Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 31s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Targeted Nano delivery Systems for Natural Antioxidants in ferulic acid Gastric Ulcer Management: Insights and Innovations

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Cite this paper as: Chetan Belwal, Dheeraj Bisht, Manoj Bharadwaj, Manoj Bisht, (2025) Targeted Nano delivery Systems for Natural Antioxidants in ferulic acid Gastric Ulcer Management: Insights and Innovations. *Journal of Neonatal Surgery*, 14 (31s), 721-731.

ABSTRACT

Gastric ulcers, a prevalent manifestation of peptic ulcer disease, are largely influenced by oxidative stress arising from reactive oxygen species (ROS). Natural antioxidants such as ferulic acid, curcumin, quercetin, and resveratrol have demonstrated promising gastroprotective effects through their antioxidant, anti-inflammatory, and cytoprotective actions. However, their clinical utility is hindered by poor solubility, instability in gastric environments, and limited bioavailability. Targeted nano delivery systems including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and dendrimers offer innovative solutions to these challenges. These nanocarriers enhance drug solubility, protect active compounds from degradation, improve mucoadhesion, enable controlled release, and facilitate site-specific delivery. This review explores the mechanisms by which nanoparticles aid in ulcer healing, evaluates various nanocarrier types employed for antioxidant delivery, and highlights case studies, particularly ferulic acid-based systems. It also addresses the translational hurdles and future directions in nano formulation-based therapy for gastric ulcer management. The integration of nanotechnology with natural antioxidant therapy holds substantial promise for advancing the efficacy and precision of ulcer treatments.

Keywords: *Gastric ulcer, oxidative stress, natural antioxidants, ferulic acid, curcumin, nanotechnology, targeted drug delivery.*

1. INTRODUCTION

1.1 Overview of Gastric Ulcers and the Role of Oxidative Stress

Gastric ulcers, a major subtype of peptic ulcer disease (PUD), are defined as open sores that develop on the gastric mucosa due to the disruption of mucosal defense mechanisms. Globally, gastric ulcers affect millions annually, with a high prevalence in developing countries due to factors such as poor sanitation and increased *Helicobacter pylori* (*H. pylori*) infections. The pathophysiology of gastric ulcers involves an imbalance between aggressive factors (like hydrochloric acid, pepsin, bile salts, and ROS) and mucosal defensive factors (such as mucus, bicarbonate, prostaglandins, and mucosal blood flow) (1).

Among these aggressive factors, oxidative stress plays a crucial role. Oxidative stress results from an imbalance between the production of ROS and the antioxidant defense system of the body. The excessive accumulation of ROS can lead to lipid peroxidation, DNA damage, protein denaturation, and cellular apoptosis, which collectively contribute to the disruption of the gastric mucosa (2). ROS, such as hydroxyl radicals, superoxide anions, and hydrogen peroxide, are produced in large amounts under pathological conditions such as NSAID use, alcohol consumption, *H. pylori* infection, and smoking (3,4). The Pathophysiological Balance Between Aggressive and Defensive Factors in Peptic Ulcer Formation with Emphasis on Oxidative Stress are mentioned below in Fig 1.

