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OVERVIEW OF THE POTENTIAL OF TRADITIONAL MEDICINAL HERBS IN THE TREATMENT OF GASTRIC ULCER AND GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

Peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD) are common chronic gastrointestinal disorders that significantly impair the quality of life of millions of people worldwide.

Although modern medical treatments, particularly proton pump inhibitors (PPIs), have demonstrated high efficacy, long-term use remains associated with concerns regarding adverse effects and drug resistance. In this context, Traditional Medicine, with its extensive pharmacopeia of medicinal herbs, offers a promising complementary and integrative therapeutic approach.

This narrative review aims to provide an overview of the potential role of Vietnamese herbal medicines in the management of PUD and GERD. The herbal formula "Da Khoi Cot" is presented as a representative case study to illustrate the multi-target therapeutic principle of Traditional Medicine, combining agents with acid-neutralizing properties (Sepiae Os), mucosal protective effects (Ardisia silvestris leaves), anti-inflammatory activity (Oldenlandia diffusa), and gastrointestinal motility regulation (Aurantii Fructus Immaturus and Paeoniae Radix Alba).

Preliminary evidence, primarily derived from preclinical studies (in vitro and animal models), has suggested these pharmacological activities. This review highlights the growing trend toward the development of standardized herbal preparations grounded in evidence-based medicine as a safe and effective adjunctive strategy in the comprehensive management of gastric disorders.

However, it must be emphasized that current evidence is insufficient for these herbal therapies to replace standard modern medical treatments, particularly given the potential malignant transformation associated with PUD and GERD.

1. INTRODUCTION

Peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD) are among the most prevalent chronic gastrointestinal disorders worldwide. Epidemiological data indicate that the prevalence of PUD accounts for approximately 5–10% of the global population, with an estimated rate of around 7% in Vietnam. These conditions are characterized by a chronic and recurrent course and not only cause distressing symptoms such as epigastric pain, heartburn, and acid regurgitation, but also carry a substantial risk of serious complications, including gastrointestinal bleeding, gastric perforation, pyloric stenosis, and even malignant transformation.

The core pathophysiological mechanism underlying both PUD and GERD involves an imbalance between aggressive factors—such as hydrochloric acid (HCl), pepsin, Helicobacter pylori infection, and nonsteroidal anti-inflammatory drugs (NSAIDs)—and protective mechanisms of the gastric mucosa, including the mucus–bicarbonate barrier, prostaglandins, and adequate mucosal blood flow. Modern medical management has achieved remarkable success, primarily through acid-suppressive therapies (H_2 receptor antagonists and proton pump inhibitors [PPIs]) and *H. pylori* eradication regimens, which together constitute the cornerstone of contemporary treatment strategies.

Nevertheless, long-term PPI use has been associated with several safety concerns, including an increased risk of enteric infections, impaired absorption of vitamins and minerals, and chronic kidney disease. In addition, the rising global prevalence of *H. pylori* antibiotic resistance has significantly compromised the efficacy of current eradication regimens. These limitations have prompted growing interest in the exploration of safe and effective

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complementary therapies derived from natural medicinal resources.

It is important to emphasize that traditional medicine–based therapies, despite their therapeutic potential, should currently be regarded as adjunctive and integrative approaches rather than substitutes for evidence-based conventional treatments. This consideration is particularly critical for PUD and GERD, which are associated with a high risk of severe complications, including gastrointestinal bleeding, perforation, obstruction, and malignant progression.

Vietnamese Traditional Medicine (VTM), with thousands of years of experience in the management of digestive disorders, represents a valuable reservoir of medical knowledge. Within the traditional medical framework, PUD and GERD are conceptualized under the syndrome category of "Vị quản thống" (epigastric pain), encompassing diagnostic patterns such as "Can khí phạm vị" (Liver Qi attacking the Stomach) and "Tỳ vị hư hàn" (Spleen–Stomach deficiency with cold). The therapeutic philosophy of VTM extends beyond simple acid neutralization (chế toan) and emphasizes the restoration of functional balance among the internal organs, particularly the Liver (Can), Spleen (Tỳ), and Stomach (Vị).

This article aims to provide a narrative overview of the therapeutic potential of Vietnamese traditional medicinal herbs in the management of PUD and GERD, to critically analyze available preclinical and clinical evidence, and to elucidate the multi-component, multi-target formulation principles of a representative traditional remedy, "Dạ Khôi Cốt."

