

Impact of herbal supplements nowadays: an overview

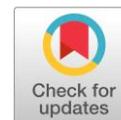
L.I. Ramirez ^{*}, O.N. Kanwugu ^{*} , M.N. Ivantsova ^{*} 

Institute of Chemical Engineering, Ural Federal University, Ekaterinburg 620002, Russia

^{*} Corresponding author: liz170496@gmail.com, nabayire@gmail.com, mivantsova@mail.ru

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Abstract

At present, people around the world are looking for more natural alternatives for treating all kinds of health conditions as well as improving the general wellbeing. As such, the consumption of herbal supplements has increased globally, generating billions in revenue. The use of these herbal products is firmly rooted in the traditional use of medicinal plants for disease prevention and treatment, practiced in several cultures. Although herbal products are recognized by the WHO as an essential component of the healthcare system, there have been increasing concerns regarding their quality and safety. Generally, herbal products are not strictly regulated as they are largely categorized under dietary supplements, thus escaping the rigorous scrutiny meted out to pharmaceuticals. Notwithstanding that many consumers generally perceive herbal products as benign and inherently safe, several reports have shown that herbal products can induce mild to acute adverse effects of clinical significance. Moreover, some herbal products on the market have been reported to be contaminated with microorganisms, environmental toxins, and adulterants. Furthermore, evidence regarding the efficacy of herbal supplements is extremely discrepant.

Keywords

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Key findings

- Herbal medicine remains an integral health resource globally, patronized in developed as well as developing countries.
- Regulation of herbal products has intensified over the years, but their classification is still inconsistent.
- Herbal products can cause adverse effects particularly if they are contaminated and should be taken with caution.

1. Introduction

With a resurgence of interest in a change in lifestyle trend towards a “return to nature”, complementary and alternative medicine (CAM) has grown steadily over the past decades to become a part of everyday life for the general population aimed at maintaining health and preventing diseases. The world health organization (WHO) recognizes CAM as an integral but often undervalued health resource, particularly in the prevention and management of chronic lifestyle-related diseases that require lifelong pharmaceutical medication [1]. Dietary supplements including botan-

icals and nutritional products are probably the most prevalent and commonly used CAM.

The use of herbal supplements, also called herbal/botanical products or phytomedicines, dates back millennia. Their usage is grounded in the traditional use of medicinal plants to prevent, alleviate, or cure various ailments in several cultures such as traditional Chinese medicine in China, Ayurvedic medicine in India, Kampo medicine in Japan, Aboriginal medicine in Australia, TeRongoā in New Zealand, Unani medicine in Muslim culture in South Asia and modern-day Central Asia, African and Native American ethnomedicines [2, 3]. Medicinal plants are endowed with a rich ensemble of biologically and pharma-

cologically active compounds, which are responsible for their renowned health benefits. In fact, a large part of existing prescription medications is derived from plants used in traditional medicine, with yet another significant portion being synthetic analogs of phytochemicals [3]. Although there is no internationally recognized definition, herbal supplements are generally products made from botanical elements and in some cases algae or fungi intended for internal use to enhance health [4]. The rising cost of conventional pharmaceuticals as well as the increasing awareness of consumers of their unwanted side effects, in part, drives the growing interests in herbal products. In addition, herbal products are perceived by many to be inherently safe as they are made from natural ingredients; moreover, they are readily available, cheap and culturally acceptable [5]. At present, there are about 30000 herbal products, if not more, available on the global market, representing the second largest dietary supplement segment after vitamins and minerals [6]. They are available as capsules, tablets, elixirs, teas, liquid extracts, oils as well as powdered and chopped “free-standing” dried material [7].

