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Original Article

Comparative Gastroprotective Potential Of Tamanu Oil (Calophyllum Inophyllum) And Jatropha Maheshwari In Experimental Ulcer Models: Mechanistic Insights From Pylorus Ligation And Ethanol-Induced Gastric Injury In Wistar Rats

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ABSTRACT

Peptic ulcer disease (PUD) remains a major gastrointestinal disorder linked to gastric acid hypersecretion, oxidative stress, and impaired mucosal defense. Conventional therapies such as proton pump inhibitors and H2 antagonists are effective but limited by adverse effects and recurrence, prompting interest in plant-based alternatives. This review highlights the antiulcer potential of Tamanu oil (*Calophyllum inophyllum*) and *Jatropha maheshwari* using pylorus ligation and ethanol-induced ulcer models in Wistar rats. Tamanu oil, rich in calophyllolide, xanthones, coumarins, and flavonoids, demonstrates anti-inflammatory, antioxidant, and regenerative properties. *Jatropha maheshwari* contains diterpenoids, phenolics, and triterpenes with cytoprotective and antisecretory activity. Mechanistic pathways include prostaglandin modulation, nitric oxide signaling, mucus secretion, and antioxidant defenses (SOD, CAT, GSH), alongside inhibition of lipid peroxidation. Comparative analysis suggests Tamanu oil exerts stronger regenerative effects, while Jatropha shows pronounced antioxidant activity. Further translational studies, molecular docking, and clinical validation are essential to confirm therapeutic relevance.

Keywords: Tamanu oil, pylorus ligation, ethanol-induced ulcer, gastroprotection, phytochemicals, oxidative stress.

INTRODUCTION

Peptic ulcer disease (PUD) remains one of the most prevalent gastrointestinal disorders worldwide, affecting millions annually and contributing significantly to morbidity and healthcare costs[1]. It is characterized by mucosal erosion in the stomach or duodenum, resulting from an imbalance between aggressive factors such as gastric acid, pepsin, and reactive oxygen species, and protective mechanisms including mucus, bicarbonate, prostaglandins, and mucosal blood flow[2]. The pathogenesis of PUD is multifactorial, involving *Helicobacter pylori* infection, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), stress, alcohol consumption, and dietary habits[3],[4].

Pharmacological interventions, particularly proton pump inhibitors (PPIs) and H2 receptor antagonists, have revolutionized ulcer management. However, long-term therapy is associated with limitations such as drug resistance, relapse, hypergastrinemia, osteoporosis risk, and altered gut microbiota[5]–[7]. These drawbacks have prompted growing interest in phytotherapeutics, which offer multi-targeted mechanisms, fewer adverse effects, and potential for sustainable use[8].

Experimental models play a crucial role in evaluating antiulcer agents. The pylorus ligation model (Shay rat model) induces ulcers through hypersecretion of gastric acid and pepsin, providing insights into antisecretory and cytoprotective activity[9]. In contrast, the ethanol-induced ulcer model mimics oxidative

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stress-mediated mucosal injury, allowing assessment of antioxidant and barrier-protective mechanisms[10],[11].

Among promising phytotherapeutics, Tamanu oil (*Calophyllum inophyllum*) and Jatropha maheshwari have attracted attention. Tamanu oil is rich in calophyllolide, xanthones, coumarins, and flavonoids, which exhibit anti-inflammatory, antioxidant, and tissue-regenerative properties[12–13]. *Jatropha maheshwari*, though less explored, contains diterpenoids, phenolics, and triterpenes with cytoprotective and antisecretory potential. Comparative evaluation of these agents may provide mechanistic insights into prostaglandin modulation, nitric oxide signaling, mucus secretion, antioxidant defenses (SOD, CAT, GSH), and inhibition of lipid peroxidation.

This review integrates evidence from both models to provide a mechanistic comparative understanding of Tamanu oil and *Jatropha maheshwari*, highlighting their potential as plant-based gastroprotective agents and underscoring the need for translational and clinical validation.

