Interactions of food and dietary supplements with drug metabolising cytochrome P450 enzymes

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SUMMARY

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Drug side effects and toxicity and often the drug efficacy are highly dependent on drug metabolism determining the activation and/or elimination of the respective compound. In humans, cytochromes P450 are the most important drug metabolizing enzymes of the first phase of drug biotransformation. Their activity can vary due to interindividual genetic differences, but it can be changed also by inhibition or induction of the enzymes by their substrates or other compounds that are not only drugs themselves and/or drugs taken concomitantly. Often, influence on drug metabolism by compounds that occur in the environment, most remarkably in the food, is forgotten. Some commonly used herbs, fruits as well as e.g. alcohol may cause failure of the therapy up to serious alterations of the patient's health. This review presents a brief overview of potentially dangerous nutrition factors including herbs (incl. teas, infusions) that should be considered when indicating individual drug therapy. Examples include primarily grapefruits, pomelo, star fruit, pomegranates and some other fruits, St John's Wort (*Hypericum perforatum*), caffeine, as well as alcohol and cigarette smoking.

Key words: cytochrome P450 – CYP – food – interaction – drug *Má*

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SOUHRN

Interakce potravin a potravních doplňků s cytochromy P450 – hlavními enzymy metabolizmu léčiv

Nežádoucí účinky léčiv, jejich toxicita a často samotná účinnost léčiv závisí významně na jejich metabolizmu, který je určujícím faktorem aktivace a/nebo eliminace příslušné látky. U lidí jsou nejvýznamnějšími enzymy metabolizujícími léčiva v první fázi jejich biotransformace cytochromy P450. Aktivita těchto enzymů se může lišit v důsledku interindividuální genetické variability, ale také může být ovlivněna indukcí nebo inhibicí enzymů jejich substráty nebo jinými látkami, a to nejen léčivy. Vedle účinků vlastního léčiva či interakcí s léčivy současně podávanými jsou opomíjeny látky, které se vyskytují v životním prostředí, nejvýznamněji v potravě, a mohou metabolizmus léčiv také ovlivnit. Některé běžně užívané rostlinné drogy, ovoce, ale stejně tak například alkohol nebo kouření mohou způsobit selhání farmakoterapie až závažné poškození zdraví pacienta. Tento článek přináší stručný přehled potenciálně nebezpečných nutričních faktorů včetně přípravků z rostlinných drog (mj. čaje, nálevy), které by měly být brány v úvahu při zavádění individuální farmakoterapie. Nejdůležitějšími rizikovými faktory ve výživě a životním stylu interagujícími s metabolizmem léčiv jsou v první řadě grapefruit, pomelo, karambola, granátová jablka a některé další exotické ovoce, třezalka tečkovaná (*Hypericum perforatum*), kofein, a rovněž alkohol a kouření cigaret.

Klíčová slova: výživa – interakce s léčivy – cytochrom P450 – CYP

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Introduction

Drug metabolism plays a crucial role in drug pharmacokinetics; by affecting the systemic level of the drug and/or its metabolites it can cause drug side effects and toxicity. Although cytochromes P450 (CYPs) are not the only enzymes involved in drug metabolism, they account for the majority of drug transformation reactions. As an advantage, from the 57 members of human CYP family only approximately one quarter metabolizes primarily xenobiotics and, moreover, 90 % of this metabolic activity belongs to only five or six CYP enzymes (CYP forms). These are CYP3A4/5, CYP2C9, CYP2C19, CYP2D6, CYP1A1/2, clinically

Tab. 1. Drugs known to be substrates of (or to interact with) the most important CYPs [3, 4]

