Ensuring Herbal Product Safety and Compliance for Biopharmaceutical Use

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Abstract

Safety and toxicological research are integral for integrating herbal items into biopharmaceutical applications. As herbal products gain prominence in pharmaceutical development, rigorous safety evaluations ensure compliance with legal standards. These studies aim to ascertain safety profiles, assess potential negative impacts and toxin levels, minimizing risks associated with herbal product usage. Prioritizing toxicity studies enhances compliance and overall product quality, guiding informed decision-making and fostering a risk-conscious approach to innovation. Given the complexity of herbal compositions, thorough safety assessments are crucial. Safety evaluations are particularly significant considering the diverse applications of herbal products in biopharmaceuticals, ranging from innovative medicine discovery to traditional therapies. In summary, research on the safety and toxicology of herbal products is paramount for shaping the future of biopharmaceutical applications, facilitating their responsible and effective utilization in medicine.

Significance | Comprehensive safety and toxicological research on herbal products might ensure regulatory compliance, promote pharmaceutical innovation, and safeguard public health

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Editor Muhammad Asif, And accepted by the Editorial Board Apr 25, 2023 (received for review Feb 25, 2023)

Keywords: Herbal products, Safety studies, Toxicology, Regulatory standards, Biopharmaceutical applications

Introduction

For millennia, the utilization of herbs and herbal medications has played a crucial role in managing health and illness across various cultures. Evidence of herbal therapy's efficacy can be traced back to ancient civilizations such as the Greeks, Indians, Mesopotamians, and Chinese (Biggs et al., 1995). In Africa, traditional medicine, transmitted orally and through native customs, has long been integrated into holistic healthcare systems (Romero-Daza, 2002). The global demand for herbal medicines has surged in recent years, with projections estimating a population surpassing 7.5 billion within the next decade to fifteen years. Particularly in the southern hemisphere, where approximately 80% of the population relies on traditional medical systems centered around herbal remedies, this growth is anticipated to be most pronounced (Ifeoma & Oluwakanyinsola, 2013). The historical use of plants as medicinal agents dates back to the earliest stages of human civilization, and contemporary efforts continue to enhance their therapeutic potential (Mosihuzzaman, 2012). Currently, there are over 200,000 recognized natural compounds derived from plants, with ongoing discoveries of additional products sourced from both higher plants and microbes (Kinghorn, 2011).

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Please cite this article:
Md Shamsuddin Sultan Khan, Mohamed Khadeer Ahamed Basheer et al. (2023). Ensuring Herbal Product Safety and Compliance for Biopharmaceutical Use, Australian Herbal Insight, 6(1), 1-10, 21073

Through continued research and exploration, the vast reservoir of botanical resources holds promise for the development of novel therapeutics and the refinement of traditional herbal remedies to address modern healthcare needs.

Certain plant-based medications, such as cardiac glycosides, boast millennia of historical use and remain irreplaceable in traditional medicine. Consequently, ongoing research into medicinal plants and their bioactive compounds remains imperative (Ifeoma & Oluwakanyinsola, 2013). This necessity is underscored by the recent surge in demand for herbal medicine within the market (Ifeoma & Oluwakanyinsola, 2013).

Herbs continue to serve as invaluable reservoirs for the discovery of bioactive compounds, which not only contribute to the development of new pharmaceuticals but also offer treatments for a wide array of human and animal ailments (Harvey, 2008). Scientific exploration of ethnomedicinal herbs used traditionally for wound healing, pain relief, and fever reduction has led to the identification of various chemical constituents. These discoveries have paved the way for the development of novel drugs targeting conditions such as cancer, hypertension, diabetes, and infectious diseases (Harvey, 2008).

Galen, a renowned Greek pharmacist and physician, is credited with providing the earliest documented account of plant toxicity. His pioneering work highlighted the dual nature of herbs, showcasing their potential therapeutic benefits alongside the presence of hazardous compounds (Cheng & Zhen, 2004). This historical insight underscores the importance of comprehensive safety evaluations in modern herbal medicine research, ensuring the development of safe and efficacious therapies.

