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Safety and Efficacy of Herbal Medicines in Modern Pharmacotherapy

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A B S T R A C T

Herbal medicines are widely popular and heavily used in developing countries, where they often provide a more accessible and affordable alternative to pharmaceutical drugs. However, the growing popularity of herbal remedies has raised concerns regarding the professionalism of practitioners and the quality, effectiveness, and safety of herbal treatments and natural products available on the market. Most research has focused on clinical and experimental aspects, such as safety, effectiveness, and mechanisms of action, as well as regulatory issues, often overlooking public health perspectives. Public health research should take into account social, cultural, political, and economic factors to maximize the role of herbal medicine in global healthcare systems. The regulatory framework for herbal medicines and dietary supplements is currently being revised. A new system for the registration of traditional herbal medicines aims to ensure that products meet safety and quality standards. Currently, the pharmaceutical quality of many complementary medicines is a concern. WHO developed guidelines for assessing herbal medicines. Herbal medicine plays a significant role in the future of alternative healthcare.

The World Health Organization (WHO) reports that nearly 70-80% of the population in developing nations depends on herbal medicines for immediate health needs, particularly in the Asian region. The discussion revolves around the scenario and perception of herbal medicine. The public's belief that herbal and natural products are safer than synthetic medications can only be verified by implementing regulatory standards for these products. This article provides a comprehensive review of herbal medicine, covering topics such as its historical context, safety, effectiveness, quality assurance, clinical trials, bioavailability, herb-drug interactions, intellectual property rights, marketing, and regulatory considerations concerning botanical therapies. The longstanding tradition of herbal medicine, deeply rooted in various cultural practices, is seeing a revival as more people seek holistic and individualized healthcare solutions. This ancient practice, handed down through generations, is gaining renewed attention as its potential advantages are increasingly recognized. This review explores the safety aspects of herbal treatments, applying thorough scientific evaluation. Furthermore, it examines the effectiveness of herbal remedies, striving to connect traditional knowledge with modern empirical evidence.

Keywords: Herbal medicines, pharmaceutical drugs, quality, safety, clinical experimental dimensions, regulatory challenges, synthetic

Introduction

Herbal medicine, also called herbalism or phytotherapy, involves using plant-based materials for healing purposes. This practice traces back to ancient cultures, where plants were highly valued for their medicinal qualities. Traditional healing systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Native American practices demonstrate the longstanding importance of herbal remedies.

Herbal medicine has consistently played a key role in primary healthcare. It's estimated that around 80% of the world's population relies on herbal treatments for their therapeutic advantages.[1,2] As of 2022, the global herbal medicine market was valued at USD 148.5 billion, with expectations to grow from USD 165.13 billion in 2023 to USD 386.07 billion by 2032. This reflects a compound annual growth rate (CAGR) of 11.20% during the forecast period from 2023 to 2032. The global COVID-19 pandemic has driven unprecedented demand for herbal medicine, with its use increasing in all regions beyond pre-pandemic levels. The rising awareness of the side effects of allopathic drugs and the benefits of herbal alternatives has contributed to this growth. Additionally, the increasing global population and the rising prevalence of chronic diseases are key factors fueling market expansion.[3,4] Approximately 70-80% of the global population, especially in developing nations, depend on alternative medicine for their primary healthcare needs, according to a report by the World Health Organization.[5] However, this growing demand has also led to an increase in fraudulent practices, such as the replacement of herbal ingredients with synthetic substances.[6,7]

Some negative effects may not just be due to adulteration, contamination, or incorrect plant identification; they can also arise from the inherent toxicity of certain plants. This highlights the need for comprehensive toxicological evaluations to address potential safety issues. Additionally, adverse effects might be caused by foreign contaminants such as pesticide residues, heavy metals, or microbial agents.[8] Adverse events associated with certain herbal remedies highlight the necessity for comprehensive clinical trials and toxicological evaluations. Regulatory bodies are increasingly focusing on the quality, safety, and effectiveness of herbal products to protect public health. Advances in science have led to the extraction and synthesis of active compounds from plants, which have become the basis for modern pharmaceuticals. Nevertheless, the holistic approach of herbal medicine, which often

employs multiple plant constituents, remains important. The field of herbal preparations has grown significantly in recent decades, leading to a wide range of products in the market used in alternative and complementary medicine. With rising consumer demand, there is increasing pressure to evaluate the efficacy and safety of these products.[9,10]

Historical background

Archaeological evidence indicates that the use of medicinal plants dates back to the Paleolithic era, around 60,000 years ago. The earliest written records of herbal remedies come from over 5,000 years ago with the Sumerians, who compiled lists of various plants. Numerous ancient cultures documented their knowledge of plants and their healing properties in texts referred to as herbals.

