Innovative Plant-Based Therapeutics and Phytochemical Interventions for the Management, Prevention, and Treatment of Gastrointestinal Disorders with Mechanistic and Clinical Insights

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Article Info

ISSN (online): 3107-393X
Volume: 01
Issue: 01
January – February 2024
Received: 05-12-2023
Accepted: 06-01-2024
Published: 08-02-2024
Page No: 197-208

Abstract
Gastrointestinal disorders, including inflammatory bowel disease, irritable bowel syndrome, peptic ulcer disease, and functional dyspepsia, affect approximately 40 percent of the global population and impose substantial socioeconomic burdens on healthcare systems worldwide. The aim of this article is to comprehensively review the therapeutic potential of plant-based compounds and phytochemical interventions in the management, prevention, and treatment of gastrointestinal pathologies, with emphasis on mechanistic insights and clinical translation. Key themes explored include the anti-inflammatory, antioxidant, antimicrobial, and gut microbiota-modulating effects of bioactive phytochemicals such as polyphenols, flavonoids, alkaloids, terpenoids, and glycosides. Preclinical evidence from *in vitro* cellular models and animal studies demonstrates that plant extracts can attenuate mucosal inflammation, reduce oxidative stress, promote epithelial barrier integrity, and favorably modulate intestinal microbial composition. Clinical trials in human subjects have reported symptomatic relief, improved quality of life, and disease remission in patients with various gastrointestinal conditions following phytotherapeutic interventions. Formulation strategies, including standardized extracts, enteric-coated capsules, nanoparticle delivery systems, and hydrogels, have been developed to enhance bioavailability, stability, and targeted delivery of phytochemicals. Safety considerations encompass toxicity profiles, herb-drug interactions, and pharmacokinetic variability. Future perspectives emphasize the integration of phytotherapeutics into conventional treatment paradigms through rigorous clinical validation, regulatory harmonization, and personalized medicine approaches. This review underscores the translational potential of plant-based therapeutics as adjunctive or alternative interventions for gastrointestinal disorders.

DOI:

Keywords: Plant-based therapeutics, Gastrointestinal disorders, Phytochemicals, Anti-inflammatory, Antioxidant, Gut microbiota, Preclinical studies, Clinical applications

Introduction

Gastrointestinal disorders encompass a heterogeneous spectrum of acute and chronic conditions affecting the digestive tract, ranging from inflammatory bowel disease and peptic ulcer disease to functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia [1]. These disorders are characterized by complex and multifactorial pathophysiological

mechanisms, including dysregulated immune responses, oxidative stress, altered gut microbiota composition, impaired mucosal barrier function, and aberrant enteric neuromuscular activity [2]. Conventional pharmacological therapies, including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, immunosuppressants, and biologics, have demonstrated efficacy in symptom management and disease remission but are frequently associated with adverse effects, treatment resistance, and high costs [3]. Consequently, there is growing interest in complementary and alternative medicine approaches, particularly plant-based therapeutics and phytochemical interventions, which have been utilized in traditional medical systems for centuries.

Plant-based therapeutics encompass whole plant extracts, isolated bioactive compounds, and formulated preparations derived from medicinal plants with documented therapeutic properties [4]. Phytochemicals, the bioactive constituents responsible for the pharmacological effects of medicinal plants, include diverse chemical classes such as polyphenols, flavonoids, alkaloids, terpenoids, saponins, glycosides, and volatile oils [5]. These compounds exert their gastrointestinal protective effects through multiple mechanisms, including modulation of inflammatory mediators, scavenging of reactive oxygen species, inhibition of pathogenic microorganisms, restoration of gut microbial homeostasis, and enhancement of mucosal repair processes [6]. The therapeutic potential of plant-based interventions is supported by extensive ethnopharmacological knowledge, preclinical investigations, and an expanding body of clinical evidence.

The rationale for exploring plant-based therapeutics in gastrointestinal disorders is multifaceted. First, many medicinal plants exhibit pleiotropic pharmacological activities that address multiple pathophysiological targets simultaneously, potentially offering advantages over single-target synthetic drugs [7]. Second, certain phytochemicals demonstrate favorable safety profiles and lower incidences of serious adverse effects compared to conventional medications [8]. Third, the growing prevalence of antibiotic resistance and concerns regarding the long-term use of immunosuppressive agents have prompted the search for alternative therapeutic strategies [9]. Fourth, patient preferences increasingly favor natural products and holistic approaches to healthcare, particularly in the context of chronic gastrointestinal conditions that require prolonged treatment [10].

This comprehensive review aims to synthesize current knowledge regarding plant-based therapeutics for gastrointestinal disorders, encompassing epidemiological and pathophysiological perspectives, mechanistic insights into phytochemical actions, preclinical and clinical evidence, formulation strategies, safety considerations, and translational potential. By critically evaluating the scientific literature, this article seeks to provide healthcare professionals, researchers, and policymakers with evidence-based information to guide the integration of phytotherapeutics into contemporary gastrointestinal disease management

Table 1: Common gastrointestinal-targeted medicinal plants, their active constituents, and traditional therapeutic uses

Plant Species	Family	Active Constituents	Traditional Therapeutic Uses	Pharmacological Activities
Curcuma longa	Zingiberaceae	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Dyspepsia, inflammatory disorders, hepatobiliary diseases	Anti-inflammatory, antioxidant, hepatoprotective
Glycyrrhiza glabra	Fabaceae	Glycyrrhizin, liquiritin, isoliquiritigenin	Peptic ulcer, gastritis, inflammatory bowel conditions	Gastroprotective, anti-ulcer, immunomodulatory
Zingiber officinale	Zingiberaceae	Gingerols, shogaols, zingerone	Nausea, vomiting, dyspepsia, gastrointestinal motility disorders	Antiemetic, prokinetic, anti-inflammatory
Mentha piperita	Lamiaceae	Menthol, menthone, rosmarinic acid	Irritable bowel syndrome, functional dyspepsia, abdominal spasms	Antispasmodic, carminative, analgesic
Matricaria chamomilla	Asteraceae	Apigenin, chamazulene, bisabolol	Gastritis, inflammatory bowel conditions, gastrointestinal cramping	Anti-inflammatory, antispasmodic, anxiolytic
Aloe vera	Asphodelaceae	Aloin, aloe-emodin, polysaccharides	Constipation, inflammatory bowel disease, wound healing	Laxative, anti-inflammatory, wound healing
Psidium guajava	Myrtaceae	Quercetin, guajaverin, tannins	Diarrhea, dysentery, gastroenteritis	Antidiarrheal, antimicrobial, astringent
Silybum marianum	Asteraceae	Silymarin, silybin, silychristin	Hepatobiliary disorders, toxin-induced liver damage	Hepatoprotective, antioxidant, anti-inflammatory

Epidemiology and Pathophysiology of Gastrointestinal Disorders

Gastrointestinal disorders represent a major global health burden, affecting individuals across all age groups, geographic regions, and socioeconomic strata.