CYP3A4		**CYP2D6**	**CYP2C9**
Alfentanil	Losartan	Ajmaline	Amitriptyline
Alpidem	Lovastatin	Amitriptyline	Antipyrine
Alprazolam	Meloxicam	Bufuralol	Diclofenac
Ambroxol	Methadone	Bupranolol	Dronabinol (THC)
Amitriptyline	Mibefradil	Captopril	Carbamazepine
Astemizole	Mifepristone	Cinnarizine	Flurbiprofen
Atorvastatin	N-hydroxyarginine	Citalopram	Glimepiride
Benzphetamine	Nevirapine	Clomipramine	Glipizide
Bupivacaine	Nicardipine	Chlorpromazine	Glibenclamide
Brotizolam	Nifedipine	Codeine	Ibuprofen
Budesonide	Niludipine	Debrisoquine	Indomethacin
Buprenorphine	Nimodipine	Deprenyl	Losartan
Carbamazepine	Nisoldipine	Desipramine	Phenytoin
Citalopram	Nitrendipine	Dextromethorphan	Piroxicam
Cisapride	Omeprazole	Dexfenfluramine	Tolbutamide
Clarithromycin	Oxodipine	Encainide	Torsemide
Clozapine	Paclitaxel (Taxol)	Flecainide	(S)-warfarin
Codeine	Pantoprazole	Fluoxetin	**CYP2C19**
Colchicine	Paracetamol	Fluvoxamine	Amitriptyline
Cortisol	Progesterone	Flunarizine	Carisoprodol
Cyclobenzaprine	Propafenone	Fluphenazin	Clomipramine
Cyclophosphamide	Proquanil	Galantamine	Diazepam
Cyclosporin A, G	Quinidine	Haloperidol	Imipramine
Dapsone	Rapamycin	Hydrocodone	Lansoprazole
Dehydroepiandrosterone	Retinoic acid (Tretinoin)	Imipramine	Omeprazole
Delaviridine	Rifabutin	Methoxyamphetamine	Proguanil
Dextromethorphan	Ritonavir	Metoprolol	Propranolol
Diazepam	Ropivacain	Mexilitine	(S)-mephenytoin
Digitoxin	Salmeterol	Mianserin	(R)-warfarin
Diltiazem	Saquinavir	Nortriptyline	**CYP1A2**
Docetaxel	Sertindole	Ondansetron	Caffeine
17ß-estradiol	Simvastatin	Paroxetine	Clomipramine
Erythromycin	Sulfamethoxazole	Perhexiline	Clozapine
Ethinylestradiol	Sulfentanil	Perphenazine	Fluvoxamine
Ethylmorphine	Tacrolimus	Propafenone	Imipramine
Etoposide	Tamoxifen	Propranolol	Naproxen
Felodipine	Teniposide	Risperidone	Ondansetron
Fentanyl	Terfenadine	Sparteine	Paracetamol
Finasteride	Terguride	Thioridazine	Phenacetin
Flutamide	Terbinafine	Timolol	Propafenone
Gallopamil	Testosterone	Tramadol	Tacrine
Gestodene	Tetrahydrocannabinol	Trifluperidol	Terbinafine
Granisetrone	Theophylline	Trimepranol	Theophylline
Haloperidol	Tolterodine	Tropisetron	Verapamil
Hypericum extract	Triazolam	Tomoxetine	(R)-warfarin
Ifosphamide	Trimethadone	Venlafaxine	**CYP2E1**
Imipramine	Troglitazone	**CYP2B6**	Chlorzoxazone
Indinavir	Troleandomycin	Bupropion	Enflurane
Irinotecan	Verapamil	Cyclophosphamide	Halothane
Ivermectin	Vinblastine	Efavirenz	Isoflurane
Lansoprazole	(R)-warfarin	Meperidine	Paracetamol
Lidocaine	Zatosetron	(S)-mephenytoin	Phenacetin
Lisuride	Zonisamide	Propofol	Sevoflurane
Loratidine	Zopiclone	Selegiline	

important are also CYP2E1 and CYP2B6 [1, 2]. This fact allows practical managing of an individual therapy in a way to avoid most of the serious drug-drug interactions and drug side effects at the metabolism level of pharmacokinetics. The principle of metabolism-based interactions are mostly based on the fact that many frequently prescribed drugs share the same metabolic pathways; second mechanism explaining drug interactions is based on an induction of a particular drug-metabolizing enzyme (e.g. elevation of the level of a particular CYP form). Today, number of drugs affecting CYP activity is commonly known and considered if multiple pharmacotherapy is used, however, there is a group of non-drug inducers and inhibitors of CYPs that are usually taken by the patients in the diet or as nutrition supplements and herbal extracts without any medical supervising. These compounds may interact with the medication causing failure of the therapy or serious side effects of the drug. Especially, herbal products became more and more popular contrary to the „chemicals", promising more natural and safe way of self-treatment, which, however, may be completely false (Table 1).

Food and dietary constituents affecting CYPs

Human diet contains many components that may show relatively higher health risk than nutrition value, some of them even miss any benefits. This is widely discussed from many aspects, as the nutrition may contribute significantly e.g. to development of metabolic disorders and other diseases including cancer. From the point of view of drug interactions, three types of nutrition can be distinguished: (i) fresh food containing endogenous substances with the potential to affect CYPs itself (ii) fresh or processed food that contains either exogenous toxic compounds or toxic compounds formed during food processing which are able to affect CYP activities as heterocyclic amines in processed meat, food additives as dyes or food preservatives, pollutants in vegetables etc. Here we could also consider alcohol intake and smoking; this second group means usually a kind of long-term load of toxic (and/or carcinogenic) compounds. Third group would contain nutrition supplements, herbal drugs and similar products. These are often taken in combination with Western medicines, considered by the patients to be safe, often without informing the physician [5].

