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EXPLORING THE SAFETY, EFFICACY, AND BIOACTIVITY OF HERBAL MEDICINES

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ABSTRACT

The safety, effectiveness, and bioactivity of these natural treatments in modern healthcare are the main topics of this review, which examines the intersection of traditional knowledge and contemporary science in the field of herbal medicines. As the movement toward more individualized and holistic healthcare gathers traction, the long history of herbal remedies which are ingrained in cultural tradition is seeing a rebirth. As the potential advantages of herbal medicine are increasingly recognized, interest, in this age old practice, which has been passed down through the centuries, is expanding. Through scientific examination, this article explores the safety profiles of herbal therapies. It also look into the effectiveness of herbal remedies in an effort to close the knowledge gap between historical stories and actual studies. Herbal compounds' complex bioactivity, which frequently includes a large number of active components, is the bioactivity, safety, and effectiveness of herbal treatments, it seeks to shed light on the changing field of herbal medicine. Recognizing the potential of herbal medicine as a useful adjunct to contemporary healthcare techniques, the objective is to combine the best aspects of both disciplines to improve global well being.

KEYWORDS: Herbal medicine; Safety; Efficacy; Bioactivity; Natural medicines; Traditional medicines; Botanical supplements.

INTRODUCTION

Herbal medicine, sometimes referred to as phytotherapy or herbalism, uses compounds derived from plants for therapeutic objectives.

This practice stretches back to ancient civilizations, where plant where revered for their

therapeutic qualities. Traditional medicinal system like Ayurveda, Traditional Chinese therapy (TCM), and Native American medicines all bore testament to the historical significance of herbal therapy.

A vital component of primary healthcare has always been herbal medicine. It is believed that 80% of people on the planet use herbal medicines for their their therapeutic effects.[1-3] The global market for herbal medicines was valued at USD 148.5 billion in 2022 and is projected to grow from USD 165.13 billion in 2023 to 386.07 billion in2032. During the projected period from 2023 to 2032, this trajectory shows a compound annual growth rate of 11.20%. The worldwide COVID-19 the epidemic has developed in an unprecedented and remarkable way, leading to a higher demand for herbal medication that before the outbreak in every geographic location. As people has been more conscious of the negative effects of allopathic medications and the medicines instead, there has been an increase in demand for herbal medical goods. Another factor influencing the market is the growing population and the rise in the prevalence of chronic illnesses.

But along with this growing demand has come an increase in dishonest tactics, such as adding synthetic substances and replacing natural material.[3,6] As a result, quality control and standardization procedure are now crucial. Furthermore, certain negative consequences can result from the inherent toxicity of particular plants rather than just adulteration, contamination. A comprehensive toxicological evaluation is required to address any possible safety issues. Additionally, foreign contaminants like pestiside residues or heavy metals, as well as microbiological organisms, can potentially have negative impacts.[7] These elements highlight the need for strict safety procedures.

The scientific community today recognizes the need for thorough safety and efficacy assessments, even though the historical usage of herbal medicines highlights their potential. Herbal treatments might interact with other pharmaceuticals and frequently lack defined dosing, in contrast to conventional drugs.[8] The necessity of comprehensive clinical trials and toxicological evaluations is highlighted by reports of unfavorable outcomes connected to specific herbal remedies. To protect the public's health, regulatory bodies are placing a higher priority on the effectiveness, safety, and quality of herbal products. As science progressed, active chemicals from plants were isolated and synthesized, creating the basis of contemporary medications. Nonetheless, herbal medicine's holistic approach which frequently makes use of several plant constituents remains important. Over the past few

decades, the phytopreparations sector has experienced significant expansion, leading to a wide range of products on the market that are used in complementary and alternative medicine settings. There is increasing pressure to evaluate the effectiveness of products and guarantee their safety in the face of increased consumer demand.

The wide range of bioactive substances that make up herbal medicine's therapeutic effects is one of its fascinating features. Alkaloids, flavonoids, and terpenes are examples of compounds that interact with biological systems to produce reactions that can treat arrange of medical diseases.[9-11] Developing a through comprehension by which these substances function is essential for formulating targeted treatments and improving formulations. The identification and characterization of these bioactive components have been greatly aided by developments in metabolomics, genetics, and analytical techniques.

The potential for toxicity and adverse effects in natural remedies, the effectiveness and bioactivity of herbal products, and the importance of comprehending drug-herb interactions are all highlighted in this review article, which explores important facets of regulation and quality control in the production of herbal medicines. Adopting knowledgeable and evidence based strategies is crucial for guaranteeing healthcare practices' efficacy and safety as herbal medicine gains popularity.

Globally renowned databases, including PubMed, Web of Science, Google Scholar, and Science Direct, were used to collect the data. Books, in-depth reviews, and primary research papers were all included in the corpus of examined material.

Safety assessment of herbal medicines Herbal drugs and their preparations

Aerial parts, flowers, fruits, leaves, seeds, stems, and underground portions including roots, bulbs, tubers, and rhizomes are all included in traditional therapeutic herbal medications.[14,15]

These materials come in a variety of forms, such as fresh, dried, raw, and extracts; occasionally, whole dried plants are used (Fig. 1).[16-18] Due to their notable clinical, economic, health, and pharmaceutical value, they are of great global significance in international trade. Their market is steadily growing as a result of the growing acknowledgement of their value, whether or not it is warranted. Nevertheless, thorough information about the quality, safety, The effectiveness of many plants, their preparations, extracts, and active ingredients are still scarce.[16] It is crucial to ensure their quality in order

to ensure their efficacy and safety.[15,19]

Safety and potential toxicity of herbal remedies

Individual viewpoints inevitably impact the concept of "toxicity". Many common foods contain ingredients that may cause allergies or be deemed harmful according to certain standards. For example.

