American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

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Palm Oil-Derived Bioactives and Surgical Recovery: Mechanistic Rationale, Evidence Gaps, and a Translational Agenda for ERAS

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To Cite This article: *Loso Judijanto*, Palm Oil-Derived Bioactives and Surgical Recovery: Mechanistic Rationale, Evidence Gaps, and a Translational Agenda for ERAS. Am J Biomed Sci & Res. 2026 32(5) AJBSR.MS.ID.004200,* **DOI:** 10.34297/AJBSR.2026.32.004200

Received: October 23, 2026 **Published:** November 06, 2026

Abstract

The physiological stress of surgery produces intertwined inflammatory, oxidative, endocrine and immune responses that can impede recovery. Enhanced Recovery After Surgery (ERAS) pathways prioritise nutritional assessment, early feeding, mobilisation and selective immunonutrition, yet the potential place of palm oil–derived bioactives remains unresolved. This qualitative literature review critically integrates 2020–2026 evidence on tocotrienols, carotenoids, squalene and oil palm phenolics with clinical perioperative nutrition research. An interpretive thematic synthesis distinguishes mechanistic plausibility, human evidence outside surgery and direct surgical evidence, while examining bioavailability, formulation, safety and research design. Tocotrienol trials show context-specific effects on selected inflammatory or metabolic markers, but pooled results are inconsistent, recent immunological studies provide additional signals without proving postoperative efficacy. Palm-derived phenolics have preliminary human antioxidant data, whereas squalene adjuvant findings and carotenoid nutrition cannot be directly transferred to oral perioperative supplementation. Evidence-based immunonutrition uses defined combinations of arginine, omega-3 fatty acids and nucleotides, not palm bioactives. A staged translational framework is proposed to prioritise product characterisation, perioperative pharmacokinetics, safety, biomarker validation and randomised trials embedded within ERAS care. Palm-derived compounds are promising research candidates but currently cannot be recommended as established ERAS immunonutrition therapies.

Keywords: Palm oil, Tocotrienols, Oil palm phenolics, Carotenoids, Squalene, Perioperative immunonutrition, Enhanced recovery after surgery, Surgical inflammation, Translational nutrition, Qualitative literature review

JEL Classification: I10, I11, I12, O31, Q16

Introduction

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Major surgery initiates tissue damage signals, autonomic activation, hormonal changes and a coordinated inflammatory response that is essential for repair but can become maladaptive. Increased glucose production, insulin resistance, protein catabolism and altered immune-cell function interact with wound healing, susceptibility to infection and physical recovery. These responses differ according to procedure, underlying malignancy, baseline nutritional status, frailty and postoperative complications. Consequently, an intervention that changes an inflammatory biomarker in an ambulatory patient cannot automatically be

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assumed to improve infection risk, anastomotic integrity or length of stay after surgery. Current surgical nutrition guidance treats nutrition as a longitudinal clinical intervention rather than an isolated supplement administered around the operating room [10,47,48]. The modern ERAS paradigm aims to attenuate avoidable surgical stress through coordinated preoperative education, selective fasting avoidance, optimised analgesia, early oral or enteral feeding, glucose management and mobilisation. These practices are not interchangeable with dietary supplement use: they comprise a multidisciplinary programme with interacting elements. Colorectal pathways provide a particularly developed evidence base, while adaptations for upper gastrointestinal and complex oncological procedures require procedure-specific judgment. Across these settings, nutrition assessment and treatment of deficiency remain essential clinical priorities. Nutraceutical innovation must therefore be assessed against a functioning ERAS standard of care, not compared with an artificial scenario of neglect or prolonged starvation [13,14,18].

Immunonutrition, From Accepted Formulations to Novel Adjuncts

The term immunonutrition is often used loosely to describe any food constituent with an apparent immunological effect. In perioperative medicine, however, it ordinarily refers to defined nutritional formulas enriched with substrates such as arginine, omega-3 fatty acids and nucleotides, studied in particular surgical populations. Recent randomised-trial syntheses support selected reductions in infectious and other complications, although pooled estimates differ according to operation, composition, timing and methodological quality. The 2025 ESPEN update favours established combination immunonutrition in major tumour surgery and emphasises appropriate indication. This specificity matters: neither a laboratory antioxidant measurement nor a generic immune-modulating label establishes therapeutic equivalence to tested products [5,11,25].

The evidence base is also less uniform than enthusiastic accounts imply. A Cochrane evaluation of preoperative nutritional interventions identified very low- or low-certainty evidence for several comparisons and underscored the need for better trials incorporating ERAS. A separate meta-analysis in colorectal cancer found more consistent signals for minor infections than for all infectious complications or hospital stay. A pancreaticoduodenectomy review and a comparison of laparoscopic and open colorectal procedures emphasise that benefits are likely conditional rather than universal. These nuances create a methodological warning for evaluating novel plant-derived ingredients: promises should be tested against meaningful perioperative outcomes, not built by combining optimistic results from unrelated conditions [33,42,49,52].

Why Palm-Derived Bioactives Merit Examination

Oil palm fruit and selected processing streams contain several biologically interesting constituents, including vitamin E isoforms known as tocotrienols, carotenoid pigments, phytosterols, squalene and phenolic compounds. Red palm oil, palm tocotrienol-rich fractions and oil palm phenolic extracts differ dramatically in chemical composition, processing history and intended use. An unrefined oil is not equivalent to a purified tocotrienol capsule, while a phenolic fraction recovered from aqueous processing streams should not be described as simply concentrated dietary palm oil. Reviews of palm composition also show why refining, oxidation and batch standardization matter when a scientific hypothesis is converted into a reproducible clinical material [22,24]. Interest in these compounds arises from three convergent needs. First, inflammatory and oxidative responses are plausible biological targets during recovery. Second, high-risk surgical patients require carefully tailored perioperative nutrition, and not all functional deficits are addressed by caloric intake alone. Third, agricultural bioresource valorization creates incentives to explore defined high-value molecules instead of undifferentiated commodity oils. Nevertheless, biological activity in another disease is not a validated surgical indication, the research opportunity is a structured translational research question, not a reason to redesign ERAS recommendations before trials have been undertaken. Ethical development must avoid the substitution of a commercial origin story for a demonstrable patient benefit [8,11,43].