Nutraceuticals, comprising nearly 1500 herbal products sold solely in the US in 2003, remain exempt from stringent preclinical efficacy and toxicity assessments by the US Food and Drug Administration (FDA) (Bent & Ko, 2004). This exemption has raised concerns regarding the potential adverse effects of these products, prompting efforts to standardize toxicity testing methods for herbal medicines globally.

Toxicological characterization of herbal medicines now relies on standardized assays tailored to assess cellular, organ, and systemic toxicity, encompassing tests for acute high-dose exposure effects and chronic low-dose toxicity (Bent & Ko, 2004). These methods aim to provide comprehensive insights into the safety profiles of herbal products.

Advancements in biotechnology have revolutionized toxicity testing techniques, particularly at the molecular and subcellular levels. Next-generation sequencing and computer-based modeling and simulation tools have emerged as invaluable resources for predicting the toxicity of novel drug candidates and herbal medicines, both individually and in combination with other substances (Bent & Ko, 2004). However, challenges persist in the comprehensive evaluation of herbal remedies, necessitating ongoing research and innovation in this dynamic field.

Toxicity of herbs

Herbal treatments are increasingly popular, yet concerns persist regarding their safety and efficacy. Stricter quality control measures are often lacking, with less than 10% of herbal products worldwide standardized to recognized active ingredients (Winsto et al., 2019). Consequently, the majority of these products lack comprehensive safety and efficacy data.

Unlike conventional medications, herbal remedies are not subjected to the same rigorous safety and efficacy standards in many countries, including the United States. This raises questions about their safety and suitability for use as medications.

To address these concerns, toxicity testing plays a crucial role in identifying potential dangers associated with herbal medicines and mitigating adverse effects. Many plants naturally produce harmful secondary metabolites as a defense mechanism against environmental stressors. These compounds, which include toxins, may not be distinguishable from therapeutically active ingredients in certain plant species relevant to toxicology and medicine, such as Digitalis purpurea, Hyoscyamus niger, Atropa belladonna, Physostigma venenosum, Podophyllum peltatum, and Solanum nigrum.

Plants, as stationary autotrophs, have evolved mechanisms to survive harsh conditions and coexist with harmful microbes and herbivores. Understanding the potential toxicity of herbal remedies is essential for ensuring their safe use in medical applications (Table 1).

Plants produce a diverse array of metabolites known as "phytoanticipins" or "general phytoprotectants," stored in specific cellular compartments and released in response to environmental stimuli such as viral infections, herbivore attacks, or nutrient deficiencies (Kennedy & Wightman, 2011). Many of these phytochemicals share structural similarities with human neurochemicals, including neurotransmitters, hormones, neuropeptides, and signaling molecules, which can either mimic or counteract their biological effects (Kawashima et al., 2007; Nässel & Winther, 2010).

Certain phytochemicals, such as alkaloids, terpenoids, flavonoids, and saponins, exert their effects by interacting with neurotransmitter systems. Alkaloids often act as feeding deterrents by modulating neurotransmitter activity, while lipid-soluble terpenes can inhibit mammalian cholinesterase and interact with the GABAergic system (Wink, 2003; Savelev et al., 2004; Rattan et al., 2010). Saponins, known for their strong surfactant properties, can disrupt the lipid-rich membranes of microbes and human erythrocytes, exhibiting potent antibacterial activity (Francis et al., 2002).

However, certain phytochemicals, like aristolochic acid found in Aristolochia species, pose significant health risks, including nephropathies and carcinogenesis (Stiborova et al., 2002). Additionally, contamination with hazardous minerals and heavy metals like mercury, arsenic, lead, and cadmium can further contribute to the toxicity of herbal products (Dwivedi & Dey, 2002). Consumption of herbal preparations contaminated with lead or mercury can lead to severe neurological impairments, while high arsenic levels in kelp seaweed have been associated with toxicosis (Amster et al., 2007).

Goals of toxicity testing of herbal drugs

Toxicological evaluations of herbal medicines aim to identify potential side effects and determine the exposure thresholds at which these effects become apparent (Gamaniel, 2000). Assessing the type and severity of adverse effects, along with the exposure level at which they occur, are critical considerations in evaluating the safety of herbal medicines. Toxicity testing plays a vital role in identifying potential hazards associated with herbal use, particularly among vulnerable populations.