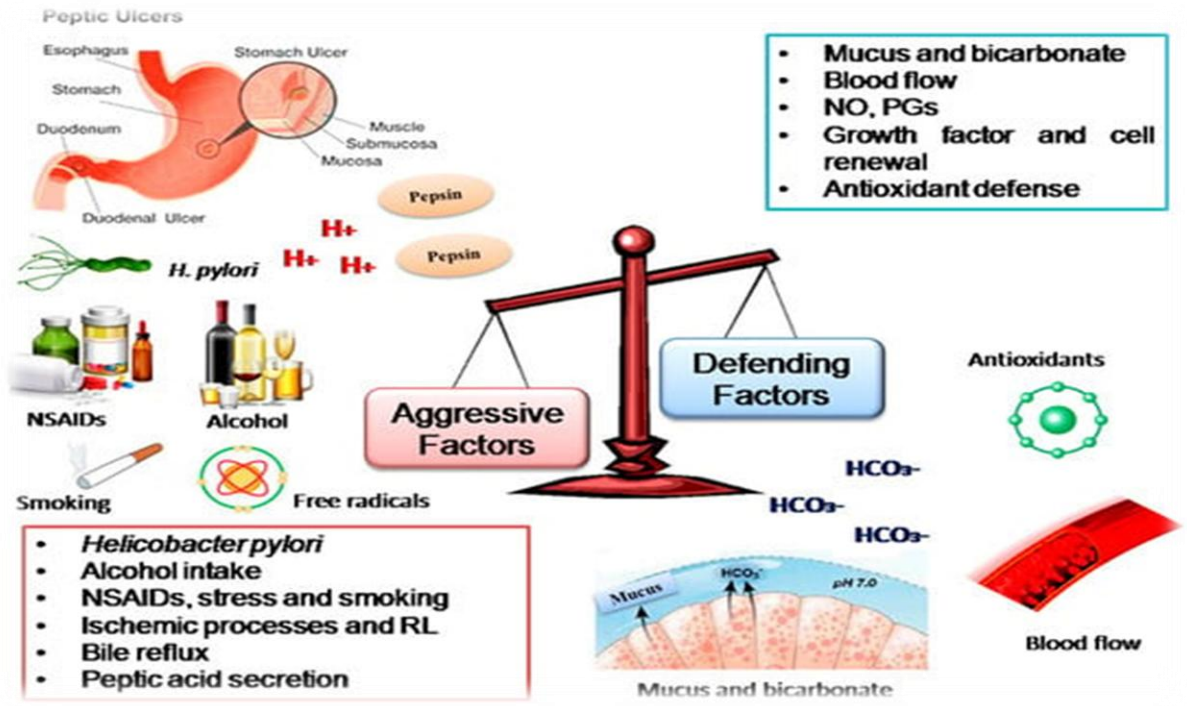


Fig 1: Pathophysiological Balance Between Aggressive and Defensive Factors in Peptic Ulcer Formation with Emphasis on Oxidative Stress.

Experimental and clinical studies have reported elevated levels of oxidative markers, such as malondialdehyde (MDA), and decreased antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) in gastric ulcer patients, further substantiating the involvement of oxidative stress in ulcerogenesis (6,62,63). These findings underline the importance of controlling oxidative stress for effective ulcer management.

1.2 Need for Effective Antioxidants

Given the pathogenic role of ROS, antioxidants have become a focal point in gastric ulcer therapy. Antioxidants neutralize ROS and prevent oxidative damage to the gastric mucosa, thereby facilitating healing and offering cytoprotection. Natural antioxidants, particularly polyphenols such as curcumin, quercetin, and ferulic acid, exhibit a broad spectrum of biological activities, including anti-inflammatory, anti-ulcer, and free radical scavenging effects (7,8).

Ferulic acid (4-hydroxy-3-methoxycinnamic acid), a phenolic compound abundantly found in plant cell walls (rice bran, oats, wheat), has demonstrated remarkable antioxidant and anti-inflammatory effects in various experimental ulcer models. It inhibits lipid peroxidation, enhances the activity of endogenous antioxidant enzymes, and downregulates pro-inflammatory cytokines like TNF-α and IL-6 (9). Despite its potential, ferulic acid exhibits poor water solubility and is rapidly metabolized and eliminated, which significantly reduces its bioavailability and therapeutic efficacy (10).

Moreover, the acidic gastric environment can degrade polyphenolic antioxidants, making their oral administration less effective. This necessitates the development of novel drug delivery strategies that can protect these molecules from degradation, improve their solubility, and ensure their controlled release at the site of action.

2. ROLE OF NANOTECHNOLOGY IN TARGETED DELIVERY

Nanotechnology has revolutionized the landscape of drug delivery by enabling the formulation of nanocarriers that protect labile drugs, enhance solubility, prolong circulation time, and provide site-specific drug delivery. Nanoparticles, typically ranging from 1–100 nm in size, offer high surface area-to-volume ratios, enabling effective interaction with biological membranes and facilitating cellular uptake (11).