Knowledge Gap and Research Contribution

Clinical evidence on palm tocotrienols is increasingly available in diabetes, fatty liver disease, metabolic conditions and inflammatory disorders, but these populations are not surrogates for patients exposed to anaesthesia, blood loss, analgesics and surgical tissue injury. The effects of tocotrienol-rich fractions also cannot be inferred from trials of isolated delta-tocotrienol, because compositions, dose-response relationships and exposure profiles vary. Notably, an overall meta-analysis of randomized studies reported no consistent pooled improvement in major cytokines, notwithstanding a C-reactive protein signal driven by a single study. This makes scientific restraint central to any perioperative proposal [17,21,38]. A second gap concerns the scale of inference. Squalene emulsion adjuvants can enhance immune responses to antigens under vaccine conditions, but that route, formulation and immunological objective differ fundamentally from oral nutrition given to surgical patients. Likewise, carotenoid status may matter for nutritional adequacy, yet carotenoid-rich palm oil is not automatically an anti-infective or wound-healing therapy. Oil palm phenolics have early human antioxidant findings but lack confirmatory surgical trials. A review that explicitly differentiates these domains can offer a more useful roadmap than an undifferentiated catalogue of bioactivities [8,28,50]. The central contribution is therefore not the proposition that antioxidant-rich material is itself an effective postoperative treatment. It is the separation of three scientific questions: whether an identifiable compound engages a relevant human mechanism, whether that engagement remains safe in perioperative physiological conditions and whether it ultimately changes complications or recovery

beyond high-quality existing care. Each question requires its own comparator, timeline and endpoint definition. Without this separation, encouraging observational or mechanistic results can be mistaken for evidence that a product belongs in an ERAS protocol [5,17,48].

Questions, Aims and Scope

This article asks which palm-derived constituents plausibly intersect with surgical stress physiology, what human evidence can and cannot establish, how formulation, timing and safety shape feasibility, which ERAS outcomes should be evaluated, and what experimental sequence could justify future recommendations. Its objectives are to synthesise the strongest relevant literature, distinguish evidence tiers, examine counterevidence and propose a feasible research programme. The emphasis is on major abdominal and oncological procedures while recognising relevant information from other surgical specialties. The review is not a systematic literature review or a meta-analysis, it offers an interpretive, argument-led qualitative synthesis whose claims remain linked to transparent sources and explicit inferential boundaries [4,10,48].

Literature Review: Conceptual and Theoretical Foundations

ERAS as a Complex, Evidence-Based Intervention

ERAS is best understood as a complex clinical intervention in which multiple practices act through overlapping physiological mechanisms. Avoiding unnecessarily long fasting reduces the burden of preoperative discomfort, early feeding supports nutritional delivery and gastrointestinal recovery, mobilisation promotes functional preservation, and multimodal analgesia may reduce barriers to breathing and activity. An isolated supplement cannot reproduce these effects. The latest ERAS and ESPEN guidance also increasingly integrates risk stratification, malnutrition, sarcopenia and frailty, making the decision to add a novel bioactive dependent on the basic quality and adherence of the underlying care pathway [13,14,48]. The therapeutic priorities of established practice are particularly visible in clinical nutrition guidelines, which distinguish patients with adequate intake from those with meaningful deficits. In poorly nourished patients, protein-energy optimisation can address a stronger causal bottleneck than speculative antioxidant dosing. A narrative review of unsettled issues in perioperative nutrition similarly emphasises uncertainty about the optimal combination, dosage and timing of interventions. Thus, any palm-derived candidate should be evaluated as an adjunct to adequate energy, protein and evidence-based micronutrient supply, rather than as a replacement for those requirements. It should also be clear whether the candidate is intended for nutritional repletion, pharmacological modulation or biomarker-directed investigation [4,10,47].

Immunological Stress, Redox Signalling and Recovery

Inflammation after surgery is simultaneously protective and potentially harmful. Neutrophil trafficking, complement activity, antigen presentation, cytokine signalling and coordinated resolution contribute to host defence and tissue repair. Excessive or prolonged inflammation may amplify organ dysfunction, yet aggressively suppressing immune responses could compromise antimicrobial protection. This duality complicates simplistic descriptions of antioxidants as universally beneficial. A credible translational hypothesis must specify which signalling pathway, immune-cell population or oxidative process should be modified, at what postoperative interval, in which type of patient and with which expected clinical consequence. Outcome selection should preserve this biological ambiguity rather than assuming that a lower cytokine concentration is necessarily desirable [6,27,31]. Nutritional prehabilitation offers an important comparator because it targets physiological reserve before the acute insult. Evidence synthesising randomised trials indicates that nutritional and exercise-based approaches can improve certain postoperative outcomes, although intervention heterogeneity limits strong universal claims. A colorectal cancer review associated preoperative nutrition with fewer infectious complications, while network evidence suggested meaningful effects from selected exercise and nutrition components. These effects do not validate a specific phytonutrient, but they show the importance of testing plausible bioactives within a clinically coherent program rather than in isolation from functional status, protein intake and physical activity [11,26,43]. More direct randomised surgical evidence further supports the importance of testing holistic recovery programs before attributing improvement to an untested ingredient. In the multicenter PREHAB trial, supervised multimodal prehabilitation was associated with fewer severe and medical complications after colorectal cancer surgery, although the prespecified six-minute walking-distance comparison at four weeks did not reach conventional statistical significance. A subsequent analysis focused specifically on functional recovery, underlining that complications, physical capacity and patient-centred recovery need not move in parallel. These studies assessed multimodal prehabilitation rather than palm-derived constituents and therefore provide a relevant clinical and methodological comparator, not efficacy evidence for palm bioactives [54,56].

