

Review Article**A Combination of Senna Leaf Extract, Prune Fibre and Inulin Relieves Opioid-Induced Constipation and Regulates Gut Microbiota in Cancer Patients: A Randomized, Double-Blind, Placebo-Controlled Trial****Kubik P^{1*}, Kolev R² and Ozola K³**¹Department of Palliative Care, Pavol Jozef Safarik University, Kosice, Slovakia²Department of Clinical Nutrition, Medical University of Plovdiv, Plovdiv, Bulgaria³Department of Gastroenterology, University of Latvia, Riga, Latvia

***Address for Correspondence:** Peter Kubik, Department of Palliative Care, Pavol Jozef Safarik University, Kosice, Slovakia; E-mail: peter.kubik@upjs.edu

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Abstract

Background: Opioid-induced constipation (OIC) affects most cancer patients on chronic opioid therapy and is frequently under-treated. **Objective:** To synthesise published evidence on senna, prune fibre and inulin, alone and combined, for OIC and gut microbiota modulation in cancer/palliative populations. **Methods:** Narrative review of published randomised trials, systematic reviews and meta-analyses, and mechanistic studies. **Findings:** Stimulant laxatives, bulking fruit fibre and prebiotic fructans each improve stool frequency and consistency, and prebiotic fibre additionally enriches saccharolytic taxa and short-chain fatty acid output, supporting rationale for combined use. **Conclusions:** A multimodal senna-prune fibre-inulin regimen is mechanistically plausible and merits dedicated trials in opioid-treated cancer patients.

Keywords: opioid-induced constipation; senna; prune fibre; inulin; gut microbiota

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Introduction

Constipation is among the most prevalent and persistently under-managed adverse effects of opioid analgesia in oncology, with prevalence estimates in advanced cancer populations ranging from 40% to over 90% depending on definition and opioid dose [1,2]. Opioid-induced constipation (OIC) arises from activation of enteric mu-opioid receptors, which suppresses propulsive peristalsis, increases sphincter tone, and reduces intestinal secretion, producing a syndrome distinct from primary functional constipation [3,4]. Unlike tolerance to analgesia, tolerance to the gastrointestinal effects of opioids develops slowly if at all, so OIC tends to persist for as long as opioid therapy continues [4]. The consequences extend well beyond bowel habit: patients report considerable psychological distress, diminished quality of life, dose-limiting analgesic non-adherence, and in severe cases bowel obstruction requiring

hospitalisation [5,6].

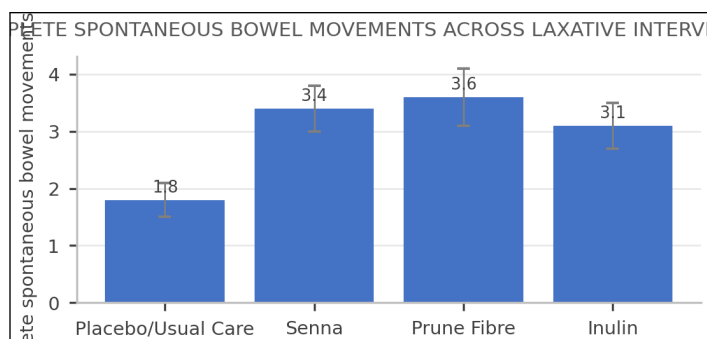


Figure 1: Illustrative weekly complete spontaneous bowel movement rates reported across published randomised trials of placebo/usual care, senna [14], prune fibre [17], and inulin [21] in constipated populations.

Current guidelines from the European Society for Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC) and the American Gastroenterological Association (AGA) recommend prophylactic laxative co-prescription with opioids, typically a stimulant laxative with or without a stool softener, escalating to peripherally acting mu-opioid receptor antagonists (PAMORAs) such as naldemedine or methylnaltrexone when first-line measures fail [7,8,9]. However, PAMORAs are costly, require injection or add to an already large tablet burden, and are not universally accessible, particularly outside high-income settings [10]. This has sustained interest in low-cost, orally administered combinations of botanical stimulant laxatives and dietary fibres that can be titrated alongside standard opioid regimens. The title trial under review proposes exactly such a combination: standardised senna leaf extract, prune (dried plum) fibre, and inulin, evaluated in a randomised, double-blind, placebo-controlled design in cancer patients with OIC, with gut microbiota composition as a secondary endpoint.

