World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2024
Volume: 3; Issue: 6
Page: 19-40

ROLE OF PHARMACOVIGILANCE OF HERBAL AND TRADITIONAL HERBAL MEDICINES

Elena Mladenovska[1], Ivana Cvetkovikj Karanfilova[2], Gjoshe Stefkov[2], Zoran Sterjev[3] and Zorica Naumovska[3*]

[1]Euro-farm Skopje, Ss. Cyril & Methodius University in Skopje, Faculty of Pharmacy North Macedonia.
[2]Ss. Cyril & Methodius University in Skopje, Faculty of Pharmacy, Institute of Pharmacognosy, Majka Tereza 47, 1000 Skopje, North Macedonia.
[3]Ss. Cyril & Methodius University in Skopje, Faculty of Pharmacy, Institute of pharmaceutical chemistry, Majka Tereza 47, 1000 Skopje, North Macedonia.

Article Received: 01 October 2024 || ***Article Revised: 23 October 2024*** || ***Article Accepted: 14 November 2024***

***Corresponding Author: Zorica Naumovska**
Ss. Cyril & Methodius University in Skopje, Faculty of Pharmacy, Institute of pharmaceutical chemistry, Majka Tereza 47, 1000 Skopje, North Macedonia. **DOI:** https://doi.org/10.5281/zenodo.14252406

How to cite this Article: Elena Mladenovska, Ivana Cvetkovikj Karanfilova, Gjoshe Stefkov, Zoran Sterjev and Zorica Naumovska (2024). ROLE OF PHARMACOVIGILANCE OF HERBAL AND TRADITIONAL HERBAL MEDICINES. World Journal of Pharmaceutical Science and Research, 3(6), 19-40. https://doi.org/10.5281/zenodo.14252406

ABSTRACT

Herbal and traditional medicines are gaining global popularity as consumers seek natural health solutions. While widely accessible and culturally significant, these products often lack standardized safety assessments. Unlike conventional medicines, herbal remedies are complex mixtures with uncertain chemical composition, making it challenging to identify specific substances responsible for adverse effects. This complexity underscores the urgent need for rigorous safety monitoring and appropriate regulatory frameworks to ensure the safety and efficacy of herbal and traditional medicines.

KEYWORDS: Natural products and preparations, Adverse event, Herbal drug interactions, Safety monitoring, Pharmacovigilance, Regulatory oversight.

CHARACTERISTICS OF HERBAL AND TRADITIONAL MEDICINES

An herbal medicine is a medical product that contains natural compounds from cut, ground or powdered plants, or parts of plants (seeds, berries, roots, leaves, bark, or flowers), as well as plants extracts. Each powdered plant raw material or extract contains compounds that are responsible for the biological-pharmacological activity that are known as active principles.[1] The term "herbal medicine" is also used to generally describe relatively crude preparations or finished

herbal products, in various forms; tinctures, tablets, capsules, topical ointments that are available for purchase without a prescription. Unlike conventional drugs, herbal drugs represent a chemically rich complex that can contain several hundred substances. For many herbal medicines, the chemical substances are unknown, and even for those with well-documented phytochemistry, the constituents responsible for pharmacological activity may not be precisely defined. The constituent profile is not uniform throughout the plant, so for many plants only a certain part of the plant, such as the root or leaves, is (or should be) used in medical purposes. In addition, the precise profile of substances may vary qualitatively and quantitatively between different batches of herbal material due to any of the following factors: 1. Variation of components within one or between different species; 2. environmental factors, such as climate or growing conditions; 3. time of harvest (harvest maturity) – the profile of constituents can vary even within a day; 4. post-harvest factors, such as drying and storage conditions. The method of processing or preparation of the raw plant material, such as the type of extraction, can also affect the precise chemical composition of the herbal preparation or product and can influence their effectiveness. Many herbal medicines contain several herbal ingredients and combinations of herbal tinctures are often prescribed, which further adds to the chemical complexity of the herbal medicine. The chemical complexity of herbal medicines creates difficulties in determining their clinical pharmacokinetics, pharmacodynamics and toxicology, so in cases where safety concerns have been identified when taking an herbal medicine, there are difficulties in determining which substance or even which herbal ingredient or a combination of them caused the problem.[2] Common definitions used in connection with herbal medicines are given in Table 1.[1]

Table 1: Definitions related to herbal medicines.

Term	Definition
Herbal medicine	Any medical product that as active components contains one or more herbal substances or one or more herbal preparations or combinations thereof; may contain added minerals and vitamins.
Herbal substances	Whole or fragmented plants, plant parts, algae, fungi and lichens in an unprocessed or dried state, rarely fresh. Certain exudates that have not undergone specific treatments are also considered herbal substances. Herbal substances are precisely defined in terms of the plant part used and the botanical name according to the binomial nomenclature (genus, species, variety, author).
Herbal preparations	Processing obtained by subjecting herbal substances to treatments such as: extraction, distillation, expression, fractionation, purification, concentration or fermentation. Herbal preparations are chopped or pulverized herbal substances, tinctures, extracts, essential oils and fatty oils, extracted juices and processed exudates.

The legislation defines another special category of "traditional herbal medicines". Traditional herbal medicines are medicines that fully meet all the listed criteria, namely:

- Have indications exclusively suitable for traditional herbal medicines and are manufactured and intended for use without the supervision of a doctor;
- Are used exclusively based on the specified strength and method of use,
- Are intended for oral use, external use and/or inhalation;
- The duration of traditional use, which can be confirmed by literary or expert evidence, is at least 30 years, including the last 15 years in the countries of the European Union;
- There are sufficient data on the traditional use of the drug, especially that it has been proven that the drug is not harmful in the prescribed way of use and that the pharmacological effects or efficacy of the drug have been proven based on long-term use and experience.[3]

Traditional herbal medicines can be used in the form of teas, infusions, decoctions or tinctures. These are traditional forms of use that are prepared as aqueous, alcoholic or aqueous-alcoholic extractive preparations. Various substances can be added to the extract in order to improve the product (preparation). These include agglutination agents, absorbents, lubricants, diluents, etc. Aromatic agents and sweeteners are added to improve the taste, antimicrobial and antioxidant agents etc. are added to improve the stability and for protection. More recently, traditional herbal medicines may be formulated as solid dosage forms, mainly using dry extracts obtained from the plant material. The most common form is capsules. In dry extracts that are intended for formulation in solid dosage forms capsules, lactose is usually added as a diluent. Lactose improves the bioavailability of plant active principles. The term phytotherapy was first established by the French doctor Henri Leclerc (Henri Leclerc, 1870-1955), who presented his entire work experience and knowledge in the work "Precis de Phytotherapie" (1927). Phytotherapy deals with the effectiveness and limitations of herbal medicines in the treatment of human diseases and covers everything used for such purposes, from herbal medicines with strong effects (digitalis, wormwood) to those with very mild effects (chamomile, peppermint). Between these two groups are the largest number of medicinal plants, such as sweet root, echinacea, St. John's wort, ginkgo and others, which are designated as medicinal plants with a medium pronounced effect.[1,4]

HERBAL AND TRADITIONAL MEDICINES: A CHALLENGE OF PHARMACOVIGILANCE

Traditional medicine has always maintained its popularity and has a long history. The use of herbal medicines, traditional remedies, and phytonutrients continues to spread rapidly across the globe, with many people turning to these products to treat various health conditions. In recent decades, there has been a significant surge in acceptance and public interest in natural therapies in both developing and developed countries. This trend has been supported by the widespread availability of herbal and traditional medicines, not only in pharmacies but also in health food stores and supermarkets. It is estimated that up to four billion people, representing 80% of the world's population, in developing countries rely on herbal medicines as their primary source of healthcare. In these communities, the use of herbs in traditional medical practices is deeply embedded in the culture.[5] One of the reasons for the growing use of herbal medicines for self-medication is the strong belief held by consumers (often motivated by the media) that these products are "natural" which is often equated with "safe". This belief is misguided, as the use of natural, herbal medicines is often associated with unwanted and potentially toxic effects. Despite this, their presence in the global market has steadily increased in recent years, largely due to the successful and highly effective marketing strategies employed by herbal medicine manufacturers. As the ubiquity and demand for traditional medicine grows rapidly, so do concerns about the quality and safety of herbal medicines. A common concept related to the safety profile of herbs is that these products should be considered safe because they have had a long history of traditional use, without significant experience and knowledge of their toxic effects. Their use is not closely monitored, making knowledge of their potential adverse effects very limited. It is also common knowledge that the safety of most herbal products is further compromised by the lack of adequate quality control, inadequate labeling and the absence of adequate patient information. It is therefore essential to provide the general public, including healthcare professionals, with adequate information to better understand the risks associated with the use of these products, but also to ensure that all medicines are safe and of adequate quality. Plants contain pharmacologically active compounds, but they can also contain toxic substances, can be contaminated with other drugs, hormones or heavy metals.[5,6] Herbal medicines that are not properly controlled can cause serious health problems and even poisoning due to the presence of many toxic substances, such as: some alkaloids (pyrrolizidine, piperidine, indolizine), glycosylates, lectins, saponins, diterpenes, cyanogenic glycosides, phytoestrogens, furanocoumarins, etc. Knowledge about the occurrence of unwanted or toxic effects of

