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Review article

# Herbal Remedies and Their Gastrointestinal Side Effects: an In-Depth Analysis

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## Abstract

The use of herbal remedies is globally increasing due to the supposed advantages of being natural means of health. Serious concerns regarding the safety and efficacy of these remedies, especially gastrointestinal (GI) side effects, have arisen. A literature search was done using Google Scholar, Web of Science, and PubMed databases with recent time frame (2002 to 2025). This review presents a comprehensive analysis of the mechanisms, prevalence, and clinical implications of herbal-induced GI disturbances. It draws critical attention to herbal medicines' increase worldwide in popularity, supported by statistical findings on their use and adverse effects, particularly of some common herbs such as *Senna alexandrina* Mill., *Aloe vera* (L.) Burm.f., and *Pulicaria burchardii* Hutch. This review illustrates the mechanisms causing herbal-induced GI disturbances, including mucosal irritation, immune-mediated inflammation, dysbiosis, oxidative stress, pharmacological toxicity. In addition, herb-herb, food-herb, and drug-herb interactions convey considerable challenges for herbal supplements, given the current lack of standardization and regulation. Mitigation strategies for GI side effects are proposed. Key research gaps are identified, along with recommendations for future research, including rigorous clinical trials, pharmacokinetic studies, and standardized quality-control protocols. The review concludes by advocating rigorous research and collaborative endeavors to inject the application of herbal remedies into modern health care with some level of assurance.

**Keywords:** gastrointestinal adverse effects; herbal medicine; herb-drug interactions; pharmacokinetics; toxicological phenomena

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## Introduction

Recent years have perceived a rapid global increase in the use of herbal remedies which arise from the growing preference for natural health solutions and traditional medicine. The safety and efficacy of many herbal products remain grossly understudied, especially concerning their gastrointestinal side effects. Herbal remedies are applied globally, with about 80% of the world population relying on traditional medicine for primary healthcare needs [1]. In developed countries, dissatisfaction with conventional therapies and preference for holistic approaches have familiarized the popularity for herbal products. In the United States, approximately 20% of the population use herbal supplements, developing a multibillion-dollar industry [2,3]. In Europe, Germany and France, people have placed herbal medicine firmly in their healthcare systems, invoking arguments for its cultural relevance and safe use [4,5]. The Mediterranean basin with diversified ecosystems has a culture of using medicinal plants, a culture that persisted through COVID-19 [6,7]. In Africa, herbal medicine is embedded with cultural and spiritual

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practices that can provide accessible and affordable healthcare solutions [8,9]. Meanwhile, Asia remains the bastion of traditional systems like Ayurveda in India and traditional Chinese medicine (TCM) in China. Over 70% of India's population is dependent on herbal remedies, and TCM contributes one-fifth of China's pharmaceutical market [10,11]. TCM's arena has been contested in Southeast Asia, especially among the Chinese diaspora, and the belt has been strengthened by projects like the belt and road initiative [12,13].

Since the inception of mankind, the remedial herbs were always accompanied with risk. World Health Organization has claimed that 20-30% of herbal remedy users do suffer some adverse effects, among which GI symptoms are the most reported [14,15] (Figure 1). In USA, the National Poison Data System documented over 30000 cases of herbal-related toxicity in 2022, of which 15% were of GI symptoms, specifically nausea, vomiting, and diarrhea [16]. The regional data throw light on the incidence of these issues. In Asia, where herbal medicine finds its roots in traditional practices, patients using berberine, existing in several medicinal plant species, reported bloating and diarrhea [17]. In Africa, almost all cases of hepatotoxicity that linked to the traditional herb *Callilepis laureola* DC. were reported alongside GI symptoms, leading to high as 20-30% mortality cases in rare severe instances [18]. In Europe, a study in 2021 reported 10% of herbal supplement users experienced GI side effects, with *Senna alexandrina* Mill., traditionally popular as a laxative, and *Aloe vera* (L.) Burm.f., traditionally popular to treat skin [19].

Considering that herb toxicity is increasing throughout the world, a 15% of annual rise in cases has been recorded in 2023, with all the difficulties driven from regulation system failure, contamination, and wrong usage of herbal products [20]. Demographic observations indicate that women have 1.5 times more likelihood to experience herbal-induced GI side effects than men, as they consume more herbals than men [21]. The elderly people are at higher risk for such effects, possibly because of polypharmacy, as well as modifications of drug metabolism associated with aging [22]. The financial impact is considerable, with an estimated annual cost of two billion Dollars in the USA for addressing herb-related adverse effects, 30% of which is attributable to GI complications [23].

This review aims to present an in-depth study of the mechanisms, prevalence, and clinical relevance of herb-induced GI disturbances. In addition, strategies to reduce these risks will be stated, and future research directions will be described to bridge the existing knowledge gaps.

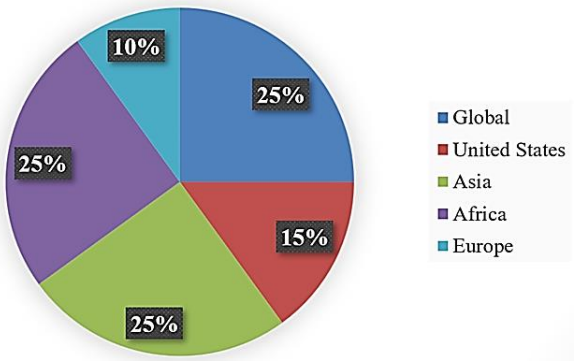


**Figure 1.** The adverse effects of herbal remedies. Percentages according to various regions in different countries [16-19].