In ancient Egypt, herbs are mentioned in medical papyri, illustrated in tomb art, and occasionally discovered in medical jars containing traces of herbs. Among these writings, the Ebers Papyrus, dated to approximately 1550 BC, stands out as one of the oldest and most comprehensive medical documents, cataloging over 700 plant-based substances.

Greek contributions to herbal literature began with Theophrastus of Eresos in the 4th century BC, who authored Historia Plantarum in Greek. This was succeeded by works from Diocles of Carystus in the 3rd century BC and Krateuas in the 1st century BC. Although only fragments of their writings remain, scholars have noted substantial similarities with the Egyptian herbals.

In Bronze Age China, archaeological findings from the Shang Dynasty (c. 1600–1046 BC) have uncovered seeds likely used for medicinal purposes. The Huangdi Neijing, an early Chinese medical text, mentions over a hundred herbs among the 224 substances it discusses.

In ancient India, traditional medicine heavily relied on herbs, with diet serving as a primary treatment method for ailments. Another significant herbal text is De Materia Medica, composed in Greek by Pedanius Dioscorides (c. 40–90 AD) from Anazarbus, Cilicia. This work remained influential for over 1,500 years until the 1600s, underscoring the enduring significance of early herbal literature.[11]

Safety assessment of herbal medicines

The common belief that herbal medications are entirely safe and free from side effects is inaccurate. Plants contain numerous compounds, some of which can be highly toxic, such as certain plant-based anti-cancer agents, digitalis, pyrrolizidine alkaloids, ephedrine, and phorbol esters. However, when used appropriately, the occurrence of adverse effects with most herbal remedies is generally lower compared to synthetic drugs. Nonetheless, well controlled clinical trials have now confirmed that side effects do indeed occur[12,13] .Two types of side effects have been associated with herbal medicines. The first type, inherent to the herbal remedies themselves, is primarily linked to predictable toxicity, overdosing, and interactions with conventional drugs, similar to side effects seen with modern pharmaceuticals. For example, many instances of allergic reactions have been reported in connection with herbal drugs.

On the other hand, most side effects linked to herbal medicines are external to the remedy itself and stem from various manufacturing issues. These include plant misidentification, lack of standardization, poor manufacturing practices, contamination, substitution or adulteration of plant materials, incorrect formulations, or improper dosing.[14,15] Traditional medicinal herbal remedies include various parts of plants, such as the above-ground parts,

flowers, fruits, leaves, seeds, and stems, as well as underground parts like roots, bulbs, tubers, and rhizomes.[16,17] They play a crucial role in global trade, having notable clinical, economic, health, and pharmaceutical significance. The growing acknowledgment of their value, whether warranted or not, is driving a consistent growth in their market. However, there is still a lack of comprehensive data on the quality, safety, and effectiveness of many plants, their extracts, preparations, and active compounds.[18]

Toxicity related to herbal medicines

The concept of "toxicity" is largely shaped by personal viewpoints. Many common foods contain substances that can provoke allergies or may be considered harmful based on certain standards. For example, alpha-gliadin found in gluten from wheat, oats, and rye; cyanogenic glycosides in the seeds of various fruits; thiocyanates in cruciferous vegetables; alkaloids in nightshade plants; and lectins in specific legumes like soy and red kidney beans are compounds present in foods that are generally deemed safe globally.[19] From a safety perspective, herbs can be classified into three main categories. The first category includes a few herbs that contain high levels of potentially dangerous compounds, similar to those found in pharmaceutical drugs. These should never be consumed by untrained individuals, except in homeopathic doses. Examples include Atropa belladonna, Arnica species, Aconitum species, and Digitalis species. The second category consists of herbs with strong effects, which may sometimes cause symptoms like nausea or vomiting. However, these herbs are generally safe when used correctly. Examples include Lobelia and Euonymus species.

