**REVIEW PAPER**

# Products of plant origin – benefits and the potential risk for the consumer

Karasiewicz Monika[1], Bogacz Anna[1, 2], Krzysztoszek Jana[3], Pędziwiatr Daniel[1],
Czerny Bogusław[1, 4]

[1] Department of Stem Cells and Regenerative Medicine, Institute of Natural Fibres and Medicinal Plants, Poznan, Poland
[2] Regional Blood Center, Poznan, Poland
[3] Chair of Health Prevention, Faculty of Health Sciences, Poznan University of Medical Sciences, Poland
[4] Department of Pharmacology and Pharmacoeconomics, Pomeranian Medical University in Szczecin, Poland

## ABSTRACT

Phytochemical compounds are widely used in traditional medicine in the treatment of many ailments. In recent years, an increasing interest is observed in the use of new natural bioactive substances and whole standardized extracts in the prevention and therapy of diseases. Some of these are the components of the diet, diet supplements or at higher doses are used as herbal medicines. Many phytochemicals have documented a beneficial effect on health, but they must be used properly. Therefore, it is important to inform about differentiating between herbal medicine and dietary supplement. Further, the possibility of interactions with synthetic drugs and the mechanisms of these effects is necessary to describe for the safety of phytotherapy. The goal of our paper is to show high prophylactic and medicinal potential of natural active compounds of plant origin. We also want to draw attention to the safety of their use by the consumer. Therefore, we present some studies on the benefical properties of natural active compounds, mainly in the prevention and treatment of cancers and neurodegenerative diseases. The results of the described studies are extensively discussed and their suitability for further testing *in vivo* and in clinical trials is examined. At the same time we show selected interaction of common medicinal plants or their raw materials with synthetic drugs.

**Keywords:** herbal products, pro-health effect, chemoprevention, herb-drug interaction.

## Introduction

Wide properties of phytochemical compounds and their multidirectional action caused that they are used in the treatment of many diseases as herbal medicines and as foods components or dietary supplements. The pharmacological action in many of them is supported by well documented studies *in vitro*, *in vivo* and in some cases tested in clinical research. Overall, awareness of the benefits from the use of herbal products is very high in society. It is worth noting that currently there is an increasing interest in the screening for natural bioactive substances and whole standardized extracts for use in new applications, especially in the treatment of cancer, neurodegenerative diseases, metabolic disorders and chronic inflammation. Beside the well-known components with numerous *in vitro* and *in vivo* studies (green tea plyphenols, quercetin, genistein from soybean and allicin from garlic), there are still new scientific evidences with promising results.

It can be also noted that consumers often believe that natural products are considered safe but this is oversimplification. Admittedly, the safety and efficacy of herbal raw materials is usually confirmed by experience during many years of use in traditional medicine

in the treatment of many common ailments or diseases. However, due to the multi-activity of products with herbal origin, the studies on their safety are needed. This is important in view of the fact that for some consumers, such as pregnant women, nursing women and children, insufficient number of well-documented research or no research supporting the safety of most herbal products is observed. Further problem is the difficulty in differentiating between a dietary supplement and herbal remedy for the treatment of a specific disease [1].

There has been a lack of sufficient knowledge of patients about the potential risks of consumption of herbal products with standard drug therapy and other adverse consequences of their abuse. The risk is particularly high in consumers with advanced and very young age, in patients with hepatic impairment and/or kidney disease, in patients dehydrated, in cases with metabolic diseases and endocrine system disorders. The consequence of the interaction may be a change in half-life synthetic drug, modification of their actions as well as other negative effects on the body. Interaction between the drug and herbal product may occur at various stages of the pharmacological processes including changes in pharmacokinetics at the absorption step, binding proteins, membrane transport, distribution, metabolism and excretion. Interactions may also occur at the stage of the biotransformation by cytochrome P450 enzymes.

The aim of this paper is to present selected new lines of research on the use of plant compounds for health purposes. On the other hand, we want to underline the possibility of occurrence of interaction between the herbal medicine and synthetic drug.

# The current state of knowledge on new applications of selected natural active compounds in the prevention and therapy

It is known that plants extracts and parts of plants or their preparations have been used in traditional medicine for several thousand years. They were used mainly by the taste properties and especially the therapeutic effect. Recently, the herbal medicines and diet supplements are commonly used in developed countries. In this paper, we have elucidated the possible pro-health effects of few natural substances of plant origin, including their potential in the prevention of diseases and treatment.