Detecting poisonous plant extracts or their derived compounds in both the pre-clinical and clinical stages of drug development from botanical sources is a key objective of toxicity testing (Gamaniel, 2000). This proactive approach allows for the identification and elimination of toxicants early in the drug development process, providing an opportunity to explore safer alternatives. Potential modifications such as dosage adjustments, chemical alterations, or structural modifications can render certain substances more tolerable and safer for use.

By conducting comprehensive toxicity assessments, researchers and regulatory bodies can better understand the potential risks associated with herbal medicines and take appropriate measures to mitigate them. This systematic approach not only ensures the safety of herbal products but also facilitates the development of effective and reliable botanical-based medications for various health conditions.

Cell-based cytotoxicity tests

Cytotoxicity assays (CTAs) utilize cultured cells, whether normal or altered, to assess potential toxicity of substances (Brien et al., 2006). These tests typically involve exposing cultured cells to test compounds for a short duration to observe their effects on basic or specialized cell processes before conducting safety studies in whole organisms. CTAs provide insights into the genotoxic and carcinogenic properties of substances and extracts derived from herbs.

The toxicity of plant extracts can be determined by assessing their ability to inhibit cellular growth and viability (Brien et al., 2006). Evaluation parameters for cytotoxic effects include reduced cell proliferation, changes in intracellular differentiation, alterations in morphology, and measures of cell viability such as metabolic activity and membrane integrity.

When conducting CTAs, it is essential to consider factors that may influence test outcomes, including cell culture systems and experimental procedures. By rigorously controlling these variables, researchers can ensure the reliability and accuracy of cytotoxicity assay results.

Prior to conducting cytotoxicity assays (CTAs), it's crucial to consider the compatibility of certain cell types with the solvent used to prepare test solutions (Malinin, 1973). Dimethylsulfoxide (DMSO) is a commonly used solvent for producing non-polar plant extracts and chemicals, but it has been documented to exhibit cytotoxic effects at certain concentrations, with varying impacts on different cell types (Malinin, 1973). Therefore, it's necessary to determine the maximum allowable solvent concentration beforehand, especially during the validation phases of CTAs. Additionally, a control group using the carrier solvent alone should be included in CTAs to assess its potential influence on cell viability.

CTAs play a crucial role in medium- and high-throughput screening of various phytochemicals across a wide range of concentrations and contribute significantly to the implementation of the three R's: replacing animals in research, refining animal test models, and reducing the number of animals used (Ukelis, 2008). Therefore, it's important to select a diverse range of cell types for testing, including normal cells of primary origin (often from rodents) and permanent cell lines, provided they demonstrate high quality and reproducibility over time (Ukelis, 2008).

Robust models for predicting genotoxicity and carcinogenicity include cytotoxicity assays (CTAs) that utilize rodent cell lines, such as Syrian Hamster Embryo cells (SHE, pH 6.7 and pH 7) and the mouse fibroblast cell line BALB/c 3T3 (Ukelis, 2008). These assays provide valuable insights into the potential cytotoxic and genotoxic effects of herbal products, allowing for informed decision-making in drug development and safety assessment.

The predictiveness of these tests is demonstrated by the fact that altered cells cause tumorigenicity when injected into x-ray-irradiated mice (Ponti et al, 2009). Moreover, these assays have been shown to be credible in the evaluation of nanoparticles, indicating their versatility in testing various substances and formulations (Ponti et al, 2009). Despite some limitations, such as the lack of sufficient evidence in testing complex combinations like herbal items, these assays can still be useful in predicting their harmful effects as long as there is adequate contact with the cells (Breheny & Massey, 2005).

Examples of normal and transformed SHE cells demonstrate the effectiveness of these assays (Figure 1). Normal colonies of cells are organized in monolayers with no criss-crossing, whereas morphologically transformed colonies comprise stacked cells that are randomly oriented, three-dimensional, and criss-crossed

throughout (Breheny & Massey, 2005). Basophilic staining is usually darker in transformed colonies, providing a visual indicator of cellular alterations (Breheny & Massey, 2005).