herbal medicines and substances in the body is well known in medicine, and their characteristic actions are usually associated with: direct toxic effect (many herbal substances have a strong physiological, chemical and/or toxic effect); indirect toxic effect (expressed due to interactions with other herbal substances and drugs, delay of the therapeutic effect, incompatibility, etc.); side effects due to the presence of toxic substances (such as contaminants), substitution or intentional falsification of products (due to lack of quality control); side effects on certain organs (liver, heart and kidneys) and systems (cardiovascular, reproductive and nervous system); carcinogenicity, mutagenicity and teratogenicity; the safety of herbal medicines on certain population groups, such as children and adolescents, elderly patients, women during pregnancy and lactation, cancer patients, surgical patients, etc. Most of the available information on the side effects and toxic effects of herbal medicines is closely related to the use of traditional Chinese, Indian and other non-European herbal medicines, mostly as a result of the complete absence of expert control or due to the absence of systemic studies regarding the potential dangers from herbal medicines. There is also clear evidence (e.g. advertisements from internet sites and brochures from "specialized" clinics) that patients with serious health problems, such as heart disease, cancer, diabetes, asthma, etc. are misled by the wrong information about the scientifically unproven and dubious effects of some herbal medicines.[7] Different traditional medical practices have been developed in different cultures in different regions, but without the parallel development of international standards and appropriate safety assessment methods. Countries face major challenges in developing and implementing regulation of traditional, complementary/alternative and herbal medicines. These challenges are related to regulatory status, safety and efficacy assessment, quality control, safety monitoring and lack of scientific knowledge of traditional, complementary/alternative and herbal medicines within national drug regulatory bodies.

CHALLENGES RELATED TO THE REGULATORY STATUS OF HERBAL MEDICINES

The definition and categorization of herbal medicines varies from one country to another. Depending on the regulations that apply to food and drugs, a medicinal plant may be categorized as a food, functional food, dietary supplement or herbal medicine in different countries. This introduces serious difficulties in defining the concept of herbal medicines for the purposes of national drug regulation, and at the same time confuses patients and consumers.[5] Due to the gap between the increased use of these products and the lack of knowledge about their risks and benefits, communication among global regulatory agencies about their respective regulatory principles is important in order to have an improved and harmonized regulatory framework to guide their safe application. A primary challenge to starting any conversation related to regulation in this area is the lack of global consensus on product definition and categorization. The problems that regulatory agencies face is that many of the herbal medicines and dietary supplements are mixtures of the same product produced in different locations, and very little is known about the supply chain. To better address quality issues, pharmacopoeias around the world, such as the United States Pharmacopoeia, the European Pharmacopoeia, and the Pharmacopoeia of the People's Republic of China, are setting quality standards for an increasing number of herbal medicinal ingredients and dietary supplements.

In 2013, the Global Coalition for Regulatory Science Research (GCRSR) was founded under the leadership of the US Food and Drug Administration (FDA). This coalition is made up of regulatory bodies from ten countries, including the European Union (EU), and aims to improve regulatory scientific research on the safety and efficacy of food and medicines.[8] To achieve these goals, annual GCRSR conferences have been established to provide a venue where regulators and researchers can meet and develop collaborations to address challenges and needs in the interest of advancing regulatory science. So far, ten conferences have been held in different countries, and GSRS20 and GSRS21

were held virtually due to the COVID-19 pandemic. The theme of the last GSRS21 conference was “Food/Drug Safety Regulatory Sciences with Real World Data and Artificial Intelligence.[9] It this review, we are summarizing and evaluating the regulatory framework and practices for monitoring the safety of herbal preparations through the pharmacovigilance system in the United States, Australia, New Zealand, Canada, China, the EU and the Republic of North Macedonia.

USA - The Food and Drug Administration (FDA) regulates products sold as dietary supplements under the Federal Food, Drug and Cosmetic Act, as amended by the Dietary Supplement Health and Education Act of 1994. Dietary supplements (except tobacco) are defined as products that are intended to supplement nutrition and contain one or more of the following dietary ingredients: vitamins; minerals; plants or their parts; amino acids; or a concentrate, metabolite, ingredient, extract or combination of any of the ingredients described above. Dietary supplements must be intended for oral use and must not be indicated for any other use (sublingual, inhalation, injection, etc.). They also must not contain ingredients that have previously been approved as drugs (unless they were marketed as dietary supplements before they were approved as drugs). Unlike FDA drug regulation, where a drug's safety and efficacy must be proven before its approval, dietary supplements are primarily regulated through post-marketing surveillance and are not submitted for approval at all. Not surprisingly, this regulatory structure has led to problems with the consistency and safety of herbal medicines. Several recent studies have documented dramatically different levels of suspected active ingredients in herbal medicines. For example, a recent analysis of 25 available ginseng products found a 15- to 200-fold variation in the concentration of 2 constituents believed to have biological activity: ginsenosides. New dietary ingredients introduced after 1994 must be submitted for safety evaluation through the New Dietary Ingredient Notification process, however there are exceptions to that requirement. Although prior approval is not required in the US to place a dietary supplement on the market, it is still the manufacturer's responsibility to ensure the safety of their product and that all necessary information (indications, side effects, warnings, etc.) is listed on the label. Dietary supplements have not approved indications: rather their use is supported particular statement such they can cure, alleviate, treat or prevent disease. For example, an echinacea product (often used to treat or prevent colds) may state that it "supports the body's natural defenses". Herbal medicines with indications: cure, relieve, treat or prevent a disease must go through the appropriate approval process before being put on the market. Currently, there are only two FDA-approved herbal medications, Veregen® (sinecatechin ointment) indicated for topical treatment of external genital and perianal warts and Mytesi® (crofelemer) used for symptomatic relief of infectious diarrhea in HIV patients / AIDS who are on antiretroviral therapy.[8,10]

In Australia, most natural products such as herbal medicines, vitamins, minerals and dietary supplements are treated as 'complementary medicines' and are referred to as 'therapeutic goods', regardless of whether they are 'Classified as supplements' or 'Classified as medicines'. These products are regulated by the Therapeutic Goods Act of 1989, which also regulates medicinal products. Some products may fall into both categories – both "Classified as Supplements" and "Classified as." medicines". The Australian Government provides a tool with guidance on how a product is characterized as a food or drug. The products are divided into two categories, "low-risk drugs" and "high-risk drugs", depending on the toxicity of the ingredients, the suggested dose, the suitability of the indications and claims for self-diagnosis and treatment, and the potential for adverse reactions, and these are listed in The Australian Register of Therapeutic Goods. Regulatory guidance is provided in the Australian Regulatory Guidance for Complementary Medicine, which describes in detail the requirements that both categories must meet. Low-risk medicines are only

"listed" in the Register of Therapeutic Products, while high-risk medicines must be marked as "registered" and must be evaluated for their quality, safety and efficacy. For comparison, complementary medicines that are only "listed" in the Register are > 11000, against ~ 40 of them that are "registered". Products "Classified as supplements" may make certain health claims, but they must contain a label stating that such claim has not been evaluated by the Therapeutic Goods Act. An important feature of risk management in Australia is that early market access for low-risk complementary medicines is supported by appropriate post-marketing regulatory activity.[8,11]

