

Medicinal Herbs in Clinical Practice: How to Prevent Adverse Effects

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Abstract

Medicinal herbs are readily available in the markets or stores as OTC products and are widely used in Turkey and all over the world. According to recent surveys, the majority of people who use herbal medicines do not inform their physicians about their consumptions which may end up in adverse effects and/or toxicity. Contrary to common beliefs that “naturals are safe”, medicinal herbs may also cause significant toxic effects, drug interactions and even morbidity or mortality just like prescription drugs. The purpose of this review article, summarizing the adverse effects, toxic effects and possible interactions with prescription drugs associated with use of medicinal herbs, is to raise the awareness of healthcare professionals.

Key words: phytotherapy, toxicity, adverse effects, drug interactions

Klinik Uygulamada Tıbbi Bitkiler: Yan Etkiler Nasıl Engellenebilir

Özet

Market veya mağazalarda reçetesiz satılan ürünler olarak satılan tıbbi bitkiler, tüm Türkiye’de ve dünyada yaygınla kullanılmaktadır. Son yapılan araştırmalar, hastaların çoğunun, advers etki ve/veya toksisiteye neden olabilecek tıbbi bitki kullanımından hekimlerine hiç söz etmediklerini ortaya koymaktadır. ‘Doğal olan zararsızdır’ şeklindeki yaygın inanışın tersine, tıbbi bitkiler de reçete edilen ilaçlar gibi önemli toksik etkilere, ilaç etkileşimlerine ve hatta mortalite veya morbiditeye yol açabilmektedir. Tıbbi bitki kullanımı ile ilişkili toksik etkiler ve reçete edilen ilaçlar ile etkileşimlerini özetleyen bu derleme makalesi, sağlık çalışanlarının bu alandaki farkındalığını artırmak amacı ile yazılmıştır.

Anahtar sözcükler: Fitoterapi, yan etkiler, toksik etkiler, ilaç etkileşimleri

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Introduction and General Information

The term “phytotherapy” refers to the use of herbs in different forms for medical purposes. History of treatment with medicinal herbs extends to Sumerian, Akkadian and Assyrian civilizations once reigned in Mesopotamia (Nineveh Tablets dating back to 3000s BC).

Supplying medicinal herbs include two main ways; either direct gathering from nature or cultivation. Actually, herbs which contain the richest active substances are generally handpicked in nature. On the other hand, plant-cultivation protects the nature, increases yield

and enables provision of standard, high-quality samples which are resistant to the diseases.

Meicinal herbs can also be reproduced via an in vitro method called “tissue culture”, by using genetically modified seeds. Heat, light, precipitation, soil composition and altitude requirements of herbs should be considered and GAP (Good Agricultural Practice) rules should be complied with as per GMP (Good Manufacturing Practice) and/or ISO (International Organization for Standardization) certification in order to cultivate high-quality and fertile products. In Turkey, medicinal herbs started to be cultivated according to the “Organic Agriculture Law” in 2004 and regulated by “Regulation on Principles and Implementation of Organic Agriculture” (Official Gazette Nr 25841) in 2005 and regulations published in 2010 (Official Gazette, n.27721). There are more than 11.000 higher plant species found in Turkey, one third of which are endemic. Approximately 2000-3000 of these

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herb species are estimated to have potential to be explored as medicinal herbs^{1,2}.

Medicinal herbs recently have become very popular in Turkey as well as in the rest of the world³⁻¹⁰. Consequently, reports of adverse reactions based on their interactions with prescribed drugs have also increased proportionally. Because medicinal herbs may also be associated with serious adverse effects and drug interactions. However, insufficient number of scientific evidences and lack of strict control by official authorities can give consumers a false sense of 'security' about herbal medicines¹¹⁻¹³. Thus the safety and quality of herbal medicines have become a very important concern for public health.

Medicinal Herb As a Drug

The World Health Organization (WHO) describes the term "drug" as the substance or mixture of substances used in the treatment, alleviation, diagnosis and prevention of diseases. A drug should have a dose-dependent and temporary effect only on pathological state and should not affect other structures and physiological activities of the organism. In the light of this concept, medicinal herbs should meet the following criteria to be regarded as drugs;

- Pharmaco-toxicologic profiles, bioavailability, pharmacokinetic and pharmacodynamic properties,
- Reliability, effectiveness and acceptable adverse effect profile,
- Standard dosage and shelf-life.