Herbal toxicokinetics

Herbal toxicokinetics, predicting the toxicity of plants or purified xenobiotics derived from them, involves pharmacokinetic disposition, genetics, or possible herb-drug interactions (Maurer, 2008). Assays utilizing human liver microsomal Cytochrome P450 (CYP) isoforms are commonly used in initial testing to detect compounds inducing toxicological modifications at any level of cellular organization (Maurer, 2008). Cytochrome P450 modification is crucial as it influences drug biotransformation into active or inert forms. Herbs stimulating these enzymes can quickly inactivate drugs dependent on them, leading to rapid clearance from the body (Maurer, 2008). Conversely, herbs suppressing enzyme function can elevate medication levels by inhibiting metabolic clearance (Maurer, 2008).

Data suggest 40% of patients on conventional therapy and herbal medications experience potential negative drug-herb interactions (Bush et al., 2007). Herb interactions with medication metabolism may reduce efficacy or increase toxicity, posing clinical risks (Bush et al., 2007). Such interactions are concerning, given 73% of medications undergo hepatic metabolism via Cytochrome P450 (Wienkers & Heath, 2005). Isoforms CYP3A4, CYP2C9, CYP2C19, CYP1A2, and CYP2D6, with extensive substrate selectivity, are frequently implicated in oxidative drug responses and are highly susceptible to inhibition (Williams et al., 2004).

Plants like ginkgo (Ginkgo biloba), ginseng (Panax ginseng), kava (Piper methysticum), garlic (Allium sativum), and St. John's Wort (Hypericum perforatum) modulate Cytochrome P450, potentially interacting significantly with co-administered medications (Izzo & Ernst, 2009). These interactions underscore the importance of understanding herb-drug interplay in clinical practice.

In vitro metabolic data offers insight into the metabolic disposition of herbal products and their potential clinically relevant effects when enzymes are inhibited or induced (Guengerich et al., 1997). Early 1990s saw the development of methods aimed at extracting maximal information from a single experiment, including protein and metabolite profiling, DNA sequencing, and microarrays for gene expression analysis (Bugrim et al., 2004).

Simulation studies and computer-based models allow for further insights into the structure-activity relationship of pure chemicals or metabolites (Bugrim et al., 2004). Integrative systems biology approaches utilize databases of genes, metabolic pathways, regulatory networks, and protein interactions for drug screening (Bugrim et al., 2004). Despite their efficiency, employing multiple assays remains crucial for predicting the metabolic fate of test molecules in humans. However, no single method is sufficient for predicting toxicokinetics in silico.

Toxicogenomic screening tools

Herbal toxicogenomics combines toxicology with various omics tools to assess potential toxic effects at multiple levels, from sub-molecular to organ levels (Youns et al., 2010). It aims to identify molecular biomarkers indicating toxicity and elucidate underlying molecular mechanisms.

DNA microarrays offer detailed insights into mechanisms by which chemical toxicants induce toxicity and predict physiological responses (Waring et al., 2002). However, data from herbal mixtures may not directly translate to existing chemical compound libraries.

Proteomics involves high-throughput screening for protein identification, offering valuable information closer to toxicology endpoints (Kennedy, 2002). It compares protein expression profiles of pure phytochemicals to existing xenobiotic databases.

Metabonomics investigates metabolic profiles and metabolite composition in response to chemical stressors (Beecher, 2002). It proves effective for in vitro metabolic profiling, animal toxicity testing, and human safety testing, aiding in the identification of safety biomarkers.

General tests

The Organization for Economic Co-operation and Development (OECD) has standardized criteria for conducting animal toxicity studies, aiming to harmonize test recommendations internationally (Alépée et al., 2014). Prior to studying the safety of herbs or their products in animals, several important considerations must be addressed:

Preparation of Test Substance: Herbal products should be quantitatively standardized according to their intended human usage, delivered in various dosage forms such as pills, capsules, lotions, or ointments.