New Zealand has two product categories - dietary supplements and medicines. Dietary supplements are regulated by the Dietary Supplements Regulations 1985, which fall under the Food Act 2014. New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) is responsible for administering the Dietary Supplement Regulations, and the Ministry for Primary Industries for the Food Act. Dietary supplements are also subject to legislation established by the Biosecurity Act of 1993. This law was enacted to protect the environment, plants and animals in New Zealand from unwanted pests and diseases. Dietary supplements in New Zealand are not submitted for pre-market approval, but, as in Australia, they are products intended for oral use only, with dosages clearly stated on the label, and should not be intended for therapeutic purposes. Dietary supplements may contain ingredients of animal origin that comply with the Animal Product Act of 1999. New Zealand also has a Supplemented Food Standard that sets out the requirements for products that are defined as food, but have been modified in some way or have had substances added to them (certain vitamins, minerals, herbs and bioactive substances) so they have a certain physiological function. The Food Act 2014 allows the Food Additives Regulations to remain in force until 1 March 2026, when a new regulatory regime is planned to be in place. New Zealand's parliament is working on a law that would encourage the use of new tools and methodologies, such as an electronic database where manufacturers would be required to list their product and provide evidence in a report format that would have confirmed all of the listed health claims.[8,12]

In Canada, most natural products are classified as a subclass of drugs in the "Classified as drugs" category, and the rest are called natural health products and are regulated by Health Canada. Natural health products are regulated under the Natural Health Products Regulations, which were enacted in 2004. These regulations refer to requirements for the product and the manufacturer, such as production, import, distribution, good manufacturing practices, reporting of adverse reactions, clinical trials, as well as special rules for labeling, with particular reference to warnings, reporting of adverse reactions and procedures in case of product recall. They require evidence of the health claims made on the labels relating to the product, which would establish its safety and efficacy, and may be in the form of a clinical trial, or references from published scientific papers or pharmacopoeias. All natural health products must be licensed before they can be marketed in Canada. To obtain an approval, applicants must provide detailed product information to Health Canada, including: medicinal ingredients, source, dosage, potency, non-medicinal ingredients and recommended use(s). Once Health Canada has evaluated the product and decided it is safe, effective and of high quality, it issues a product license along with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), which must appear on the label. This number is proof that the product has been evaluated and approved by Health Canada. Health Canada has also published a set of monographs on natural health products, which an applicant can cite as a single source of evidence for the safety and efficacy of their product. Natural health products are submitted for approval before they are placed on the market, and their full documentation is evaluated by Health Canada, which ensures monitoring of the manufacturing process, as well as post-marketing follow-up. In Canada there is a huge overlap between herbal medicines and dietary supplements. Clearly delineating the regulatory classification of these products is

challenging because it is based on the product's intended use, public perception, and use history. Herbal medicines can be sold with preventive and therapeutic claims, except for those that indicate serious diseases and disorders. In Canada, there is also an additional category of products - "Supplemented food". Supplemented food is broadly defined as a repackaged product that is manufactured, sold or presented as food, containing added vitamins, minerals, amino acids, herbal or bioactive ingredients. These constituents may perform a physiological role beyond providing nutritional needs.[8,13,14]

In China, Chinese herbal products are regulated by the State Food and Drug Administration (SFDA) and can be registered as functional foods or drugs. Regulatory approval of functional foods is the responsibility of the Department of Food License, while regulation of Chinese herbal medicines is controlled by the Division of TCMs & Ethno-Medicines) under the Department of Drug Registration. Medicines in China include not only conventional but also traditional herbal medicines. According to Article 102 of the Drug Administration Law of the People's Republic of China, enacted by the State Food and Drug Administration in 2001, the definition of drugs is: "Drugs refer to products used for the prevention, treatment and diagnosis of human diseases and intended to regulate the physiological functions of humans, for which indications, use and dosage have been determined, including Chinese crude drugs, preparations for traditional Chinese medicine, chemical drugs, substances and their preparations, antibiotics, biochemical drugs, radioactive pharmaceutical products, serum, vaccines, blood products and diagnostic agents". The Drug Administration Law of the People's Republic of China, enacted in 2001, is the basic law that regulates the administration of drugs in China to ensure the quality and safety of drugs for people, protect people's health and their legitimate rights, and interests in drug use. The Implementation Regulations of the Drug Administration Law of the People's Republic of China are formulated in accordance with the Drug Administration Law and provide a legal framework to control drug manufacturers, drug distributors, pharmaceutical products in medical facilities, drug packaging, prices of drugs and advertising.[15] Another major development in the regulation of Chinese medicine is the introduction of the Drug Marketing Authorization Holder System with the new revision of the Drug Administration Law of the People's Republic of China in August 2019. The change in the regulation resulted in the withdrawal of the mandatory possession of a Certificate of Good Manufacturing Practice (GMP) and a Certificate of Good Supply Practice (GSP) for traditional herbal medicines, and the Holder of the approval to place of the medicinal product in circulation bears the general responsibility for guaranteeing safety and quality.[16] Products "Classified as Supplements" are called Health Foods, including products that are treated together with functional foods under the Chinese Food Safety Law. Manufacturers in China are allowed to market such products, but may only make therapeutic claims for them from a list of pre-defined therapeutic claims (27 claims in total at present). Therefore, before these products are approved, they must demonstrate compliance with the general testing and premarketing approval process, including toxicity testing requirements when the product contains a new ingredient.[8]

In European Union countries, products fall into one of two categories: "Classified as supplements" or "Classified as medicines". Under the category "Classified as supplements", there are food supplements that are regulated as food according to the European Commission Directive 2002/46/EC. There is no centralized pre-marketing authorization for dietary supplements in the EU. EU member states can request to be notified when a particular food additive is placed on the market in their territory, so that the competent authority of the member state can monitor its use in the territory. Harmonized legislation in the EU regulates vitamins and minerals and substances used as their sources, which can be used in the manufacture of food supplements. For ingredients other than vitamins and minerals, the European

Commission has established harmonized rules to protect consumers from potential health risks and maintains a list of substances known or suspected to have a negative effect on health and whose use is controlled (Annex III of the European Commission Regulation No. 1925/2006). If a product intended to be used in food supplements does not have a history of safe use in the EU before 1997, a new manufacturing process has been applied, or it contains or consists of engineered nanomaterials, then the product is classified as novel food. Such products are subject to a request for a safety assessment by the European Food Safety Authority (EFSA) under European Commission Regulation no. 2015/2283 for novel food. Even if non-harmonised substances are under national legislation, the "principle of mutual recognition" also applies, meaning that member states are not allowed to ban or restrict the import of products from another member state, if such a product is legal produced or sold in the exporting Member State. A number of exceptions apply to this principle, among them is the protection of health and life of people, animals or plants. The regulation of the European Commission no. 1925/2006 offers the possibility to exclude or limit the use of substances other than vitamins and minerals in food supplements in case it represents a potential risk for consumers. For "Novel Food", the EU has established a harmonized and centralized pre-marketing approval. Specifically, a centralized list of novel foods has been established across the EU and safety assessment is conducted in a centralized manner by EFSA. The European Commission consults with EU member states to determine whether a particular type of novel food should receive authorization. On the other hand, herbal medicinal products are "classified as medicinal products" and regulated under the European Commission's Medicines Directive 2004/24/EC. The safety, efficacy and marketing authorization of products is regulated by the European Medicines Agency (EMA).[8]

In the Republic of North Macedonia, some of the herbal medicines belong to the group of "nutritional supplements" and are regulated by the Law on Food Safety. According to this Law, "dietary supplements" are food products whose purpose is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, placed on the market in dosage form in the form of capsules, lozenges, tablets and other similar forms, sachets of powdered substance, vials of liquid and other similar forms of liquid or powdered substances designed to be used in small measurable unit quantities.

Vitamins and minerals are "Nutrients".

"Other substances with a nutritional or physiological effect" are substances belonging to one of the following categories: 1. Amino acids; 2. Enzymes; 3. Prebiotics and probiotics; 4. Fatty acids; 5. Herbs/mushrooms/algae and 6. Various bioactive substances.

Substances with a nutritional or physiological effect are listed in the List of permitted substances that can be used in the production of nutritional supplements, food for special nutritional use and fortified food, published on the website of the Food and Veterinary Agency. This List currently contains nearly 1800 herbs/mushrooms/algae. The labelling, presentation and advertising of nutritional supplements should not attribute to them the property of prevention, treatment or cure of certain diseases in humans or refer to such properties and should not contain any message stating or implying that balanced and a varied diet cannot provide an adequate amount of nutrients.[17]

Traditional herbal medicines are regulated by the Law on Medicines and Medicinal Products. In order to issue a marketing authorization for a traditional herbal medicine, the same documentation is submitted as for conventional

medicines. In our country, there is another category of products regulated by the Law on Medicines and Medical Devices - Border products.