# Chemoprevention and cancer treatment

Chemoprevention of cancer focuses on the factors affecting the early stages of cell transformation. Naturally occurring phytochemicals have a wide range of cellular effects including carcinogens protection and the detoxification of reactive molecules. Moreover, they may enhance innate immune surveillance and improve the elimination of transformed cells. Further, phytochemicals have several impacts on the mechanisms of DNA repair and can cause the inhibition of cell proliferation pathways [2]. Numerous reports, including clinical studies suggest the beneficial effects of medicinal herbs and their active compounds in combination with conventional therapeutics on the survival, immune modulation and quality of life of cancer patients. Scientists examine the possibility of using the herbal materials mainly in the chemotherapy resistance and in the reduction of side effects. Moreover, among the new applications of active compounds with plant origin is treatment of diseases, the blood-brain barrier modulation and as a chemotherapeutic agent sensitizers.

Based on preclinical studies it can be assumed that curcumin, a polyphenol derived from the roots of *Curcuma longa* plant, may be useful for the prevention and/or treatment of several diseases, such as colorectal cancer, cystic fibrosis, inflammatory diseases and Alzheimer's disease [3]. Curcumin seems to have anti-tumor properties by inducing cell cycle arrest and apoptosis most importantly through pleiotropic modulation on nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), STAT-3 and cyclin D1 in *in vitro* models [2,4–7]. Further, several phase I clinical trials confirmed safety of curcumin in patients (up to 8 g/day, p.o.) [2, 3, 8]. However, excessive use of curcumin can damage the intestinal microflora, disrupt the normal physiology and immune response [9]. The bioavailability of curcumin after oral administration is relatively low and mainly metabolites are detected in plasma [3, 10]. On the other hand, measurable biological effects have been demonstrated in patients with different types of malignancies including pancreatic cancer, multiple myeloma and advanced colorectal cancer resistant to standard chemotherapy [11–13].

Another known active compound is quercetin found in a wide variety of foods including capers, apples, onions, berries, green and black tea, and red wine [14]. This flavonoid showing antioxidant properties acts

mainly by scavenging reactive oxygen species. In addition, anticancer, antiviral, anti-inflammatory, and anti-amyloidogenic activities of quercetin have been extensively analyzed [15, 16]. Rivera et al [17] showed that combination of polyphenols (resveratrol, quercetin and catechin) reduces breast cancer growth and metastasis in mice. Further, quercetin (15mM) caused the inhibition of proliferation similar to the combination of all three of polyphenols. In mice with very severe immunodeficiency (SCID) a reduction of tumor growth by about 70% was observed after administration of quercetin (15 mg/ kg body weight). In conclusion, quercetin appears to be a promising polyphenol for future development as therapeutic preparation for breast cancer. It has been reported that quercetin (doses up to 1 g/day) had no adverse effects on blood parameters, liver and kidney function, hematology, or serum electrolytes in human [3, 14]. But the elimination of quercetin metabolites from plasma is quite slow (half-lives ranging from 11 to 28 h), which means the accumulation of this compound in the body in daily uptake [3, 18].

Epigenetic changes in neoplastic cells are frequently observed in carcinogenesis. Therefore, new therapies could restore the correct pattern of methylation of oncogenes and tumor suppressor genes. Recent reports indicate that resveratrol in breast cancer restore the hypomethylated and hypermethylated status of key tumor suppressor genes and oncogenes, respectively. The authors showed that the corresponding changes were also noted in mRNA expression [19]. It is known that resveratrol is the most common phytoalexin tested in modern health care. It is a polyphenolic compound belonging to the stilbenes and is produced in a several plant after exposure to stress, injury, fungal infection, or UV radiation [3]. Resveratrol shows antioxidant, neuro- and cardio- protective properties and may also act as a factor retarding the aging process, antifungal, antibacterial, antiviral, anti-inflammatory and a chemoprevention agent. Moreover, resveratrol can inhibit tumor growth at the initiation, promotion and progression step. Early studies identified that resveratrol can induce cancer cell apoptosis by affecting signaling pathways in transformed cells [2, 20, 21]. Recently it was described that resveratrol may repress collagen deposition in the vasculature, heart, lung, kidney, liver, and esophagus in animal models. Some data suggest that lung fibroblasts and prostate fibroblast to myofibroblast phenoconversion can be both repressed and reversed by resveratrol *in vitro* treatment [22]. This may indicate that the antifibrotic