In gastric ulcer therapy, nanocarrier systems like polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and dendrimers have been utilized to encapsulate antioxidants and improve their pharmacokinetic profiles (12,13). These systems enhance mucoadhesion, increase residence time in the stomach, and allow for sustained or stimuli-responsive drug release. Additionally, the use of gastroretentive formulations ensures prolonged contact between the therapeutic agent and the gastric mucosa, maximizing therapeutic effects. (62)

Advanced nanocarriers such as pH-sensitive nanoparticles and enzyme-responsive nanogels are also being explored. These "smart" systems can release their cargo in response to environmental stimuli specific to the ulcer site like pH drop or presence of inflammatory enzymes—thereby providing precise and effective therapy (16).

The biocompatibility and biodegradability of nanocarrier materials such as chitosan, alginate, PLGA, and lipid-based systems further support their application in gastric ulcer therapy. Additionally, surface modification techniques (e.g., PEGylation or ligand conjugation) can be employed to further improve stability, mucosal adhesion, or targeting ability. (63)

Nanotechnology provides a powerful tool to enhance the therapeutic potential of natural antioxidants in gastric ulcer management. By addressing issues of solubility, stability, and bioavailability, nanocarriers can optimize drug performance and patient outcomes. The development of ferulic acid-loaded nanoparticles represents a significant step forward in natural antioxidant therapy, and continued research in this area promises to revolutionize the treatment strategies for gastric ulcers.

2.1 Nanoparticles and Their role in Gastric Ulcer Treatment

Nanoparticles (NPs), ranging from 1 to 100 nm in size, have emerged as promising carriers for targeted and effective drug delivery in gastric ulcer management. Their small size, large surface area, and ability to be functionalized enable them to overcome several physiological barriers in the gastrointestinal (GI) tract. These features make NPs ideal for improving the therapeutic efficacy of conventional and natural anti-ulcer agents that suffer from low solubility, rapid metabolism, or instability in acidic environments (17,18). The are mentioned below in **Table-1.**

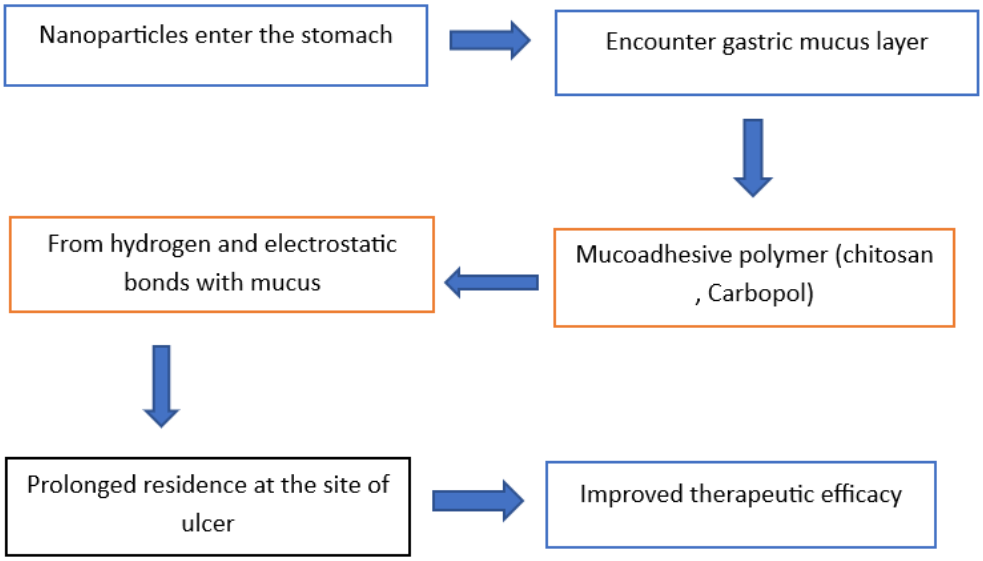
Table 1: Specific Targets of Nanoparticles in Gastric Ulcer Therapy.