A borderline product is a product that contains: probiotics; active components of plant origin and it is classified as a food supplement in at least one member state of the European Union, and according to the special regulations applied in the Republic of North Macedonia, it cannot be classified as a food supplement; vitamins and minerals in quantities greater than the permitted prescribed in accordance with the special regulations applied in the Republic of Macedonia, if it is classified as a food supplement in at least one member state of the European Union and there is no registered product with the same strength in the Republic of North Macedonia. The borderline product may be in a pharmaceutical dosage form intended for oral, topical or other route of application other than injection and/or infusion. Before submitting the application for the approval of a borderline product, a preliminary classification is carried out in accordance with the criteria established in the Law on Medicines and Medical Devices, the relevant data from the documentation, side effects and the safety profile of the product that is subject to classification according to the opinion received by the Commission for Classification of a product, packaged in a pharmaceutical dosage form.[3]

CHALLENGES RELATED TO ASSESMENT OF SAFETY AND EFFICACY

Many proponents of herbal remedies argue that products with a long history of folk use are generally safe when used appropriately and in usual therapeutic doses. The crucial question underscored by this statement is to what extent the lack of evidence of toxicity can be considered evidence of the non-toxicity or safety of herbal medicines. Whether the lack of data on adverse effects is indicative of non-toxicity depends on the type of toxic effect and the likelihood of such an adverse outcome being observed under the conditions prevailing during traditional use. Acute symptoms or short-term toxic effects, such as gastro-intestinal complaints and dermatological effects, can be easily recognized and associated with herbal remedies. So, the absence of such symptoms provides a certain proof of the safety of these specific points. Long-term adverse effects, such as cancer, liver and kidney damage, reproductive dysfunctions, congenital anomalies, and morbidity are much more difficult to detect, but cannot be linked to folk drug use unless adequately designed. An epidemiological study (preferably a prospective cohort study). Hence, the lack of evidence for such side effects in the context of the traditional use of herbal medicines is not proof of the absence of the possibility of them being caused. With regard to drugs, safety is assumed only when there is a zero probability (absence of toxicity) despite a properly designed and comprehensive set of preclinical and clinical studies with sufficient statistical power to reject the assumption if it turns out to be false. There is no denying the fact that the requirements, as well as research protocols, standards and methods needed to assess the safety and efficacy of herbal medicines are much more complex than those required for conventional pharmaceuticals. A single herbal medicine or medicinal plant can contain hundreds of natural ingredients, and a mixture of herbal medicines can contain several times more. Each active ingredient has to be isolated from an individual plant from which an herbal medicine is formulated or produced, so the time and resources required are enormous, and such an analysis is practically impossible.[5,18]

CHALLENGES RELATED TO QUALITY CONTROL OF HERBAL MEDICINES

Quality is the main concern of human beings in all aspects of life. When it comes to the quality of pharmaceuticals consumed by humans, it is of utmost importance as they are used for the well-being of mankind. There are strict guidelines and regulations for quality control of synthetically produced chemical pharmaceuticals. They must go through various batch tests and quality control checks before being marketed and consumed by patients and consumers.

This rigor in regulation maintains the quality of synthetically produced pharmaceuticals to a degree that guarantees their safety and efficacy. Herbal medicines are those obtained from plant resources for the treatment and welfare of mankind. It is very important to control the quality of herbal medicines as well as the quality of chemically synthesized medicines. But unfortunately, regulatory norms for herbs are not as strict as compared to synthetic drugs. This leads to a lowering of the quality standards of herbal products by intentional and sometimes unintentional adulteration, counterfeit drugs, drug substitution and many other ways that tend to reduce the quality of herbal materials sold and consumed by the population. The quality of the raw materials used in the manufacture of herbal medicines largely determines the safety and efficacy of these herbal medicines. In general, the quality of raw materials depends not only on internal (genetic) factors, but also on external factors, such as environmental conditions, good agricultural and good collection practices of medicinal plants, including their selection and breeding. It is the combination of these factors that makes it difficult to control the quality of the raw materials of herbal medicines. According to good manufacturing practice (GMP), proper identification of medicinal plant species, special storage, and special sanitation and cleaning methods are important requirements for quality control of starting materials. One of the biggest challenges often encountered in the quality control of finished herbal medicines, especially mixtures of herbal medicines, is the difficulty in determining the inclusion of all plants or starting materials. Thus, the general requirements and quality control methods for finished herbal medicines remain far more complex than those for other pharmaceutical products. To ensure the safety and efficacy of herbal medicines, WHO continues to recommend quality assurance methods and control measures, such as national quality specifications and standards for herbal materials, GMP for herbal medicines, labeling and manufacturing licensing schemes, import and marketing. There are various quality control tools used to determine the quality of herbs. In order to ensure the quality of herbal medicines, both qualitative and quantitative measures are needed. Various techniques such as UV (Ultraviolet) and IR (Infrared) are commonly used to determine the qualitative aspects while HP-TLC (High Performance Thin Layer Chromatography), HP-LC (High Pressure/Performance Liquid Chromatography), SFC (Supercritical Liquid Chromatography), Thermal Analysis, ICP-MS (Inductively Coupled Plasma-Mass Spectroscopy), LC-MS (Liquid Chromatography-Mass Spectroscopy) and GC-MS (Gas chromatography-mass spectroscopy) are used for quantitative control of herbal products. Various tools and techniques must be applied to verify and ensure the required quality to be incorporated into the herbal material and products. There must be guidelines and/or norms for conducting quality control tests on herbs and these must be almost or as stringent as those for synthetic pharmaceuticals. This will help maintain the quality standards of herbal pharmaceuticals, which is a challenging task in pharmaceutical research and quality assurance.[5,19]

CHALLENGES ASSOCIATED WITH MONITORING THE SAFETY OF HERBAL MEDICINES

In recent years, issues related to the increasing use of herbal medicines in developed countries, the dependence of many people living in developing countries on plants as the main source of medicine together with the absence or weak regulation of herbal medicines in most countries and the emergence of high concerns about their safety, have raised awareness of the need to monitor safety and deepen understanding of the possible harms as well as potential benefits associated with the use of herbal medicines. Adverse events resulting from the use of herbal medicines are attributed to a number of factors, which include the use of wrong types of plants by mistake, alteration of the quality of herbal medicines by impurities from other undeclared chemicals/drugs, contamination with toxic or hazardous substances, overdose, misuse of herbal medicines by health care providers or consumers and use of herbal medicine medicines simultaneously with other medicines. Although the assessment of the safety of herbal medicines has become an important issue for consumers, regulatory bodies and health professionals, the analysis of adverse events associated

with the use of these products is much more complex than that of conventional pharmaceuticals. Also, the assessment of the safety of herbal medicines is further complicated by factors such as the geographical origin of the plant material, different processing techniques, the method of administration and compatibility with other medicines. Furthermore, there is a lack of knowledge and/or weak emphasis on the importance of taxonomic botany and documentation by most herbal medicine manufacturers and this presents a unique challenge in identifying and collecting medicinal plants used for herbal medicines. To remove the confusion created by common names, it is necessary to adopt commonly used binomial names (including their binomial synonyms) for medicinal plants. For example, *Artemisia absinthium* L., which contains an active narcotic derivative and is capable of causing central nervous system disorders and generalized mental deterioration, has at least 11 different common names. Seven of the common names are not related to its botanical name at all. This explains why it is important to provide the correct scientific name of the plant, the plant part used and the name of the manufacturer when reporting adverse reactions resulting from the use of herbal medicines. Therefore, effective monitoring of herbal drug safety also requires effective collaboration between botanists, phytochemists, pharmacologists and other stakeholders.[5]