therapeutics might be efficacious for the treatment of lower urinary tract dysfunction (LUTD). However, the low bioavailability (2%) and a rapid biotransformation to less active metabolites limit the possibilities of resveratrol use in medicine. Therefore, researchers are working on resveratrol derivatives whose biological properties have proved to be higher as compared to their natural precursor [23]. Clinical trials have also defined the safety, pharmacokinetics and metabolism of resveratrol and showed that adverse effects, including abdominal pain, diarrhea, and nausea occur at doses above one gram daily [24]. On the other hand, it was demonstrated that a dose of 1 gram per day for four weeks significantly inhibit the plasma cytochrome P450 and induces CYP1A2 in healthy volunteers. Thus, resveratrol perhaps may affect the metabolism of drugs, and raises concerns about the combined use with pharmaceuticals [2, 25].

The fact that diet is important for health confirms another report indicating that the 1.5% polymeric black tea polyphenols (PBPs) have chemopreventive effect through inhibition of cellular proliferation, inflammation and induction of apoptosis. This effect was observed after 28 weeks of treatment in mice with induced lung cancer. The histopathological evaluation of lung showed decrease in tumor multiplicity which was also correlated with different molecular markers such as reduced Cox-2 expression. Moreover, PBPs down-regulated the cell proliferation induced earlier by tobacco carcinogens [26].

Epidemiologic data indicate that Asian diets containing high amounts of soy products, reduce a women's risk of breast cancer. On the other hand, it has been difficult to dissociate the benefits of soy from others environmental and lifestyle factors. Moreover, soybean isoflavones are phytoestrogens that reduce menopausal symptoms and decrease the risk of certain chronic diseases, such as cancer and cardiovascular diseases. Despite the widespread use of soybean isoflavones as functional food and dietary supplements, data regarding the safety as well as herb-drug interactions, remain scarce. Daidzein, genistein, glycitine and equol are major food-derived phytoestrogens. They bind weakly to estrogen receptors. Therefore, it has been proposed that soy isoflavones can reduce breast cancer risk by interfering with the binding of endogenous estrogens to estrogen receptors [27]. Animal and population studies have indicated that soy intake may also reduce the risk of lung cancer [28, 29]. It seems that dietary isoflavones, may protect against several cancer types, without exerting toxic effects on

normal cells [30]. Especially, genistein showed ability to increase the anti-neoplastic activity of certain chemotherapy drugs in multiple tumor types. On the other hand, some researchers say that dietary soy isoflavones increase metastases to lungs in a model of breast cancer and significantly increased cell proliferation in breast cancer patients who used soy supplementation [31, 32].

So far, it is known that soy isoflavones sensitize non-small cell lung carcinoma cancer cells (NSCLC) to radiation both *in vitro* and *in vivo* studies [33]. On the other hand, radioprotection was demonstrated of normal lung tissues in the lung tumor model [34]. Furthermore, it was shown that soy can protect against radiation-induced injury to normal lung tissue [34]. It is postulated that the use of soy isoflavones as radioprotectors is attractive because they were proven to be safe in controlled human clinical trials [35, 36]. Therefore, in non-randomized, open label clinical trial no NCT01958372 the soy isoflavones may promote radiation therapy, cisplatin, pemetrexed sodium, and etoposide work better by making tumor cells more sensitive to the drug. Soy isoflavones may also protect normal cells from the side effects of radiation therapy and chemotherapy in patients with stage IIIA-IIIB NSCLC. It was also described that combination of genistein and low concentrations of cisplatin induced significantly greater growth inhibition and increased apoptosis in lung cancer cells compared with either agent alone. In addition, the use of both substances together suppress tumor growth *in vivo* compared with either agent alone [30]. A similar synergistic effect of genistein and cisplatin was observed in hepatocellular carcinoma [37]. Moreover, genistein may sensitize estrogen receptor-positive breast cancer cells to tamoxifen treatment [38].

