

ETHICAL ASPECTS OF PHYTOTHERAPY

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The review is devoted to safety issues of herbal medicinal products. Apart from the most known adverse effects such as allergic reactions and irritation of mucous membranes, use of a number of herbal medicines results in hormonal disturbances, organotoxic reactions and CNS disturbances. The problem of intoxication is pressing in case of uncontrolled administration of herbal remedies, which is often accompanied by a carefree attitude towards them as natural and thus safe agents. This assurance is developed in the result of non-ethical advertising of dietary supplements in mass media. Finally, an important factor of safe therapy is comprehensive accounting of potential herb-herb and herb-drug interactions. The purpose of the article is to attract attention to a weighted attitude towards phytotherapy concerning its safety both in administration of traditional herbal medicinal products by doctors and during self-treatment by patients.

Key words: phytotherapy, adverse reactions, overdose, drug interactions

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ЭТИЧЕСКИЕ АСПЕКТЫ ФИТОТЕРАПИИ

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Обзор посвящен вопросам безопасности лекарственных растительных средств. Помимо наиболее известных нежелательных эффектов — аллергических реакций, раздражения слизистых оболочек, при применении целого ряда растительных средств могут возникать гормональные нарушения, органотоксические реакции, расстройства ЦНС. Актуальной является проблема интоксикации при бесконтрольном приеме препаратов растительного происхождения, зачастую обусловленная легкомысленным отношением к ним как «натуральным», а значит безопасным средствам. Такая убежденность возникает в том числе в результате неэтичной рекламы БАД в СМИ. Наконец, немаловажным фактором безопасности терапии является всесторонний учет потенциальных лекарственных взаимодействий фитопрепаратов между собой и с синтетическими лекарственными средствами. Цель статьи — привлечь внимание к более взвешенному отношению к фитотерапии с точки зрения ее безопасности, как при назначении лекарственных препаратов врачами, так и при самолечении пациентами.

Ключевые слова: фитотерапия, нежелательные реакции, передозировка, лекарственные взаимодействия

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Medicinal plants (MP) include wild and cultivated plants used to prevent and treat diseases that affect humans and animals. About 20 thousand of MP are currently used. According to WHO, about 70% of the world population treat herbal remedies as additional or alternative medicine [1]. A significant growth of consumption of MP both in traditional and official medicine has been found during the last years. This growth is due to several factors: over-the-counter sale of herbal medicinal products (HMP), use of MP as part of dietary supplements and affordability, in a number of cases (as compared with synthetic drugs). However, for the majority of phytotherapy apologists, an opinion about safety of plant-derived drugs is a determining factor while selecting a medication.

This can be explained by advertising of these agents and dietary supplements in mass media, which is sometimes far from being ethical. HMP are commonly used by population not by a doctor's prescription, but for self-treatment.

Along with certain advantages HMP have significant disadvantages associated with standards of their quality, safety and therapeutic effectiveness.

The issue of MP safety is of a great practical value, as in the Russian Federation, HMP account for up to 30% of the pharmacy assortment and are dispensed without a prescription [2]. Many consumers of HMP do not consult a doctor regarding safety and effectiveness of these products and take them in an uncontrollable manner, without considering indications and contraindications, concomitant diseases and drug interactions both between the active ingredients of separate plants if several herbal medicines are taken or, for instance, home-made herbal mixtures are used, and with conventional synthetic drugs.

Moreover, manufacture of HMP is associated with potential risks that influence effectiveness and safety of therapy: erroneous identification of MP (during collection, supply of raw material, etc.), raw material contamination (waste products of rodents, insects, pollen of other plants, etc.) or mixtures of similar plants (that are not biologically active at the most), instability of active ingredients, and variability of raw material collection [3].

Extensive experimental and clinical material that characterizes toxicity of certain biologically active substances

contained in MP has been accumulated lately. However, these data are not unified and not included into any national or international regulatory documents [4].

