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The role of biotransformation processes in mediating interactions between psychotropic drugs and natural products

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ABSTRACT

Many patients are not aware that natural products such as fruit juices or plant infusions can cause significant interactions with several drugs, some of which can be dangerous, especially when the medical treatment is for neurological or psychiatric disorders. Among the most predisposed for interacting with drugs are citric juices, particularly grapefruit and plant infusions, especially St John`s wort (Hypericum perforatum). Understanding the mechanism and the frequency of this type of interaction helps to avoid it. The goal of this research was to identify and summarize the most relevant reports on interactions between psychotropic drugs and natural beverages, in order to raise awareness among physicians that they should invest more time in educating patients how to administer drugs properly, thus reducing the likelihood of such unwanted events. For the purpose of this study, an electronic search of PubMed database was conducted until September 2019. We concluded that natural beverage consumption along side medical treatment is a widespread practice and the main mechanism generating interactions is related to the functioning of biotransformation enzymes.

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Introduction

Often physicians are asked if drugs can be taken with drinks other than water, such as fruit and vegetable juices or tea, for better compliance, especially by pediatric and geriatric patients. The latest research in the field shows that concomitant use of single drugs and certain juices or plant infusions can influence the efficiency of medicines decreasing it or even worse, enhancing it excessively [1-4].

How can this type of phenomenon be explained? As we know, drugs are used for their pharmacological effect, but most are foreign substances for the human body and undergo various biotransformations in order to be inactivated and eliminated. It is well known that most drugs are metabolized with the help of vital enzymes called liver microsomal enzymes (cytochrome P450), but also with other blood or tissue enzymes [5-9].

Discussions

Cytochrome is a complex protein, containing iron and a prosthetic group represented by the heme, often called hemoprotein. The group was first described in 1886 by C.A. MacMunn as the histohematin, but its role in living cells remained unclear until 1925 when the group had been reanalyzed by D. Keilin [10,11]. Since then, vast knowledge about cytochromes has accumulated regarding their role in living organisms.

Cytochromes are widespread in plant and animal cells and in some microorganisms, such as yeasts and some facultative anaerobes. Linked to mitochondrial membranes, endoplasmic reticulum, chloroplasts and chromatophores, they play an important role in many processes that occur in living organisms, such as cellular respiration, photosynthesis and microsomal oxidation [12, 13].

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All cytochromes are able to donate and accept electrons through a reversible change in the valence of iron atoms in heme molecules. Combined in short or long chains, depending on the potential of the final electron acceptor, cytochromes transport electrons from dehydrogenases to final acceptors. The transport of electrons from cytochrome to cytochrome allows the cell to use the energy of chemical compounds or sunlight in all vital processes. For example, as part of the mitochondrial respiratory enzyme chain, cytochromes, together with cytochrome oxidase, carry out the final oxidation steps of the substrates. The energy released in this process is used to form adenosine triphosphate (ATP) or to generate a membrane potential. Cytochromes in the endoplasmic reticulum form non-phosphorylated short chains that are part of a system responsible for metabolizing and neutralizing aromatic compounds [14-16].

The cytochromes are divided into four types - a, b, c and d - depending on the spectral characteristics, the chemical structure of the heme side chains and the nature of the link between the heme and the protein molecule. Each type, in turn, is further subdivided into several subtypes. The cytochromes whose individuality has been established are designated by a Latin letter in lowercase, indicating the group to which the cytochrome belongs and with an index number, for example, cytochrome c1. In a reduced state, cytochromes form a distinct spectrum with three pronounced absorption bands, characteristic of each type of cytochrome and useful in identifying cytochromes by spectrophotometric methods [17-19].

About 30 cytochromes are known, but only a few have been obtained as individual proteins. It is difficult to obtain highly purified cytochromes as they are strongly bound to membranes and can only be separated by treatment with surfactants or proteolytic enzymes. Cytochromes b3 and c are exceptions because they can be easily extracted with saline solutions [19, 20].