Animal Welfare Considerations: Guidelines for using clinical indicators as humane endpoints for experimental animals should be followed, ensuring that animals are treated ethically throughout the study (ASSAY et al., 2004).

Animal Selection: Animal toxicity testing involves various rodent and non-rodent species, with justification needed for the species or strain chosen. Animals must be housed in suitable environments and receive adequate care in accordance with established standards (IOLAR, 1986).

Regulatory Requirements: Animal experiments are subject to review, approval, and supervision by independent committees dedicated to animal ethics, ensuring compliance with animal care regulations.

Acute Systemic Toxicity Testing: This test assesses an organism's toxicological response to a single or brief exposure to a test chemical (OECD, 1994). It utilizes standardized techniques to determine the median lethal dose (LD50) of a substance, involving various routes of exposure such as oral gavage, inhalation, cutaneous contact, or

injection. Animals are monitored closely for toxic effects following administration, with additional care provided if delayed toxicities occur.

By addressing these considerations, researchers can conduct animal toxicity studies effectively and ethically to evaluate the safety of herbal products.

Chronic toxicity/carcinogenity

Similar to subchronic studies, chronic toxicity testing involves a larger number of animals to identify toxicity that may develop from exposure to a chemical for up to 24 months or a lifetime. Depending on the intended application in humans, the main routes for these tests are oral, cutaneous, or inhalation. Long-term investigations identify the mutagenic and carcinogenic properties of test compounds and the potential organs where these substances may accumulate. Endpoints studied in these tests include dose limits of toxicity (NOAEL - No Observed Adverse Effect Level), mortality, food consumption, water intake, hematology and clinical biochemistry measurements, organ gross necropsy, and histopathology. Additional details on research design and implementation can be found in the OECD's draft guidance document on the planning and conduct of long-term toxicity and carcinogenicity studies (Ifeoma & Oluwakanyinsola, 2013).

These tests are tailored to reveal specific toxicities such as reproductive toxicity, developmental toxicity, eye and skin irritancy (Draize test), neurotoxicity, and genotoxicity.

Ocular/Skin Irritancy Test: Developed in the mid-20th century by US Food and Drug scientist John Draize, this test involves the topical application of the test material to the skin or cornea of rabbits. Unlike permanent damage (such as rust), irritability can be reversed. However, due to its subjective grading system and perceived cruelty to rabbits, this test has lost favor and shows high interlaboratory variability (Balls et al., 1995). A more recent short-term exposure test using Statens Seruminstitut Rabbit Cornea (SIRC) cells may serve as a viable alternative to the traditional rabbit eye irritancy test (Takahashi et al., 2008).

Neurotoxicity: Some phytomedicines can cause convulsions and other neurological symptoms after acute systemic exposure. Subacute, subchronic, and chronic toxicity testing can reveal more severe conditions such as encephalopathy, psychosis, and cerebrovascular accidents. Notably, herbal remedies may exhibit heightened neurotoxicity if they contain high concentrations of metals (Ifeoma & Oluwakanyinsola, 2013). Efficient methods for removing heavy metal contamination from herbal extracts include chelation with dithizone and microbial biosorptive removal using granulated Cladosporium cladosporioides (Pethkar et al., 2001).

Genotoxicity: Genotoxicity, which is often the hardest toxicity to identify, involves mutations or changes in the structure and/or segregation of genetic material that are chemically induced. The European Medicines Agency has drafted guidance on assessing the genotoxicity of herbal remedies (Bunel et al., 2014). The first step typically involves the Ames test with S. Typhimurium. However, some potent genotoxins, such as vincristine (from Catharanthus roseus) and taxol (from Taxus brevifolia), may not be accurately detected at this stage. Furthermore, products high in flavonoids, like quercetin, may produce false positive results. More conclusive tests, such as the mouse lymphoma assay (MLA) and the mouse micronucleus test, are also employed (Bunel et al., 2014).