Tocotrienols Versus Tocopherols

Tocotrienols and tocopherols belong to the vitamin E family, but their structural differences affect membrane behaviour, transport, distribution and biological responses. Palm-derived tocotrienol-rich fractions generally contain multiple isoforms and may include tocopherols, while purified delta-tocotrienol represents a different intervention. Mechanistic discussions commonly address redox balance, inflammatory transcriptional signalling, lipid metabolism and cellular stress pathways; however, the outcome of an animal or cell experiment depends on concentrations that may not be reached in humans. Reviews of NF-kappaB regulation and endoplasmic-reticulum stress provide useful mechanistic hypotheses, not direct demonstrations of surgical benefit [1,32,34]. Human supplementation findings are heterogeneous. A clinical

trial in type 2 diabetes reported changes in glycaemic indices, inflammation and selected microRNAs with delta-tocotrienol, while trials in fatty liver disease reported improvements in several liver-related and inflammatory measurements. A study combining delta-tocotrienol with resveratrol cannot isolate the independent tocotrienol contribution. These data support the proposition that specific forms can be biologically active in humans, but chronic cardiometabolic conditions, intervention durations of many weeks or months and nonoperative endpoints limit transferability to a 7- or 30-day postoperative outcome [9,23,36,37]. Broader evidence supports caution. A systematic review and meta-analysis of randomised trials did not find consistent pooled reductions in interleukin-6, tumour necrosis factor-alpha or malondialdehyde, despite a C-reactive protein finding dominated by one trial. A later review of palm tocotrienol-rich fraction studies described promise but also called for work on dose, formulation and treatment duration. Evidence in chronic kidney disease and metabolic syndrome similarly suggests context-dependent biological signals rather than a reproducible cross-population anti-inflammatory effect. Accordingly, tocotrienols should be framed as candidates requiring perioperative investigation rather than established anti-inflammatory pharmaceuticals [17,21,29,46].

Carotenoids and Red Palm Oil

Red palm oil is distinguished from highly refined palm oil by retention of carotenoid pigments, particularly alpha- and beta-carotene. Carotenoid-derived vitamin A plays a physiological role in epithelial integrity and immunity, but its relevance depends on baseline intake and deficiency status. Restoring a nutrient deficit is conceptually different from giving supraphysiologic antioxidant doses to a replete surgical population. Food-matrix effects, lipid co-ingestion, intestinal absorption and conversion efficiency further complicate any assumption that measured carotenoid content guarantees a predictable tissue exposure. The research question is therefore whether a defined carotenoid intervention corrects a documented need or delivers an independently verified benefit, not whether red palm oil is generally described as healthy [22,24].

Squalene: A Crucial Route-Of-Administration Distinction

Squalene is an endogenous lipid precursor and a minor constituent of several plant-derived oils. Its best-established immunological application in the present literature involves formulated oil-in-water vaccine adjuvants, sometimes combined with other constituents including alpha-tocopherol. Experimental work demonstrates modulation of dendritic-cell responses, antigen uptake and antibody generation under particular immunization conditions. Other preclinical studies report antioxidant or anti-inflammatory activity in nonhuman systems. These observations identify mechanistic possibilities but do not establish that orally administered palm-derived squalene will exert comparable effects, or that immune stimulation would be desirable during a vulnerable postoperative period [3,28,50,53].

Oil Palm Phenolics and Compositional Complexity

Oil palm phenolics are commonly discussed as recovered fractions from processing-related aqueous streams rather than major constituents of the edible triglyceride matrix. Their biological effects depend on constituent identification, enrichment, stability and delivery. A recent phase-one human trial of encapsulated oil palm phenolics reported selected blood-pressure and antioxidant-related signals in healthy adults, but it did not assess surgical patients, infection, tissue healing or ERAS outcomes. The early-stage nature of these findings matters because polyphenol-rich extracts may contain chemically heterogeneous molecules with distinct pharmacokinetic behaviour. Standardisation and contaminant testing should precede broad claims about immune rescue or postoperative organ protection [8,24].

Translational Theory and the Evidence Ladder

The conceptual model used here treats translation as a sequence of evidentiary gates: chemically characterised material, plausible and reproducible mechanism, achievable human exposure, acceptable perioperative safety, consistent biomarker engagement and finally patient-important benefit. Evidence that clears one gate does not automatically clear the next. A vaccine adjuvant experiment addresses pharmacodynamic potential under immunisation conditions, a chronic-disease tocotrienol trial demonstrates human exposure and possible context-specific modulation, a surgical randomised trial is needed to establish effects on postoperative outcomes. This gatekeeping framework reduces the risk that independent pieces of supportive evidence will be combined as though they constituted a single causal chain [32,40,48].

Figure 1 brings together the four candidate bioactive classes, the surgical stress response and the minimum translational checks that connect chemical plausibility to a patient-centred outcome. Its arrows represent testable hypotheses, not causal effects already confirmed in surgical populations. The Figure distinguishes ingredient identity from the evidence needed to justify administration during ERAS, including exposure and perioperative safety [40,48] (Figure 1).

Figure 1 should be interpreted from top to bottom as a sequence of hypotheses: surgery creates biological vulnerability, each chemically distinct ingredient has a proposed but incompletely tested pathway, and only well-characterised, safe, human-exposed products can proceed toward clinical outcome testing. The figure deliberately does not claim that reducing oxidative stress alone improves postoperative results.



Figure 1: Candidate palm-derived bioactives and hypothesized links to ERAS endpoints (conceptual synthesis).

Clinical Outcomes Versus Surrogate Endpoints

Postoperative infections, anastomotic leakage, organ dysfunction, functional recovery, duration of hospital stay, readmission and patient-reported quality of recovery have direct relevance to clinical decisions. Inflammatory biomarkers can illuminate mechanism, but they are not universally validated surrogates for those endpoints. A postoperative fall in interleukin-6, for example, must be interpreted alongside the degree of tissue injury, sampling time, infection surveillance and immune competence. Studies of prehabilitation and established immunonutrition demonstrate why outcomes should cover both biological and functional domains. In a clinical trial, a biomarker-only positive result should not be presented as proof of ERAS success [2,6,25].

Methods: Qualitative Literature Review

Design and Epistemological Orientation

This review employs a Qualitative Literature Review (QLR), using a critical, configurative and interpretive synthesis rather than a Systematic Literature Review (SLR). The purpose is to construct a coherent cross-disciplinary explanation of how a set of heterogeneous research traditions may inform a surgical translational agenda. The analysis therefore integrates guidelines, randomised trials, meta-analyses, pharmacokinetic reports, mechanistic reviews and selected experimental studies according to the contribution each makes to a specified conceptual question. No claim is made that every eligible publication has been exhaustively identified, and the present work does not report pooled effect estimates, PRISMA flow counts or formal trial-level risk-of-bias scores.

