



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Gastroprotective Phytomedicine And Nanoparticle-Based Delivery Platforms for Targeted Gastric Therapy-A Comprehensive Review on Phytochemistry, Bioavailability, And Mechanistic Insights

Snehal Rahate*, Varsha Jadhav, Vilas Ghawate, Kangare Aradhana, Shejul Jayashri

Department of Pharmacognosy, Mula education society's college of pharmacy sonai

ARTICLE INFO

Published: 19 May. 2026

Keywords:

Gastroprotective
phytomedicine, nanoparticle
drug delivery, mucoadhesive
nanoparticles,
bioavailability enhancement,
gastric mucosal protection,
Helicobacter pylori

DOI:

10.5281/zenodo.20290759

ABSTRACT

Peptic ulcer disease, gastritis, and gastroesophageal reflux disease are gastric mucosal diseases that pose a significant health burden on the global population; the existing pharmacological treatment of these diseases continues to face increasing limitations due to drug adverse effects, resistance to antibiotics, and poor patient adherence. The long-standing use of medicinal plants throughout the context of traditional medicine systems includes the treatment of gastric malady, and an increasing scientific literature now confirms their presence as gastroprotective agents by means of rigorously described mechanisms. This review critically analyzes the basis of the selection and extraction methodologies of major gastroprotective herbs such as Terminalia chebula, Glycyrrhiza glabra, Curcuma longa, Zingiber officinale, Emblica officinalis, and Camellia sinensis besides the extensive phytochemical profiling of the major bioactive components of their extracts in terms of tannins, flavonoids, alkaloids, terpenoids, and polyphenols. The mechanistic attributes of gastroprotective activity are critically assessed at crossroad along diverse axes such as mucosal defense improvement, anti-secretory, antioxidant, anti-inflammatory signaling, and anti-Helicobacter pylori. The pharmacokinetic constraints of the oral bioavailability of these phytoconstituents are discussed systematically and a detailed evaluation of the nanoparticle-based delivery platforms with special reference to the mucoadhesive polymeric systems as solutions to these limitations is made. Future translational prospects, safety, and toxicity, and regulatory factors are also discussed. This review identifies the targeted gastroprotective therapy delivered with the help of nanoparticles as a promising and scientifically sound approach to delivering pharmaceuticals.

***Corresponding Author:** Snehal Rahate

Address: Department of Pharmacognosy, Mula education society's college of pharmacy sonai.

Email ✉: snehalrahate@outlook.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



INTRODUCTION

Gastrointestinal disorders, especially gastric mucosa disorders are one of the greatest and most commonly observed health burdens in the modern world [1]. Peptic ulcer disease, gastritis, gastroesophageal reflux disease (GERD) and stress-induced mucosal damage are only some of the conditions that affect hundreds of millions of people worldwide, and the World Health Organization only identifies peptic ulcer disease as a condition that affects about 10 percent of the world population at some time in their life [2]. There is a significant socioeconomic burden associated with these conditions, including direct healthcare expenses, productivity losses, and decreased life quality, and the burden is especially high in low- and middle-income countries as the access to specialized care is still very limited [3]. The pathophysiology of gastric mucosal injury is inherently based on a disruption of the balance between the aggressive factors and natural defence mechanisms of the gastric mucosa [4]. The factors that are aggressive are hypersecretion of the hydrochloric acid, pepsin activity, non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, bile salts, reactive oxygen species (ROS), and infection by *Helicobacter pylori*, the gram-negative bacterium that has now come to be recognized as a primary causative agent in most cases of peptic ulcers and as a carcinogen of the first rank contributing to the pathogenesis of gastric cancer [5]. On the other hand, defensive mechanisms include the mucus-bicarbonate secretion, synthesis of prostaglandin, mucosal blood flow, epithelial cell regeneration, and antioxidant enzyme complex. The consequence of breaking of this balance is the erodic appearance of the mucosa, ulceration, and, in the chronic condition, the transition to more serious gastrointestinal pathology [6].

Existing pharmacological interventions that are used to manage gastric diseases are proton pump inhibitors (PPIs): omeprazole and lansoprazole, histamine H₂-receptor blockers: ranitidine and famotidine, antacids, sucralfate, and antibiotics as part of the *H. pylori* elimination regimens [7]. Even though these agents have been shown to offer both symptomatic relief and ulcer healing to a significant percentage of patients, there are various adverse effects that are linked to their chronic use that restrict their clinical usage [8]. Long-term PPI therapy, e.g. has been linked with hypomagnesemia, vitamin B12 deficiency, and a heightened risk of *Clostridium difficile* infection, and possible gastric cancer after long-term use. The increase in the prevalence of multidrug-resistant *H. pylori* strains, especially to clarithromycin and metronidazole, has also made eradication difficult treatment a challenge with treatment failure rates that are becoming harder to manage using the existing clinical guidelines [9]. Such restrictions have increased concern in plant-based therapeutic agents as substituents or complements to traditional pharmacotherapy. The use of such a broad range of herbal preparations in managing gastric complaints has long been a practice in the ethnomedicinal traditions of Asia, Africa and Latin America and a current scientific literature is now finding several of these traditional applications confirmed by extensive in vitro and in vivo experimental protocols and regimens [10]. Medicinal plants provide a chemically varied source of bioactive compounds such as polyphenols, flavonoids, tannins, alkaloids, terpenoids, and saponins, which have been shown to provide multifarious gastroprotective effects such as anti-secretory, antioxidant, anti-inflammatory, antimicrobial, and cytoprotective activity. One of these, the fruit-bearing tree, *Terminalia chebula*, of the family Combretaceae, used in Ayurvedic, Unani and traditional Chinese medicine has received specific scientific interest



due to the presence of hydrolysable tannins like chebulagic acid, chebulinic acid and ellagic acid, compounds that have displayed strong gastro protective effects in a variety of mechanistic actions [11]. Though the therapeutic potential of these phytoconstituents cannot be underestimated, their clinical translation has been seriously impaired by inbuilt pharmacokinetic difficulties. Most gastroprotective phytochemicals are poorly soluble in aqueous solvents, poorly absorbed in the gastrointestinal system, prone to enzymatic and acidic pH-mediated degradation in the gastrointestinal compartment, undergo first-pass metabolism and have small biological half-lives [12]. All these lead to inadequate oral bioavailability which compromises the attainment of therapeutic concentrations that can be attained at the gastric mucosal surface when such drugs are isolated during the conventional oral route of delivery. In response to such biopharmaceutical deficits, it has become a focus of attention to develop gastroprotective therapies using phytomedicine [13]. Over the last few decades, nanoparticle-based drug delivery systems have positioned themselves as robust platforms by conquering the bioavailability constraints of chemically diverse therapeutic agents, and their use in delivering phytomedicine is growing faster than ever. Among possible nanoparticle architectures that have been investigated in this regard, polymeric nanoparticles made of biopolymers like chitosan and alginate have become of particular interest to gastric drug delivery through their mucoadhesive properties, pH-responsive drug delivery properties, biocompatibility, biodegradability, and ability to preserve encapsulated phytoconstituents when subjected to the hostile physicochemical conditions of the gastrointestinal tract [14]. Nanoparticles formed by ionic gelation of chitosan and alginate interact well with the gastric mucus layer and increased stay at the mucosal surface

facilitating prolonged, targeted biomolecule release following encapsulation of bioactives [15]. The purpose of the present review is to offer a synthetic, integrated overview of the current body of knowledge regarding gastroprotective phytomedicine, with specific reference to the selection of herbs and their extraction procedure, phytochemical profiling, mechanistic capacity of understanding gastroprotective activity, the pharmacokinetic/bioavailability issues of phytoconstituents delivery, the application of a nanoparticle platform in terms of addressing these issues, as well as safety, regulatory and future translational aspects of this fast-developing line of usage.

2. Gastroprotective Herbs Selection Criteria and Extraction Methods

A combination of ethnopharmacological knowledge, preclinical experimental data, abundance of phytochemical constituents, safety data, and access to standardizable active constituents inform the selection of medicinal herbs to be used as gastroprotectives [16]. Surveys of traditional medicine systems (such as Ayurveda, Traditional Chinese Medicine (TCM), Unani and other African and Latin American herbal traditions) have repeatedly described a list of central plants whose application in the treatment of gastric complaints over long history provides a starting point of a long history of scientific inquiry on the topic. Scientific selection criteria also demand that the candidate herbs should possess demonstrated anti-ulcer, anti-inflammatory, anti-secretory or anti-oxidant activity in verified experimental studies in ethanol-induced, indomethacin-induced or pylorus-ligation ulcer models in rodents, and in other independent research populations [17]. One of the best-researched and scientifically proven gastroprotective herbs in the Ayurvedic



pharmacopoeia is *Terminalia chebula* Retz., widely referred to as haritaki in the Sanskrit and black myrobalan in English. Hydrolysable tannins, gallic acid, ellagic acid, chebulagic acid, and chebulinic acid are bioactives present in the dried fruits of this tree and that have proven to have cytoprotective, anti-*H. pylori*, antioxidant, and healing properties of the mucosal across various experimental platforms [18]. *Glycyrrhiza glabra* (licorice) is an extract of the root that contains glycyrrhizin and its aglycone, glycyrrhetic acid and flavonoids, including liquiritin and isoliquiritin, and has been used in the treatment of peptic ulcer disease over several decades, and its carbenoxolone derivative is one of the bioactives of the first plant origin to receive regulatory approval in this category of therapies. Aloe vera gel, a source of acemannan, aloesin, and other anthraquinones, has been shown to have strong gastroprotective effects by stimulating mucus secretion and inhibiting gastric acid secretion, whereas *Zingiber officinale* (ginger), and its major bioactives, 6-gingerol and 6-shogaol, to possess strong anti-*H. pylori* and anti-inflammatory gastroprotective activity [19]. *Curcuma longa*, containing curcumin, is perhaps the best-investigated phytochemical in relation to gastrointestinal inflammation and its effects in inhibiting NF-kb signaling, cyclooxygenase-2 (COX-2) expression, and *H. pylori* adhesion to gastric epithelial cells are thoroughly reported in literature [20]. Another Ayurvedic herb used as a base ingredient, *Emblica officinalis* (amla) contains a powerful combination of vitamin C, emblicanin A and B, punigluconin and pedunculagin, which correspondently possess powerful antioxidant, anti-ulcer and mucoprotective properties [21]. *Camellia sinensis* (green tea) provides epigallocatechin gallate (EGCG) and similar catechins which avoid *H. pylori* virulence factor and decrease gastric mucosal oxidative stress. The contribution of each

