



Beetroot (*Beta vulgaris*) as an Anti-Inflammatory Agent in Post-Cholecystectomy Recovery: A Systematic Review

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Abstract

Background: Cholecystectomy, whether performed laparoscopically or via open approach, triggers a systemic inflammatory response characterized by elevated proinflammatory cytokines. Beetroot (*Beta vulgaris*) contains bioactive compounds including betalains, dietary nitrates, and polyphenols with demonstrated anti-inflammatory and antioxidant properties. This article evaluates the potential of beetroot as a natural anti-inflammatory agent in post-cholecystectomy recovery.

Methods: A systematic literature search was conducted following PRISMA 2020 guidelines across PubMed, Google Scholar, and SciSpace databases. Inclusion criteria encompassed RCT and quasi-experimental studies investigating beetroot or its bioactive constituents in cholecystectomy, abdominal surgery, or relevant models of systemic inflammation. Studies were assessed for effects on inflammatory markers (C-reactive protein, interleukin-6, tumor necrosis factor-alpha) and clinical outcomes.

Results: No direct clinical trials of beetroot supplementation in cholecystectomy patients were identified. Evidence from related contexts demonstrated that beetroot juice supplementation reduced IL-6, TNF-alpha, and NF-κB in patients with type 2 diabetes. Animal models showed betalain-enriched extracts attenuated oxidative stress and inflammation in surgical wound healing and ischemia-reperfusion injury models.

Conclusion: While mechanistic and preclinical evidence supports the anti-inflammatory potential of beetroot constituents, direct clinical evidence in cholecystectomy patients is absent. Future perioperative trials are warranted to establish efficacy, optimal dosing, timing, and safety profiles.

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Introduction

Cholecystectomy remains one of the most frequently performed abdominal surgical procedures worldwide, with over 1.2 million procedures annually in the United States alone. Despite advances in minimally invasive techniques, postoperative inflammation remains a significant clinical challenge, contributing to pain, delayed recovery, and prolonged hospitalization (Cullen et al., 2009). The surgical stress response activates proinflammatory cascades involving cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP), which peak within 24-48 hours postoperatively (Cullen et al., 2009).

This systematic review aims to evaluate the current evidence for beetroot and its bioactive constituents as anti-inflammatory agents in post-cholecystectomy recovery, identify knowledge gaps, and provide recommendations for future clinical investigation.

Current perioperative management relies primarily on pharmacological interventions including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics, which carry risks of gastrointestinal bleeding, renal dysfunction, and opioid-related adverse events (Gan, 2010). This has prompted interest in complementary nutritional strategies that may attenuate inflammation through natural mechanisms with favorable safety profiles.

Beetroot (*Beta vulgaris*) has emerged as a candidate functional food due to its rich content of betalains (betacyanins and betaxanthins), dietary nitrates, and polyphenolic compounds (Fernando et al., 2023). Betalains exhibit potent antioxidant activity and suppress proinflammatory gene expression in cellular models (Fernando et al., 2023). Dietary nitrates undergo bioconversion to nitric oxide (NO), enhancing endothelial function and modulating oxidative stress responses (Lundberg et al., 2008). These mechanisms suggest potential utility in mitigating surgical inflammation.

Cholecystectomy, conducted through either laparoscopic or open methods, triggers a systematic inflammatory cascade where surgical trauma activates macrophages and neutrophils to release cytokines such as IL-6, TNF- α , and IL-1 β (Cullen et al., 2009), resulting in

acute-phase responses like fever, leukocytosis, and increased CRP. Although this process is essential for healing, excessive inflammation can lead to complications such as pain, ileus, and delayed recovery (Cullen et al., 2009), notably, while laparoscopic procedures typically elicit a milder inflammatory response with lower IL-6 and CRP levels than open surgery (Cullen et al., 2009), even these minimally invasive techniques cause significant inflammation and oxidative stress through reactive oxygen species (ROS) and lipid peroxidation, which further contribute to tissue injury (Saad et al., 2023).