Literature Identification and Boundaries

Literature published between January 2020 and October 2026 was examined through targeted searches and citation tracing focused on PubMed-indexed biomedical publications, recognized clinical nutrition and surgery journals, and directly accessible publisher records. Indicative combinations included perioperative nutrition, enhanced recovery, immunonutrition, surgical stress, prehabilitation, tocotrienols, palm bioactives, carotenoids, squalene, polyphenols, oxidative stress, pharmacokinetics and inflammation. Priority was placed on guideline updates, clinical trials, high-level syntheses and research explicitly concerning the chemical identity or formulation of palm-derived compounds. This approach is purposive and transparent but is not a reproducible exhaustive search strategy.

Inclusion Logic and Source Appraisal

Sources were retained when they illuminated at least one of five questions: evidence-based ERAS nutrition, human effects of a specified palm bioactive, pharmacokinetic feasibility, a biologically relevant pathway, or the design and measurement of translational research. The analysis assigned different interpretive weight to direct surgical intervention evidence, evidence from nonoperative humans and nonhuman or formulation studies. Protocols were considered evidence of research priorities and feasibility rather than efficacy, and secondary publications describing the same guideline were not treated as independent clinical datasets. Animal results were used to define mechanisms, not to estimate surgical treatment effects.

Coding and Iterative Thematic Analysis

An initial coding matrix classified studies by bioactive identity, source and product characteristics, study population, exposure route, dose or duration where reported, principal outcomes, evidence tier and limitations. Codes were then grouped into seven themes: established surgical nutrition, tocotrienol immunometabolism, other palm bioactives, oxidative and inflammatory mechanisms, formulation and bioavailability, perioperative safety, and clinical trial translation. Contradictory studies were retained as analytical cases. Where recent guidelines and meta-analyses disagreed in emphasis, the interpretation explored their population and intervention definitions instead of selecting the most favorable conclusion.

Interpretive Safeguards and Limitations

The review adopts four safeguards. First, it avoids conflating all vitamin E compounds or all palm products. Second, it separates route-specific pharmacology from oral nutrition, particularly for squalene adjuvants. Third, it does not infer that favorable biomarkers imply fewer clinical complications. Fourth, it avoids numerical effect estimation beyond accurately attributed results from source studies. Nevertheless, purposive selection is subject to author judgment, publication bias and the limitations of individual papers. The thematic framework is proposed as a reasoned research synthesis, not as a validated clinical algorithm.

Results: Thematic Findings

Theme 1 — Established Perioperative Immunonutrition has a Specific Evidence Base

The strongest clinical evidence identified concerns standard perioperative nutritional management, not palm-derived supplements. The 2025 ESPEN update offers specific recommendations for surgical nutritional risk, early feeding and immunonutrition in major tumour surgery, while ERAS Society guidance specifies procedure-sensitive nutritional actions. A meta-analysis across head-and-neck and gastrointestinal cancer operations reported reductions in total and infectious complications with immunonutrition compared with standard nutrition. More recent evidence aggregating gastrointestinal cancer trials also suggests benefits for several infection endpoints and hospital stay when arginine, nucleotides and omega-3 fatty acids are combined. Those associations apply to studied formulas and populations, not to substitute botanicals. A contemporary trial comparing preoperative immunonutrition with conventional oral supplements in colorectal surgery reinforces why the comparator itself must be defined [5,13,25,35,48]. The distinction between tested formulas and exploratory palm-derived additives is illustrated by the scale and specificity of a recent gastrointestinal cancer meta-analysis. Budai, et al., (2026) [5] examined 90 randomized controlled trials, of which 55 contributed to meta-analysis, encompassing 7,462 patients. Formulas combining arginine, nucleotides and omega-3 fatty acids were associated with lower odds of several postoperative complications, including anastomotic leakage (odds ratio 0.62, 95% confidence interval 0.50–0.76), but this evidence neither establishes a benefit for isolated omega-3 supplementation nor provides evidence for palm-derived molecules. Because operation types, formula compositions and underlying care differ, even these quantitative results warrant setting-specific interpretation [5].

The high-level evidence is qualified by differences in certainty and setting. A Cochrane review was unable to establish confident benefits for several broad preoperative nutrition comparisons, whereas other meta-analyses identified benefits in particular intervention classes. Colorectal research found a signal for minor infectious complications but not consistent effects across all outcomes, and trials in highly complex surgeries show why intervention timing and clinical context require attention. A preliminary randomized study of enteral immunonutrition and intestinal microbiota illustrates emerging mechanistic endpoints, while an updated synthesis of gastrectomy ERAS trials demonstrates effects of an entire recovery pathway rather than a specific supplement. Thus, the evidence is best read as support for specified nutritional pathways and selected formulas rather than proof that any material marketed as immunonutrition will improve recovery [16,20,33,42,45,49].

Theme 2 — Nutritional Reserve may be more Important than Untested Bioactive Additions

Across surgical studies, preoperative malnutrition, insufficient protein intake and reduced functional reserve emerge as practical vulnerabilities. A randomised trial in sarcopenic patients undergoing major hepatectomy found better postoperative morbidity results with structured nutrition-plus-exercise prehabilitation, while a trial involving older esophageal cancer patients demonstrated preservation of selected muscle outcomes during preoperative treatment. Such studies indicate that the consequences of nutritional interventions depend on baseline deficits and a combination of behavioural and biological inputs. Patients with adequate nutritional status are less likely to benefit in the same way as patients with substantial deficits. A short-course esophageal prehabilitation trial also reminds readers that improved protein intake need not consistently improve the primary cardiopulmonary endpoint [2,15,43,44]. Intervention implementation also changes measured results. A pragmatic randomized prehabilitation class embedded in colorectal ERAS improved aspects of protein adequacy and functional recovery without clearly reducing length of stay, this distinction shows why adherence and selected endpoints matter. Research on individualized versus standard prehabilitation further suggests that immune-cell signalling can change with a broader program that includes physical, nutritional and psychological components. None of these trials evaluated palm bioactives. Their significance is methodological: a future bioactive trial must account for the surrounding nutrition and prehabilitation program before attributing postoperative changes to its investigational ingredient [6,12,26]. Implementation evidence now extends beyond closely supervised trials. In a nationwide multicenter cohort study of

colorectal cancer surgery, Sabajo, et al., (2026) [55] compared standardized multimodal prehabilitation with matched historical controls and observed lower complication rates and shorter hospitalization in participating patients. The historical-comparator design leaves room for residual confounding and changes in care over time, so the study should not be interpreted as proving causality equivalent to randomization. Nevertheless, its real-world setting reinforces the need to measure adherence, health-system readiness and the clinical value added by any proposed novel supplement beyond nutrition and exercise programmes already available to surgical teams [54,55].