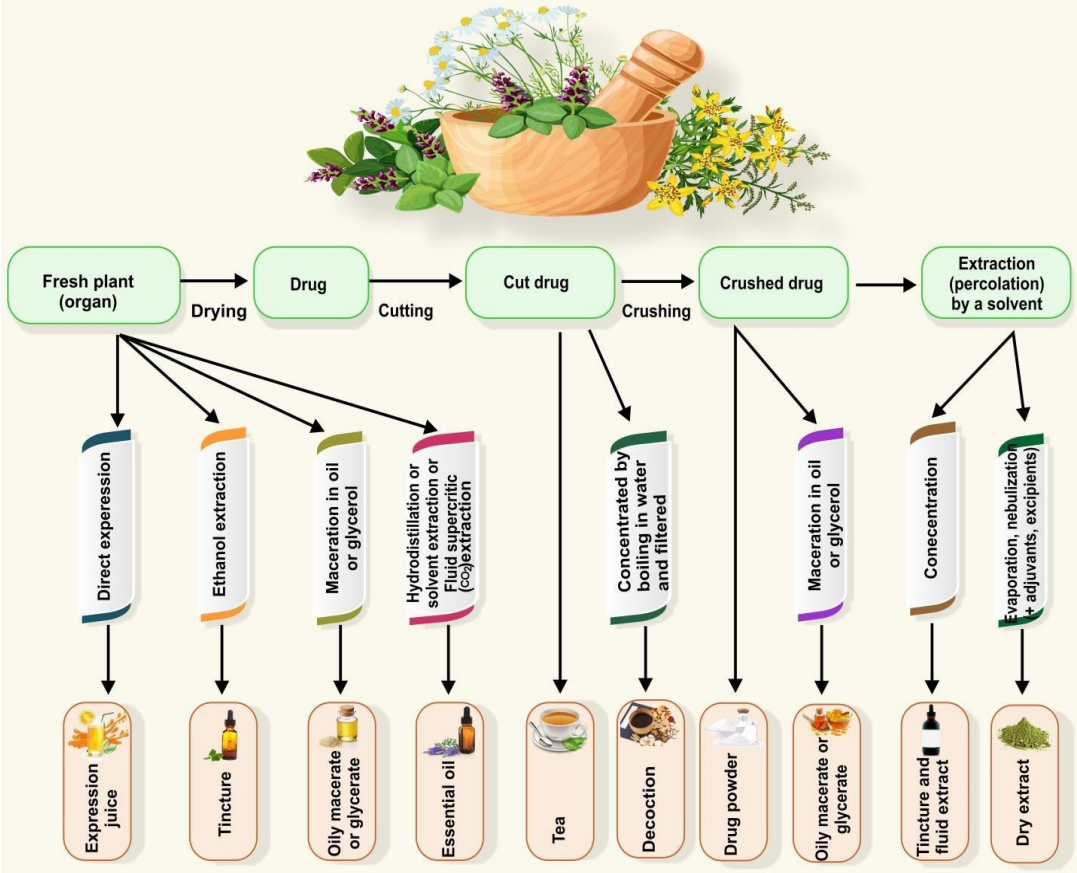

Fig. 1: The major types of herbal preparations.

components found in foods that are generally accepted as safe around the world include alpha-gliadin in wheat, oat, and rye gluten; cyanogenic glycosides in different fruit seeds thiocyanates in Brassica vegitables; Alkaloids in Solanaceae plants; and lectins in certain legumes like soy and red kidney beans.[20]

Similarly, excessive consumption of even life sustaining chemicals like oxygen and water can be fatal, highlighting the need of dose as a critical aspect.[21,22] From a safety perspective, however, it is possible to divide herbs into three groups. A small number of plants in the first group have significant concentrations of potentially dangerous chemicals, similar to those found in pharmaceuticals. Untrained people should never consume them, unless they are in

homeopathic preparations. Atropa belladonna, Arnica species, Aconitum species, and Digitalis species are a few examples. Herbs in the second category have strong effects and can occasionally cause symptoms like nausea or vomiting. But when utilized properly, these herbs are safe. Lobelia And Eonymus species are two examples.

It's interesting to note that laws governing certain herbs vary from one nation to another; for example, ephedra is prohibited in the UK yet easily accessible in the USA, maybe for good cause.[23-25] The third category includes herbs that have been shown to have particular forms of toxicity by science. Notably, plants like Comfrey (Symphytum) that contain pyrrolizidine alkaloids are notoriously hepatotoxic. Other examples are Corynanthe (Yohimbe), Viscum (Mistletoe), and Dryopteris (Male Fern). It is advised that laypeople refrain from ingesting any of these herbs.[3,20,26]

In conclusion, a number of criteria determine whether a substance is considered poisonous; in the context of herbal medicine, different herbs display differing levels of toxicity and possible hazards. To guarantee safety and reduce potential danger, it is imperative to use caution, follow the right usage instructions, and consult a specialist before consuming any herbs, especially those in the first and third groups. Regulatory supervision of manufacturing procedures and quality standards is frequently deficient, and the introduction and broad availability of herbal medications and their derivatives in many nations sometimes take place without required safety or toxicological evaluations. As a result, people can simply obtain these herbal products without a prescription. Regrettably, there are serious risks due to the overestimated possible problems connected to inferior herbal products.[24,26-29] Herbal medications are becoming more and more popular worldwide, as seen by the high rates of use in Asian nations, such as China (40%) and India (65%). Canada, France, and Belgium also provide usage percentages of 31%, 49%, and 70%, in that order.[30-32] Concerns regarding the safety of herbal therapies persist even if patients have favorable opinions of them, are happy with their therapeutic results, and frequently voice discontent with the effectiveness and safety of traditional allopathic pharmaceuticals. The unfavorable responses of pharmaceuticals and natural treatments are contrasted in Table 1. A holistic approach that takes into account mental, emotional, and spiritual components is what distinguishes herbal therapy, and naturopathic techniques heavily emphasize lifestyle factors. Although normal pharmacological actions and side effects are generally absent from herbal remedies, clinical trials for suitable medical applications and informed knowledge of the effects of medicinal

plants are crucial. It has been suggested that while addressing the usage of herbs, we refer to them as indications and contraindications rather than side effects.[24, 33, and 35]

Anticipating adverse effects and toxicities: understanding herbal medicine usage

When it comes to herbal medicine and nutritional supplements, misuse is frequently the cause of negative side effects and toxicities. There are multiple reasons for these occurrences, including improper use, improper preparation, overuse, or chronic use of herbs and supplements, among other things.[26,36] physician must therefore exercise caution when patients disclose a history of such use, since this could point to the possibility of toxicities. For example, hypercalcemia has been associated with excessive vitamin D intake, which is frequently caused by overzealous milk fortification. Likewise, chronic overconsumption of vitamin A can result in adverse outcomes like osteoporosis and hepatotoxicity.[37-39]

It's critical to realize that the main goal of herbal remedies is to preserve the body's equilibrium rather than to instantly alleviate symptoms. Because this could imply deliberate adulteration with pharmaceutical chemicals, healthcare practitioners should be concerned when goods claim to provide immediate symptom alleviation. Toxic responses and consequences may result from such adulteration. These tainted goods are typically offered as consumable or, on occasion, topical final products.

Research has revealed instances of adulteration in herbal medicines. For instance, a Taiwanese survey that examined 2,609 herbal samples discovered that 23.7% of them were tampered with pharmaceuticals. In a similar vein, a California investigation that looked at 243 proprietary products revealed that 7% of them had unidentified prescription components. According to a 1999 examination of 3,320 TCM herbal products in Singapore, 1.2% of them contained unreported medications. Although there are instances of several adulterations, usually only one adulterant is found. Another type of adulteration is when a plant with a less desirable safety profile is replaced with one that is more affordable.

