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Review Article

Exploring the Safety, Efficacy, and Bioactivity of Herbal Medicines: Bridging Traditional Wisdom and Modern Science in Healthcare

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Abstract

This review explores the convergence of traditional wisdom and modern science in the realm of herbal medicines, focusing on the safety, efficacy, and bioactivity of these natural remedies in contemporary healthcare. The rich history of herbal medicines, deeply embedded in cultural traditions, is witnessing a resurgence as the quest for holistic and personalized healthcare gains momentum. Herbal medicine, a time-honored practice passed down through generations, is experiencing renewed interest amid the growing acknowledgment of its potential benefits. This review delves into the safety profiles of herbal remedies, subjecting them to rigorous scientific scrutiny. Additionally, it investigates the efficacy of herbal interventions, aiming to bridge the gap between historical anecdotes and empirical research. The complex bioactivity of herbal compounds, often containing numerous active ingredients, is a focal point, unraveling the mechanisms through which these natural substances interact with the human body. In a world where the synthesis of traditional wisdom and modern science holds promise for advancing healthcare, this review contributes to the ongoing dialogue. By critically examining the safety, efficacy, and bioactivity of herbal remedies, it aims to illuminate the evolving landscape of herbal medicine. The goal is to integrate the best of both worlds to enhance global well-being, acknowledging the potential of herbal medicine as a valuable complement to modern healthcare practices.

Introduction

Herbal medicine, also known as herbalism or phytotherapy, involves employing plant-based substances for therapeutic purposes. This practice dates back to ancient civilizations, where plants were revered for their healing properties. Traditional medical systems like Ayurveda, Traditional Chinese Medicine (TCM), and Native American remedies all bear witness to the historical significance of herbal medicine.

Herbal medicine has perpetually represented a crucial element of primary healthcare. Approximately 80% of the global population is estimated to use herbal medicinal products for their therapeutic benefits.[1–3] As of 2022, the global Herbal Medicine Market Size was assessed at USD 148.5 billion, and it is anticipated to ascend from USD 165.13 billion in 2023 to reach USD 386.07 billion by 2032. This trajectory indicates a compound annual growth rate of 11.20% throughout the forecasted period from 2023 to 2032. The global COVID-19 pandemic has unfolded in an unparalleled and remarkable manner, resulting in a heightened demand for herbal medicine in all geographical regions, surpassing prepandemic levels. The demand for herbal medicinal goods has grown as people have become more aware of allopathic medications' side effects and the advantages of using herbal medicines instead. The expanding population, coupled with an increase in the prevalence of chronic diseases, is another market driver impacting market

Keywords: Herbal medicine; Safety; Efficacy; Bioactivity; Natural remedies; Traditional medicine; Botanical supplements.

Abbreviations: ACE, angiotensin-converting enzyme; Akt, protein kinase B; BP, blood pressure; CNS, central nervous system; CYP, cytochrome P450; ED_{50}, effective dose for 50% of the population; ERK, extracellular-signal regulated kinase; FAERS, FDA's Adverse Event Reporting System; FDA, The Food and Drug Administration; GACP, Guidelines on Good Agricultural and Collection Practices; HDIs, herb-drug interactions; IL, interleukin; JNK, c-Jun N-terminal kinase; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; TCM, traditional Chinese medicine; TD_{50}, median toxic dose of a drug at which toxicity occurs in 50% of cases.

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growth.[4,5]

However, this increasing demand has also witnessed a rise in fraudulent practices, including the substitution of herbal material and the addition of synthetic compounds.[3,6] Consequently, standardization and quality control processes have become paramount. Additionally, some adverse effects are not solely attributable to adulteration, contamination, or misidentification of plant species; they can also stem from the intrinsic toxicity of certain plants. This necessitates a thorough toxicological assessment to mitigate potential safety concerns. Furthermore, adverse effects can also be triggered by foreign contaminants such as chemicals like pesticide residues or heavy metals, or microbiological agents.[7] These factors underscore the necessity for rigorous safety protocols.

While the historical use of herbal medicines underscores its potential, the contemporary scientific community acknowledges the imperative for rigorous safety and efficacy evaluations. Unlike pharmaceutical drugs, herbal products often lack standardized dosages and can interact with other medications.[8] Instances of adverse events linked to certain herbal preparations underscore the need for thorough clinical trials and toxicological assessments. Regulatory agencies are increasingly prioritizing the quality, safety, and efficacy of herbal products to safeguard public health. Scientific advancements over time led to the isolation and synthesis of active compounds from plants, forming the foundation of modern pharmaceuticals. However, the holistic approach inherent in herbal medicine, often utilizing multiple plant constituents, continues to retain its significance. The industry of phyto-preparations has witnessed substantial growth over recent decades, resulting in a diverse array of products available in the market, which are utilized in alternative and complementary medicine contexts. Amidst heightened consumer demand, there is mounting pressure to assess product efficacy and to ensure their safety.

One of the intriguing facets of herbal medicine lies in its diverse array of bioactive compounds that contribute to its therapeutic effects. Compounds like alkaloids, flavonoids, and terpenes interact with biological systems, eliciting responses that can address various health conditions.[9–11] Gaining a comprehensive understanding of the mechanisms through which these compounds operate is pivotal for optimizing formulations and developing targeted treatments. Advances in analytical techniques, genomics, and metabolomics have played a pivotal role in identifying and characterizing these bioactive components.[12,13]

This review article delves into crucial aspects of regulation and quality control in herbal medicine production, highlighting the potential for toxicity and side effects in natural remedies, the efficiency and bioactivity of herbal products, and the significance of understanding interactions between drugs and herbs. With the growing popularity of herbal medicine, adopting informed and evidence-based approaches becomes paramount for ensuring both safety and efficacy in healthcare practices.

Data acquisition was executed through the utilization of globally recognized databases, namely, PubMed, Web of Science, Google Scholar, and Science Direct. The corpus of scrutinized literature encompassed primary research articles, comprehensive review articles, and books.

Safety assessment of herbal medicines

Herbal drugs and their preparations

Traditional medicinal herbal drugs encompass various plant parts such as aerial parts, flowers, fruits, leaves, seeds, stems, and subterranean components like roots, bulbs, tubers, and rhizomes.[14,15] These materials exist in diverse forms, including raw, fresh, dried, and extracts, with occasional use of entire dried plants (Fig. 1).[16–18] They hold significant global importance in international trade, featuring noteworthy clinical, economic, health, and pharmaceutical value. The escalating recognition of their worth, whether justified or not, is contributing to a steady expansion of their market. However, comprehensive data concerning the quality, safety, and efficacy of numerous plants, their extracts, preparations, and active compounds remain limited.[16] Ensuring their quality is of paramount importance to guarantee their safety and effectiveness.[15,19]

Safety and potential toxicity of herbal remedies

The notion of "toxicity" is inherently influenced by individual perspectives. Numerous everyday foods contain components that could trigger allergies or might be classified as toxic based on specific criteria. For instance, alpha-gliadin in gluten from wheat, oats, and rye; cyanogenic glycosides in various fruit seeds; thiocyanates in Brassica vegetables; alkaloids in Solanaceae plants; and lectins in select legumes such as soy and red kidney beans are constituents present in foods generally regarded as safe worldwide.[20]