However, unlike vitamins and minerals, the evidence for the effectiveness of these plant-based products is extremely discrepant and in most cases is not supported by hard data [8]. In addition, compared to conventional drugs as well as vitamins and minerals, the regulatory requirements of herbal products are less stringent. Depending on the legislation of the country they are being marketed in, herbal products are presented under several descriptions, including traditional medicines, herbal medicines, natural health products, dietary supplements, plant food supplements, nutraceuticals, food supplements, etc., contributing to the poor regulation of these products on the global market [2]. As the uses of herbal products are increasingly becoming prevalent around the world, several issues are raised concerning their quality, safety and efficacy. The preparation of these products is not standardized, and they may vary in consistency, constituents, quality and efficacy between batches and among manufacturers. Besides, it is known that the composition as well as the concentration of phytochemicals in the same plant species is greatly influenced by the cultivation conditions, geographical location, part and age of plant [3].

Beyond these, while most of the phytochemicals in medical plants used in herbal products have therapeutic properties, some are inherently toxic, exhibiting hepatotoxic and nephrotoxic effects among others. Some herbal products may as well be contaminated with environmental toxins and microorganisms. In addition, some have been found to be adulterated with banned ingredients [9]. Thus, notwithstanding that these products are generally promoted as natural and assumed by many consumers to be always safe, several reports have shown that herbal products can induce mild to clinically significant adverse effects including gastrointestinal discomfort, allergic reactions, nausea, vomiting, diarrhea, chronic toxicity and, most importantly, interaction with drugs [10]. It was re-

ported that about a quarter of patients use herbal products and conventional drugs simultaneously [11]. Like prescription medications, herbal products contain chemically and biologically active substances; thus, there is a possibility of herb-drug interaction when they are present concurrently in the body. These interactions affect the pharmacological and toxicological effects of these substances and could be potentially deleterious [6].

This article discusses the usage of herbal supplements, their regulation as well as the associated safety issues.

2. Global usage and market

For thousands of years, several cultures have developed and used herbal medicine for the maintenance of health and in prevention and treatment of diseases, as part of the traditional medical systems, particularly in Eastern countries and the African continent [2]. However, the western world, until recently, has used herbal products only for the treatment of minor medical symptoms like cold and stomach upset [12]. In recent times, the general increase in wealth and improvements in living standards have resulted in a greater investment in health care and healthcare products [13]. With hopes of preventing chronic diseases, particularly those related to lifestyle, the use of herbal products is, nowadays, globally widespread but recognized in varying degrees in different countries. In Asia and Africa, for instance, traditional medicine, particularly herbal medicine, generally coexists with modern medicine in the healthcare sector as a complementary or alternative therapy; however, there is tension and collision between these two in Europe and particularly the US [2, 14]. All the same, complementary/alternative therapies are progressively being integrated into the healthcare system of the West, as the number of patients demanding herbal therapy keeps growing [15].

It is estimated that about 80% of the global population and as much as 95% of the population in developing countries to some extent rely on herbal medicine for their primary healthcare needs [3]. In the US, it is estimated that about 50% of the population use herbal products [16]. On the other hand, more than two thirds of the population in Canada and Germany have used herbal medicine at least once [3]. Likewise, in other developed countries such as France, Australia, and Belgium at least one-third of the population is estimated to have used CAM at least once for healthcare [10], with herbal medicine likely constituting a core of it. In China, herbal medicines are projected to account for between 30% to as much as 50% of total drug consumption. Similarly, about 30% of Malaysians use traditional herbal medicine for their health needs [9]. In most African countries like Ghana, Nigeria, Mali and Zambia, however, herbal medicine is the major treatment option at home, representing up to 60% or perhaps more of home remedies [3]. In the Western world where herbal medicine is used not as a primary therapy but more of a

health-conscious lifestyle habit, its use is prevalent among females, the young and the middle aged, the affluent and the erudite [13, 15]. Unsurprisingly, there is a rise in herbal products and CAM usage among children as a result of increased parental awareness of CAM therapies and a conscious desire by parents to limit the amount of drugs consumed by children [13]. The use of herbal products is also common among cancer patients and people living with HIV/AIDS; it is reported that 32–70% of cancer patients and 75% of HIV/AIDS patients use herbal formulations [3, 13].

