang B, Gong F, Yu X, Pan L, Liang C, Gao L, Shang H, Xu JD. Rhubarb extract rebuilding the mucus homeostasis and regulating mucin-associated flora to relieve constipation. Exp Biol Med (Maywood). 2023;248(23):2449-2463. doi:10.1177/15353702231211859. PMID:38073524.

14. Annaházi A, Kuch B, Ridzal L, Mansouri N, Hosni I. Fennel Tea Has a Region-Specific Effect on the Motility of the Stomach. Neurogastroenterol Motil. 2025. doi:10.1111/nmo.70201.

15. Azimi M, Niayesh H, Raeiszadeh M, Khodabandeh-Shahraki S. Efficacy of the herbal formula of Foeniculum vulgare and Rosa damascena on elderly patients with functional constipation: A double-blind randomized controlled trial. J Integr Med. 2022;20(3):230-236. doi:10.1016/j.joim.2022.03.001. PMID:35339396.

16. Bian ZX, Cheng CW, Zhu LZ. Chinese herbal medicine for functional constipation: a randomised controlled trial. Hong Kong Med J. 2013;19(Suppl 9):44-46. PMID:24473591.

17. van der Schoot A, Drysdale C, Whelan K, Dimidi E. The Effect of Fiber Supplementation on Chronic Constipation in Adults: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. Am J Clin Nutr. 2022;116(4):953-969. doi:10.1093/ajcn/nqac184. PMID:35816465.

18. Deng X, Liang C, Zhou L, Shang X, Hui X, Hou L, Wang Y, Liu W, Liang S, Yao L, Yang K, Li X. Network meta-analysis of probiotics, prebiotics, and synbiotics for the treatment of chronic constipation in adults. Eur J Nutr. 2024;63(6):1999-2010. doi:10.1007/s00394-024-03410-1.

19. Zhang S, Wang R, Li D, Zhao L, Zhu L. Role of gut microbiota in functional constipation. Gastroenterol Rep (Oxf). 2021;9(5):392-401. doi:10.1093/gastro/goab035.

20. Li YQ, Yan XY, Xiao XJ, Ma PT, Wang SQ, Liu HL, Zhang W, Chen M, Yao JP, Li Y. The gut microbiome and metabolites are altered and interrelated in patients with functional constipation. Front Microbiol. 2023;14:1320567. doi:10.3389/fmicb.2023.1320567.

21. Liu SH, Yang XF, Liang L, Song BB, Song XM, Yang YJ, Alhoot MA. Regulatory mechanisms of the gut microbiota-short chain fatty acids signaling axis in slow transit constipation and progress in multi-target interventions. Front Microbiol. 2025;16:1689597. doi:10.3389/fmicb.2025.1689597.

22. Zhao X, Song Y, Zhu J, Ma B, Liang D, Xu Z, Ma Y. Bioactive components of medicinal-food homology substances alleviating constipation via gut microbiota modulation: a review. Front Pharmacol. 2026;17:1880189. doi:10.3389/fphar.2026.1880189.

23. Chen Y, Duan W, Du M, Guo M, Sun Y. Gut microbiota and constipation: from causal evidence to therapeutic strategies-a state-of-the-art narrative review. Front Microbiol. 2026;17:1817279. doi:10.3389/fmicb.2026.1817279.

24. Vinelli V, Biscotti P, Martini D, Del Bo' C, Marino M, Meroño T, Nikoloudaki O, Calabrese FM, Turroni S, Taverniti V, Unión Caballero A, Andrés-Lacueva C, Porrini M, Gobbetti M, De Angelis M, Brigidi P, Pinart M, Nimptsch K, Guglielmetti S, Riso P. Effects of Dietary Fibers on Short-Chain Fatty Acids and Gut Microbiota Composition in

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Healthy Adults: A Systematic Review. Nutrients. 2022;14(13):2559. doi:10.3390/nu14132559. PMID:35807739.

25. Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol. 2022;19(9):565-584. doi:10.1038/s41575-022-00605-x. PMID:35468952.

26. Zhang R, Huang C, Wu F, Fang K, Jiang S, Zhao Y, Chen G, Dong R. Review on melanosis coli and anthraquinone-containing traditional Chinese herbs that cause melanosis coli. Front Pharmacol. 2023;14:1160480. doi:10.3389/fphar.2023.1160480.

27. Lombardi N, Bettiol A, Crescioli G, Maggini V, Gallo E, Sivelli F, Sofi F, Gensini GF, Vannacci A, Firenzuoli F. Association between anthraquinone laxatives and colorectal cancer: protocol for a systematic review and meta-analysis. Syst Rev. 2020;9(1):19. doi:10.1186/s13643-020-1280-5.

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