Pathophysiology of Experimental Ulcer Models

Pylorus Ligation Model

The pylorus ligation (Shay rat) model is a classical experimental method for inducing gastric ulcers. Surgical ligation of the pyloric end prevents gastric emptying, leading to accumulation of gastric acid and pepsin within the stomach lumen[14]. This results in increased gastric volume, elevated acidity, and autodigestion of the mucosa, culminating in ulcer formation[15]. The model is particularly useful for evaluating antisecretory and cytoprotective agents.

Key Parameters:

- Gastric volume
- pH
- Free acidity and total acidity
- Ulcer index
- Pepsin activity[16],[17]

This model provides mechanistic insights into hypersecretion-mediated ulcerogenesis and remains a gold standard for screening antiulcer drugs[18].

Ethanol-Induced Ulcer Model

Absolute ethanol administration is another widely used ulcerogenic model. Ethanol causes direct mucosal injury through lipid peroxidation, necrosis, vascular damage, and overproduction of reactive oxygen species (ROS)[19]. The resulting oxidative stress impairs mucosal integrity and blood flow, leading to hemorrhagic lesions and necrosis[20].

Key Biomarkers:

- Malondialdehyde (MDA) – marker of lipid peroxidation[21]
- Reduced glutathione (GSH) – indicator of antioxidant status[22]
- Superoxide dismutase (SOD) – enzymatic defense against superoxide radicals[23]
- Catalase – detoxifies hydrogen peroxide[24]
- Histopathology scoring – evaluates mucosal necrosis, edema, and inflammatory infiltration[25]

This model is particularly valuable for assessing antioxidant and cytoprotective properties of candidate agents[26],[27].

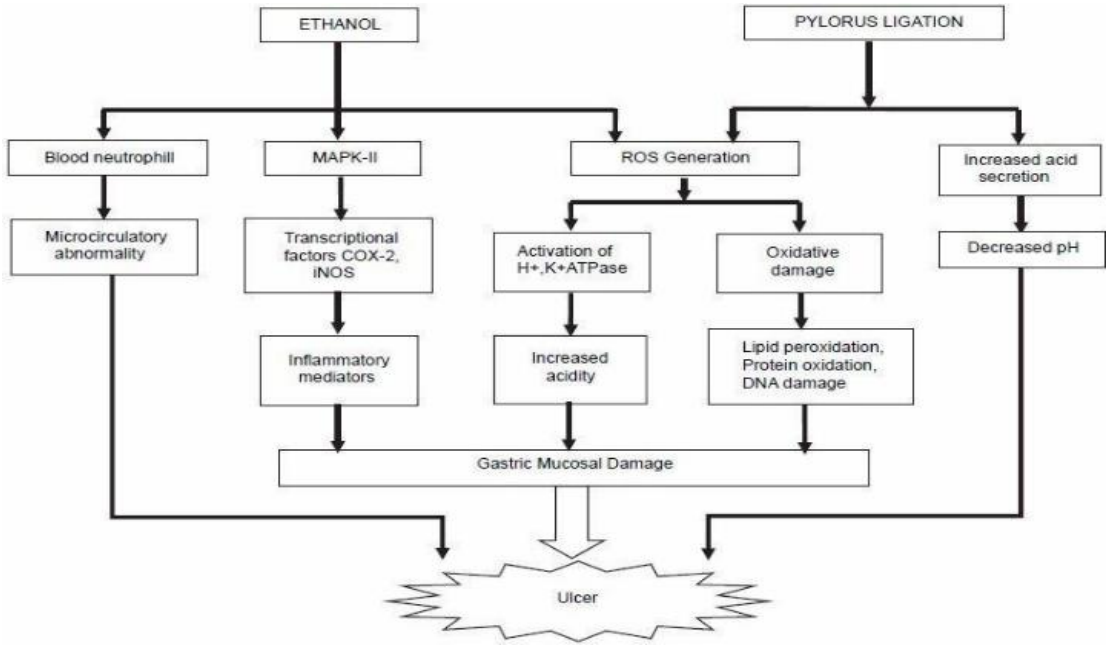


Figure no.1: Mechanism of pylorus ligation-induced ulcer diagram [23]