Epidemiological studies indicate that functional gastrointestinal disorders alone affect approximately 40 percent of the global population, with irritable bowel syndrome being the most prevalent condition, estimated to affect 9 to 23 percent of adults worldwide [11]. Inflammatory bowel disease, comprising Crohn's disease and ulcerative colitis, demonstrates increasing incidence rates in newly industrialized countries while maintaining high prevalence in Western nations, with current estimates suggesting over 6.8 million individuals affected globally [12]. Peptic ulcer disease continues to affect approximately 5 to 10 percent of the population during their lifetime, although incidence rates have declined in some regions due to improved Helicobacter pylori eradication strategies and reduced nonsteroidal anti-inflammatory drug use [13]. Gastroesophageal reflux disease affects approximately 13 percent of the global population, with higher prevalence observed in Western countries and significant impacts on quality of life and healthcare utilization [14].

The pathophysiology of gastrointestinal disorders involves complex and interconnected mechanisms that vary according to the specific condition but share common pathological features. Chronic inflammation represents a cardinal pathophysiological hallmark, characterized by dysregulated production of pro-inflammatory cytokines such as tumor

necrosis factor-alpha, interleukin-1 beta, interleukin-6, and interleukin-17, along with enhanced expression of adhesion molecules, chemokines, and matrix metalloproteinases [15]. Oxidative stress, resulting from imbalanced production of reactive oxygen species and antioxidant defense mechanisms, contributes to cellular damage, lipid peroxidation, protein oxidation, and DNA damage in gastrointestinal tissues [16]. The gut microbiota plays a pivotal role in gastrointestinal health and disease, with dysbiosis, defined as alterations in microbial diversity, composition, and metabolic activity, being implicated in inflammatory bowel disease, irritable bowel syndrome, and other gastrointestinal pathologies [17].

Impairment of the intestinal epithelial barrier represents another critical pathophysiological mechanism, involving disruption of tight junction proteins, increased intestinal permeability, and translocation of luminal antigens and microorganisms across the mucosal barrier [18]. This barrier dysfunction triggers immune activation and perpetuates inflammatory responses in susceptible individuals. Altered gastrointestinal motility, visceral hypersensitivity, and dysregulated brain-gut axis signaling contribute to symptom generation in functional gastrointestinal disorders, with neurotransmitter imbalances, altered enteric nervous system function, and psychological factors playing important roles [19]. Genetic susceptibility factors, environmental triggers including diet and lifestyle, psychological stress, and infectious agents interact in complex ways to initiate and perpetuate gastrointestinal pathology [20].

Understanding these pathophysiological mechanisms provides the foundation for identifying therapeutic targets amenable to phytochemical intervention. Plant-based therapeutics have demonstrated capacity to modulate multiple pathways simultaneously, including inflammatory signaling cascades, oxidative stress responses, microbial composition, barrier function, and neuromuscular activity, thereby offering potential advantages in addressing the multifactorial nature of gastrointestinal disorders [21].

Bioactive Phytochemicals and Mechanisms of Action

Phytochemicals represent structurally diverse secondary metabolites synthesized by plants that exhibit a wide range of biological activities relevant to gastrointestinal health. Polyphenols constitute one of the largest and most extensively studied classes of phytochemicals, encompassing flavonoids, phenolic acids, stilbenes, and lignans [22]. Flavonoids, including quercetin, kaempferol, apigenin, luteolin, and catechins, demonstrate potent anti-inflammatory effects through inhibition of nuclear factor-kappa B signaling, suppression of cyclooxygenase and lipoxygenase enzymes, and modulation of mitogen-activated protein kinase pathways [23]. These compounds also exhibit antioxidant properties by directly scavenging free radicals, chelating metal ions, and upregulating endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [24].

Curcumin, the principal curcuminoid from Curcuma longa, has been extensively investigated for its gastrointestinal protective effects. This polyphenol inhibits nuclear factor-kappa B activation, reduces expression of inducible nitric oxide synthase and cyclooxygenase-2, and suppresses production of inflammatory cytokines [25]. Curcumin also modulates multiple cellular signaling pathways including Janus kinase-signal transducer and activator of transcription, phosphatidylinositol 3-kinase-protein kinase B, and Wnt-beta-catenin pathways, which are implicated in intestinal inflammation and carcinogenesis [26]. Furthermore, curcumin demonstrates antimicrobial activity against enteric pathogens and favorably influences gut microbiota composition by promoting beneficial bacterial populations [27].

Fig 1: Representative plant species used for gastrointestinal disorders, highlighting leaves, roots, and extracts

Alkaloids represent another important class of bioactive phytochemicals with gastrointestinal activities. Berberine, an isoquinoline alkaloid found in several plant species including Berberis vulgaris and Coptis chinensis, exhibits antimicrobial properties against Helicobacter pylori and other gastrointestinal pathogens, anti-inflammatory effects through adenosine monophosphate-activated protein kinase activation, and beneficial effects on gut microbiota composition [28]. Terpenoids, including monoterpenes and sesquiterpenes, demonstrate antispasmodic, carminative, and anti-inflammatory properties. Menthol from Mentha piperita acts as a calcium channel blocker in gastrointestinal smooth muscle, producing antispasmodic effects beneficial in irritable bowel syndrome [29]. Bisabolol from Matricaria chamomilla exhibits anti-inflammatory activity through inhibition of leukotriene synthesis and demonstrates gastroprotective effects in experimental models [30].

Saponins, including glycyrrhizin from Glycyrrhiza glabra, possess anti-inflammatory, anti-ulcer, and immunomodulatory properties. Glycyrrhizin inhibits phospholipase A2 activity, reduces prostaglandin production, and enhances mucus secretion in gastric mucosa [31].