Theme 3 — Tocotrienol Effects in Humans Are Reported but Population- and Preparation-Specific

Among palm-associated compounds, tocotrienols have the most developed clinical research portfolio in the reviewed period. Studies involving diabetes, fatty liver disease, metabolic syndrome and rheumatoid arthritis have reported favorable changes in selected inflammatory, metabolic or symptomatic measurements. A randomized six-month rheumatoid arthritis trial using a palm tocotrienol-rich fraction offers a particularly interesting human immunomodulatory signal, but it remains a chronic inflammatory disease model. Duration, background treatment, disease activity and mechanism differ sharply from the immediate postoperative environment [23,36,37,51]. The same literature contains important boundaries. A meta-analysis of randomized tocotrienol trials found no pooled effect on several major inflammatory biomarkers, while a review of palm tocotrienol-rich fractions highlighted variability in dose and formulations. A trial in chronic kidney disease reported limited and subgroup-dependent changes, whereas an older-adult beverage study and a metabolic-syndrome food intervention evaluated different functional outcomes. This variation makes a universal dose or class effect implausible. A surgical study needs to specify whether the test product is a tocotrienol-rich fraction, a purified isoform or a whole-food matrix, otherwise positive and negative results cannot be interpreted comparably [17,21,29,41,46]. A recent randomized vaccination study found enhanced antibody and selected T-helper-cell responses following palm-derived tocotrienol-rich-fraction supplementation in healthy volunteers. This is more directly immunological than many metabolic trials, but its primary challenge was vaccination, not surgical tissue injury or bacterial infection. Vaccine immune responsiveness, immunological balance after anaesthesia and wound-site host defense are distinct outcomes. These results strengthen the argument for measuring cellular immune endpoints in future clinical studies while offering no direct proof that tocotrienols reduce postoperative pneumonia, wound infection or anastomotic failure [7,21].

Theme 4 — Bioavailability and Exposure are Unresolved Translational Bottlenecks

The bioactivity of tocotrienols depends on more than the nominal milligram dose. Lipophilic solubility, food intake, intestinal transport, interactions with the lipid matrix, isoform composition and rapid clearance influence systemic exposure. Human pharmacokinetic synthesis and more recent formulation research emphasize inconsistent oral bioavailability and the need for carefully engineered delivery systems. These challenges become acute around surgery because fasting, gastrointestinal dysfunction, nausea and changes in feeding route may alter absorption. An intervention administered before surgery may yield different exposure from the same dose given during early postoperative feeding [32,40,48]. Formulation also creates interpretive and regulatory issues. A tocotrienol supplement containing multiple vitamin E isoforms cannot be compared directly with purified delta-tocotrienol, and a lipid emulsion with vaccine adjuvant properties cannot be relabeled a nutritional beverage without new safety and exposure data. Studies in which tocotrienols were administered alongside other active compounds further complicate ingredient attribution. Chemical fingerprints, contaminant profiles, stability under storage and administration conditions, and human pharmacokinetic measurements should therefore be prerequisites to efficacy testing. This is particularly important if trial participants are receiving anaesthetics, anticoagulants, chemotherapy or multiple perioperative medicines [9,32,39].

Theme 5 — Oil Palm Phenolics are at an Early Human-Evidence Stage

The clinical maturity of oil palm phenolics remains substantially lower than that of surgical immunonutrition. A human phase-one study of encapsulated oil palm phenolics recorded selected changes in blood pressure and antioxidant markers among healthy volunteers, supplying evidence that a standardized extract may be studied in people. However, this does not validate enhanced immune defense or expedited surgical recovery. Different extraction methods can yield different mixtures, and polyphenols may behave differently across tissues and metabolic states. Translation requires identity and dose controls, validated exposure or metabolite markers, and evidence that a targeted perioperative mechanism is engaged without disrupting host defense [8,24]. The agricultural origin of the extract introduces an additional methodological issue: composition and quality should be evaluated independently of the marketing language used to describe by-products or circular-economy value creation. Bioactive recovery may provide environmental or industrial value, but clinical efficacy is a separate claim. Particularly for extracts intended for vulnerable postoperative patients, screening for residual process chemicals, oxidation products, microbial contamination and batch variability should be treated as part of research validity rather than only manufacturing compliance. The correct comparison is a characterized intervention against matching placebo and guideline-concordant care [8,22,24].

Theme 6 — Carotenoids and Squalene Require Distinct Research Pathways

Carotenoids in red palm oil offer a plausible nutritional role, especially when dietary vitamin A provision is inadequate, but evidence of deficiency correction must not be repurposed into a claim of faster postoperative recovery. The immediate research

priority is to determine whether target surgical patients have relevant deficiency or exposure gaps and whether a defined formulation improves nutritional status safely. In patients who are nutritionally replete, adding carotenoids solely for antioxidant protection requires new outcome-oriented evidence. Carotenoid absorption and conversion add uncertainty, and the triglyceride matrix of whole red palm oil has metabolic implications beyond the measured pigment content [22,24]. For squalene, the strongest available experimental immune data concern vaccine emulsion adjuvants and immunization models. Formulated squalene emulsions have been shown to influence antigen uptake, dendritic-cell maturation and antibody responses, experimental work in aquatic organisms suggests antioxidant signalling under induced stress. These observations are not demonstrations of benefit from oral squalene in surgical patients. The differences encompass source, route, dose, antigen context, carrier composition and clinical intention. Further, stimulating a vaccine response is not the same as safely resolving postoperative inflammation. Squalene should therefore remain a separate exploratory branch of the proposed research agenda [3,28,50,53].

Theme 7 — Safety, Interactions and Implementation Define Feasibility

Perioperative nutritional intervention occurs in an unusually complex therapeutic environment. Participants may have bleeding risk, altered liver or kidney function, insulin resistance, immunosuppression, bowel dysmotility, enteral intolerance, active malignancy and multiple drug exposures. A supplement tolerated in healthy adults over months may not share that profile during the first postoperative days. Tocotrienol supplementation alongside anticancer chemotherapy has been evaluated in a phase-II colorectal study, but a non-significant primary endpoint and nonoperative treatment setting limit what may be concluded. Any early surgical trial should prospectively assess bleeding, liver biochemistry, gastrointestinal tolerance, medication changes and clinically adjudicated adverse events [39,40,48]. Potential commercial adoption must be considered separately from proof of clinical value. ERAS programmes already require staff coordination, education, nutrition screening and postoperative monitoring, an investigational capsule should not displace basic care or impose an unmeasured adherence burden. Trials should explicitly record ERAS compliance and standard nutritional provision. This is especially important in lower-resource settings, where improving access to adequate food, standard oral nutritional supplements and perioperative clinical services may produce larger gains than adding relatively costly unvalidated bioactives. Implementation and opportunity cost are therefore ethical as well as economic variables [4,12,19].