Table 1: Contrasting adverse reaction between pharmaceuticals and herbal medication.

Herbal Product	Adverse Reactions	Interactions
Ginseng	Ginseng abuse syndrome (hypertension, agitation, insomnia, stomach upset, nervousness), estrogen effects (breakthrough bleeding, breast tenderness, gynecomastia)[14]	Increased effect of antidiabetic drugs, antiplatelet drugs, estrogen products[14] Reduced effect of warfarin[14] Increased risk of insomnia, mania, and agitation with antidepressants, dopamine agonists, lithium, neuroleptics[13]
Qing bu liang	Gastrointestinal distress from dried polygonatum Reduced blood glucose levels from pearl barley	Reduced effect of corticosteroids[7] Reduced absorption of various medications[7]
Lycium fruit	None reported	Increased effect of warfarin[15]
Dioscorea	Emesis[13]	None reported
Dong quai	Photosensitivity, possible carcinogenicity of safrole component[7]	Increased effect of warfarin[7]

Pharmaceuticals designed to relieve uncomfortable sensations, such as antihistamines and nonsteroidal anti-inflammatory medications, are among the most prevalent adulterants. In the world of steroids and sexually stimulating medications, adulteration is a widespread problem, and sildenafil is frequently implicated.[42-45] Such adulterations can have disastrous results because the additional medications frequently involve high toxicity concerns. For example, drugs such as corticosteroids, phenylbutazone, phenytoin, and sulfonylurea can have serious side effects that could be fatal.[41] These tainted products can cause allergic reactions, Addisonian crisis, and Cushing's syndrome, which are all brought on by inadvertently consuming goods that contain additional steroids.[46] Additionally, people who use nitrates to treat heart ischemia may unintentionally use products tainted with sildenafil and suffer from hypotension. Furthermore, severe or even fatal hypoglycemia can result from the careless use of drugs containing sulfonylurea.[39,47,48]

Aside from this, species substitution and adulteration are the main causes of additional quality issues that are common in the market for herbal medicines.[28] Customers may respond negatively to such contaminations and substitutes. Sennosides were inadvertently consumed as a result of Senna alexandrina's presence in Hypericum perforatum products, which had a laxative effect.[49]

Because juglone is a poisonous chemical, the discovery of Juglans nigra in ginkgo and echinacea products caused worry. Additionally, because Aristolochia fangchi contains aristolochic acid, replacing Stephania tetrandra in TCM goods may result in cancer and kidney damage. There are significant hazards associated with using Brugmansia arborea to

adulterate Datura stramonium in Ayurvedic medicine.[28,50,51]

Given the difficulties outlined above, it is essential to accurately identify medicinal plant components in order to guarantee their safety. Furthermore, a lot of producers of herbal remedies are ignorant of or undervalue the importance of taxonomy botany and documentation, which creates special difficulties in identifying and gathering medicinal plants for use in herbal treatments. Adopting commonly used binomial names for medicinal plants, together with their synonyms, is crucial to addressing misunderstanding caused by common names. For example, Artemisia absinthium L., which is well-known for its potent narcotic derivative and capacity to cause diseases of the central nervous system as well as widespread mental decline, has at least 11 different popular names, seven of which are completely unrelated to its botanical name. The need to provide the exact scientific name of the plant is highlighted by the fact that Heliotropium Europaeum (heliotrope), which contains strong hepatotoxic pyrrolidine alkaloids, is commonly confused with Valerian officinalis (garden heliotrope), which contains sedative and muscle relaxant valepotriates. Because of this, effective supervision of the safety of herbal medicines requires strong collaboration between pharmacologists, botanists, phytochemists, and other important contributors.[26]

Both the original herbal ingredients and the final commercialized products must be authenticated in order to protect customers. Although conventional techniques like as morphological, microscopic, and chemical identification have long been used as instruments for authentication, new strategies have surfaced and gained popularity in the last ten years. These developments offer new ways to ensure the authenticity and safety of herbal treatments.[52]

Regulation and quality controle

Guidelines and criteria for the manufacturing of herbal medicines are established in large part by organizations like the World Health Organization. Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants and Guidelines for Assessing the Quality of Herbal Medicines with Reference to Contaminants and Residues, for instance, provide crucial information about cultivation and quality control procedures, guaranteeing the worldwide observance of safety and efficacy standards.[52,53] In contrast to pharmaceutical medications that go through extensive premarket testing, Due to differences in cultivation, harvesting, processing, and storage, herbal products have inconsistent quality and standardization; regulatory actions are necessary to address these issues and protect consumer

health. Climate, soil composition, and geographic location all affect the variability of phytochemical constituents, which makes standardization difficult. Growing problems like adulteration and substitution of herbal drugs, which are frequently connected to increased deforestation, also jeopardize the safety of herbal products. The safety, effectiveness, and bioactivity of herbal medications Future Integr Med and these products' effectiveness. Key obstacles in getting authentic herbal pharmaceuticals include adulteration, replacement, and a shortage of competent workers. To guarantee the quality of medicinal herbal products, it is essential to implement cutting-edge quality control methods and standards.[54,55]

A thorough and accurate pharmacognostical assessment forms a scientific foundation for evaluating the quality of traditional herbs and Ayurvedic products.[56-58] The World Health Organization has established guidelines for herbal drug standardization, incorporating critical evaluation parameters like organoleptic properties, ash values, moisture content, microbial contamination, and chromatographic and spectroscopic assessments.[56-58] Modern analytical techniques are essential for the global acceptance of traditional herbs and Ayurvedic products. Pharmacognostic schemes, physicochemical investigations, and organoleptic testing are essential for standardization and authentication. 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]

Nowadays, one or two indicators or pharmacologically active ingredients are frequently used to assess the quality of herbal medications. However, as several ingredients frequently function in concert, this might not offer a through grasp of a product’s therapeutic effects. Assessment is made more difficulty by variations in chemical composition brought on by elements such as plants origin, harvest season, and drying procedures. It is recommended that a wider range of phytochemical constituents be identified in order to guarantee the validity of pharmacological and clinical research as well as the quality of a final product. This will necessitate the use of chromatographic techniques such as capillary electrophoresis, gas chromatography, high performance liquid chromatography, and thin layer chromatography analysis. Chromatography fingerprints, which stand for common chemical components, can be used as a comprehensive technique for evaluating the quality of herbal medications. These fingerprints need to show both the consistency and variations among various samples.

Togather with chemometric techniques, hyphenated chromatography spectrometry approaches such as capillary electrophoresis diode array detection, gas chromatography mass spectrometry, and high performance liquid chromatography diode array detection offer improved separation, selectivity, and precision for qualitative and structural analysis. These chromatographic fingerprints are essential for quality control since they are thought to be dimensionally beneficial.