Tannins, polyphenolic compounds with astringent properties, demonstrate antidiarrheal effects by precipitating proteins in the intestinal mucosa, reducing inflammation, and exhibiting antimicrobial activity [32]. Mucilaginous polysaccharides from plants such as Aloe vera and Plantago ovata provide protective coating effects on gastrointestinal mucosa, enhance mucus production, and demonstrate prebiotic properties that promote beneficial gut bacteria [33].

The mechanisms through which phytochemicals exert gastrointestinal protective effects are multifaceted and involve modulation of numerous molecular targets and cellular processes. At the level of inflammatory signaling, phytochemicals interfere with pattern recognition receptor activation, inhibit transcription factor nuclear factor-kappa B and activator protein-1, suppress inflammatory enzyme expression, and reduce production of prostaglandins, leukotrienes, and inflammatory cytokines [34]. Antioxidant mechanisms include direct free radical scavenging, metal chelation, enhancement of endogenous antioxidant defenses through nuclear factor erythroid 2-related factor 2 pathway activation, and inhibition of pro-oxidant enzyme systems [35].

Phytochemicals modulate gut microbiota through selective antimicrobial effects against pathogenic bacteria, prebiotic activities that promote beneficial microbial growth, and direct interactions with microbial metabolic pathways [36].

Additional mechanisms include enhancement of intestinal barrier function through upregulation of tight junction proteins including occludin, claudins, and zonula occludens proteins, promotion of epithelial cell proliferation and wound healing, modulation of intestinal secretion and motility, inhibition of mast cell degranulation and histamine release, and regulation of enteric nervous system function [37]. Many phytochemicals also demonstrate anti-carcinogenic properties relevant to prevention of gastrointestinal malignancies through mechanisms including cell cycle arrest, apoptosis induction, angiogenesis inhibition, and suppression of metastatic processes [38].

Preclinical Evidence: *In vitro* and Animal Studies

Preclinical investigations utilizing *in vitro* cellular models and *in vivo* animal studies have provided substantial evidence supporting the gastrointestinal protective effects of plant-based therapeutics. *In vitro* studies employing intestinal epithelial cell lines have demonstrated that various phytochemicals preserve barrier integrity, reduce inflammatory mediator production, and protect against oxidative damage. Treatment of Caco-2 cells with quercetin and other flavonoids has been shown to enhance transepithelial electrical resistance, increase expression of tight junction proteins, and reduce lipopolysaccharide-induced inflammatory cytokine production [39]. Curcumin treatment in intestinal epithelial cells inhibits nuclear factor-kappa B activation, reduces reactive oxygen species generation, and prevents barrier dysfunction induced by inflammatory stimuli [40].

Animal models of inflammatory bowel disease, particularly dextran sulfate sodium-induced colitis and trinitrobenzene sulfonic acid-induced colitis in rodents, have been extensively employed to evaluate anti-inflammatory and therapeutic effects of plant extracts. Administration of turmeric extract or curcumin in these models consistently demonstrates reduction in disease activity indices, attenuation of histological damage, decreased expression of inflammatory cytokines and mediators, and preservation of intestinal barrier function [41]. Ginger extract administration in experimental colitis models has shown similar beneficial effects, including reduced macroscopic and microscopic inflammation scores, decreased myeloperoxidase activity as a marker of neutrophil infiltration, and suppression of nuclear factor-kappa B pathway activation [42].

Peptic ulcer disease models, including ethanol-induced, nonsteroidal anti-inflammatory drug-induced, and stress-induced gastric ulcers in rodents, have been utilized to assess gastroprotective effects of medicinal plants. Licorice extract administration demonstrates significant reduction in ulcer index, enhancement of gastric mucus production, increase in prostaglandin E2 levels, and improvement in mucosal blood flow [43]. Chamomile extract exhibits gastroprotective effects in experimental ulcer models through anti-inflammatory mechanisms, antioxidant activity, and enhancement of mucosal defensive factors. Studies investigating peppermint oil in animal models have demonstrated antispasmodic effects on gastrointestinal smooth muscle, reduction in visceral pain responses, and improvement in gastrointestinal transit parameters.

Table 2: Preclinical studies of plant extracts in gastrointestinal disorder models, including observed effects and experimental details

Plant Extract/Compound	Experimental Model	Dose and Duration	Observed Effects	Proposed Mechanisms
Curcumin	DSS-induced colitis in mice	50-200 mg/kg for 7 days	Reduced DAI, decreased histological damage, lowered MPO activity, suppressed TNF-α and IL-1β	NF-κB inhibition, antioxidant activity
Ginger extract	TNBS-induced colitis in rats	100-400 mg/kg for 7 days	Decreased macroscopic scores, reduced inflammatory cell infiltration, lowered oxidative stress markers	COX-2 suppression, ROS scavenging
Licorice extract	Ethanol-induced gastric ulcer in rats	200-400 mg/kg single dose	Reduced ulcer index, enhanced mucus secretion, increased PGE2 levels	Mucus enhancement, prostaglandin synthesis
Peppermint oil	Visceral pain model in mice	0.2-0.4 mL/kg for 14 days	Reduced pain responses, decreased visceral hypersensitivity	Calcium channel blockade, antispasmodic
Quercetin	Caco-2 barrier dysfunction model	10-50 μM for 24 hours	Increased TEER, enhanced tight junction protein expression, reduced IL-8	Barrier protection, anti-inflammatory
Berberine	H. pylori infection model *in vitro* and *in vivo*	50-200 mg/kg for 4 weeks	Reduced bacterial colonization, decreased gastric inflammation, improved histology	Antimicrobial, NF-κB inhibition
Aloe vera gel	Acetic acid-induced colitis in rats	100-400 mg/kg for 7 days	Decreased lesion scores, reduced inflammatory markers, improved healing	Anti-inflammatory, wound healing
Silymarin	Carbon tetrachloride-induced hepatotoxicity in rats	100-200 mg/kg for 21 days	Reduced liver enzymes, decreased oxidative stress, improved histopathology	Antioxidant, hepatoprotective

Studies investigating effects of plant-based therapeutics on gut microbiota in animal models have revealed important insights into microbiota-modulating properties. Berberine administration in high-fat diet-fed mice demonstrates restoration of microbial diversity, enrichment of beneficial bacterial species including Akkermansia muciniphila and Lactobacillus species, and reduction in endotoxin-producing bacteria. Polyphenol-rich extracts from green tea, grapes, and berries have shown prebiotic-like effects in animal studies, promoting growth of beneficial bacteria and enhancing production of short-chain fatty acids with anti-inflammatory and metabolic benefits.