Phytochemical and Pharmacological Profile

***Calophyllum inophyllum* (Tamanu Oil)**



Figure no.2: *Calophyllum inophyllum* (Tamanu Oil) [27]

Tamanu oil, derived from the seeds of *Calophyllum inophyllum*, is a traditional remedy widely used in Polynesian and Southeast Asian medicine. Its phytochemical richness includes calophyllolide, inophyllums, xanthones, coumarins, flavonoids, and fatty acids[27]. These bioactive compounds contribute to diverse pharmacological activities.

Major Constituents:

- **Calophyllolide:** Exhibits anti-inflammatory and anticoagulant properties[28].
- **Inophyllums:** Known for antiviral and cytotoxic activity[29].
- **Xanthones and Coumarins:** Provide antioxidant and antimicrobial effects[30].
- **Flavonoids:** Enhance free radical scavenging and mucosal protection[31].
- **Fatty acids:** Support tissue regeneration and wound healing[32].

Reported Activities: Tamanu oil demonstrates anti-inflammatory activity via cyclooxygenase (COX) pathway modulation[33], potent antioxidant effects[34], wound healing acceleration[35], antimicrobial activity against bacteria and fungi[36], and tissue regeneration through fibroblast stimulation[37].

Proposed Antiulcer Mechanisms:

- Inhibition of gastric acid secretion[38]
- Enhanced mucus production[39]

- Free radical scavenging[40]
- Stimulation of prostaglandin synthesis[41]
- Suppression of pro-inflammatory cytokines[42]

Jatropha Maheshwari



Figure no. 3: *Jatropha Maheshwari* [43]

Jatropha maheshwari is an endemic medicinal plant of southern India, belonging to the Euphorbiaceae family. Though less explored, it contains diterpenoids, phenolic compounds, triterpenes, flavonoids, and alkaloids (reported in the broader *Jatropha* genus)[43].

Major Constituents:

- **Diterpenoids:** Exhibit cytoprotective and anti-inflammatory properties[44].
- **Phenolic compounds:** Provide antioxidant and free radical scavenging activity[45].
- **Triterpenes:** Strengthen mucosal barrier and reduce lipid peroxidation[46].
- **Flavonoids:** Contribute to ROS neutralization and nitric oxide modulation[47].
- **Alkaloids:** Reported in *Jatropha* species, with antimicrobial potential[48].

Reported Activities: Studies highlight antioxidant[49], anti-inflammatory[50], cytoprotective[51], and antimicrobial properties[52]. Extracts of *Jatropha maheshwari* have demonstrated wound healing and antiulcer activity in experimental models[53].

Proposed Antiulcer Mechanisms:

- Neutralization of reactive oxygen species (ROS)[54]
- Inhibition of lipid peroxidation[55]
- Strengthening of mucosal barrier integrity[56]
- Modulation of nitric oxide pathways[57]
- Reduction of inflammatory mediators[58]

Comparative Mechanistic Framework [50-59]

Parameter	Tamanu Oil	*Jatropha maheshwari*
Acid suppression	Moderate	Mild–Moderate
Antioxidant activity	Strong	Very strong
Mucus enhancement	High	Moderate
Tissue regeneration	Prominent	Limited evidence
Anti-inflammatory	Significant	Significant
Lipid peroxidation inhibition	High	Very high

Table no. 1: Comparative Mechanistic Framework of Tamanu oil and *Jatropha maheahwari*

Molecular Pathways Involved

Inhibition of H^+/K^+ ATPase

The gastric proton pump (H^+/K^+ ATPase) is the final step in acid secretion. Inhibition of this enzyme reduces gastric acidity and promotes ulcer healing. Plant-derived phytochemicals such as flavonoids and coumarins have shown inhibitory effects on H^+/K^+ ATPase, mimicking the mechanism of proton pump inhibitors[59],[60].