of these herbs to a specific phytochemical profile and mechanism renders them interesting on their own, whether as a constituent or combination entities of phytomedicine strategy [22]. The extraction methodology used significantly affects extract yield, composition, biological properties and stability of the amplified phytochemical extract, and the selection of extraction methodology must hence be well-coordinated with the physicochemical characteristics of the bioactives of interest and the final intended use of the extract [23]. Maceration, Soxhlet extraction, and hydrodistillation are traditional extraction techniques that are still widely used in research and industry due to the simplicity, low-cost equipment, and well-developed methodology. The technique of maceration, which is the wetting of plant material with a solvent (e.g. water, ethanol, methanol or combinations thereof) over prolonged periods is especially suited to thermolabile bioactives but is characterized by long extraction times and partial degradation of the plant matrix. Soxhlet extraction that uses solvent recycle and high temperatures has higher extraction yields but is likely to cause thermal degradation in thermosensitive compounds like some flavonoids and volatile terpenoids [24]. High-performance extraction methods have become increasingly popular in studies of phytochemistry due to their efficiency, selectivity, speed, and solvent use. The Ultrasound-assisted extraction (UAE) uses the principle of acoustic cavitation to break the plant cell walls and increase mass transfer of bioactives to the solvent phase, yielding the same or better products compared to more traditional methods, in a fraction of the time and lower temperatures [25]. Microwave-assisted extraction (MAE) employs the dielectric heating to provide rapid and selective heating of the plant matrix and the solvent and leads to faster extraction kinetics and lower solvent volumes [26]. CO₂-based SFE provides outstanding selectivity with lipophilic bioactives



and does not leave any traces of solvents in the extract, so it is of special interest in pharmaceutical contexts where extract purity and extract safety are critical factors [27]. In enzyme-assisted extraction (EAE), cell wall-degrading enzymes like cellulases and pectinases are used to enhance the extraction of intracellular bioactives to obtain extracts with a higher bioactivity profile. Time and again, hydroalcoholic extractions of the fruits of

Terminalia chebula prepared using ethanol concentrations of 50-70% have been shown to yield optimally bioactive hydrolysable tannins without affecting their content and bio-integrity; therefore, the standardization of such extracts on the basis of chebulagic acid or gallic acid content by HPLC-based assays is now regarded as a matter of due procedure in the context of both research and product development [28].

Table 1: Comparative Overview of Key Gastroprotective Herbs [29–36]

Herb (Botanical Name)	Plant Part Used	Major Phytoconstituents	Extraction Method	Reported Gastroprotective Activity
<i>Terminalia chebula</i>	Fruit	Chebulagic acid, chebulinic acid, ellagic acid, gallic acid	Hydroalcoholic (50–70% EtOH), Soxhlet	Anti-ulcer, anti- <i>H. pylori</i> , antioxidant, mucosal healing
<i>Glycyrrhiza glabra</i>	Root	Glycyrrhizin, glycyrrhetic acid, liquiritin, isoliquiritin	Aqueous, hydroalcoholic	Anti-secretory, cytoprotective, anti-inflammatory
<i>Curcuma longa</i>	Rhizome	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Ethanol, supercritical CO ₂	NF-κB inhibition, COX-2 suppression, anti- <i>H. pylori</i>
<i>Zingiber officinale</i>	Rhizome	6-Gingerol, 6-shogaol, zingerone	Hydroalcoholic, UAE	Anti- <i>H. pylori</i> , anti-inflammatory, mucoprotective
<i>Aloe vera</i>	Leaf gel	Acemannan, aloesin, anthraquinones	Aqueous, cold-press	Mucus stimulation, anti-secretory, wound healing
<i>Emblica officinalis</i>	Fruit	Emblicanin A&B, punigluconin, gallic acid, vitamin C	Aqueous, hydroalcoholic	Antioxidant, anti-ulcer, mucoprotective
<i>Camellia sinensis</i>	Leaf	EGCG, epicatechin, catechin, theaflavins	Hot water, ethanol	Anti- <i>H. pylori</i> , antioxidant, mucosal protection
<i>Withania somnifera</i>	Root	Withanolide A, withaferin A, sitoindosides VII–X	Hydroalcoholic (70% EtOH), methanol	Mucosal cytoprotection, anti-inflammatory, stress-induced ulcer prevention
<i>Azadirachta indica</i>	Leaf, bark	Nimbolide, azadirachtin, quercetin, β-sitosterol	Hydroalcoholic, aqueous, ethanol	Anti- <i>H. pylori</i> , anti-ulcer, anti-secretory, antioxidant
<i>Tinospora cordifolia</i>	Stem	Berberine, tinosporin, palmatine, giloin	Aqueous, hydroalcoholic	Anti-ulcer, cytoprotective, immunomodulatory, antioxidant
<i>Coptis chinensis</i>	Rhizome	Berberine, coptisine, palmatine, jatrorrhizine	Aqueous, ethanol	Anti- <i>H. pylori</i> (VacA/CagA inhibition), NF-κB suppression, mucosal repair
<i>Astragalus membranaceus</i>	Root	Astragalosides, calycosin, formononetin, polysaccharides	Aqueous, hydroalcoholic	Mucosal healing, anti-inflammatory, gastroprotection via prostaglandin upregulation

<i>Panax ginseng</i>	Root	Ginsenosides Rb1, Rg1, Rg3, panaxydol	Aqueous, ethanol	Anti-ulcer, anti- <i>H. pylori</i> , mucosal regeneration, antioxidant
<i>Maytenus ilicifolia</i>	Leaf, bark	Friedelan-3 β -ol, lupeol, tannins, flavonoids	Hydroalcoholic, aqueous	Anti-ulcer, anti-secretory, mucus stimulation, cytoprotective
<i>Croton cajucara</i>	Bark	trans-Dehydrocrotonin, alkaloids, terpenes	Ethanol, hydroalcoholic	Anti-secretory, anti-ulcer, prostaglandin-mediated cytoprotection
<i>Allium sativum</i>	Bulb	Allicin, ajoene, quercetin, S-allyl cysteine	Aqueous, hydroalcoholic, cold-press	Anti- <i>H. pylori</i> , antioxidant, mucosal protection, anti-inflammatory
<i>Nigella sativa</i>	Seed	Thymoquinone, thymohydroquinone, carvacrol, nigellidine	Cold-press oil, methanol, ethanol	Anti-ulcer, anti- <i>H. pylori</i> , antioxidant, COX inhibition, mucoprotective

3. Phytochemical Profiling of Gastroprotective Herbs

The analytical backbone of any organized attempt to comprehend, standardize and clinicalize the gastroprotective action of herbs is phytochemical profiling. The detailed description of the phytochemical compounds of a particular plant extract, including its identity, concentration, structural properties, and interactions, forms the scientific backbone on which mechanistic hypotheses can be developed, bioactivity-directed fractionation can be performed, and extract standardization can be evaluated in terms of quality [37]. The major groups of phytochemicals involved in gastroprotective activity are chemically diverse, with each group playing a different contribution to the protective mechanisms of action, which are altogether involved to explain the multiprotective actions that are seen in clinical and experimental practice. Tannins form the majority phytochemical in *Terminalia chebula* and other key gastroprotective plants, and in mucosal protection, their role is multifaceted on a mechanistic basis [38]. Hydrolysable tannins Gallic acid ellagic acid Gallotannin and ellagitannin One of the hydrolysable tannins is a gallic acid or ellagic acid

ester around a polyol core, which in this case is a glucose. Benzopyranone-type ellagitannins, chebulagic acid and chebulinic acid have also been shown to inhibit activity of *H. pylori* urease, suppress gastric acid secretion and inhibit apoptosis in gastric epithelial cells caused by oxidative stress. Grape and Camellia seed extracts and other berry extracts contain condensed tannins (proanthocyanidins) which can generate protective protein tannin complexes on the mucosal wall, making it less permeable to acid and pepsin. This is exactly the same ability to precipitate the proteins of the mucosal surface and establish a mechanical barrier against the irritant agents, which is indicated by the astringent quality of tannins, long known empirically in traditional medicine [39]. Another significant group of gastroprotective phytochemicals are the flavonoids which include quercetin, rutin, kaempferol, luteolin and catechins and the catechins are the most widely researched in a gastric mucosal protective role. Quercetin which is found in large amounts in onion, apple and several pharmaceutical herbs has also shown anti-ulcer activity in a number of experimental models through various mechanisms such as inhibition of secretion of acid in the stomach, stimulation of

mucus production, increase in production of prostaglandins E2 and direct antioxidant action [40]. The flavanols of green tea especially EGCG, have been reported to prevent *H. pylori* adhesion against gastric epithelial cells not only by preventing expression of bacterial adhesins on the surface, but also by preventing the expression of pro-inflammatory cytokines, such as interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-Young, 2020) [41]. Berberine, found in Berberis species and *Coptis chinensis*, and piperine found in *Piper nigrum* are examples of alkaloids which possess pronounced anti-*H. pylori* effects and anti-inflammatory effects applicable to gastroprotection. Specifically, Berberine has been demonstrated to suppress *H. pylori* vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA) virulence factors, inflammatory responses in the gastric mucosa by inhibiting the NF-KB pathway, and has been shown to induce the growth of gastric epithelial cells. Terpenoids and saponins, including the compounds like ursolic acid, oleanolic acid, and glycyrrhizin, are gastroprotective due to anti-inflammatory effects, anti-secretory effects, and cytoprotective effects, and the anti-secretory effects of glycyrrhizin inhibiting 11-beta-hydroxysteroid dehydrogenase and thus controlling prostaglandin metabolism are best studied [42]. Phytochemical profiling today is based on a complex repertoire of hyphenated and non-hyphenated analytical methods which allow simultaneous detection and measurement of complex multi-component mixtures. The best method of quantitative profiling of phenolic compounds, tannins, and flavonoids in plant extracts is high-performance liquid chromatography (HPLC) with photodiode array (PDA) or mass spectrometric (MS) detection. High-resolution liquid chromatography-mass spectrometry (HRLCMS) based on the quadrupole time-of-flight (QTOFT) or the Orbitrap mass analyzers allows the annotation of metabolites at

the level of molecular formula with mass accuracy of less than 5 ppm, thereby making it possible to dereplicate known compounds and enable the tentative identification of novel metabolites in complex matrix samples of herbals [43]. One- and two-dimensional nuclear magnetic resonance spectroscopy (NMR) can offer conclusive structural explanation of isolated pure compounds and has been utilized in metabolomics based methods of phytochemical profiling so that primary and secondary metabolites can be characterized simultaneously without initial chromatographic separation [44]. The structure-activity relationship (SAR) analysis has increasingly shed light on the structural characteristics of phytochemicals that are of utmost importance in determining their gastroprotective activity. In the case of polyphenolic compounds, it has been found that the antioxidant activity, affinity to proteins, and anti-*H. pylori* effect depend on the number and the position of hydroxyl groups within an aromatic ring system, the extent of polymerization in the case of condensed tannins, and the nature of the ester linkages in hydrolysable tannins. Concepts of SAR are also starting to influence computationally-guided strategies on phytochemical screening, where molecular docking with *H. pylori* urease, gastric H⁺/K⁺-ATPase, and other inflammatory mediators, including COX-2, are being used to rank the resources used in experimental validation [45].