## Methods

A broad literature overview was carried out using Google Scholar, Web of Science, and PubMed databases to identify publications best fitting the sought themes of studies on herbal remedies and their GI side effects. The literature examined included studies that addressed topics including "herbal remedies," "gastrointestinal side effects," "mucosal irritation," "immune-mediated inflammation," "dysbiosis," "oxidative stress," "pharmacological toxicity," "herb-herb interactions," "food-herb interactions," and "drug-herb interactions." Specific herbs that are commonly implicated in GI disturbances were also searched-for terms such as *Senna alexandrina*, *Aloe vera*, and *Berberis vulgaris* L. Searches were limited to English publications and were kept general in order to include both historical and contemporary data. Studies were filtered for mechanisms, prevalence, and clinical implications of herbal-induced GI disturbances. Moreover, data regarding the safety and efficacy and related regulatory challenges of herbal supplements were also extracted. Complementary to the literature review, the study underscores the need for robust clinical trials, advanced pharmacokinetic studies, and standardized quality-control protocols to fill some critical gaps in the current knowledge. The time frame for the study search was (2002 to 2025).

## Results and Discussion

### Mechanisms of herbal-induced GI complications

Herbal medicines can produce GI disorders by different interconnected mechanisms. Knowledge of these pathways will help in minimizing the risks and providing the safe use of herbal products (Figure 2).

### Mucosal irritation

Through the irritant properties on the GI mucosa, mucosal irritation constitutes an important source of GI disturbance in herbal medicine. Herbal drugs with bioactive substances such as alkaloids, tannins, and saponins can irritate the GI mucosa. *Aloe vera*, is an example of these herbs which is used for laxative purposes. It contains anthraquinones, believed to stimulate intestinal motility and fluid secretion, thus inducing cramping and diarrhea [24]. *Senna alexandrina*, a common herbal laxative, also causes mucosal damage and inflammation on prolonged use [25].

### Immune-mediated inflammation

Immune-mediated inflammation constitutes yet another crucial mechanism underlying herbal-induced GI disturbances. Certain herbal compounds may act as haptens, binding to endogenous proteins and triggering hypersensitivity reactions. *Echinacea purpurea* (L.) Moench. which has a reputation for immunomodulation, has been cited to stimulate intestinal epithelial cells to release pro-inflammatory cytokines, causing nausea, abdominal pain, and diarrhea among hypersensitive individuals [26,27]. Contaminants in herbal products, such as allergens or microbial toxins, may also aggravate the immune responses and contribute to GI inflammation [28]. The inflammation may compromise the integrity of the intestinal epithelial barrier, leaving the person predisposed to further GI disorders. Any mode of herbal medicines influencing an immune response can plausibly be injurious to the GI tract. Furthermore, *Echinacea purpurea* normally contributes in stimulating the immune system, yet in some individuals, it causes too much stimulation, leading to GI inflammation and discomfort [29].

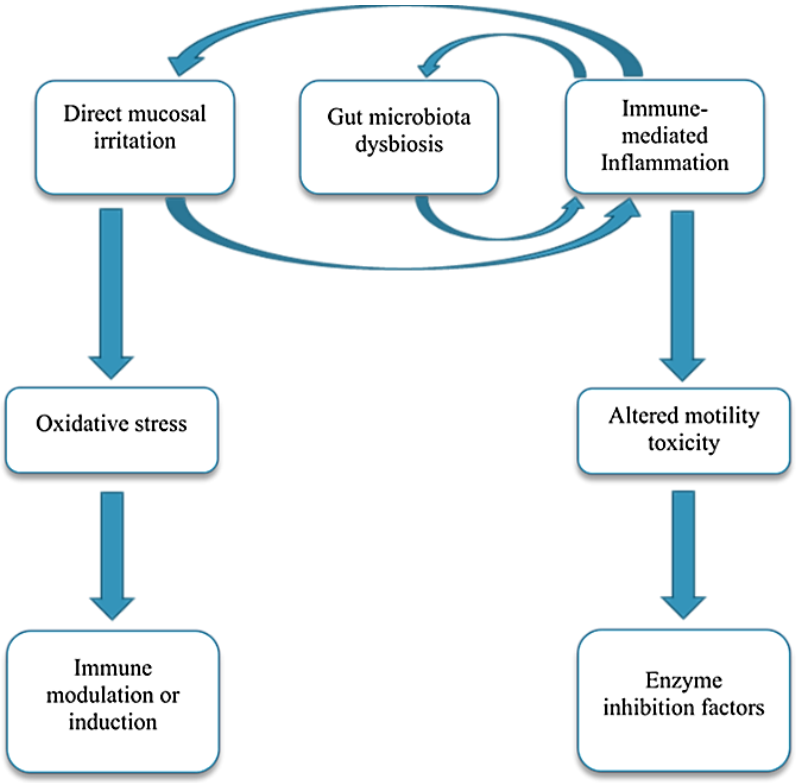


**Figure 2.** Mechanisms in herbal-induced GI disturbance

Likewise, herbs with immunomodulatory activity, such as *Curcuma longa*, may create disturbances in the cytokine profiles of symptomatic patients suffering from inflammatory bowel disease [26,30]. Some individuals may experience hypersensitivity to herbal substances which would lead to immune-mediated GI inflammation. The immunostimulatory activity of *Echinacea purpurea* has been reported to cause nausea and abdominal pain in sensitive persons [27]. The advent of contamination through herbal products may lead to allergic reactions or toxic hepatitis and influence GI function indirectly [28].

**Dysbiosis and disruption of gut microbiota**

Gut microbiota serves a cardinal role in maintaining GI homeostasis; any disruption of dysbiosis entails a chief mechanism in herbal-induced GI disturbances. Herbal compounds with antimicrobial effects, such as berberine, can selectively inhibit beneficial gut bacteria, leading to an imbalance in microbial populations [29]. Impairment of gut barrier function, increased intestinal permeability, and promotion of systemic inflammation due to this dysbiosis may manifest as bloating, diarrhea, and abdominal pain [31]. Alterations in microbial metabolites due to dysbiosis, including short-chain fatty acids, may further aggravate GI dysfunction and induce chronic inflammatory conditions. Berberine, the alkaloid driven from *Berberis aristata* DC., has an antimicrobial effect which can adversely reduce beneficial gut bacteria, potentially inducing diarrhea and bloating [29]. Dysbiosis possibly hampers the gut barrier function, permitting an increased chance of inflammation and GI symptoms [31].