Mechanistic studies utilizing knockout mice and specific inhibitors have helped elucidate molecular pathways mediating phytochemical effects. Nuclear factor erythroid 2-related factor 2 knockout mice demonstrate attenuated protective effects of curcumin and other polyphenols against oxidative stress-induced intestinal injury, confirming the importance of this transcription factor in mediating antioxidant responses. Studies using nuclear factor-kappa B reporter mice have demonstrated that various plant extracts suppress inflammatory signaling through this critical pathway in intestinal tissues. Investigations utilizing germ-free mice have revealed that certain beneficial effects of phytochemicals are microbiota-dependent, underscoring the importance of gut microbiota in mediating therapeutic responses.

Safety and toxicity assessments in animal models generally support favorable safety profiles for most plant extracts at therapeutic doses. However, some phytochemicals demonstrate dose-dependent toxicity, and certain plants contain toxic constituents that necessitate careful quality control and standardization. Long-term feeding studies in rodents with turmeric, ginger, and peppermint extracts at doses substantially exceeding therapeutic levels have shown minimal adverse effects on organ function, hematological parameters, or histopathology. Nevertheless, extracts from some plants, particularly those containing pyrrolizidine alkaloids or high concentrations of certain glycosides, have demonstrated hepatotoxicity or other organ toxicity in animal studies, highlighting the importance of appropriate safety evaluation.

Clinical Evidence and Human Trials

Clinical trials investigating plant-based therapeutics in gastrointestinal disorders have expanded considerably over the past two decades, providing evidence for efficacy, safety, and optimal clinical applications. In patients with irritable bowel syndrome, peppermint oil has been extensively studied through multiple randomized controlled trials. A meta-analysis of nine trials involving 726 patients demonstrated that enteric-coated peppermint oil capsules significantly improved global irritable bowel syndrome symptoms compared to placebo, with a pooled odds ratio of 2.39 for symptom improvement. Individual symptom parameters including abdominal pain, bloating, and stool frequency showed significant improvements, with favorable safety profiles characterized by minimal adverse effects, primarily mild heartburn in some patients.

Curcumin supplementation has been evaluated in several clinical trials for inflammatory bowel disease and other gastrointestinal conditions. A randomized controlled trial in 89 patients with ulcerative colitis demonstrated that curcumin administration at 3 grams daily in combination with standard mesalamine therapy resulted in significantly higher clinical remission rates compared to mesalamine alone, with 53.8 percent versus 0 percent achieving remission after six months. Endoscopic improvement and quality of life measures also showed significant benefits in the curcumin group. In patients with irritable bowel syndrome, curcumin supplementation for eight weeks resulted in significant improvements in abdominal pain scores and quality of life compared to placebo, with 56 percent of curcumin-treated patients reporting symptom improvement versus 28 percent in the placebo group.

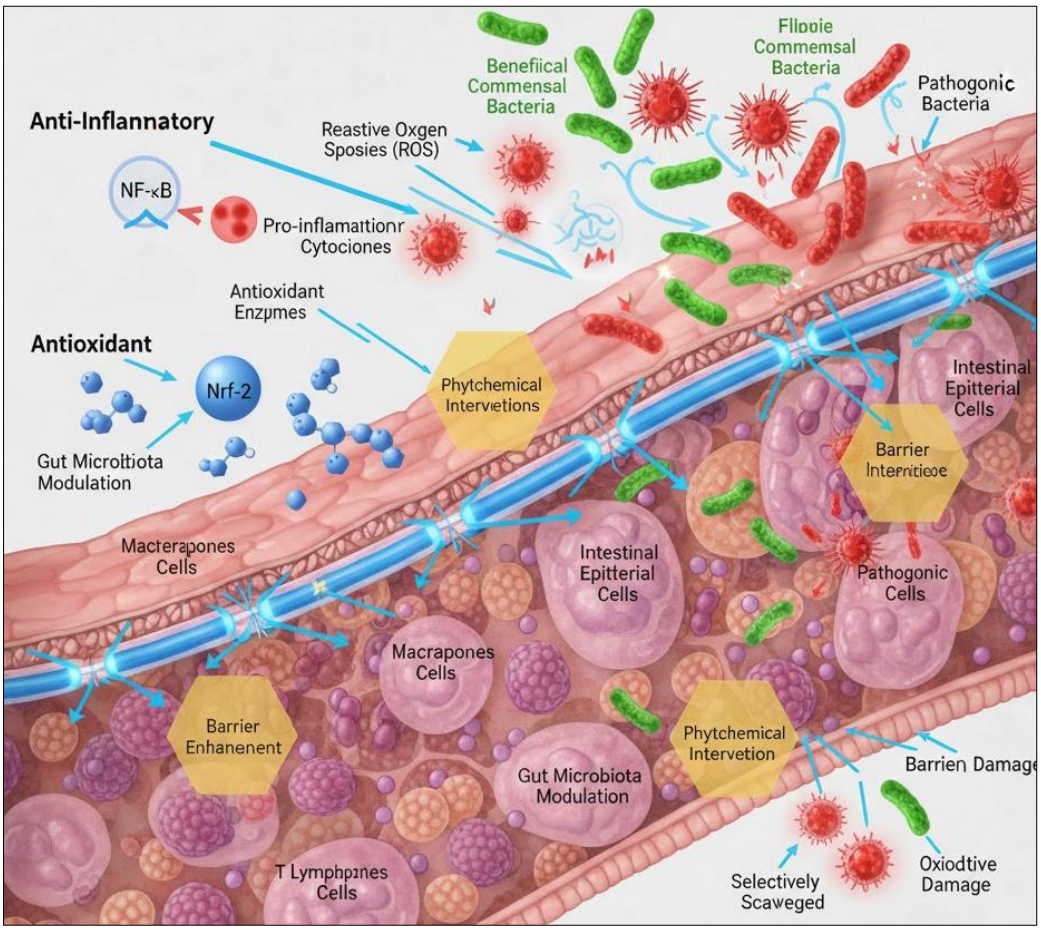

Fig 2: Mechanisms of action of plant-derived compounds in modulating gut inflammation, oxidative stress, and microbiota balance

Ginger has been investigated primarily for nausea, vomiting, and functional dyspepsia in clinical trials. A systematic review of randomized controlled trials concluded that ginger effectively reduces nausea and vomiting in various clinical contexts including pregnancy, postoperative recovery, and chemotherapy, with doses ranging from 1 to 2 grams daily showing efficacy comparable to conventional antiemetics but with fewer side effects. In patients with functional dyspepsia, ginger supplementation at 1.2 grams daily for 28 days significantly accelerated gastric emptying and reduced dyspeptic symptoms compared to placebo.

