Products of Plant and Animal origin as Modifiers of Active Systems Drug Metabolism: Pharmacogenetic Aspect

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ABSTRACT

The paper deals with the topical issue of the drug's interactions with components of commonly used food and remedies of traditional medicine (folk medicine). Similar studies are needed for a personalized approach to the treatment. In particular, the effect of traditional and new food, plants, which are used in traditional medicine, the characteristics of the person's lifestyle on the activity of enzymes of the family of cytochrome P-450 involved in the metabolism of drugs and actively studied in pharmacogenetic studies has been shown. Presented problematics is the basis for a thorough gathering of the medical history referring to the ways of life (food, bad habits) of the patient in the appointment of appropriate therapy.

Keywords: drugs, pharmacogenetics, cytochromes P-450, food, remedies of the traditional medicine.

Modern official medicine is faced with a growing number of interactions of drugs with components of food, which is commonly used and remedies of the traditional medicine. Particular attention is paid to their influence on the activity of extensive system enzymes of family cytochrome P-450, which are involved in the metabolism of many drugs and which are actively studied in pharmacogenetic research. The **aim** of the present study was to analyze the available information about potential interactions of the drugs and products of plant and animal origin, which are used in human nutrition and as remedies of the traditional medicine. Similar studies are needed for a personalized approach to the treatment.

MATERIALS AND METHODS

The information search, analysis and generalization, system analysis were used in the paper.

RESULTS AND DISCUSSION

In addition to individual pharmacogenetic differences in reactions to drugs and food products, the situation is complicated by the possible interactions of these components regardless of the genotypic characteristics of the patient, which are illustrated below.

Positive and negative results of such interaction in preclinical and clinical practice in a number of cases are predictable, but sometimes have unpredictable nature. The reduction of

neurotoxicity of cytotoxic drugs while the simultaneous application of plant and animal origin is the example of conditionally positive drug interactions. Thus, neuropathic effects of oxaliplatin are reduced when administered to mice injections of diluted bee venom [15], rats – eel calcitonin [1], salmon calcitonin [2], turmeric [3], and green tea extract [10]. The use of grapefruit juice (a potent inhibitor of CYP3A4) during therapy with drugs that are substrates of cytochrome CYP3A4 refers to the examples of the negative nature of the interaction. It was first time such an unexpected interaction has been described for the simultaneous use of felodipine and alcoholic drink, in which the grapefruit juice was added to mask the taste. Subsequent studies have shown that grapefruit juice reduced first-pass metabolism of felodipine by selective post-translational reduction of the expression of CYP3A4 in the intestinal wall. In particular, the 24-hour duration of action on the organism of a grapefruit and grapefruit-based products results in the fact that their repeated consumption contributes to a significant increase of the oral bioavailability and a cumulative increase of AUC and C_{max} in the several simultaneous use of drugs, in particular, most of dihydropyridine calcium channel antagonists, terfenadine, saquinavir, cyclosporine, midazolam, triazolam, verapamil, lovastatin, cisapride, astemizole et al. [5]. It is known that such action of a grapefruit is associated with the presence furanocoumarin bergamotin in it. This active component is in other products used by man, in particular, limes, on the activity of CYP3A4 and on the pharmacokinetics of several drugs is affecting in the same way [6]. Potential drug interactions are typical for the more modern drugs, which include targeted drugs and biologics, many of which continue to be at different stages of clinical trials. Thus, during the treatment by tyrosinekinase inhibitor bosutinibom urged to avoid the use of grapefruit in the form of fruit and juice, as well as related citrus fruits (eg, bitter oranges) [4].

In addition to grapefruit in Ukraine became available other exotic fruits and vegetables, which are consumed by the population in large numbers in the recent years. At the same time, reception of drugs whose metabolism is associated with the cytochrome system and the simultaneous use of these products may not be innocuous. For example, the effect on the activity of several cytochrome P450 (CYP1A1, CYP1A2, CYP2E1 and CYP3A11) of six tropical fruits, namely, banana, mangosteen, guava, pineapple, mango and papaya was investigated in a recent study in mice. The pineapple juice appeared the most potential inhibitor against these enzymes, so the consumption of it in large quantities over a long period of time can lead to side effects in the case of the use of drugs - substrates of these options cytochromes [7].

It was shown a possible effect on drugs metabolism of traditional plant products of local population, such as cranberries. In particular, the use of cranberries and cranberry juice in the treatment of warfarin can lead to increase international normalized ratio (INR), which is a key measure of blood clotting [8].

Another important problem is the uncontrolled use of a population of herbal tinctures and teas as a means of national folk medicine during concomitant therapy. The classic and most-studied example is the induction of the activity CYP3A4 by the components of St. John's wort, often used to treat depression. [12]. Thus, the Office of the Food and Drug USA (FDA) does not recommend the combined use of St. John's wort extract with oral contraceptive drugs, selective serotonin reuptake inhibitors and inhibitors of HIV protease.

Familiar foods of animal origin, in particular, honey, can also have an effect on the concomitant medication, and these effects may have an individual ethno-geographical nature. Thus, in vitro study, it was shown that the wild honey Tualang, found in Malaysia inhibited CYP2C8 activity [13], at the level of macroorganism could potentially lead to a change in the metabolism of drugs, which are metabolized by this enzyme, in particular, a potent opioid buprenorphine. In another study, the effect of honey produced in the highlands of the Western Ghats (South India) on the enzyme activity of CYP3A4, CYP2D6 and CYP2C19 was studied on the volunteers within 7 days. It has been found that the use of honey led to the induction of only variant CYP3A4 [14].

At the same time, there are screening tests, indicating the absence of potential interactions between foods commonly used in the population, which is at the same time the remedies of traditional medicine, with drugs. In particular, the study on human volunteers did not reveal the effect of garlic extract on the activity of the enzymes CYP2D6 and CYP3A4 [11].

We should not underestimate the fact that in addition to food and remedies of traditional medicine, bad habits rights, in particular, the use of alcohol and nicotine may influence on the drug metabolism. In particular, it was shown the effect of nicotine on neuroleptic metabolism of clozapine and olanzapine in connection with the induction of the enzyme CYP1A2 in schizophrenic patients [9].

Thus, the simultaneous use of several drugs, except of which are not narcotic drugs and antidepressants, and use certain foods and remedies of traditional medicine may contribute to the temporary change in metabolizer's phenotype and, accordingly, the risk of side effects, even when using the information about the respective genotyping. A presented problem is the basis for a thorough medical history analysis in the order of the ways of life (food, bad habits) of the patient in the appointment of appropriate therapy.

CONCLUSIONS

1. The analysis of interactions of drugs with components commonly used food and traditional medicine was conducted.

2. The influence of food, plants used in traditional medicine, features the image of a person's life on the activity of enzymes of the family of cytochrome P-450, which are involved in the metabolism of drugs.

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