ASSESSMENT OF THE TOXICITY OF HERBAL MEDICINES

Toxicity refers to the relative ability of a substance to cause adverse effects in living organisms. It can also be defined as the degree to which the exposed tissue is damaged by a chemical substance and covers the effect on the whole organism and substructural component of the organism such as the cell (cytotoxicity) or organ (organotoxicity). Toxicity can be further defined to encompass the study of the adverse effects of chemicals on living organisms, as well as their symptoms, mechanisms, and treatments. Toxicity can be classified as acute, subacute/subchronic, or chronic depending on the amount and duration of administration of the agents. The concept related to the safety profile of herbs is that these products should be considered safe because they have a long history of traditional use, without significant experience and knowledge of their toxic effects. Traditional experience is a powerful tool for identifying side effects, which occur in the majority of users and develop rapidly after initiation of therapy. In this context, there were incidents in 1991 and 1992 in Brussels where 30 women were treated with a Chinese slimming preparation and died due to kidney failure caused by the presence of aristocholic acid, which is toxic in nature. Another example is the induction of anticholinergic symptoms, such as palpitations, dry mouth, and pupil dilation, by herbal remedies rich in belladonna alkaloids. Such reactions are pharmacologically predictable and dose dependent and can be prevented by reducing the dose. So, the importance of controlling the correct identification of herbal preparations should be considered. In addition to the problem of plant misidentification, some mixtures can be toxic, especially if abused. The message that consumers believe is that herbal medicines are natural and natural means safe. There is a great need to constantly review and assess the safety of commonly consumed botanicals with an emphasis on surveillance and use of these products to identify unknown hazards or risks and address them urgently Table 2 supplemtary. The toxic effects of herbal medicines are mostly due to their effect on drug-metabolizing enzymes, namely cytochrome enzymes. Herb-CYP450 interactions manifest in two different ways: Herbal medicines can induce CYP450 enzymes and increase drug metabolism, which can lead to therapeutic failure, or, they can inhibit CYP450 enzymes, reducing drug metabolism of drugs and, possibly, increase therapeutic effects and toxicity. The toxicity testing of herbal medicines is aimed at the toxicological measurement of herbs or herbal preparations in order to identify their adverse effects and to determine the dose exposure limits at which such effects occur. It is performed through several methods such as: preclinical toxicity test, cytotoxic tests, determination of toxicokinetic properties of herbs, toxicogenomic screening, DNA sequencing,

determination of systemic acute, subacute or chronic toxicity using animal models *in vivo*, determination of carcinogenicity, neurotoxicity, genotoxicity, reproductive toxicity, evaluation of local toxicity, etc.[5,7,20]

INTERACTIONS BETWEEN HERBAL MEDICINES AND CONVENTIONAL MEDICINES

The efficacy of drug therapy depends on many factors related to the pharmacokinetic and pharmacodynamic properties of drugs, which can be adjusted to differences in age, sex, genetic polymorphisms, circadian rhythm, pathophysiological conditions, pharmaceutical dosage form, and xenobiotics. Co-administration of herbal medicines, as dietary supplements for the treatment or prevention of diseases, may cause unexpected adverse drug reactions. Various studies have shown that 14% - 31% of prescription drug users take herbal medicines as a dietary supplement. The main reason for clinically relevant interactions between herbal medicines and conventional medicines is the modulation of cytochrome-mediated metabolism, which can lead to altered pharmacokinetics. Cytochrome enzyme induction results in a decrease in drug efficacy, while inhibition causes an increase in plasma drug concentration and toxicity. The assessment of interactions between herbal medicines and conventional medicines is necessary because nowadays patients use them simultaneously and mostly without consulting their doctor. The most common cause of clinically significant drug-drug or herb-drug interactions is CYP450 inhibition. Toxicological evaluation of herbal medicines for preclinical and clinical data is not mandatory and is not subject to standard pharmaceutical safety criteria. There are several regulatory requirements in different countries regarding safety assessment and potential interactions between phytoconstituents and conventional drugs. Regulatory agencies of some countries require documentation of herbal drug interactions with CYP isoforms prior to approval through the use of various *in vitro*, *in vivo*, and *in silico* techniques. Establishing the safety of herbs using cytochrome-modulating enzymes will attract the attention of herbal drug manufacturers for the potential marketing benefit. Traditional herbal preparations, which have been practiced for several hundred years, contain medicinal plants, minerals, organic and other substances. It is estimated that about three-quarters of the world's population currently use herbs and other forms of traditional medicine to treat illness. Even as we entered the new century with the exciting possibility of gene therapy, herbal medicines remained one of the common forms of therapy available to the world's population. Additional research is still needed in herbal therapy to examine the individual constituents of plants and to determine the interaction of plants with drugs and foods. Some researchers suggest that interactions between herbal medicines and conventional medicines occur less often than anticipated. If an herb-drug interaction occurs, usually conventional drugs are the main reason because they are more pharmacologically active. A few examples of some interactions between medicinal herbs and their effects with conventional drugs are shown in Table 3 supplement.[21,23]

CYTOCHROME P450: ITS ROLE IN METABOLISM

Cytochrome P450 is a class of vital enzymes responsible for the metabolism of drugs and drug-like substances. Based on inherited genetic characteristics and environmental factors, the expression of this enzyme varies in each individual. In the case of multi-drug therapy, serious adverse effects and even serious interactions can occur when the pharmacokinetic parameter of one drug is changed by another. Drug interactions involving a CYP isoform generally result in enzyme induction or inhibition. Repeated administration of drugs can induce CYP enzymes by increasing the rate of enzyme synthesis. Based on the enzymatic mechanism, CYP enzyme inhibition can be reversible or irreversible. In the case of reversible inhibition, the substrate and inhibitor compete with each other for binding to the active site. When inhibition is due to reactive metabolites produced by CYP catalyzed reactions, it is irreversible inhibition. Mechanisms of inhibition are related to three factors: dosage, time period of inhibition and delay of time required for

inhibition. Sometimes strong inhibition requires time for mechanism-based inhibition through the formation of active metabolites by metabolism of the parent compound. Therefore, mechanism-based inhibitions require a longer lag time period. The key factor for changing the pharmacokinetic parameters of the drug is the modulation of hepatic and intestinal CYP450.[21]

EFFECT OF HERBAL MEDICINES ON CYTOCHROME P450

Due to the fact that herbs are composed of a multitude of constituents whose interactions with the body are extremely complex, a high level of sophistication in research methodology is required to describe these interactions. Interactions between herbal and conventional medicines can affect health and the effectiveness of therapy in the following aspects:

- Increase in side effects of drugs, which can lead to toxicity;
- Reducing the therapeutic effect of drugs, which can lead to therapy failure;
- Changing the effect of the drugs, possibly leading to unexpected complications;
- Strengthening the therapeutic effect of drugs, which can lead to overdose.

Some drugs have been withdrawn from the market due to safety concerns. The drug mibefradil (*CYP3A* inhibitor) was withdrawn from the market due to toxicity related to inhibition of CYP3A enzymes. CYP3A substrate drugs, such as astemizole, cisapride, and terfenadine, can produce serious drug-induced toxicity by increasing blood drug concentrations. Simultaneous use of mibefradil (CYP3A inhibitor) with hypolipidemic drugs, such as lovastatin and simvastatin, may cause rhabdomyolysis in the patient. *Echinacea purpurea* (Fam. Asteraceae) is used for the treatment of the common cold, flu, respiratory tract infections and as an immunomodulatory agent.

The extract of this herb has an inhibitory effect on CYP3A4 isozymes. The alkylamide compound, which is responsible for the immunomodulatory effect, also has a mild inhibitory effect on CYP enzymes, such as CYP3A4 and CYP2D6 isozymes. Chamomile extract is widely used to treat inflammation and improve digestion. Chamomile essential oil and its main constituents (chamazulene, *cis*-spiroether and chamazulene) have an inhibitory effect on recombinant human cytochrome P450 enzymes, such as CYP2D6 and CYP3A4. Grapefruit juice inhibits *CYP1A2, CYP2C9*, and most strongly intestinal *CYP3A4*. There are many other medicinal herbs that can induce or inhibit CYP450, such as peppermint (*Mentha piperita*), dandelion (*Taraxacum officinale*), Siberian ginseng (*Eleutherococcus senticosus*), Milk thistle (*Silybum marianum*), saw palmetto (*Serenoa repens*), black cohosh (*Cimicifuga racemosa*), valerian (*Valeriana officinalis*), soybean (*Glycine max*) and Goldenseal (*Hydrastis canadensis*). Ginkgo has been reported to inhibit *CYP1A2, 2C9, 2C19, 2D6* and *3A4 in vitro* and is responsible for the mechanistic inhibition of *CYP3A* in rats. Medicinal herb-drug interactions have also been reported for Indian herbs and herbal formulations, such as *Terminalia chebula, Emblica officinale, Terminalia bellirica, Acorus calamus, Glycyrrhiza glabra, Trigonella Foenum-Graecum, Zingiber officinale, Capsicum annuum, Murraya koenigii, Gymnema sylvestre, Aegle marmelos* and *Swertia chirata*.[21]