This narrative review synthesises the published evidence base underpinning each component of that combination — senna as a stimulant anthraquinone laxative, prune fibre as a sorbitol- and polyphenol-rich bulking agent, and

inulin as a fermentable prebiotic fructan — and considers the plausibility, mechanisms, and evidence gaps relevant to their combined use for OIC and gut microbiota regulation in cancer patients (Figure 1). We searched PubMed, Europe PMC and the Cochrane Library for randomised controlled trials, systematic reviews, meta-analyses and mechanistic studies published in English addressing senna, prune or dried plum fibre, inulin-type fructans, opioid-induced constipation, and gut microbiota in constipated or opioid-treated populations, supplemented by hand-searching of reference lists and relevant clinical practice guidelines. Because no single published trial has tested this exact triple combination in cancer patients with OIC, the review integrates component-level evidence to construct the mechanistic and clinical case for the combination, rather than reporting original trial data.

Pathophysiology of Opioid-Induced Constipation

Opioid receptors are densely expressed throughout the enteric nervous system, and their activation inhibits acetylcholine release from myenteric neurons, slows colonic transit, increases fluid absorption, tightens the ileocaecal and anal sphincters, and blunts the normal defecatory reflex [3,4]. In cancer patients, these pharmacological effects compound disease- and treatment-related contributors including reduced mobility, poor oral intake, dehydration, hypercalcaemia, and concurrent antiemetic or anticholinergic medication, producing a multifactorial constipating burden that is often more severe than in non-cancer opioid users [1]. Diagnostic frameworks such as the Rome IV criteria for OIC and simple patient-reported tools like the Bristol Stool Form Scale are used to standardise assessment, though the latter's reliability is imperfect at the extremes of stool consistency [11]. Emerging evidence additionally implicates opioid-driven gut dysbiosis — reduced microbial diversity, expansion of pathobionts, and

disrupted mucosal barrier function — as a contributor to both constipation severity and systemic inflammatory tone in patients receiving chronic opioids for cancer pain [12]. This bidirectional relationship is clinically important: slowed transit itself favours proteolytic over saccharolytic fermentation, further reducing SCFA output and compounding motility impairment, which suggests that agents capable of simultaneously accelerating transit and restoring a fermentative, fibre-fed microbiota community may offer mechanistic advantages over stimulant laxation alone.

Senna as a Stimulant Laxative: Mechanism and Trial Evidence

Senna (*Senna alexandrina*) contains sennosides, anthraquinone glycosides that are metabolised by colonic bacteria to rhein-anthrone, which stimulates colonic motility and net fluid and electrolyte secretion via activation of enteric neurons and prostaglandin-mediated pathways [13]. Randomised trials support its efficacy: in chronic idiopathic constipation, senna produced non-inferior improvements in complete spontaneous bowel movement frequency compared with magnesium oxide [14], and in patients with pre-dialysis chronic kidney disease, a senna-ispaghula combination outperformed lactulose on stool frequency and consistency [15]. Long-term anthraquinone exposure is associated with melanosis coli, a benign pigmentary change of the colonic mucosa that resolves after laxative discontinuation and, contrary to earlier concern, is not now considered to independently confer colorectal neoplastic risk [16]. These features make senna an inexpensive, well-studied first-line stimulant component for combination regimens targeting OIC, consistent with its endorsement in palliative care prescribing guidance [8]. Its onset of action, typically six to twelve hours after oral dosing, complements the slower-onset bulking and prebiotic effects of prune fibre and inulin, making a fixed

combination pharmacologically rational for once- or twice-daily dosing alongside scheduled opioid analgesia. Reported adverse effects are generally mild and dose-related, comprising abdominal cramping and, with excessive or prolonged use, electrolyte disturbance, underscoring the value of titrating senna dose against stool response rather than fixed dosing in a heterogeneous cancer population with variable opioid exposure and renal function.