## Impact of plant-derived substances on neurodegenerative diseases

The pathologies of the central nervous system (CNS) may be caused by toxic agents, traumatic injury, or may be the result of neuronal degeneration associated with degenerative disease or aging. Currently available drugs make it possible to alleviate the symptoms of Parkinson's disease (PD). While the search for new substances to achieve therapeutic benefit in patients with PD and Alzheimer's disease (AD), including plant origin is the subject of many recent investigations, it has been shown that a diet rich in flavonoids reduces the risk of neurodegenerative diseases in humans,

induced the neuroprotective effects in rodents and increased the cognitive function in an animal model. Flavonoids induce large effect on neurons and glial cells in culture and in a model for neurodegenerative diseases *in vitro*. In this regard they can be considered as potential neuroprotectors agents and neuroimmunomodulators *in vivo*. Flavonoids also induced neuronal differentiation of mouse embryonic stem cells and human pluripotent stem cells [39].

Polyphenolic compounds (flavonoids, phenolic acids, stilbenes, and lignanes) and terpenes have established effects against Parkinson's disease. The mechanisms of action of the active compounds are various. Parkinson's disease is a neurodegenerative disease associated with loss of dopaminergic neurons in the substantia nigra and with accumulation of aggregated α-synuclein in specific central nervous system (CNS) regions [40]. The complex of flavonolignans obtained from the seeds of *Silybum marianum* and known as silymarin is widely used as an antioxidant and tissue regenerative agent, especially in the treatment of hepatic disorders induced by alcohol, viral hepatitis and the toxin. Besides, it was recently demonstrated that silymarin probably posesses neuroprotective properties against many neurological diseases, including Alzheimer's and Parkinson's diseases, and cerebral ischemia. It was shown that 100 mg / kg of silymarin administered over five days intraperitoneally diminished the number of apoptotic cells and preserved dopaminergic neurons in the substantia nigra in PD model in mice [41].

The flavonoid silibinin is the major active constituent of silymarin. Some authors suggest that silibinin protects mitochondria in PD models and that it offers a starting point for the development of treatments that ameliorate the symptoms of PD. Silibinin pretreatment alleviates motor disorders and loss of dopaminergic neurons. *In vitro* studies showed that silibinin may be considered for use as a potential method for treating PD and other disorders related to neuroinflammation [42]. Pretreatment with silymarin, dose-dependently (1–10μg / kg, i.v.) reduces cerebral ischemic / reperfusion brain infarction by 16–40% and improved neurological deficits in rats with a stroke. Elevated biomarkers for induced brain injury, including lipid peroxidation, protein nitrosylation, and oxidative stress, were all reduced after the application of silymarin. Moreover, expression of inflammation-associated proteins including inducible nitric oxide synthase, cyclooxygenase-2 and myeloperoxidase, and transcriptional factors (nuclear factor (NF)-kappa B and signal transducer and

activator of transcription (STAT-1), as well as proinflammatory cytokine level (interleukin-1β and tumor necrosis factor-α) was significantly prevented by silymarin. Consequently, it seems that silymarin displays beneficial effects of preventing inflammation-related neurodegenerative disease, stroke including but needs further investigation and clinical evidences [43].

Alzheimer's disease (AD) is the one of the most common neurodegenerative disorder with reduced therapeutic or prophylactic treatment. AD histopathologically is manifested by the presence of β-amyloid (Aβ) deposits and formation of neurofibrillary tangles [3]. Medicinal plants are firstly important source of protective compounds against AD and further using the structure of active substances with plant origin as templates for synthetic drugs provides a wide variety of potential neuroprotective compounds. *In vitro* and *in vivo* studies suggest that the neurobiological effects of active compounds of plant origin may contribute to the clinical benefit in a model of Alzheimer's disease.

One of neuroprotective natural substances is bilobalide (BB), the main terpenoid of *Ginkgo biloba* leaves. This compound has the protective effects on neurons and Schwann cells. However, it should be noted that this sesquiterpene trilactone induces some xenobiotics metabolizing enzymes (CYP3A1 and CYP1A2) in liver which may be associated with interactions between *G. biloba* and pharmaceutical drugs or other herbal medicines [3]. Bilobalide in the range of concentrations *in vitro* (25–100 mM) blocked reactive oxygen species (ROS)-induced apoptosis in early stages and decreased the elevated levels of *apoptotic* factors. In addition, some authors suggest that bilobalide can inhibit the β-amyloid production [44]. However, it suggested that excessive dose of BB can cause adverse reactions [45].