Discussion and Analysis

Answering the Mechanistic Question: Plausible Does not Mean Established

The reviewed evidence provides a coherent but incomplete mechanistic rationale. Tocotrienols can affect redox-related and inflammatory pathways in experimental settings and selected clinical populations, polyphenols can influence antioxidant readouts, carotenoids participate in nutritional and cellular biology, and squalene-containing vaccine emulsions have formulation-specific immunological effects. However, these are different mechanisms supported at different levels, not a validated shared pathway that predicts superior surgical recovery. The most defensible answer to the first research question is therefore conditional: palm-derived constituents may intersect with stress physiology, but the target pathway, product exposure and clinical benefit have not yet been jointly demonstrated in perioperative patients [1,8,28,34]. A second challenge is the biological meaning of inflammation reduction. It is tempting to equate diminished cytokine concentrations with protection, but postoperative healing needs appropriately timed innate and adaptive immune responses. A future hypothesis should distinguish excessive systemic inflammation from effective wound-site immunity and from the later resolution phase. It should examine immunophenotypes or clinically interpretable biomarker trajectories rather than a single postoperative marker. The immune profiling observed with personalized prehabilitation offers an example of higher-resolution measurement, but not a ready-made target threshold for a tocotrienol intervention. This distinction prevents the research programme from simply maximizing the appearance of an anti-inflammatory response [6,7,31].

Human Evidence Transferability: An Explicit Hierarchy

An evidence hierarchy resolves much of the apparent contradiction in the literature. At the strongest and most directly actionable tier sit clinical guidelines and randomized surgical nutrition trials using specified standard formulas. A second tier includes randomized human studies of tocotrienols or oil palm phenolics in nonoperative populations, demonstrating possible human biological activity but not surgical effectiveness. A third tier includes pharmacokinetic, biochemical and preclinical studies that establish feasibility hypotheses. Results from a lower tier may justify work at the next tier but should not be promoted to clinical guidance by rhetorical similarity. The hierarchy is a practical interpretive device, not a numerical grading instrument [5,8,21,48]. As shown in Figure 2, the existing evidence must be sorted by proximity to the actual perioperative decision. Established clinical nutrition guidance and trials of defined surgical formulas are more directly informative than chronic-disease supplementation studies, while mechanistic findings serve primarily to identify hypotheses. The diagram uses qualitative categories rather than an invented numerical certainty estimate [17,48] (Figure 2).

Figure 2 illustrates the inferential distance between the strongest existing evidence on standard perioperative nutrition and the exploratory evidence on palm-derived compounds. The tiers are categorical judgments about clinical directness, not invented numerical certainty scores. They explain why findings from a vaccine formulation or chronic metabolic disorder cannot independently support a perioperative recommendation.



Figure 2: Qualitative evidence-tier map: direct clinical evidence is distinct from nonsurgical human and mechanistic findings.

Figure 2 must not be read as assigning a universal quality score to every paper in a category. It maps the directness of evidence for a perioperative clinical decision, which is different from judging internal trial validity. Consequently, an impeccably conducted vaccine-immunology study can occupy a lower translational tier for postoperative infection prevention than a smaller but appropriately controlled surgical nutrition trial. This distinction prevents apparent methodological precision from obscuring the mismatch between a source study and the clinical question [5,7].

This hierarchy also explains why even fairly large nonoperative randomized studies do not resolve the perioperative question. A six-month rheumatoid arthritis study tests inflammation during relatively stable chronic disease management. A metabolic study tests glucose and lipid pathways over weeks, and a vaccination study deliberately creates a specific antigenic stimulus. Surgery instead combines acute sterile injury, variable microbial exposures, anaesthesia, analgesia, catabolism and organ-specific complications. Neither study duration nor background pathophysiology is comparable. The distinction should be made in evidence tables and abstracts so that readers do not confuse proof of activity with proof of clinical utility [7,38,51].

Integration Into ERAS: where a Candidate Might Fit

A potential palm-bioactive program would be most rational in carefully selected elective procedures permitting preoperative optimization. One hypothetical design might supplement an already adequate nutrition and exercise prehabilitation programme with a standardized tocotrienol-rich fraction, beginning sufficiently before surgery to characterize adherence and exposure. Postoperative continuation could be evaluated only where enteral tolerance and medication safety permit. This design is a research proposal, not an endorsed clinical dose or timing schedule. It deliberately preserves early feeding, protein-energy targets and standard immunonutrition when indicated. Any resulting benefit would be measured as incremental rather than as a substitute for guideline-based recovery measures [11,13,48]. Patient stratification is essential. A frail or sarcopenic patient may derive measurable benefit from nutrition and exercise regardless of additional bioactive supplementation, an already well-nourished person may have little room for nutritional improvement. Patients with diabetes, metabolic liver disease, kidney impairment or inflammation-related conditions may also have different baseline signalling and pharmacokinetics. Trials should prespecify these characteristics as effect modifiers rather than combine them indiscriminately in small exploratory studies. The successful functional endpoints reported in prehabilitation research reinforce the necessity of retaining capacity and recovery outcomes alongside laboratory measurements [2,30,44].

Why Source Identity and Dose Cannot be Treated as Minor Details

The language of palm oil bioactives often conceals product heterogeneity. Crude or red palm oil, refined edible palm oil, mixed tocotrienol-rich fractions, purified tocotrienols, squalene-rich material and aqueous phenolic extracts belong to different chemical and regulatory categories. Pooling them as a single intervention is scientifically indefensible. A trial report must specify botanical source, processing, active constituent identities, compositional ranges, batch-to-batch repeatability, storage stability and dose calculation. The placebo must be appropriately matched without becoming an active comparator through its own lipid composition.