Reproductive/Developmental Toxicity Studies: These studies originated from the discovery that millions of children born to mothers who took thalidomide for morning sickness suffered severe birth abnormalities (Botting et al., 2002). It was later hypothesized that thalidomide reduces the transcription effectiveness of genes involved in angiogenesis in the fetus's developing limb bud, leading to limb truncation (Stephens et al., 2000). To determine the effects of a herb on reproductive function and/or developing offspring, a large number of animals are used. These animals are dosed repeatedly with increasing doses of the herbal test substance before mating, during gestation, and after delivery up to the lifetime of the offspring. Toxicity endpoints include birth abnormalities, early delivery, and spontaneous abortion.

Clinical testing: Clinical/safety trials

Studying a herbal product in pre-clinical settings can lead to additional research with human subjects once adequate basic data has been gathered. These kinds of research are termed clinical trials (CTs), and they are conducted in four phases: I through IV (Wang, 2005).

Phase I: These are specially prepared CTs in which a minimal number of human volunteers willingly agree to participate to evaluate the effect of using the herbal product on important physiological indices. The safety and maximum acceptable doses of the investigational chemical are typically determined during this initial round of testing in healthy individuals. However, this step may not be necessary for some herbs with a long history of use (Wang, 2005).

Phase II: Also known as feasibility studies, these involve a small number of participants to assess clinical efficacy. Doses that have been found to be reasonably safe are used in this trial, and participants are monitored for the occurrence of side effects (Wang, 2005).

Phase III: This phase involves a larger number of participants across multiple centers and is designed as a double-blind, randomized, controlled trial. This study serves to validate the herbal product's clinical efficacy, often by contrasting it with a conventional intervention (Wang, 2005).

Phase IV/Post-marketing Surveillance: This phase involves keeping an eye out for uncommon side events that might have gone

unreported in Phases I through III but could manifest themselves after the product is released onto the market (WHO, 2002).

The World Health Organization has published guidelines regarding the clinical trial of herbal products (Wang, 2005). Several important considerations must be made to justify these trials:

Chemistry-Manufacturing-Control: Unlike conventional medications, herbal remedies are often polyherbal or monoherbal with a wide range of chemical constituents. Standardization methods must be employed to ensure that the product is representative of the final product, recognizing that the compounds in the product may act synergistically and that isolating an active component is not always necessary. If the active principle is known, it can act as the product's marker. If unknown, a sufficient quantity of a chemical marker or the full product's chemical fingerprint may be used within certain bounds. The herbal medicine preparation for clinical trial delivery must follow WHO requirements for good manufacturing practices (WHO, 2007). Additionally, information about the herbal product and substance is crucial. This includes details on the plant's origin, processing, shelf life, and storage conditions, as well as the product's ingredients, dosage form, analytical parameters for chemical markers or active compounds, storage conditions during the trial's duration, and specifications that will be evaluated before the release of clinical trial material.

Non-Clinical Considerations: These considerations provide a supportive background for a clinical investigation. Generally, this includes information on pharmacokinetics, toxicity, and efficacy that has been proven or acquired from reliable literature sources, such as pharmacopeias and journal articles. Whenever possible, a thorough analysis of previous studies on the same or a related herb should be conducted to identify any gaps that can be addressed in the planned experiment.

Clinical Considerations: Ethical norms and quality requirements must be adhered to during the trial. Human subjects recruited within the inclusion parameters—based on gender, weight, age, and health status—are monitored for adverse effects associated with escalating dosages of the test substance in a phase 1 safety study. Table 2 provides an overview of the fundamental safety parameters that are monitored. The product itself is typically the conventional intervention. To reduce bias, the study may be double-blinded, randomized, blinded, or placebo-controlled.

Ethics Considerations: Before any experiments can be conducted, all clinical trial (CT) protocols must be approved by the regional ethics board. Fundamental ethical principles and good clinical practice guidelines must be followed in any research involving human subjects, including clinical trials (Sadoh, 2006). Informed consent must be obtained from all participants or from the guardians of minors participating in the study. Every participant must be fully informed about any concerns they may have regarding the herbal trial product, particularly with respect to any rarely recognized interactions or known adverse effects. To minimize risks to participants, skilled ethical investigators, particularly medical professionals who can quickly recognize and manage adverse events, must be engaged as CT investigators.