**Additional mechanisms**

Herbal compounds can create oxidative stress conditions in the gastrointestinal tract (GIT) by generating reactive oxygen species and/or by reducing or consuming the antioxidant defense mechanism. Some herbs with high content of polyphenols or alkaloids might actually lead to cellular injury in the intestinal epithelium in an outwardly pro-oxidative manner [32]. Oxidative stress can disrupt intestinal integrity, increase permeability, and further incite inflammatory reactions to manifest symptoms of gut distress such as abdominal cramping and diarrhea [24].

Specific herbal agents have a direct effect on the GI motility either through stimulant action on GI smooth muscle contractions or inhibition of such contractions. The anthraquinone-containing *Aloe vera* and *Senna alexandrina* promote peristalsis and thereby expedite colonic transit causing diarrhea and cramping [33]. By contrast, herbs such as *Atropa belladonna* L., which exert their action by blocking receptors for the neurotransmitter acetylcholine, slow down GI motility thereby contributing to conditions of constipation and bloating [28]. The dynamics involved in this mechanism are generally dose-dependent and may vary upon the individual's own sensitivity.

Herbal remedies can potentiate conventional medicines frustrating their GI side effects. *Ginkgo biloba* L. might aggravate the likelihood of bleeding in patients taking anticoagulants almost leading to GIT hemorrhage [34]. Whilst *Hypericum perforatum* L induces cytochrome P450 enzymes modifying the metabolism of drugs and thereby inducing possible GIT discomfort [30]. Again, certain herbal substances show direct toxicity against the GIT lining; pyrrolizidine alkaloids originating from plants such as *Symphytum officinale* L. may produce hepatotoxicity by involving secondary GI symptoms such as nausea, vomiting, and abdominal pain [35].

Herbal preparations that have been contaminated with heavy metals or pesticides may in turn provide direct detoxification effects to the GIT mucosa, inducing acute or chronic disturbances in the GI tract [27]. Heavy metals, pesticides, or microbial pathogens during cultivation and processing could net direct toxic effects on the GI tract, explaining symptoms ranging from nausea and vomit to diarrhea [35]. The pathophysiology of herbal-induced degradation of GIT function is multifactorial, including direct mucosal irritation, disruption of gut homeostasis by the gut microbiota, immune-mediated responses, pharmacological mechanisms of interaction, and contamination. The passive perception of herbal remedies being absolutely safe has encouraged their possible adverse effects on the GI tract; hence prudent usage, strict control of quality, further studies are needed to validate the safety of herbal remedies and their efficacy.

**Interplay between mechanisms**

Interaction between the mucosal irritative action, immune-mediated inflammatory responses, and dysbiosis perpetuate a vicious cycle that maintains GI dysfunction (Figure 3).

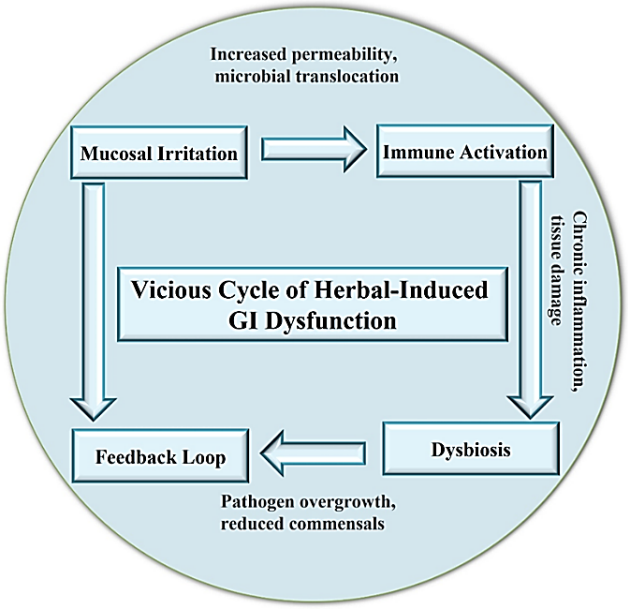


**Figure 3.** Vicious cycle of GI dysfunction induced by herbs

Thus, for instance, direct mucosal irritative action may compromise epithelial integrity with the subsequent translocation of microbial components triggering immune activation [36]. At the same time, dysbiosis can exacerbate inflammation by fostering the growth of pathogenic bacteria, while decreasing anti-inflammatory commensals [37]. This synergy is a vast confirmation of the many interlocked avenues fortifying an herbal-induced pseudo-GI pathology [38]. The salient mechanisms of herbal-induced GI issues-i.e., irritation, inflammation, and dysbiosis-are intertwined and collectively lead to the onset and progression of GI symptoms [39]. Understanding these pathways will help to design interventions to limit the negative effects of herbal medicine and allow for safer practice [40]. Further studies need to uncover the exact mechanisms and individual risk factors behind these processes [26,41].

## Common herbal remedies and their GI side effects

Though herbal remedies are used for many therapeutic effects, they may cause GI side effects due to active compounds and the mechanisms of action (Table 1). *Aloe vera* and *Senna alexandrina* can cause diarrhea and abdominal pain [24,25], whereas *Berberis vulgaris* and *Curcuma longa* may also induce bloating and dysbiosis [29,31].

Some of the herbs, such as *Echinacea purpurea*, *Ginkgo biloba*, and *Hypericum perforatum*, induce nausea or discomfort in the GIT, as well as *Symphytum officinale* also augments this scenario with nausea and abdominal pain by causing hepatotoxicity [27,30]. Pseudoaldosteronism is caused with *Glycyrrhiza glabra* L. roots; *Mentha piperita* L. leads to heartburn; *Zingiber officinale* Roscoe. may cause abdominal discomfort when taken in higher doses; while *Allium sativum* L. is associated with bloating and flatulence [42-45]. In a meta-analysis in 2022, *Senna alexandrina* was found to cause diarrhea in 40% and abdominal pain in 20% of users [46]. *Aloe vera* similarly caused 30% of participants in another study to suffer from cramping and diarrhea in 2021 [47]. In 2023 clinical trial, 25% of patients used berberine suffered from bloating and diarrhea [48]. Traditional poisonous medicinal plants pose hazardous risk, *Aconitum* species containing aconitine, account for 5% of herbal toxicity cases in China, and cause severe GI symptoms like nausea and vomiting [49]. The tropane alkaloids from *Atropa belladonna* resulted in constipation and dry mouth in 3% of herbal toxicity cases in Europe [50].