The size of international market for herbal products and dietary supplements as a whole is massive and continues to increase, with a current global market value of roughly over US\$ 60 billion [16]. As far back as 2000 a BBC survey reported that UK users spend on average £13.6 per month on CAM including, but not limited to, herbal products, resulting in a projected annual expendi-

ture of £1.6 billion nationwide [17]. Between 2007 to 2009 the market of complementary medicines (such as herbal products, essential oils etc.) is estimated to have grown by 18% in the UK [4]. As of 1997, the sales of herbal products in France and Germany amounted to US\$ 1.1 billion and US\$ 1.8 billion respectively [4]; it thus reasonable to project that the current market value of herbal products in these countries exceeds the aforementioned values. In the US, consumers spent an estimated US\$ 8 billion in 2018 and 9.6 billion in 2019 on herbal supplements [18]. Similarly, in China, trade volume of herbal medicine products was pegged at around US\$ 6.2 billion in 2019, a significant increase from that of 2018 [19]. In Malaysia, the market value of the herbal industry is estimated to grow by 8–15% annually and was projected to hit MYR 32 billion in 2020 [9]. Some of the commonly used herbal supplements are presented in Table 1.

Table 1 Commonly used herbal products.

Common Name (Scientific name)	Applications	References
Aloe Vera (<i>Aloe Vera</i>)	Used topically for burns, psoriasis and osteoarthritis. It also used in the oral form for digestive issues such as gastritis or constipation.	[20]
Black cohosh (<i>Actaea racemosa</i>)	Used to treat hot flashes, night sweats, vaginal dryness, menopausal symptoms, dysmenorrhea and vaginitis.	[21, 22]
Chamomile (<i>Matricaria recutita</i>)	Used topically for skin conditions. Also used to treat anxiety, stomach upset, gas and diarrhea.	[23]
Echinacea (<i>Echinacea purpurea</i>)	It is colds, bronchitis, flu, and respiratory infections. Additionally, it is used as an immune booster.	[21]
Flaxseed (<i>Linum usitatissimum</i>)	It has long been used for cardiovascular protection and as a laxative. It is also used for managing hyperlipidemia, atherosclerosis, diabetes mellitus, obesity, menopausal symptoms and premature labor. It is a good source of fiber and omega-3s.	[23]
Ginkgo (<i>Ginkgo biloba</i>)	Used to treat memory and cognitive problems particularly those associated with aging. It is also an effective adjuvant therapy for schizophrenia. Additionally, it is used in asthma, autism spectrum disorder, chronic obstructive pulmonary disease and depression.	[21, 23]
Peppermint oil (<i>Mentha piperita</i>)	Used to treat digestion problems such as nausea, indigestion, stomach problems and bowel conditions.	[24]
Soy (<i>Glycine max</i>)	Used to treat menopausal symptoms, memory problems and high cholesterol levels.	[25]
St. John's Wort (<i>Hypericum perforatum</i>)	Used to treat depression and anxiety. It is also reported to be effective in the treatment of menopausal symptoms, somatoform disorders, attention-deficit hyperactivity disorder, (ADHD), angioplasty, glioma, migraine headaches, obsessive-compulsive disorder, polycystic ovary syndrome, and premenstrual syndrome.	[23]
Tea tree oil	Used topically to treat several conditions including, acne, athlete's foot, nail fungus, wounds, infections, lice, oral yeast infection (thrush), cold sores and dandruff.	[26]
Evening primrose (<i>Oenothera biennis</i>)	It is used to treat ADHD, asthma, atopic dermatitis, chronic fatigue syndrome, dry eye syndrome, dyslexia, hyperlipidemia, obesity, premenstrual syndrome, diabetes mellitus, rheumatoid arthritis, and ulcerative colitis.	[23]
Feverfew (<i>Tanacetum parthenium</i>)	It is commonly used for treating migraine headaches and menstrual cramps. It has also been used to treat allergies, arthritis, psoriasis, fever, headache, tinnitus, vertigo, menstrual irregularities.	[23]
Garlic (<i>Allium sativum</i>)	Garlic is generally used for cardiovascular conditions, including high cholesterol and triglyceride levels associated with the risk of atherosclerosis.	[27]
Ginseng (<i>Panax quinquefolius</i> L. <i>Panax ginseng</i> , and <i>Panax japonicus</i>)	Used as a general tonic to increase overall body tone. It is considered helpful in elevating energy levels, enhancing physical and mental performance as well as improving resistance to stress. It also used to treat erectile dysfunction, and strengthen the immune response.	[21, 22]
Goldenseal (<i>Hydrastis canadensis</i>)	It is famous for its healing and antiseptic properties and used commonly for colds and flu. It is also popular for soothing the nose lining when it is inflamed or sore. In addition, treat skin and eye infections and gastrointestinal irritation.	[21, 22]
Hawthorn (<i>Crataegus monogyna</i>)	It is used mostly for managing heart-related conditions such as treatment of angina, atherosclerosis, heart failure, and high blood pressure.	[21]
Saw palmetto (<i>Serenoa repens</i>)	It is currently being used to treat enlarged prostate. It has also been used to treat genitourinary symptoms, relieve inflamed mucous membranes, increase testicular function and increase breast size.	[21]