Fresh food: fruits and fruit juices

It is well known that grapefruits and grapefruit juice (GFJ) cause clinically important inhibition of the activity of intestinal CYP3A subfamily, mainly of the CYP3A4 form, and thus increase the oral bioavailability of many CYP3A4 substrates that undergo high presystemic metabolism even if consumed in normal quantities [6, 7]. GFJ was proved to enhance remarkably the oral bioavailability of drugs metabolized preferentially by CYP3A4 as carbamazepine, cyclosporine, amlodipine, felodipine (up to more than 250% compared to water), nifedipine, nitrendipine, nisoldipine, nimodipine, midazolam, triazolam, terfenadine, risperidone, cisapride and benzodiazepines [8–13], but the most important interaction was found with statines, e. g. atorvastatine, cerivastatine, lovastatine, simvastatine [11, 14, 15]. As an example, GFJ administration increased the mean peak plasma concentration (c_{max}) of simvastatin about 9-fold (range, 5.1-fold to 31.4-fold; $P<0.01$) and its mean area under curve (AUC) 16–fold (range, 9.0-fold to 37.7-fold; $P<0.05$). The mean c_{max} and AUC of simvastatin acid were both increased about 7-fold ($P<0.01$) [15]. Another significant increase was observed with buspirone: c_{max} raised 4.3-fold (range, 2-fold to 15.6-fold; $P<0.01$) and buspirone AUC 9.2-fold (range, 3-fold to 20.4-fold; $P<0.01$) [16]. In halofantrine, the risk subsist the halofantrine-induced QT interval prolongation that follows an increased level of this CYP3A4 substrate [17] (Table 2).

The compounds responsible for CYP3A4 inhibition are furanocoumarins, namely, 6',7'-dihydroxybergamottin (DHB), bergamottin (BG) and bergaptol (BT). BG seems to have a slower onset of action than DHB and exhibits substrate-dependent inhibition [18], but its enzyme inhibiting effect might be not limited only to CYP3A4

*Tab. 2. Overview of the most important interactions of the grapefruit juice (GFJ) with some drugs: relative ratio of c_{max} in group given GFJ to c_{max} of the control group (*important interaction, **middle important interaction, ***very important interaction) [14]*

Drug	Dose of drug	GFJ (ml)	c_{max} change (folds)	Drug	Dose of drug	GFJ (ml)	c_{max} change (folds)
Albendazole*	10 mg/kg	250	3.20	Ivermektin*	0.15 mg/kg	750	1.39
Amiodarone**	17 mg/kg	300	1.85	Lovastatin**	40 mg	200	1.65
Artemether**	100 mg	350	2.59	Methyl-prednisolon*	16 mg	200	1.27
Atorvastatin**	40 mg	200	2.57	Nifedipine*	20 mg	200	2.00
Buspiron***	10 mg	200	4.29	Nisoldipine*	20 mg	300	3.50
Celiprolol**	100 mg	200	-1.95	Nitrendipine**	20 mg	300	2.06
Cisapride***	10 mg	250	1.34	Pranidipine*	2 mg	250	1.53
Diazepam*	5 mg	250	1.54	Sertralin*	55 mg	240	1.47
Felodipine*	10 mg	250	2.46	Simvastatin***	40 mg	200	12.04
Fluvoxamine*	75 mg	250	1.33	Terfenadine**	60 mg	250	1.17
Halofantrine**	500 mg	250	2.77	Triazolam*	0.25 mg	250	1.25

since BG was also identified as a mechanism-based, NADPH-dependent and irreversible inactivator of CYP2B6 and CYP3A5 in the reconstituted system [19] and of CYPs 1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 in human liver microsomes [20]. Some other citrus fruits contain the same furanocoumarins, too, e.g. pomelo or Seville oranges [7, 21]. Seville orange juice and GFJ interact with felodipine by a common mechanism, which is based on inactivation of intestinal CYP3A4 [22].