Target Site	Nanoparticle Action
Ulcerated Gastric Epithelium	Enhanced mucoadhesion, increased retention, epithelial healing (19)
Gastric Mucus Layer	Prolongs residence time, protects from acid, supports mucus secretion (20)
Helicobacter pylori Infection Zones	Targeted delivery to bacterial colonization sites (via ligand conjugation) (21)
Gastric Capillary Endothelium	Anti-inflammatory actions and improvement of mucosal blood flow (22)
Gastric Immune Cells (e.g., macrophages)	Delivery of anti-inflammatory agents to suppress cytokine storms (23)

2.2 Mechanisms by Which Nanoparticles Aid in Ulcer Healing

Mucoadhesive nanoparticles improve the therapeutic efficacy of drugs used in gastric ulcer treatment. When these nanoparticles are orally administered, they enter the stomach and encounter the gastric mucus layer, which serves as a protective barrier over the stomach lining. To ensure effective delivery of the encapsulated drug, nanoparticles are often formulated using mucoadhesive polymers such as chitosan and Carbopol. These polymers enable the nanoparticles to interact with the mucus through hydrogen bonding and electrostatic interactions. Specifically, positively charged groups on the polymers bind with negatively charged sialic acid and other residues in the mucin network. This mucoadhesive property allows the nanoparticles to anchor firmly to the gastric mucosa, especially at ulcerated sites (24).

As a result of this strong adhesion, the nanoparticles achieve prolonged residence time in the stomach, allowing for sustained and localized release of the therapeutic agent. This targeted presence enhances the drug's ability to exert antioxidant, anti-inflammatory, and mucosal protective effects precisely where needed, thereby promoting ulcer healing. Ultimately, this approach leads to improved therapeutic efficacy, better patient outcomes, and potentially reduced dosing frequency. This mechanism is particularly valuable in overcoming the limitations of conventional therapies, which often suffer from rapid clearance and poor bioavailability in the harsh gastric environment (25).



The therapeutic benefits of nanoparticles in gastric ulcer management are achieved through multiple mechanisms. The Mechanisms by Which Nanoparticles Aid in Ulcer Healing are mentioned below in **Fig 2.**

- **Protection from gastric acid degradation**: NPs can encapsulate acid-labile compounds (like polyphenols) and prevent degradation in the stomach (26).
- **Improved mucoadhesion**: Certain polymers like chitosan and Carbopol confer mucoadhesive properties, prolonging gastric residence time (27).
- **Controlled and sustained release**: NPs can release drugs over time, reducing dosing frequency and maintaining therapeutic concentrations (28).
- **Targeted delivery**: Surface modification enables targeting of ulcerated tissue or *H. pylori*-infected sites (29).
- **Enhanced permeability and retention**: Small NP size facilitate better absorption and penetration into inflamed gastric tissues (30).