4. Mechanisms of Gastroprotective Activity

Various levels of action of gastroprotective effects of phytoconstituents include direct physicochemical interactions between phytoconstituents with the gastric mucosal lining multiple intricate intracellular signaling cascades via expression of genes that regulate mucosal integrity, inflammation, and cell survival. The



study of these mechanisms does not only confirm the therapeutic rationale of phytomedicine-based gastroprotective modalities but also provides a mentality of how combination formulations may be recruited to exploit more than a single pathogenic pathway at a time [46]. The gastric mucosa is safeguarded against autodigestion by a complex multi-layered defensive system, the first line of which is the mucus-bicarbonate barrier, a viscoelastic layer of gels about 500 micrometers thick, which is secreted by surface mucous cells, and contains mucin glycoproteins, immunoglobulin A, trefoil factor peptides, and bicarbonate ions neutralizing acid diffusing through the unstirred layer. There is a variety of gastroprotective phytoconstituents that are known to stimulate mucus directly and increase the biochemical composition and gel making properties of gastric mucus. Flavonoids like quercetin and rutin have been found to elevate mucus secretion in experimental models whereas tannins of *Terminalia chebula* have been reported to elevate the expression of MUC5AC, which is the major mucin glycoprotein of the gastric mucus surface, in gastric epithelial cell lines in contact with *H. pylori* lipopolysaccharide. Preparations of licorice, and especially those derived by removing gluconeogenic sugars (degree of glycyrrhization) to create compounds called deglycyrrhized glycyrrhized licorice (DGL) preparations, have been found to promote the secretion of mucus independently of the effects of prostaglandins, rendering them safe even in those patients whose mucosal inflammation is partially induced by NSAID-generated prostaglandin suppression [47]. Another significant axis of mechanistic localization of phytoconstituents is the role of anti-secretory action, i.e., the inhibition of secretions of gastric acid. The main object of the acid suppressive action of modern pharmacotherapy is the gastric proton pump ($H^+ / K^+ -ATPase$) which is on the lumen of parietal cells secretory

canaliculi and a number of phytoconstituents have been shown to inhibit this enzyme with varying levels of success and selectivity. Enzymatic assay has demonstrated $H^+ / K^+ -ATPase$ inhibitory properties with flavonoids, such as quercetin, naringenin and hesperidin, and molecular docking analysis has indicated that their catechol and resorcinol cores may bind the catalytic site of the enzyme in a similar way PPIs may. Green tea polyphenols and *Terminalia chebula* have also been demonstrated to inhibit histamine-induced acid secretion in isolated gastric glands, which implicate effects either directly at the histamine H_2 receptor or at the histamine H_2 receptor-induced effector molecules [48]. The antiinflammatory component of phytoconstituent-mediated gastroprotection is specifically well defined and mechanistically endowed, owing to the pivotal position of gastric ulcer disease pathogenesis in terms of mucosal inflammation, particularly in regard to *H. pylori* infection and nonsteroidal anti-inflammatory drugs. NF- κ B takes a central role in the inflammatory process of gastric mucosal injury, which is triggered by *H. pylori* virulence factor such as CagA, VacA, and lipopolysaccharide triggers a downstream program of pro-inflammatory gene expression including COX-2, inducible nitric oxide synthase (iNOS), IL-1 β , IL-6, IL-8, and TNF- α . Curcumin is recognized as one of the strongest phytochemicals that activate NF- κ B, so far, which inhibits the I κ B kinase activity and thus inhibits the translocation of nuclear p65 NF- κ B subunits in the gastric epithelial cells. Ellagic acid of *Terminalia chebula* has also been found to suppress NF- κ B-mediated inflammatory signaling in gastric mucosal tissue, and EGCG of green tea inhibits the AP-1 transcription factor pathway which has collaborated with NF- κ B in the regulation of COX-2 in cells infected with *H. pylori* [49].

The benefit of reactive oxygen species in gastric mucosal injury has been dealt with through the antioxidant effect of gastroprotective phytoconstituents. Superoxide anion, hydrogen peroxide, hydroxyl radical and lipid peroxidation products are the direct causes of the damage of gastric epithelial cell membranes, DNA, and proteins as well as the depletion of endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase, and glutathione peroxidase by oxidative stress produced by *H. pylori* infection, NSAID use, intake of ethanol, and ischemia-reperfusion. Among the best-characterized natural antioxidants are polyphenols of *Terminalia chebula*, *Embllica officinalis* and *Camellia sinensis* whose antioxidant power is defined by the capacity of their multiple phenolic hydroxyl groups to donate hydrogen atoms to free radical and chelate transition metal ions catalyzing the Fenton reaction. Experimental ulcer models have found that treatment with *T. chebula* extract has been linked to remarkable recovery of gastric tissue SOD and catalase activity, malondialdehyde as a lipid peroxidation marker, and decreased reduced glutathione content [50]. Anti-*H. pylori* effects constitute a mechanistically discrete but clinically very urgent aspect in the scope of phytoconstituent gastroprotection because *H. pylori* infection afflicts half the world population and is the major etiological agent of peptic ulcer disease, chronic atrophic gastritis and gastric cancer. Several phytoconstituents have shown direct bactericidal or bacteriostatic action on *H. pylori* via a variety of different mechanisms such

as urease inhibition (the enzyme that forms ammonia out of urea and is necessary to help the bacterium survive in the acidic gastrointestinal milieu), destabilization of bacterial cell wall integrity, inhibitor of bacterial adhesion to gastric epithelial cells, and interference with *H. pylori* virulence factor expression. *T. chebula* provides chebulagic acid and chebulinic acid with potent urease inhibitory activity at introduced IC₅₀ values in the low micromolar range, equivalent to the reference urease inhibitor acetohydroxamic acid, as well as direct bactericidal activity against both clarithromycin sensitive and clarithromycin resistant *H. pylori* clinical isolates [51]. The gastroprotective effects of the gastroprotective phytoconstituents include stimulation of endogenous production of prostaglands, stimulation of heat shock proteins, stimulation of anti-apoptotic signaling and migration and proliferation of the gastric epithelial cells in wound healing. Gastric mucosal cells constitutively produce prostaglandins E₂ and I₂ through the COX-1 pathway and play an essential role in mucosal protection by cytoprotecting the mucous membrane, causing it to secrete mucus and bicarbonate, sustaining blood flow to the mucosa, and inhibiting mucosal secretion of parietal cell acid. Prostaglandin production in gastric tissue has been suggested to be promoted by several flavonoids and terpenoids, which have a mechanistic explanation of their cytoprotective effect independent and additive to direct antioxidant and anti-inflammatory activity [51].

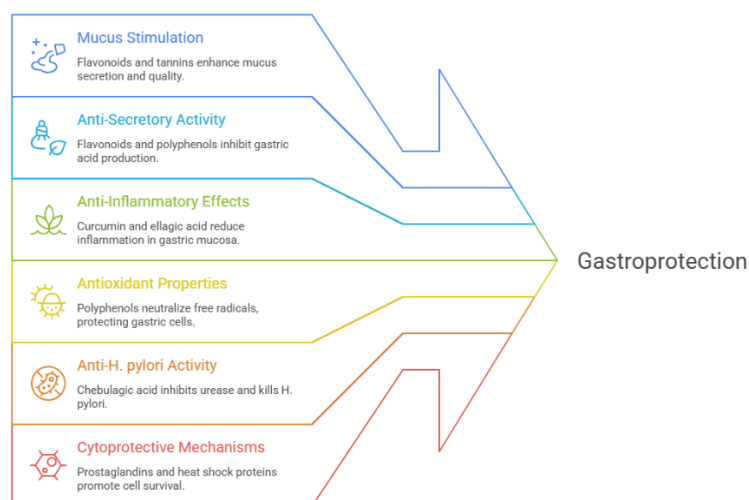


Figure 1: Phytoconstituent Pathways to Gastric Health

5. Bioavailability and Pharmacokinetic Challenges of Phytoconstituents

The therapeutic potential of gastroprotective phytoconstituents is often hampered in clinical practice by the uphill forces of pharmacokinetics that curtail their oral bioavailability, which is the factor that ultimately predicts the systemic and local concentrations that can be reached at the site of action after administration. The rational design of delivery systems that can circumvent them and convert in vitro bioactivity into clinically significant therapeutic effects is therefore a requirement based on the comprehension of the microspecific pharmacokinetic constraints of key phytochemical classes [52]. Polyphenols (which comprise most of the most significant gastroprotective phytoconstituents such as tannins, flavonoids, phenolic acids, and stilbenes) are reported to be a group, whose oral bioavailability is limited and highly variable due to the interplay of multiple pharmacostasis barriers. Most polyphenols are insoluble in water, especially the aglycone flavonoid aglycones and large molecular weight tannins, which restricts the rate of dissolution in the gastrointestinal fluids and, therefore, the impulse behind intestinal absorption. In cases where aqueous solubility is satisfactory,