2. LITERATURE REVIEW METHIDOLOGY AND CLASSIFICATION OF EVIDENCE

2.1. Search Strategy

Relevant literature was systematically searched from major electronic academic databases, including PubMed, Google Scholar, ScienceDirect, as well as specialized Vietnamese medical journals. The primary keywords used in the search strategy included: traditional herbal medicine, traditional medicine, Vietnamese herbal medicine, peptic ulcer disease, gastroesophageal reflux disease, GERD, PUD, Dạ Khôi Cốt, Sepiae Os, Ardisia sylvestris, Dạ cẩm, Chỉ thực, Bạch thược, Thảo quả, combined using Boolean operators (AND, OR). Priority was given to studies published within the past 10–15 years (2008–2023). However, classical references and historically significant publications were also considered when they provided foundational or essential information.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria comprised original research articles, review papers, textbooks, and conference proceedings that were directly related to the pathology, pathogenesis, and treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD), with particular emphasis on experimental pharmacology and clinical studies of the Vietnamese medicinal herbs discussed in this review.

Exclusion criteria included studies that were not directly relevant to the topic, non–peer-reviewed publications (such as preprints), and sources lacking sufficient methodological or outcome data for critical evaluation.

2.3. Study Selection and Data Synthesis

Articles were initially screened based on titles and abstracts to assess relevance. Potentially eligible studies were then reviewed in full text to extract detailed data. The collected information was systematically synthesized, analyzed, and organized according to pharmacological effects and Traditional Medicine formulation principles, consistent with the structural framework of this review.

2.4. Classification of Evidence

In this narrative review, we clearly distinguish between preclinical evidence and clinical evidence to provide an objective assessment of the reliability and translational value of the available data.

- Preclinical evidence: This category includes findings from in vitro studies (cell culture and tissue-based models) and in vivo studies (animal models). Preclinical research is essential for elucidating mechanisms of action, screening pharmacological activities, and guiding subsequent clinical investigations. However, such findings cannot be directly extrapolated to human efficacy and safety due to physiological, pharmacokinetic, and pathological differences between animals and humans.

- Clinical evidence: Clinical evidence is derived from studies conducted in human subjects, particularly randomized controlled trials (RCTs). This type of evidence provides the most direct and reliable information regarding therapeutic efficacy, safety, dosage, and treatment regimens in humans and is considered the gold standard for evaluating real-world clinical effectiveness.

3. CONCEPTS OF TRADITIONAL MEDICINE REGARDING GASTRIC DISORDERS

According to Vietnamese Traditional Medicine (VTM), the Stomach (Vị) plays a fundamental physiological role in receiving, ripening, and transforming food and fluids (chủ thu nạp và hủ thục thủy cốc). Its normal functional characteristic is described as the downward movement of Qi (khí chủ giáng), which facilitates the descent of digested contents. Disruption of this physiological function may lead to various gastric disorders.

The syndrome known as Vị quản thống (epigastric pain) has a complex pathogenesis but can generally be classified into several principal etiological patterns:

- Liver Qi Invading the Stomach (Can khí phạm vị – stress and emotional factors):

This is the most prevalent pattern in modern society. Prolonged emotional stress, anxiety, or depression may

impair the Liver's function of Qi dispersion, leading to Liver Qi stagnation. The stagnant Liver Qi becomes rebellious and overacts on the Stomach (Wood overacting on Earth), preventing the normal descent of Stomach Qi. Clinically, this manifests as epigastric pain, belching, and acid regurgitation. If Qi stagnation persists over time, it may transform into Fire, resulting in burning sensations and epigastric discomfort.

- Spleen–Stomach Deficiency with Cold (Tỳ Vị hư hàn – impaired digestive function):

This pattern arises from irregular dietary habits, excessive consumption of cold or raw foods, or constitutional weakness. These factors weaken the Yang Qi of the Spleen and Stomach, impairing their warming and transformative functions. Cold stagnation in the Middle Jiao leads to dull, persistent epigastric pain that is characteristically alleviated by warmth or pressure.

- Blood Stasis (Huyết ứ):

Chronic or unresolved epigastric pain may obstruct the normal circulation of Qi and Blood, resulting in Blood stasis in the epigastric region. This pattern is characterized by severe, fixed, and localized pain. From a Traditional Medicine perspective, therapeutic strategies focus on restoring systemic balance. Depending on the specific syndrome pattern, treatment principles may include soothing the Liver and regulating Qi (sơ can lý khí), warming the Middle Jiao and dispelling Cold (ôn trung tán hàn), and invigorating Blood circulation while resolving stasis (hoạt huyết hóa ứ).