There are also notable differences in the regulations surrounding these herbs in different countries; for example, Ephedra is banned in the UK but is readily available in the USA, likely for valid reasons [20, 21]. The third group includes herbs that demonstrate certain forms of toxicity, backed by scientific research. For instance, plants with pyrrolizidine alkaloids, like Comfrey (Symphytum), are widely recognized for their liver toxicity. Other examples are Dryopteris (Male Fern), Viscum (Mistletoe), and Corynanthe (Yohimbe). It is recommended that nonexperts avoid consuming herbs from this group internally.[22,23,24] The classification of a substance as toxic depends on several factors. In herbal medicine, different herbs have varying levels of toxicity and risk. It's important to be cautious, follow proper usage guidelines, and get professional advice before taking herbs, especially those in the first and third groups, to stay safe and avoid harm. Many herbal medicines and their products are widely available in many countries without required safety or toxicology tests. There is often little regulation of how these products are made or the quality standards they follow. As a result, these herbal products are easily available to consumers without a prescription. Sadly, the risks associated with low-quality herbal products are often underestimated, posing serious dangers.[25,26,27]

Clinical trials of herbal medicines

The basic principles of clinical trials for herbal medicines are much like those for synthetic drugs. These trials generally aim to: Confirm the safety and effectiveness of the herbal medicine.

1. Develop new herbal medicines.
2. Investigate new uses for existing herbal medicines.
3. Test changes in dosage or how the medicine is taken.

Sometimes, trials also evaluate the effects of purified or partially purified substances from herbs. The World Health Organization (WHO) has issued guidelines on the regulatory requirements for conducting these trials

The new Appendix IB in Schedule Y lists the information that needs to be submitted when applying to conduct a clinical trial for imported or manufactured phytopharmaceutical drugs in India. This is the first time the term "Phytopharmaceutical drug" has been officially defined. It refers to a purified and standardized extract from a medicinal plant that contains at least four specific bio-active or phytochemical compounds, both qualitatively and quantitatively measured.For a New Drug Application involving a phytopharmaceutical drug, the regulatory requirements include standard safety and pharmacological data from human or epidemiological studies. Specifically, applicants must provide:

- Information on the plant's identification, authentication, source, and quality.

- Details about the extraction process, fractionation, purification, and bio-active constituents.

- Formulation details, manufacturing process, route of administration, dosages, and therapeutic class.

- Published literature on the composition, process, dosage, and method of use, as well as the proportion of active ingredients.

- Published literature on safety and pharmacological studies.

- Information on any contraindications and side effects.

- Stability data.

- Results from dose-finding studies and Phase I clinical trial protocols.

Phase I clinical trials determine the highest dose that can be tolerated and any related side effects in healthy volunteers. Phase II trials assess the drug's effectiveness and side effects in patients with the specific disease the drug is meant to treat. Data from both Phase I and II trials, along with the study

protocol, must be submitted for exploratory clinical trials.If the phytopharmaceutical drug has been on the market for over five years or has strong published safety evidence, the study requirements may be simplified or adjusted.[28]

Challenges in Clinical Trials

Herbal medications consist of various chemical compounds (phyto-constituents) that have been used for centuries and are known for their pharmacological effects on the body. These remedies are widely accepted and utilized globally, suggesting their perceived safety and efficacy. However, many herbal products lack comprehensive pharmacokinetic, pharmacological, and clinical data, leading to uncertainties regarding their safety and effectiveness. The challenge of regulating herbal drugs is compounded by significant gaps in meeting statutory research criteria for these products.

There is insufficient scientific evidence to evaluate the safety and efficacy of herbal medications. It's crucial to assess the quality of trial drugs for consistency in active ingredients across different batches. Creating active and control groups that match the color, smell, and taste of herbal medications poses a challenge, as these attributes are difficult to replicate in a placebo. Employing the latest clinical research methodologies and protocols can help mitigate these issues.