In a similar vein, even life-sustaining substances such as water and oxygen can become lethal when consumed in excessive quantities, underscoring the significance of dosage as a pivotal factor.[21,22] Nonetheless, from a safety standpoint, it is feasible to categorize herbs into three distinct groups. The first group comprises a few herbs that contain high levels of potentially harmful substances, akin to pharmaceutical compounds. These should never be ingested by untrained individuals, except in homeopathic preparations. Examples include *Atropa belladonna*, *Arnica* spp., *Aconitum* spp., and *Digitalis* spp. The second group includes herbs with potent effects that may sometimes lead to symptoms like nausea or vomiting. However, these herbs are safe when used appropriately. Examples include *Lobelia* and *Eonymus* spp. Interestingly, there are contradictions in the regulations of these herbs across different countries; for instance, *Ephedra* is restricted in the UK but readily available in the USA, possibly with valid reasons.[23–25] The third group consists of herbs that exhibit specific types of toxicity, supported by scientific evidence. Notably, plants containing pyrrolizidine alkaloids, such as Comfrey (*Symphytum*), are well known for their hepatotoxicity. Other examples include *Dryopteris* (Male Fern), *Viscum* (Mistletoe), and *Corynanthe* (Yohimbe). It is advisable for laypeople to avoid internal consumption of herbs from this group.[3,20,26]

In summary, the classification of a substance as toxic hinges on various factors; in the realm of herbal medicine, different herbs exhibit varying degrees of toxicity and potential risks. It is crucial to exercise caution, adhere to appropriate usage guidelines, and seek professional advice when considering the ingestion of herbs, particularly those in the first and third groups, to ensure safety and minimize potential harm. The introduction and widespread availability of herbal medicines and their derivatives in many countries often occur without mandatory safety or toxicological assessments, and regulatory oversight of manufacturing practices and quality standards is often lacking. Consequently, these herbal products are easily accessible to consumers without requiring prescriptions. Unfortunately, the underestimated potential hazards associated with substandard herbal products pose significant risks.[24,26–29] There has been a growing global interest in and usage of herbal medicines, exemplified by substantial consumption rates in Asian countries, with India at 65% and China at 40%. Likewise, Belgium, France, and Canada report usage percentages of

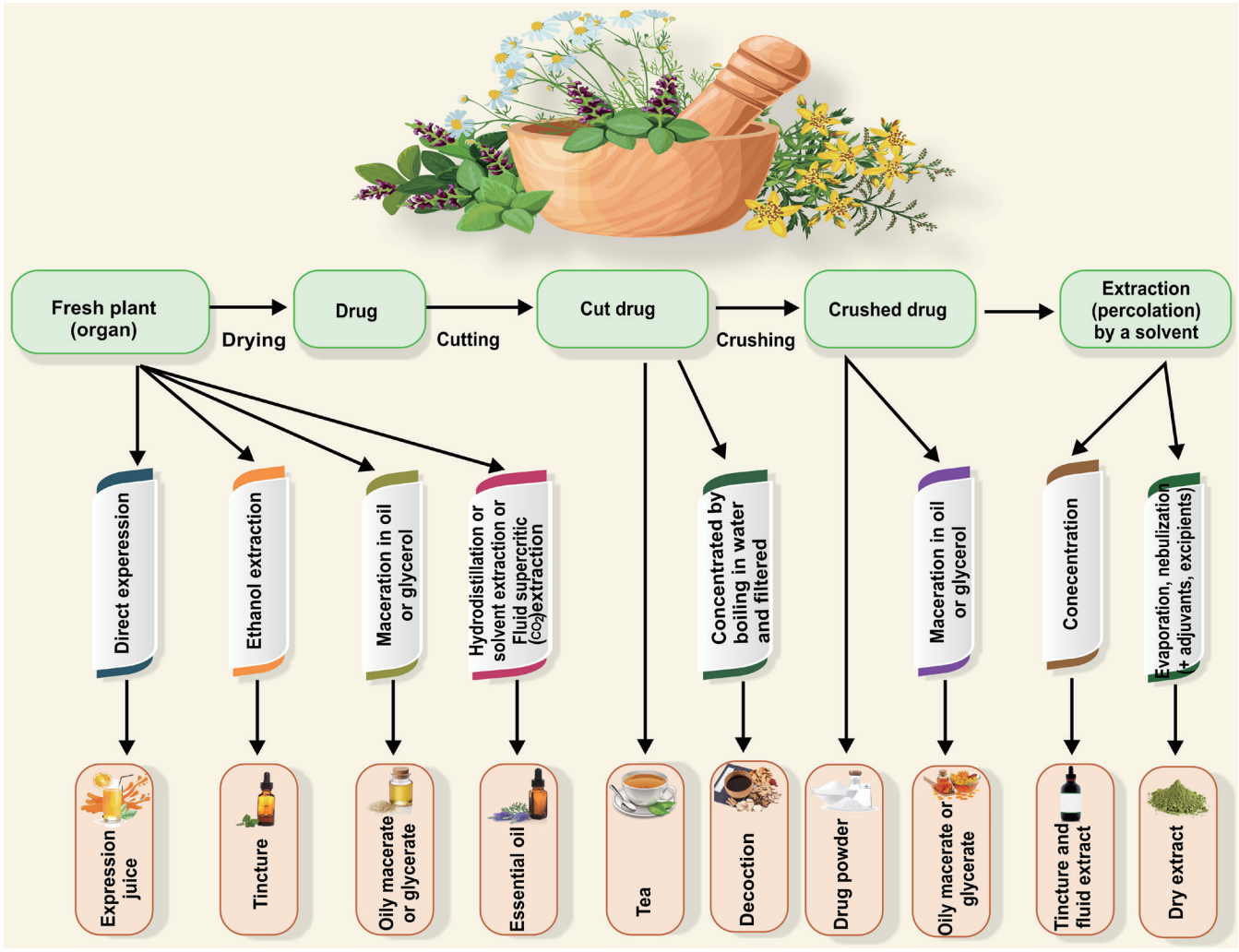

Fig. 1. The major types of herbal preparations.

31%, 49%, and 70%, respectively.[30–32] Although patients hold positive perceptions of herbal medicines, express satisfaction with their therapeutic outcomes, and often harbor dissatisfaction with the efficacy and safety of conventional allopathic medications, apprehensions about the safety of herbal remedies endure. Table 1 illustrates contrasting adverse reactions between pharmaceuticals and herbal medications. Herbal therapy is characterized by a holistic approach, encompassing emotional, mental, and spiritual aspects, with lifestyle considerations being integral to naturopathic practices. Generally, herbal treatments do not entail typical drug actions or adverse effects, but informed knowledge of medicinal plant effects and clinical trials for appropriate medical applications are essential. It has been recommended that we use the terms indications and contraindications instead of side effects when discussing herb consumption.[24,33–35]

Anticipating adverse effects and toxicities: understanding herbal medicine usage

In the realm of herbal medicine and dietary supplements, the occurrence of adverse effects and toxicities often stems from improper usage. These incidents can be attributed to several factors, including the inappropriate application of herbs and supplements, their incorrect preparation, excessive dosages, or prolonged utilization.[26,36] Consequently, it is crucial for physicians to remain vigilant when patients report a history of such usage, as it may indicate the potential for toxicities. For instance, an excess intake of vitamin D, often driven by overly enthusiastic fortification in milk, has been linked to hypercalcemia. Similarly, the prolonged and excessive consumption of vitamin A can result in adverse outcomes like osteoporosis and hepatotoxicity.[37–39]

It is important to understand that herbal medicines primarily focus on maintaining the body's balance rather than providing immediate symptom relief. Therefore, when products claim to offer rapid symptom relief, it should raise concerns among healthcare professionals, as this could indicate intentional adulteration with pharmaceutical substances. Such adulteration can lead to complications and toxic reactions. These adulterated products are usually available in the form of ingestible or occasionally topical finished products.