intestinal permeability has frequently been an inhibitory factor, where the hydrophilic nature and high molecular weight of most polyphenolic compounds prevent passive transmembrane diffusion across the enterocyte surface, and where active transport systems of these compounds are limited in capacity and prone to saturation at high doses [53]. There are other physicochemical and enzymatic challenges on the stability and absorption of phytoconstituents in the gastrointestinal environment. Gastric acid, although possibly helpful in the dissolution of some basic phytochemicals, facilitates the hydrolysis of ester-linked compounds such as hydrolysable tannin chebulagic acid, which releases Gallic acid moieties and ellagic acid moieties which might possess alternative bioavailability characteristics to the parent compound. The chemical structure of phytoconstituents is also altered further by the alkaline pH of the small intestine, the presence of pancreatic enzymes and intestinal brush border enzymes that hydrolyze flavonoid glycosides to aglycones prior to absorption. Colonic microbiota imposes extensive transformative action on unabsorbed polyphenols that reach large intestine transformed on complex tannins and flavonoids to simple phenolic acids and products of ring fission

whose bioactivity profile and bioavailability characteristics are markedly different than that of the parent phytochemicals [54]. One important factor in systemic bioavailability of most phytoconstituents is first-pass metabolism in the intestinal epithelium and liver. The oxidative metabolism of flavonoids and phenolic acids by cytochrome P450 enzymes especially CYP1A1, CYP1A2 and CYP3A4 in the intestinal enterocyte and hepatocyte produces metabolites which may have a significantly lower pharmacological activity than the parent molecule. Phase II conjugation reactions such as glucuronidation by UDP-glucuronosyltransferases (UGTs), sulfation by sulfotransferases (SULTs) and methylation by catechol-O-methyltransferase (COMT) also alter circulating polyphenols to generate conjugating metabolites with reduced membrane permeability and binding specificity of target. P-glycoprotein (P-gp) which is highly expressed on the apical cell surface of intestine is actively pumped by efflux wherein many polyphenols are pumped back into the intestinal lumen following absorption and this reduces net absorption [55]. The pharmacokinetic issues are especially reported to exist in the case of the key bioactives of *Terminalia chebula*. One of the major bioactive degradation products of chebulagic and chebulinic acid is ellagic acid, which attains low plasma concentrations after oral delivery of *T. chebula* extract in rodent systems, and it has been reported that even the absolute oral bioavailability of ellagic acid of less than 1%. This low systemic exposure can be explained by the low aqueous Solubility of ellagic acid (about 2 µg/mL in water, at physiological pH), the tendency of ellagic acid to crystallize quickly in the gastrointestinal tract, and the extensive metabolism and conjugation of the acid after absorption [56]. The canonical example perhaps of a phytoconstituent with excellent in vitro bioactivity and pathetically poor oral bioavailability, with absolute bioavailability

values less than 1% in humans treated with conventional curcumin preparations, is curcumin, whose gastroprotective and anti-inflammatory effects are well documented. Most polyphenolic phytoconstituents have a relatively low biological half-life after absorption, which is generally approximately 1-4 hours in the case of flavonoid aglycones and their major metabolites, and therefore it often requires constant dosing to retain therapeutic levels, and clinical viability of traditional oral preparations may be limited by this. In the case of gastroprotective applications in particular, the problem is further complicated by the requirement to attain therapeutic concentrations of phytoconstituents at the gastric mucosal surface, a site that is notoriously inaccessible to the activities of standard oral dosage forms due to the normally brief gastric residence time and the rapid passage of liquid and small solid dosage forms through the stomach [57]. All these factors serve to highlight the need to implement superior delivery mechanisms that could help in increasing the gastrointestinal residence time, avoiding the destruction of phytoconstituents by the gastric environment, and achieving active and controlled release of bioactives on the mucosal environment [58].

6. Nanoparticle-Based Delivery Platforms for Gastroprotective Phytomedicine

The pharmacokinetic constraints mentioned above have prompted intensive research activities on the design of nanoparticle-based delivery systems with the aim of improving the bio-pharmacological efficacies of gastroprotective phytoconstituents [59]. Nanoparticles, described in general as colloidal systems with at least one dimension between 1-1000 nanometers, possess a set of physicochemical and biological characteristics that are especially beneficial to gastric drug delivery, such as high surface areas-



volume ratios to enhance dissolution and absorption, compatibility with functionalization of surfaces to generate mucoadhesive or targeting properties, shielding of encapsulated drug to the severe gastric environment, and the ability to form a set of controlled or stimuli responsive shapes of drug release that correlates with the biological needs. Polymeric nanoparticles of different types have received a long history of research-based interest in phytomedicine delivery due to their versatility, not particularly challenging synthesis, tunable surface chemistry, and compatibility with a variety of hydrophilic and lipophilic phytoconstituents. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have widely been utilized in the delivery of curcumin, quercetin and berberine, with significant enhancement of oral bioavailability compared to its free form achieved by combination of technology of resattement in dissolution, protection against metabolism-induced degradation, and transectose across intestinal epithelial cells by endocytosis. Nonetheless, PLGA nanoparticles do not exhibit inherent mucoadhesive property, and must be surface functionalized with mucoadhesive polymers to attain significant interactions with the gastric or intestinal mucus layer [60]. Chitosan, a cationic linear polysaccharide, resulting as a partial deacetylation product of chitin, found in crustacean shells and fungal cell walls, has various attributes that make it highly suitable in the preparation of mucoadhesive nanoparticles to deliver drugs to the gastrointestinal tract. The electrostatic interactions enhanced between its negative sialic acid residues and chitosan-based nanoparticles driven by its positive surface charge at acidic and neutral pH, which is caused by the protonation of its amino groups (pKa approximately 6.5), give this material the capacity to interact strongly with the negatively charged gastric mucin glycoproteins [61]. Chitosan, the other polysaccharide, also possesses passive

antimicrobial effect against *H. pylori* via cell membrane integrity disruption, and contributes directly to therapy in addition to its carrier action. Biocompatibility, biodegradability, low toxicity and acceptance as a food additive and a pharmaceutical excipient in various regulatory authorities broadens its appeal as a nanoparticle matrix material. An anionic polysaccharide with complementary properties to chitosan, such as alginate, a brown seaweed-derived polysaccharide consisting of mannuronic acid and guluronic acid residues can be used with chitosan in complementary nanoparticle systems. The pH-dependent conformational changes of alginate result in obtaining rigid gels at low pH as a result of protonation of carboxylates and in expanding to release the cargo stored within it as the pH rises toward the neutral values found in the small intestine. Such pH-responsive characteristics render alginate-based systems highly attractive to gastric-targeted delivery, in which the drug retention ability during the low-pH gastric environment with subsequent targeted release in the rising small intestine may be a required feature. The chitosan and alginate nanoparticle architecture of a core-shell or polyelectrolyte complex is based on the synergistic properties of the two polymers, where the cationic chitosan polymer serves as mucoadhesive and the anionic alginate polymer as a structural and pH-responsive polymer with a secondary advantage as a secondary barrier to premature drug release [62]. Chitosan-alginate nanoparticles are most frequently prepared by ionic gelation, which is a gentle aqueous procedure that does not require the use of organic solvents and high temperatures that may damage the integrity of thermolabile phytoconstituents. Within the ionic gelation procedure, under magnetic stirring, the solution of chitosan is added in drops to an alginate solution that includes the dissolved or dispersed phytochemical extract, leading to the self-



assembly of a polyelectrolyte complex nanoparticles due to electrostatic interaction between the oppositely charged polymers. Parameters such as the molecular weight and degree of deacetylation of chitosan, mannuronic to guluronic acid ratio of the alginate, polymers concentration ratio, extract-polymer ratio, pH of the medium used to prepare the nanoparticles, and stirring rate and time are critically important in determining the size, zeta potential, encapsulation efficiency, and profile of drug release of the final nanoparticles. These parameters can be optimized by experimental design methods including Box-Behnken design or central composite design to identify the conditions of the formulation that produce maximum encapsulation efficiency and place the spectroscopic size of the particle within the optimal mucoadhesive range of 200-600 nanometres [63]. Particularly driven by the pharmacokinetic profile of its major bioactives presented in the previous section, the pharmacokinetics of the encapsulation of the hydroalcoholic extract of *Terminalia chebula* in chitosan-alginate nanoparticles are best explained by an inability to encapsulate the hydroalcoholic extract of *Terminalia chebula* in chitosan-alginate nanoparticles. The nanoparticle matrix shields the chebulagic acid, chebulinic acid, and ellagic acid against the acidic hydrolysis and enzyme postulations they would experience in the gastric lumen, and the mucoadhesive chitosan surface enhances close contact of the nanoparticle with the gastric mucosa and extends local drug concentrations at the mucosal surface. In vitro

drug release studies of such systems generally have a biphasic release profile, in which surface-associated or loosely encapsulated drug initially released rapidly followed by near-constants release of the encapsulated fraction over the span of 8-24 hours, which is desirable both to a rapid attainment of local therapeutic levels and to long-lasting mucosal exposure. In addition to nanoparticle polymer-based nanoparticles, other classes of nanoparticles have been investigated as gastroprotective delivery of phytomedicine with unique advantages and disadvantages [64]. Compared to polymeric systems, lipid-based nanocarriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes have better encapsulation capacity of lipophilic phytoconstituents e.g. curcumin and β -caryophyllene and its lipid constituent can be optimized to take advantage of the lymphatic absorption route as a method of avoiding hepatic first-pass metabolism. Preclinical studies of self-nanoemulsifying drug delivery systems (SNEDDS) have shown an extraordinary increase of curcumin oral bioavailability by at least 185 times due to improved solubilization of curcumin, increased intestinal permeability and partial P-glycoprotein efflux inhibitory effects. Organic cationic nanoparticles, especially mesoporous silica nanoparticles (MSNs) with its great surface-area, size-pore tuneability, and surface functionalization have been discussed as plots to adsorptively load polyphenols such as quercetin and ellagic acid, with an increased dissolution rate and mucosal gastrointestinal absorption [65].

Table 2: Summary of Nanoparticle Systems Used for Gastroprotective Phytomedicine Delivery [66–69].