A comparison of the amino acid sequence of the protein part of the cytochrome c molecule obtained from different organisms reveals that the amino acid residue sequences of 35 and 11 in different parts of the chain remain unchanged. The number of exchanges in other parts of the protein chain of this cytochrome obtained from different species of organisms is directly related to the phylogenetic differences between species [21]. For example, the molecules of cytochrome c from horse and yeasts differ in 48 amino acid residues, while ducks and chickens differ only in two; those of pigs, cows and sheep are identical.

Through these enzymes a very important role is played by the complex of hepatic cytochrome P 450 divided into several sub-families: A, C, E. The basic role of this cytochrome is to ensure the metabolism of xenobiotics. However, the activity of these enzymes can be modified by the xenobiotic itself as well as by many other factors such as additional drugs, plant juices, ethanol, various foods or even cigarette smoke [1, 22-25]. The nature of these changes can be in the direction of intensifying the activity, as well as in diminishing it. The process of intensifying the activity of such an enzyme system is known as enzymatic induction and results in a faster metabolization of a xenobiotic, which in turn may lower the intensity and duration of its pharmacological effect. The process of reducing the activity of a biotransformation enzyme system is known as enzymatic inhibition and results in a slower metabolization of a xenobiotic, which in turn may increase the intensity and duration of its pharmacological effect [26, 27].

Based on these considerations, any substance administered concurrently with a drug may alter its efficacy and this would require reviewing the dosage of the drug or the time between 2 consecutive doses. The CYP3A4 cytochrome is responsible for the biotransformation of most xenobiotics and is highly susceptible to enzymatic induction or inhibition. Therefore, any food or beverage, being a xenobiotic, can influence the activity of cytochrome P450 enzymes [28, 29].

Taking into account that many nutritionists encourage natural juice consumption on a daily bases due to the undeniable richness in various nutrients, vitamins and microelements in these products, it is pertinent to wonder whether they influence the efficacy of drugs [30].

Daily consumption of fruits and vegetables, preferably raw or in the form of salads or juices is part of a normal, healthy and balanced diet, which promotes the proper functioning of the immune system [31] and can prevent the onset of many nutrition related illnesses such as obesity and diabetes, which are increasingly studied by researchers to develop new pharmacological remedies [32,33]. However, a rising number of studies are revealing that medical treatment can be significantly influenced by some compounds found in various natural beverages or foods.

Scientists have observed for several decades that drugs administered with grapefruit juice, containing naringin (that turns to naringenin in the liver) or orange juice, containing hesperidin, both substances inhibitors of cytochrome P450, will metabolize at a slower speed. This phenomenon can occur even after the ingestion of no more than 200 mL of juice. Administering drugs at standard intervals when biotransformation processes are slowed down can lead to their accumulation in the body. This amplifies side effects and can even trigger drug overdose [34-38].

Thus, for example, if a patient uses grapefruit juice while taking some statins for lowering cholesterol blood levels, a fraction of the drug fails to metabolize, increasing the risk of liver and muscle damage, which could lead, finally, to renal failure [39, 40]. It turns out that the grapefruit juice inhibits several hepatic microsomal

enzymes responsible for the inactivation of at least 40 drugs administered in humans [41]. Pomegranate juice has also shown CYP3A4 inhibition properties, just like grapefruit juice [42].

It has also been demonstrated that, alongside grapefruit juice, other fruit juices, especially apple and orange juice, can also significantly alter the efficacy of many drugs [43, 44]. It is assumed that they are inhibitors of the intestinal organic anion transporting polypeptide (OATP), which helps in the absorption process of some drugs [45-47]. Inhibiting the intestinal OATP results in reduced absorption and increased probability of low serum levels of drugs transported by OATP [48-50]. Other studies have shown that citric juices also inhibit the intestinal efflux P-glycoprotein (PGP), thus increasing the oral bioavailability of other drugs [51].