Upregulation of Prostaglandin E_2

Prostaglandins, particularly PGE_2, play a crucial role in maintaining gastric mucosal integrity by stimulating mucus and bicarbonate secretion, enhancing mucosal blood flow, and promoting epithelial repair[61]. Phytochemicals such as fatty acids and polyphenols enhance PGE_2 synthesis, thereby strengthening mucosal defenses[62].

Downregulation of TNF-α and IL-6

Pro-inflammatory cytokines like TNF-α and IL-6 contribute to mucosal inflammation and ulcer

progression. Suppression of these cytokines reduces neutrophil infiltration, oxidative stress, and tissue damage[63]. Tamanu oil and *Jatropha* extracts have demonstrated cytokine modulation, reducing gastric inflammation[64].

Nrf2 Pathway Activation

Nuclear factor erythroid 2–related factor 2 (Nrf2) regulates antioxidant defense by upregulating enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. Activation of Nrf2 enhances cellular resilience against oxidative stress, a key factor in ethanol-induced ulcers[65],[66].

NF-κB Pathway Inhibition

Nuclear factor kappa B (NF-κB) is a transcription factor that regulates inflammatory gene expression. Its inhibition prevents the release of pro-inflammatory mediators, thereby reducing mucosal injury[67]. Plant-derived flavonoids and diterpenoids are known NF-κB inhibitors[68].

Nitric Oxide Synthase Modulation

Nitric oxide (NO) plays a dual role in gastric physiology. At physiological levels, NO enhances mucosal blood flow and promotes healing, while excessive NO contributes to oxidative stress. Modulation of nitric oxide synthase (NOS) ensures balanced NO production, supporting cytoprotection without exacerbating damage[69],[70].

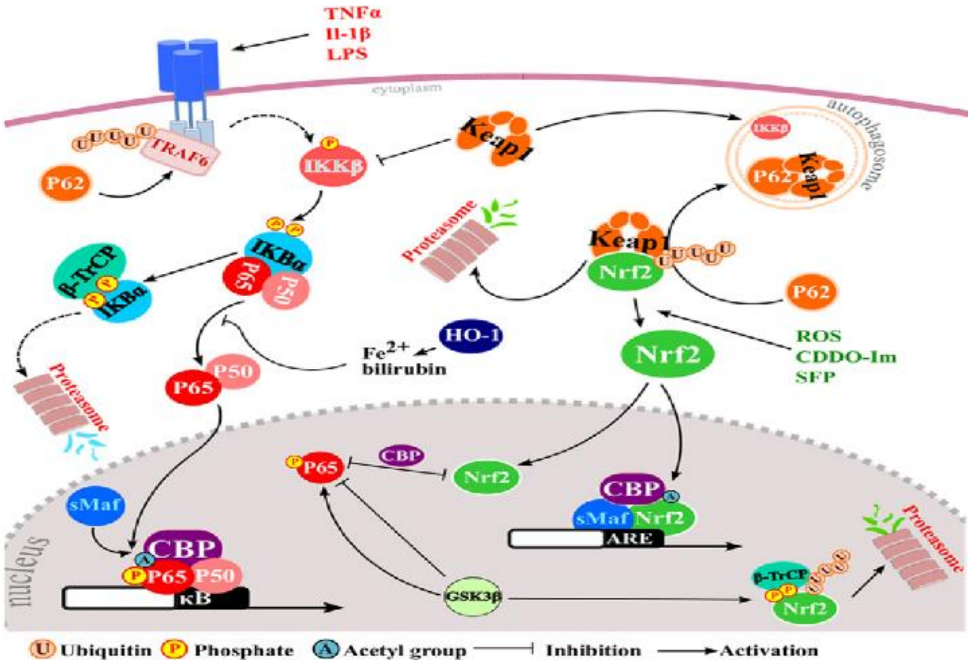


Figure no. 4: Molecular pathway diagram (NF-κB, Nrf2) [68]