Most important factors to be considered as an effective and reliable phytotherapy applications are the quality and reliability of the products, successful management of product-control mechanisms, and successful detection of individual features of consumers.

Lack of sufficiently updated information and evidence in this field sometimes results mainly from insufficiency of both related knowledge of healthcare professionals and of the number and method of adverse effect records and empirical/clinic findings. Also it is a huge necessity to detect and describe possible risks which can arise during the use of herbs along with the present drugs in a detailed and cautious manner. So there could be some necessary measures to minimize such risks. Patients fail to duly inform their physicians about medicinal herbs they consume and, in turn, physicians fail to question such information, which generally results in failure to notice herb-drug interactions¹⁴.

Adverse Effects Associated with Medicinal Herbs

An adverse effect is a harmful, undesired reaction resulting from a drug administered in normal dosage for diagnostic, prophylactic or treatment purposes or to change a physiological response. In phytotherapy, toxic effects may result from interactions of many foreseeable and unforeseeable factors between herbs, drugs and patients. Adverse effects associated with herbal medicines can occur in several ways (Table 1):

Table 1. Adverse effects associated with herbal medicines

1. Individual reactions	respiratory irritation, contact dermatitis
2. Adulteration and contamination	substances or molecules included, microbiological contamination
3. Pharmacologic and toxic reactions	side/toxic effects, excessive dosages or use for a longer-than-recommended period
4. Lack of quality control	environmental conditions, agricultural factors, production technologies
5. Medicinal herb-prescribed drug interactions	increased or decreased metabolism, interacting with drug

1. Individual reactions

Children, pregnant, patients who have organ failures or aged people as well as atopic persons could be more vulnerable and consuming of medicinal herbs should be made in caution or limited for this population. Most severe and frequent adverse effects observed in phytotherapy are recorded to be allergic reactions. In a hospital-based study, 15% of the self-poisoned cases were recorded as the possible toxic effects of traditional herbs¹⁵.

In oral or topical administrations, it is also possible to see reactions resulting from individual sensibilities. For instance, essential oil odour in aromatherapy may lead to some problems particularly due to respiratory irritation. Contact dermatitis cases were recorded in use of feverfew for migraine attacks¹⁶.

2. Adulteration and contamination

Some herbal preparations may contain undeclared foreign substances which called as adulteration. Moreover, due to deliberate inclusion of a substance or contamination may also lead to the effect as well as to adverse-toxic effects. For instance; amount of sibutramine included in Lida (a weight loss drug) has been

found to be three times higher than the prescription dosages¹⁷.

Different substances or molecules can be included, particularly, in ginseng and in green tea formulations (Figure 1, 2). At least 3-4 weeks are required generally to see the physiological effects of ginseng. For this reason; "caffeine", "cola extract" or similar mixtures are sometimes added into ginseng to prevent users from giving up its consumption before the specified period, up to when it is possible to see the physiological effects. Any person who consumes "Additive-containing Ginseng" formulation develops addiction to this product from the very first day on one hand and may be exposed to typical side effects of caffeine on the other hand. Significant amounts of caffeine can also be added into green tea formulations. Upon development of recurrent and persistent hypoglycemic attacks in a diabetic patient who had been taking a preparation called "ZhenQi" for the last five years for his diabetes, the mentioned preparation was found to contain glibenclamide (glyburide, SU)¹⁸. Similarly in England, glycemic control could not be achieved in a 48-year old patient despite shifting from oral antidiabetic treatment to insulin+metformin treatment. The patient, whom glycemic control improved after his travel to India, suggested 3 herbal products he used in India as the reason behind such improvement. However, as these three products were examined, it was found to contain chlorpropamide¹⁹.



Figure 1. Camellia sinensis (green tea)



Figure 2. Panax ginseng

Samples collected from 53 Asia-origin products sold in Vietnam, Hong Kong, Florida, New York and New Jersey were analysed in terms of heavy metal addition. This analysis revealed that these products contained arsenic, lead and mercury at dosages significantly above the acceptable levels and/or even at toxic level²⁰.