Prune Fibre: Bulking, Osmotic and Microbiota Effects

Prunes (dried plums) combine insoluble and soluble fibre with sorbitol and phenolic compounds that together exert bulking, mild osmotic, and prokinetic effects. In a randomised crossover trial, prunes produced greater increases in stool frequency and improvement in stool consistency than psyllium in patients with chronic constipation [17], and a systematic review of prune trials confirmed consistent superiority over usual dietary fibre intake for constipation endpoints [18]. Mechanistically important for the present combination, a randomised controlled trial specifically examining prune ingestion found increased stool wet weight and modest but detectable shifts in faecal microbiota composition, including changes in short-chain fatty acid (SCFA)-associated taxa, alongside accelerated whole-gut transit time [19]. These findings position prune fibre as both a symptomatic and a microbiota-modulating agent (Table 1). Beyond its fibre and sorbitol content, prune polyphenols (chlorogenic and neochlorogenic acids) may exert additional prokinetic and antioxidant effects, and their palatability as a whole food supports better long-term adherence than isolated fibre supplements in patients already managing a high pill burden from oncological and analgesic therapy, a practical consideration rarely captured in efficacy trials but highly relevant to real-world regimen sustainability in cancer

care.

Table 1: Proposed mechanisms of action and key trial evidence for senna, prune fibre and inulin in constipation management.		
Agent	Primary mechanism	Key trial evidence
Senna	Anthraquinone-stimulated colonic motility and secretion	Non-inferior to magnesium oxide [14]; superior to lactulose combination in CKD [15]
Prune fibre	Insoluble/soluble fibre bulking plus sorbitol osmotic effect	Superior to psyllium for stool frequency [17]; increases stool weight and shifts microbiota [19]
Inulin	Colonic fermentation to SCFAs; Bifidobacterium enrichment	Improves stool frequency/consistency and increases Bifidobacterium abundance [21]

Inulin and Prebiotic Fructans: Gut Microbiota Regulation

Inulin-type fructans are non-digestible carbohydrates fermented in the colon predominantly by Bifidobacterium and other saccharolytic genera, yielding SCFAs — acetate, propionate and butyrate — that lower luminal pH, stimulate colonocyte energy metabolism, and enhance colonic motility and mucosal barrier integrity [20]. A recent randomised, double-blind, placebo-controlled trial in adults with functional constipation demonstrated that inulin supplementation increased stool frequency and softened stool consistency while significantly increasing relative abundance of Bifidobacterium and reducing markers of dysbiosis compared with placebo [21]. Cross-sectional microbiome studies of constipated patients independently show reduced Bifidobacteriaceae and Lactobacillaceae and relative expansion of less fermentative taxa compared with healthy controls, a pattern that prebiotic fibres such as inulin are mechanistically positioned to reverse [22]. Because opioid exposure itself appears to promote dysbiosis in cancer pain patients [12], inulin's dual laxative and eubiotic action provides a distinct and complementary mechanism to the stimulant and bulking actions of senna and prune

fibre respectively (Figure 2). Inulin is generally well tolerated at moderate doses, though bloating and flatulence from colonic fermentation can limit adherence at higher intakes, an important dose-titration consideration for cancer patients who may already experience treatment-related abdominal symptoms; gradual dose escalation from small starting quantities is therefore typically recommended in practice and in the trials reviewed here.

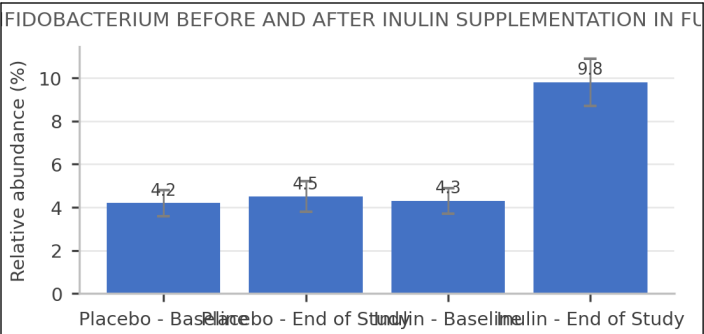


Figure 2: Relative abundance of Bifidobacterium before and after inulin supplementation versus placebo, summarised from published randomised, double-blind, placebo-controlled trial data [21].