Research has revealed instances of adulteration in herbal medicines. For example, a survey conducted in Taiwan analyzed 2,609 herbal samples and found that 23.7% of them were adulterated

Table 1. Contrasting adverse reactions between pharmaceuticals and herbal medications

	Pharmaceutical drugs	Herbal drugs
Reporting System	A robust system exists for reporting and tracking adverse reactions to pharmaceutical drugs. Healthcare providers and pharmaceutical companies must report such events, resulting in comprehensive databases of drug-related adverse events.	Adverse reactions linked to herbal drugs are less systematically reported compared to pharmaceuticals, often leading to underreporting due to a lack of awareness among consumers and healthcare providers.
Data on adverse reactions	In 2020, the FDA's Adverse Event Reporting System (FAERS) recorded 5.8 million adverse event reports associated with pharmaceutical drugs, encompassing a spectrum from mild side effects to severe and life-threatening reactions.	Monitoring herbal drug adverse reactions is less robust than for pharmaceuticals. Despite potential underreporting, the documented instances of serious or life-threatening adverse reactions to herbal medicines remain exceptionally rare.
Common adverse reactions	Common adverse reactions to pharmaceutical drugs include nausea, vomiting, headache, dizziness, and skin rashes. In severe cases, they can cause organ damage or even death	The lack of comprehensive reporting systems makes it challenging to compile accurate data on adverse reactions to herbal drugs.

FDA, The Food and Drug Administration.

with pharmaceuticals. Similarly, a study examining 243 proprietary products in California showed that 7% contained undisclosed pharmaceutical ingredients. In Singapore, screening of 3,320 TCM herbal products in 1999 revealed that 1.2% of them contained undisclosed pharmaceuticals. Typically, only one adulterant is detected, although there are cases of multiple adulterations. Another form of adulteration involves substituting a cheaper or more readily available herb for another, even if it has a less favorable safety profile.[39–42]

Among the most common adulterants are pharmaceuticals intended to alleviate discomforting symptoms, including nonsteroidal anti-inflammatory drugs and antihistamines. Adulteration is a pervasive issue in the realm of steroids and sexual-enhancing drugs, with Sildenafil being a commonly reported culprit.[42–45] The consequences of such adulterations can be dire, as the added drugs often carry significant risks of toxicity. For instance, substances like sulfonylurea, phenylbutazone, phenytoin, and corticosteroids can lead to severe and potentially life-threatening adverse effects.[41] Issues originating from these adulterated items include allergic responses, Addisonian crisis, and Cushing's syndrome, all stemming from unintentional ingestion of products containing added steroids.[46] Moreover, individuals employing nitrates for cardiac ischemia may experience hypotension when unknowingly using items contaminated with Sildenafil. Furthermore, unsuspicious utilization of products containing sulfonylurea can lead to severe or fatal hypoglycemia.[39,47,48]

Apart from this, other quality challenges prevalent in the herbal medicinal products market primarily stem from species substitution and adulteration.[28] Such contaminations and substitutions can result in adverse reactions in consumers. For instance, the presence of *Senna alexandrina* in *Hypericum perforatum* products led to unintended ingestion of sennosides, causing a laxative effect.[49] The discovery of *Juglans nigra* in *Ginkgo* and *Echinacea* products raised concerns due to the toxic compound juglone. In addition, substituting *Stephania tetrandra* with *Aristolochia fangchi* in TCM products may lead to renal toxicity and cancer due to the presence of aristolochic acid. Adulterating *Datura stramonium* with *Brugmansia arborea* in Ayurvedic medicine also poses serious risks.[28,50,51]

In light of the aforementioned challenges, the accurate identification of medicinal plant materials is imperative to ensure their safety. Additionally, many manufacturers of herbal medicines lack knowledge or place insufficient emphasis on the significance of taxonomic botany and documentation, which presents unique challenges during the identification and collection of medicinal plants used in herbal remedies. To address confusion stemming from common names, it is essential to adopt widely accepted binomial names, including their synonyms, for medicinal plants. For instance, *Artemisia absinthium* L., known for its active narcotic derivative and potential to induce central nervous system disorders and generalized mental deterioration, has no fewer than 11 distinct common names, with seven bearing no resemblance to its botanical name. Given the prevalence of common names, *Heliotropium europaeum* (heliotrope), containing potent hepatotoxic pyrrolidine alkaloids, is frequently mistaken for *Valerian officinalis* (garden heliotrope), which contains sedative and muscle relaxant valepotriates, emphasizing the necessity of providing the precise scientific name of the plant. Hence, the proficient oversight of herbal medicine safety necessitates robust cooperation among botanists, phytochemists, pharmacologists, and other prominent contributors.[26]

To safeguard consumers, the authentication of both the initial herbal constituents and the ultimate commercialized items remains imperative. While traditional methods, including morphological, microscopic, and chemical identification, have traditionally served as authentication tools, novel approaches have emerged and garnered prominence over the past ten years. These innovations provide fresh avenues for guaranteeing the safety and genuineness of herbal remedies.[52]

Regulation and quality control

Organizations such as the World Health Organization play a pivotal role in establishing guidelines and standards for the production of herbal medicines. For example, "Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues" and "Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants" offer essential insights into quality control and cultivation practices, ensuring the global adherence to safety and efficacy standards.[52,53] Unlike pharmaceutical drugs that undergo rigorous premarket testing, herbal products exhibit variable standardization and quality due to disparities in cultivation, harvesting, processing, and storage. Regulatory measures are essential to address these challenges and safeguard consumer health. The variability in phytochemical constituents is influenced by factors such as climate, soil composition, and geographical location, contributing to challenges in standardization. Rising issues like adulteration and substitution of herbal drugs, often linked to increased deforestation, also compromise the safety

and efficacy of these products. Key challenges in obtaining genuine herbal drugs include adulteration, substitution, and a shortage of skilled personnel. Implementing advanced quality control techniques and standards is crucial to ensure the quality of medicinal herbal products.[54,55]

The World Health Organization has established guidelines for herbal drug standardization, incorporating critical evaluation parameters such as organoleptic properties, ash values, moisture content, microbial contamination, and chromatographic and spectroscopic assessments.[56–58] Modern analytical techniques are indispensable for the global acceptance of traditional herbs and Ayurvedic products. A comprehensive and precise pharmacognostical assessment forms a scientific foundation for evaluating the quality of traditional herbs and Ayurvedic products. Organoleptic tests, physicochemical studies, and pharmacognostic schemes are paramount for authentication and standardization. Microscopic and macroscopic studies provide data to prevent the adulteration of authentic herbal materials and assist in their identification. Furthermore, the identification of secondary metabolites like alkaloids, tannins, glycosides, saponins, and flavonoids serves as a valuable tool for standardization.[59–62]