Challenges and Future Recommendations:

Conducting thorough safety and toxicological investigations on herbal medicines for biopharmaceutical applications presents complex challenges (Smith et al., 2020). The complex composition of herbal products and variations in plant constituents necessitate the development of standardized guidelines for study design and interpretation (Jones & Brown, 2019). Future recommendations should integrate advanced analytical techniques such as genomics and metabolomics to provide a comprehensive understanding of potential dangers (Chen et al., 2021).

Recent studies suggest that harmonizing modern scientific methodologies with traditional knowledge is crucial for a thorough safety assessment (Lee & Wang, 2022). Long-term safety evaluations are particularly essential for chronic illnesses where prolonged use of herbal products is typical (Miller et al., 2018). Cooperation between regulatory agencies and researchers is vital to ensure that study procedures align with evolving standards (FDA, 2021). Encouraging transparency and data sharing across the scientific community accelerates research and fosters collective knowledge (EMA, 2022).

Education programs for researchers, healthcare professionals, and consumers enhance understanding and promote appropriate use of herbal products (WHO, 2019). Conducting risk-benefit analyses helps balance therapeutic advantages and potential hazards (EMA, 2020). Traditional safety investigations are supplemented by in silico methods for early risk identification (Chen & Wang, 2017). The implementation of ongoing monitoring systems allows for timely adjustments to new scientific discoveries and legal obligations (ICH, 2023).

These recommendations, based on extensive research and official regulations, aim to address the complex issues surrounding the safety of herbal products in biopharmaceutical applications and provide a robust foundation for their ethical incorporation into medical practice (Figure 2).

Conclusion:

In summary, the following schematic represents the procedures involved in the toxicological assessment of complex herbal extracts/mixtures and chemically defined isolated components. Notably, while compound databases are available for data comparison, only chemically defined phytocompounds are currently viable candidates for Quantitative Structure-Activity Relationship (QSAR) investigations and high-throughput toxicogenomic experiments.

Table 1. Potential toxic effects associated with some common herbal medicines marketed for different indications

Common name	**Plant source/parts used**	**Intended indications**	**Potential toxicity**
Ginseng	Panax ginseng roots	Relieves stress, promotes mental and physical activity	Central nervous system stimulation, hypertension, skin eruptions
St. John's wort	Hypericum perforatum aerial parts	Antidepressant, mood stabilizer	Highly potent cytochrome P450 enzyme inducer which affects drug metabolism. Also causes hepatotoxicity and nephrotoxicity in pregnancy and lactation
Kava kava	Piper methysticum roots	Sedative, anxiolytic	Hepatotoxic, cytochrome P450 enzyme inhibitor
Ginkgo	Ginkgo biloba leaves	Impotence, vertigo, circulatory disorders, improves mental alertness	Gastric irritability, spontaeneous bleeding
Danshen	Salvia miltiorrhiza exterior taproot	Angina pectoris, antihyperlipidemic, ischemic stroke	Bleeding, anticoagulant effects
Hawthorn	Crataegus oxycantha Flowers, roots, berries	Mild to moderate congestive heart failure	Cardiac arrythmias, lowered blood pressure
Comfrey	Symphytum officinale leaves	Anti inflammatory, antidiarrhoel and treatment of thrombophlebitis	Carcinogenic, nephrotoxic, hepatotoxic
Licorice	Glycyrrhiza glabra roots	Antiulcer, anti inflammatory, antihypertensive	Hypotension, seizures
Chaparral, creosote bush	Larrea tridentata leaves and twigs	Blood thinner, weight loss, antioxidant, anticancer, anti arthritis	Symptoms resembling digitalis toxicity
Mistletoe	Phoradendron spp., Viscum album leaves and young twigs	Digestive aid, heart tonic, sedative	Arsenic poisoning, Hyperthyroidism
Squill	Urginea maritima bulbs	Anti-arthritic, bronchial expectorant	Cardiotoxicity, thyrotoxicosis, seizures
Kelp (seaweed)	Liminaria digitata	Metabolic tonic, thyroid tonic, anti inflammatory	Skeletal and cardiac muscle degeneration, hepatotoxicity, neurotoxicity
Ma-huang	Ephedra	Promotes weight loss, mental and physical alertness	Cytogenetic toxicity