Nanoparticle Type	Encapsulated Phytoconstituent	Preparation Method	Particle Size (nm)	Encapsulation Efficiency (%)	Key Findings
Chitosan-alginate NPs	<i>Terminalia chebula</i> extract	Ionic gelation	200–450	68–82	Enhanced mucoadhesion, sustained tannin release, improved gastroprotection vs. free extract

PLGA NPs	Curcumin	Nanoprecipitation	150–300	75–90	6–8× improved oral bioavailability, enhanced anti- <i>H. pylori</i> activity
Solid lipid NPs	Quercetin	Hot homogenization	100–250	70–85	Sustained release, enhanced intestinal permeation, improved antioxidant activity in gastric tissue
Liposomes	EGCG (green tea)	Thin film hydration	80–200	60–78	Protected from gastric degradation, enhanced anti- <i>H. pylori</i> efficacy
Chitosan NPs	Berberine	Ionic gelation	150–350	72–88	Prolonged gastric residence, 3× improved bioavailability, anti- <i>H. pylori</i> synergy
Mesoporous silica NPs	Ellagic acid	Adsorption loading	100–300	65–80	Enhanced dissolution rate, improved mucosal penetration
SNEDDS	Curcumin	Self-emulsification	50–200 (droplet)	>90	Up to 185-fold bioavailability enhancement, lymphatic absorption
NLC	6-Gingerol	Melt emulsification	120–280	75–88	Enhanced chemical stability, improved gastric mucosal anti-inflammatory activity

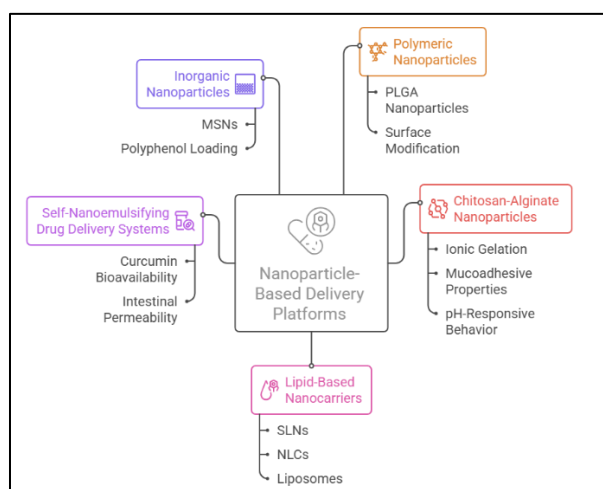


Figure 2: Nanoparticle-Based Delivery Platforms for Gastroprotective Phytomedicine

7. Safety, Toxicity, and Regulatory Considerations

The safety profile of any therapeutic agent that is planned to be used in clinics has to be properly described via systematic preclinical and clinical

testing, and it will be no less valid to phytomedicine-based nanoformulations as the gastroprotective agent. The common belief that natural origin is inherently safe is a consistent myth that should be actively disproved given that most the plant-based compounds show the dose-

related toxicity, herb-drug interaction, and organ-specific toxicity that need to be systematically characterized [70]. Although the long-term history of traditional use of gastroprotective herbs through Ayurvedic, Traditional Chinese Medicine, and Unani systems offer some preliminary clue of human tolerability it must be complemented with stringent toxicological data obtained based on ICH and OECD protocols. Acute oral toxicity tests of the most studied gastroprotective herbs such as *Terminalia chebula*, *Glycyrrhiza glabra*, *Embolica officinalis*, *Curcuma longa* and *Zingiber officinale* have metacutely spoken in general with all of them falling in GHS Category 4 or 5 of acute oral toxicity. Similar subacute and subchronic 28 and 90 day toxicity studies have also not resulted in significant adverse effects on body weight, hematological parameters, serum biochemistry or organ histopathology at therapeutically relevant doses. Nonetheless, there are some phytoconstituents that should be given particular attention. Long-term use of glycyrrhizin-containing *Glycyrrhiza glabra* preparations has been linked with pseudoaldosteronism, which is sodium retention, hypokalemia, and hypertension, an effect that has been effectively managed by the use of deglycyrrhizinated licorice preparations, which lose the main safety risk but with otherwise similar gastroprotective activity. Alopha has single formula Aloe vera latex preparations containing anthraquinone which also need close dose control because of electrolyte imbalance and carcinogenicity seen at high doses over long term animal experiments resulting in regulatory prohibition in some jurisdictions [71]. Genotoxic studies on the use of Ames test, chromosomal aberration assay and on the micronucleus test have implicated mainly negative outcomes on the major classes of gastroprotective phytoconstituents such as tannins, flavonoid and phenolic acids at therapeutically relevant dosages. The occasional weak positive hints of curcumin and quercetin in

some in vitro procedures at excessive physiological concentrations have never been replicated in vivo and the overall body of empirical information corroborates their non-toxicity of therapeutic levels of their action [72]. A potentially untapped safety aspect of herb-drug interactions distributivism is a clinically significant but often under-recognized safety factor, with polyphenolic phytoconstituents such as quercetin, EGCG, and curcumin having demonstrated the ability to alter the activity of cytochrome P450 enzymes and P-glycoproteins in vitro, making the theoretical risk of pharmacokinetic interactions of these compounds with co-administered drugs a potentially relevant consideration during product development in a product design process, especially when designing products intended to be Chitosan is safe and has a history of use as a nanocarrier in FDA-approved pharmaceutical preparations, and is biodegraded to non toxic-glucosamine and N-acetylglucosamine, and is not immunogenic so has no danger to the safety of oral delivery. Alginate is also established and safe as a food additive and pharmaceutical excipient with an acceptable daily intake that was approved by JECFA. PLGA, lipid-based excipients in solid lipid nanoparticles and nanostructured lipid carriers, and pharmaceutical surfactants in nanoemulsion systems all have demonstrated safety histories in the case of the right concentration. The use of ionic gelation technique to prepare chitosan- alginate nanoparticles is especially beneficial in the process of eliminating toxic chemical cross-linkers like glutaraldehyde that has been found to provoke safety concerns in other polymeric nanoparticles systems [73]. Herbal nanoformulations regulations differ significantly across jurisdictions. In the United States of America, FDA regulates botanical drug products under special botanical drug guidance that demands showing safety and efficacy in clinical proof. In the EMA 'traditional



herbal medicine product route' framework an easier approval route containing traditional usage proof is accessible, whereas in India the CDSCO and the Ministry of AYUSH are urging to establish evidence-based creation of updated customized transformations under Drugs and Cosmetics Act. Nanoparticle-based herbal products have not yet received regulatory guidance on a case-by-case basis, and so developers are forced to stand at the intersection of herbal drug and nanomedicine regulation. The technical challenges of pharmaceutical-grade standardization of phytomedicine nanoformulations: Due to the chemical complexities and natural variability of herbal extracts, a combination of the analytical sensitivity of multiple marker compounds making up phytomedicine mixtures with indicators of physicochemical quality such as particle size, zeta potential, encapsulation efficiency, and drug release profile are both required as components of product specifications and stability programs [74].

8. Future Prospects and Challenges

Nanoparticle delivery of gastroprotective agents based on phytomedicine-based nanoparticles represents a potentially exciting but challenging crossroads in nanotechnology history, with the combination of a blistering nanotechnology breakthrough, a growing body of mechanistic insight into gastric mucosal biology, a growing body of phytochemical knowledge, and an increasing enthusiasm of medical interest in plant-based therapeutics providing both a call to arms across multiple scientific fields and a call to concerted action. Among the greatest challenges to translation of chitosan-alginate and other polymeric nanoparticle systems loaded with phytoconstituents is how to move the volume of preliminary work done in laboratories to scalable processes of manufacturability and quality and consistency criteria demanded by clinical testing

and ultimate commercialization of the products [75]. The most widely used chitosan-alginate nanoparticle preparation method, ionic gelation, is fundamentally vulnerable to batch-to-batch effects, due to small variations in polymer viscosity, mixing dynamics and polymer solution composition, and its scaling to continuous manufacturing platforms, e.g. microfluidic or membrane-based mixing systems that provide significantly better control and scalability of the process, is the subject of active study and development efforts. Long term physical and chemical stability of phytoconstituent-loaded nanoparticles during storage, transportation and handling is another practical limitation, as the colloidal instability, aggregation of particles, and oxidative or hydrolytic degradation of encapsulated phytochemicals can compromise the products quality during the shelf life, requiring the formulation of suitable stabilization measures such as lyophilization with cryoprotectants, controlled atmosphere storage and addition of antioxidant excipients [76]. Perhaps the most serious lacuna between the impressive preclinical body of research and clinical translation is the lack of clinical support of phyto-based nano-formulations in gastroprotective formulations. The large number of studies that have shown gastroprotective efficacy of phytoconstituent-loaded nanoparticles have been done in rodent ulcer models the predictive power of which in human gastric disease, albeit having been reasonably well proven in a few outcomes, is not without significant limitations. The clinical trial design to address the heterogeneity of human gastric disease in etiology, severity, *H. pylori* status, comorbid medications, and genetic background presents challenges with careful consideration on patient stratification, choice of endpoints and comparators [77]. Regulatory authorities in large markets now insist on strong clinical demonstrations of effectiveness and safety



of novel gastroprotective agents notwithstanding their natural location, and the effort needed to produce such demonstrations using well-powered randomized controlled trials is a significant obstacle to the significantly academic research community that's currently promoting innovation in the area. The inclusion of computational methods such as molecular docking and molecular dynamics simulation, ADME prediction, and artificial intelligence-based phytochemical screening are increasingly seen as a tool to speed up the drug discovery pipeline in the context of phytomedicine-based gastroprotective agents by prioritizing candidate compounds in silico, predicting their metabolic profiles and any associated drug interactions, and optimizing nanoformulation design parameters before experimental works (which were resource intensive) is approached. The use of network pharmacology methodologies, predicting the interplay between multiple phytoconstituents and multiple gastric disease-relevant targets at the same time, is yielding novel insights into the synergy processes involving the gastroprotective action of complex herbal extracts and consequently guiding the rational design of standardized extract cocktails with preferred multi-target activity profiles [78]. Precision medicine-based gastroprotective therapy is a promising future direction of phytomedicine, acknowledging that each person differs in terms of the composition of professionals, metabolic enzyme genotype, the amount of gastric acid secretion, and immune response phenotype, all of which have a large impact on the pharmacokinetic profiles of phytoconstituents and the progression of gastric disease. Gastroprotective phytotherapy

may be approached with greater individuality and efficacy through application of pharmacogenomic profiling to identify the best-responding patients to particular phytomedicine formulations, and microbiome analysis analysis that predicts the colonic metabolic conversion of colonic phytoconstituents to bioactive urolithins and other metabolites. Intellectually compelling Next-generation gastric drug delivery systems that can react to disease-specific cues in the gastric microenvironment, including increased proteolytic activity and altered pH of the mucosa in an *H. pylori*-infected gastrointestinal cancer environment to induce localized drug release, are smart nanoparticle systems, but may need complex manufacturing, regulatory, and safety assessment bottlenecks to be overcome before translation to the clinic [79]. A particularly compelling approach to near-term clinical translation of a phytoconstituent of phytomedicine-based nanoformulations is in combination with conventional anti-*H. pylori* eradication regimens, whereby the complementary anti-*H. pylori* actions, mucosal healing effects, and microbiome-protective effects of phytoconstituents such as that of *Terminalia chebula* were harnessed to enhance the effectiveness of standard anti-helminthic regimens alongside possible alleviating the side effects of standard anti-helm This will require the rigorous appraisal of such combination modalities in well-designed clinical trials, and the scientific community will be limited in its ability to do so by its ability to provide nanoformulations of standardized, analytically well-characterized phytomedicine, which will owe its success to its ability to meet the quality challenge posed by the discipline [80].