4. EXPERIMENTAL EVIDENCE ON THE PHARMACOLOGICAL EFFECTS OF VIETNAMESE HERBS IN THE "DẠ KHÔI CỐT" FORMULA

The "Dạ Khôi Cốt" formulation represents a typical traditional Vietnamese polyherbal prescription, developed from long-standing empirical experience for the treatment of "Vị quản thống" (epigastric pain) corresponding to the Liver Qi attacking the Stomach pattern. The therapeutic efficacy of this formula arises from the synergistic interaction among its constituent herbs, whose pharmacological activities have been validated through various experimental and preclinical studies in modern biomedical research.

4.1. Group of acid-neutralizing and mucosal-protective herbs

- Ô tắc cốt (Sepia esculenta Hoyle): Ô tặc cốt is the internal shell of the cuttlefish, with calcium carbonate ($CaCO_3$) as its principal component.

According to Traditional Medicine (TM), it possesses a salty flavor and warm nature, and exerts the functions of "chế toan chỉ thống" (acid neutralization and pain relief) and "thu liễm chỉ huyết" (astringing ulcers and hemostasis).

+ Experimental evidence: Multiple studies have confirmed the acid-neutralizing capability of calcium carbonate. In addition, organic compounds and mucopolysaccharides in Sepiae Endoconcha can form a protective colloidal layer covering the ulcer surface, shielding the gastric mucosa from acid and pepsin aggression, thereby facilitating ulcer healing. In an indomethacin-induced gastric ulcer model in rats, treatment with Sepiae Endoconcha powder significantly reduced the ulcer index compared with the control group.

- Lá khôi (Ardisiae sylvestris Pitard) : According to Traditional Medicine, Ardisiae sylvestris Pitard has a neutral nature and mild taste, exhibiting effects of acid suppression, ulcer contraction, and pain alleviation. Experimental evidence: The primary bioactive constituents include tannins and glycosides. Studies conducted at the National Institute of Materia Medica (Vietnam) demonstrated that Ardisia sylvestris extract reduces gastric acid secretion and intestinal motility. Tannins precipitate proteins at the ulcer surface, forming a protective layer that helps stop bleeding and promote mucosal regeneration. In the Shay rat model of gastric ulcer, the extract markedly decreased both gastric juice volume and free acidity compared with controls.

4.2. group of anti-inflammatory, analgesic, and *anti-H. pylori herbs*

- Dạ cẩm (Oldenlandia eapitellata Kuntze): According to Traditional Medicine (TM), Dạ cẩm has a sweet and slightly bitter taste, with a neutral nature, and is known for its effects in clearing heat, detoxifying, relieving pain, and reducing inflammation.

+ Experimental evidence: The roots of Dạ cẩm contain alkaloids, saponins, and tannins. Experimental studies have demonstrated significant anti-inflammatory activity of Dạ cẩm extracts in the carrageenan-induced paw edema model in rats. Its analgesic effect has also been confirmed in the acetic acid–induced writhing test. Notably, several in vitro studies reported that Dạ cẩm extract inhibited the growth of Helicobacter pylori, a major etiological agent of gastritis and peptic ulcer disease. These findings suggest that Dạ cẩm may possess multi-target gastroprotective potential through anti-inflammatory, analgesic, and antimicrobial mechanisms.

4.3. group of liver–spleen–stomach function regulators (qi-regulating and liver-soothing herbs)

- Chỉ thực (Fructus Aurantii immaturus): According to Traditional Medicine (TM), Chỉ thực has a bitter and pungent taste, with a slightly cold nature, and exerts actions of "breaking stagnant Qi, resolving food accumulation, and eliminating phlegm". It is considered a strong Qi-moving herb, commonly used to treat symptoms of abdominal distension and indigestion due to Qi stagnation. In the pattern of Liver Qi attacking the Stomach (Can khí phạm vị), Chỉ thực helps to disperse constrained Liver Qi, thereby restoring the downward flow of Stomach Qi and alleviating epigastric discomfort.