On the other hand, it has been documented that common orange juice is incapable of inhibiting the catalytic activity of CYP3A4 [10]. For bioavailability of some drugs (e.g. cyclosporine or vinblastine), also inhibition of intestinal P-glycoprotein (drug efflux transporter) activity by GFJ may be a more important determinant for increasing the bioavailability [7, 23]. However, GFJ does not enhance the absorption of digoxin, a prototypical P-glycoprotein substrate, possibly because of its high inherent oral bioavailability [6]. Pomelo juice increases the bioavailability of cyclosporine as well, inhibiting CYP3A or P-glycoprotein activity (or both) in the gut wall [24]. Seville orange juice doesn't interact with cyclosporine, suggesting that it does not inhibit intestinal P-glycoprotein, just selectively inhibits CYP3A4 [22]. Egashira and his colleagues recently reported a case of increase in the blood level of tacrolimus following intake of pomelo in a renal transplant recipient and confirmed CYP3A4 and P-glycoprotein inhibition by pomelo juice [25, 26]. Finally, a very recently citrus flavonoids were identified, naringin in grapefruits and resperidin in oranges, as responsible for drug transport modulation by GFJ and orange juice through inhibition of human enteric organic anion-transporting polypeptide (OATP1A2). This type of inhibition was examined in a clinical study documenting a significantly lowered oral bioavailability of fexofenadine [6]. Drug transporters expression (OATP1A2 or multi-drug resistant protein – MDR1) is not affected by short-term GFJ consumption. This food-drug interaction appears to be novel and may be relevant to other fruit juices and drugs [27–29].

To conclude, grapefruit and potentially other citrus fruits and their juices have a true clinical importance and should be considered hazardous if consumed during drug therapy. The mechanisms of action include inhibition of CYP3A4, P-glycoprotein and OATP1A2, which can affect the pharmacokinetics of antiallergics, antibiotics, anticoagulants, antimalaria drugs (e.g. halofantrine, antiparasitic drugs, sedative-hypnotics, calcium channel blockers, HIV protease inhibitors, antitumor drugs, HMG-CoA reductase inhibitors, beta-blockers, hormones, immunosuppressants, antiarrythmics and other drugs [30]. Especially for drugs with a narrow therapeutic index, as e.g. carbamazepine, which bioavailability is increased by GFJ by approx. 40 %, patients should be instructed by clinicians not to consume grapefruits and other citrus fruits to avoid undesirable side effects [9].

This recommendation should be also valid for a star fruit (carambola) that was found (besides a serious nephrotoxic and neurotoxic effect in patients with renal insufficiency [31, 32]) to have even stronger potential to inhibit CYP3A enzyme activity *in vitro* and *in vivo* (this inhibition does not seem to be mechanism-based) than the grapefruit juice, although there is only a limited number of studies to-date. Similarly the pomegranate juice has been shown to be another strong inhibitor of human CYP3A4; it was shown to alter significantly carbamazepine pharmacokinetics in rats [33]. For midazolam, pomegranate juice does not impair clearance of oral or intravenous applied drug contrary to the grapefruit juice administered to human volunteers [34]. From other tropical fruits tested as common papaw, dragon fruit, kiwi fruit, mango, passion fruit, rambutan, also the papaw had inhibited *in vitro* CYP3A activity at least as much as white grapefruit. Dragon fruit, kiwi, mango, passion fruit, rambutan and Valencia orange didn't affect CYP3A activity in a clinically important way [35].

Vegetables: broccoli and others

Vegetables are highly heterologous group of food. Some of the botanical species can affect significantly human health, including metabolism of drugs by CYP enzymes; however, this effect can be ameliorated by consumption of a different type of vegetable. For example, CYP1A2 activity was shown to be induced by brassicaceous vegetables but inhibited by apiaceous vegetables [36]. A mixed diet containing vegetables with adverse effects can be difficult to evaluate, as seen in epidemiological studies. Anyway, some of the vegetables might be of our interest because of their high potential to induce or inhibit cytochromes P450, especially CYP1A family. Induction of CYP1A enzymes is suggested mainly to be caused by indolyl glucosinolates produced by *Cruciferae* family, and particularly the genus *Brassica* (e.g., cabbage, radishes, cauliflower, broccoli, Brussels sprouts, and daikon radish). The major ones are glucobrassicin and neoglucobrassicin and glucobrassicin derivative indole-3-carbinol (I3C), which oligomeric products (among which 3,3'-diindolylmethane is the major component) are thought to be responsible for biological effects [37, 38]. In two similar studies, a diet enriched in cruciferous vegetables (radish, Brussels sprouts, cauliflower, broccoli and cabbage) for 6 days caused a pronounced increase in the CYP1A2 activity (N–acetyltransferase and xanthine oxidase activities were not affected) in human volunteers [39, 36]. Kall et al. [40], observed the induction of human CYP1A2 and other CYP enzymes involved in estrone 2-hydroxylation by dietary broccoli. In fact, changes of CYP activities may vary among different cultivars and growth conditions of the broccoli [38].