Current quality evaluation of herbal medicines often relies on one or two markers or pharmacologically active components. However, these may not provide a comprehensive understanding of a product's therapeutic effects, as multiple constituents often work synergistically. Variability in chemical composition due to factors like harvest season, plant origin, and drying processes further complicates assessment. To ensure pharmacological and clinical research reliability and product quality, it is suggested that a broader range of phytochemical constituents should be determined, requiring chromatographic techniques like high-performance liquid chromatography, gas chromatography, capillary electrophoresis, and thin-layer chromatography analysis. Chromatographic fingerprints, representing common chemical components, can serve as a holistic quality assessment tool for herbal medicines. These fingerprints should demonstrate both the uniformity and differences in different samples. Hyphenated chromatography-spectrometry approaches, such as high-performance liquid chromatography–diode-array detection, gas chromatography-mass spectrometry, and capillary electrophoresis–diode-array detection, along with chemometric techniques, offer enhanced separation, selectivity, and precision for qualitative and structural analysis. Such chromatographic fingerprints, regarded as dimensionally advantageous, are pivotal for quality control.[3,54,55]

The absence of robust regulation can result in various issues within the herbal products industry, including adulteration, contamination, and inconsistencies in potency. Regulatory frameworks play a vital role in establishing guidelines for good manufacturing practices, ensuring that herbal medicines adhere to specific quality standards and promoting accurate labeling for informed consumer choices. However, regulatory standards for herbal medicines vary widely between countries, with some implementing stringent regulations while others adopt more lenient approaches. This divergence can result in disparities in product quality and safety, where herbal remedies from different countries may not conform to the same quality standards. Harmonizing global regulatory standards remains an ongoing challenge, necessitating collaboration among international organizations, regulatory bodies, and governments. To enhance the authentication of herbal products, future studies should align with established formulation processes, incorporating microscopic and macroscopic analyses, substance identification (for both adulterants and authentic components), physicochemical parameter assessments (e.g., moisture content, acid-insoluble ash, and water-soluble ash), and the incorporation of novel parameters.[63–65]

Drug-herb interactions

The interactions between herbal remedies and conventional medications can have significant implications for patient safety and treatment outcomes. Certain herbs can alter the pharmacokinetics and pharmacodynamics of prescription drugs, potentially reducing their efficacy or causing adverse effects.

The use of herbal remedies is widespread. The growing global use of herbal medicinal products raises public health concerns about their safety and efficacy. Estimating risks is challenging due to misconceptions, lack of communication, low-grade products, and counterfeit supplies. Ensuring herbal medicine safety is crucial. The pharmacological or toxicological effects of either substance may be increased or decreased as a result of interactions between herbs and medications. The long-term administration of drugs may become more difficult due to synergistic therapeutic effects. Less than 40% of patients notify their doctors that they use herbal supplements, and many medical professionals are oblivious to the potential harmful effects of herb-drug combinations.[66] Negative side effects and interactions have not been reported, which is probably a result of both underreporting and the largely innocuous nature of the plants used. A study of 1,000 elderly patients found that 538 were exposed to 1,087 interactions, with 30 experiencing adverse effects.[67]

The common specificity of substrates in biotransformational paths is the primary cause of drug-drug, food-drug, and herb-drug interactions (HDIs). Pharmacodynamic drug interactions involve chemical moieties interacting with receptor sites and altering the physiological environment, while pharmacokinetic interactions arise from altered absorption, distribution interference, and metabolic and excretory pathway changes (Fig. 2). Pharmacokinetic HDIs involve the induction or inhibition of metabolic enzymes, particularly the cytochrome P450 (CYP) enzyme family, in the intestines and liver, and similar effects on drug transporters and efflux proteins.[68–71] CYP and efflux proteins' presystemic activity can affect oral bioavailability, causing co-administered herbal products to significantly reduce or increase drug levels.[72]

Pharmacokinetic and pharmacodynamic HDIs are mechanisms that alter gastrointestinal functions, drug absorption, metabolic enzymes, transport proteins, and renal excretion of drugs. HDIs often involve CYP oxidative metabolism or P-glycoprotein efflux, affecting the oral bioavailability of medications when combined with soluble and insoluble fibers like psyllium, tea, pomegranate, cinnamon, and rhubarb. Grapefruit also has been found to significantly increase the serum drug concentration due to its irreversible inhibition of CYP3A4 activity.[67,71,72]

The combination of herbs and drugs can result in various adverse effects, including the following: an increased risk of bleeding with warfarin when used alongside ginkgo, garlic, dong quai, or danshen; the potential for mild serotonin syndrome when serotonin-reuptake inhibitors are mixed with St. John's wort; decreased bioavailability of medications like digoxin, theophylline, cyclosporine, and phenprocoumon when taken concurrently with St. John's wort; the risk of inducing mania in depressed patients by combining antidepressants with *Panax ginseng*; exacerbation of extrapyramidal effects when neuroleptic drugs are paired with betel nut; an elevated hypertension risk when tricyclic antidepressants are combined with Yohimbine; increased corticosteroid po-