Furthermore a beneficial effect on AD seems to have quercetin (QCT). To improve the penetration of the compound across the blood brain barrier the solid lipid nanoparticles (SLNs) of quercetin were prepared. Behavioral studies confirmed a better neuroprotective effect of this formulation [46]. *In vitro* study showed that QCT (10 µM) can exert anti-amyloidogenic effects by inhibiting the formation of Aβ fibrils [47] or at lower doses (5–20 µM) significantly attenuated apoptosis in hippocampal cultures. At the same time, quercetin may induce cytotoxicity at high doses (40 µM) [48]. QCT combination with BB could significantly enhance the level of brain-derived neurotrophic factor (BDNF) which plays important role in neurogenesis, neuronal

survival, neuronal differentiation, and synaptic plasticity in mice brain [49].

Epigallocatechin gallate (EGCG) is the most abundant catechin from *Camellia sinensis* leaves. As a flavonoid it has antioxidant properties and has been the subject of many studies in cancer, atherosclerosis, and neurodegenerative diseases. The elimination half-life of EGCG is about 3 h [50]. Orally administered EGCG at a dose of 10 mg / kg could reduce acetylcholinesterase activity, glutathione peroxidase activity, nitric oxide metabolites and ROS content in model of dementia [51]. In other study, EGCG (3 mg/kg in water) enhanced memory formation and α-secretase activity, and suppressed γ-secretase activity in AD mice [52]. At higher doses the EGCG improved the cognitive abilities of mice. EGCG also prevented lipopolysaccharide -induced memory impairment and apoptosis, astrocytes activation and inflammatory factors. Moreover, *in vitro* and *in vivo* studies described by Dragicevic et al [53] showed that EGCG and luteolin were the main two mitochondrial restoration compounds among 25 tested flavonoids.

Rosmarinic acid (RA) is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid which is the main phenolic compound in *Lamiaceae* family used commonly as culinary herbs, such as lemon balm (*Melissa officinalis*), rosemary (*Rosmarinus officinalis*), oregano (*Origanum vulgare*), sage (*Salvia officinalis*), thyme and peppermint. Rosmarinic acid possesses many biological activities including antiviral, antibacterial, antioxidant, anti-inflammatory, anticancer, and neuroprotective effects. Several human studies investigated the potential beneficial effects of RA on cognitive function [54]. Based on a review of literature it may be noted that the RA (0.25–4 mg / kg, i.p.) significantly prevented β-amyloid -induced memory impairments, mainly by NF-κB and TNF-α. In other study RA (1–10 µM) could inhibit apoptotic pathways by decrease of ROS formation, caspase-3 activation, and DNA fragmentation. Generally, no severe side effect has been described for RA application [55–57].

Natural products of plant origin can be considered as pharmaceuticals or future therapy complementary to conventional therapeutic approaches to mitigate adverse effects and improve the effectiveness in the treatment of neurodegenerative diseases. Previously well-designed clinical trials are needed to assess the safety and therapeutic benefits of phytochemicals for the patient. Despite the fact that some neuroprotective compounds derived from natural sources are attractive in the treatment of neurodegenerative dis-

ease, the poor bioavailability and low clinical efficacy are the serious problems. Possibly, the advanced pharmaceutical technologies and medicinal chemistry will use the opportunity to prepare novel formulations or design new compounds based on natural templates.

## Herb-drug interaction as a potential risk for the consumer

It is known that some components of the herbal products can modulate xenobiotic metabolism and transport systems which play an important role in the absorption and disposition of drugs. Interaction between the drug and herbal remedies may occur on the various stages including pharmacokinetic: absorption, binding proteins, membrane transport, distribution, metabolism and excretion. Studies have shown that interactions are often caused by the modification of the cytochrome P450 (CYP-450) isoenzymes in phase I biotransformation of drugs. CYP isoforms carry out conversion of the lipophilic compounds, including drugs to the hydrophilic metabolites to facilitate its excretion in the urine or bile. Cytochrome P-450 isoenzymes are expressed at the highest level in the liver. Inhibition of the CYP450 isoform activity leads an increased drug concentration in plasma and intensifying its action and toxicity. The induction of the enzyme causes the opposite effect, the decline in plasma concentrations and reduced the effectiveness of therapy. It is recognized that approximately 70–80% of all currently prescribed drugs are metabolized by the CYP system. Briefly, the CYPs most active in drug metabolism are CYP2C, CYP2D and CYP3A subfamilies. It has been shown that CYP3A4 isoforms involved in the metabolism of nearly 50% of clinically used drugs. While the CYP1A, CYP2A and CYP2E subfamilies metabolize, besides drugs, also many protoxins and procarcinogens. Therefore, modifications of their activities by phytochemicals can have clinical relevance.