Garlic and related *Alliaceae* plants as onion or leek contain a spectrum of organic compounds with various biological effects. Garlic is studied mostly because of its anti–carcinogenic properties that are mediated through a number of mechanisms, such as the scavenging of radicals, increasing glutathione levels, increasing the activities of enzymes such as glutathione S-transferase, catalase, DNA repair mechanisms, prevention of chromosomal damage but also an inhibition of

cytochrome P450 2E1 [41]. Diallylsulfide, diallyldisulfide and allylmethylsulfide are the most effective garlic compounds in terms of shutting down the CYP2E1 protein activity, indicating that the presence of an allylic side chain coupled to single sulphur atom is necessary for this effect. The propyl allyl compounds, however, are not effective as inhibitors for CYP2E1 [42]. Since the biologically active vegetables were rarely tested for possible vegetable-drug interactions, future studies are needed to confirm the safety of their consumption with e.g. CYP1A2 and CYP2E1 substrates. Data collected up to date show that garlic changes pharmacokinetics of paracetamol, decreases blood concentrations of warfarin and may cause more frequent hypoglycaemia when used concomitantly with chlorpropamide (a sulphonylurea drug used to treat type 2 diabetes mellitus) [43].

Processed meat

Char grilled meat contains carcinogenic heterocyclic amines (HAAs) and polycyclic aromatic hydrocarbons (PAHs) that are substrates of CYP1A and CYP3A enzymes and of P–glycoprotein. HAAs arise during the cooking of meats, fish, and poultry, and they also occur in tobacco smoke and diesel exhaust. Chemical analysis of foods shows that flame–grilling can form both PAHs and HAAs, and that frying forms predominantly HAAs [44]. Creatinine, amino acids, and sugars are the precursors of these compounds [45]. Many HAAs are carcinogenic as demonstrated *in vivo* and confirmed in a number of epidemiologic studies, moreover, they also induce human CYP1A2 [46]. One of the most potent inducers of CYP1A2 protein and activity is dibenz(a,h)anthracene [47]. Phenylimidazo[4,5-b]pyridine (PhIP) induces CYP1A1, 1A2 and 2B2 in rats [48]. Food-drug interactions of processed meat have probably not been described although they are not excluded. Just a few old studies in 1980s and 1990s have described a modest induction effect of consumption of a char grilled meat diet on CYP1A [46, 49]. Sinha et al.[46] proved increased CYP1A2 activity in 47 of 65 (72 %) subjects consuming high temperature-cooked meat ($P<0.0002$) compared to low temperature-cooked meat 7 days after ingestion. A 7-day char grilled meat diet caused CYP1A2 induction in duodenal biopsies in ten healthy subjects [50]. Insufficient knowledge on the effect of char grilled meat on CYPs may be partially caused by the lack of useful experimental tool for discerning CYP1A2-mediated metabolism *in vivo* in humans [51]. Anyway, frequent consumption of fried and charcoal broiled meat cannot be recommended from any aspect.

Alcohol

Acute and chronic ethanol treatment has been shown to increase the production of reactive oxygen species, to lower the cellular antioxidant levels, and to enhance oxidative stress in many tissues, especially liver, where it may produce a fulminant damage [52, 53]. One of the most important effects of alcohol is induction of CYP2E1, which brings other implications for metabolism of its pharmacologically and/or toxicologically important substrates, e.g. paracetamol (acetaminophen). Paracetamol has a toxic metabolite, N–acetyl–p–benzoquinone imine (NAPQI) that can bind to hepatic and renal proteins. Glutathione detoxifies NAPQI and therefore glutathione levels are altered if NAPQI is accumulated [3, 54, 55]. Production of NAPQI by induced CYP2E1 is enhanced by alcohol intake, although this reaction might be to certain degree suppressed if alcohol is still present in the system by the mechanism of competitive inhibition of CYP2E1 [54–56]. Reviewers consider the restrictions on paracetamol use by patients consuming alcohol greater than necessary and recommend its use with no effusive fear considering its possible benefits against e.g. NSAIDs [57].