*Symphytum officinale* accounts for 2% of herbal toxicity cases in the USA resulting in hepatotoxicity and other associated GI symptoms [51]. Global case studies provide further evidence of the worldwide nature of herbal-induced GI issues.

**Table 1.** Common herbal remedies with common GI side effects

| Herbal remedy | Active compound (s) | Benefits | Common GI side effects | Pharmaceutical form | Dosage | Mechanism of action | Ref. |
|---|---|---|---|---|---|---|---|
| ***Aloe vera*** | Anthraquinones | Anti-inflammatory, wound-healing, and laxative properties | Diarrhea, cramping, dehydration | Capsule, gel, juice | 250-500 mg/day | Stimulates intestinal motility and fluid secretion; irritates mucosa | [24] |
| ***Senna alexandrina*** | Sennosides (anthraquinones) | Effective laxative for constipation | Diarrhea, abdominal pain | Tablet, tea, capsules | 15-30 mg/day | Direct mucosal irritation; increased peristalsis | [25] |
| ***Berberis vulgaris*** | Berberine | Antimicrobial, anti-inflammatory, and metabolic benefits | Bloating, diarrhea | Capsule, tincture | 500-1000 mg/day | Antimicrobial effects disrupt gut microbiot; induces dysbiosis | [29] |
| ***Echinacea purpurea*** | Alkamides, polysaccharides | Immune-boosting and anti-inflammatory properties | Nausea, abdominal pain | Tablet, liquid extract | 300-500 mg/day | Immune-mediated inflammation; cytokine release | [27] |
| ***Ginkgo biloba*** | Flavonoids, terpenoids | Cognitive enhancement and antioxidant properties | Nausea, vomiting, diarrhea | Capsule, tablet | 120-240 mg/day | Inhibits cytochrome P450 enzymes; interacts with medications | [30] |
| ***Hypericum perforatum*** | Hypericin, hyperforin | Antidepressant and anxiolytic effects | GI discomfort, diarrhea | Capsule, tea | 300-600 mg/day | Induces drug-metabolizing enzymes; alters drug metabolism | [30] |
| ***Curcuma longa*** | Curcumin | Anti-inflammatory, antioxidant, and anticancer properties | Bloating, diarrhea (in high doses) | Capsule, powder, extract | 500-1500 mg/day | Immune modulation; alters cytokine profiles | [31] |
| ***Symphytum officinale*** | Pyrrolizidine alkaloids | Anti-inflammatory and wound-healing properties | Nausea, vomiting, abdominal pain | Tea, ointment | Traditionally used as an external application only | Hepatotoxicity; secondary GI effects | [28] |
| ***Glycyrrhiza glabra*** | Glycyrrhizin | Anti-inflammatory and gastroprotective properties | Nausea, abdominal pain, pseudoaldosteronism | Capsule, tea, extract | 250-500 mg/day | Inhibits 11β-hydroxysteroid dehydrogenase; causes sodium retention and potassium loss | [42, 55] |
| ***Mentha piperita*** | Menthol | Relieves IBS symptoms | Heartburn | Essential oil, capsule, tea | 100-200 mg/day | Relaxes smooth muscles in the GI tract; may lower esophageal sphincter pressure | [43] |
| ***Zingiber officinale*** | Gingerols, shogaols | Reduces nausea and vomiting | Abdominal discomfort (in high doses) | Capsule, powder, fresh root | 1000-2000 mg/day | Modulates serotonin receptors; antiemetic effects | [56] |
| ***Allium sativum*** | Allicin, sulfur compounds | Cardiovascular and antimicrobial properties | Nausea, bloating, flatulence | Capsule, fresh cloves | 500-1000 mg/day | Irritates GI mucosa; sulfur compounds cause gas production | [44, 45] |

IBS: inflammatory bowel syndrome

A 2022 study in China reported 500 herbal-induced liver injury cases, among which 30% showed GI symptoms manifested as nausea and vomiting, primarily associated with *Fallopia multiflora* (Thunb.) Haraldson [52]. In India, a 2021 survey showed that 20% of patients using Ayurvedic medicine showed GI side effects, primarily due to *Senna alexandrina* and *Aloe vera* [53]. The use of *Callilepis laureola* in South Africa has been reported to be linked with herbal

toxicity in 50 cases of hepatotoxicity per year, with 40% of the patients having GI symptoms [54]. A list of specific herbs, their benefits, side effects, mechanism, and case studies are presented in Table 1.

**Case reports of GI side effects**

Various gastrointestinal side effects have been reported for herbal remedies in individual case reports. *Aloe vera* use for more than three months caused severe diarrhea and electrolyte imbalances in a 45-year-old woman [51]. Taking *Senna alexandrina* for two years induced melanosis coli in a 60-year-old man [20]. In another case, *Berberis vulgaris* supplementation caused bloating and diarrhea after four weeks in a 40-year-old woman [57]. It has been found that, ten days after using *Echinacea purpurea*, a 30-year-old man reported nausea and abdominal pain [58]. Nausea and diarrhea were observed in a 55-year-old woman after three weeks of using *Ginkgo biloba* [59]. *Hypericum perforatum* use caused diarrhea in a 25-year-old woman after two months [60]. Furthermore, a 50-year-old man experienced bloating and diarrhea after one month of high-dose *Curcuma longa* supplementation [61]. Male, 45 years old, after three weeks of *Symphytum officinale* tea, developed nausea and abdominal pain [62]. Abdominal pain and hypertension arose after six months of *Glycyrrhiza glabra* intake in a 35-year-old woman [63]. A 28-year-old male with IBS experienced worsening heartburn after four weeks of *Mentha piperita* [64]. *Zingiber officinale*, in high doses over two weeks, caused abdominal discomfort in a 32-year-old woman [65]. Lastly, *Allium sativum* was linked to severe bloating and flatulence in a 50-year-old woman after two months of use [66].