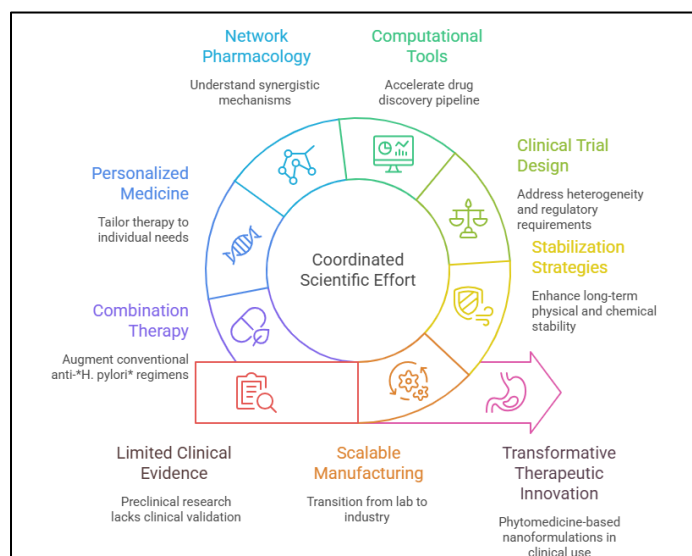


Figure 3: Advancing Phytomedicine for Gastroprotection

CONCLUSION

Historically Gastroprotective phytomedicine medications Gastroprotective phytomedicine is a scientifically promising area of therapeutic practice that can connect centuries of ethnomedicinal usage to modern pharmaceutical science. This current review has reviewed the landscape of gastroprotective herbs, and it has been demonstrated that plants like *Terminalia chebula*, *Glycyrrhiza glabra*, *Curcuma longa*, *Zingiber officinale*, *Emblica officinalis*, *Aloe vera*, and *Camellia sinensis*, the diverse arsenal of bioactive phytoconstituents comprised tannins, flavonoid, alkaloid, terpenoid, and polyphenol, which have multifaceted protective effects on the gastric mucosa, encompassing These mechanistic contributions work jointly to take care of the major pathogenic agents of gastric mucosal damage in a way that cannot be duplicated to date by any single conventional pharmacological agent. Nevertheless, these phytoconstituents have not been translated into clinical, due to low oral bioavailability due to low solubility, enzyme degradation, high first-pass elimination, and low biological half-lives, highlighting the immense importance of novel delivery vehicles.

Nanoparticle-contained vehicles, especially mucoadhesive polymeric vehicles that take advantage of the complementary forces of chitosan and alginate, have turned out to be potent agents in safeguarding the phytoconstituent against gastrointestinal breakdown, extending the period of stay in the mucosal gut and facilitating targeted drug delivery. The safety of both phytoconstituents and nanocarrier excipients is generally positive over the therapeutic dose percentage, but interactions between herbs and drugs still should be observed carefully. In future directions, the space needs urgently a shift towards a preclinical evidence-supported demonstration of proof-of-concept to carefully designed clinical studies, with the support of standardized nanoformulations, harmonised regulatory frameworks, and a combination of computational tools to optimise rational multi-target phytomedicine applications, to put phytomedicine-based nanoparticle platforms in a truly promising position in terms of gastroprotective therapy.

REFERENCES

1. Wang Y, Huang Y, Chase RC, Li T, Ramai D, Li S, et al. Global Burden of Digestive



- Diseases: A Systematic Analysis of the Global Burden of Diseases Study, 1990 to 2019. *Gastroenterology* 2023;165:773-783.e15. <https://doi.org/10.1053/j.gastro.2023.05.050>.
2. Wang R, Li Z, Liu S, Zhang D. Global, regional, and national burden of 10 digestive diseases in 204 countries and territories from 1990 to 2019. *Front Public Health* 2023;11. <https://doi.org/10.3389/fpubh.2023.1061453>.
3. Bai Z, Wang H, Shen C, An J, Yang Z, Mo X. The global, regional, and national patterns of change in the burden of nonmalignant upper gastrointestinal diseases from 1990 to 2019 and the forecast for the next decade. *Int J Surg* 2025;111:80. <https://doi.org/10.1097/JS9.0000000000001902>.
4. Wang F, Hu D, Sun H, Yan Z, Wang Y, Wang L, et al. Global, regional, and national burden of digestive diseases: findings from the global burden of disease study 2019. *Front Public Health* 2023;11. <https://doi.org/10.3389/fpubh.2023.1202980>.
5. Danpanichkul P, Suparan K, Tothanasurongroj P, Dejvajara D, Rakwong K, Pang Y, et al. Epidemiology of gastrointestinal cancers: a systematic analysis from the Global Burden of Disease Study 2021. *Gut* 2025;74:26–34. <https://doi.org/10.1136/gutjnl-2024-333227>.
6. Mohammadi MJ, Baratifar M, Asban P, Kiani F, Hormati M, Kazemi Bareh Bichast R. The Effect of Air Pollutants on Chronic Gastrointestinal Diseases: A Comprehensive Review. *J Hum Environ Health Promot* 2024;10:1–10. <https://doi.org/10.61186/jhehp.10.1.1>.
7. Karunarathna I, Gunathilake S, Ekanayake U, Hapuarachchi T, Ranasinghe S, Senanayaka S, et al. Clinical Use of H2 Receptor Antagonists: Pharmacology, Indications, Safety, and Best Practices in Gastrointestinal Disorders 2025.
8. Kuril AK. Multifaceted Strategies for Managing Gastroesophageal Reflux Disease: A Study of Pharmacological and Non-Pharmacological Interventions. *Arch Gastroenterol Res* 2025;Volume 6:45–52. <https://doi.org/10.33696/Gastroenterology.6.066>.
9. Lamsaouri H. The role of the pharmacist in the prevention of peptic ulcer disease and its complications. Роль фармацевта в профілактиці виразкової хвороби та її ускладнень 2024.
10. Tan J, Jeffries S, Carr R. A Review of Histamine-2 Receptor Antagonist and Proton Pump Inhibitor Therapy for Gastroesophageal Reflux Disease in Neonates and Infants. *Pediatr Drugs* 2023;25:557–76. <https://doi.org/10.1007/s40272-023-00580-z>.
11. Bulbul MRH, Chowdhury MNU, Naima TA, Sami SA, Imtiaj MS, Huda N, et al. A comprehensive review on the diverse pharmacological perspectives of Terminalia chebula Retz. *Heliyon* 2022;8. <https://doi.org/10.1016/j.heliyon.2022.e10220>.
12. Khare A, Singh R. Effect of Exotic Indian Spices on Gastrointestinal Disorders. *Med. Spices Herbs India*, Apple Academic Press; 2024.
13. Golzardi M, Glamočlija U. Solubility of phytochemicals and challenges in in vitro studies: a literature review. *Period Eng Nat Sci* 2025;13:417–24. <https://doi.org/10.21533/pen.v13.i2.456>.
14. Abdelhafez OH, Shady NH, Hisham M, Essawad K, Hashem RA, Fouad RA, et al. A Comprehensive Overview on the Role of Phytocompounds as Gastroprotective Agents. *Nat Prod Commun* 2025;20:1934578X251329870. <https://doi.org/10.1177/1934578X251329870>.