Table 2. Basic physiological parameters monitored in phase 1 clinical trial

Organ/system **Neurological:**	**Safety parameter** **lack of neurologic symptoms**
Musculoskeletal	Lack of arthritis or myalgias, normal values of CPK
Skin	Clinical evidence of lack of allergic reactions
Gastrointestinal:	Clinical evidence of tolerability
Liver	normal values of SGOT or SGPT, alkaline phosphatase, total bilirubin,
Kidney	Normal values of BUN or creatinine
Endocrine system and metabolism:	normal values of albumin or total protein, uric acid, glucose, cholesterol, amylase or lipase, sodium/potassium, calcium
Cardiovascular:	Normal EKG and blood pressure
Haematopoietic:	Normal values of complete blood count
Additionally:	More intensive investigation of any organ system likely to be affected by the product

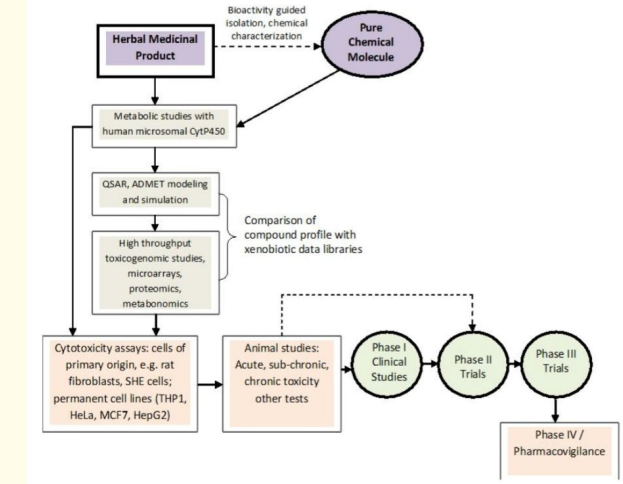

Figure 2. Schematic processes involved in evaluating and establishing the toxicity of medicinal herbs. The broken arrow indicates that for some herbal medicines, phase 1 clinical trials may not always be necessary.

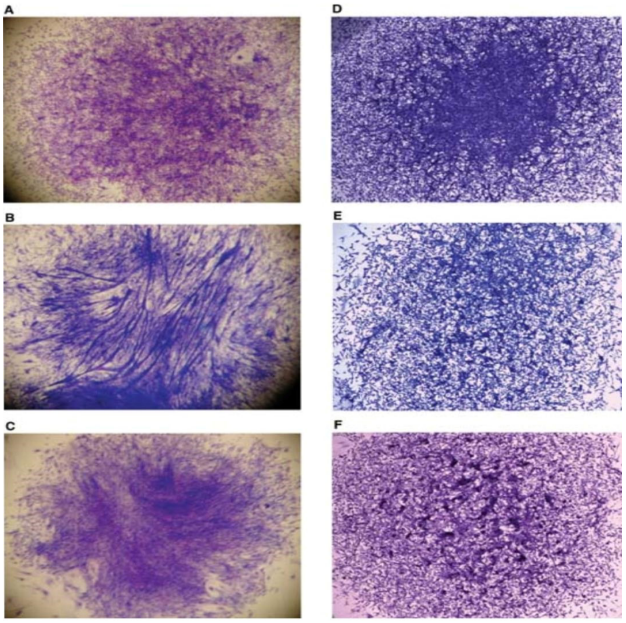

Figure 1. Sample

Author contributions

M.S.S.K., M.K.A.B., A.M.S.A.M., and F.S.R.A. contributed equally to this work. M.S.S.K. conceived the study and designed the experiment. M.K.A.B. conducted the data analysis and interpretation. A.M.S.A.M. wrote the initial draft of the manuscript and provided critical revisions. F.S.R.A. assisted with data collection and contributed to the literature review. All authors reviewed and approved the final version of the manuscript.

Acknowledgment

Author was grateful to their department.

Competing financial interests

The authors have no conflict of interest.

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