**Dose-response relationships and the parameters of safe usage**

The dosage of herbal remedy often determines therapeutic efficacy and safety. Often, such benefits are derived from low to moderate doses, and toxic effects occur at high doses with GI tract toxicity (Figure 4). In this concern, numerous reports showed that doctors are supposed to prescribe dosages and be watchful for any adverse effects. On the contrary, *Aloe vera* is generally considered safe within a dosage range of 50–200 mg/day for a maximum duration of 10 days [24]. However, prolonged use requires careful monitoring, as it may lead to electrolyte imbalance and mucosal damage [25].

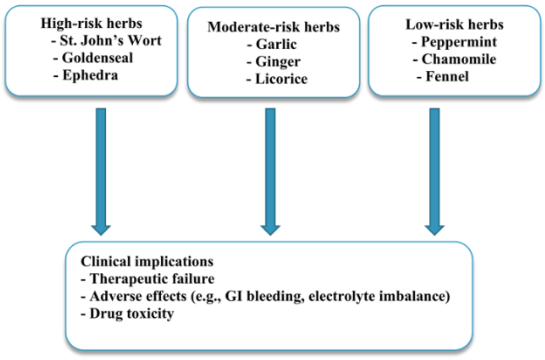


**Figure 4.** Risk stratification; Plants are categorized according to risk and the way they might cause clinical problems. The downward arrows indicate that all have clinical relevance irrespective of their level of risk.

*Senna alexandrina* is commonly supplemented with sennosides at a dose of 15–30 mg per day for a duration of 1 to 2 weeks to achieve full laxative effectiveness [67]. However, prolonged use can result in dependence and melanosis coli [28]. Furthermore, *Glycyrrhiza glabra* root, when consumed at concentrations of 100 mg/day glycyrrhizin for up to four weeks, presents potential risk factors such as pseudoaldosteronism, necessitating caution in its administration [28]. *Mentha piperita* oil is recommended 0.2-0.4 mL/day for IBS [35]; *Zingiber officinale* is effective at 1-2 g/day for nausea or vomiting [53]. Thus, their concentrations are quite safe around such ranges but would lead to GI discomfort if taken in higher concentrations. These have demonstrated how essential is to adhere to safe dosage guidelines in order to maximize benefits and reduce risks.

**Interactions between herb-herb, food-herb, and drug-herb**

Concerns are emerging in anticipation of the widespread global adoption of herbal medicines, particularly regarding potential possible herb-herb, food-herb, and drug-herb interactions. Such interactions can probably change both the pharmacokinetics and pharmacodynamics of the supplements, resulting in therapeutic failure or adverse effects (Table 2). Interaction of herb-herb mostly occurs when two or more herbal products are combined resulting in synergistic, additive, or antagonistic effects. In the case of anticoagulants, *Panax ginseng* C.A. Mey. may intensify the effect with its combination with *Ginkgo biloba*

[68]. Certain combinations that reduce the effectiveness of medications include substances with conflicting pharmacological effects, like the combination of stimulant herbs and sedative herbs [69]. Moreover, the regulation of cytochrome P450 (CYP) enzymes in connection with P-glycoprotein (P-gp) transporters is widely regarded as a crucial factor in facilitating drug-drug interactions [70].

Food-herb interaction refers to the interaction in the diet and the herbal product. For example, grapefruit juice acts as an inhibitor for CYP3A4 enzyme and modifies the metabolism of those herbs such as *Hypericum perforatum*, with an increased possibility for toxicity [71]. Similarly, high-fat meals can additionally enhance the bioavailability of lipophilic herbal compounds like curcumin, resulting in unintended effects as the absorption of the herbal compound improves [72]. Such interactions are beneficial in populations that consume functional foods as part of their diets or herbal supplements.

Drug-herb interaction is the most clinically impactful because it lowers the efficacy of the conventional medication and safety. From the herbs inducing liver CYP enzymes is *Hypericum perforatum*, which induces CYP3A4 and P-gp, leading to lowered plasma concentrations of drugs, including warfarin, cyclosporine, and oral contraceptives [73]. *Allium sativum* supplement exhibit anti-platelet aggregation activity, which can be beneficial for cardiovascular health. However, when used inappropriately or in excess, especially by patients taking anticoagulant medications, this effect can increase the risk of bleeding, highlighting both its therapeutic potential and safety concern [74]. Similarly, *Hydrastis canadensis* L. inhibits CYP enzymes, which in turn may enhance toxicity from the drug [75]. Such effects become critical in patients suffering from chronic diseases that use polypharmacy regimens. *Valeriana officinalis* L. increase the potency of benzodiazepine and place individuals at risk of central nervous system (CNS) depression [76]. Stimulating effects are antagonized by herbs such as *Ephedra sinica* Stapf. Elderly patients, pregnant women, and people with chronic diseases are particularly at risk for herb-drug interactions because of altered pharmacokinetics and polypharmacy. Laxative herbs, including *Senna alexandrina* and *Rhamnus purshiana*, may lead to diarrhea or electrolyte imbalances when taken alongside other laxatives or high-fiber foods [77]. Likewise, use of *Zingiber officinale* during pregnancy is associated with some antiemetic medication, thus requiring close monitoring [78]. Management strategies in reducing risk include quality control, monitoring, avoiding interactions, starting with low doses and building up to full dose to minimize adverse effects [79], using protective agents to maintain gut microbiota balance [80], and patient education regarding potential dangers and the importance of using standardized products [81].

