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Review Article

Profiling the toxicological landscape of herbal drugs

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ABSTRACT

Herbal drugs, also known as phytochemicals or botanical medicines, are a cornerstone of traditional healthcare, with the World Health Organization (WHO) noting their reliance by approximately 80% of the global population. Despite their historical and widespread use, the assumption of their inherent safety due to natural origins is misleading. The significance of toxicological profiling and standardization to ensure the safe use of herbal medicines. Challenges such as species substitution and adulteration highlight the urgent need for regulatory oversight and stringent quality control. Various bioactive compounds in herbs can pose severe health risks, necessitating comprehensive toxicity evaluations using OECD guidelines. Regulatory frameworks across different regions, including the FDA in the United States, EMA in Europe, and the Ministry of AYUSH in India, are pivotal in maintaining the safety and efficacy of these products. Strategies to mitigate herbal drug toxicity include standardization of manufacturing processes, adherence to Good Manufacturing Practices (GMP), robust regulatory compliance, extensive research on toxicity profiles, education of stakeholders, and vigilant monitoring of adverse events. These measures are essential to fostering the responsible use of herbal medicines and safeguarding public health.

1. Introduction

Herbal drugs, alternatively referred to as botanical medicine, are defined by the World Health Organization (WHO) as encompassing herbs, herbal materials, herbal preparations, and finished herbal products. These formulations comprise active ingredient parts derived from plants or other plant materials, individually or in combination. Traditional herbal medicine has consistently served as a crucial element of primary healthcare. Roughly 80% of the global population is believed to rely on herbal medicinal products for their therapeutic benefits. Herbal medicine is commonly viewed as a fundamental aspect of dietary supplements. The increasing interest in herbal medicine is driven by its extensive historical use and the widespread belief that herbs are inherently natural and safe. In recent times, there has been a growing trend in the use of herbal remedies as dietary supplements for disease prevention and as alternative or complementary medicine (CAM) for treating illnesses. A diverse array of herbal medicines and products is readily accessible in markets worldwide.[1] Many people think herbal medicines are safer than conventional ones because they come from nature. However, it's important to realize that some components in herbal medicines can be harmful in large amounts and may have negative effects if used for a long time.[2] The significance of herbal drug toxicology lies in the necessity to confirm the safety of traditional herbal medicines before employing them in clinical settings. This is particularly vital in initial clinical trials, where it's essential to understand and assess the toxic effects of herbs and plants. Additionally, there is an increasing concern

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about the absence of scientific evaluations regarding the toxicity of herbal medicines.[3] Toxicological profiling is essential for assessing potential risks and adverse effects associated with the use of herbal drugs. Through systematic toxicity studies, scientists can comprehensively evaluate the safety and efficacy of herbal drugs. This process serves to validate the authenticity of herbal remedies and provides evidence-based information crucial for informing healthcare professionals and regulatory bodies.[4] Toxicological profiling of herbal drugs entails a thorough examination of their toxicity profiles. This process encompasses identifying the toxic dose, evaluating potential adverse effects, and understanding the mechanisms of action and potential drug interactions associated with these herbal remedies. By conducting toxicological profiling, researchers can pinpoint potential toxic components or interactions that may harm human health. Additionally, this process enables the establishment of safe dosage guidelines and the identification of potential drug-drug interactions, especially when herbal drugs are used concurrently with conventional medicines.

2. The Importance of Standardization for Safety and Toxicity Profiling of Herbal Medicine

In recent decades, research has highlighted issues related to the substandard quality of herbal medicinal products found in the market. Challenges such as species substitution and adulteration have been identified as key contributors to these problems. This can have serious consequences for consumers, as contaminations and substitutions may result in adverse reactions. For instance, some *Hypericum perforatum* products were found to contain Senna alexandrina, leading to a laxative effect with symptoms like diarrhea and abdominal pain. Additionally, the presence of *Juglans nigra* in Ginkgo and Echinacea products poses risks, given that *Juglans nigra* contains the toxic compound juglone, which could be hazardous, especially for individuals with nut allergies. Moreover, the substitution of *Stephania tetrandra* with *Aristolochia fangchi* in traditional Chinese medicine products carries the potential for renal toxicity and cancer due to the presence of aristolochic acid, a known carcinogenic and nephrotoxic substance.[5]

3. Herbal Drug Constituents and Toxicity

3.1. Toxicity evaluation

The toxicity associated with medicinal plants and herbal medicinal products is intricately linked to the presence of bioactive compounds within the plant material and their inherent toxic characteristics. This complexity is further heightened when dealing with heterogeneous and intricate mixtures of herbs, which can give rise to unpredictable effects. Numerous examples underscore the