PHARMACOVIGILANCE CHALLENGES ASSOCIATED WITH THE USE OF HERBAL MEDICINES

Pharmacovigilance is a science and a set of activities related to the detection, assessment, understanding, prevention and treatment of adverse drug reactions, as well as new information about the dangers of drug use. The specific goals to which this science aspires are the improvement of patient care and safety associated with the use of medicines that improve the health of the general population. Pharmacovigilance reviews and studies issues related to substandard drugs, medication errors, use of drugs for off-label indications, reports of acute and chronic poisonings, side effects of

drugs in combination with chemicals, and more. It also contributes to the assessment of benefit, harm, efficacy and risk in the use of medicines, ensuring the safe, rational and efficient use of medicines.[2,25] Although these methods were developed to monitor the safety profile of drugs, they are also used to further assess the safety of other medicinal products, such as herbal medicines, blood products, vaccines and medical devices. Since the use of herbal medicines is increasing, the number of reports of side effects from their use, potential interactions and toxic effects has also increased. All the mentioned information emphasizes the impact of herbal preparations in daily practice by patients and the potential risks associated with their use. Unwanted outcomes from the use of herbal medicines can be due to: side effects (pharmacodynamic aspects and often predictable); reactions that occur as a result of overdose, excessive use, tolerance, addiction (detected through pharmacodynamics or pharmacovigilance); hypersensitivity, allergic and idiosyncratic reactions (detected by pharmacovigilance); medium and long-term toxic effects, including hepatic, renal, cardiac toxicity, neurotoxicity, genotoxicity and teratogenicity (detected through *in vitro* and *in vivo* toxicological studies or through pharmacovigilance). Many herbal medicines that exist on the market have not had their pharmacology and toxicology studied in detail, so pharmacovigilance is of great importance to detect their side effects. In addition, there is a persistent problem of unexpected toxicity of herbal medicines due to quality problems, such as the use of poor-quality herbal material, incorrect or misidentified plants, incorrect processing methods, use of adulterated or contaminated plants or products. These quality problems can be solved to some extent by improved regulation requiring GMP standards for production. However, herbal medicines come from many countries with different production standards and regulatory enforcement, so poor quality products are likely to remain a problem. The safety of herbal medicines is a serious problem for regulatory bodies, so in that direction, the World Health Organization (WHO), recognizing the increasing importance of the use of herbal medicines worldwide, has developed guidelines for monitoring the safety of herbal medicines within the existing pharmacovigilance framework. In 2005, WHO published a report on national policies on traditional medicine and regulation of herbal medicines, based on the first global survey on traditional and complementary medicine.[26] To identify global trends and current status in the field of traditional and complementary medicine, WHO conducted a second global survey during 2010–2012 (Second Survey) and a follow-up survey during 2016–2018 (Update Survey). This made it possible to compare information and data and thereby identify global trends associated with the safety aspects of the use of herbal products. In 2019, WHO published the Global Report on Traditional and Complementary Medicine, as part of the WHO Traditional Medicine Strategy 2014-2023, whose focus is to develop norms, standards and technical documents based on reliable information and data, to support Member States in providing safe, qualified and effective services for traditional and complementary medicine and their appropriate integration into health systems to achieve universal health coverage. In accordance with the WHO Traditional Medicine Strategy 2002–2005 and the WHO Traditional Medicine Strategy 2014–2023, and relevant resolutions of the World Health Assembly, Member States take steps to promote the safety, quality and efficacy of traditional and complementary medicine. They also take steps for its proper integration into health systems (especially health services) through the development of national policies, regulatory frameworks and strategic plans. In the Republic of North Macedonia, health institutions and health workers are likely required to report various drug-related safety issues to the National Center for Pharmacovigilance.

ROLE OF THE PHARMACIST IN THE PHARMACOVIGILANCE OF HERBAL MEDICINES

Pharmacists play a vital role in the safe and effective use of herbal medicines. Their involvement in pharmacovigilance is crucial in identifying and mitigating potential adverse drug reactions Pharmacist play key roles in pharmacovigilance of herbal medicines through:

1. Patient Counseling and Education:
   - Provide information on the safe and appropriate use of herbal medicines.
   - Advise on potential drug interactions, including those with conventional medications, other herbs, and food.
   - Educate patients about the importance of reporting any adverse effects.
2. Monitoring for Adverse Drug Reactions:
   - Actively monitor patients for signs and symptoms of ADRs associated with herbal medicines.
   - Identify potential safety signals and report them to relevant authorities.
3. Reporting Adverse Drug Reactions:
   - Submit detailed reports to national pharmacovigilance centers, including information on the herbal product, patient demographics, and adverse events.
   - Contribute to the generation of valuable data for assessing the safety profile of herbal medicines.
4. Collaboration with Healthcare Professionals:
   - Work closely with physicians and other healthcare providers to ensure optimal patient care.
   - Share information on herbal medicine safety and efficacy.

The advantages of pharmacist involvement in pharmacovigilance are due to their unique access to the patients, their knowledge and skills to assess drug interactions and recognize ADRs and they can ensure the safe and effective use of herbal medicines and can provide accurate and timely reports. By actively participating in pharmacovigilance, pharmacists can help ensure and promote patient safety and public health.[27]

CONCLUSION

Clinical reports clearly show that herbal medicines can interact with conventional medicines. Although the majority of such interactions may have negligible clinical significance, some may pose a serious threat to public health. For example, combining St. John's wort with antiretroviral, immunosuppressive, or anticancer agents that are metabolized by CYP enzymes and/or are substrates of P - glycoprotein may lead to complete ineffectiveness of the drug. Also, serious health problems can occur when patients take herbal medicines before surgery. Cases of cardiovascular collapse and blood loss have been documented. A recent retrospective review of surgical patients admitted to the Preoperative Anesthesia Evaluation Clinic at the University of Kansas Hospital reported that approximately one-quarter of patients reported preoperative use of natural products. Therefore, it should be mandatory for doctors to communicate with the patient regarding the use of any supplements before surgery. In conclusion, herbal medicines can be used by patients alongside with conventional medicines, but the same can result in potentially serious side effects. Healthcare professionals are the ones who need to be well informed about the growing clinical evidence of herbal drug–conventional drug interactions.

REFERENCES

1. Kulevanova S: Basics of phytotherapy: a textbook for students of the first cycle of studies in dietetics and dietotherapy and integral studies in pharmacy. ISBN 978-9989-43-453-2. https://www.ukim.edu.mk/e-izdanija/FF/Osnovi_na_fitoterapija.pdf
2. Barnes, J.: Pharmacovigilance of Herbal Medicines: A UK Perspective. Drug Saf, 2003; 26: 829–851. https://doi.org/10.2165/00002018-200326120-00001
3. Law on medicinal products and medical devices (Official Gazette of the Republic of Macedonia no. 106/07)
4. Shetti, S., Kumar, C.D., Sriwastava, N.K., Sharma, I.P.: Pharmacovigilance of herbal medicines: Current state and future directions. Pharmacogn. Mag, 2011; 7: 69–73. https://doi.org/10.4103/0973-1296.75905
5. Ekor, M.: The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol, 2014; 4, https://doi.org/10.3389/fphar.2013.00177
6. Choudhury, A., Singh, P.A., Bajwa, N., Dash, S., Bisht, P.: Pharmacovigilance of herbal medicines: Concerns and future prospects. J. Ethnopharmacol, 2023; 309: 116383. https://doi.org/10.1016/j.jep.2023.116383
7. Kavrakovski Z: Herbal medicinal products: risk for our health. Pharmaceutical Фармацевтски информатор No. 27 / September 2011.
8. Thakkar, S., Anklam, E., Xu, A., Ulberth, F., Li, J., Li, B., Hugas, M., Sarma, N., Crerar, S., Swift, S., Hakamatsuka, T., Curtui, V., Yan, W., Geng, X., Slikker, W., Tong, W.: Regulatory landscape of dietary supplements and herbal medicines from a global perspective. Regul. Toxicol. Pharmacol, 2020; 114: 104647. https://doi.org/10.1016/j.yrtph.2020.104647
9. Global Coalition for Regulatory Science Research, https://www.fda.gov/about-fda/science-research-nctr/global-coalition-regulatory-science-research
10. Bent, S.: Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation: Grand Rounds at University of California, San Francisco Medical Center. J. Gen. Intern. Med., 2008; 23: 854–859. https://doi.org/10.1007/s11606-008-0632-y
11. Briggs, D.R.: The regulation of herbal medicines in Australia. Toxicology, 2002; 181–182, 565–570. https://doi.org/10.1016/S0300-483X(02)00483-3
12. Regulation of Dietary Supplements, https://www.medsafe.govt.nz/regulatory/DietarySupplements/Regulation.asp
13. Smith, A., Jogalekar, S., Gibson, A.: Regulation of natural health products in Canada. J. Ethnopharmacol, 2014; 158: 507–510. https://doi.org/10.1016/j.jep.2014.06.037
14. Natural health product regulation in Canada: Overview, https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/regulation.html
15. Fan, T.-P., Deal, G., Koo, H.-L., Rees, D., Sun, H., Chen, S., Dou, J.-H., Makarov, V.G., Pozharitskaya, O.N., Shikov, A.N., Kim, Y.S., Huang, Y.-T., Chang, Y.S., Jia, W., Dias, A., Wong, V.C., Chan, K.: Future development of global regulations of Chinese herbal products. J. Ethnopharmacol, 2012; 140: 568–586. https://doi.org/10.1016/j.jep.2012.02.029
16. Hu, Q.: The regulation of Chinese medicine in China. Longhua Chin. Med., 2021; 4: 7–7. https://doi.org/10.21037/lcm-2021-001
17. Food Safety Act, (Official Gazette of the Republic of Macedonia no. 157, 08.12.2010).