+ Experimental evidence: Phytochemical analyses have identified essential oils and flavonoids (notably hesperidin) as the principal active constituents of Chỉ thực. Experimental studies demonstrated that Chỉ thực extract modulates gastrointestinal motility in a dose-dependent manner. At low doses, it can enhance gastric

contractions, accelerate gastric emptying, and reduce gastroesophageal reflux. Conversely, at higher doses, it exerts smooth muscle relaxant effects, helping to alleviate spasm-induced abdominal pain.

– Bạch thược (Radix Paeoniae lactiflorae): According to Traditional Medicine (TM), Bạch thược has a bitter and sour taste, with a slightly cold nature, and functions to "nourish Blood, soften the Liver, and relieve pain by relaxing spasms." While Chỉ thực acts as a potent Qi-dispersing herb ("offensive" in nature), Bạch thược plays a gentle and harmonizing role. It nourishes Liver Yin and Blood, helping to alleviate Liver Qi overactivity and restore its smooth regulation, thereby reducing muscular tension and epigastric pain.

+ Experimental evidence: The principal bioactive compound of Bạch thược is paeoniflorin. Pharmacological studies have demonstrated its antispasmodic, anti-inflammatory, and hepatoprotective properties. In stress-induced gastric ulcer models, Bạch thược extract showed significant gastroprotective effects, potentially mediated through modulation of the brain–gut axis and attenuation of stress responses.

– Thảo quả (Amomum aromaticum Roxb): According to Traditional Medicine, Thảo quả possesses a pungent taste and warm nature, acting to "dry dampness, warm the Middle burner, and resolve phlegm." It helps strengthen the Spleen and Stomach, dispelling cold-damp stagnation and relieving symptoms such as bloating, indigestion, and nausea.

+ Experimental evidence: The essential oils extracted from Thảo quả have been shown to exhibit antibacterial, antifungal, and mild gastro-stimulant activities. Studies indicate that it can enhance gastric secretion, promote bile flow, and facilitate digestive processes, thereby improving overall gastrointestinal function.

5. PRINCIPLE OF HERBAL SYNERGY AND FORMULATION DESIGN IN THE "DẠ KHÔI CỐT" PRESCRIPTION

- Lá Khôi (Ardisia sylvestris) serves as the sovereign (principal) herb in the formula, exerting the primary therapeutic effect. According to Traditional Medicine (TM) theory, it functions to soothe the Liver and relieve Qi stagnation (sơ can giải uất), detoxify, reduce gastrointestinal motility, suppress gastric acid secretion, promote mucosal healing, and exert antibacterial activity, including activity against Helicobacter pylori.

- In the pattern of Vị quản thống attributed to Liver Qi stagnation invading the Stomach (Can khí phạm vị), the pathogenesis is characterized by constrained Liver Qi disrupting normal Stomach function. Therefore, Lá Khôi is employed to disperse Liver Qi stagnation, restore the harmonious relationship between the Liver and Stomach, and address the root cause of the disorder.

- Bạch thược (Radix Paeoniae lactiflorae) functions as the minister herb, assisting Lá Khôi in treating the underlying etiology. As a Yin-nourishing herb with actions of nourishing the Blood, softening the Liver, and relieving pain (dưỡng huyết, nhu can, chỉ thống), Bạch thược alleviates Liver constraint by moderating excessive Liver Qi activity and relieving tension.

- The combination of Lá Khôi and Bạch thược produces a synergistic effect: Lá Khôi disperses constrained Liver Qi, while Bạch thược softens the Liver and nourishes Yin, together facilitating smooth Liver Qi flow and relieving epigastric pain.

- Chỉ thực (Fructus Aurantii immaturus) acts to break up stagnant Qi, resolve food accumulation, and eliminate phlegm. Dạ cẩm (Oldenlandia capitellata Kuntze) clears heat and toxins, relieves pain, reduces inflammation, and promotes diuresis. Thảo quả (Amomum aromaticum Roxb) dries dampness, resolves phlegm, promotes digestion, and alleviates abdominal distension.

- These three herbs collectively serve as assistant (adjuvant) components, primarily targeting the clinical manifestations of Vị quản thống due to Qi stagnation, such as severe epigastric pain, abdominal fullness and distension, acid regurgitation, and belching.

- Ô tặc cốt (Sepia esculenta Hoyle) functions as the envoy (courier) herb, with actions of neutralizing gastric acidity, absorbing dampness, and harmonizing the formula. By moderating acidity and enhancing the cohesion and coordination among the constituent herbs, Ô tặc cốt contributes to the overall balance of the prescription.