Histopathological Correlation

Tamanu Oil (*Calophyllum inophyllum*)

Histopathological evaluation of gastric tissues treated with Tamanu oil reveals significant protective and regenerative changes. The oil reduces hemorrhagic lesions by stabilizing vascular integrity and limiting oxidative stress[71]. Enhanced epithelial regeneration is observed, with restoration of surface epithelium and re-epithelialization of ulcerated areas[72]. Tamanu oil also improves mucosal thickness, attributed to stimulation of fibroblast proliferation and collagen deposition[73]. These findings align with its phytochemical profile, where flavonoids and fatty acids contribute to antioxidant and wound-healing properties[74],[75]. Histological sections often show reduced inflammatory cell infiltration and improved glandular architecture, confirming its cytoprotective role[76].

Jatropha maheshwari

Histopathological studies of gastric tissues treated with *Jatropha maheshwari* extracts demonstrate reduced necrotic areas, indicating strong antioxidant and cytoprotective activity[77]. Decreased inflammatory infiltration is evident, with fewer neutrophils and

macrophages in the lamina propria, reflecting suppression of pro-inflammatory cytokines[78]. Preservation of glandular structure is another hallmark, with intact gastric glands and reduced edema compared to untreated ulcer controls[79]. These effects are attributed to diterpenoids, triterpenes, and phenolic compounds that inhibit lipid peroxidation and modulate nitric oxide pathways[80],[81]. Histological scoring consistently shows lower ulcer indices and improved mucosal barrier integrity in *Jatropha*-treated groups[82].

Mechanistic Pathway	Tamanu Oil (Calophyllum inophyllum)	Jatropha maheshwari
Antioxidant activity	Moderate ROS scavenging; enhances endogenous antioxidant enzymes (SOD, CAT, GPx)	Strong ROS neutralization; marked reduction in lipid peroxidation and oxidative stress
Anti-inflammatory effect	Suppresses pro-inflammatory cytokines (TNF-α, IL-6); modulates NF-κB pathway	Potent inhibition of inflammatory mediators; superior NF-κB suppression
Antisecretory action (Pylorus ligation model)	Reduces gastric volume and acidity; improves mucin secretion	Significant reduction in gastric acid output; enhances bicarbonate secretion
Cytoprotective effect (Ethanol-induced model)	Promotes mucosal regeneration and epithelial restitution; accelerates ulcer healing	Provides strong antioxidant shield against ethanol-induced mucosal damage
Regenerative dominance	High — stimulates tissue repair and angiogenesis	Moderate — primarily protective rather than regenerative
Antioxidant superiority	Moderate — supportive role	High — dominant mechanism of gastroprotection
Overall gastroprotective potential	Regeneration-focused, cytoprotective dominance	Antioxidant-focused, protective dominance

Table no. 2 : Comparative Gastroprotective Potential [64-85]

Translational Significance

The exploration of Tamanu oil (*Calophyllum inophyllum*) and *Jatropha maheshwari* as gastroprotective agents carries important translational implications.