Clinical trials of licorice-containing preparations have been conducted primarily for peptic ulcer disease and functional dyspepsia. A randomized controlled trial comparing deglycyrrhizinated licorice with antacid therapy in 100 patients with peptic ulcer disease demonstrated comparable healing rates of approximately 78 percent in both groups after six weeks, suggesting potential as an alternative or adjunctive therapy. However, concerns regarding mineralocorticoid effects of glycyrrhizin have led to preferential use of deglycyrrhizinated preparations in clinical practice. Studies of combination herbal formulations containing licorice along with other herbs have shown benefits in functional dyspepsia, with symptom improvement reported in 60 to 70 percent of treated patients.

Aloe vera has been evaluated in clinical trials for inflammatory bowel disease and irritable bowel syndrome. A randomized placebo-controlled trial in 44 patients with mild to moderate ulcerative colitis demonstrated that oral aloe vera gel at 100 milliliters twice daily for four weeks resulted in clinical remission in 30 percent of patients compared to 7 percent in the placebo group, with improvements in histological scores and reductions in inflammatory markers. However, subsequent larger trials have yielded mixed results, highlighting the need for further investigation with standardized preparations.

Psyllium husk, derived from Plantago ovata, has been extensively studied for constipation-predominant irritable bowel syndrome and chronic constipation. Multiple randomized controlled trials have demonstrated that psyllium supplementation at doses of 10 to 30 grams daily significantly improves stool frequency, consistency, and ease of passage compared to placebo, with efficacy comparable to or exceeding that of other fiber supplements. A meta-analysis of seven trials in irritable bowel syndrome patients showed that soluble fiber including psyllium significantly improved global symptoms with a relative risk of 1.56 for symptom improvement compared to placebo.

Combination herbal formulations have also been investigated in clinical trials, often showing synergistic benefits. A standardized nine-herb formulation was evaluated in a randomized controlled trial of 208 patients with irritable bowel syndrome, demonstrating significant improvements in abdominal pain and quality of life compared to placebo, with 75.1 percent of herbal formula patients reporting adequate relief versus 42.3 percent in the placebo group. Chinese herbal medicine formulations individualized according to traditional diagnostic patterns have shown benefits in irritable bowel syndrome patients in several trials, although heterogeneity in formulations limits generalizability of findings.

Table 3: Clinical trials of plant-based therapeutics: study design, outcomes, formulation, and safety observations

Study/Intervention	Study Design	Patient Population	Dose and Duration	Primary Outcomes	Safety Observations
Peppermint oil	RCT, double-blind, placebo-controlled	90 IBS patients	225 mg enteric-coated capsules TID for 4 weeks	75% symptom improvement vs 38% placebo	Mild heartburn in 10% patients
Curcumin	RCT, double-blind, placebo-controlled	89 UC patients	3 g daily with mesalamine for 6 months	53.8% clinical remission vs 0% placebo	No serious adverse events
Ginger extract	RCT, double-blind, placebo-controlled	126 FD patients	1.2 g daily for 28 days	Improved gastric emptying, reduced dyspepsia scores	Minimal side effects
Aloe vera gel	RCT, double-blind, placebo-controlled	44 UC patients	100 mL twice daily for 4 weeks	30% clinical remission vs 7% placebo	Mild diarrhea in some patients
Psyllium husk	RCT, double-blind, placebo-controlled	170 IBS-C patients	10 g twice daily for 12 weeks	Increased bowel movement frequency, improved stool consistency	Transient bloating initially
Nine-herb formula	RCT, double-blind, placebo-controlled	208 IBS patients	Standardized capsules TID for 8 weeks	75.1% adequate relief vs 42.3% placebo	Well tolerated, no serious events
Curcumin	RCT, double-blind, placebo-controlled	207 IBS patients	72-144 mg daily for 8 weeks	Reduced abdominal pain, improved QOL	No significant adverse effects
Chamomile extract	Open-label trial	79 diarrhea-predominant IBS patients	3 cups chamomile tea daily for 8 weeks	Reduced stool frequency, improved consistency	Well tolerated

Challenges in interpreting clinical trial data for plant-based therapeutics include variability in extract standardization, differences in formulation and delivery systems, heterogeneity in patient populations and disease severity, variations in study duration and outcome measures, and limited sample sizes in many trials. Publication bias favoring positive results and inadequate reporting of adverse events in some studies further complicates evidence synthesis. Despite these limitations, the accumulated clinical evidence supports the potential of several plant-based therapeutics as effective and safe interventions for various gastrointestinal disorders, either as monotherapy in mild to moderate disease or as adjunctive therapy in combination with conventional treatments.

Formulation Strategies: Extracts, Capsules, and Novel Delivery Systems

The translation of plant-based therapeutics from traditional preparations to modern pharmaceutical formulations requires careful consideration of extraction methods, standardization approaches, and delivery system design to optimize bioavailability, stability, and therapeutic efficacy. Traditional preparations including decoctions, infusions, tinctures, and crude powders have been largely replaced or supplemented by standardized extracts, concentrated formulations, and novel delivery systems that address limitations of conventional preparations.

Extraction methodologies significantly influence the composition, potency, and quality of plant-based therapeutics. Conventional extraction techniques including maceration, percolation, Soxhlet extraction, and reflux extraction utilize various solvents such as water, ethanol, methanol, or their mixtures to extract bioactive compounds from plant materials. The choice of extraction solvent influences the profile of extracted compounds, with polar solvents preferentially extracting glycosides, alkaloids, and phenolic compounds, while nonpolar solvents extract lipophilic constituents including terpenoids and volatile oils. Modern extraction techniques including supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, and pressurized liquid extraction offer advantages of reduced extraction time, lower solvent consumption, higher extraction efficiency, and better preservation of thermolabile compounds.