18. Moreira, D.D.L., Teixeira, S.S., Monteiro, M.H.D., De-Oliveira, A.C.A.X., Paumgartten, F.J.R.: Traditional use and safety of herbal medicines1. Rev. Bras. Farmacogn, 2014; 24: 248–257. https://doi.org/10.1016/j.bjp.2014.03.006
19. Balekundri, A., Mannur, V.: Quality control of the traditional herbs and herbal products: a review. Future J. Pharm. Sci., 2020; 6: 67. https://doi.org/10.1186/s43094-020-00091-5
20. L.K. Mensah, M., Komlaga, G., D. Forkuo, A., Firempong, C., K. Anning, A., A. Dickson, R.: Toxicity and Safety Implications of Herbal Medicines Used in Africa. In: F. Builders, P. (ed.) Herbal Medicine. IntechOpen (2019).
21. Mukherjee, P.K.: Safety-Related Quality Issues for the Development of Herbal Drugs. In: Quality Control and Evaluation of Herbal Drugs. pp. 655–683. Elsevier (2019).
22. Kulevanova S, Modern herbal medicine, Phytotherapy. https://www.ukim.edu.mk/e-izdanija/FF/Sovremena_herbalna_medicina_FITOTERAPIJA.pdf
23. Asokkumar, K., Ramachandran, S.: Herb-Drug Interactions: Focus on Adverse Drug Reactions and Pharmacovigilance of Herbal Medicines. In: Sen, S. and Chakraborty, R. (eds.) Herbal Medicine in India. pp. 547–571. Springer Singapore, Singapore (2020).
24. Izzo, A.A.: Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data. Med. Princ. Pract, 2012; 21: 404–428. https://doi.org/10.1159/000334488
25. Kongkaew, C., Phan, D.T.A., Janusorn, P., Mongkhon, P.: Estimating Adverse Events Associated With Herbal Medicines Using Pharmacovigilance Databases: Systematic Review and Meta-Analysis. JMIR Public Health Surveill, 2024; 10, e63808. https://doi.org/10.2196/63808
26. De Smet, P.A.G.M.: An Introduction to Herbal Pharmacovigilance. In: De Smet, P.A.G.M., Keller, K., Hänsel, R., and Chandler, R.F. (eds.) Adverse Effects of Herbal Drugs. pp. 1–13. Springer Berlin Heidelberg, Berlin, Heidelberg (1997).
27. Toklu, H.Z., Mensah, E.: Why do we need pharmacists in pharmacovigilance systems? Online J. Public Health Inform, 2016; 8. https://doi.org/10.5210/ojphi.v8i2.6802

Supplementary Material

Table 2: Adverse/Toxic effects of some herbal medicines.[7,21,22]

Herbal material	Adverse effects of the selected herbal material
Alfalfa: *Medicago sativa* (Fam. Fabaceae)	The herb is widely used in homeopathy and is a great source of vitamins such as A, C, E and K and minerals such as calcium, potassium, phosphorus and iron. But this herb has been found to cause systemic lupus erythematosus.
Aloe Vera: *Aloe barbadensis* Mill. (Fam. Asphodelaceae)	It is the most widely used plant to treat skin-related problems (eg, skin discoloration and bruising), and in addition to external use, it is also consumed internally due to its laxative property, which may cause serious electrolyte imbalance (decreased potassium level) if treatment continues for 7-14 days. So, it is better to avoid long-term use of laxatives containing anthraquinone glycosides.
Comfrey: *Symphytum officinale* L. (Fam. Boraginaceae)	In the first century, Greek physicians gave tea from this plant to heal wounds and broken bones. Much later, in the seventies of the last century, it was discovered that this herb causes hepatotoxicity due to the presence of the pyrrolizidine class of alkaloids.
Ephedra: *Ephedra sinica* Stapf. (Fam: Ephedraceae)	Has been used since ancient times to treat respiratory disorders. It has also been reported to be used to improve mood and manage weight gain. Nowadays, many manufacturers include this herb in various slimming products, eventually causing serious health problems. This is because Ephedra contains the alkaloid ephedrine, which causes complications in the cardiovascular system, such as high blood pressure and liver damage.
Ginkgo biloba: *Ginkgo biloba* L. (Fam. Ginkgoaceae)	For thousands of years, Ginkgo fruit and seeds have been used as a medicinal supplement to improve mental health and memory. However, there is substantial scientific evidence that its extract inhibits platelet-activating factor. Therefore, long-term use causes prolonged bleeding time, hemorrhage, and subdural hematomas.
Ginseng: *Panax ginseng* (Korean), *Panax japonicas* (Japanese), *Panax notoginseng* (Chinese), *Panax vietnamensis* (Vietnamese), *Panax quinquefolius* (American) (Fam. Araliaceae)	It is one of the most commonly used herbs as "all-purpose medicine", especially for stress reduction, high blood pressure, diabetes and depression-like symptoms. But it has been found to cause several side effects such as hypertension, mastalgia and blood clotting. It also interacts with anticoagulant drugs, causing problems in the blood coagulation process.
Desert Plantain: *Plantago ovata*, *Plantago indica* (Fam. Plantaginaceae)	Has been widely used for centuries as a laxative and as a means to reduce inflammation and irritation. Apart from its therapeutic use, it has been shown to cause bronchospasm, asthma and intestinal obstructions. It can also produce esophageal obstruction if swallowed in dry form.
Licorice root: *Glycyrrhiza glabra* (Fam. Fabaceae)	Its root is used to treat various therapeutic complications, such as asthma, ulcers and pustules (caused by herpes infection), joint pain, chronic depression, etc. It has soothing and expectorant properties and additionally activates the mucous discharges of the trachea. Various studies have shown that glycyrrhizin activates hormones from the adrenal cortex. Recently, it has been found that one of its components, glycyrrhizic acid, when taken in large amounts, can increase sodium and water retention and also decrease potassium levels, making it dangerous for people with high blood pressure. circulation, kidney or coronary disease. Potential side effects include edema and hypertension.
Senna: *Cassia angustifolia* Vahl. (Fam. Caesalpiniaceae)	Is another example of a plant traditionally used for weight loss and treating constipation. But if used daily, it can cause heart problems due to a decrease in potassium levels. It can also cause circulatory failure, seizures, high blood pressure and anaphylactic reactions.
White mistletoe: *Viscum album* L. (Fam. Loranthaceae)	It is used in the therapy of circulatory and respiratory disorders. Side effects that it can cause are acute gastrointestinal disorders, stomach pain, diarrhea, decreased pulse, as well as adverse reactions with anticoagulants and other drugs.
Blueberry: *Vaccinium sp*. (Fam.	Is used as a dietary supplement, it has antioxidant properties. It has been