When a product contains a mixed vitamin E fraction, isoform-specific pharmacology also becomes relevant to interpretation [22,32,24]. Human exposure is another necessary bridge. Perioperative fasting restrictions, the schedule of oral feeding, altered bile delivery, malabsorption or intolerance can affect the relationship between administered dose and circulating levels. Pharmacokinetic work should determine preoperative trough and peak exposure and how these change when patients resume oral intake. A purely preoperative regimen could avoid some absorption uncertainty but might fail to engage the intended postoperative window. These possibilities should be resolved through pilot studies, ideally combining exposure profiles with a modest set of prespecified mechanistic biomarkers. Only then is a larger clinical endpoint trial scientifically justified [10,32,40].

Antioxidant Promise, Contradictory Biomarkers and Clinical Risk

The tocotrienol literature provides a useful cautionary case. Individual studies have reported reductions in particular inflammatory markers, but a meta-analysis did not confirm consistent effects on several central cytokines across randomised trials. Contradiction does not establish the absence of every biological effect, it signals intervention, population and outcome heterogeneity. A plausible translational programme should therefore select one standardized product and a bounded mechanistic hypothesis instead of testing a shifting combination of endpoints until favorable findings emerge. Researchers should preregister clinical and mechanistic outcomes separately, with correction for multiple testing where appropriate [17,23,37]. Safety should not be inferred from the general dietary use of palm oil. Concentrated fractions administered at doses much higher than ordinary diet, or formulated with novel carriers, may have different pharmacological properties. Prior tolerability in metabolic populations can inform safety monitoring but does not resolve interaction risks in patients receiving perioperative drugs or organ support. A phase-II trial combining delta-tocotrienol with colorectal cancer chemotherapy illustrates the importance of reporting the primary result as non-significant even when selected secondary observations appear promising. Equivalent discipline is required in any ERAS trial, especially if a favorable biomarker coexists with unchanged infections, readmissions or recovery [39,46,48].

A Staged Translational Clinical Research Programme

The first research stage should characterize three distinct candidate classes rather than begin with an undifferentiated palm supplement. Tocotrienol-rich fractions have the strongest human-exposure foundation and are reasonable first candidates for carefully controlled mechanistic investigation. Standardized oil palm phenolics may merit parallel work on product identity and early exposure, while carotenoid interventions should be directed primarily toward documented nutritional need. Squalene should remain at the formulation and route-specific experimental stage until a clinically credible oral immunonutrition hypothesis exists. These recommendations reflect maturity and interpretability of evidence, not a claim that any class is already clinically effective [3,8,21,22].

Figure 3 operationalizes the proposed research agenda as five decision gates, beginning with analytical identification and progressing toward trials with clinically important outcomes. At each transition, the preceding evidence requirement must be satisfied before advancing to a more expensive and risk-bearing study. Standard nutrition care, ERAS fidelity and transparent reporting apply throughout the development sequence [32,48] (Figure 3).



Figure 3: Stage-gated translational research sequence for candidate palm bioactives in ERAS.

As Figure 3 shows, product identity and achievable exposure precede any claim of biological target engagement or clinical benefit. Negative findings at an earlier gate should trigger redesign or discontinuation rather than an escalation to large efficacy trials. This staged approach also makes safety monitoring, accepted comparators and ERAS protocol fidelity integral to the research pathway. The second stage consists of pilot perioperative pharmacokinetic and safety studies in a narrowly defined elective surgical population. Investigators should record baseline nutritional risk, procedure, ERAS compliance, medication exposures and relevant comorbidities. Mechanistic measurements might include circulating tocotrienol isoforms, oxidative stress markers, inflammatory trajectories and selected immune-cell functional assays. The primary outcome of such a pilot would be feasibility and safety, not a definitive clinical efficacy claim. The trial should specify whether sampling intervals capture the anticipated biological phase and should include an independent clinical adjudication procedure for adverse events [6,32,40]. Only after these conditions are met should a multicenter randomised trial assess patient-important outcomes. A suitable design would compare standardized adjunctive supplementation with an indistinguishable placebo, both delivered alongside high-quality ERAS and established nutrition. Randomization should be stratified by major predictors such as nutritional risk or procedure, with a prespecified primary endpoint and blinded outcome assessment. Infection definitions, Clavien-Dindo complication severity, anastomotic leakage, length of stay, readmission, quality of recovery and functional testing are candidate endpoints, not outcomes that all need to be included as coprimary measures. An economic evaluation could determine whether incremental benefit justifies manufacturing and delivery costs [13,14,25].

Research Design Priorities and Counterfactual Comparators

Choosing the comparator is a conceptual as well as practical decision. A study that compares a bioactive-rich oral formula with no nutritional intervention may identify an effect of energy, protein or general nutritional attention rather than the bioactive itself. The credible comparison is an isocaloric, isonitrogenous or otherwise suitably matched formulation when the research question concerns incremental biological activity. Where the target population qualifies for established immunonutrition, withholding clinically indicated care would be inappropriate, the test compound must be added to, or directly compared under a defensible noninferiority framework with, accepted practice. Product source and comparator composition must be clearly registered before randomization [19,42,48]. An early proof-of-concept design should avoid inferring too much from underpowered exploratory endpoints. One practical sequence is feasibility and pharmacokinetics, followed by a biomarker-engagement trial and finally a larger clinical trial. A pilot can measure process indicators such as acceptability, supplement adherence, oral tolerance, completion of blood sampling and protocol fidelity. It can also estimate variance for later sample-size calculation without declaring clinical success. The absence of adverse events in a small cohort is not evidence that uncommon complications cannot occur. Reviews of perioperative nutrition and prehabilitation repeatedly demonstrate the value of disciplined study architecture and realistic endpoint selection [10,12,26]. Trial protocols should also separate efficacy claims from implementation claims. Evidence from the PREHAB randomised trial and its functional-outcome analysis shows that complication endpoints, exercise capacity and quality of recovery can differ in responsiveness and therefore should not be bundled into an ambiguous unregistered composite. Observational evidence from broader rollout can inform acceptability and external validity, but it cannot remove confounding from an unrandomized intervention evaluation. For a palm-derived adjunct, a prespecified primary clinical outcome, transparent adverse-event reporting and independent endpoint adjudication should remain mandatory even when mechanistic biomarkers appear favorable [54,55,56].