In the herbal products sector, a lack of strong control can lead to a number of problems, such as contamination, adulteration, and inconsistence potency. In order to ensure that herbal medicines meet certain quality requirements, provide rules for acceptable manufacturing methods, and encourage proper labeling so that consumers may make educated decisions, regulatory frame works are essential. The legal requirements for herbal remedies, however, differ greatly between nations; some have stricter laws, while others take a more relaxed stance. Due to this divergence, herbal treatments from other nations might not meet the same quality standards, which could to lead differences in product safety and quality. Governments, regulatory agencies, and international organizations must work together to address the continuous issue of harmonizing global regulatory norms. Future research should follow known formulation procedures to improve the authentication of herbal products. This includes physiochemi, ingredients identification (for both genuine and adulterants), microscopic and macroscopic examinations. Evaluations of several criteria (such as moisture content, water soluble ash, and acid insoluble ash), as well as the addition of new parameters.[63-65]

Drugs herbs interactions

Patient safety and treatment results may be significantly impacted by combinations between natural medicines and prescription medications' pharmacokinetics and pharmacodynamics can be changed by certain herbs, which may lessen their effectiveness or have unfavorable effects.

Herbal medicines are used extensively. Public health concerns over the safety and effectiveness of herbal therapeutic items are heightened by their increasing use worldwide. It difficult to estimate risks because of miss understandings, poor communication, subpar goods, and fake supply. It is essential to ensure the safety of herbal medicines. Herbs and pharmaceuticals may interact to promote or diminish the pharmacological or toxicological effects of either substance. Synergistic therapeutic effects may make long term drug

administration more challenging. Many medical personnel are unaware of the possible negative effects of herbs drug combos, and less than 40% of patients tell their doctors that they take herbal supplements.[66] There have been no reports of adverse interactions or side effects, which is likely due to both underreporting and the generally harmless nature of the plants employed. Out of 1000 senior individuals, 538 were exposed to 1087 interactions, 30 of which had negative impacts, according to the study.[67]

Interactions between drugs, foods, and herbs are mostly caused by the shared specificity of substrates in biotransformational pathways (HDIs). While pharmacokinetic interactions result from changes in the metabolic and excretory pathways, altered absorption, and interference with distribution, pharmacodynamics drug interactions entail chemical moieties interacting with receptor sites and changing the physiological environment (Fig. 2). Pharmacokinetic HDIs include effects on drug transports and efflux proteins, as well as the activation or inhibition of metabolic enzyme in the liver and intestines, especially the cytochrome P450 (CYP) enzyme family.[68-71] The presystemic activity of CYP and efflux proteins can impact oral bioavailability, leading to a considerable decrease or rise in medication levels when co- administered herbal supplement are used.[72]

Pharmacodynamic and pharmacokinetic concepts HDIs are processes that change renal drug excretion, metabolic enzymes, gastrointestinal processes, and drug absorption. When paired with soluble and insoluble fibers such as psyllium, tea, pomegranate, cinnamon, and rhubarb, HDIS can impact the oral bioavailability of pharmaceuticals by either CYP oxidative metabolism or P- glycoprotein efflux. Because grapefruits irreversibly inhibits CYP3A4 function, it has also been shown to dramatically raise the serum drug levels.[67,71,72]

Combing herbs and medications can have a number of negative effects, such as: a higher risk of bleeding when taking warfarin with ginkgo, garlic, dong quai, or danshen; a mild case of serotonin syndrome when taking serotonin reuptake inhibitors with St. John's wort; a decrease in the bioavailability of drugs such as digoxin, theophylline, cyclosporine, and phenprocoumon when taken concurrently with St. John's wort; the potential for antidepressant and Panax ginseng to cause mania in depressed patients; the escalation of extrapyramidal symptoms when neuroleptic medications are taken with betel nut; a higher risk of hypertension when Yohimbine is taken alongside tricyclic antidepressants; elevated levels of corticosteroids tency with licorice; lower blood levels of prednisolone when combined with Chinese herbal remedies; and lower levels of phenytoin when combined with

the Ayurvedic formulation shankhapushpi.[67,73–77]

In both healthy human and animal models, ginko biloba and garlic have been shown to induce CYP2C19 dependent omeprazole metabolism.[78,79] Furthermore, it has been discovered that the flavonoid content of grapefruit juice inhibits CYP, which has prompted more research into medicinal herbs.[80,81] By obstructing the electron transfer of heme iron, rotenone, a naturally occurring phytochemical present in plants such as the jicama vine, also reduces CYP activity.[82,83]

Herbal extracts have demonstrated the ability to increase HDIs and decrease a variety of enzymes. It has been demonstrated that curcumin, a herbal antioxidant with anti-inflammatory and antitumor qualities, increases the activity of quinone reductase and glutathione S-transferase in the livers of ddy mice. Furthermore, it has been shown that valerian, a herbal supplement used to treat insomnia, may induce HDIs by inhibiting the activity of uridine 5-diphospho- glucuronosyltransferase. More study is needed to fully understand the working and therapeutic applications of these herbal remedies.[71]

Plants that contain anthranoid (such as rhubarb, cassia, and cascara) and soluble fibers can reduce drug absorption by increasing the transit time of the gastrointestinal tract and boosting its motility. These plants may cause increased intestinal transit and fluid accumulation by inhibiting Na+/K+ Adenosine Triphosphatase and increasing nitic oxide synthase activity, which is harmaful to the gut epithelium. Compounds derived from garlic are through to be chemoprotective against chemical carcinogense because they have been shown to increase the activity of glutathione transferase in the rat gastrointestinal effects of ginseng may have an impact on its pharmacokinetics HDIs. Rhein and danthron may improve the water-soluble medications, according to in vitro research. It has been demonstrated that chinese herbal plants, like Polugonum paleaceum, decrease gastrointestinal motility, inhibit the defection reflex, and avoid gastroparesis. By sequestering bile acids, high-fiber herbal products can decrease drug absorption.[67,71] The impact of drug-herb interactions is depicted in Figure 3.

Herbal remedies and prescription medications may have additive or synergistic effects because of their affinity for comparable receptor sites.[71,77,84] Investigating the mechanisms by which HDIs occur may provide support for phytotherapies when an integrated medicine approach is desired.[85]

Fig. 3: Effects of drug-herb intractions ACE stands for angiotensin-converting enzyme; BP for blood pressure; and CNSfor central nervous system.

Efficacy of herbal medicines

Traditional herbal medicine has been a vital component of human culture and medical procedures for thousands of years. It has its roots in ancient knowledge and includes a long tradition of healing techniques that have been handed down through the ages. But in the present day, the effectiveness of herbal remedies is being examined more closely and put to the test against the standards of scientific study. This changing relationship between conventional wisdom and scientific data emphasizes the necessity of bridging the gap between traditional medical treatment.