Smoking

Cigarette smoking remains highly prevalent in most countries. Cigarette smoking can affect the drug therapy pharmacokinetically by PAHs and pharmacodynamically by nicotine [58]. Polycyclic aromatic hydrocarbons in tobacco smoke induce rat CYP1A1 and CYP1A2 (but not CYP2B1/2, 2E1 or 3A2) which increases the risk of cancer by enhancing the metabolic activation of carcinogens and alters the drug metabolism [59]. Estrogens [60, 61] and theophylline [61–64] are inactivated faster in smokers. Premenopausal female smokers show significantly increased estrogen 2-hydroxylation, which may be the reason for the anti–estrogenic effects of cigarette smoking [60]. The body clearance of theophylline in smokers (1–2 packs/day) was shown to be approximately two times faster than in non–smokers (100±44 ml/min/1.73 m^2 compared to 45±13 ml/min/1.73 m^2) [62]. Smokers metabolize 40% more pentazocine than non-smokers [65]. Induction of liver enzymes was reported to increase the metabolism of imipramine, meprobamate and phenylbutazone [61] and propranolol [64, 66]. Higher dosages may be needed to balance altered subcutaneous absorption of insulin because of cutaneous vasoconstriction [67, 64]. Also insulin clearance is lowered suggesting to be the cause of hyperinsulinemia in smoking type 2 diabetic patients [68]. Warfarin clearance is increased without a significant change in prothrombin time, but the study was carried with sub-therapeutical doses [61, 69]. On the contrary, an increased metabolism of heparin (possibly due to activation of thrombosis with enhanced heparin binding to antithrombin III) may require a somewhat higher dosage [64, 70]. Smokers could not profit from the GI ulcers treatment with histamine H2-receptor, antagonists, blockers; sucralfate is probably more useful, as the healing rates of ulcers in smokers and non-smokers are indistinguishable [71]. Smoking reduces diuretic effect of furosemide, but it probably does not act through affecting furosemide pharmacokinetics [72].

Among the drugs used in psychiatry, a large review over the effect of smoking on their metabolism was done by Desai et al.[73] The authors have concluded that cigarette smoking increases the metabolism and decreases the plasma concentrations of imipramine, clomipramine, fluvoxamine and trazodone due to the

induction of hepatic enzymes. An increased clearance was observed with tiotixene, fluphenazine, haloperidol, olanzapine, alprazolam, lorazepam, oxazepam, diazepam and demethyl-diazepam.[73] A decrease of olanzapine level in a heavy smoking schizophrenic patient caused an exacerbation of his clinical symptoms, probably due to an induction of CYP1A2 [74]. Zevin and Benowitz [64] presented pharmacokinetic drug interactions based on induced metabolism also for tacrine, flecainide, propoxyphene and chlordiazepoxide. According to the authors, these interactions might have clinically important consequences. Cigarette smoking reduces plasma concentrations of chlorpromazine and clozapine [75, 76]. Smokers have been also reported to have reduced drowsiness if using chlorpromazine or benzodiazepines, compared with non-smokers which may be due to induction of metabolizing enzymes by certain compounds present in cigarette smoke [77] or due to diminished end-organ responsiveness [61]. Haslemo and his colleagues [78] recommend a 50 % lower starting dose of clozapine and olanzapine in non–smokers to avoid side effects. It was found that metabolism of both the drugs is maximally induced already with a daily consumption of 7–12 cigarettes. Reversely, smoking cessation can significantly increase levels of the drugs [12]. As a summary, smoking as well as smoking cessation should be in any case considered in the individual drug therapy management, although there is a lack of recent, well-designed studies to confirm the interactions presented. The authors of review articles refer often to the results from one or a few studies performed even more than 30 years ago. Further studies should be done to prove the validity of all the data used before any kind of (often "popular") conclusion and recommendation is given.

Food supplements and herbal products

Herbal products are widely used in both the adult and children population and are taken by women during pregnancy and lactation. The consumption of these products has even risen in recent years; they are often used concomitantly with drug medications, usually without any professional supervising. This fact, however, may cause adverse effects or failure of the therapy as well as variable outcomes of clinical trials where the concomitant use was not controlled. There is growing concern that there is a lack of disclosure of herbal use by patients to doctors [79]. According to outcomes from the "Drug Interactions with Herbal Products & Food" symposium in Washington 2002, supported by American Society for Clinical Pharmacology and Therapeutics and the US Food and Drug Administration (FDA), 20% Americans take prescription medications concurrently with at least one herbal product or a high-dose vitamin, or both [80].

Various pre-clinical and *in vitro* investigations on a series of other herbal remedies were performed; clinical relevance of some of them remains to be established [81]. The prevailing botanicals are ginkgo (*Ginkgo biloba*), St John's Wort (*Hypericum perforatum),* ginseng *(Panax ginseng),* garlic *(Alium sativum),* echinacea *(Echinacea augustifolia, E. purpurrea, E. pallida),* saw palmetto *(Serenoa repens)* and kava *(Piper methysticum).* The most important interactions are observed with St John's Wort (SJW). More than 50 papers were published in past few years regarding SJW interactions with synthetic drugs; SJW is proved to decrease significantly plasma levels of indinavir, cyclosporine, irinotecan, warfarin, phenprocoumon, alprazolam, dextrometorphane, amitriptyline, simvastatin, theophylline and digoxin. Moreover, it causes intermenstrual bleeding or therapy failure (pregnancies) of oral contraceptives (ethinylestradiol/desogestrel, ethinylestradiol/norethindrone) and delirium or mild serotonin syndrome if used with loperamide or selective serotonin-reuptake inhibitors (SSRI: sertaline, paroxetine, nefazodone) [43, 80, 82–84].