Special Considerations for Cancer Surgery

Cancer surgery is a particularly relevant setting because immunonutrition evidence is relatively rich, yet the biology is unusually complex. Patients may experience chronic inflammation, chemotherapy-associated gastrointestinal symptoms, compromised muscle reserves and altered immune function. Tocotrienol observations from patients receiving systemic anticancer therapy cannot be assumed to generalize to operative recovery. A prospective surgical intervention would also need to clarify potential effects on anticancer treatment tolerability and scheduling. Study protocols should minimize disruption to standard oncological care and avoid mechanistic narratives implying anticancer efficacy without direct evidence [5,25,39]. The relative priority of a new supplement should also depend on whether current nutrition is adequate. Clinical trials of nutritional support and immunonutrition suggest that surgical risk, deficit severity, formulation and treatment timing influence observed effects. Results from prehabilitation in hepatobiliary and esophageal surgery indicate possible gains from integrated interventions without requiring an exotic ingredient. Thus, the appropriate research contribution is not a new universal supplement recommendation but the definition of a subgroup and biological window in which a particular palm-derived molecule could provide demonstrable additional benefit [2,44,52].

Mechanistic Figures, Evidence Maps and Falsifiable Propositions

Figure 1 displays the proposed connection between surgical stress and candidate biochemical mechanisms while emphasizing that clinical endpoints remain to be established. Figure 2 separates existing nutrition recommendations from the evidence tiers for palm-derived candidates. Figure 3 translates this appraisal into sequential research decisions. These conceptual figures deliberately avoid invented treatment effect sizes, unsupported causal arrows and implied equivalence between oral supplements and vaccine adjuvants. Their purpose is to make the assumptions underlying

future studies visible and falsifiable, rather than to present a completed therapeutic model [7,21,48] One falsifiable proposition is that a characterized tocotrienol-rich fraction administered before elective surgery can achieve reproducible circulating exposure without compromising perioperative safety. A second is that such exposure changes a prespecified biologically meaningful trajectory compared with an exposure-matched control, beyond the changes produced by good ERAS care alone. A third, much stronger, proposition is that biologic target engagement improves a clinically relevant postoperative endpoint in an adequately powered randomised trial. Failure at any stage should narrow or discontinue development, rather than motivate retrospective selection of an alternative biomarker as the main success claim [13,17,32].

Equity, Regulation and Implementation

Translation has implications beyond biomarker selection. Palm cultivation and processing generate commercial opportunities, but health-system purchasing decisions should be driven by reproducible benefit, safety and value. A raw material's geographic origin or sustainability narrative does not establish a clinical advantage. When selecting supply chains, manufacturers and health institutions should consider product quality, traceability, environmental performance and equitable access while keeping those assessments separate from therapeutic efficacy. This distinction allows nutritional innovation and resource valorization to proceed responsibly without confusing industrial desirability with clinical proof [22,24,48]. Access is especially important where perioperative malnutrition and care-resource limitations coexist. Established actions such as nutritional assessment, availability of adequate protein-energy support, trained ERAS teams and postoperative follow-up have evidence-based rationale. A high-cost adjunct requiring specialized testing could divert resources from these foundations unless it provides incremental patient benefit. Future economic assessments should therefore record cost per complication avoided, opportunity cost, ease of procurement, product stability and feasibility of implementation. Equity assessments should include whether patients in lower-resource centers are systematically excluded from studies despite substantial surgical risk [11,47,48].

Integrative Answers to the Research Questions

The evidence answers the proposed questions in a qualified sequence. Palm-derived tocotrienols show the strongest human biological evidence, but their perioperative effectiveness remains unproven, carotenoid-rich products have a clearer nutrient-adequacy rationale than a direct ERAS therapeutic claim, oil palm phenolics warrant additional standardization and early human research, and squalene vaccine-adjuvant results are not transferable to oral postoperative nutrition. The relevant ERAS outcomes are well described but have not been tested directly for these candidate compounds. Dose, timing, absorption, comedication and product identity remain important uncertainties, and the required evidence pathway moves from product characterization to safe human exposure and then randomized surgical effectiveness [8,21,22,28]. Established immunonutrition cannot be redefined merely by analogy. Its stronger clinical evidence is tied to tested substrate combinations and procedure-specific indications. Even that literature contains uncertainty and heterogeneity, reinforcing the need for appropriate controls and cautious interpretation of novel adjuncts. The proposed contribution is therefore an explicit hierarchy of translational readiness, a mechanism-aware evidence map and a staged clinical research design. This synthesis avoids both premature therapeutic enthusiasm and the opposite error of dismissing informative human and laboratory work simply because definitive surgery trials are not yet available [5,25,33,42].

Conclusion and Recommendations

The translational potential of palm oil–derived bioactives lies in their chemical diversity and selected human biological signals, not in an established ability to accelerate recovery after surgery. Tocotrienols offer the strongest immediate research case, supported by nonoperative clinical trials and mechanistic investigations, but their effects vary by isoform, formulation, population and endpoint. Carotenoids may be relevant when nutritional inadequacy is documented, oil palm phenolics have preliminary clinical signals requiring replication, and squalene's formulation-specific vaccine adjuvant research cannot be translated directly into oral perioperative recommendations. None of these classes should presently be presented as a proven substitute for evidence-based ERAS or established perioperative immunonutrition. The first priority is to preserve comprehensive surgical care: nutritional-risk screening, adequate energy and protein, procedure-appropriate early feeding, prehabilitation when indicated and standardized ERAS delivery. Future studies of palm-derived compounds should begin with compositional quality, bioavailability and perioperative safety before seeking efficacy. Investigators should select clinically meaningful endpoints and credible nutritional comparators, distinguish mechanistic biomarkers from patient benefit, and report null or conflicting findings transparently. International collaboration across surgery, anesthesiology, nutrition, pharmacology and food science will be necessary to translate a plausible molecule into a testable intervention. A successful research programme should also incorporate product traceability, cost-effectiveness, environmental responsibility and equitable access without conflating these goals with clinical effectiveness. Clinicians should not extrapolate doses from metabolic-disease trials to perioperative practice, while policymakers and manufacturers should avoid making unverified postoperative recovery claims. The responsible conclusion is not that palm bioactives lack promise, but that their role in surgical recovery remains a hypothesis requiring sequential validation. A positive clinical recommendation will become justified only when standardized products demonstrate reproducible exposure, acceptable safety and patient-important benefit in adequately controlled surgical populations.

Acknowledgement

None.

Conflict of Interest

None.

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