Standardization of plant extracts is essential to ensure consistent therapeutic efficacy and reproducible clinical outcomes. Standardization involves quantification of marker compounds or active constituents to specified concentrations, typically using chromatographic techniques including high-performance liquid chromatography, gas chromatography, or thin-layer chromatography. For example, turmeric extracts are commonly standardized to contain 95 percent curcuminoids, while ginger extracts may be standardized based on gingerol content. Some extracts are standardized to multiple marker compounds to ensure comprehensive quality control. Standardization also encompasses control of botanical identity, absence of adulterants and contaminants, consistent processing methods, and documentation of batch-to-batch variability.

Conventional solid dosage forms including tablets and capsules remain the most common formulations for oral administration of plant-based therapeutics. Immediate-release capsules containing powdered extracts or concentrated preparations provide simple and economical delivery but may result in rapid release and potential degradation in the harsh gastric environment. Enteric-coated formulations designed to resist gastric acid and release contents in the intestinal environment are particularly relevant for gastrointestinal applications, protecting acid-labile compounds and enabling targeted delivery to intestinal sites of action. Sustained-release and controlled-release formulations utilizing matrix systems, reservoir systems, or osmotic pump mechanisms extend duration of action and may improve therapeutic outcomes by maintaining optimal drug concentrations and reducing dosing frequency. Bioavailability enhancement represents a critical challenge for many phytochemicals that exhibit poor aqueous solubility, low membrane permeability, extensive first-pass metabolism, or rapid elimination. Nanotechnology-based delivery systems offer promising approaches to overcome these limitations. Nanoparticles including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid

carriers, and nanoemulsions can enhance solubility, protect bioactive compounds from degradation, improve cellular uptake, and enable targeted delivery. Curcumin-loaded nanoparticles have demonstrated significantly improved bioavailability compared to conventional curcumin formulations, with some nanoformulations showing up to 20-fold enhancement in plasma concentrations.

Liposomal formulations encapsulate phytochemicals within phospholipid bilayers, providing protection from degradation, enhanced membrane permeability, and improved bioavailability. Liposomal curcumin and quercetin formulations have shown superior pharmacokinetic profiles and enhanced therapeutic efficacy in preclinical and clinical studies. Phytosomes, also known as herbosomes, represent complexes between phytochemicals and phospholipids that demonstrate enhanced lipophilicity and bioavailability. Silymarin-phospholipid complexes exhibit significantly improved absorption and hepatoprotective efficacy compared to unformulated silymarin.

Self-emulsifying drug delivery systems spontaneously form fine oil-in-water emulsions upon contact with gastrointestinal fluids, enhancing solubilization and absorption of lipophilic phytochemicals. These systems have been successfully applied to improve bioavailability of curcumin, quercetin, and other poorly soluble compounds. Cyclodextrin complexation represents another approach to enhance aqueous solubility and stability of phytochemicals through formation of inclusion complexes within the cyclodextrin cavity. Beta-cyclodextrin complexes of curcumin and other flavonoids demonstrate improved dissolution rates and bioavailability.

Hydrogel formulations offer advantages for topical or local gastrointestinal applications. Plant extract-loaded hydrogels can provide sustained release, mucoadhesive properties for prolonged residence time, and protective effects on gastrointestinal mucosa. Injectable hydrogels or hydrogel-based rectal formulations have been investigated for targeted delivery in inflammatory bowel disease. Mucoadhesive tablets and films designed to adhere to gastrointestinal mucosa enable prolonged contact time and localized delivery of therapeutic agents at sites of inflammation or ulceration. Co-administration strategies including combination with absorption enhancers, efflux pump inhibitors, or metabolic enzyme inhibitors can improve bioavailability of phytochemicals. Piperine from black pepper is commonly used as a bioenhancer due to its ability to inhibit drug-metabolizing enzymes and enhance absorption of curcumin and other compounds. Formulation scientists continue to develop innovative delivery systems including microspheres, microparticles, transdermal patches, and targeted delivery platforms utilizing ligand-conjugated nanocarriers to optimize therapeutic outcomes while minimizing adverse effects.

Safety, Toxicity, and Herb–Drug Interactions

While plant-based therapeutics are often perceived as safe due to their natural origin and long history of traditional use, comprehensive safety evaluation remains essential to identify potential toxicities, adverse effects, and interactions with conventional medications. Acute and chronic toxicity studies in animal models provide important safety data, but differences in metabolism, dosing, and species-specific sensitivities necessitate cautious extrapolation to humans. Clinical safety monitoring in human trials and post-marketing surveillance further contribute to understanding of safety profiles.

Most commonly used medicinal plants for gastrointestinal disorders demonstrate favorable safety profiles when used at recommended doses. Turmeric and curcumin have been consumed as dietary spices for millennia, and clinical trials report minimal adverse effects at doses up to 12 grams daily, with occasional mild gastrointestinal symptoms including nausea or diarrhea. However, high doses may increase bleeding risk due to antiplatelet effects, necessitating caution in patients on anticoagulant therapy. Ginger is generally well tolerated with mild side effects limited to heartburn or gastrointestinal discomfort in some individuals, though concerns exist regarding potential effects on bleeding parameters and interactions with anticoagulants. Peppermint oil demonstrates excellent safety in clinical trials when administered in enteric-coated formulations, with adverse effects primarily limited to mild heartburn, perianal burning, or allergic reactions in sensitive individuals. Non-enteric formulations may cause gastroesophageal reflux or esophageal irritation. Licorice root, while demonstrating therapeutic benefits, contains glycyrrhizin that can cause pseudoaldosteronism characterized by hypertension, hypokalemia, and edema when consumed in excessive quantities or for prolonged periods. Deglycyrrhizinated licorice preparations eliminate this risk while retaining gastroprotective properties.

Aloe vera gel for oral consumption is generally considered safe, though anthraquinone-containing aloe latex has laxative effects and potential for dependency with chronic use. Safety concerns regarding potential carcinogenicity of whole-leaf aloe preparations containing aloin have led to recommendations for using purified gel preparations. Psyllium husk demonstrates excellent safety but requires adequate fluid intake to prevent esophageal or intestinal obstruction, particularly in individuals with swallowing difficulties or intestinal strictures.

Hepatotoxicity represents the most serious safety concern associated with certain herbal products. While most gastrointestinal-targeted herbs demonstrate hepatoprotective rather than hepatotoxic effects, some traditional preparations and dietary supplements have been associated with liver injury. Green tea extract in high doses has been linked to hepatotoxicity in susceptible individuals, though the mechanism remains incompletely understood. Herbal products containing pyrrolizidine alkaloids, found in certain Boraginaceae and Asteraceae species, carry hepatotoxic and carcinogenic risks and should be avoided. Contamination with heavy metals, pesticides, mycotoxins, or adulterants in poorly manufactured products poses additional safety concerns, emphasizing the importance of quality control and regulatory oversight.