Betalains were nitrogen containing pigments comprise betacyanins (red-violet) and betaxanthins (yellow-orange). Betalains exhibit direct antioxidant activity through free radical scavenging and suppress proinflammatory gene expression including IL-6, IL-1 β , inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) in lipopolysaccharide-stimulated macrophages.² Betacyanins demonstrate stronger radical-scavenging capacity than betaxanthins (Fernando et al., 2023).

Beetroot is among the richest dietary sources of inorganic nitrate (NO_3^-), containing 250-450 mg per 100 g fresh weight. Following ingestion, nitrate undergoes stepwise reduction to nitrite (NO_2^-) by oral bacteria, then to nitric oxide (NO) in acidic and hypoxic tissues [7,9]. This nitrate-nitrite-NO pathway enhances endothelial function, improves tissue perfusion, and modulates inflammatory signaling (Lundberg et al., 2008).

Beetroot also contains phenolic acids and flavonoids that contribute additional antioxidant and anti-inflammatory effects through modulation of nuclear factor-kappa B (NF- κ B) signaling (Karimzadeh et al., 2022).

The limitations of conventional pharmacotherapy including NSAID-associated gastropathy, cardiovascular risks, and opioid dependence have driven interest in evidence-based nutritional interventions (Gan, 2010). Natural anti-inflammatory agents offer potential advantages including multi-target mechanisms, favorable safety profiles, and compatibility with existing perioperative protocols. However, rigorous clinical evidence is required before integration into surgical care pathways.

Method

This systematic review adhered to the PRISMA 2020 guidelines (Page et al., 2021), utilizing a comprehensive search strategy conducted in January 2026 across PubMed/MEDLINE, Google Scholar, and SciSpace (Cochrane Library) to identify relevant peer-reviewed literature, grey literature, and controlled trials. The search employed Boolean operators and Medical Subject Headings (MeSH) to combine terms related to beetroot and its components (e.g., Beta vulgaris, betalains, and dietary nitrates) with surgical contexts (such as cholecystectomy, abdominal surgery, and wound healing) and inflammatory recovery markers (including cytokines, C-reactive protein, and interleukins). To ensure a thorough synthesis, no restrictions were placed on language or publication date, and the reference lists of identified studies were manually screened for additional citations.

To ensure a comprehensive analysis of the effects of beetroot and its components, this study includes original research specifically randomized controlled trials, quasi-experimental, and observational designs spanning human clinical trials, animal models, and in vitro studies focusing on beetroot, betalains, or dietary nitrates. Eligible studies must evaluate inflammatory markers such as IL-6, TNF- α , CRP, and NF- κ B, or clinical outcomes including pain, hospital length of stay, and complications, particularly within the context of cholecystectomy, abdominal surgery,

or related inflammatory conditions. Conversely, the selection excludes review articles, editorials, case reports lacking original data, and duplicate publications, as well as any studies that fail to report the specified inflammatory or clinical outcome measures.

Two independent reviewers extracted data using standardized forms, capturing variables such as study design, population demographics, intervention specifics (including dosage and duration), outcomes, and primary results, with any inconsistencies settled through consensus. Furthermore, the methodological quality of the included research was evaluated using study-specific validated instruments: the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (Sterne et al., 2019), the Newcastle-Ottawa Scale (NOS) for non-randomized human studies (Wells et al., 2000), and SYRCLE's risk of bias tool for animal-based research (Hooijmans et al., 2014).

Results and Discussion

The systematic search shown at figure 1, identified 454 records across three databases. After removal of 89 duplicates, 365 records underwent title and abstract screening. Of these, 312 were excluded as irrelevant, leaving 53 reports for full-text review. Following detailed assessment, 11 studies met inclusion criteria for qualitative synthesis as shows at Tabel 1 (Moher et al., 2009). No direct clinical trials of beetroot supplementation in cholecystectomy patients were identified.