The rich history of traditional herbal medicine practices

The history of traditional herbal medicine is long and varied, spanning continents and cultures. Herbs and botanicals have long been used by ancient societies like the Egyptians, Chines, Greeks, and Indigenous peoples of different areas to treat illnesses and advance health. These customs were frequently founded on observations, and accumulated knowledge that was transmitted verbally or in writing.[86,87] Herbs are viewed as holistic solutions that take into account the balance of the body, mind, and spirit in traditional system as TCM, Native American herbalism, and Indian Ayurveda. This all encompassing how all facets of health are interrelated and how crucial it is to preserve bodily harmony.

The importance of validating traditional knowledge with modern scientific research

Despite the fact that traditional herbal medicine has endured and frequently helped countless people, its reputation has become increasingly skewed due to the prevalence of modern medicine. As a result, there is now a critical nexus between conventional wisdom and empirical data. 88 Ensuring the safety and effectiveness of herbal remedies is one of the main goals of scientific scrutiny. Current research techniques make it possible to identify the active ingredients in herbs, optimize dosage, and comprehend possible adverse effects or drug interactions. Integrating herbal medicine into traditional healthcare systems requires this knowledge. Additionally, bridging the gap between various healthcare paradigms is facilitated by substantiating traditional knowledge with scientific evidence. It helps patients who might prefer or benefit from herbal treatments by facilitating the integration of efficient herbal remedies into conventional medicine. Along with guaranteeing the best possible care, it also protects the priceless knowledge of traditional healers. In order to produce validated data regarding safety and efficacy, controlled clinical trials are essential. Even though clinical trial results are encouraging, more thorough clinical research is necessary to confirm the method's effectiveness. Obesity, diabetes, heart disease, and bronchial asthma have all been successfully treated with ayurvedic preparations. ma and respiratory conditions, 93,94 ischemic heart disease, rheumatoid arthritis, and.[95–97. 98, 99]

Examples of some common herbs scientifically proven to be effective

Curcumin is a potent anti-inflammatory and antioxidant compound found in turmeric, a mainstay of Indian Ayurvedic medicine. Its efficiency in treating inflammatory conditions like arthritis and digestive problems has been validated by scientific research. When given Curcuma longa extract instead of a placebo, patients with osteoarthritis of the knee showed significant improvements in a number of health indicators over the course of a four-month randomized, double-blind, placebo-controlled trial. Among these enhancements were notable decreases in biomarker levels like 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 radiationinduced 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] Additionally, the potential of ginkgo biloba extract to treat hearing loss and tinnitus was investigated. After receiving Ginkgo biloba extract for 90 days, patients with hearing loss showed notable improvements in the loudness and intensity of their tinnitus in a randomized controlled, double-blind, three-arm study.[105]

A double-blind clinical study found that Ginkgo biloba extract improved patients' Mini-Mental State Examination and Wechsler Memory Scale Recipe III scores for mental health conditions and cognitive function, especially for older patients, with no discernible adverse effects.[106] Additionally, a multi-center, double-blind, randomized controlled trial assessed the efficacy, safety, and dependability of Ginkgo biloba extract in treating vertigo brought on by cerebral arteriosclerosis.[107] Similarly, a 24-week randomized, double-blind, positive-controlled, prospective study examined whether an aqueous extract of Terminalia bellerica could reduce creatinine and uric acid levels in people with hyperuricemia and chronic kidney disease. These markers showed notable declines during the trial.[108] In a different clinical study, patients with type 2 diabetes who received an aqueous extract of Terminalia chebula as opposed to a placebo experienced a significant reduction in cardiovascular risk factors.[109]

The antimicrobial qualities of garlic (Allium sativum) have long been used in a variety of traditional systems. It was examined in an eight-week randomized-controlled study for its potential as a supplemental treatment in addition to standard care, as evidenced by its ability to improve lipid markers in women with polycystic ovary syndrome.[110] In addition, compared to Vaseline treatment, the application of a 30% garlic ointment showed better wound healing with less obvious scarring[111] Furthermore, it was discovered that adding raw crushed garlic to a regular diet helped people with metabolic syndrome, suggesting that it could be used as a preventative adjunctive treatment[112]

A randomized, double-blind, placebo-controlled clinical study found that supplementing with aged garlic extract changed immunity and inflammation in obese people[113] To elaborate, a 12- week double-blind, randomized, placebo-controlled, dose-response study found that using aged garlic extract to treat hypertensive patients was both successful and well-tolerated.[114]

The adaptogenic qualities of ginseng, a well-known herb in TCM, can help the body manage stress while also possibly increasing energy and enhancing mental clarity.

People with idiopathic chronic fatigue showed antifatigue effects from Korean red ginseng (Panax ginseng) in a randomized, double-blind, placebo-controlled study.[115] Without directly influencing endothelial function, a combined treatment involving enriched Korean Red ginseng (P. ginseng) and American ginseng (Panax quinquefolius) improved central systolic blood pressure and certain aspects of pulse waveform in patients with type 2 diabetes and hypertension in another randomized study.[116] Additionally, American ginseng reduced exercise-induced muscle damage in physically active males by modifying the inflammatory response and lipid peroxidation in a randomized, double-blind, crossover, placebo-controlled study.[117] P. ginseng's effect on genitourinary syndrome in postmenopausal women was evaluated in a different randomized, double-blind, crossover, placebo-controlled trial. Following four weeks of the study, related symptoms showed improvement. Furthermore, a four-week clinical study showed that, in comparison to those given a placebo, Korean red ginseng decreased allergic symptoms and total immunoglobulin E levels in patients with allergic rhinitis.[118]

In conclusion, traditional herbal medicine has a wealth of wisdom and knowledge that has been used for centuries to benefit humanity.

To guarantee safety and effectiveness, however, its incorporation into contemporary healthcare necessitates thorough scientific validation. In addition to preserving long-standing healing customs, the continuous integration of scientific data and traditional knowledge deepens our comprehension of the medicinal properties of herbs. We open up a wider range of therapeutic options for the benefit of people and societies everywhere as we investigate the synergy between tradition and science.

Bioactivity of herbal medicines

Particularly in herbs used for culinary, medicinal, or therapeutic purposes, bioactive

compounds represent an intriguing realm of naturally occurring chemical compounds within plants. These substances have unique physiological or biological effects on the human body, providing a range of health advantages and being essential to both conventional and alternative medicine.[119,120]

The Greek word "bios," which means "life," and the Latin word "activus," which means dynamic, vivacious, or involved in activity, are the roots of the term "bioactive." Bioactive compounds are a broad category of naturally occurring substances that have both essential and non-essential properties. the capacity to impact human health. These substances can come from a variety of natural sources, such as plants and animals.