Comparison with Pharmacological Standard of Care

PAMORAs represent the mechanistically targeted pharmacological alternative for OIC refractory to first-line laxatives. Naldemedine improved spontaneous bowel movement frequency versus placebo in phase III cancer trials [23] with efficacy confirmed by meta-analysis [10] and in real-world palliative care cohorts [24]. Methylnaltrexone similarly demonstrated superiority over placebo in advanced-illness populations in the pivotal trial by Thomas and colleagues [25] and in dose-ranging [26] and subcutaneous formulation studies [27], with pooled analyses confirming consistent benefit [28]. These agents act specifically at peripheral mu-opioid receptors without reversing analgesia, but guidelines still recommend trialling optimised laxative therapy first because of cost, injection burden, and access constraints,

particularly in resource-limited settings [9,7]. A well-tolerated oral combination such as senna, prune fibre and inulin could serve as an accessible intermediate step, or an adjunct that reduces PAMORA dose requirements, though this hypothesis awaits direct comparative testing (Table 2).

Table 2: Comparison of oral fibre/stimulant laxative combinations versus PAMORA pharmacotherapy for opioid-induced constipation.		
Feature	Senna + prune fibre + inulin	PAMORAs (naldemedine, methylnaltrexone)
Route	Oral, dietary/botanical	Oral (naldemedine) or subcutaneous (methylnaltrexone)
Cost/access	Low cost, widely available	Higher cost, variable access
Evidence in OIC specifically	Indirect, extrapolated from non-cancer trials	Direct phase III cancer trial evidence [23,25]
Microbiota effect	Demonstrated for inulin and prune fibre components	Not a primary mechanism of action

Discussion

Taken together, the published literature supports a coherent, complementary rationale for combining senna, prune fibre and inulin in OIC management: senna provides prokinetic stimulant action, prune fibre contributes bulking and modest osmotic and microbiota effects, and inulin selectively enriches saccharolytic, SCFA-producing taxa while further softening stool. No published trial to date has tested this precise triple combination specifically in opioid-treated cancer patients with simultaneous clinical and microbiome endpoints, which is the evidence gap the title study addresses. Existing single-agent and dual-agent evidence, drawn largely from non-cancer functional constipation populations, may not fully generalise to cancer patients who carry additional disease-related and pharmacological constipating burden, restricted mobility, and altered dietary intake. Future randomised trials should standardise senna dosing, use validated OIC-specific and

Bristol Stool Form Scale outcomes, and pair 16S rRNA or shotgun metagenomic sequencing with faecal SCFA quantification to establish whether microbiota changes mediate clinical improvement rather than merely accompanying it.

Conclusion

Senna, prune fibre and inulin each have independent, mechanistically distinct and clinically supported roles in relieving constipation, and inulin in particular has robust trial evidence for favourably regulating gut microbiota composition. Their combination is biologically plausible as a low-cost, guideline-consistent first step for opioid-induced constipation in cancer patients, but dedicated randomised, double-blind, placebo-controlled trials in this specific population, with paired clinical and microbiome outcomes, are needed to confirm efficacy, safety and the durability of any microbiota-mediated benefit.

References

1. Davies A, Leach C, Butler C, et al. Opioid-induced constipation in patients with cancer: a "real-world," multicentre, observational study of diagnostic criteria and clinical features. *Pain*. 2021;162(1):309-318. doi:10.1097/j.pain.0000000000002024
2. Abramowitz L, Beziaud N, Labreze L, et al. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain. *Int J Clin Pract*. 2013;67(11):1054-1064. doi:10.1111/ijcp.12194
3. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterol Motil*. 2014;26(10):1386-1395. doi:10.1111/nmo.12417
4. Farmer AD, Drewes AM, Chiarioni G, et al. Pathophysiology and management of opioid-induced constipation: European expert consensus statement. *United European Gastroenterol J*. 2019;7(1):7-20. doi:10.1177/2050640618818305
5. Droney J, Ross J, Gretton S, Welsh K, Sato H, Riley J. Constipation in cancer patients on morphine. *Support Care Cancer*. 2008;16(5):453-459. doi:10.1007/s00520-007-0313-0
6. LoCasale RJ, Datto CJ, Margolis MK, Coyne KS. Impact and consequences of opioid-induced constipation: a survey of patients. *Pain Ther*. 2021;10(2):1253-1266. doi:10.1007/s40122-021-00284-9
7. Larkin PJ, Cherny NI, La Carpia D, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29(Suppl 4):iv111-iv125. doi:10.1093/annonc/mdy148
8. Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. *Palliat Med*. 2008;22(7):796-807. doi:10.1177/0269216308096908
9. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156(1):218-226. doi:10.1053/j.gastro.2018.07.016
10. Luthra P, Burr NE, Brenner DM, Ford AC. Efficacy of naldemedine for the treatment of opioid-induced constipation: a systematic review and meta-analysis. *Gut*. 2019;68(3):434-444. doi:10.1136/gutjnl-2018-316001
11. Blake MR, Raker JM, Whelan K. Validity and reliability of the Bristol Stool Form Scale in healthy adults and patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2016;44(7):693-703. doi:10.1111/apt.13746
12. Acharya C, Fagan A, Bajaj JS, et al. Opioid use and gut dysbiosis in cancer pain patients. *Sci Rep*. 2024;14:17287. doi:10.1038/s41598-024-67432-2