Mechanism of SJW action includes potent induction particularly of CYP3A4 and/or P–glycoprotein; the component responsible for this effect is hyperforin, content of which was shown to correlate strongly with the enzyme induction efficiency of the SJW extracts. However, even SJW preparations with low hyperforin amount (<1 %) reveal a therapeutic effect equivalent to imipramine or fluoxetine in the treatment of moderate forms of depression indicating that hyperforin is probably not the main active compound in treatment of depression [84, 85].

Crude extracts of SJW demonstrated inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 *in vitro*; the last three being more sensitive. From the major SJW extract constituents, which are anthraquinone-derivative hypericin, flavonoid 13,118–biapigenin, flavonoid (flavonol) quercetin and chlorogenic acid, only the 13,118–biapigenin was shown to be a potent, competitive inhibitor of CYP2C9 and 1A2, while hyperforin was a strong noncompetitive inhibitor of CYP2D6 and competitive inhibitor of CYP2C9 [86]. The effects on CYP isoforms other then CYP3A4 would deserve a systematic examination.

SJW was proven to remarkably decrease level of cyclosporine (substrate of CYP3A4), which has an apparent clinical consequence, since low cyclosporine levels are associated with an increased risk of rejection of a transplanted organ. Two cases of heart rejected in two transplant patients due to a metabolic interaction of SJW and cyclosporine were already reported by Ruschitzka et al.[84, 87] SJW doesn't affect only CYP3A4, it was found to induce also CYP2C19 in healthy volunteers and thus enormously decrease plasma concentrations of omeprazole, which is metabolized by both the CYP isoforms [88]. Coadministration of SJW increases significantly the clearance of S-warfarin (by up to 40 %) in healthy volunteers while Asian **ginseng** produces only a moderate increase (by approx. 14 %) [83]. According to another author, ginseng lowers plasma concentrations of warfarin and alcohol, and if used concurrently with phenelzine, a monoaminoxidase inhibitor (IMAO), it can intensify mental and/or physical hyperactivity (mania) as a side effect of the antidepressant therapy [43]. The biologically active compounds of ginseng root constitute of at least seven steroidal saponins

*Tab. 3. Overview of the most important interactions of the St John's Wort (SJW) extract with some drugs: relative ratio of c_{max} in group given SJW to c_{max} of the control group (*important interaction, **middle important interaction, ***very important interaction)*[14]

Drug	Dose of drug	SJW extract (ml)	c_{max} change (folds)
Cyclosporin*	2.8 mg/kg	300	-1.42
Desogestrel/ ethinylestradiol*	0.15 mg/ 0.02 mg	600	-1.18
Efavirenz**	?	?	↓
Fexofenadin	2.5 mg/kg	300	-1.39
Imatinib**	400 mg	300	-1.18
Midazolam*	2.5 mg/kg	300	-1.53
Nevirapin**	?	?	↓
Simvastatin*	10 mg	300	-1.28
Takrolimus*	0.1 mg/kg	300	-1.23
Telithromycin***	?	?	?
Verapamil*	120 mg	250	-1.80

? – doses applied were not specified in the respective studies
↓ – decrease in c_{max} where exact data were not published

ginsenosides. Some of them were shown to increase CYP2C9 or CYP3A4 activity *in vitro*, but as ginseng had not affected the urinary 6-ß-OH-cortisol/cortisol ratio in human, it is not considered to induce the CYP3A4 enzyme [89] (Table 3).

Ginkgo biloba extract interacts with warfarin increasing its levels and hence the risk of bleeding, and with thiazide diuretics, where it may heighten the blood pressure [43]. An interpretation of these effects in more detail remains to be done. A coma was reported due to an interaction with trazodone [90]. *In vivo*, standardized extract of ginkgo caused a decrease in plasma concentrations of propranolol by accelerated conversion of parental drug due to induction of CYP1A2. It also significantly induced CYP2B1/2 and CYP3A1 in the rat, suggesting potential interactions with substrate drugs for these two enzymes [91]. In the case of ginkgo extract, the occurrence of bleeding has been reported in patients who used it with anticoagulant drugs such as aspirin, rofecoxib, or warfarin at the same time [92]. Another study had shown that the simultaneous and continuous intake of ginkgo extract significantly affects the hypoglycemic action of tolbutamide, possibly via a hepatic CYP enzyme-mediated mechanism, particularly in the aged rats [92].