15. Vélez LA, Delgado Y, Ferrer-Acosta Y, Suárez-Arroyo IJ, Rodríguez P, Pérez D. Theoretical Prediction of Gastrointestinal Absorption of Phytochemicals. *Int J Plant Biol* 2022;13:163–79. <https://doi.org/10.3390/ijpb13020016>.
16. Ben Mansour R, Wasli H, Serairi-Beji R, Bourgou S, Dakhlaoui S, Selmi S, et al. In vivo gastroprotective effect and biological potentialities of six Tunisian medicinal plants using multivariate data treatment. *Plant Biosyst - Int J Deal Asp Plant Biol* 2022;156:152–63. <https://doi.org/10.1080/11263504.2020.1845840>.
17. Boeing T, de Souza J, Vilhena da Silva R de C, Mariano LNB, Mota da Silva L, Gerhardt GM, et al. Gastroprotective effect of *Artemisia absinthium* L.: A medicinal plant used in the treatment of digestive disorders. *J Ethnopharmacol* 2023;312:116488. <https://doi.org/10.1016/j.jep.2023.116488>.
18. 1Dr. Nimitha Benny 2Dr Sreelakshmy K. HARITAKI (TERMINALIA CHEBULA RETZ.) IN AYURVEDA: A CLASSICAL REVIEW WITH SCIENTIFIC PERSPECTIVES 2025. <https://doi.org/10.5281/ZENODO.17951397>.
19. Cerulli A, Masullo M, Montoro P, Piacente S. Licorice (*Glycyrrhiza glabra*, *G. uralensis*, and *G. inflata*) and Their Constituents as Active Cosmeceutical Ingredients. *Cosmetics* 2022;9:7. <https://doi.org/10.3390/cosmetics9010007>.
20. Chou A-H, Lee H-C, Liao C-C, Yu H-P, Liu F-C. ERK/NF-kB/COX-2 Signaling Pathway Plays a Key Role in Curcumin Protection against Acetaminophen-Induced Liver Injury. *Life* 2023;13:2150. <https://doi.org/10.3390/life13112150>.
21. Bhattacharyya J, Saikia L, Kalita V, Dutta PP. An Updated Review on the Anti-Inflammatory Potential of *Phyllanthus* Genus. *Chem Biodivers* 2025;22:e202402483. <https://doi.org/10.1002/cbdv.202402483>.
22. Martins-Gomes C, Nunes FM, Silva AM. Natural Products as Dietary Agents for the Prevention and Mitigation of Oxidative Damage and Inflammation in the Intestinal Barrier. *Antioxidants* 2024;13:65. <https://doi.org/10.3390/antiox13010065>.
23. Jaicharoensub J, Sakpakdeejaroen I, Panthong S. Validation of HPLC method for quantitative determination of active compounds in Thai traditional herbal medicine to treat gastrointestinal disease. *Talanta Open* 2023;7:100227. <https://doi.org/10.1016/j.talo.2023.100227>.
24. Teterovska R, Skotele RE, Maurina B, Sile I. Medicinal Plants in Food Supplements for Gastrointestinal Disorders: Critical Assessment of Health Claims on Gastric Acid Regulation. *Nutrients* 2025;17:3674. <https://doi.org/10.3390/nu17233674>.
25. Darwin R, Valmon R, Chithanna S, Galla SH, Syed SH, Mohathasim Billah AA, et al. Sustainable Extraction and Purification of Phytochemicals: A Review of Green Solvents and Techniques. *Chem Methodol* 2025. <https://doi.org/10.48309/chemm.2025.504050.1892>.
26. Kapadia P, Newell AS, Cunningham J, Roberts MR, Hardy JG. Extraction of High-Value Chemicals from Plants for Technical and Medical Applications. *Int J Mol Sci* 2022;23:10334. <https://doi.org/10.3390/ijms231810334>.
27. Razgonova MP, Nawaz MA, Ivanova EP, Cherevach EI, Golokhvast KS. Supercritical CO₂-Based Extraction and Detection of Phenolic Compounds and Saponins from the Leaves of *Three Medicago varia* Mart. Varieties by Tandem Mass Spectrometry.

- Processes 2024;12:1041.
<https://doi.org/10.3390/pr12051041>.
28. De Laet E, Bernaerts T, Morren L, Vanmarcke H, Van Loey AM. The Use of Different Cell Wall Degrading Enzymes for Pectin Extraction from Carrot Pomace, in Comparison to and in Combination with an Acid Extraction. *Foods* 2025;14:435. <https://doi.org/10.3390/foods14030435>.
29. Banerjee) SG (nee, Karmakar S, Brahmachari K, Sarkar P, Sharma N, Ghosh M, et al. Gastroprotective Potential of Indian Medicinal Plants- A Comprehensive Review. *Mathews J Gastroenterol Hepatol* 2024;9:1–37. <https://doi.org/10.30654/MJGH.10023>.
30. Cherrada N, Chemsal AE, Gheraissa N, Laib I, Gueboudji Z, EL-Shazly M, et al. Gastroprotective Efficacy of North African Medicinal Plants: A Review on Their Therapeutic Potential for Peptic Ulcers n.d. <https://doi.org/10.1002/fsn3.4536>.
31. Nugraha MIA, Harfiani E, Pramesyanti A. Systematic Review: Potensi Kurkumin Dalam Rimpang Kunyit (*Curcuma Longa* Linn) Sebagai Anti-Inflamasi Pada Gastritis Akibat Infeksi *Helicobacter Pylori*. *Semin Nas Ris Kedokt* 2022;3.
32. Elbestawy MKM, El-Sherbiny GM, Moghannem SA, Farghal EE. Antibacterial, Antibiofilm, and Anti-Inflammatory Activities of Ginger Extract against *Helicobacter pylori*. *Microbiol Res* 2023;14:1124–38. <https://doi.org/10.3390/microbiolres14030075>.
33. Mohamed AO, Abd-Elghaffar SKh, Mousa RA, Kamel AA. Aloe vera gel confers therapeutic effect by reducing pyroptosis in ethanol-induced gastric ulcer rat model: Role of NLRP3/GSDMD signaling pathway. *Mol Biol Rep* 2024;51:401. <https://doi.org/10.1007/s11033-024-09329-4>.
34. Matalqah L, Matalqah S, Al Tawaha AR, Kozuharova E, Radaideh L, Mhaidat Q, et al. Update in the therapeutic role of Complementary and Alternative Medicine (CAM) in peptic ulcer. *Egypt J Intern Med* 2026;38:10. <https://doi.org/10.1186/s43162-026-00590-6>.
35. Altemani FH, Elmaidomy AH, Abu-Baih DH, Zaher AMA, Mokhtar FA, Algehainy NA, et al. *Tamarix aphylla* derived metabolites ameliorate indomethacin-induced gastric ulcers in rats by modulating the MAPK signaling pathway, alleviating oxidative stress and inflammation: In vivo study supported by pharmacological network analysis. *PLOS ONE* 2024;19:e0302015. <https://doi.org/10.1371/journal.pone.0302015>.
36. Banerjee) SG (nee, Karmakar S, Brahmachari K, Sarkar P, Sharma N, Ghosh M, et al. Gastroprotective Potential of Indian Medicinal Plants- A Comprehensive Review. *Mathews J Gastroenterol Hepatol* 2024;9:1–37. <https://doi.org/10.30654/MJGH.10023>.
37. Swati, Kumar B, Pandey HK, Kaur R, Mishra S, Kalam MA. Phytochemical profiling, antioxidant capacity, acute toxicity, and gastroprotective potential of *Angelica glauca* root: A promising high-altitude medicinal herb. *Fitoterapia* 2025;183:106565. <https://doi.org/10.1016/j.fitote.2025.106565>.
38. Atchan APN, Monthe OC, Tchamgoue AD, Singh Y, Shivashankara ST, Selvi MK, et al. Anti-Inflammatory, Antioxidant Activities, and Phytochemical Characterization of Edible Plants Exerting Synergistic Effects in Human Gastric Epithelial Cells. *Antioxidants* 2023;12:591. <https://doi.org/10.3390/antiox12030591>.
39. Enciso-Roca EC, Arroyo-Acevedo JL, Común-Ventura PW, Tinco-Jayo JA, Aguilar-Felices EJ, Ramos-Meneses MB, et al. The

- Phytochemical Profile and Antioxidant and Gastroprotective Effects of Three Varieties of *Chenopodium quinoa* Willd. Sprouts Cultivated in Peru. *Sci Pharm* 2025;93:10. <https://doi.org/10.3390/scipharm93010010>.
40. Márquez-Flores YK, Ayala-Velasco J, Correa-Basurto J, Estrada-Pérez A, Meléndez-Camargo ME. *Peperomia campyloptropa* A.W. Hill: Ethnobotanical, Phytochemical, and Metabolomic Profile Related to Its Gastroprotective Activity. *Molecules* 2025;30:772. <https://doi.org/10.3390/molecules30040772>.
 41. Amira H, Mamache W, Benchikh F, Benabdallah H, Ouaret A, Amira I, et al. Evaluation of the safety, gastroprotective activity and possible mechanisms of action of *Ziziphora hispanica* L. methanol extract. *Fitoterapia* 2026;190:107171. <https://doi.org/10.1016/j.fitote.2026.107171>.
 42. Walter UG, Assumpta EO, Kelvin E-IO, Ifeanyi EF, Chika MJ. Gastroprotective Properties and Phytochemical Constituents of Leaf Methanol Extract of *Phyllanthus discoideus* on Diclofenac-Induced Gastric Ulcers in Rats. *Afr J Pharm Altern Med* 2025;4:227–40. <https://doi.org/10.58460/ajpam.v4i2.171>.
 43. Tan B, Chiranthan N, Chansakaow S, Sireeratawong S, Khonsung P, Nimlamool W, et al. Gastroprotective effects of Pikad Tri-phol-sa-mut-than herbal remedy on multiple gastric ulcer models in rats. *Heliyon* 2023;9. <https://doi.org/10.1016/j.heliyon.2023.e19297>.
 44. Hamoud N-E-H, Maammeri Z. PRETREATMENT WITH *HYSSOPUS OFFICINALIS* ETHYL ACETATE LEAF EXTRACT MITIGATES GASTRIC MUCOSAL INJURY: A POTENTIAL GASTROPROTECTIVE STRATEGY. *Acta Pol Pharm* 2025;82:305. <https://doi.org/10.32383/appdr/208281>.
 45. Bellard e Silva R, Martins JLR, Almeida D de S, Ferreira GV, Ribeiro KR, Coimbra MC, et al. Quality-by-design Development of *Celtis iguanaea* Microparticles with In vivo Gastroprotective Efficacy. *Rev Bras Farmacogn* 2025;35:1209–30. <https://doi.org/10.1007/s43450-025-00692-2>.
 46. Singh MP, Chawla V, Kaushik D, Chawla PA, Sisodia SS. Pharmacodynamic Stance of Phytoconstituents as a Gastric Ulcer Protective Mechanism: An Overview. *Curr Mol Med* 2022;22:431–41. <https://doi.org/10.2174/1566524021666210806161835>.
 47. Alcântara IS, Pessoa RT, Silva LYS da, Silva TM, Menezes IO, Martins AOBPB, et al. Mechanisms of Action Involved in the In Vivo Gastroprotective Response of Fruits: A Systematic Review. *Food Front* 2026;7:e70117. <https://doi.org/10.1002/fft2.70117>.
 48. Shahzad N, Ibrahim IAA, Alzahrani AR, Al-Ghamdi SS, Alanazi IMM, Ahmad MdP, et al. A comprehensive review on phytochemicals as potential therapeutic agents for stress-induced gastric ulcer. *J Umm Al-Qura Univ Appl Sci* 2024;10:793–808. <https://doi.org/10.1007/s43994-024-00140-2>.
 49. Oladele JO, Ojuederie OB, Oladele OT, Ajayi EIO, Olaniyan MD, Atolagbe OS, et al. Gastroprotective mechanism of *Talinum triangulare* on ethanol-induced gastric ulcer in Wistar rats via inflammatory, antioxidant, and H⁺/K⁺-ATPase inhibition-mediated pathways. *Drug Chem Toxicol* 2025;48:281–93. <https://doi.org/10.1080/01480545.2024.2365435>.
 50. Ansari P, Reberio AD, Ansari NJ, Kumar S, Khan JT, Chowdhury S, et al. Therapeutic