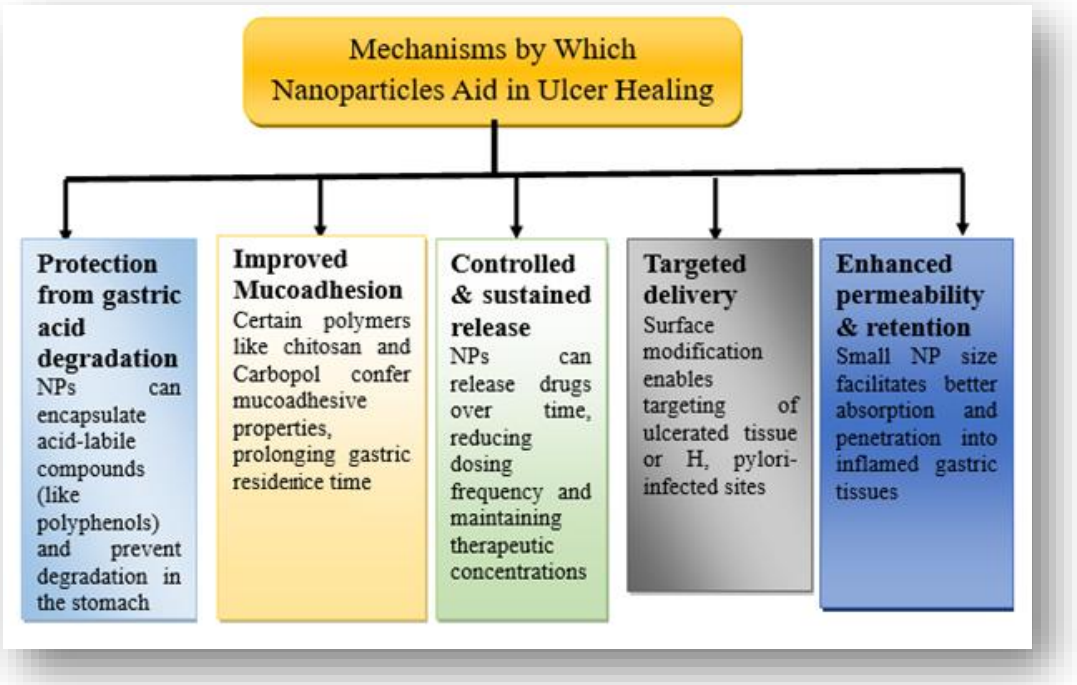


Fig.2: Mechanisms by Which Nanoparticles Aid in Ulcer Healing.

2.3 Types of Nanoparticles Used in Gastric Ulcer Treatment

2.3.1 Polymeric Nanoparticles

Polymeric NPs, particularly those made of PLGA, chitosan, and Eudragit, are widely used due to their biocompatibility and biodegradability. For instance, ferulic acid-loaded PLGA nanoparticles showed significant ulcer index reduction in ethanol-induced ulcer models by enhancing antioxidant activity and tissue protection (31). Chitosan-based NPs not only enhance mucosal adhesion but also stimulate mucus production and tissue regeneration (32). The Schematic Representation of Different Lipid-Based Nanocarriers are mentioned below in **Fig 3.**

2.3.2 Solid Lipid Nanoparticles (SLNs)

SLNs are composed of solid lipids that remain solid at both room and body temperatures. They offer excellent biocompatibility and are particularly suitable for hydrophobic drugs. A study on **quercetin-loaded SLNs** showed improved gastroprotective activity, reduced ulcer area, and suppressed oxidative stress markers in ulcer models (33).

2.3.3 Nanostructured Lipid Carriers (NLCs)

NLCs, an advancement over SLNs, incorporate both solid and liquid lipids, providing higher drug loading and stability. For example, resveratrol-loaded NLCs demonstrated enhanced antioxidant activity and mucosal protection in aspirin-induced gastric ulcers (34).

2.3.4 Metallic Nanoparticles

Metallic NPs like zinc oxide (ZnO) and silver nanoparticles (AgNP**s)** have been studied for their antimicrobial and wound-healing properties. ZnO NPs showed significant ulcer healing by reducing *H. pylori* load, stimulating angiogenesis, and modulating cytokine levels (35). However, metallic NPs require careful assessment due to their potential cytotoxicity and accumulation.

2.3.5 Liposomes

Liposomes are phospholipid bilayer vesicles that can encapsulate both hydrophilic and lipophilic drugs. They are known for biocompatibility and membrane fusion properties. Liposome-encapsulated curcumin demonstrated improved antioxidant and anti-inflammatory effects in rat ulcer models, enhancing epithelial regeneration (36).

2.3.6 Dendrimers

Dendrimers are hyperbranched, tree-like polymers capable of multivalent drug loading. Their surface functionalization allows for targeted delivery. Although less explored in ulcer therapy, dendrimers have shown promise in enhancing the solubility of poorly soluble flavonoids and polyphenols (37). The Advanced Types of Nanoparticles Used in Gastric Ulcer Treatment are mentioned below in **Table-2.**