The juices from lemon and pomelo are susceptible to drug interactions similar to grapefruit by inhibiting intestinal CYP3A4 [52]. Recently it has been shown that even tomato juice, used extensively in the food industry, also has an inhibitory action on cytochrome P450 CYP3A4 [22].

It should be noted that the amount of microsomal enzymes varies from person to person and is genetically determined [53]. Accordingly, juices can influence the efficacy of drugs differently in people who receive the same medicine but are of different ages or ethnic groups.

A wide range of drugs used in daily psychiatric practice undergo phase I oxidation with CYP3A4, CYP1A2 or CYP2C19 such as anxiolytics, antidepressants, mood stabilizers, antipsychotics or neurotonic compounds and are susceptible to interactions with several natural products. The highest number of reports regarding such interactions is related to grapefruit juice and the mechanism of interaction has to do with the influence of some ingredients from grapefruits on hepatic metabolism but also on enteric absorption pathways using PGP and OATP, as we have already shown. The risk of dangerous consequences is particularly important when taking psychotropic drugs with natural products that can alter the pharmacological effect of drugs. For instance, grapefruit juice consumption increases the mean peak plasma concentrations and the area below the concentration – time curve of sertraline [54] and fluvoxamine [55]. Therefore, grapefruit juice is generally contraindicated to patients under psychiatric treatment and it is advised to inform patients about the nature of these possible interactions [56].

Antidepressant activity of monoamine oxidase inhibitors (MAOIs) was initially noted in the 1950s. Although older MAOIs are effective in the treatment of depressive disorders, they are under-utilized in clinical practice due to concerns about interaction with tyramine-containing food (matured cheese, red vine, ripened bananas, yogurt, shrimp paste and salami) – the so called "cheese reaction", since it can induce a hypertensive crisis in patients taking MAOIs [57].

The first-generation MAOIs such as phenelzine and isocarboxazid were largely nonselective inhibitors of both subtypes of MAO: MAO (A) and MAO (B). These drugs carried with them dietary restrictions [58]. Tyramine is an indirectly acting sympathomimetic agent, is degraded by MAO but in the presence of nonselective MAOIs, it escapes degradation and reaches the systemic circulation where it produces vascular constriction, leading to a hypertensive crisis [59]. However, MAOIs have been well established as an effective intervention for people with treatment-resistant depression, and transdermal formulations of selective MAO (B) inhibitors may provide a valuable therapeutic option and minimize the drug-food interactions [60].

Taking into account that the prevalence of anxiety disorders, depression and even epilepsy is rising around the world, it is important to assess and underline the risk of interactions between the most prescribed drugs for these illnesses and the most consumed natural products such as citric juices or herbal infusions:

Benzodiazepines – There have been mixed reports on the degree to which grapefruit juice interacts with a variety of anxiolytics. A Turkish research group revealed that one glass of grapefruit juice more than triples the bioavailability of *diazepam* [61], while a Swiss study [62] has shown grapefruit juice increasing the bioavailability of oral *midazolam* by 50%. Hukkinen et al [63] showed an increase in the serum concentration of *triazolam* by a factor of 1.3. These studies, however, are contradicted by Vanakoskiet et al who found no effect on bioavailability of midazolam or triazolam by grapefruit juice [64].

Another natural beverage with a significant potential to influence the effect of benzodiazepines is the Hypericum perforatum infusion. An open-label crossover study conducted on 12 healthy volunteers revealed a 2-fold decrease in the area under the curve for *alprazolam* plasma concentration vs time and a 2-fold increase in *alprazolam* clearance after a 2-week period of St John`s wort tea consumption [65].

For the above mentioned 4 benzodiazepines, patients should avoid drinking grapefruit juice or John`s wort tea during treatment in order to avoid similar interactions.