Microbiological contamination; pathogenic bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella* sp., etc.) or toxins (aflatoxins, bacterial endotoxins); or inclusion of the herbal/chemical compounds which have toxic effects; environmental wastes (agricultural chemicals, pesticides, fumigants, ethylene oxide, methyl bromide, etc); and radiation exposure may also lead to some adverse/toxic effects. It was reported in a previous study that 9 of 12 heavy metal poisoning cases resulted from Asian herbal preparations²¹.

3. Pharmacologic and toxic reactions

Each herb is composed of many of components and each component may have a different physiological effect. These effects may be beneficial as health preventive, or remedial but sometimes also toxic. Adverse effect risk, which can only be observed in active use period of a drug, may also be recorded -even at lower frequencies- in herbal drugs used for hundreds of years. The low-effect capacity of high number of components results in lower adverse effect risk, which is an advantage for medicinal herbs. However, synergism between multiple components in a plant remedy may increase desired effect on one hand but may also potentialize some undesired effects on the other hand. However, no sufficient clinical evidence has been achieved to clarify this issue.

Improper use of herbal preparations frequently leads to some adverse effects as well. For instance, it is possible to see side/toxic effects resulting from excessive dosages or use for a longer-than-recommended period. A 85-year old patient with longer-than-5 years of constipation complaint was examined for possible reasons of constipation²². Then it was found that the patient used to drink senna tea every other day for 6 months. This senna formula included

senna, fennel, licorice, cumin and hibiscus. It was concluded that paralytic ileus developed in this patient was due to improper use of this herbal product.

4. Lack of quality control

There are many factors affecting the herb constituents, in turn, the quality of the herbal medicine product. Therefore the quality of active substances in medicinal herbs is affected by many factors such as environmental conditions (climate, humidity, heat/light exposure), agricultural factors (soil/ground properties, irrigation/fertilization, harvest time, growth process of the herb), and production technologies (drying-processing-storage conditions). In addition, deliberate or undeliberate applications and packaging may result in destruction of the product purity. In this case, either adulteration or allopathy occurs.

It is generally quite impossible to know whether the informed content and/or labels of the herbal products exactly match with the real product content. Some additives are not documented in the packages. Moreover, it is still impossible for official authorities of many countries to prohibit introduction of the product into the market without "toxicity warning" on them. Unfortunately, dietary supplements-herbs in the market cannot be intervened until they have been found to have harmful effects.

Adverse and/or toxic effects may also be caused accidentally by use of 'wrong' herbs. For instance, use of *Aristolochia manchuriensis* (Ma Tong) and *Aristolochia fangchi* (Fang-chi) rather than *Stephania tetrandra* in a slimming clinic in Brussels in 1993 resulted in hundreds of nephrotoxicity cases²³. These patients required dialyses and other renal procedures (Aristolochic acid nephropathy).

When prepared or mixed unconsciously, multi-compound formulations may give raise to adverse effect risks. Some products marketed in New Zealand and in many other countries under the name "bomb" or "ecstasy" were analyzed due to reported side effects of palpitation, drowsiness and hypertension. Drug was decided to be withdrawn from the market since the analysis revealed ephedrine content of the drug²⁴.

In phytotherapy, it is also possible to encounter some adverse effects resulting from wrong processing of herbs. For instance, lupine has been reported to have anticholinergic toxicity induced by lupine alkaloids²⁵.

5. Medicinal herb-prescribed drug interactions

Possible interactions of medicinal herbs with prescribed drugs may also induce some adverse and/or toxic effects. These effects may manifest themselves through a few mechanisms. By affecting the metabolism of the drug used, some medicinal herbs may reduce or increase the foreseeable effects of the drug. For instance; guar gum may delay gastric discharge and, in turn, reduce digoxin absorption. Similarly, herbs containing mucilage, pectin and polysaccharides (such as flaxseed and wheat bran) may also prevent absorption of, for example digoxins or statins from intestines and reduce their effects. St. John's Wort may also prevent absorption of cyclosporine and digoxin from intestines and/or speed up metabolism and discharge of the same. Moreover, St. John's Wort may also reduce bioavailability of verapamil and lead to increased metabolism of warfarin. When used with SSRIs (sertraline, paroxetine, etc.), St. John's Wort causes an increase in serotonergic effect and when administered together with MAOI (phenelzine), it may lead to headache and tremor²⁶.