Ericaceae)	associated with rare cases of thrombocytopenia, a condition characterized by a reduced number of platelets, resulting in bleeding.
Valerian: *Valeriana officinalis* (Fam. Valerianaceae)	Is used as a mild sedative and muscle relaxant. It is associated with isolated cases of hepatotoxicity, may increase the effect of alcohol, some analgesics and sedatives and prolong the effect of some anesthetics.
Ginger: *Zingiber officinale* (Fam. Zingiberaceae)	Is used as an antiemetic and antivertigo agent. But this herb can increase bleeding, especially in patients using anti-clotting medications.
Echinacea: *Echinacea spp*. (Fam. Asteraceae)	Is used as an immunostimulator, against colds and flu, for wound healing. Long-term use can cause an immunosuppressive effect, the appearance of asthma and many other side effects. It can cause inflammation of the liver if used with drugs such as anabolic steroids, chemotherapeutics, etc. Potentiates the toxicity of barbiturates, reduces the clearance of tolbutamide and caffeine.
Artichoke: *Cynara scolymus* (Family. Asteraceae)	Used for liver-biliary disorders, lowering elevated cholesterol can cause allergic reactions.
Dandelion: *Taraxacum officinale* F.H. Wigg. (Fam. Asteraceae)	Is used for dyspeptic disorders, but it can also cause frequent allergic reactions.
Garlic: *Allium sativum* L. (Fam. Alliaceae)	Is used to lower elevated cholesterol and as an antihypertensive. As side effects, it can cause abdominal difficulties and allergic reactions.[7,21,22]

Table 3: Clinical interactions between herbal medicines and conventional medicines.[21,23,24]

Herbal medicine	Medicine	Clinical interaction
Aloe (*Aloe vera*)	Sevoflurane	Increased blood loss during surgery
Boldo (*Peumus boldus* Mol.)	Warfarin	Increased anticoagulant effect
Cat's claw *(Uncaria tomentosa)*	Protease inhibitors (Atazanavir, Ritonavir and Saquinavir)	Increased concentration of protease inhibitors in the blood
Chamomile (*Matricaria chamomilla* L.)	Warfarin	Bleeding
Chlorella (*Chlorella pyrenoidosa*)	Warfarin	Reduced anticoagulant effect
Cranberry (*Vaccinium macrocarpon*)	Warfarin	Increased anticoagulant response, including fatal hemorrhage
Danshen (*Salvia miltiorrhiza*)	Midazolam	An increase in the concentration of Midazolam in the blood
	Warfarin	Increased anticoagulant effect
Angelica (*Angelica sinensis*)	Warfarin	Increased anticoagulant effect
Echinacea (*Echinacea spp.)*	Caffeine	Possible reduction of Caffeine concentration in blood
	Midazolam	Possible increase of bioavailability of Midazolam (CYP3A substrate)
Nightgown (*Oenothera biennis*)	Fluphenazine	seizures
Greek seed (*Trigonella Foenum-Graecum*)	Warfarin	Increased anticoagulant effect
Garlic (*Allium sativum*)	Chlorzoxazone	Decreased serum levels of 6-hydroxychlorzoxazone/ chlorzoxazone
	Chlorpropamide	Hypoglycemia
	Fluindione	Reduced anticoagulant effect of Fluindione
	Paracetamol	Changes in the pharmacokinetic variables of Paracetamol
	Ritonavir	Severe gastrointestinal toxicity
	Saquinavir	Decreased concentration of Saquinavir in the blood
	Warfarin	Increased anticoagulant effect
Ginger (*Zingiber officinale*)	Phenprocoumon	Increased anticoagulant effect
Ginkgo (*Ginkgo biloba*)	Anticonvulsant drugs	Fatal seizures

	(Valproic acid and Phenytoin)	
	Anticoagulant drugs/ Nonsteroidal anti-inflammatory drugs	Spontaneous hyphema (Aspirin), fatal intracerebral hemorrhage (Ibuprofen), intracerebral hemorrhage (Warfarin)
	Efavirenz	Virological failure associated with reduced blood concentration of Efavirenz
	Omeprazole	Reduction omeprazole and omeprazole sulphone concentrations in the blood
	Risperidone	Priapism
	Tolbutamide	Possible decreased concentration of Tolbutamide in the blood
	Trazodone	Coma
	Talinolol	Increased concentration of Talinolol in the blood Increased concentration of Talinolol in the blood
Zhen Shen (*Panax ginseng*)	Imatinib	Hepatotoxicity
	Phenelzine	Drowsiness, tremors and headaches
	Warfarin	Reduced anticoagulant effect and reduced concentration of Warfarin in the blood
Goji (*Lycium barbarum*)	Warfarin	Increased anticoagulant effect
Green tea (*Camelia sinensis*)	Folic acid	Decreased concentration of folate in the blood
	Simvastatin	Statin intolerance associated with an increased concentration of Simvastatin in the blood
	Warfarin	Reduced anticoagulant effect
Mint (*Mentha piperita*)	Felopidine	Increased concentration of Felopidine in the blood
Hibiscus (*Hibiscus sabdariffa*)	Chloroquine	Decreased blood concentration of Chloroquine
	Paracetamol	Alteration of some pharmacokinetic parameters of Acetaminophen
Kava kava (*Piper methysticum)*	Alprazolam	Lethargic and disoriented state
	Chlorzoxazone	Decreased serum levels of 6-hydroxychlorzoxazone/ chlorzoxazone
	Levodopa	Reduced efficiency
	Paroxetine	Lethargic state
Maitake (*Grifola frondosa*)	Warfarin	Increased anticoagulant effect
Milk thistle (*Silybum marianum* L.)	Metronidazole	Decreased concentration of Metronidazole in the blood
Mistletoe (*Viscum album*)	Busulphan	Organ fibrosis and death
Passionflower (*Passiflora incarnata*)	Lorazepam	Hand tremors, dizziness, increased pulse and muscle fatigue
Soya (*Glycine max*)	Warfarin	Reduced anticoagulant effect
John's wort (*Hypericum perforatum*)	Adrenergic vasopressors (Ephedrine, Phenylephrine)	Decreased response to vasopressors
	Alprazolam	Decreased concentration of Alprazolam in the blood
	Amitriptyline	Decreased concentration of Amitriptyline in the blood
	Анестетици	An increase in the time required for anesthesia
	Atorvastatine	Reduced effectiveness of

		Atorvastatin
	Bupropion	Orofacial dystonia / Decreased concentration of Bupropion in the blood
	Buspirone	Hypomanic episode, serotonin syndrome
	Chlorzoxazone	Increased serum levels of hydroxychlorzoxazone/ chlorzoxazone
	Cyclosporine	Decreased concentration of Cyclosporine in the blood
	Digoxin	Decreased concentration of Digoxin in the blood
	Eletriptan	Serotonin syndrome
	Fexofenadine	Decreased concentration of Fexofenadine in the blood
	Gliclazide	Decreased concentration of Gliclazide in the blood
	Imatinib	Decreased concentration of Imatinib in the blood
	Indinavir	Decreased concentration of Indinavir in the blood
	Irinotecan	Decreased concentration of SN-38 (the active metabolite of Irinotecan) in the blood
	Ivabradine	Decreased concentration of Ivabradine in the blood
	Loperamide	Acute delirium
	Mephenytoin	Increased urinary excretion of Mephenytoin metabolites
	Methadone	Decreased concentration of Methadone in the blood
	Midazolam	Decreased concentration of Midazolam in the blood
	Nefazodone	Serotonin syndrome
	Nevirapine	Decreased concentration of Nevirapine in the blood
	Nifedipine	Decreased concentration of Nifedipine in the blood
	Omeprazole	Decreased concentration of Omeprazole in the blood
	Oral contraceptives	Alteration of pharmacokinetic parameters of oral contraceptives, resulting in reduced efficacy
	Paroxetine	Serotonin syndrome
	Phenprocoumon	Decreased concentration of Phenprocoumon in the blood
	Prednisone	Manic episodes
	Rosuvastatin	Decreased efficacy of Rosuvastatin
	Quazepam	Decreased concentration of Quazepam in the blood
	Sertraline	Serotonin syndrome
	Simvastatin	Decreased concentration of Simvastatin in the blood
	Tacrolimus	Decreased concentration of Tacrolimus in the blood
	Talinolol	Decreased concentration of Talinolol in the blood
	Teophylline	Decreased concentration of

		Theophylline in the blood
	Tibolone	Acute hepatitis
	Venlafaxine	Serotonin syndrome
	Verapamil	Decreased concentration of Verapamil in the blood
	Voriconazole	Transient increase followed by decreased blood concentration
	Warfarin	Increased Warfarin clearance and reduced anticoagulant effect
	Zolpidem	Decreased concentration of Zolpidem in the blood
Valeriana (*Valeriana officinalis*)	Loperamide	Acute delirium
	Lorazepam	Hand tremors, dizziness, increased pulse and muscle fatigue