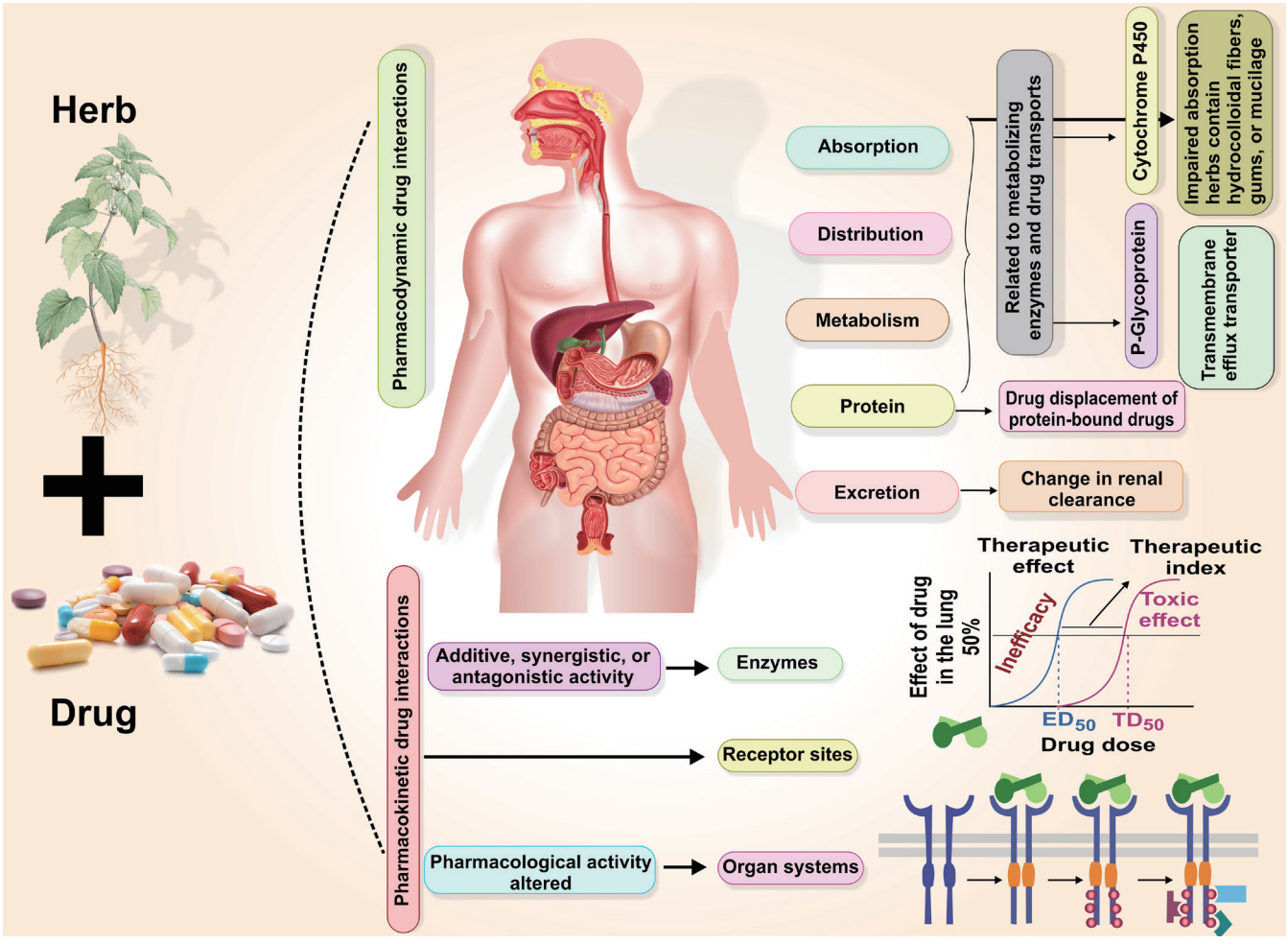

Fig. 2. Pharmacokinetic and pharmacodynamic mechanistic insights of herb-drug interactions. ED_{50}, effective dose for 50% of the population; TD_{50}, median toxic dose of a drug at which toxicity occurs in 50% of cases.

tency with licorice; decreased prednisolone blood concentrations when paired with Chinese herbal products; and reduced phenytoin concentrations when taken alongside shankhapushpi, an Ayurvedic formulation.[67,73–77]

Ginko biloba and garlic have been found to induce CYP2C19-dependent omeprazole metabolism in healthy humans and animal models.[78,79] In addition, grapefruit juice's flavonoid content has been found to inhibit CYP, leading to further research in medicinal herbs.[80,81] Rotenone, a naturally occurring phytochemical found in plants like the jicama vine, also inhibits CYP activity by interfering with the electron transfer of heme iron.[82,83]

Herbal extracts have shown potential in reducing various enzymes and promoting HDIs. Curcumin, an herbal antioxidant with anti-inflammatory and antitumor properties, has been shown to increase glutathione S-transferase and quinone reductase activity in the livers of ddY mice. Moreover, valerian, an herbal supplement for treating insomnia, has demonstrated the possibility of inducing HDIs through the inhibition of uridine 5′-diphospho-glucuronosyltransferase activity. To further comprehend the mechanisms and therapeutic uses of these herbal treatments, more research is required.[71]

Anthranoid-containing plants (e.g., cassia, cascara, and rhubarb) and soluble fibers can decrease drug absorption by increasing the gastrointestinal transit time and increasing gastrointestinal motility. These plants might be detrimental to the gut epithelium (inhibits Na^+/K^+ Adenosine triphosphatase) and increase nitric oxide synthase activity, leading to increased intestinal transit and fluid accumulation. Garlic-derived compounds have been found to enhance the activity of quinone reductase and glutathione transferase in the rat gastrointestinal tract; therefore, these compounds are considered chemoprotective against chemical carcinogens. Ginseng's pharmacokinetic HDIs may be influenced by its gastrointestinal effects, specifically its inhibitory effects on gastric secretion. *In vitro* studies have demonstrated the possibility of rhein and danthron to enhance the absorption of the least water-soluble drugs like furosemide. Chinese herbal plants, such as *Polygonum paleaceum*, have been shown to reduce gastrointestinal motility and prevent the defecation reflex as well as gastroparesis. High-fiber herbal products can reduce the absorption of drugs through the sequestration of bile acids.[67,71] Figure 3 illustrates the impact of drug-herb interactions.

Due to their affinity for similar receptor locations, herbal drugs and conventional pharmaceuticals might have additive or synergistic effects.[71,77,84] When an integrated medicine strategy is desired, researching the processes through which HDIs take place may give a justification for combining conventional and phytotherapies.[85]

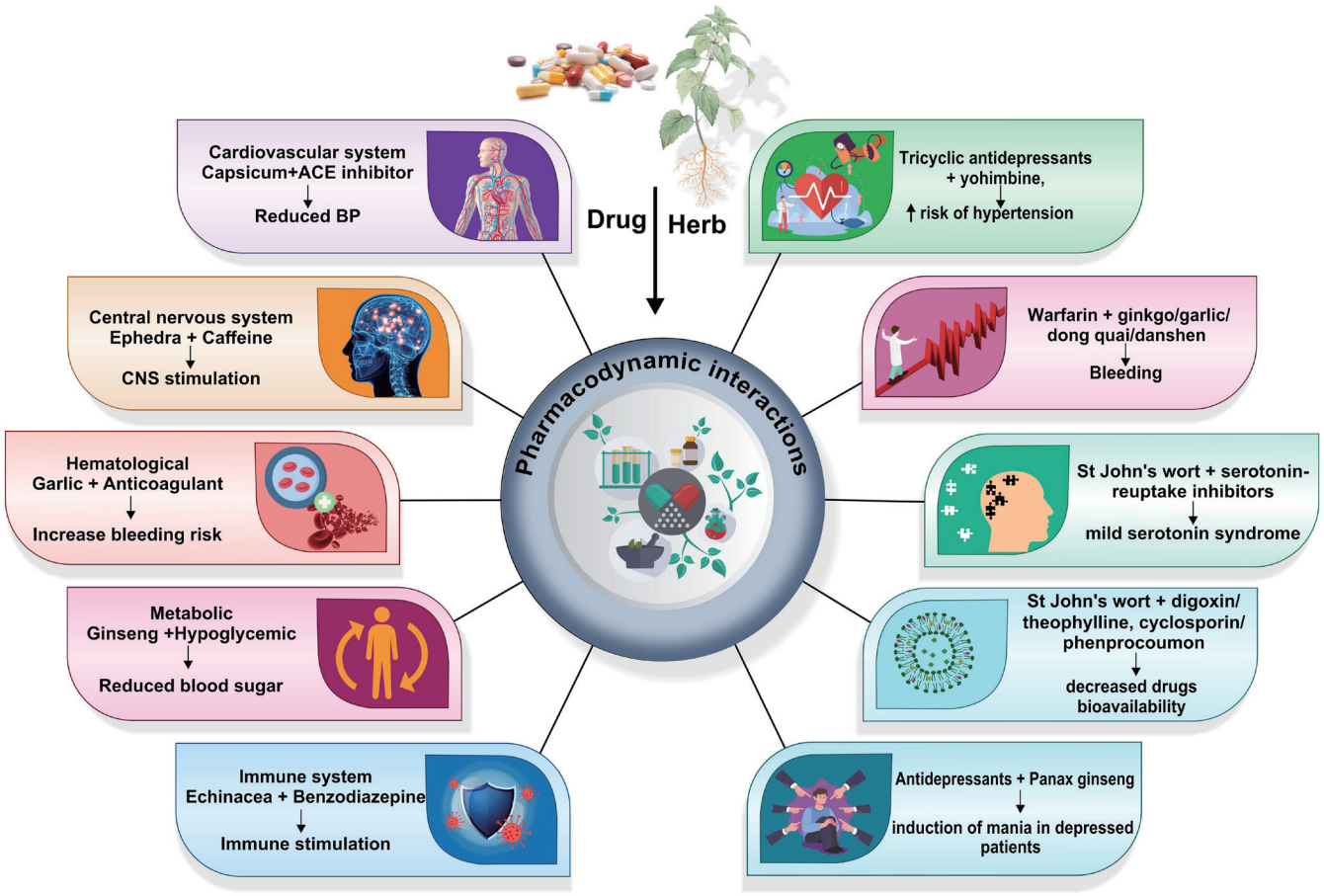

Fig. 3. Impact of drug-herb interactions. ACE, angiotensin-converting enzyme; BP, blood pressure; CNS, central nervous system.