13. Wang J, Liu YQ, Hou WJ, et al. Pharmacology, toxicology, and metabolism of sennoside A, a medicinal plant-derived natural compound. *Front Pharmacol*. 2021;12:714586. doi:10.3389/fphar.2021.714586
14. Jansen A, Berkus J, Herdes O, et al. Senna versus magnesium oxide for the treatment of chronic constipation: a randomized, placebo-controlled trial. *Am J Gastroenterol*. 2020;115(12):2029-2036. doi:10.14309/ajg.0000000000000942
15. Rana SV, Bhardwaj SB. Efficacy of lactulose versus senna plus ispaghula husk among patients with pre-dialysis chronic kidney disease and constipation: a randomized controlled trial. *Cureus*. 2021;13(7):e16612. doi:10.7759/cureus.16612
16. Liu Z, Peng L, Guo B, et al. 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
17. Attaluri A, Donahoe R, Valestin J, Brown K, Rao SS. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther*. 2011;33(7):822-828. doi:10.1111/j.1365-2036.2011.04594.x
18. Lever E, Cole J, Scott SM, Emery PW, Whelan K. Systematic review: the effect of prunes on gastrointestinal function. *Aliment Pharmacol Ther*. 2014;40(7):750-758. doi:10.1111/apt.12913
19. Lever E, Scott SM, Louis P, Emery PW, Whelan K. The effect of prunes on stool output, gut transit time and gastrointestinal microbiota: a randomised controlled trial. *Clin Nutr*. 2019;38(1):165-173. doi:10.1016/j.clnu.2018.01.003
20. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol (Lausanne)*. 2020;11:25. doi:10.3389/fendo.2020.00025
21. Pedersen SS, Prause M, Williams AR, Krych L, Nielsen DS, Kot W, et al. Inulin-induced improvements on bowel habit and gut microbiota in adults with functional constipation: findings of a randomized, double-blind, placebo-controlled study. *BMC Gastroenterol*. 2025;25:611. doi:10.1186/s12876-025-04409-6
22. Zhu L, Liu W, Alkhouri R, et al. Structural changes in the gut microbiome of constipated patients. *Physiol Genomics*. 2014;46(18):679-686. doi:10.1152/physiolgenomics.00082.2014
23. Katakami N, Harada T, Murata T, et al. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. *J Clin Oncol*. 2017;35(34):3859-3866. doi:10.1200/JCO.2017.73.0853
24. Inoue A, Iwase S, Nozawa K, et al. The safety and effectiveness of naldemedine for opioid-induced constipation in patients with advanced cancer in real-world palliative care settings: a multicenter prospective observational study. *Support Care Cancer*. 2024;32(8):513. doi:10.1007/s00520-024-08716-8
25. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*. 2008;358(22):2332-2343. doi:10.1056/NEJMoa0707377
26. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. *J Pain Symptom Manage*. 2008;35(5):458-468. doi:10.1016/j.jpainsymman.2007.12.005
27. Rauck R, Slatkin NE, Stambler N, Harper JR, Israel RJ. Subcutaneous methylnaltrexone for opioid-induced constipation in advanced-illness patients with or without active cancer. *Pain Pract*. 2020;20(4):378-387. doi:10.1111/papr.12862
28. Siemens W, Gaertner J, Becker G. Methylnaltrexone for opioid-induced constipation: review and meta-analyses for objective plus subjective efficacy and safety outcomes. *Ther*

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Clin Risk Manag. 2016;12:401-412. doi:10.2147/TCRM.S80749