## Issues associated with alternative medicine

Alternative therapies, such as botanical treatments and dietary supplements, are widely regarded as efficacious and healthier alternatives to social medicines (conventional pharmaceuticals and medically prescribed treatments used in mainstream healthcare). However, these alternative approaches come with multiple hazards, which include but are not limited to non-regulation and lopsidedness, adverse effects, drug interference, delays in traditional treatment (postponing or avoiding established medical interventions, potentially leading to worsening health outcomes due to late diagnosis or missed therapeutic windows), adulteration and falsification, and variation in maintenance.

**Table 2.** Summary of herb-herb, food-herb, drug-herb and other interactions

| Interaction Type | Examples | Mechanism | Clinical implications | Ref. |
|---|---|---|---|---|
| **Herb-Herb** | *Panax ginseng* + *Ginkgo biloba* | Enhanced anticoagulant effects; increased bleeding risk | Monitor for bleeding, especially in patients on anticoagulants | [68] |
| **Food-Herb** | *Citrus paradisi* Macfad + *Hypericum perforatum* | Inhibition of CYP3A4; increased toxicity | Avoid grapefruit juice with CYP3A4-metabolized herbs | [71] |
| **Drug-Herb** | - *Hypericum perforatum* + warfarin | - Induction of CYP3A4 and P-gp; reduced drug efficacy | - Monitor international normalized ratio; adjust warfarin dosage | [73] |
| | - *Senna alexandrina* + laxatives | - Increased bowel motility; diarrhea | - Avoid their combination stimulant | [77] |
| | - *Zingiber officinale* + antiemetics (pregnancy) | - Potentiation of antiemetic effects; risk of over-sedation | - Monitor for excessive sedation; adjust dosage | [78] |

Understanding these risks is crucial for healthcare providers and patients to assure safe and effective use. Lack of regulation and standardization: Most alternative medicines do not dispense strict regulatory jurisdiction, unlike conventional medicines. The absence of strict regulations leads to varying quality and potency of the products and purity [2]. For example, studies indicate that some herbal supplements either contain contaminants or have not included the ingredients advertised in their labels; that gives rise to concerns over safety and efficacy [82]. Adverse reactions due to herbal remedies begin from mild and can be severe sometimes. The GI disturbance, allergic reactions, and hepatotoxicity are commonly found among herbal adverse effects [83]. One among the notable examples is *Piper methysticum* G.Forst., which is used in anxiety but has severe liver damage cases associated with it [84]. These adverse effects present again emphasizes much careful use and monitoring when taking alternative medicines.

Drug interactions: Alternative medicine, like conventional drugs, can interact with prescription medications, potentially leading to harmful effects if not used appropriately. *Hypericum perforatum,* which is popularly used in treating depression, can also bring reduced effectiveness of other medical treatment such as oral contraceptives and anticoagulants [85]. Such kinds of drug interactions should knock the door of healthcare providers to be mindful of alternative therapies that patients use and, hence, educate patients about the possible risks involved.

Delayed conventional treatment: Failure to seek conventional medical treatment and opting for alternative therapies could result in considerable delays in the disease diagnosis and management of serious conditions. This eventually leads to progressive disease and poorer health outcomes [86]. Patients should be encouraged towards evidence-based therapies with securing a visit to their healthcare promoter before adopting any alternative therapies. Mislabeling and contamination: Mislabeling and contamination leave a stake of concerns. A few products may even be contaminated with heavy metals, pesticides, and, in some cases, prescription drugs [87]. Most of them pose serious health hazards. For example, a certain study found out that some dietary supplements contained undisclosed pharmaceutical ingredients which put infinitely higher risk to adverse effects developments [88].

Inconsistent dosages: Due to its non-standardization in alternates, such a big variability in dosages could make it impossible to attain therapeutic effect. Due to the considerable variability, odds of overdose or under dose are also tremendously increased. It thus makes their safe use complicated [89]. For example, synonymous with high-risk alternatives is *Ephedra sinica*. Popular for weight loss and athletic performance, once this herb was banned in the United States for associating with cardiovascular events as heart attacks or strokes [90]. *Aristolochia* species which are now used in traditional Chinese medicine also have been linked to kidney failures and urinary tract cancers due to thier nephrotoxic and carcinogenic properties [91]. Benefits can be accrued from alternative medications; however, it is imperative to understand the underlying potential danger. All risk features should be emphasized by healthcare providers and practice-based treatments encouraged. Consulting healthcare professionals about alternative medication is also encouraged to ensure safety and effectiveness.

**Counteracting GI side effects**

Herbal medicines, functional foods, and dietary supplements are gaining popularity fast. Therefore, evidence-based approaches must be taken to alleviate GI complications arising from interactions between herbs and foods, herbs and drugs, and food and drugs. An excellent clinical approach involves a mix of patient education, pharmacovigilance, and interdisciplinary approaches to ensure optimal therapeutic outcomes and safety (Table 3). It is incumbent on health-care providers to identify herb-drug and food-herb combinations deemed high-risk and likely to produce GI side effects. For instance, *Camellia sinensis* (L.) Kuntze, rich in tannins, could cause an irritative reaction on the GI mucosa, with subsequent nausea or gastritis in some patients [92]. Both dose and time adjustment of herbal products may lessen GI insult. The use of low doses with slow upward titration allows for better GI tolerance, reducing adverse effects [79]. Administering herbs like *Curcuma longa* or *Zingiber officinale* with food increases tolerability via mucosal irritation reduction [72].

Probiotics should also be administered at the same time to help in maintaining gut microbiota balance, thereby counteracting diarrhea induced by some herbal products [80]. Mucosal

protectants like *Aloe vera* or sucralfate could protect the GI tract from tannin-induced irritation [74]. Monitoring symptoms such as diarrhea, constipation, or abdominal pain on the regular basis is important. Mild to moderate GI symptoms can be controlled with hydration and antiemetics (e.g., ondansetron); however, immediate medical intervention is warranted for severe cases [73,75].