Efficacy of herbal medicines

For millennia, traditional herbal medicine has been an integral part of human culture and healthcare practices. Rooted in ancient wisdom, it encompasses a rich history of healing methods passed down through generations. However, in the modern era, the efficacy of herbal remedies is increasingly scrutinized and tested against the rigors of scientific research. This evolving dynamic between traditional knowledge and scientific evidence highlights the need to bridge the gap between ancient wisdom and contemporary healthcare.

The rich history of traditional herbal medicine practices

Traditional herbal medicine has an extensive and diverse history that stretches across cultures and continents. Ancient civilizations such as the Egyptians, Chinese, Greeks, and Indigenous peoples of various regions have long relied on herbs and botanicals to treat ailments and promote well-being. These practices were often based on observations, trial and error, and accumulated wisdom passed down orally or through written texts.[86,87] In traditional systems like Ayurveda in India, TCM, and Native American herbalism, herbs are seen as more than just remedies; they are regarded as holistic solutions that consider the balance of the body, mind, and spirit. This holistic approach emphasizes the interconnectedness of all aspects of health and the importance of maintaining harmony within the body.

The importance of validating traditional knowledge with modern scientific research

While traditional herbal medicine has stood the test of time and has often provided relief to countless individuals, the skepticism surrounding it has grown in the face of modern medicine's dominance. This has led to a crucial intersection between traditional knowledge and scientific evidence.[88] One of the primary reasons for subjecting herbal remedies to scientific scrutiny is to ensure safety and efficacy. Modern research methods allow for the identification of active compounds within herbs, dosage optimization, and understanding of potential side effects or interactions with other medications. This knowledge is vital for integrating herbal medicine into conventional healthcare systems. Additionally, validating traditional knowledge with scientific evidence helps bridge the gap between different healthcare paradigms. It facilitates the incorporation of effective herbal remedies into mainstream medicine, benefiting patients who may prefer or benefit from herbal treatments. It also preserves the valuable wisdom of traditional healers while ensuring the highest standard of care. Controlled clinical trials play a crucial role in generating substantiated data concerning safety and effectiveness. While the outcomes of clinical trials are promising,[89] additional extensive clinical investigations are essential to validate the efficacy of the approach. Ayurvedic preparations have been successfully evaluated for the treatment of obesity,[90] diabetes,[91] cardiovascular diseases,[92] bronchial asth-

ma and respiratory disorders,[93,94] rheumatoid arthritis,[95–97] and ischemic heart disease.[98,99]

Examples of some common herbs scientifically proven to be effective

Turmeric, a staple in Indian Ayurvedic medicine, contains curcumin, a powerful anti-inflammatory and antioxidant compound. Scientific studies have confirmed its effectiveness in managing inflammatory disorders, such as arthritis and digestive issues. In a four-month randomized, double-blind, placebo-controlled trial, patients suffering from osteoarthritis of the knee displayed notable improvements in various health markers when treated with *Curcuma longa* extract compared to the placebo group. These improvements included significant reductions in the levels of biomarkers such as interleukin (IL) 1b, reactive oxygen species (ROS), and malondialdehyde, as well as enhancements in their visual analog scale and Western Ontario and McMaster University Osteoarthritis index scores.[100] Another study, this time focusing on patients with nonalcoholic fatty liver disease, found that curcumin, a natural polyphenol derived from turmeric, had a substantial impact on health. In a randomized placebo-controlled trial, curcumin was shown to reduce the body mass index and lower the serum levels of glucose, glycated hemoglobin, aspartate aminotransferase, alanine aminotransferase, triglycerides, and total cholesterol when compared to the placebo group.[101] Curcumin was also investigated in a triple-blind, placebo-controlled study focusing on young women suffering from premenstrual syndrome and dysmenorrhea. The results revealed that curcumin significantly improved vitamin D and liver function enzyme tests, though it had no effect on the blood sugar levels.[102] Likewise, according to the results of a triple-blind, pilot randomized controlled trial, a mouthwash containing 0.1% curcumin was found to effectively delay the onset of radiation-induced oral mucositis in patients with head and neck cancer, although it could not fully prevent it.[103] Shifting the focus to mental health, a 12-week randomized, double-blind, placebo-controlled study among healthy subjects indicated that the consumption of *C. longa* extract resulted in reduced chronic low-grade inflammation and improved mental health and mood disorders.[104]

Furthermore, *Ginkgo biloba* extract was examined for its potential to address tinnitus and hearing loss. In a randomized-controlled, double-blind, three-arm trial, patients with hearing loss experienced significant improvements in tinnitus loudness and intensity after 90 days of *Ginkgo biloba* extract treatment.[105] For psychiatric disorders and cognitive function, a double-blind clinical study revealed that *Ginkgo biloba* extract led to improvements in patients' Mini-Mental State Examination and Wechsler Memory Scale Recipe III scores without any observed side effects, particularly benefiting older patients.[106] Moreover, *Ginkgo biloba* extract was also evaluated for its effectiveness, safety, and reliability in treating dizziness caused by cerebral arteriosclerosis in a multi-center, double-blind, randomized controlled trial.[107] Similarly, a 24-week randomized, double-blind, positive-controlled, prospective trial investigated the potential of an aqueous extract of *Terminalia bellerica* to lower uric acid and creatinine levels in individuals with chronic kidney disease and hyperuricemia. The trial found significant reductions in these markers.[108] In another clinical study, the aqueous extract of *Terminalia chebula* dramatically reduced the cardiovascular risk factors in patients with type 2 diabetes when compared to placebo.[109]

Garlic (*Allium sativum*) has a long history of being utilized for its antimicrobial properties in various traditional systems. In an eight-week randomized-controlled trial, it was investigated for its potential to enhance lipid markers in women suffering from polycystic ovary syndrome, suggesting its potential as a complementary therapy alongside standard care.[110] Furthermore, the application of a 30% garlic ointment demonstrated superior wound healing with less noticeable scars compared to Vaseline treatment.[111] Additionally, incorporating raw crushed garlic into a standard diet was found to provide benefits to individuals with metabolic syndrome, making it a potential adjunctive remedy for prevention.[112] In a randomized, double-blind, placebo-controlled clinical study, aged garlic extract supplementation in individuals with obesity altered inflammation and immunity.[113] Expanding on this, the implementation of aged garlic extract in the treatment of hypertensive patients proved to be an effective and well-tolerated approach in a 12-week double-blind, randomized, placebo-controlled, dose-response trial.[114]