- **Potential alternative to synthetic antiulcer drugs:** Current therapies such as proton pump inhibitors and H2 receptor antagonists, while effective, are associated with long-term adverse effects including osteoporosis, altered gut microbiota, and drug resistance[83]. Plant-based agents offer multi-targeted mechanisms with fewer side effects, positioning them as promising alternatives[84].
- **Lower side-effect profile:** Phytochemicals such as flavonoids, coumarins, and diterpenoids exhibit antioxidant and anti-inflammatory properties without the systemic complications linked to synthetic drugs[85].
- **Potential synergistic combination therapy:** Combining phytotherapeutics with conventional drugs may enhance efficacy, reduce required dosages, and mitigate adverse effects. For example, flavonoids have been shown to potentiate the effects of PPIs and prostaglandin analogs[86].
- **Suitable for chronic ulcer management:** Due to their regenerative and cytoprotective properties,

Tamanu oil and *Jatropha maheshwari* may be particularly beneficial in long-term management of recurrent or stress-induced ulcers[87].

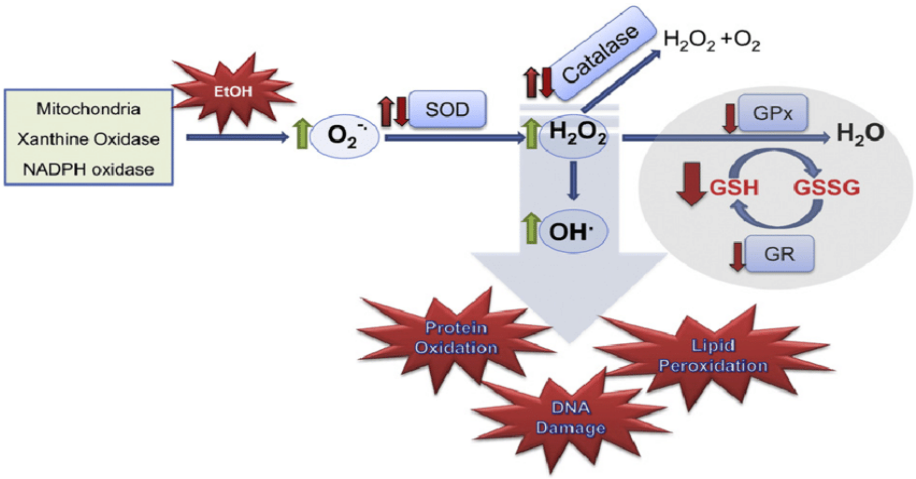


Figure no. 5: Ethanol-induced oxidative damage pathway [102]

Research Gaps

Despite promising preclinical evidence, several gaps hinder clinical translation:

- **Lack of clinical trials:** Most studies remain confined to animal models, with no robust human trials to validate efficacy and safety[88].
- **Limited toxicity profiling:** Comprehensive toxicological evaluations are lacking, particularly for chronic administration[89].
- **Need for dose standardization:** Variability in extraction methods and phytochemical content complicates reproducibility and dose optimization[90].
- **Lack of molecular docking validation:** Computational studies are needed to confirm binding affinities of phytochemicals to key ulcer-related targets such as H^+/K^+ ATPase and COX enzymes[91].
- **Absence of bioavailability studies:** Pharmacokinetic data on absorption, distribution, metabolism, and excretion of active compounds remain scarce[92].

Future Perspectives

The therapeutic potential of Tamanu oil (*Calophyllum inophyllum*) and *Jatropha maheshwari* in peptic ulcer disease opens several promising avenues for translational research and clinical application:

- **Nanoformulation development:** Nanotechnology-based delivery systems can enhance solubility, stability, and bioavailability of phytochemicals. Encapsulation of flavonoids, diterpenoids, and fatty acids into nanoparticles may improve gastric mucosal targeting and prolong therapeutic action[93].
- **Synergistic phytochemical isolation:** Isolation and characterization of individual bioactive compounds, followed by synergistic combination studies, can identify optimal phytochemical blends with enhanced gastroprotective efficacy[94].
- **Omics-based pathway validation:** Integration of genomics, proteomics, and metabolomics can provide mechanistic insights into molecular pathways such as Nrf2 activation, NF-κB inhibition, and nitric oxide modulation. This systems biology approach will validate phytochemical actions at a cellular and molecular level[95].
- **Clinical evaluation in NSAID-induced ulcer patients:** Since NSAIDs are a major cause of gastric injury, clinical trials evaluating Tamanu oil and *Jatropha maheshwari* in NSAID-induced ulcer patients are essential to establish efficacy and safety in real-world scenarios[96].