## Healthcare provider and patient guidelines

An extensive examination of the medical history, medications, and eating habits is obligatory. Patients with already established GI diseases (for example, IBS and peptic ulcers) harbor more risks and need individualized management [26,69]. Keeping a record of all prescription drugs, over-the-counter medicines, and herbal supplements will help detect interactions, such as, grapefruit juice which cause metabolic inhibition of *Hypericum perforatum* [70,71]. Therefore, giving education to the patient relating to herb-drug interaction and adherence to the dosing protocol becomes pivotal [81]. Henceforth, this becomes an interdisciplinary approach where physicians, pharmacists, and dietitians work together. Pharmacists will address the pharmacokinetic interactions, while the dietician will prescribe dietary modifications to lessen such risks [76]. Patients should consult their healthcare provider before taking any herbal products, especially if they are on prescription medications [89]. Choosing standardized products from well-known brands minimizes contamination risk [78]. Avoiding overdoing it and combining multiple herbs without professional assistance may lead to adverse effects [79]. Symptom diaries can help the patient monitor their symptoms while applying self-care strategies such as hydration and diet modifications for mild GI symptoms, but if symptoms are severe or persist, medical attention is warranted [80,74]. By means of dose adjustments, protective agents, and education of patients, proactive intervention can reduce the burden of GI side effects, which may arise from herb-herb, food-herb, or drug-herb interactions. Interdisciplinary collaboration and pharmacovigilance for practitioners should maximize patient safety. Researches in the future will need to standardize protocols and improve reporting systems to tackle the increasing administration of herbal products [68,69].

## Gaps in existing knowledge

As herbal treatments and food supplements have surpassed scientific research in their safety and effectiveness, especially concerning interactions with other herbs, food, or drugs, some well-established interactions are known while numerous others still pose possible harm to patients. Therefore, this often unrewarding section will address these possibilities and examine critically the lacunae in existing knowledge, with a view toward presenting an agenda for addressing those areas of research.

Most work on herb-herb interactions has depended on preclinical data and reports of individual cases, with far too few attempts at proper design and implementation of clinical trials. For example, while the combination of *Panax ginseng* and *Ginkgo biloba* is known to increase anticoagulant effects, the clinical importance of this interaction remains dubious [68]. Also, in need of more consideration are the synergistic or antagonistic effects of other distinguished herbal pairings, *Curcuma longa* and *Piper nigrum* commonly employed [72].

Unfortunately, food-herb interactions cannot be sufficiently studied if the focus is mainly on assessing the effects of food components upon the bioavailability and efficacy of herbal products.

**Table 3.** Strategies for counteracting herbal-induced GI side effects

| Strategy | Description | Examples |
|---|---|---|
| **Dose Regulation** | Using herbal remedies within recommended dosages | *Aloe vera*, *Senna alexandrina* |
| **Quality control** | Ensuring herbal products are free from contaminants | *Ginkgo biloba* |
| **Monitoring** | Regular monitoring for adverse effects during herbal use | *Berberis vulgaris*, *Curcuma longa* |
| **Avoiding interactions** | Avoiding concurrent use of herbs and medications with known interactions | *Hypericum perforatum*, *Ginkgo biloba* |
| **Patient education** | Educating patients about potential risks and proper use of herbal remedies | All herbal remedies |
| **Medical intervention** | Adjusting prescription medications or screening for drug-herb interactions. | *Camellia sinensis* |
| **Probiotic prescription** | Using probiotics to mitigate herb-related GI disturbances. | *Curcuma longa*, *Zingiber officinale* |

For example, high-fat meals enhance the absorption of lipophilic entities, such as curcumin, but the effects of such interaction over time remain to be substantiated [79]. Also, further appraisal of functional food influence, such as probiotics and prebiotics, is required to understand herb metabolism [80] (Table 4).

A large number of proposed herb-drug interactions remain poorly characterized due to the unavailability of pharmacokinetics-pharmacodynamics studies. While *Hypericum perforatum* is known to induce CYP3A4 and P-gp, its effects on specific drugs vary widely across studies [73]. Also, mechanisms for GI side effects from tannin-rich herbs such as *Camellia sinensis* are not well elucidated [92].

Variation in composition and quality of herbal products makes it harder in doing research in clinical trial settings. Variation in extraction methods, plant parts used, and storage conditions can dramatically change the bioactive constituents of herbs, causing them to exhibit different results in studies and unpredictable outcomes [70]. There is an urgent need for the standardization of the methods used for herbal product preparation along with quality controls.

## An update on future research directions

Our understanding of herbal products and their safe uses goes beyond prescribing the next set of recommendations for future research: rigor clinical trials, further pharmacokinetic and pharmacodynamic research, predictive modeling, development of standards and quality control, and patient-centered research (Table 5). Robustly designed clinical trials are critical to establish safety and efficacy profiles, as well as possible interactions, for herbal products.

**Table 4.** Limited understanding of mechanisms underlying herbal remedies and GI side effects

| Mechanism | Description | Examples of herbs | Research gaps | Ref. |
|---|---|---|---|---|
| **Mucosal irritation** | Bioactive compounds like tannins and saponins irritate the GI mucosa, leading to inflammation. | *Camellia sinensis*, *Glycyrrhiza glabra* | Specific molecular pathways and long-term effects of mucosal irritation are unclear. | [93,94] |
| **Altered gut motility** | Herbs stimulate or inhibit intestinal smooth muscle, affecting bowel movements. | *Senna alexandrina*, *Rhamnus purshiana* | Mechanisms of action on enteric nervous system and smooth muscle are poorly understood. | [95,96] |
| **Microbiome disruption** | Herbal compounds alter gut microbiota composition, potentially leading to dysbiosis and GI symptoms. | *Berberis vulgaris* | Long-term effects on gut microbiota and implications for GI health are unknown. | [97-99] |
| **Enzyme and transporter modulation** | Herbs modulate CYP enzymes and P-gp, affecting drug metabolism and absorption. | *Hypericum perforatum*, *Hydrastis canadensis* | Extent of modulation and clinical significance in GI side effects require further study. | [100-102] |
| **Immune modulation** | Some herbs may trigger immune responses in the GI tract, leading to inflammation or hypersensitivity. | *Echinacea purpurea*, *Curcuma longa* | Role of immune modulation in herb-induced GI side effects is understudied. | [103,104] |