Ginseng, a prominent herb in TCM, is known for its adaptogenic properties, which can aid the body in managing stress while potentially boosting energy levels and improving mental clarity. In a randomized, double-blind, placebo-controlled trial, Korean red ginseng (*Panax ginseng*) exhibited antifatigue effects in individuals with idiopathic chronic fatigue.[115] In another randomized study, a combined treatment involving enriched Korean Red ginseng (*P. ginseng*) and American ginseng (*Panax quinquefolius*) led to improvements in central systolic blood pressure and aspects of pulse waveform, without directly affecting endothelial function in individuals with hypertension and type 2 diabetes.[116] Besides, in a randomized, double-blind, crossover, placebo-controlled trial, exercise-stimulated muscle damage in physically active males was attenuated by American ginseng through modulation of the inflammatory response and lipid peroxidation.[117] A separate randomized, double-blind, crossover, placebo-controlled trial was conducted to assess the impact of *P. ginseng* on genitourinary syndrome in postmenopausal women, revealing an improvement in associated symptoms after four weeks of the study. Additionally, a four-week clinical trial demonstrated that Korean red ginseng reduced allergic symptoms and total immunoglobulin E levels in patients with allergic rhinitis compared to individuals receiving a placebo.[118]

In summary, traditional herbal medicine carries with it a wealth of knowledge and wisdom that has served humanity for centuries. However, its integration into modern healthcare requires rigorous scientific validation to ensure safety and efficacy. The ongoing collaboration between traditional knowledge and scientific evidence not only preserves ancient healing traditions but also expands our understanding of the therapeutic potential of herbs. As we continue to explore the synergy between tradition and science, we unlock a broader spectrum of healing possibilities for the benefit of Individuals and societies worldwide.

Bioactivity of herbal medicines

Bioactive compounds found in herbs represent a fascinating realm of naturally occurring chemical compounds within plants, particularly in herbs utilized for culinary, medicinal, or therapeutic purposes. These compounds possess distinctive biological or physiological effects on the human body, offering various health benefits and playing a pivotal role in traditional and alternative medicine.[119,120]

The term bioactive is derived from the Greek word "bios," meaning "life," and the Latin word "activus," signifying dynamic, energetic, or engaged in activity. Bioactive compounds encompass a wide spectrum of substances, including both essential and nonessential compounds, which are naturally occurring and have

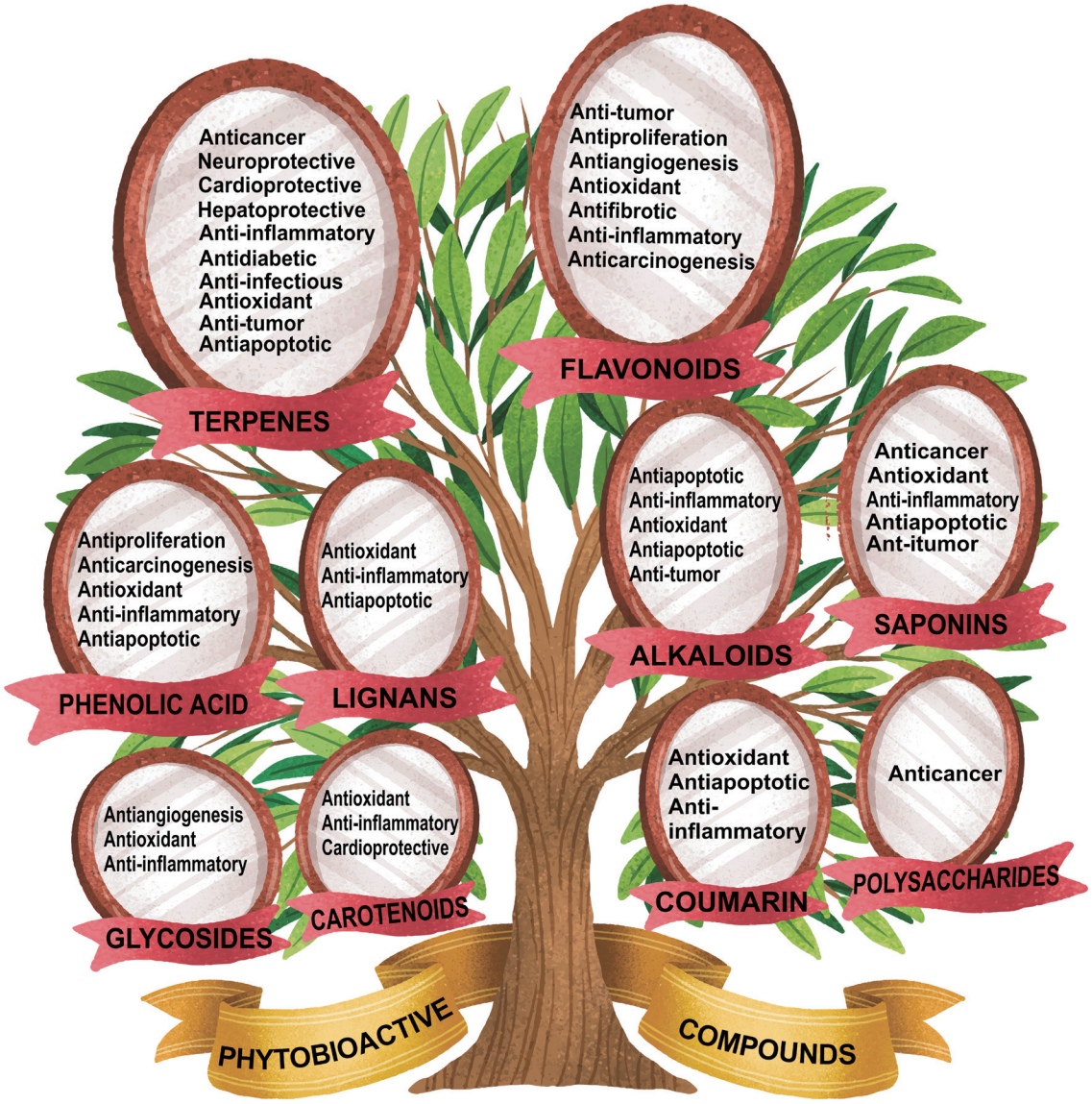

Fig. 4. Overview of the therapeutic potential of bioactive compounds.

the potential to influence human health. These compounds can be sourced from diverse natural origins, including plants and animals. Frequently found in trace amounts within their natural origins, these active biological compounds are dispersed across different plant components, including leaves, roots, barks, tubers, wood, gums, oleoresin exudations, fruits, figs, flowers, rhizomes, berries, twigs, and even the entire plant. Extraction procedures may be required after harvesting to refine or separate the specific bioactive compounds of interest.[10]

Diverse array of bioactive compounds

Bioactive compounds in herbs encompass a rich diversity of chemical constituents, including alkaloids, terpenoids, coumarins, flavonoids, nitrogen-containing compounds, organosulfur compounds, phenolics, and more. Each of these compounds possesses unique effects on the human body and has been harnessed for centuries in traditional medicine systems like Ayurveda, TCM, and Indigenous healing practices due to their medicinal properties. These bioactive compounds are the very essence that imparts color, flavor, and aroma to herbs, while also offering a profound impact on human health when consumed. They contribute to a spectrum of bioactivities, such as anti-inflammatory, immunostimulatory, anticancer, antioxidant, antiproliferation, apoptosis, antifibrotic, and antimicrobial properties (Fig. 4). Additionally, they may support digestive health, bolster the immune system, or aid in the management of chronic conditions.[11]

The complex mechanisms of bioactive compounds

The mechanisms through which bioactive compounds exert their effects on the human body are multifaceted and can vary widely. For instance, the antioxidants present in herbs serve to neutralize harmful free radicals, while anti-inflammatory compounds can alleviate inflammation and pain. The bioavailability of these compounds can be influenced by various factors, including cooking

methods, processing, and the digestive process, all of which affect their absorption and utilization within the body. Herbalists and traditional healers often prescribe herbs based on the bioactive compounds they contain to address specific health conditions. Modern scientific research also has delved into the therapeutic potential of bioactive compounds in herbs, shedding light on their mechanisms of action and potential applications in healthcare.