THE ISSUE OF TOLERANCE AND SPECIFIC ADVERSE REACTIONS OF HMP

Allergic reactions belong to the most frequent adverse effects of HMP. An irritant effect produced on the mucous membranes of the GIT and skin is quite common while taking HMP [5].

The MP that contain toxic substances are potentially dangerous. These MP are often included into herbal preparations; some of the preparations contain two potentially toxic substances. For instance, herbal mixtures to treat bronchopulmonary diseases can contain both marsh Labrador tea (*Ledum palustre*) and coltsfoot (*Tussilago farfara*). Even therapeutic doses of Ledole contained in marsh Labrador tea essential oils can produce an irritant effect and result in inflammation of the GIT mucous membrane [6]. Pyrrolizidine alkaloids within coltsfoot have a pronounced hepatotoxic effect [7]. Some mixtures used for therapy of gastrointestinal diseases contain three potentially toxic MP: absinthe (thujone), sweet flag (β -azarone) and peppermint (pulegone at minor concentrations). For instance, owing to thujone, absinthe can be responsible for vomiting, gastric and intestinal spasms. β -azarone, which is contained in sweet flag rhizome essential oils, has mutagenic and cancerogenic properties, whereas pulegone produces a hepatotoxic action [7]. It is dangerous because the majority of these substances are accumulated in the body, and their toxic effect is developed slowly [2].

Over 40 currently known medicinal herbs can cause hormonal changes in the body. Only some of them are used to produce medicinal agents and dietary supplements. In particular, products based on *Pygeum africanum*, *Serenoa repens*, *Vitex agnus-castus* and *Cimicifuga racemosa* are used to treat endocrine disturbances and diseases such as menstrual disorders, premenstrual syndrome, mastodynia, blood circulation and autonomic dysfunction during pre- and post-menopause, prostatic adenoma and prostatitis. In other medicinal products hormonal activity is taken as an adverse effect. Thus, herbs with oxytocin-like activity induce abortion (*Verbena officinalis*, *Harpagophytum procumbens*, *Cytisus scoparius*); medicinal herbs with corticosteroid activity increase blood pressure and cause electrolyte disbalance (*Panax ginseng*, *Eleutherococcus senticosus*, *Glycyrrhiza glabra*, *Myrica cerifera*); plants with a predominant estrogenic activity can cause microcirculation disturbances and thromboembolic complications (*Anisum vulgare*, *Asclepias tuberosa*, *Trifolium pratense*, *Ferula foetida*, *Glycine max*, *Humulus lupulus*, *Cimicifuga racemosa*) [8].

Intrinsic hormonal activity of such plants as *Anisum vulgare*, *Trigonella foenum-graecum*, *Verbena officinalis*, *Harpagophytum procumbens*, *Cytisus scoparius*, *Ferula assa-foetida* is found in *in vitro* and *in vivo* experiments. Hormonal activity of *Panax ginseng*, *Trifolium pratense*, *Pygeum africanum*, *Serenoa repens*, *Glycyrrhiza glabra*, *Glycine max*, *Humulus lupulus*, *Cimicifuga racemosa* and *Eleutherococcus senticosus* is confirmed both on animals and in clinical studies [9, 10].

It should be noted that some plants with intrinsic hormonal activity are widely used in food industry as well. For instance, humulus is widely used in brewing while fenugreek in cheese-making.

Some plants contain substances with a direct organotoxic activity. For instance, *Ledum palustre*, *Berberis vulgaris* and *Ruta graveolens* possess nephrotoxicity. *Artemisia absinthium*,

Petroselinum crispum and *Dryopteris filix-mas* have a neurotoxic action [2]. It means that patients have to be informed about the adverse effects by medical specialists.