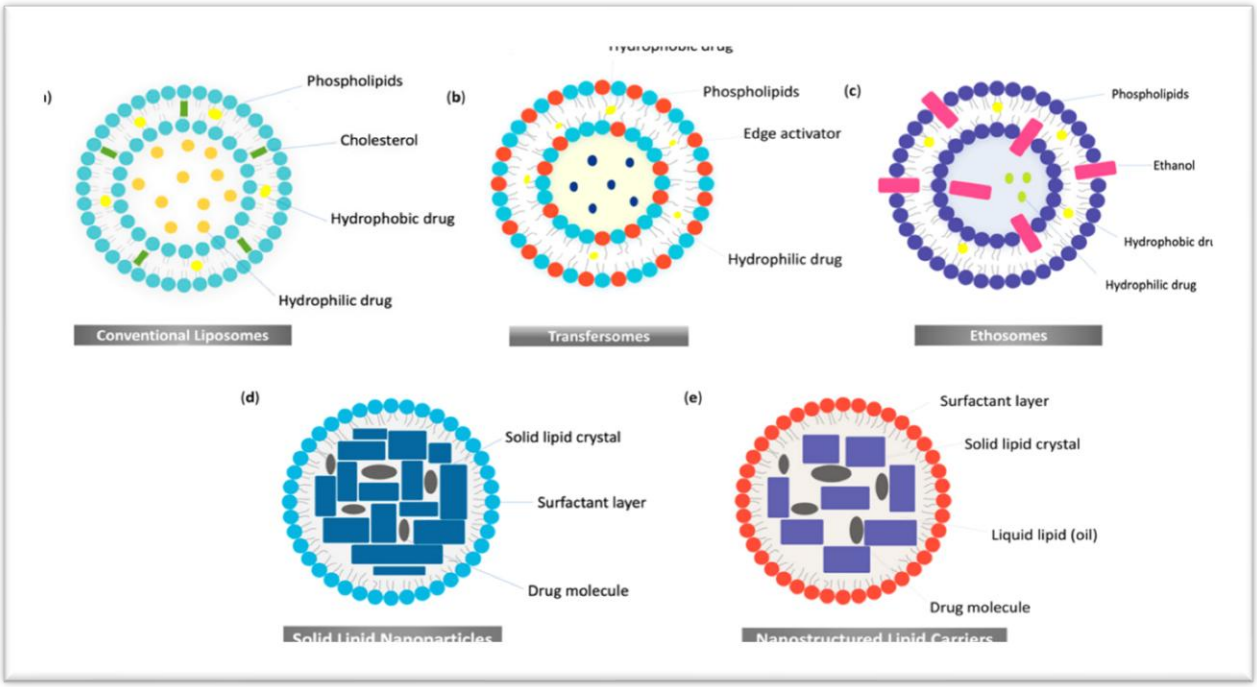


Fig 3- Schematic Representation of Different Lipid-Based Nanocarriers.

Table 2: Advanced Types of Nanoparticles Used in Gastric Ulcer Treatment.

Type	Key Features	Recent Innovations
Polymeric Nanoparticles (e.g., PLGA, Chitosan)	Biocompatible, controlled release, surface functionalizable	Development of pH-sensitive PLGA nanoparticles for targeted delivery of antibiotics to *Helicobacter pylori*, enhancing treatment efficacy and reducing side effects (39).
Solid Lipid Nanoparticles (SLNs)	Suitable for hydrophobic drugs, stable, enhances oral bioavailability	Formulation of quercetin-loaded SLNs using stearic acid and Arabic gum, improving physicochemical properties and cellular uptake for gastric ulcer therapy (40).
Nanostructured Lipid Carriers (NLCs)	Increased drug loading, stable structure	Co-delivery of curcumin and omeprazole in chitosan-coated hydrogel beads, providing synergistic effects and sustained release for enhanced gastric ulcer treatment (41).
Metallic Nanoparticles (e.g., ZnO, AgNPs)	Antibacterial, wound-healing properties	Green synthesis of ZnO nanoparticles using plant extracts like neem and lemongrass, reducing toxicity and enhancing antimicrobial activity against *H. pylori*. (42)
Liposomes	Can carry both hydrophilic/lipophilic drugs, biocompatible	Development of PEGylated liposomes for mucus-penetrating delivery of curcumin, improving bioavailability and therapeutic efficacy in gastric ulcer models. (43)
Dendrimers (e.g., PAMAM)	Highly branched, multivalent surface, targetable	Utilization of PAMAM dendrimers conjugated with polyphenols to enhance antioxidant activity and promote gastric mucosal healing (44).
Mesoporous Silica Nanoparticles (MSNs)	High surface area, tunable pore size, pH-sensitive release	Enzyme-responsive MSNs designed for targeted delivery of ferulic acid, releasing the therapeutic agent in response to gastric ulcer-specific enzymes (45).