Herbal drug research faces numerous obstacles, including financial constraints, ethical considerations, product standardization (quality control), study design, and regulatory compliance, all of which must be addressed before progressing to large Phase III studies. Another significant challenge in randomized clinical trials of herbal medicines is selecting appropriate controls. The controls must be as similar to the intervention group as possible, as comparability is essential for demonstrating the specific effects of the herbal treatment.

Factors such as color, odor, dosage frequency, patient perception of the therapy, and the physical conditions under which treatments are administered should be carefully regulated. For instance, finding a matching control for certain herbal substances, like ginger, which has a distinctive aroma, can be particularly challenging.[29]

Regulation and quality control of herbal medicines

focus on standardizing Regulatory bodies are crucial for setting standards for herbal medicines and ensuring they work as intended. They, ensuring quality, and controlling these products to make them safer and more effective. They also check how herbal remedies affect gut health and how they might interact with regular medications.

NAFDAC's regulatory practices and enforcement strategies include several key activities. These involve:

1. Ensuring Product Safety and Quality: NAFDAC conducts inspections of manufacturing facilities and lab tests on herbal products to make sure they are safe and meet quality standards.

2. Registration and Listing: The agency manages the registration process for herbal products, ensuring that their labeling, packaging, and advertising meet required standards.

3. Post-Market Surveillance: NAFDAC monitors herbal medicines even after they are on the market to track any adverse reactions or issues.

4.Enforcement Actions: When products do not comply with regulations, NAFDAC can seize them, impose penalties, or take legal action.

5. Training and Public Education: The agency offers training and educates the public on how to use herbal products safely and effectively.

6.Collaboration: NAFDAC works with local and international partners to improve the regulation and quality of herbal medicines in Nigeria..

Stronger Laws and Policies: Create and enforce strict rules for herbal medicines, covering aspects like production quality, labeling, product registration, and marketing. Update these laws regularly to include new scientific findings and trends in the herbal medicine industry.

Training and Skill Development: Provide resources for creating training programs and workshops for NAFDAC staff to improve their knowledge about herbal medicines. Focus on areas like quality checks, safety evaluations, and enforcing regulations. Work with universities and international agencies to share knowledge and enhance skills.

Public Awareness and Education: Launch campaigns to educate consumers, healthcare workers, and traditional medicine practitioners about herbal medicines. Provide clear and accurate information on their benefits, risks, and proper use through workshops, seminars, social media, and printed materials.

Collaborating with Partners: Create strong connections with local and international groups such as herbal medicine makers, sellers, traditional healers, industry experts, research institutions, universities, and global organizations. Work together to address issues, share good practices, and agree on regulatory methods. This teamwork can also help with research, development, and testing of new herbal products. Set up advisory groups or task forces to keep communication and cooperation ongoing.

Enhancing Safety Monitoring Set up a strong and well-resourced team to monitor and track any negative effects of herbal medicines. This team should act quickly when issues arise. Also, educate and encourage both consumers and healthcare professionals to report any problems they notice with herbal medicines.[30]

Drug herb interaction

Interactions between herbal remedies and conventional medications can pose serious risks to patient safety and treatment effectiveness. Certain herbs may affect how prescription drugs are absorbed, metabolized, and eliminated, potentially reducing their efficacy or causing harmful side effects.

The widespread use of herbal remedies raises public health concerns regarding their safety and effectiveness. Evaluating these risks can be complicated due to misunderstandings, poor communication, low-quality products, and counterfeit items. Ensuring the safety of herbal medicines is vital, as interactions can either enhance or diminish the effects of both herbs and medications.

Prolonged use of pharmaceuticals may also become more intricate because of these interactions. Fewer than 40% of patients report their use of herbal supplements to healthcare providers, and many practitioners may not be fully aware of the potential risks linked to herb-drug combinations. Some adverse effects and interactions go underreported, perhaps due to the perception that many herbs are harmless.

A study of 1,000 elderly patients found that 538 experienced 1,087 interactions, with 30 reporting adverse effects. Herbal-drug interactions (HDIs) can change how medications are absorbed or processed in the body, thereby affecting their effectiveness. These interactions often involve liver enzymes, especially CYP, or transport proteins, which can alter drug concentrations in the bloodstream. For instance, grapefruit can markedly increase blood levels of certain medications by inhibiting the CYP3A4 enzyme.