The MP, that cause severe and life-threatening reactions or those with experimentally established cancerogenic, mutagenic and embryotoxic effects give rise to serious security problems. Thus, in accordance with available data, *Acorus calamus*, *Aristolochia franchi*, *Tussilago farfara*, *Symphytum officinale*, *Centella asiatica* have a potential cancerogenic effect [11]. These adverse reactions are developed slowly (for several weeks-months-years) and do not have clinically pronounced symptoms during the development.

OVERDOSAGE OF HERBAL MEDICINAL PRODUCTS

Adverse effects of MP are often developed in case of overdose of their active ingredients. Overdose of the majority HMP is characterized by typical mild general toxic adverse reactions: headache, nausea, vomiting, etc. However, long-term intake of increased dosages of such popular MP as lavender and ginger can result in more serious consequences such as CNS depression and respiration, seizures and cardiac arrhythmias.

Overdose of other HMP causes specific complications. For instance, uncontrolled administration of turmeric preparations (*Curcuma longa*) can lead to internal bleedings. Long term administration of alder buckthorn bark extract (*Frangula alnus*) can result in hypokalemia, reduced bowel motility, albuminuria and hematuria. If large dosages of stimulating HMP, for instance, ginseng extract/tincture (*Panax ginseng*), are used, arterial hypertension, increased excitability and insomnia can evolve [12]. Large doses of marsh Labrador tea (*Ledum palustre*) inhibit CNS and cause spastic paralyzes, including respiratory paralysis [6].

Long-term use of absinthe (*Artemisia absinthium*) in doses higher than therapeutic ones can cause seizures and hallucinations [7].

Liquorice (*Glycyrrhiza gabra*) is a popular plant used in conventional and traditional folk medicine as an expectorant. If the recommended dosages are exceeded and taken on a long-term basis, specific adverse effects (hyperaldosteronism (elevation in BP, edema, hypokalemia), encephalopathy, muscular weakness, retinopathy, cardiac dysfunction) can evolve [12].

DRUG INTERACTIONS OF HERBAL MEDICINAL PRODUCTS

At least 30% of patients receiving long-term pharmacotherapy take additional HMP. Only 20% of them inform their attending physician thereof. Up to 70% of patients who used phytotherapy are not informed of possible adverse reactions, including the ones occurring due to drug interactions. Serious adverse events occur in 16% of cases. Nevertheless, no significant data about the frequency and nature of drug interactions with HMP are available. A physician should know that at least 80 MPs have clinically significant interactions with conventional drugs [13]. At the same time, doctors are not even aware of a possible herb-drug interactions due to a number of reasons. Many qualified doctors lack sufficient knowledge about HMP pharmacology, and, in particular, their potential drug interactions. Moreover, while collecting medication history, doctors often ignore questions about HMP intake, whereas patients do not inform a doctor hereof proactively [14].

Additional issues can be associated with the nature of HMP, for instance, content of mixtures with an additional (not expected) pharmacological activity (see above).

HMPs have both pharmacodynamic (without a change in the substance concentration in the blood) and pharmacokinetic (with a change in the substance concentration in the blood) drug interactions with synthetic drugs. The favorable or unfavorable drug interactions result in a stronger or weaker effect of a drug taken along with the HMP.

The capability of a synergic action of MP and conventional medicinal agents is used during manufacture of combined preparations and expectorants, in particular. For instance, a combination of ambroxol hydrochloride, sodium bicarbonate, sodium glycyrrhizinate, and thermopsis dry extract in a medicinal product sold under the trade name "Codelac Broncho" in Russia possesses expectorant and anti-inflammatory action. Similarly, administration of separate drugs of ambroxol or bromhexine in combination with HMP of althea, thyme and ivy, etc. to intensify an expectorant action is an example of beneficial pharmacodynamic interaction [15]. On the contrary, administration of expectorant mixtures along with antitussive drugs, especially the ones that significantly suppress the cough center (codeine, butamirate), is an example of antagonistic interaction and irrational therapy of bronchitis, which can be complicated with "bronchi waterlogging". Another example of pharmacodynamic antagonism is simultaneous administration of HMP obtained from plants with a hemostatic action (stinging nettle (*Urtica dioica*), shepherd's purse (*Capsella bursa-pastoris*), great burnet (*Sanguisorba officinalis*) and antithrombotic for instance, acetylsalicylic acid to prevent thrombosis [14].