These active biological compounds, which are often present in trace amounts in their natural habitat, are distributed throughout various plant parts, such as leaves, roots, barks, tubers, wood, gums, oleoresin exudations, fruits, figs, flowers, rhizomes, berries, twigs, and even the entire plant. Following harvesting, extraction techniques might be necessary to separate or refine the particular bioactive compounds of interest. 10.

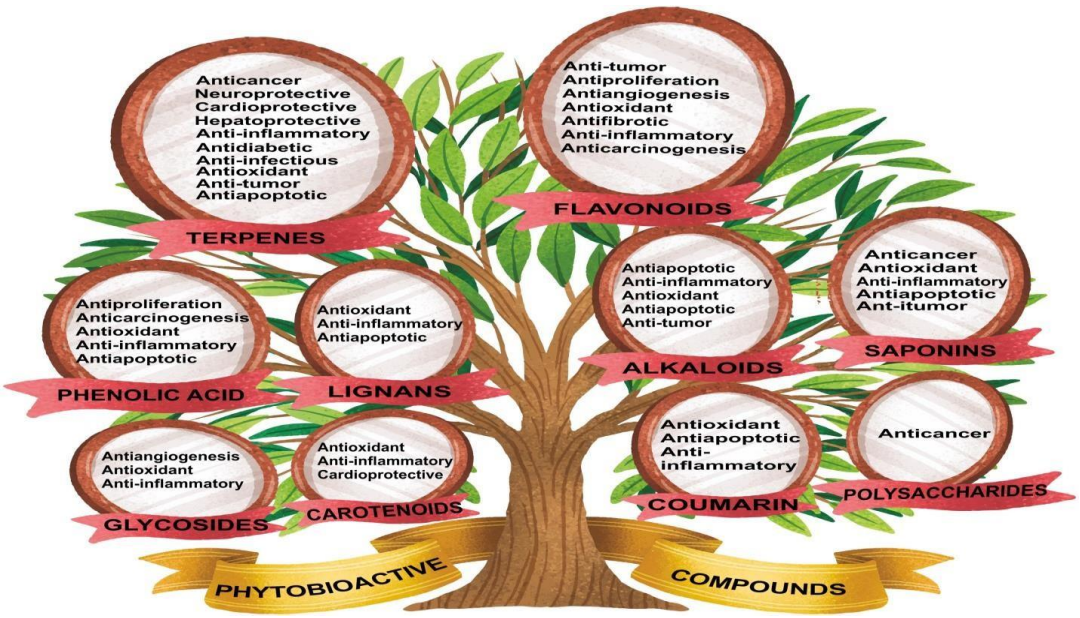

Fig. 4: Overview of the therapeutic potential of bioactive compounds.

Diverse array of bioactive compounds

Herbs contain a wide range of chemical components known as bioactive compounds, such as phenolics, alkaloids, alkaloids, terpenoids, coumarins, flavonoids, nitrogen containing compounds, and organosulfur compounds. Because of their distinct effects on the human

body, these substances have been used for centuries in traditional medical systems such as Ayurveda, TCM, and In dignified medical procedures because of their therapeutic qualities. These bioactive substances are what give herbs their color, flavor, and aroma. When ingested, they also have a significant effect on human health. Anti-inflammatory, immumostimulatory, anticancer, antioxidant, antiproliferation, apoptosis, antifibrotic, and antimicrobial qualities are just a few of the many bioactivities they support (Fig. 4). They might also strengthen the immune system, promote digestive health, or help manage long term illness.[11]

The complex mechanisms of bioactive compounds

The ways in which bioactive substance affect the human body are complex and can differ greatly from one another. Antioxidants found in herbs, for example, help to counteract dangerous free radicals, and anti-inflammatory substances can reduce pain and inflammation. Cooking is one of factors that can affect these compounds' bioavailability. Techniques, processing, and digestion, all of which have an impact on how well they are absorbed and used by the body. To treat particular medical conditions, herbalists and traditional healers frequently recommend herbs based on the bioactive compounds they contain. The therapeutic potential of bioactive compounds found in herbs has also been studied by contemporary scientists, who have provided insight into their modes of action and possible uses in medicine.

Although bioactive compounds have many advantages, it's important to remember that they can also have negative effects and interfere with prescription drugs. Thus, it is essential to use herbs and herbal supplements sparingly and under the supervision of medical professionals. It is always important to take into account possible contraindications and appropriate dosages.

Mechanistic insight of bioactive compounds

Numerous diseases are affected differently by phenolic compounds such as curcumin, 6-gingerol, gallic acid, ellagic acid, and chlorogenic acid. By controlling mitochondrial pathways, gallic acid causes antiproliferation and apoptosis, whereas ellagic acid inhibits cancer by eliminating free radicals and stopping DNA fragmentation.[27,34] By deactivating extracellular- signal regulated kinase (ERK) 1/2, inhibiting the expression of matrix metalloproteinase (MMP) 2 and MMP9, and enhancing antioxidant capacity, chlorogenic acid prevents proliferation, profibrogenesis, and progression.[121]

6-gingerol reduces oxidative stress and prevents cell death (upregulates phosphoinositide 3-

kinase (PI3K)/protein kinase B (Akt) signaling pathway expression), whereas curcumin reduces oxidative damage and prevents apoptosis in the myocardium (Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway).[122,123]

Anthocyanins, flavonols, flavanones, flavones, and isoflavonoids are among the flavonoids that have particular bioactivity. Through a variety of mechanisms, anthocyanins, on the other hand, demonstrate antitumor, amtiproliferation, apoptosis, anti-angiogenesis, antioxidant, antifibrotic, and anti-inflammatory properties.[124,125] Flavanols have anticarcinogenic properties by controlling the hedgehog/glioma 1 and wingless related integration site/ beta catenin pathways and associated genes, inhibit metastasis by lowering osteopontin, and induce apoptosis and antiproliferation through the inhibition of receptor tyrosine kinase, the down regulation of PI3K/Akt, and the inactivation of nuclear factor kappa B (NFkB) through the down regulation of Bcl-2 alpha and Bcl-xl.[126-128] Flavanones prevent invasion and metastasis by suppressing MMP9 transcription, lowering MMP9 expression, and controlling mitochondrial pathways.[129-131] By up regulating poly (ADP-ribose) polymerase and Bcl-2-associated X protein, down regulating Bcl-2 protein, and preventing mitochondria-activated apoptosis from activating hepatic stellate cells, flavones cause apoptosis. Additionally, they prevent carcinogenesis by up regulating p53 and Bcl-2-associated X protein, preventing MMP activation from activating hepatic stellate cells, and controlling the balance of antifibrogenec and profibrogenic molecules. By blocking p21-activated kinase 1 and mitogen activated protein kinase/ERK, flavonols also prevent the development of hepatocellular carcinoma. They also prevent metastasis by reversing the epithelial- mesenchymal transition.[123-134]

Glycosides and lignans have a number of anti-inflammatory and antioxidant qualities. Glycosides such as resveratrol inhibit the expression of vascular endothelial growth factor, genes linked to profibrogenesis, and the activation of hepatic stellate cells, whereas lignans inhibit the pathways of p38 phosphorylation and c-Jun N-terminal kinase (JNK) death,[135,136] Resveratrol inhibits NFκB and controls hepatocyte growth factor/cMet signaling. Au is promoted by polydatin tophagic flux, reduces ROS, and cell death, while lignans inhibit p38 phosphorylation and JNK death.[137-139]

Terpene, or triterpenoid, has a number of cardioprotective and anticancer effects. By blocking the PI3K/Akt and Src/focal adhesion kinase/ERK signaling pathways, it prevents cell migration, proliferation, angiogenesis, and apoptosis. It also triggers apoptosis by

activating the ERK/JNK/p38 pathway and suppressing NFκB.