While bioactive compounds offer a wealth of benefits, it is essential to acknowledge that they can also carry side effects and may interact with medications. Therefore, the judicious use of herbs and herbal supplements under the guidance of healthcare professionals is crucial. Appropriate dosages and potential contraindications should always be considered.

Mechanistic insight of bioactive compounds

Phenolic compounds like gallic acid, ellagic acid, chlorogenic acid, curcumin, and 6-gingerol have various effects on many diseases. Gallic acid induces antiproliferation and apoptosis by regulating mitochondrial pathways, while ellagic acid prevents cancer by removing free radicals and preventing DNA fragmentation.[27,34] Chlorogenic acid inhibits proliferation, profibrogenesis, and progression by inactivating extracellular-signal regulated kinase (ERK) 1/2, suppressing matrix metalloproteinase (MMP) 2 and MMP9 expression, and improving antioxidant capacity.[121] Curcumin decreases oxidative damage and inhibits apoptosis in the myocardium (Janus kinase 2/ signal transducer and activator of transcription 3 signaling pathway),[122] while 6-gingerol alleviates oxidative stress and inhibits cell death (upregulates phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway expression).[123]

Flavonoids, including anthocyanins, flavanols, flavanones, flavones, flavonols, and isoflavonoids, possess specific bioactivity. Meanwhile, anthocyanins exhibit antitumor, antiproliferation, apoptosis, anti-angiogenesis, antioxidant, antifibrotic, and anti-inflammatory activities through various mechanisms.[124,125] Flavanols inhibit metastasis by reducing osteopontin, exhibit anticarcinogenic activity by regulating the hedgehog/glioma 1 and wingless-related integration site/beta-catenin pathways and related genes, and induce apoptosis and antiproliferation by receptor tyrosine kinase inhibition, PI3K/Akt downregulation, and inactivation of nuclear factor kappa B (NFκB) via downregulation of Bcl-2 alpha and Bcl-xl.[126–128] Flavanones inhibit metastasis by reducing the expression of MMP9, regulating mitochondrial pathways, and inhibiting invasion and metastasis by suppressing MMP9 transcription.[129–131] Flavones induce apoptosis by upregulating poly(ADP-ribose) polymerase and Bcl-2-associated X protein, downregulating Bcl-2 protein, and inhibiting hepatic stellate cell activation by mitochondria-activated apoptosis. They also inhibit carcinogenesis by upregulating Bcl-2-associated X protein and p53, inhibiting hepatic stellate cell activation by MMP activation, and regulating the antifibrogenic/profibrogenic molecule balance. Flavonols also inhibit hepatocellular carcinoma development by inhibiting p21-activated kinase 1 and mitogen-activated protein kinase/ERK as well as block metastasis by reversing the epithelial-mesenchymal transition.[132–134]

Lignans and glycosides have various anti-inflammatory and antioxidant properties. Lignans inhibit p38 phosphorylation and c-Jun N-terminal kinase (JNK) death pathways,[135,136] while glycosides like resveratrol inhibit vascular endothelial growth factor expression, profibrogenesis-related genes, and hepatic stellate cell activation. Resveratrol regulates hepatocyte growth factor/c-Met signaling and downregulates NFκB. Polydatin promotes autophagic flux, reduces ROS, and cell death, while lignans inhibit p38 phosphorylation and JNK death.[137–139]

Triterpenoid (terpene) has various anticancer and cardioprotective properties. It inhibits cell proliferation, migration, angiogenesis, and apoptosis by inhibiting the Src/focal adhesion kinase/ERK and PI3K/Akt signaling pathways. It also suppresses NFκB and induces apoptosis by activating the ERK/JNK/p38 pathway. It exhibits neuroprotective activity by downregulating IL6, IL1β, and tumor necrosis factor alpha, Bcl-2-associated X protein, and upregulating Bcl. Furthermore, it inhibits apoptosis and antiapoptotic effects by inhibiting the transforming growth factor beta-activated kinase 1–JNK pathway. It prevents microglial migration towards neurons and removes intracellular ROS. It also has antioxidant effects by inhibiting mitogen-activated protein kinase/mitochondrial-dependent apoptotic pathways and reducing myocardial hypertrophy. It also expresses hepatoprotective activity by suppressing protein kinase RNA-like endoplasmic reticulum kinase/activating transcription factor 6 and iron regulatory protein 1 pathway activation, preventing liver fibrosis. It also has anti-inflammatory activity by inhibiting NFκB pathway activation and the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome. It also has anti-infectious activity by stimulating the anti-inflammatory cytokines granulocyte-macrophage colony-stimulating factor, IL10, and IL12 as well as inhibiting the expression of proinflammatory cytokines.[140,141]

Sesquiterpene lactone (artemisinin) and diterpene lactone (ginkgolide B) have various anti-inflammatory, antioxidant, and antitumor properties. Artemisinin suppresses nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome activation, while diterpene lactone inhibits apoptosis induced by endoplasmic reticulum stress via PI3K/Akt/mammalian target of rapamycin signaling.[142] Alkaloids promote proliferation, attenuate apoptosis, and inhibit ROS production.[136] Saponins exert antioxidant, anticancer, anti-inflammatory, antitumor, and antiapoptotic properties.[143,144] Polysaccharides block P-selectin-mediated neutrophil rolling on the vessel wall,[145] while carotenoids inhibit inflammation and ROS accumulation.[146] Coumarin expresses antioxidant, antiapoptotic, and anti-inflammatory activity by inhibiting the inhibitor of nuclear factor kappa B alpha/NFκB signaling pathway and high-mobility group box 1 expression.[147]

Scientific exploration into the potential health benefits of bioactive compounds in herbs is an ongoing endeavor. Researchers are continually working to unravel the intricacies of their mechanisms of action and their applicability in diverse healthcare contexts. As research unfolds, we gain a deeper understanding of how bioactive compounds in herbs can be harnessed for the betterment of human health.

Conclusion

In conclusion, the resurgence of interest in herbal medicine highlights the necessity of reconciling traditional wisdom with contemporary scientific rigor. The pursuit of safe, effective, and evidence-based herbal remedies necessitates collaborative efforts across disciplines such as botany, pharmacology, clinical research, and regulatory oversight. As ongoing research continues to unveil the intricacies of herbal bioactivity, it is anticipated that herbal medicine will solidify its position as a valuable component of comprehensive healthcare. This will cater to the evolving needs of individuals who seek holistic and natural approaches to well-being.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (AB), acquisition of data (SS, AK), analysis and interpretation of data, drafting of the manuscript (DS, NS), critical revision of the manuscript for important intellectual content (NS), administrative, and study supervision (VA). All authors have made a significant contribution to this study and have approved the final manuscript.

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