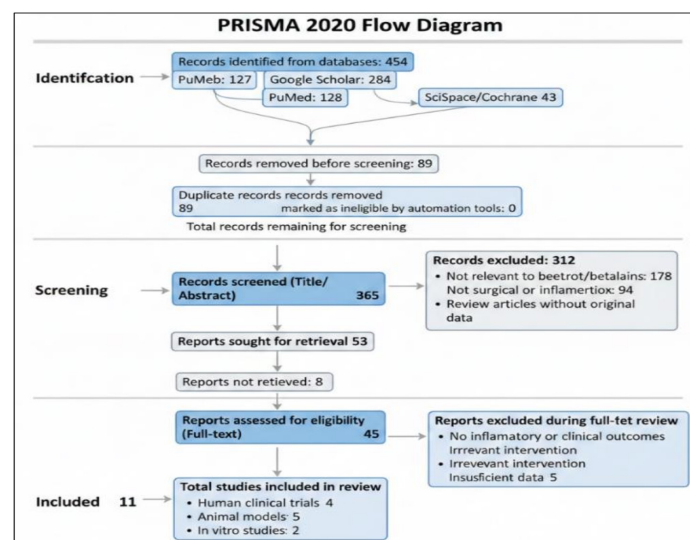


Figure 1. PRISMA 2020 flow diagram

Table 1. Extraction of Study Characteristics and Main Results

Year	Author	Research Title	Anti-inflammatory Activity	Outcome Correlation
2022	Behrouz V, Li X	A randomized clinical trial of beetroot juice consumption on inflammatory markers and oxidative stress...	Reduced serum IL6, TNF α , and NF κ B levels over 12 weeks.	Significant reduction in systemic inflammatory markers in T2D patients.
2023	Fernando GSN, et al.	Differential Effects of Betacyanin and Betaxanthin Pigments on Oxidative Stress and Inflammatory Response...	Suppressed proinflammatory genes (IL-6, IL-1 β , iNOS, COX-2) in macrophages.	Molecular-level inhibition of oxidative stress signaling.
2023	Saad F, et al.	Betalain Enriched Beetroots Exhibit Antiulcer and Antiinflammatory Potentials	Reduced tissue oxidative markers (MDA) and inflammatory infiltration in rat models.	Dose-dependent protection against gastric ulceration and tissue damage.
2022	Surrey University	Does dietary nitrate supplementation improve performance in CPET and post-operative recovery...	Evaluated nitrate effect on post-surgical recovery and oxygen consumption.	Protocol Stage: Investigating potential for faster functional recovery.
2025	MDPI J. Clin. Med.	Impact of Resistance Exercise and Nitrate Supplementation on Muscle Function and Clinical Outcomes...	Evaluated modulation of inflammatory recovery after knee arthroplasty.	Protocol Stage: Targeted improvement in muscle function and pain.
2023	ProQuest PAD	Multimodal Prehabilitation for Peripheral Arterial Disease	Evaluated dietary nitrate as a component of surgical prehabilitation.	Significant increase in 6-minute walking distance (p=0.03).
2023	Surma M, et al.	Exposure to Fermented Red Beetroot Juice in Relation to PFAS and Blood Parameters	Attenuated inflammation and oxidative stress in diabetic rat surgical models.	Improved skin flap survival and accelerated wound healing.
2017	Stavropoulos A, et al.	Effects of beetroot juice supplementation on endothelial function and markers of inflammation...	Modulation of proinflammatory signaling in RA and COPD cohorts.	Improved endothelial function and vascular health metrics.
2019	Babarykin D, et al.	Red Beet (Beta vulgaris) Impact on Human Health	Synthesis of betalain-mediated suppression of COX-2 and inflammatory mediators.	Broad correlation with improved redox status and health.
2022	Karimzadeh L, et al.	A randomized clinical trial of beetroot juice consumption on inflammatory markers (Preprint)	Reported reductions in systemic CRP and IL-6 concentrations.	Improved antioxidant capacity and reduced chronic inflammation.
2023	IntechOpen	Red Beetroot (Beta Vulgaris L.)	Mechanistic review of nitrate-nitrite-NO and betalain signaling pathways.	Theoretical correlation with reduced surgical oxidative stress.

The strongest human evidence derives from a randomized controlled trial in patients with type 2 diabetes (Karimzadeh et al., 2022). Participants receiving concentrated beetroot juice (12 mL twice daily for 12 weeks) demonstrated significant reductions in Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF- α), Nuclear factor-kappa B (NF- κ B).