3. POTENTIAL OF NATURAL ANTIOXIDANTS IN GASTRIC ULCER MANAGEMENT AND CHALLENGES FOR FORMULATION

Naturally occurring antioxidants offer promising therapeutic potential due to their multifaceted actions against oxidative stress and inflammation, along with generally favorable safety profiles (46,47). Some of the most widely studied natural antioxidants include ferulic acid, curcumin, quercetin, and resveratrol, each of which acts through distinct yet overlapping mechanisms:

3.1 Ferulic Acid

Ferulic acid, found in cereals, coffee beans, fruits, and vegetables, exhibits robust free radical scavenging activity. It enhances endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while concurrently inhibiting pro-inflammatory mediators like TNF-α, IL-1β, IL-6, COX-2, and inducible nitric oxide synthase (iNOS). Additionally, it demonstrates anti-apoptotic properties and may enhance mucus secretion (48). However, ferulic acid suffers from low water solubility and undergoes rapid phase II metabolism (glucuronidation and sulfation), resulting in poor systemic bioavailability after oral administration. These issues limit its therapeutic efficacy, necessitating delivery strategies such as nanoparticle encapsulation to protect it from degradation and enhance gastric retention and absorption (Zhao & Moghadasian, 2008; Shah et al., 2018.

3.2 Curcumin

Curcumin, the major curcuminoid in turmeric, is a potent antioxidant and anti-inflammatory agent. It scavenges ROS and RNS, upregulates GSH, SOD, and CAT, and suppresses inflammation via NF-κB inhibition. Moreover, curcumin exhibits anti-*H. pylori* effects, supports epithelial regeneration, and promotes mucus secretion (49).

The clinical application of curcumin is significantly delayed by its extremely poor aqueous solubility, chemical instability at physiological pH, and rapid biotransformation through glucuronidation and sulfation. These factors contribute to its negligible oral bioavailability. Moreover, curcumin undergoes extensive first-pass metabolism, and its active concentration in systemic circulation is often insufficient for therapeutic action. To overcome these limitations, various nanotechnology-based strategies such as nanoparticles, liposomes, micelles, and solid lipid nanocarriers have been developed to enhance its solubility, protect it from degradation, and promote targeted delivery at the ulcer site (50).

3.4 Quercetin

Quercetin, a flavonoid present in onions, apples, and berries, acts as an ROS scavenger and metal chelator. It modulates antioxidant enzymes and reduces inflammation by inhibiting NF-κB and MAPK pathways. Additionally, it improves microcirculation, strengthens the mucus barrier, exhibits mild anti-secretory activity, and possesses anti-*H. pylori* properties (51).

However, the clinical utility of quercetin is restricted by its extremely low aqueous solubility, poor permeability, and susceptibility to metabolic degradation. Its bioavailability is further reduced due to rapid conjugation reactions and active efflux by P-glycoprotein transporters. Quercetin's instability under physiological pH and enzymatic conditions also limits its residence time in the gastrointestinal tract. To address these challenges, formulation approaches such as polymeric nanoparticles, phospholipid complexes, and nanoemulsions have been explored to enhance its solubility, protect it from degradation, and improve mucosal targeting (52).

3.5 Resveratrol

Resveratrol, found in grapes, berries, and red wine, combines direct free radical scavenging with indirect antioxidant effects by activating the Nrf2/ARE pathway. It upregulates SOD, CAT, GPx, and GSH, inhibits NF-κB and AP-1, and protects against apoptosis through SIRT1 activation. Its Vaso protective actions improve mucosal blood flow, and it also exhibits potential anti-*H. pylori* activity (53).

Despite its therapeutic promise, resveratrol faces critical formulation issues, including poor water solubility, high photosensitivity, and rapid metabolism via glucuronidation and sulfation. Its low oral bioavailability and chemical instability significantly limit its effectiveness when administered through conventional dosage forms. Advanced drug delivery systems such as PEGylated liposomes, dendrimers, solid lipid nanoparticles, and encapsulation in biocompatible polymers have been investigated to enhance resveratrol's stability, prolong its circulation time, and increase its accumulation at the gastric site (54).