3. Regulation of herbal products

In general, the classification and, consequently, regulation and legislation regarding herbal products varies among countries, even among those within the same political and economic region such as the EU [16, 28]. They are generally classified as either dietary supplements or over-the-counter drugs; nevertheless, their regulations are largely different from those governing pharmaceutical drugs – they are less stringent [9, 23]. Compared to Germany, Japan and China, herbal supplements are less strictly regulated in the US.

The FDA considers herbal supplements as foods and not drugs; for this reason, they are not subject to the same regulations and standards of testing, manufacturing and labeling as conventional drugs. According to the FDA, “dietary supplements are not intended to diagnose, treat, cure, or prevent disease” [23]. As a result manufacturers of herbal products are currently at liberty to make structure-function claims that explain how the product can influence different actions in the body without pre-approval of the FDA. The FDA, however, prohibits disease treatment claims by herbal products since they have not been subjected to rigorous clinical trials. Unlike pharmaceuticals, new herbal products do not require premarket approval by the FDA before they hit the market; they only need to conform with the Dietary Supplement Health Education Act of 1994 [16, 23]. Although, currently, the FDA mandates manufacturers to adhere to the Good Manufacturing Practices (GMPs) established in 2007, evaluation of product safety and accurate labeling before products are sold on the market remain the responsible of the manufacturers. The FDA only has the authority to evaluate and recall these products in case of violations after they appear on the market [23].

Under the umbrella of the EU, herbal products considered as medicine fall within the jurisdiction of the European Medicines Agency and are governed according to the European Guideline 65/65/EEC. However, with regards to other herbal products except for spices and flavouring agents, there is no unified EU legislation and thus herbal products are largely regulated according to national laws. In general, at the national level, products that make health/therapeutic claims or are deemed to have therapeutic activity by the regulatory body are classified as medicine and, as such, full registration, including the information about quality, safety and efficacy, is required, according to national legislations [28, 29]. This notwithstanding, legislation and regulation of herbals vary greatly from country to country, with each having its own list of exemptions. Some countries, such as Germany and the UK, make extra provisions to recognizing and regulate other herbals, which do not fit the above category as dietary supplements; countries like France and Ireland, on the other hand, treat all herbals equally as medicinal products [28]. As a result of this, some herbals are marketed as

dietary supplement in some EU-member countries and as drugs in others [29].