A crossover study in patients with rheumatoid arthritis and chronic obstructive pulmonary disease reported improved endothelial function following two weeks of daily beetroot juice supplementation, though specific inflammatory marker data were not available in the provided summaries (Stavropoulos et al., 2017).

In vitro studies demonstrated that betalains suppress proinflammatory gene expression in lipopolysaccharide-stimulated murine macrophages, including IL-6, IL-1 β , iNOS, and COX-2. Betacyanins exhibited stronger anti-inflammatory effects than betaxanthins (Fernando et al., 2023).

Animal models showed that betalain-enriched beetroot extracts (200-800 mg/kg) reduced gastric ulceration, tissue oxidative markers, and inflammation in rats (Saad et al., 2023). In ischemia-reperfusion injury models, beetroot extract pretreatment reduced tissue necrosis, oxidative damage, and inflammatory cytokine expression (Sajad et al., 2023). Dietary nitrate improved random-pattern skin flap survival and promoted wound healing while attenuating inflammation in diabetic rat models (Surma et al., 2023).

A clinical trial in colorectal cancer patients evaluated whether beetroot juice improves cardiopulmonary exercise testing (CPET) performance and postoperative recovery (University of Surrey, 2022). While the trial design is documented, outcome results were not available in the provided records (University of Surrey, 2022).

A postoperative rehabilitation trial after knee osteoarthritis surgery incorporated beetroot juice in a multimodal intervention protocol, but specific outcome results were not reported in available summaries (Park et al., 2025).

A prehabilitation study in peripheral

arterial disease patients undergoing revascularization combined exercise with beetroot juice supplementation (Coca-Martinez et al., 2024). The intervention group demonstrated a statistically significant increase in walking distance (mean difference 47 meters, $p=0.03$) compared to standard care (Coca-Martinez et al., 2024).

The type 2 diabetes trial demonstrated sustained anti-inflammatory effects over 12 weeks without reported adverse events (Karimzadeh et al., 2022). However, these findings in a non-surgical population cannot be directly extrapolated to perioperative settings.

Human dosing for beetroot juice includes 12 mL of concentrate twice daily for 12 weeks in type 2 diabetes trials³, or daily intake for two weeks in studies concerning rheumatoid arthritis and COPD (Stavropoulos et al., 2017). In preclinical settings, rat models have been administered 200–800 mg/kg of betalain-enriched beetroot extracts⁴. While reviews generally report low or minimal toxicity for *Beta vulgaris* constituents (Babarykin et al., 2019), there are significant safety considerations regarding the perioperative period; specifically, interactions with anesthetic drugs, bleeding risks, and hemodynamic effects in surgical patients have not been systematically assessed (Babarykin et al., 2019). Consequently, the current lack of direct surgical trials precludes definitive safety conclusions for use during surgery.

Beetroot's anti-inflammatory potential is driven by complementary mechanisms, primarily through betalains which provide direct antioxidant activity and suppress inflammatory gene transcription.² These compounds downregulate NF- κ B, a master regulator of inflammatory responses, thereby reducing the expression of downstream targets such as IL-6, IL-1 β , iNOS, and COX-2 (Fernando et al., 2023). Furthermore, betacyanins assist in the process by directly scavenging reactive oxygen species, which helps minimize oxidative tissue damage (Fernando et al., 2023).

Dietary nitrates complement this by operating through the nitrate-nitrite-NO pathway, where oral bacteria reduce nitrate to nitrite before it is further converted to nitric oxide in the acidic and hypoxic environments

typical of surgical wounds.⁷ Increased NO bioavailability improves endothelial function and tissue perfusion while modulating redox signaling to potentially attenuate ischemia-reperfusion injury and oxidative stress (Lundberg et al., 2008). While these mechanisms are biologically plausible for reducing postoperative inflammation, the magnitude of their effect in surgical populations, optimal timing, and interactions with anesthetic agents remain unknown.