By upregulating Bcl and downregulating IL6, IL1β, tumor necrosis factor alpha, and Bcl-2-associated X protein, it demonstrates neuroprotective activity. Additionally, by blocking the transforming growth factor betaactivated kinase 1–JNK pathway, it prevents apoptosis and antiapoptotic effects. It eliminates intracellular ROS and stops microglia from migrating toward neurons. By reducing myocardial hypertrophy and blocking mitogen-activated protein kinase/mitochondrial-dependent apoptotic pathways, it also has antioxidant effects. Additionally, it exhibits hepatoprotective activity by inhibiting the activation of the iron regulatory protein 1 pathway, protein kinase RNA-like endoplasmic reticulum kinase/activating transcription factor 6, and thereby preventing the activation of the NFkB pathway and the protein 3 inflammasome's nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain, it also exhibits anti-inflammatory properties. 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 pro inflammatory cytokines.[140,141]

Diterpene lactone (ginkgolide B) and sesquiterpene lactone (artemisinin) both have anti-inflammatory, antioxidant, and anti-tumor qualities. Diterpene lactone prevents apoptosis brought on by endoplasmic reticulum stress through PI3K/Akt/mammalian target of rapamycin signaling, while artemisinin inhibits the activation of the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome.[142] Alkaloids suppress apoptosis, encourage proliferation, and prevent the generation of ROS. 136 Antioxidant, anticancer, anti-inflammatory, antitumor, and antiapoptotic qualities are all exhibited by saponins.[143,144] While polysaccharides prevent neutrophils from rolling on the vessel wall due to P-selectin, carotenoids prevent inflammation and the buildup of reactive oxygen species.[146] Coumarin exhibits anti-inflammatory, anti-apoptotic, and antioxidant properties by blocking the expression of high-mobility group box 1 and the inhibitor of nuclear factor kappa B alpha/NFκB signaling pathway.[147]

Research into the possible health advantages of the bioactive substances found in herbs is still being conducted. The complexities of their mechanisms of action and their suitability for use in various healthcare contexts are being worked out by researchers on a constant basis. We learn more about the potential applications of bioactive compounds found in herbs to improve

human health as research progresses.

CONCLUSION

To sum up, the renewed interest on herbal medicine emphasizes the need to balance conventional knowledge with modern scientific research. Collaboration between fields like botany, pharmacology, clinical research, and regulatory oversight is necessary in the search of safe, efficient, and evidence based herbal medicines. Herbal medicine is expected to firmly establish itself as an important part of all encompassing healthcare as more research reveals the complexities of herbal bioactivity. This will meet the changing needs of people looking for natural and holistic ways to improve their well- being.

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Conflict of interest

Regarding this publication there are no conflicts of interest for the writers.

REFERENCE

1. Aware CB, Patil DN, Suryawanshi SS, Mali PR, Gurav RG, et al. Natural bioactive products as promising therapeutics: A review of natural product-based drug development. S Afr J Bot, 2022; 151: 512-528. Doi; 10.1016/j. sajb. 2022.05.028.
2. Islam SU, Dar TUH, Khuroo AA, Bhat BA, Mangral ZA, Tariq L, et al. DNA barcoding aids in identification of adulterants of Trillium govanianum Wall. ex D. Don. J Appl Res Med Aromat Plants, 2021; 23: 100305.doi:10.1016/j.jarmap.2021.100305.
3. Jităreanu A, Trifan A, Vieriu M, Caba IC, Mârțu I, Agoroaei L. Current trends in toxicity assessment of herbal medicines: A narrative review. Processes, 2022; 11(1): 83. doi:10.3390/pr11010083.

4. Tulunay M, Aypak C, Yikilkan H, Gorpelioglu S. Herbal medicine use among patients with chronic diseases. J Intercult Ethnopharmacol, 2015; 4(3): 217–220. doi:10.5455/jice.20150623090040, PMID:2640 1410.
5. Peltzer K, Pengpid S. The use of herbal medicines among chronic disease patients in Thailand: a cross-sectional survey. J Multidiscip Healthc, 2019; 12: 573–582. doi:10.2147/JMDH.S212953, PMID: 31413584.
6. Tnah LH, Lee SL, Tan AL, Lee CT, Ng KK, Ng CH, et al. DNA barcode database of common herbal plants in the tropics: a resource for herbal product authentication. Food control, 2019; 95: 318–326. doi:10.1016/j.foodcont.2018.08.022.
7. Jordan SA, Cunningham DG Marles RJ. Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol, 2010; 243(2): 198-216. doi: 10.1016/j.tapp. 2009.12.005, PMID: 20018204.
8. Brantley SJ, Argikar AA, Lin YS, Nagar S, Paine MF. Herb-drug interactions: challenges and opportunities for improved predictions. Drug Metab Dispos, 2014; 42(3): 301–317. doi:10.1124/dmd.113.055236, PMID:24335390.
9. Singh S, Bansal A, Singh V, Chopra T, Poddar J. Flavonoids, alkaloids and terpenoids: a new hope for the treatment of diabetes mellitus. J Diabetes Metab Disord, 2022; 21(1): 941–950. doi:10.1007/s40200-021-00943-8, PMID:35673446.
10. Roy A, Khan A, Ahmad I, Alghamdi S, Rajab BS, Babalghith AO, et al. Flavonoids a Bioactive Compound from Medicinal Plants and Its Therapeutic Applications. Biomed Res Int, 2022; 2022: 5445291. doi:10.1155/2022/5445291, PMID:35707379.
11. Riaz M, Khalid R, Afzal M, Anjum F, Fatima H, Zia S, et al. Phytobioactive compounds as therapeutic agents for human diseases: A review. Food Sci Nutr, 2023; 11(6): 2500– 2529. doi:10.1002/fsn3.3308, PMID:37324906.
12. Fernández-Ochoa Á, Leyva-Jiménez FJ, De la Luz Cádiz-Gurrea M, Pimentel-Moral S, Segura-Carretero A. The Role of High-Resolution Analytical Techniques in the Development of Functional Foods. Int J Mol Sci, 2021; 22(6): 3220. doi:10.3390/ijms22063220, PMID:33809986.
13. Rinschen MM, Ivanisevic J, Giera M, Siuzdak G. Identification of bioactive metabolites using activity metabolomics. Nat Rev Mol Cell Biol, 2019; 20(6): 353–367. doi:10.1038/s41580-019-0108-4, PMID:30814649.
14. Fu Y, Yang JC, Cunningham AB, Towns AM, Zhang Y, Yang HY, et al. A billion cups: The diversity, traditional uses, safety issues and potential of Chinese herbal teas. J Ethnopharmacol, 2018; 222: 217–228. doi:10.1016/j.jep.2018.04.026, PMID:29730132.
15. Zhao J, Deng JW, Chen YW, Li SP. Advanced phytochemical analysis of herbal tea in China.