Buspirone is an azapirone anxiolytic agent that produces less sedation and impairment of psychomotor performance than benzodiazepines do. It has poor bioavailability due to extensive first-pass metabolism. Moderate quantities of grapefruit juice have been shown to raise the mean peak plasma concentration of buspirone 4.3-fold and the mean area under the plasma buspirone concentration-time curve 9.2-fold [66]. It would be wise to counsel patients to avoid the co-administration of buspirone with grapefruit juice, particularly in large amounts (more than 3 glasses per day).

Sertraline, a selective serotonin reuptake inhibitor used in the treatment of depression, panic disorder, and obsessive-compulsive disorder, undergoes first-pass metabolism by CYP3A4. A thorough study has shown both in vitro and in vivo evidence of grapefruit juice inhibiting this metabolism [67]. Four of the study's 5 patients had sertraline levels increased by approximately 1.5-fold when 1 glass of regular-strength grapefruit juice was drunk daily.

Hypericum perforatum infusion has also been found to influence the activity of antidepressant drugs as well as anxiolytics active on the serotonin transmission, such as buspirone [68]. Studies have shown that some active ingredients in this plant inhibit MAO activity and induce an up-regulation of 5-HT_2 receptors in the frontal cortex [69]. Under these circumstances, consuming a tea containing a St John`s wort infusion while under treatment with serotonin reuptake inhibitors may trigger a serotoninergic syndrome [70].

Clomipramine is a tertiary tricyclic amine antidepressant also used in the treatment of obsessive-compulsive disorder. Oesterheld and Kallepalli [71] reported their experience of using grapefruit juice to elevate the drug levels of clomipramine and improve efficacy in 2 children with obsessive-compulsive disorder. The authors postulated that in some patients, demethylation of clomipramine may be largely mediated by the CYP3A4 system. However, in most patients, up to 5 isoforms of cytochrome P450 with different sensitivities to enzymatic inhibitors are involved in the biotransformation of this drug [72].

In the case of psychotropic drugs, the inhibitory effect of grapefruit juice on the CYP3A4 cytochrome is of equal importance with its influence on OATPs and especially PGPs due to the fact that PGP is one of the most important transporters for drugs active in the central nervous system, regulating their absorption and elimination [73, 74].

Methadone is a synthetic μ-opioid receptor agonist used for treating the withdrawal syndrome in heroin addicts, but also for chronic pain. The main biotransformation pathway of this drug is via CYP3A4 which is significantly induced by St John`s wort. A study investigating the influence of this natural product on methadone serum concentrations uncovered an average decrease of 47% when patients ingested St John`s wort tea repeatedly [75]. On the other hand, in the presence of grapefruit juice, the area under the concentration – time curve increases by an average of 17% which could lead to symptoms of overdosing in some patients [76].

Carbamazepine, an anticonvulsant widely used in the treatment of epilepsy, when co-administered with a large glass (300 mL) of fresh grapefruit juice increased the steady-state peak concentration of carbamazepin by 40% and the area under the plasma concentration-time curve by 41%, leading to drowsiness and confusion [77]. Given carbamazepine's narrow therapeutic index, it is wise to avoid the potential toxic effects induced by the co-administration of grapefruit juice.

Highlights

Biotransformation enzymes play an important role in determining the intensity and duration of the pharmacological effect of drugs.

Several natural juices or plant infusions contain compounds capable to influence the activity of biotransformation enzymes, thus altering drug pharmacokinetics and pharmacodynamics, causing either relative overdosing, or relative underdosing.

Conclusions

In light of the above findings we can conclude that people under treatment with various drugs, especially psychotropic drugs, should consult their doctor before administering them with fruit juices or plant infusions. Underdosing or overdosing psychotropic drugs can lead to unpredictable consequences, and therefore extreme caution is required. Taking into account the fact that many interactions are not yet fully known, patients should be given the medication only with water if possible, and should be encouraged to report any new side effect that occurs when drugs are administered with natural beverages other than water.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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