Herb-drug interactions represent clinically important safety considerations that can result in altered pharmacokinetics or pharmacodynamics of conventional medications.

Mechanisms of interaction include modulation of cytochrome P450 enzymes, drug transporters including P-glycoprotein, or pharmacodynamic effects such as additive or antagonistic actions. St. John's wort, though not primarily used for gastrointestinal disorders, exemplifies clinically significant herb-drug interactions through induction of CYP3A4 and P-glycoprotein, leading to reduced efficacy of numerous medications including immunosuppressants, anticoagulants, and hormonal contraceptives.

Curcumin and piperine inhibit various cytochrome P450 isoforms and may increase plasma concentrations of drugs metabolized by these enzymes, potentially enhancing both therapeutic and adverse effects. Ginger demonstrates antiplatelet activity and may potentiate effects of anticoagulant and antiplatelet medications, increasing bleeding risk. Green tea catechins may reduce iron absorption and interfere with certain chemotherapeutic agents. Licorice can reduce effectiveness of antihypertensive medications and potentiate effects of corticosteroids through inhibition of 11-beta-hydroxysteroid dehydrogenase.

Risk mitigation strategies include comprehensive medication history taking, patient education regarding potential interactions, therapeutic drug monitoring when appropriate, gradual introduction of herbal products with observation for adverse effects, and consultation with healthcare providers knowledgeable in both conventional and botanical medicine. Healthcare providers should maintain awareness of commonly used herbal products, potential interaction mechanisms, and resources for interaction checking. Pregnant and lactating women, pediatric patients, elderly individuals with polypharmacy, and patients with significant hepatic or renal impairment warrant particular caution regarding herbal product use due to altered pharmacokinetics, increased vulnerability to adverse effects, or limited safety data in these populations.

Regulatory, Standardization, and Quality Control Considerations

The regulatory landscape for plant-based therapeutics varies considerably across different countries and jurisdictions, reflecting diverse approaches to classification, approval requirements, and quality standards. In the United States, most herbal products are regulated as dietary supplements under the Dietary Supplement Health and Education Act, which does not require premarket approval for safety and efficacy but prohibits disease claims without Food and Drug Administration approval. This regulatory framework differs substantially from the rigorous approval process required for pharmaceutical drugs, resulting in variability in product quality and limited regulatory oversight. Some plant-derived compounds that demonstrate sufficient evidence may be developed as botanical drugs through the FDA's botanical drug development guidance, requiring comprehensive preclinical and clinical data similar to conventional drugs.

The European Union regulates herbal medicinal products through the Traditional Herbal Medicinal Products Directive, which establishes a simplified registration procedure for traditional herbal medicines with demonstrated traditional use of at least 30 years, including 15 years within the European Union. This framework recognizes traditional knowledge while requiring evidence of safety and traditional use. The European Medicines Agency's Committee on Herbal Medicinal Products develops monographs providing scientific guidance on quality, safety, and efficacy of herbal substances. Germany's Commission E monographs have historically provided authoritative evaluations of herbal medicines, though these have been partially superseded by European Union harmonization efforts.

Other countries including China, India, and Japan have developed regulatory frameworks that integrate traditional medicine systems with modern pharmaceutical regulation. Traditional Chinese Medicine and Ayurvedic preparations are subject to specific regulatory pathways that acknowledge historical use while implementing quality and safety standards. The World Health Organization has developed guidelines for quality control of herbal medicines and traditional medicine regulation to promote harmonization and ensure public health protection.

Quality control of plant-based therapeutics encompasses multiple dimensions including botanical authentication, chemical standardization, contaminant testing, stability assessment, and good manufacturing practices compliance. Botanical authentication verifies the identity of plant species used in products, employing techniques including macroscopic and microscopic examination, organoleptic evaluation, chemical profiling, and DNA barcoding. Misidentification or adulteration represents significant quality concerns, with studies revealing that substantial percentages of commercial herbal products contain plant species different from those listed on labels.

Chemical standardization, as discussed previously, quantifies marker compounds or bioactive constituents to ensure consistent potency. Pharmacopoeial standards including those published by the United States Pharmacopeia, European Pharmacopoeia, and other national compendia provide official quality specifications for selected botanical materials. However, many plants used in traditional medicine lack pharmacopoeial monographs, necessitating development of in-house or industry standards. Contaminant testing screens for heavy metals including lead, cadmium, mercury, and arsenic; pesticide residues; microbial contamination including pathogenic bacteria and fungi; mycotoxins including aflatoxins; and residual solvents from extraction processes.

Stability testing evaluates how quality attributes change over time under various storage conditions, establishing appropriate shelf life and storage recommendations. Good manufacturing practices compliance ensures that products are consistently produced and controlled according to quality standards, covering aspects including facility design, equipment qualification, process validation, personnel training, documentation, and quality management systems. Third-party certification programs and quality seals provide consumers with additional assurance of product quality, though proliferation of certification schemes has created complexity in the marketplace.

Challenges to ensuring quality and standardization include the inherent variability of plant materials due to genetic diversity, environmental conditions, harvesting practices, and post-harvest handling; complexity of plant extracts containing hundreds of compounds; limited analytical resources and expertise in many manufacturing facilities; economic incentives for adulteration or substitution; and globalization of supply chains increasing vulnerability to quality lapses. Emerging technologies including metabolomics, DNA barcoding, hyperspectral imaging, and blockchain traceability systems offer potential solutions to enhance quality assurance.

Pharmacovigilance systems for monitoring adverse events associated with herbal products remain underdeveloped in many countries, resulting in underreporting of safety concerns. Strengthening post-market surveillance, establishing herb-drug interaction databases, and improving communication between conventional healthcare providers and patients regarding herbal product use represent important public health priorities. Education of healthcare professionals regarding botanical medicine, quality considerations, and

evidence-based use can improve appropriate integration of plant-based therapeutics into clinical practice.

Future Perspectives and Translational Potential

The future of plant-based therapeutics in gastrointestinal disorders encompasses multiple promising directions including discovery of novel bioactive compounds, elucidation of mechanisms through systems biology approaches, development of optimized formulations and delivery systems, conduct of rigorous clinical trials, integration with personalized medicine paradigms, and establishment of appropriate regulatory frameworks. Advances in analytical chemistry, molecular biology, and computational methods are accelerating the pace of discovery and development in this field.