**Table 5.** Recommendations for future research on herbal products

| Research Area | Key objectives | Methods/tools | Target outcomes | Ref. |
|---|---|---|---|---|
| **Robust clinical trials** | Establish safety, efficacy, and interactions of herbal products | RCTs, longitudinal studies | Evidence-based guidelines for herb-herb, food-herb, and drug-herb interactions in high-risk groups | [69,81] |
| **Advanced pharmacokinetics/ pharmacodynamics studies** | Elucidate PK and PD mechanisms of herb-related interactions | Investigate effects on CYP enzymes, drug transporters, and gut microbiota | Predictive insights into herb-drug interactions and metabolic pathways | [71,75] |
| **Development of predictive models** | Predict potential interactions and adverse effects | In silico screening tools, machine learning algorithms | High-risk herb-drug combination identification and improved clinical decision-making | [71,74,75] |
| **Standardization and quality control** | Ensure consistency and quality of herbal products | HPLC, mass spectrometry, GMP | Standardized protocols for herbal product preparation and quality assurance | [70] |
| **Patient-centered research** | Address real-world challenges and patient outcomes | RWE, PROs | Improved understanding of herb-related interactions and their impact on quality of life | [80,77] |

These should be randomized controlled trials (RCTs) that determine whether an herb-herb, food-herb, or drug-herb interaction has clinical significance in target high-risk populations such as the elderly and pregnant women [69]. Such study designs could also be longitudinal in nature, to be able to define the cumulative results of chronic herb consumption and its interaction with medications [81].

Future research efforts would include establishing an understanding of the pharmacokinetics and pharmacodynamics mechanisms driving herb-related interactions. This should involve detailed research on the effects of herbal products on CYP enzymes and drug transporters, which could predict or prevent those interactions [75]. Another critical aspect would be to investigate how gut microbiota would play a role in metabolizing herbal compounds and modulating their effects [74].Computational and in silico models can help predict potential interactions and aid the clinical approach. For instance, in silico screening tools use molecular interactions to detect herb-drug relationships with a greater likelihood of risk [71]; whereas, large data sets can be assessed by machine-learning algorithms for predicting herb adverse effects due to interactions [76].

Such research must also be prioritized towards developing standard protocols for preparing and controlling the quality of herbal products. The bioactive constituents of herbal products can be characterized using advanced analytical techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry [89]. Adequate regulations concerning good manufacturing practices (GMP) for herbal product production will offer assurances of consistency and quality in production [78].

Research methods must start using patient-oriented approaches in addressing real-life scenarios. Real-world evidence (RWE), gathered from clinical environments, can be very useful in complementing the result of controlled trials [77]. The incorporation of patient-reported outcomes (PROs) will ensure assessment of and by herb-interactions on quality-of-life issues [80]. Future directions should be focused on filling the gaps in our current knowledge on herb-herb, food-herb, and drug-herb interactions through a multidisciplinary approach with robust clinical trials and advanced pharmacokinetics/ pharmacodynamics studies culminating in the development of predictive models. Excellent focus on these research areas will not only improve our understanding of herb-related interactions but will also contribute to higher patient safety and optimized therapeutic outcomes. The well-structured collaboration between researchers, health professionals, and regulatory agencies will be essential for these goals to be achieved.

## Conclusion

Most herbs offer a range of therapeutic effects, yet they can become hazardous, especially with respect to the gastrointestinal tract. This review has shown that herbal products may worsen GI side effects via different biological mechanisms: mucosal damage, inflammation (immune-mediated), dysbiosis, and oxidative stress. Unbearable to mention, nearly 30% of herbal remedy users worldwide have claimed GI upset symptoms, based on large case studies and epidemiological data. Upregulation, contamination, and improper dosages in the herbal supplement industry certainly pose danger and make a much stronger case for the immediate need for the global implementation of standardized quality control and surveillance. Interference of herbal products with the conventional medications raises extra hurdles, where herb-drug interactions can lead to therapeutic failure or severe side effects. Attending to the safe use of the herbal remedy, therefore involves education at the healthcare provider level, provision for dose alteration, and possibly adding moderately acceptable substances such as probiotics. Collaborative efforts among the physicians, pharmacists, and dietitians would ensure that all avenues have been optimized to determine therapeutic outcome(s) and patient safety. Despite increasing evidence, there are still considerable gaps in knowledge regarding herb-herb and food-herb interactions and the pharmacokinetics and pharmacodynamics of many herbal compounds. Future studies should focus on the implementation of strong clinical trials, sophisticated mechanistic studies, and the establishment of predictive models to further understand and properly manage these interactions. Standardization of herbal products and improved reporting systems are crucial in addressing the challenges associated with its widespread use. Therefore, while herbal

medicines are potentially promising, their potential GI effects and interactions with conventional medicines necessitate stringent use and further research in such parameters. Meeting these challenges will ensure a safe and effective integration of herbal medicine into the global healthcare system, thus improving outcome-based practice and public health.

## AI tools

Reference management and deduplication were performed using the AI-based tool (DeepSeek) to ensure consistency and eliminate redundancy.

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## Author Contributions

Abdalsalam Kmail performed the study conception and design, data collection and analysis, wrote the review paper, read and approved the final manuscript and agreed to be accountable for all aspects of the work. Abdalsalam Kmail is corresponding author and responsible for correctness reviewing data.

## Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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## Abbreviations

GI: gastrointestinal; TCM: traditional Chinese medicine; GIT: gastrointestinal tract; IBS: inflammatory bowel syndrome; CYP: cytochrome P450; P-gp: P-glycoprotein; CNS: central nervous system; RCTs: randomized controlled trials; HPLC: high-performance liquid chromatography; GMP: good manufacturing practices; RWE: real-world evidence; PROs: patient-reported outcomes