Other noteworthy natural antioxidants with gastroprotective roles include:

- **Silymarin** (from milk thistle)
- **Epigallocatechin gallate (EGCG)** (from green tea)
- **Thymoquinone** (from *Nigella sativa*, black seed oil)

These agents primarily act via antioxidant, anti-inflammatory, and, in some cases, anti-*H. pylori* pathways. The Key Natural Antioxidants for Gastric Ulcer Management - Mechanisms & Delivery Challenges are mentioned below in **Table-3.**

Table 3: Key Natural Antioxidants for Gastric Ulcer Management - Mechanisms & Delivery Challenges.

Antioxidant	Sources	Mechanisms of Action	Delivery Challenges	Reference
Ferulic Acid	Rice bran, oats, fruits	↑ SOD, CAT, GPx; ↓ TNF-α, IL-6, COX-2; ↑ mucus; antioxidant & anti-apoptotic	Low water solubility, rapid conjugation	(55)
Curcumin	Turmeric	↓ NF-κB, COX-2, iNOS; ↑ GSH, mucus; anti-H. pylori, anti-inflammatory	Poor solubility, pH instability	(56)
Quercetin	Onion, apple, berries	↑ GSH, ↓ NF-κB/MAPK; anti-apoptotic; improves blood flow, mucus	P-gp efflux, low oral bioavailability	(57)
Resveratrol	Grapes, red wine	↑ Nrf2 → SOD/CAT; ↓ NF-κB; ↑ SIRT1, NO-mediated blood flow	Photo-instability, rapid metabolism	(58)
Silymarin	Milk thistle	↓ fibrosis, ↑ GSH, membrane stabilizing	Poor solubility of silybin	(59)
EGCG	Green tea	↓ NF-κB, ↑ antioxidant enzymes, anti-H. pylori	Oxidation sensitivity, pH degradation	(60)
Thymoquinone	Black seed oil	Anti-inflammatory, anti-secretory, antioxidant	Low solubility	(61)

4. CONCUION N FUTURE SCOPE-

This comprehensive review highlights the significant strides already made in the formulation of nanotechnology-based delivery systems for natural antioxidants in gastric ulcer therapy. The successful application of polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and dendrimers has provided compelling preclinical evidence for their efficacy in enhancing the solubility, stability, and bioavailability of antioxidants such as ferulic acid, curcumin, quercetin, and resveratrol.

Building upon this strong foundation, future formulation efforts should focus on translating these promising laboratory findings into clinically viable therapies. Advanced systems such as stimuli-responsive or enzyme-triggered nanocarriers, which can respond to the unique microenvironment of gastric ulcers, represent the next frontier. Additionally, hybrid delivery platforms, scalable and eco-friendly manufacturing processes, and co-delivery strategies involving both natural and conventional therapeutic agents offer exciting opportunities for innovation.

As this body of work has demonstrated the feasibility and benefits of targeted Nano delivery systems, it serves as a launchpad for the development of novel, patient-friendly, and commercially scalable gastroretentive formulations. With continued interdisciplinary research and clinical validation, these advanced formulations hold the potential to redefine the therapeutic landscape of gastric ulcer management.

Acknowledgement

The authors express their gratitude towards Head and Faculty members of Department of Pharmacy, Devsthali Vidyapeeth College of Pharmacy, Lalpur Rudrapur , Uttarakhand, India, for providing research environment and all necessary facility for conducting research.

Author Contributions:- Conceptualization, D.B., C.B and M.B., **Validation**, C.B., D.B, M.B., **Investigation**: D.B., C.B., and M.B, R**esources**, M.B., C.B **Data Curation;** D.B, and M.B,. **Writing—original draft preparation;** C.B **Review and Editing, and Visualization;** D.B., and M.B., C.B; **Supervision;** D.B., M.B, M.B.,. All the authors read and approved the final version of the manuscript. No paper mill and artificial intelligence was used for preparation of this manuscript.

Statements and declarations:-

No potential conflict of interest was reported by the author(s) and ethics approval and consent to participate Not applicable.

Named funding statement

The author(s) did not receive any potential funding for their review project work.

Conflict of Interest

The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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