Table 1: Herbal drugs with their reported toxicity

Constituent Type	Example	Source	Therapeutic Use	Potential Toxicity
Alkaloids	Morphine	Opium poppy (*Papaver somniferum*)	Analgesic (pain relief)	Respiratory depression and overdose
Flavonoids	Quercetin	Various fruits, vegetables, and herbs	Antioxidant, anti-inflammatory	High concentrations may cause gastrointestinal upset
Terpenoids	Thujone	Sage, wormwood	Traditionally used for digestive issues	Excessive amounts can cause neurotoxic effects
Glycosides	Digoxin	Foxglove plant (*Digitalis purpurea*)	Cardiac glycoside used in heart conditions	Overdose can lead to severe cardiac issues, arrhythmias

existence of toxic endogenous compounds in the plant kingdom. These include pyrrolizidine alkaloids (known for hepatotoxic, genotoxic, cytotoxic, and phototoxic effects), furan derivatives (associated with hepatotoxicity and potential carcinogenicity), epoxy-diterpenoids (known for hepatotoxic effects), anthraquinones (recognized for hepatotoxicity), bis-benzylisoquinoline alkaloids (linked to pulmonary toxicity), alkenylbenzenes (acknowledged for genotoxic and carcinogenic properties), and ginkgolic acids (identified as embryotoxic, cytotoxic, and neurotoxic). In response to the proven toxic potential of these phytometabolites, regulatory authorities responsible for overseeing the quality and safety of herbal medicines have instituted concentration limits. These limits serve as protective measures to mitigate potential risks associated with the presence of these toxic compounds.[5]

4. Acute/Sub-Acute/Chronic Toxicity Evaluation

The preclinical assessment of toxicity in herbal medicines employs a combination of in vitro and in vivo models. Animal models are commonly utilized to assess both acute and chronic toxicity, as illustrated in the figure. Guidelines for evaluating the toxicity of chemical compounds have been developed by the Organization for Economic Cooperation and Development (OECD).[5]

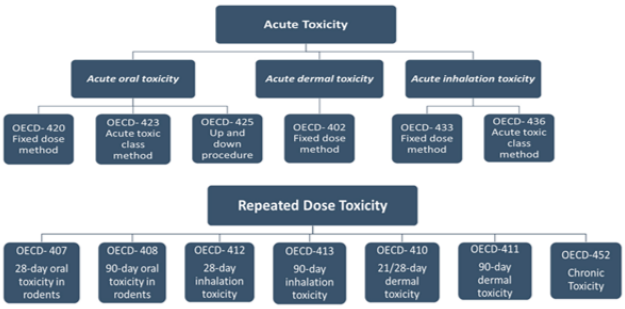

Figure 1: OECD guidelines for toxicology studies.

5. Legal and Regulatory Framework for Herbal Drugs

The legal and regulatory framework for herbal drugs varies across countries and regions. In many places, including the United States, Europe, and various Asian countries, there are specific regulations and guidelines in place to oversee the production, marketing, and use of herbal drugs.

In the United States, for example, the Food and Drug Administration (FDA) regulates herbal products as dietary supplements. These products are subject to certain regulations, including good manufacturing practices (GMP) to ensure quality and safety. The Dietary Supplement Health and Education Act (DSHEA) of 1994 provides the legal framework for the regulation of dietary supplements, including herbal products.

In Europe, herbal medicinal products are regulated under the European Medicines Agency (EMA). The Committee on Herbal Medicinal Products (HMPC) assesses the safety and efficacy of herbal medicines, and products are granted a Traditional Herbal Registration (THR) or a marketing authorization based on scientific evidence.

In India, the regulatory authority for herbal drugs is the Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy). The Drugs and Cosmetics Act, of 1940, and the Drugs and Cosmetics Rules, of 1945, outline the regulatory requirements for the manufacturing and sale of herbal medicines.

6. Strategies for Minimizing Herbal Drug Toxicity

Strategies for Minimizing Herbal Drug Toxicity	Description
Standardization of Herbal Products	Implement standardized manufacturing processes to ensure consistent quality and concentration of active ingredients in herbal products
Quality Assurance Through Good Manufacturing Practices (GMP)	Adhere to GMP to maintain high standards in the production, packaging, and labelling of herbal drugs, reducing the risk of contamination
Regulatory Oversight and Compliance	Establish and enforce regulatory frameworks for herbal drugs, ensuring compliance with safety and quality standards
Research and Documentation of Toxicity Profiles	Conduct thorough research on the toxicity profiles of herbal drugs and document potential adverse effects to provide evidence-based information
Education and Awareness	Educate healthcare professionals, herbalists, and consumers about the potential risks associated with herbal drugs, emphasizing responsible use.
Monitoring and Reporting of Adverse Events	Establish systems for monitoring and reporting adverse events related to herbal drug use, facilitating early detection of potential toxicity.

7. Conclusion

In conclusion, the intricate composition of herbal formulations, coupled with the inherent variability in bioactive compounds, underscores the importance of systematic toxicological profiling. Rigorous evaluation, by OECD guidelines, becomes imperative to ensure the safety and efficacy of herbal medicines. The existing challenges of substandard quality and the potential presence of toxic constituents emphasize the critical role of standardization and regulatory frameworks. By implementing strategies such as standardization, quality assurance, and robust regulatory oversight, the potential risks associated with

herbal drug toxicity can be mitigated, fostering responsible use and safeguarding public health.

8. Source of Funding

None.

9. Conflict of Interest

None.

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