Combining herbs with medications can lead to various complications, such as:

- Increased bleeding risk with warfarin when used alongside ginkgo, garlic, dong quai, or danshen.
- Mild serotonin syndrome when St. John's wort is combined with serotonin-reuptake inhibitors.
- Reduced effectiveness of drugs like digoxin, theophylline, cyclosporine, and phenprocoumon when taken with St. John's wort.
- Mania in depressed patients when antidepressants are paired with Panax ginseng. - Worsened movement disorders when neuroleptic drugs are used with betel nut.
- Increased blood pressure risks when tricyclic antidepressants are combined with Yohimbine.
- Enhanced corticosteroid effects with licorice.
- Decreased prednisolone levels when used with Chinese herbal products.
- Lowered phenytoin levels with shankhapushpi, an Ayurvedic remedy.

Certain herbal extracts, such as curcumin (known for its antioxidant and anti-inflammatory benefits) and valerian (commonly used for insomnia), have shown potential to affect enzyme activity and drug interactions[31].

Enzyme induction can result in lower plasma drug concentrations, while altered metabolic processes may lead to toxicity. Herbal products can either inhibit or stimulate the enzymes responsible for metabolizing synthetic drugs, resulting in HDIs. These enzymes are crucial for breaking down, deactivating, or conjugating drugs for elimination. When herbs influence enzyme activity, HDIs occur.

Enzyme Inhibition

It happens when an herb binds to the enzyme's active site, preventing the synthetic drug from attaching. Irreversible or quasi-irreversible inhibition involves time-dependent effects, where the herb permanently modifies the enzyme, often necessitating new protein synthesis for recovery.

Enzyme Induction

results in elevated blood levels of drugs due to the activation of drug transporters. When herbs induce enzymes, this can lower serum drug concentrations, and if the metabolites produced are active, toxicity may ensue.

Garlic (Allium sativum):

Two pharmacokinetic studies demonstrated that garlic consumption significantly boosted duodenal P-glycoprotein expression by 131%. Consequently, the average AUC and Cmax of the antiviral drug saquinavir decreased by up to 51% and 54%, respectively, when taken with garlic. After a 10-day washout period, these values returned to approximately 60–70% of their original levels.

Ginkgo (Ginkgo biloba):

Clinical trials revealed that taking G. biloba extract reduced the AUC for tolbutamide by 16% compared to prior levels. While this interaction is considered minor, it is advisable to exercise caution when using them concurrently.

Green Tea (Camellia sinensis):

An in vivo study indicated that catechins in green tea extract inhibit folic acid absorption by acting as competitive inhibitors of dihydrofolate reductase (DHFR), adversely affecting folate uptake. Human studies showed that the Cmax and AUC of folic acid decreased by 58.4% and 43.9%, respectively,

when taken with green tea, leading to reduced bioavailability of folic acid. The likely mechanism for this interaction is the inhibition of carrier-mediated absorption of folates.[32]

Efficacy of herbal medicines

Turmeric

Curcuma longa, commonly known as Turmeric, is a perennial herbaceous plant in the Zingiberaceae family. Native to India, it is also cultivated in China, Sri Lanka, West and East Africa, and other tropical regions. . Turmeric is utilized for various health purposes, including the treatment and management of conditions such as cancer, coughs, diabetes, arthritis, diarrhea, inflammation, psoriasis, liver diseases, skin disorders, and stomach ulcers. It is known for its ability to enhance blood circulation, relieve stagnation, reduce depression, and serve as a natural colouring and flavouring agent in food.

Research has demonstrated that C. longa and its active compounds offer a range of pharmacological benefits, including antioxidant, hepatoprotective, anti-osteoarthritis, anti-inflammatory, anticancer, anti-arthritic, neuroprotective, antidiabetic, antidiarrheal, antimicrobial, anti-atherosclerotic, antidepressant, anti-aging, wound healing, and memory-enhancing effects. The therapeutic uses of Turmeric are attributed to its diverse array of over 300 biologically active compounds, such as polyphenols, sesquiterpenes, diterpenes, triterpenoids, sterols, and alkaloids.[33]

Ginkgo biloba

Ginkgo biloba L (Ginkgoaceae), often referred to as a "living fossil," has a rich history of medicinal use. Both its leaves and seeds have been commonly prescribed for a range of conditions, including respiratory illnesses, alcohol dependence, bladder inflammation, heart and lung issues, and skin infections.