- Together, these herbs form a comprehensive formula that treats Vị quản thống characterized by Liver Qi stagnation, addressing both the root pathogenesis and the associated symptoms.

6. RESEARCH AND DEVELOPMENT TRENDS

Research on herbal medicines for the treatment of gastric disorders is increasingly evolving toward modern scientific approaches, aiming to transform empirical traditional remedies into standardized and widely recognized therapeutic products.

From empirical experience to scientific evidence: The implementation of well-designed experimental studies, as outlined above, represents an inevitable trend in the modernization of traditional medicine. These studies provide preliminary scientific evidence that serves as a foundation for subsequent clinical trials in humans.

Elucidation of molecular mechanisms: Modern research has progressed beyond the observation of ulcer indices alone and now focuses on elucidating underlying molecular mechanisms, including:

- Evaluation of inhibitory activity against the H^+/K^+-ATPase enzyme (proton pump).

- Measurement of the expression levels of pro-inflammatory mediators (such as TNF-α and IL-6) as well as anti-inflammatory factors.

- Determination of anti-Helicobacter pylori activity and associated antimicrobial mechanisms.

- Investigation of modulatory effects on the brain–gut axis.

- Standardization and development of modern dosage forms:

- To ensure consistent quality, safety, and therapeutic efficacy, traditional herbal formulations must be standardized throughout the entire production process, from raw material sourcing in accordance with Good Agricultural and Collection Practices (GACP) to manufacturing processes compliant with Good Manufacturing Practice (GMP) standards.

- The development of modern, convenient dosage forms such as capsules, tablets, and instant granules can significantly enhance patient adherence compared with traditional decoction-based preparations. The formulation of "Dạ Khôi Cốt" as a liquid extract represents a practical example of this modernization trend.

Integration of Traditional and Modern Medicine: The most sustainable approach lies in the establishment of integrated treatment protocols. For instance, traditional herbal formulations may be used as adjunctive therapies alongside modern eradication regimens to improve eradication rates, reduce antibiotic -related adverse effects, and prevent recurrence. Additionally, traditional medicines may offer therapeutic benefits in managing non-acid reflux conditions, in which proton pump inhibitors (PPIs) demonstrate limited efficacy.

7. CONCLUSION

Peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD) represent major challenges to modern healthcare, particularly due to their potential for serious complications such as gastrointestinal bleeding, perforation, and malignancy. Vietnamese Traditional Medicine, with its rich herbal resources and holistic therapeutic philosophy, offers a valuable foundation for the development of safe and effective adjunctive treatment strategies. Evidence from preclinical studies has progressively elucidated and substantiated the pharmacological properties of many classical Vietnamese medicinal herbs. The Da Khoi Cot formula serves as a representative example of a multi-target herbal combination, with supportive therapeutic potential suggested by existing preclinical evidence. The future of gastric disease management using herbal medicine lies in the close integration of traditional medical knowledge with modern scientific research methodologies.

However, it is critically important to emphasize that herbal preparations, including Da Khoi Cot, currently serve only as adjunctive therapies and should not be used as substitutes for standard modern medical treatments. In particular, for cases of PUD and GERD with a high risk of severe complications or malignant transformation, strict adherence to evidence-based modern medical protocols is mandatory, and any complementary therapies must be considered with caution. The advancement of raw material standardization (GACP), manufacturing processes (GMP), the conduct of high-quality randomized controlled trials (RCTs), and the development of modern dosage forms will be essential to establishing herbal medicinal products as reliable options within integrative treatment regimens. Such efforts may contribute to improved disease management outcomes and enhanced quality of life for millions of patients, under close medical supervision and appropriate clinical guidance.

8. STATEMENT ON SELECTIVE EVIDENCE BIAS

This review is a narrative review focusing on a specific Traditional Medicine formulation (Da Khoi Cot). Although efforts were made to search for and present the available evidence objectively, the possibility of selection bias in the inclusion of studies cannot be completely excluded.

Conflict of interest:

The authors declare that there are no conflicts of interest related to the conduct of this research or the publication of this article.

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Author contributions:

- Kieu Hoang Yen: Major contribution to literature collection, content analysis, and drafting of the initial manuscript.

- Tran Thi Hong Ngai: Contribution to conceptualization and structuring of the manuscript, scientific content review, and final manuscript editing.

Ethical considerations:

This review is based exclusively on the analysis of previously published literature and does not involve new studies conducted on human participants or animals. Therefore, approval from an institutional ethics committee was not required.

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