J Chromatogr A., 2013; 1313: 2-23. Doi: 10.1016/j. chroma. 2013.07.039, PMID: 23906802.

16. Dori D, Méda N, Gbaguidi FA, Quetin-Leclercq J, Semdé R. [Wholesale distribution and delivery of plant-based medicinal products through the pharmaceutical system of Burkina Faso]. Ann Pharm Fr., 2020; 78(2): 179–188. doi:10.1016/j.pharma.2019.12.003, PMID:32037029.
17. Petitet F. Interactions pharmacocinétiques entre préparation à base de plantes et médicament: une revue de l'importance Clinique. Phytothérapie, 2012; 10(3): 170–182. doi:10.1007/s10298-012-0705-2.
18. Sahoo N, Manchikanti P, Dey S. Herbal drugs: standards and regulation. Fitoterapia, 2010; 81(6): 462–471. doi:10.1016/j.fitote.2010.02.001, PMID:20156530.
19. Muyumba NW, Mutombo SC, Sheridan H, Nachtergael A, Duez P. Quality control of herbal drugs and preparations: The methods of analysis, their relevance and applications. Talanta Open, 2021; 4: 100070. doi:10.1016/j.talo.2021.100070.
20. George P. Concerns regarding the safety and toxicity of medicinal plants-An overview. J Appl Pharm Sci, 2011; 1(6): 40–44.
21. Boullata JI, Nace AM. Safety issues with herbal medicine. Pharmacotherapy, 2000; 20(3): 257–269. doi:10.1592/phco.20.4.257.34886, PMID:10730682.
22. Ernst E. Herbal medicines: balancing benefits and risks. Novartis Found Symp, 2007; 282: 154–167. doi:10.1002/9780470319444.ch11, PMID:17913230.
23. Mardani S, Nasri H, Rafieian-Kopaei M, Hajian S. Herbal medicine and diabetic kidney disease. J Nephropharmacol, 2013; 2(1): 1–2. PMID:28197432.
24. Karimi A, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; beliefs and facts. J Nephropharmacol, 2015; 4(1): 27-30. PMID: 28197471.
25. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol, 2014; 4: 177. doi:10.3389/fphar.2013.00177, PMID:24454289.
26. Ifeoma O, Oluwakanyinsola S. Screening of herbal medicines for potential toxicities. In: Gowder S (ed). New insights into toxicity and drug testing. Rijeka: IntechOpen, 2013; 63–88. doi:10.5772/54493.
27. Jagan S, Ramakrishnan G, Anandakumar P, Kamaraj S, Devaki T. Antiproliferative potential of gallic acid against diethylnitrosamineinduced rat hepatocellular carcinoma. Mol Cell Biochem, 2008; 319(1-2): 51–59. doi:10.1007/s11010-008-9876-4, PMID:18629614.
28. Msomi NZ, Simelane MB. Herbal medicine. In: Builders PF (ed). Herbal Medicine. Rijeka: IntechOpen, 2019; 215–227. doi:10.5772/ intechopen.72816.
29. Mirzaeian R, Sadoughi F, Tahmasebian S, Mojahedi M. Progresses and challenges in the

traditional medicine information system: A systematic review. J Pharm Pharmacogn Res, 2019; 7(4): 246–259. doi:10.56499/jppres19.662_7.4.246.

30. Ahmad Khan MS, Ahmad I. Chapter 1-Herbal medicine: current trends and future prospects. In: Ahmad Khan MS, Ahmad I, Chat- topadhyay D (eds). New Look to Phytomedicine: Advancements in Herbal Products as Novel Drug Leads. Cambridge: Academic Press, 2019; 3–13. doi:10.1016/B978-0-12-814619-4.00001-X.
31. Wake GE, Fitie GW. Magnitude and Determinant Factors of Herbal Medicine Utilization Among Mothers Attending Their Antenatal Care at Public Health Institutions in Debre Berhan Town, Ethiopia. Front Public Health, 2022; 10: 883053. doi:10.3389/fpubh.2022.883053, PMID:35570953.
32. Nasri H. Cisplantin therapy and the problem of gender-related nephrotoxicity. J Nephropharmacol, 2013; 2(2): 13-14. PMID: 28197436. Nasri H. Cisplatin therapy and the problem of gender-related nephrotoxicity. J Nephropharmacol, 2013; 2(2): 13–14. PMID:28197436.
33. Rafieian-Kopaei M. Medicinal plants for renal injury prevention. J Renal Inj Prev, 2013; 2(2): 63–65. doi:10.12861/jrip.2013.21, PMID:25340130.
34. Chang YJ, Hsu SL, Liu YT, Lin YH, Lin MH, Huang SJ, et al. Gallic acid induces necroptosis via TNF-α signaling pathway in activated hepatic stellate cells. PLoS One, 2015; 10(3): e0120713. doi:10.1371/journal. pone.0120713, PMID:25816210.
35. Welz AN, Emberger-Klein A, Menrad K. Why people use herbal medicine: insights from a focus-group study in Germany. BMC Complement Altern Med, 2018; 18(1): 92. doi:10.1186/s12906-018-2160-6, PMID:29544493.
36. Mulholland CA, Benford DJ. What is known about the safety of multivitamin- multimineral supplements for the generally healthy population? Theoretical basis for harm. Am J Clin Nutr, 2007; 85(1): 318S–322S. doi:10.1093/ajcn/85.1.318S, PMID:17209218.
37. Jacobus CH, Holick MF, Shao Q, Chen TC, Holm IA, Kolodny JM, et al. Hypervitaminosis D associated with drinking milk. N Engl J Med, 1992; 326(18): 1173- 1177. Doi: 10.1056/NEJM199204303261801, PMID: 1313547.