Ginkgo extracts contain active compounds that provide a range of beneficial effects on the body. These extracts improve blood circulation, prevent clot formation, fortify capillary walls, and safeguard neural cells during periods of oxygen deprivation. Ginkgo leaf extracts are frequently used to address symptoms of dementia, such as issues with concentration and memory. They also offer anti-asthmatic properties, support wound healing, and have neuroprotective effects. Additionally, Ginkgo biloba is utilized to manage stomach pain, cognitive impairments, bronchitis, asthma, tuberculosis, and

various other conditions. Clinical evaluations have confirmed its efficacy as a nutritional supplement and medicinal aid for enhancing memory, as well as a therapeutic or preventive measure for Alzheimer's disease and other neurological conditions.

Furthermore, Ginkgo has demonstrated potential as a treatment for cardiovascular issues due to its immunomodulatory, anti-inflammatory, neuroprotective, and antioxidant properties. Ginkgo leaf extracts are available in various formats, including film-coated tablets, oral solutions, and injectable forms, in Europe and America. These extracts are widely incorporated into herbal pharmaceuticals, dietary supplements, and complementary therapies.[34]

Garlic

Garlic was widely used in ancient times to address a range of health issues. Garlic is recognized as a valuable remedy (with antibiotic properties) for treating infections, gynecological issues, toothaches, persistent coughs, constipation, parasitic diseases, snake and insect bites, and rheumatoid arthritis. During the Renaissance, Europe began to focus more on garlic's health benefits.

Despite many misconceptions about its health-promoting properties, garlic has gained significant attention in contemporary medicine. Sales of garlic supplements now rival those of popular prescription drugs in several Western countries. Substantial epidemiological evidence supports garlic's medicinal and preventative effects. A variety of clinical and experimental studies have documented the multiple health benefits of garlic and its derivatives. Key factors contributing to these benefits include: reduced cardiovascular and metabolic risk; lowered cancer risk; antioxidant effects; antimicrobial properties; and enhanced detoxification and liver protection.[35]

Ginseng

Ginseng, often referred to as the "king of herbs," has been utilized for thousands of years in East Asian traditional medicine to treat various ailments. Over the past thirty years, it has gained immense popularity around the globe. Today, ginseng is incorporated into agricultural products, dietary supplements, and medicines in numerous countries. Its primary bioactive compounds are ginsenosides, which are a type of triterpene saponin. However, the health benefits of ginseng are not solely attributed to ginsenosides. Recently, gintonin, another active compound, has been identified. Despite this, most research in pharmacology and medicine has concentrated mainly on ginsenosides. To date, nearly 200 different ginsenosides have been documented, with some of the most significant being Rb1, Rb2, Rc, Rd, Re, and Rg1.[36]

Conclusion

The renewed interest in herbal medicine underscores the need to align traditional knowledge with modern scientific standards. To ensure that herbal remedies are safe, effective, and grounded in evidence, it is crucial to foster collaboration among experts in botany, pharmacology, clinical research, and regulatory affairs. As research continues to explore the complex effects of herbal substances, it is expected that these remedies will become a valued part of a holistic healthcare approach, meeting the growing demand for natural and integrative health solutions.

Despite the positive outcomes reported in clinical studies, more comprehensive research is necessary to standardize dosages, clarify potential drug interactions, and guarantee uniform quality. The evolving regulations and heightened scrutiny of herbal products highlight the need for a robust, evidence-based framework for their use.

Ultimately, the successful incorporation of herbal medicines into modern pharmacotherapy hinges on a cooperative effort among herbalists, pharmacologists, and healthcare providers. By emphasizing thorough research and strict quality control, we can effectively integrate herbal remedies into contemporary treatment regimens, optimizing their benefits while minimizing potential risks for patients.

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