4. Quality and safety concerns

In general, it is expected that any pharmacologically active agent has the potential to elicit adverse reactions due to the functional or structural connection with or because of the similarity in sensitivity to off-target processes [30]. Given that herbal products are not strictly regulated by the authorities and scientific information on their dosage and toxicity is scanty, usage of herbals is associated with an increased risk of side effects. In fact, it has been reported in medical literature that commonly used herbals such as ginkgo, garlic and St. John’s wort can cause mild to severe adverse effects [23]. The Uppsala Monitoring Centre of the WHO reported that over a period of 20 years (1968–1997) a total of 7874 cases of adverse health effects involving herbal medicines were recorded in 55 countries, with anaphylactic reactions being the major recorded adverse effect. However, 21 deaths were reported to be associated with these adverse effects during this period. The other reported adverse health effects associated with herbal medicines included face oedema, bronchospasm, circulatory failure, hypertension and intestinal obstruction. Most of the reported adverse effects were associated with opium alkaloids total, evening primrose oil, peppermint oil, psyllium hydrophilic mucilloid and senna [31]. Also, in a 5-year toxicity study of Traditional Remedies and Food Supplements, Shaw et al. reported 12 confirmed cases of adverse effects, 10 of which were related to Chinese and Indian herbal products [32]. Furthermore, out of 491 patients who admitted to taking at least one herbal component in a 5-month survey at an urban university general hospital in Italy, 9.6% reported adverse effects related to gastrointestinal (associated with dandelion, propolis, and fennel), cardiovascular (associated with liquorice, ginseng, and green tea), dermatological (in connection with propolis, thyme, arnica, and passion-flower) as well as neurological problems (linked with guarana and liquorice) [33].

These adverse effects arising from the use of herbal products are attributed to two factors: intrinsic and extrinsic toxicities [10]. Herbal products generally consist of a plethora of phytochemicals, responsible for their often-remarked multi-target effects, any of which could interfere with off-target pathways leading to undesirable effects [4, 6]. Also, metabolism of these compounds in herbals could lead to long-term organ (i.e. liver, kidney) damage. These side effects are the results of the inherent components of the herbals, which can be exacerbated by overdosing, considering that there is generally no clinically-backed evidence for the dose of these herbal products [10]. Besides, extrinsic factors particularly related to product quality such as misidentification of starting

herbal materials, contamination and adulteration could lead to major adverse health effects [34]. It is interesting to note that most of the severe adverse effects related to the use of herbals have to do with the product quality [30]. Although manufacturers are expected to abide by the GMP, poor handling and storage as well as unhygienic production processes result in herbal products being contaminated with microorganisms, particularly fungi and bacteria, as well as mycotoxins [10]. The issue of microbial contamination is an age-old problem of the food industry, and herbal preparations are no exception. For instance, Hong Kong's Department of Health at one point had to recall 17 proprietary Chinese medicines because they had been found to contain total bacterial count more than the maximum permitted limit, while in Croatia, fungal contamination was found to be high in the samples of medicinal plant materials and herbal teas [4].

Also, since herbal materials are cultivated on land, they can be contaminated with pesticides and heavy metals. Several studies have shown that a considerable number of commercially available herbal products are contaminated with heavy metals of special public health concern such as lead, arsenic and mercury beyond permissible recommended limits [4]. Additionally, pesticide residues have been reported in medicinal plants [35]. Adulteration of herbal products is likewise a serious quality and safety concern globally. Indeed, there have been reports of adulteration in almost every country. In a recent review by Ichim et al., the authors observed that over a quarter of 2386 commercial herbal products sold in 37 countries were reported to be adulterated [36]. The adulterants in these cases included fillers, banned substances, and substituted species, with some products completely lacking labeled botanical ingredients. Many herbal products have been reported to be adulterated with active pharmaceuticals such as corticosteroids, non-steroidal anti-inflammatory drugs, analgesics, benzodiazepines, and many others [30]. In Taiwan, for instance, it was reported that around 23.7% of commercially sold traditional Chinese medicines are adulterated with drugs [10]. Because the adulterants are always not declared, there is a high possibility of overdose.

Considering that herbal products are often used in conjunction with conventional prescription medicines, one of the major clinically significant safety concerns that has been in the limelight is the issue of potential adverse drug-herbal interaction. The evidence to this effect is, however, still limited, with majority of information coming from only the case reports. This notwithstanding, possible drug-herbal interactions based on these clinical reports and theoretical knowledge of the interaction between specific classes of compounds are available (Figure 1).