Pharmacokinetic interactions of HMP with conventional drugs can occur at any stage (absorption, distribution, metabolism and excretion). However, drug interactions during metabolism and biotransformation enzymes (mainly, cytochromes) modulation are of the greatest value. CYP1, CYP2, CYP3 and CYP4 cytochromes are most involved in drug metabolism. CYP3A4 isoform prevails and metabolizes up to 60% of drugs [16].

It is known that St. John's wort (*Hypericum*) can induce at least two isoforms of P450 (CYP3A4, CYP2C9) owing to hyperforin [17, 18]. On the contrary, echinacea inhibits the microsomal system (CYP1A, CYP2C9, CYP3A4) [19]. These properties of the MP can be of a clinical significance in concomitant administration of HMP with CYP substrates, of which there are several hundreds in various therapeutic areas. Increased activity (induction) of cytochromes will result in accelerated metabolism of CYP substrates and a decrease of its effective plasma concentration. Inhibited activity of cytochromes can slow down metabolism of a drug and increase its plasma concentration leading to overdosage symptoms.

For instance, concomitant administration of HMP containing ginkgo (*Ginkgo biloba*) with warfarin or clopidogrel can lead to an excessive increase of plasma concentrations of the drugs and bleedings [13]. It is necessary to take into account these

interactions in patients with subsequent surgeries. On the contrary, combined administration of ginseng or hypericum with warfarin can decrease warfarin plasma concentration and increase the risk of thrombotic complications.

Another important but underestimated mechanism of pharmacokinetic interactions is represented by the influence on activity of P-glycoprotein, a transporter of xenobiotics out of cells into the extracellular environment. In particular, P-glycoprotein releases drugs from an enterocyte back into the intestinal lumen and from the cerebral capillary endothelium back into blood. Inhibition of P-glycoprotein results in increased absorption of its substrates from the intestine and increases their penetration into the brain. Induction of P-glycoprotein causes opposite consequences. For instance, St. John's wort, which is a known inducer of P450, is also an inducer of P-glycoprotein. In particular, it can decrease absorption of oxycodone from the GIT and accelerate its metabolism. This finally reduces the analgesic effect [20]. Amitriptyline is another drug, which is a substrate of both CYP3A4 and intestinal P-glycoprotein. Amitriptyline plasma concentration may be reduced in concomitant administration with St. John's wort (herbal antidepressant) when it's required to accelerate or intensify a therapeutic effect [21].

It should be noted that risk factors of adverse effects observed when HMP are administered together with conventional drugs include age (children and elderly), concomitant diseases (especially liver or kidneys failure), polypharmacy (unjustified use of five and more medicinal products), pregnancy and lactation.

CONCLUSION

The current situation makes it necessary to attract attention and use a complex of measures that increase safety of phytotherapy. First, HMP leaflets should contain unified sections describing safety of the drug including all established adverse reactions, contraindications, warnings and drug interactions in detail. This is especially true for herbal mixtures' leaflets, which contain a few or no adverse effects or lack data about their possible administration together with other medicinal products. Instructions for use of HMP should include the indications solely based on clinical data which are obtained using criteria of evidence-based medicine (placebo-controlled or comparative clinical trials). Second, there is a need in more stringent requirements to advertising of herbal medicines and dietary supplements with obligatory detailed covering of safety issues not limited to a disclaimer about required consultations of a doctor and/or potential harm to health. Third, educational programs have to be updated and increased attention to the issues of safety of phytotherapy is required when doctors and pharmaceutical workers are being educated.

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