- Potential of Medicinal Plants and Their Phytoconstituents in Diabetes, Cancer, Infections, Cardiovascular Diseases, Inflammation and Gastrointestinal Disorders. *Biomedicines* 2025;13:454. <https://doi.org/10.3390/biomedicines13020454>.
51. Kmail A. Mitigating digestive disorders: Action mechanisms of Mediterranean herbal active compounds. *Open Life Sci* 2024;19. <https://doi.org/10.1515/biol-2022-0857>.
 52. Landge MM. Analysing The Distribution, Metabolism, Excretion, And Absorption Of Phytoconstituents. *Libr Prog-Libr Sci Inf Technol Comput* 2024;44:7867.
 53. Kaur G, Dogra K, Sunil NS, Kurl S. Harnessing Nanocarriers to Overcome Bioavailability Barriers of Herbal Actives: A Comprehensive Review 2026. <https://doi.org/10.2174/0122117385412374251111045823>.
 54. Ribeiro SM. Biochemical and pharmacokinetic insights into a single plant-derived phytocompound used in chronic inflammatory conditions. *J Phytopharm Phytochemistry* 2026;3:13–6. <https://doi.org/10.33545/30810620.2026.v3.i1.A.37>.
 55. Bhatt J, Dhyani A, Kukreti G, Durgapal S, Kumar G. Self-emulsifying Drug Delivery Systems as a Paradigm for Enhancing Bioavailability of Phytoconstituents. *J Solut Chem* 2026. <https://doi.org/10.1007/s10953-026-01564-6>.
 56. Idakwoji PA, Tukur U, Onwukwe BO, Agboola JB, Onugwu EO, Iyiola AT, et al. Phytochemicals as promising lead compounds for drug discovery: A comprehensive review of mechanisms and pharmacological potentials. *Lett Drug Des Discov* 2026:100363. <https://doi.org/10.1016/j.lddd.2026.100363>.
 57. Chou P, Shannar A, Pan Y, Dave PD, Xu J, Kong A-NT. Application of Physiologically-Based Pharmacokinetic (PBPK) Model in Drug Development and in Dietary Phytochemicals. *Curr Pharmacol Rep* 2025;11:45. <https://doi.org/10.1007/s40495-025-00427-w>.
 58. de Albuquerque Mendes MK, dos Santos Oliveira CB, da Silva Medeiros CM, dos Santos LR, Lopes Júnior CA, Vieira EC. Challenges and Strategies for Bioavailability of Curcumin. In: Rai M, Feitosa CM, editors. *Curcumin Neurodegener. Dis. Tradit. Transl. Med.*, Singapore: Springer Nature; 2023, p. 21–37. https://doi.org/10.1007/978-981-99-7731-4_2.
 59. Nanoparticle-based delivery systems of phytochemicals for gut-related disorders. *Phytochem. Gut Health*, Academic Press; 2026, p. 123–48. <https://doi.org/10.1016/B978-0-443-36372-6.00007-0>.
 60. Bawankar A, Zawar L. RECENT ADVANCES IN PHYTOCHEMICAL-BASED NANOPARTICLES FOR COLON-SPECIFIC DRUG DELIVERY n.d.
 61. Shree D, Patra CN, Sahoo BM. Emerging Nanoparticle-Based Herbal Drug Delivery Systems for Colon Targeting Therapy. *Int J Gastroenterol Hepatol Dis* 2024;3:E26662906317495. <https://doi.org/10.2174/0126662906317495240827080916>.
 62. [62] Alabi TD, Badmus JA. Antidiabetic Plant Products and Their Nanoparticle-Based Delivery. *Adv. Phytonanotechnology Treat. Var. Dis.*, CRC Press; 2023.
 63. Attia RT, Babker A, Nafie MS, Saleh FA, Abdelwareth MA, Loutfy EM, et al. Mucoadhesive chitosan-coated boswellic acids nanoparticles as promising gastroprotective nanoagents via modulation



- of the RAS/ERK signaling pathway. *Discov Nano* 2025;20:190. <https://doi.org/10.1186/s11671-025-04375-8>.
64. Gupta J, Kumar D, Gupta R, Kumar S, Kumar M. Emerging Trends in the Pharmacological and Therapeutic Potential of Ginger: From Traditional Medicine to Nanotechnological Innovations. *Curr Pharm Des* 2025;31:2995–3016. <https://doi.org/10.2174/0113816128372023250324050304>.
65. Barik S, Patra M, Gorain S, Biswas SJ. Nanotechnology in Cancer Chemoprevention: In Vivo and In Vitro Studies and Advancement in Biological Sciences. In: Malik JA, Sadiq Mohamed MJ, editors. *Mod. Nanotechnol. Vol. 2 Green Synth. Sustain. Energy Impacts*, Cham: Springer Nature Switzerland; 2023, p. 203–30. https://doi.org/10.1007/978-3-031-31104-8_9.
66. Mittal G, A P, Dhali A, Prasad R, S Y, Nurani KM, et al. Plant extracts with antioxidant and hepatoprotective benefits for liver health: A bibliometric analysis of drug delivery systems. *World J Gastroenterol* 2025;31:105836. <https://doi.org/10.3748/wjg.v31.i18.105836>.
67. Anter HM, Abu Hashim II, Awadin W, Meshali MM. Novel chitosan oligosaccharide-based nanoparticles for gastric mucosal administration of the phytochemical “apocynin.” *Int J Nanomedicine* 2019;14:4911–29. <https://doi.org/10.2147/IJN.S209987>.
68. Abd-Allah H, Youshia J, Abdel Jaleel GA, Hassan A, El Madani M, Nasr M. Gastroprotective Chitosan Nanoparticles Loaded with Oleuropein: An In Vivo Proof of Concept. *Pharmaceutics* 2024;16:153. <https://doi.org/10.3390/pharmaceutics16010153>.
69. Zhang X, Wu W. Novel Drug Delivery Systems for Phytomedicines. *Pharmaceutics* 2024;16:1059. <https://doi.org/10.3390/pharmaceutics16081059>.
70. Karthikeyan M, Mehta A, Kumar SS, Mohan H, Usha B. Safety, Dosage, and Regulatory Aspects in the Use of Phytochemicals. In: Kuca K, Patocka J, Kumar V, Dhalaria R, editors. *Med. Plants Their Bioact. Hum. Dis.*, Cham: Springer Nature Switzerland; 2025, p. 207–33. https://doi.org/10.1007/978-3-032-01356-9_10.
71. Phytochemicals: Extraction process, safety assessment, toxicological evaluations, and regulatory issues. *Funct. Preserv. Prop. Phytochem.*, Academic Press; 2020, p. 341–61. <https://doi.org/10.1016/B978-0-12-818593-3.00011-7>.
72. Phytopharmaceuticals and herbal drugs: prospects and safety issues in the delivery of natural products. *Phytopharm. Herb. Drugs*, Academic Press; 2023, p. 215–48. <https://doi.org/10.1016/B978-0-323-99125-4.00006-8>.
73. Singh S, Thakur A, Kiran V, Dulta K, Sharma AJ, Choudhury MD. Safety, Toxicity, and Regulation in Use of Medicinal Plants. In: Kuca K, Patocka J, Kumar V, Dhalaria R, editors. *Med. Plants Their Bioact. Hum. Dis.*, Cham: Springer Nature Switzerland; 2025, p. 41–57. https://doi.org/10.1007/978-3-032-01356-9_2.
74. Samal IP, Jena S, Jyotirmayee B, Mahalik G, Das IJ, Samal HB. Safety, Dosage, and Regulatory Aspects in the Use of Phytochemicals Against Cancer. In: Kuca K, Patocka J, Kumar V, Dhalaria R, editors. *Med. Plants Their Bioact. Hum. Dis.*, Cham: Springer Nature Switzerland; 2025, p. 331–51. https://doi.org/10.1007/978-3-032-01356-9_14.

75. Singh V, Punia A, Gupta S, Thakur A, Kumar R, Singh Chauhan N. Chemopreventive Strategies in Herbal Medicine Practice: Current Aspects, Challenges, Prospects, and Sustainable Future Outlook. *Herb. Med. Phytochem.*, Springer, Cham; 2024, p. 1–27. https://doi.org/10.1007/978-3-031-21973-3_58-1. <https://doi.org/10.1080/14656566.2025.2597281>.
76. Wahid A, Khan SA, Huang J, Cai Z, Xu G, Sun G. NanoPhyto formulations: A promising approach for targeted therapy of gastrointestinal infections, clinical advancements, and future perspectives. *Curr Opin Pharmacol* 2026;87:102617. <https://doi.org/10.1016/j.coph.2026.102617>.
77. Paulraj RS, Sathiyaseelan A, Perumal P, Ramachandran A, Paulraj SG. A Comprehensive Analysis of Therapeutic Potential of Medicinal Plant Extracts to Treat Ethanol-Induced Gastric Ulcer. *Biomedicines* 2026;14:562. <https://doi.org/10.3390/biomedicines14030562>.
78. Komolafe K, Komolafe TR, Crown OO, Ajiboye B, Noubissi F, Ogungbe IV, et al. Natural Products in the Management of Gastroesophageal Reflux Disease: Mechanisms, Efficacy, and Future Directions. *Nutrients* 2025;17:1069. <https://doi.org/10.3390/nu17061069>.
79. Kumar R, Kumar K, Kaur A, Gill DNS. HERBAL APPROACHES TO GASTRIC ULCER TREATMENT: CURRENT CHALLENGES AND FUTURE DIRECTIONS n.d.
80. Lambiase C, Usai Satta P, Bassotti G, Giacomelli L, de Bortoli N, Bellini M. Iberogast in functional dyspepsia: yesterday, today, and tomorrow – a narrative review of a multitarget phytomedicine. *Expert Opin Pharmacother* 2025;26:1867–76.

HOW TO CITE: Snehal Rahate*, Varsha Jadhav, Vilas Ghawate, Kangare Aradhana, Shejul Jayashri, Gastroprotective Phytomedicine And Nanoparticle-Based Delivery Platforms for Targeted Gastric Therapy- A Comprehensive Review on Phytochemistry, Bioavailability, And Mechanistic Insights, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 5, 5052-5076. <https://doi.org/10.5281/zenodo.20290759>