Some medicinal herbs may increase bleeding risk. For instance, herbs with anticoagulant (fenugreek, garlic, Dong-Quai) and antiplatelet effect (Ginkgo biloba) may potentiate the anticoagulant effects of warfarin²⁷. For this reason, use of such herbs should be stopped during the peri-operation period and warfarin therapy. By interacting with anaesthetics, some other medicinal herbs may affect anaesthesia process and/or increase bleeding risk. For instance, Valerian and Kava -both of which have sedative effects- have the capacity to potentiate the effects of anaesthetics.

Green tea has been recorded to possibly reduce the effect of warfarin²⁸. One hundred gram of green tea (*Camellia sinensis*) leaves consists of 1428 mcg Vitamin K²⁹. Depending on the amount and concentration of green tea consumed, Vitamin K levels in blood circulation may change. Due to its hypertensive effects, *Siberian Ginseng* may decrease the effects of antihypertensive drugs. Since *Panax ginseng* may reduce warfarin effect, have oestrogen-like, and hypoglycaemic effects and decrease the effects of furosemide, warning should be made with related prescription drugs³⁰⁻³².

Discussion and Conclusion

Medicinal herbs have healing effects like all other drugs. Therefore special attention should be paid for the dosage, indications and contraindications of medicinal herbs and their interactions with each other or prescription

drugs. Unfortunately, these interactions have not been studied very well up to now.

Sources of herbs in the market and sold in herbalists should be analysed carefully. For instance, different herbs can be collected and marketed under the same vernacular name. In addition, cultivation period as well as harvesting, storage and transfer conditions (important in terms of aflatoxin contamination, pesticide residue, moisture content etc.) of an herbal drug may affect the preservation and/or toxicity of its agent.

One of the most important issues in the scope of control, certification and consumption monitoring of medical herbs is dosage standardization. To prevent any surprises in efficiency and drug interaction, medicinal herbs should be put up for sale in appropriate pharmaceutical forms and each form should be standardized. In other words, same physiological response should be created in the body by each unit of medical herb. Rather than subjective measures such as "hand full" or "a pinch of"; if necessary, these medicinal herbs should be processed appropriately with an additive with no effects on body and be developed into tablet, capsule, dragee or syrup forms.

Stabilization of medicinal herbs, i.e. setting a shelf life for these herbs, is also an important issue. Safety of a medicinal herb should be determined not only by its type of package or name of company, but also by scientific documents. Reliability of data written on the labels should be controlled and regulated by the laws. Herbal treatments should be considered as drug treatments and should be monitored by the Ministry of Health. All these measures could serve to diminish these concerns. As there is a growing tendency for the use of herbal preparations. On the contrary, tendency not to regard medicinal herbs as drugs can give rise to many problems for public health. It may not always be true to make comments such as "it is natural" "it has no side effects", "it is harmless" or "it has no effect at all" for any medicinal herb. Regardless of its source, any herb has the potential and possibility to show side effects/toxicity depending on its amount, administration period, individual properties and drug interactions. Similarly, herbs which contain highly-effective molecules with narrow therapeutic dosage range should not be used casually. However, books and publications prepared by herbalists and non-specialized individuals without any scientific control promote medicinal herbs and society is directed towards uncontrolled consumption of such

herbs. Therefore, presence of such herbs in herbalists and similar places may sometimes be quite dangerous.

Although there is a worldwide interest in using medicinal herbs, especially in our country where clinicians frequently encounter medicinal herb use, toxicity-cases induced by these preparations are not increasing significantly. This fact may be due to poor questioning of patients from this point of view, which leads to ignoring this matter or knowledge.

Training healthcare professionals about medicinal plants during medical college and postgraduate education might be critically important for raising the awareness in this issue. Also regulation and monitoring of medicinal herbs is of utmost importance in terms of general health.

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