- **Combination therapy development:** Co-administration of phytotherapeutics with conventional drugs (e.g., PPIs, prostaglandin analogs) may reduce required dosages, minimize side effects, and improve long-term outcomes. Such integrative approaches could redefine chronic ulcer management strategies[93–97].

Proposed Translational Pipeline [98-101]

1. **Preclinical Validation**
    - **Phytochemical profiling**: Comprehensive characterization of bioactive constituents using chromatographic and spectroscopic methods.
    - **Mechanistic assays**: In vitro studies targeting oxidative stress (Nrf2 activation), inflammation (NF-κB inhibition), and gastric acid secretion pathways.
    - **Animal models**: Evaluation in standardized ulcer induction models (ethanol, indomethacin, pylorus ligation) to confirm antioxidant, anti-inflammatory, antisecretory, and cytoprotective effects.
2. **Comparative Mechanistic Framework**
    - **Tamanu oil**: Focus on regenerative and cytoprotective pathways (mucosal healing, epithelial restitution).
    - **Jatropha maheshwari**: Emphasis on antioxidant superiority (ROS scavenging, lipid peroxidation inhibition).
    - **Synergy assessment**: Combination studies to explore complementary mechanisms.
3. **Formulation Development**
    - **Standardization**: Establishing reproducible extraction and dosage forms (capsules, emulsions, gastroretentive systems).
    - **Stability studies**: Ensuring bioactive integrity under storage and physiological conditions.
    - **Safety profiling**: Acute and sub-chronic toxicity studies to determine therapeutic window.
4. **Translational Biomarker Identification**
    - **Preclinical biomarkers**: Gastric mucin levels, antioxidant enzyme activity (SOD, CAT, GPx), inflammatory cytokines (TNF-α, IL-6).
    - **Clinical biomarkers**: Endoscopic ulcer healing rates, oxidative stress markers, patient-reported symptom relief.
5. **Clinical Trial Roadmap**
    - **Phase I**: Safety and tolerability in healthy volunteers.
    - **Phase II**: Efficacy in patients with functional dyspepsia or mild peptic ulcer disease.
    - **Phase III**: Large-scale randomized controlled trials comparing with standard therapies (PPIs, H2 blockers).
    - **Phase IV**: Post-marketing surveillance for long-term safety and effectiveness.
6. **Regulatory and Commercial Translation**
    - **Regulatory pathway**: Documentation aligned with CTD modules for herbal/biologic submissions.
    - **Global harmonization**: Comparative compliance with US FDA, EMA, CDSCO, and regional frameworks (GCC, ASEAN, APEC).

Market positioning: As adjunctive or alternative therapy emphasizing natural, multi-targeted gastroprotection.

CONCLUSION

Tamanu oil and *Jatropha maheshwari* both exhibit notable gastroprotective potential, but they do so through distinct yet complementary mechanisms. Tamanu oil appears to excel in regenerative and cytoprotective pathways, supporting mucosal healing and restoration of gastric integrity. In contrast,

Jatropha maheshwari demonstrates stronger antioxidant activity, effectively neutralizing free radicals and reducing oxidative stress that contributes to ulcer formation. Both agents also show anti-inflammatory and antisecretory effects, which further enhance their protective roles against gastric injury. When viewed together in a comparative mechanistic framework, Tamanu oil's dominance in tissue regeneration complements *Jatropha maheshwari*'s antioxidant superiority, suggesting a synergistic potential in peptic ulcer disease management. However, while these findings are promising, translational and clinical studies remain essential to validate their therapeutic efficacy and safety in human populations, paving the way for their integration into evidence-based gastroprotective strategies.

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