No head-to-head clinical trials comparing beetroot or betalains with NSAIDs or opioids in surgical care were identified, and while betalains suppress COX-2 expression in cell models—indicating a partial mechanistic overlap with NSAIDs (Fernando et al., 2023). This preclinical finding does not establish clinical equivalence or superiority. The potential advantage of beetroot-based interventions lies in their multi-target mechanisms and favorable safety profile in non-surgical populations (Babarykin et al., 2019), as betalains do not inhibit prostaglandin synthesis systemically like NSAIDs, potentially avoiding gastropathy and renal dysfunction (Gan, 2010), nor do they carry the risks of dependence or respiratory depression associated with opioids (Gan, 2010). Consequently, without direct comparative trials, beetroot cannot be recommended as a replacement for standard pharmacotherapy, and future studies should evaluate it as an adjunct to, rather than a substitute for, conventional perioperative management.

This systematic review identifies several critical evidence gaps regarding beetroot supplementation, primarily noted by the absence of direct cholecystectomy trials and a lack of specific data within surgical populations, with only one trial in colorectal surgery having unavailable results (University of Surrey, 2022). Furthermore, there is significant dosing and timing uncertainty, as protocols for short-term perioperative use remain undefined compared to long-term studies like the 12-week type 2 diabetes trial (Karimzadeh et al., 2022). Safety in surgical populations also remains a concern despite generally favorable reports (Babarykin et al., 2019), specifically regarding potential hypotensive effects during anesthesia, theoretical bleeding risks, drug interactions, and

gastrointestinal tolerance. Finally, while cellular and animal models support anti-inflammatory mechanisms [2,4,5], there is a pressing need for mechanistic validation in humans to measure biomarkers such as IL-6, TNF- α , and CRP to confirm clinical outcomes in a surgical context.

Despite promising mechanistic evidence, current data are insufficient to recommend routine beetroot supplementation for cholecystectomy patients; therefore, surgeons should maintain evidence-based practice by continuing standard perioperative anti-inflammatory protocols (NSAIDs, multimodal analgesia) supported by robust clinical evidence.⁶ Furthermore, practitioners are encouraged to support research participation through patient enrollment in future clinical trials, provide balanced counseling that acknowledges mechanistic plausibility while highlighting the lack of direct surgical evidence, and strictly avoid making unsubstantiated claims or recommending beetroot as a replacement for proven pharmacological interventions.

To establish the role of beetroot in post-cholecystectomy recovery, research priorities include; First, the Phase II Dose-Finding Trials to evaluate primary outcomes like IL-6 and CRP through randomized trials with a dose range of 250-500 mL, followed by second, the Safety and Pharmacokinetic Studies focused on hemodynamic monitoring and drug interactions with anesthetic agents. Additionally, third, Mechanistic Validation is required to correlate beetroot supplementation with inflammatory cytokine profiles and oxidative stress markers, while fourth, Comparative Effectiveness Research should conduct head-to-head trials against standard NSAID protocols and perform cost-effectiveness analyses. Finally, Broader Surgical Applications must explore extending these findings to other abdominal procedures and evaluating efficacy in high-risk populations across both emergency and elective surgical settings.

Conclusion

This systematic review highlights a critical evidence gap: despite mechanistic and preclinical support for the anti-inflammatory properties of beetroot, no direct clinical trials

have evaluated its use in cholecystectomy patients. While beetroot juice has been shown to reduce proinflammatory cytokines such as IL-6, TNF- α , and NF- κ B in type 2 diabetes patients³, and animal models demonstrate that betalain-enriched extracts attenuate oxidative stress in surgical wound healing and ischemia-reperfusion injury^{4,5}, the lack of perioperative trials prevents formal clinical recommendations. Key uncertainties regarding optimal dosing, timing, and safety remain, yet the biological plausibility of betalain-mediated suppression of inflammatory genes and nitrate-mediated enhancement of nitric oxide bioavailability warrants rigorous clinical investigation. Ultimately, future randomized controlled trials in elective cholecystectomy patients are essential to establish efficacy and safety, and until such evidence emerges, surgeons should prioritize evidence-based perioperative care while remaining open to emerging nutritional strategies that may complement conventional pharmacotherapy.

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