High-throughput screening methodologies enable systematic evaluation of large numbers of plant extracts and compounds for specific biological activities, identifying promising candidates for further development. Virtual screening using molecular docking and quantitative structure-activity relationship modeling can predict interactions between phytochemicals and molecular targets, guiding rational selection of compounds for experimental validation. Metabolomics approaches provide comprehensive chemical fingerprints of plant extracts and enable correlation of chemical profiles with biological activities, facilitating quality control and identification of bioactive constituents. Systems biology and network pharmacology approaches recognize the multi-target nature of plant-based therapeutics and employ computational methods to map interactions between phytochemical constituents and multiple biological targets, pathways, and networks. These approaches align well with the holistic philosophy of traditional medicine systems and provide mechanistic insights into synergistic effects of complex formulations. Integration of genomics, transcriptomics, proteomics, and metabolomics data generates comprehensive understanding of how plant-based therapeutics modulate biological systems at multiple levels. Microbiome research represents a particularly promising frontier for understanding mechanisms and optimizing applications of plant-based therapeutics. Recognition that gut microbiota serves as a critical interface between phytochemicals and host biology has spurred investigation of microbiota-mediated biotransformation of phytochemicals, production of bioactive metabolites by gut bacteria, and reciprocal effects of phytochemicals on microbial composition and function. Personalized nutrition and medicine approaches may stratify patients based on microbiome profiles to predict responses to specific plant-based interventions, optimizing therapeutic outcomes. Clinical trial methodologies require refinement to address unique challenges of evaluating plant-based therapeutics. Pragmatic trial designs that reflect real-world clinical practice, inclusion of traditional diagnostic categories alongside conventional disease classifications, use of patient-reported outcome measures that capture holistic health benefits, and development of appropriate comparison groups are important considerations. Comparative effectiveness research evaluating plant-based therapeutics against conventional treatments and investigation of combination approaches integrating herbal and pharmaceutical interventions provide clinically relevant evidence to guide practice.

Regulatory evolution toward science-based frameworks that recognize unique characteristics of botanical medicines while maintaining rigorous safety and efficacy standards represents an important goal. The botanical drug development pathway in the United States and similar initiatives in other countries provide models for translating promising traditional medicines into approved therapeutics. Harmonization of international regulatory standards, establishment of regional cooperation mechanisms, and capacity building in quality control and pharmacovigilance strengthen the global botanical medicine ecosystem.

Education and training of healthcare professionals in integrative approaches that combine conventional and botanical medicine enable informed decision-making and appropriate patient counseling. Development of evidence-based clinical practice guidelines incorporating plant-based therapeutics for specific gastrointestinal conditions, establishment of specialty clinics integrating conventional gastroenterology with botanical medicine expertise, and fostering of interdisciplinary collaboration between physicians, pharmacists, herbalists, and researchers promote optimal patient care.

Sustainability considerations regarding cultivation, harvesting, and processing of medicinal plants merit attention as demand increases. Overharvesting of wild populations threatens biodiversity and traditional medicine resources, necessitating cultivation programs, sustainable harvesting practices, and conservation initiatives. Ethical considerations regarding intellectual property rights, benefit sharing with indigenous communities, and preservation of traditional knowledge systems require ongoing dialogue and appropriate policy frameworks.

The potential for developing novel therapeutics from plant sources remains vast, with the majority of plant species insufficiently explored for bioactive constituents. Ethnobotanical knowledge from traditional medicine systems provides valuable leads for drug discovery, while random screening of biodiversity expands the chemical space for therapeutic discovery. Semisynthetic modification of natural product scaffolds and bioprospecting in underexplored ecosystems including marine environments and extremophiles offer additional opportunities for therapeutic innovation.

Integration of artificial intelligence and machine learning approaches accelerates various aspects of plant-based therapeutic development including prediction of bioactive properties from chemical structures, optimization of extraction and formulation parameters, analysis of complex datasets from omics studies, and identification of patient subgroups likely to respond to specific interventions. Digital health technologies including mobile applications for symptom tracking, telemedicine consultations, and decision support systems may facilitate appropriate use of plant-based therapeutics and monitoring of therapeutic responses.

Conclusion

Plant-based therapeutics represent a valuable and increasingly evidence-based approach to the management, prevention, and treatment of gastrointestinal disorders. The extensive body of preclinical research demonstrates that bioactive phytochemicals exert protective effects through multiple mechanisms including anti-inflammatory activity, antioxidant capacity, antimicrobial properties, microbiota modulation, and enhancement of mucosal defense mechanisms. Clinical trials, while varying in quality and

scope, provide support for the efficacy and safety of several plant-based interventions in conditions including irritable bowel syndrome, inflammatory bowel disease, peptic ulcer disease, and functional dyspepsia.

The multitarget nature of phytochemicals offers potential advantages in addressing the complex and multifactorial pathophysiology of gastrointestinal disorders. Rather than viewing plant-based and conventional therapeutics as mutually exclusive approaches, integration of evidence-based herbal interventions as adjunctive therapy or, in selected cases, as primary treatment for mild to moderate disease represents a rational strategy. Continued research efforts are necessary to strengthen the evidence base, optimize formulations and delivery systems, establish appropriate dosing regimens, identify patient populations most likely to benefit, and develop personalized treatment approaches.

Critical challenges that must be addressed include ensuring quality, standardization, and authentication of plant-based products; establishing robust pharmacovigilance systems for adverse event monitoring; educating healthcare professionals and patients regarding appropriate use and potential interactions; and developing regulatory frameworks that balance accessibility with safety and efficacy standards. Advances in analytical technologies, delivery systems, and understanding of mechanisms continue to enhance the therapeutic potential of plant-based interventions.

The future of plant-based therapeutics in gastrointestinal medicine lies in rigorous scientific investigation that builds upon traditional knowledge while employing modern research methodologies. Systems biology approaches, microbiome research, personalized medicine paradigms, and integration with conventional therapeutic modalities offer promising directions for advancing this field. As global interest in natural products and integrative medicine continues to grow, plant-based therapeutics are poised to play an increasingly important role in comprehensive gastrointestinal care, offering patients additional options for managing their conditions while potentially reducing adverse effects and healthcare costs associated with conventional treatments.

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