Soy-derived products are used for the treatment of menopause in women due to the content of phytoestrogens (mainly isoflavones) that are functionally similar to 17ß-estradiol. These products popularity is raising as the side effects of traditional hormone replacement therapy are suspected. Cytochromes P450 should be affected by two major soy isoflavones, genistein and daidzein, which may inhibit CYPs *in vitro*, mainly CYP1A [93]. Genistein inhibits also P-glycoprotein activity *in vitro* [94]. The majority of the isoflavones in plasma are in the unhydrolyzed form that produced very little inhibition with CYPs 1A2, 2A6, and 2D6 and slight activation of CYP3A4. The hydrolyzed soy isoflavones do not inhibit CYP activities. Soy extract containing both daidzein and genistein have not affected mRNA level of rat hepatic CYP1A1, CYP1A2, CYP2B1/2, CYP2C11, CYP2E1, CYP3A1, CYP3A2 and CYP4A1 [95]. Genistein increased relative bioavailability of orally administered paclitaxel from 1.26- to 1.55-fold [96]. Soy extract as a complex have not altered the urinary 6-ß-OH-cortisol/cortisol ratio in men significantly, suggesting that unlike St. John's Wort, it is not CYP3A inducer [89].

Kava is used for its anxiolytic, antistress and sedative properties. The psychoactive activity in kava is contained in a series of about 18 compounds called kavalactones of which six (kavain, yangonin, methysticin, dihydrokavain, desmethoxyyangonin and dihydromethysticin) account for about 95% of the lipid extract and the activity [97]. Some of its constituents (desmethoxyyangonin, dihydromethysticin, and methysticin) significantly inhibited one or more of CYPs *in vitro* at concentrations of less than 10 μM. They were sometimes more potent inhibitors of the isoforms 1A2, 2C19, and 2C19 than the positive controls used in each assay (furafylline, sulfaphenazole, and tranylcypromine, respectively), which are known to produce clinically significant drug interactions [98]. In clinical practice, kava was shown to increase "off" periods in patients treated for Parkinson's disease with levodopa. If taken concurrently with alprazolam, it may cause a semi comatose state [43, 99].

Saw palmetto extract (which is used in the treatment of benign hyperplasia of prostate) and echinacea extract were not proven to cause any significant interactions with synthetic drugs [43]. However, *in vitro*, saw palmetto extract showed a potential for strong adverse interactions as a potent inhibitor of CYP3A4, 2D6, and 2C9 and *Echinacea purpurea* extract demonstrated mild inhibition of CYP3A4 activity with 7–benzyloxy–4–trifluoromethylcoumarin as the model substrate. Little effect on CYP2D6 and moderate inhibition of CYP2C9 was seen with *E. purpurea* [100]. In human volunteers, saw palmetto extract did not alter CYP2D6 activity and at generally recommended doses is unlikely to alter the disposition of coadministered medications primarily dependent on the CYP2D6 or CYP3A4 pathways for elimination [101].

Recently, Hellum et al. [5] found that the common **valerian** increases the activity of CYP3A4 and surprisingly also of the CYP2D6, which is known to be

non-inducible. Despite previous reports that have found no effect on either CYP3A4 or CYP2D6 the authors suggest a potential for an inductive effect on intestinal CYP3A4 metabolism and, hence, on a decreased drug bioavailability. These researchers observed also a general inhibitory potential of **horse chestnut** and common **sage** and showed for the first time that ginkgo biloba may exert opposite and biphasic effects on CYP1A2 and CYP2D6 metabolism, when induction of CYP1A2 and inhibition of CYP2D6 were found at low concentrations; the opposite was observed at high concentrations.[5)] Some other herb extracts were also tested for their potential to interact with other drugs metabolism, e. g. *Citrus aurantium* or milk thistle, but they appear to pose a minimal risk for CYP-mediated herb-drug interactions in humans [102)].

CONCLUSION

Food-drug and herb-drug interactions may occur and cause pronounced side effects of the drug as well as failure of the therapy. Clinicians should be familiar with the most important inducers and inhibitors of cytochrome P450 enzymes that are present not only among drugs but also in the environment and nutrition of their patients: the most important are grapefruit juice and some other citrus and tropical fruits and Saint John's Wort. Anyway, their clinically proved importance relate to only a few drugs, thus allowing good drug therapy management. An effusive fear should not be present when prescribing most of the common drugs. Medical professionals would probably profit from more relevant recommendations than available. Although there is quite a lot of data from animal as well as human studies, inconsistency of particular conclusions is remarkable and valid recommendations are not given. The summaries of product characteristics (SmPC or SPC) of medicinal products that are authorized by the European health authorities do not fulfill the current recommendations in this field and are a suboptimal source of information for food-drug interactions [103)]. More systematic approach to this field is necessary to alleviate the common risk of food- and herb–drug interactions.

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