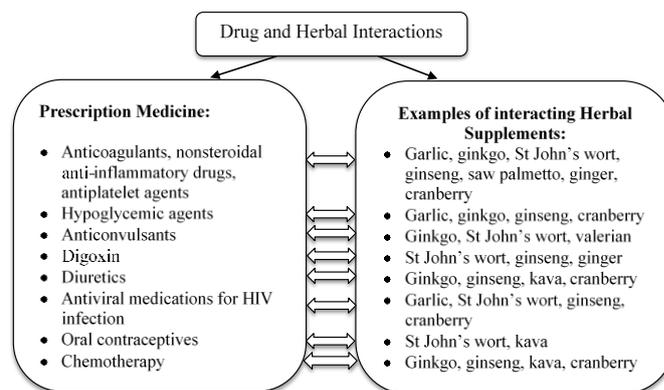


Figure 1 The drug-herbal interactions.

5. Pharmacokinetic and pharmacodynamic Drug-herbal Interactions

Herb-drug interactions may manifest in either pharmacodynamic or pharmacokinetic manner. Pharmacodynamic interactions, in general, occur less frequently and involve direct pharmacologic actions of the interacting agents that are unrelated to changes in blood concentrations of the herb or drug. Risk of a pharmacodynamics interaction occurs when an herbal supplement has a direct effect on the mechanism of action of a co-administered drug by manipulating molecular targets involved in the physiological responses of the drug. This may antagonize or exacerbate the drug's clinical effects without changing its concentration. In most cases, a change in drug dosage does not counter a pharmacodynamics herb-drug interaction [6, 10, 37].

Clinically important herb-drug interactions typically manifest as pharmacokinetic interactions, which affect both the drug's concentration in the blood and the pharmacologic action. This type of interaction involves movement of the drug through the body from absorption to excretion [23]. Risk of a pharmacokinetic interaction occurs when the herbal supplement shares the same mechanism of absorption, distribution, metabolism, or excretion as a co-administered drug [38]. Competition between the herbal supplement and the drug for a shared ADME mechanism may result in a change in the drug's concentration at the site of action [39]. In many cases, pharmacokinetic interactions can be safely countered by adjusting the drug's dosage.

6. Conclusions

Herbal supplements are used extensively worldwide for the treatment and management of many diseases. Many consumers consider them safe and good for them due to their natural ingredients; this, however, is not necessarily true. There have been several reported adverse effects of herbals, ranging from mild side effects to clinically significant conditions, resulting from acute toxicity or chronic/cumulative toxicity. These toxicities could be intrinsic, related to the inherent components of herbal or extrinsic, related to microbial/chemical contamination and adultera-

tion. The most significant adverse effects usually occur due to pharmacokinetic/pharmacodynamic herbal-drug interactions. Aside from this, herbs products do not go through the same rigorous control and testing as conventional medicines. Thus, although herbal supplements are, at present, an essential part of our everyday life, care should be taken about their consumption. In addition, governing bodies should step-up the regulation of these products.

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Author contributions

Conceptualization: L.I.R., O.N.K., M.N.I.

Data curation: M.N.I.

Formal Analysis: L.I.R., O.N.K., M.N.I.

Funding acquisition: L.I.R., O.N.K., M.N.I.

Investigation: L.I.R.

Methodology: L.I.R., O.N.K., M.N.I.

Project administration: O.N.K., M.N.I.

Resources: L.I.R., O.N.K., M.N.I.

Software: L.I.R., O.N.K., M.N.I.

Supervision: M.N.I.

Validation: L.I.R., O.N.K., M.N.I.

Visualization: L.I.R., M.N.I.

Writing – original draft: L.I.R., O.N.K.

Writing – review & editing: O.N.K., M.N.I.

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The authors declare no conflict of interest.

Additional information

Authors' IDs:

Kanwugu, Osman N., Scopus ID [57195573903](https://orcid.org/0000-0001-9148-1000);

Ivantsova, Maria N., Scopus ID [6507519617](https://orcid.org/0000-0001-9148-1000).

Website of

Ural Federal University: <https://urfu.ru/en>.

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