The multidrug resistance protein (P-glycoprotein) is ATP-dependent protein in the apical membrane of intestinal epithelium, hepatocytes, kidney proximal tubule epithelium, and brain capillary endothelium. In these structures P-gp pumps a variety range of xenobiotics into the intestinal lumen, bile duct, renal tubule, and brain capillary, respectively. In this regard it plays an important role in the intestinal absorption, distribution in the central nervous system and excretion of drugs. Thus, inhibition or induction of CYP enzymes and/or P-gp by administration of prescribed drugs

with some herbs can cause pharmacokinetic interactions potentially leading to failure of therapeutic agents [58]. In this paper we draw attention only to some of the commonly used medicinal or dietary herbs as factors causing drug interactions.

Extracts and preparations of the leaves of *Ginkgo biloba* are used for the treatment of cerebrovascular dysfunctions, dementia, memory impairment (120–240 mg/day), and peripheral vascular disorders [58, 59]. *G. biloba* has anti-platelet activities and among the interactions mentioned the possibility of bleeding during the use of the extract with other anti-platelet agents (warfarin, aspirin) or herbal remedies possessing similar anti-platelet activities (garlic or ginseng) are worth noting [60]. Data from *in vitro* studies suggest the existence of interaction of *G. biloba* on the stage of biotransformation of xenobiotics by changes in the activity of cytochrome P450 isoforms [61]. It is possible that terpenoid fraction of *G. biloba* extract (EGb 761) inhibited CYP2C9 while flavonoids decrease the activity of CYP2C9, CYP1A2, CYP2E1 and CYP3A4 [62]. Generally, it has been shown that the level of CYP2B1 / 2 and 3A1/2 are induced in the rats under the influence of *G. biloba* while CYP1A1/2, 2C11, 2E1 and 4A1 do not change significantly. In the human CYP3A4 and CYP1A2 grows, but CYP2C9 and CYP2E1 falls under the influence of *G. biloba* extract. It is believed that the induction of CYP3A4 may be due to the interaction of ginkgolide A via pregnane X receptor. Further, the activity of human P-gp was significantly reduced by *G. biloba* extract in the *in vitro* or *in vivo* studies [58]. On the other hand, Li et al. showed that ginkgolide A and B induce hepatic P-gp while flavonoids and bilobalide do not influence P-gp activity [63]. Long-term use of extract in rats decrease bioavailability of cyclosporine which may affect the modulation of P-gp activity [64].

*Allium sativum* (garlic) is widely used as a medicinal and dietary product, which has a wide pharmacological activity such as antimicrobial, hypolipidemic, antihypertensive, procirculatory, antidiabetic, and anti-immunoenhancing efficacy [58]. Chemopreventive properties of garlic are not fully understood, but it is suggested that that this may be an inhibiting effect on CYP2E1 and induction of phase II metabolism of xenobiotics. Among the active compounds include alliin, allicin, diallyl disulfide, and diallyl sulfide. There are studies indicating that uncontrolled dosage *A. sativum* is not always safe, and necrotic changes in the histopathological study of the liver and kidney in rats after administration of high doses of garlic [1000 mg / kg] for 30 days have been observed [66]. There-

fore, according to some authors, the recommended daily dose of fresh garlic is about 4 g or 600–900 mg garlic powder standardized to 1.3% of the alliin [58, 59]. Some studies suggest that garlic can modify the pharmacokinetics of paracetamol and cause hypoglycemia together with the chlorpropamide dosage [67]. Well described interaction is the impact of garlic with a CYP2C9 substrate warfarin, which is probably due to antiplatelet activity of garlic [68]. Therefore, garlic should not be taken with anticoagulants due to the increasing risk of bleeding. Administration of the enteric coated 2g/dose x twice a day for two weeks garlic does not alter the pharmacokinetics of warfarin and its effects in healthy males but the chronic (above 21 days) consumption of garlic powder increases clearance saquinavir, CYP3A4 and P-glycoprotein substrate [69–71]. In general, garlic extract inhibited *in vitro* CYP2C9 * 1, 2C19, 3A4, 3A5 and 3A7 activity, but does not alter the CYP2D6, and increased CYP2C9 * 2 activity in recombinant human CYP isozyme system. Administration of the garlic oil causes an induction of rat CYP2B1 activity in mice. Moreover, the clinical studies show the lack of connection between the intake of garlic extract and CYP2D6 and CYP3A4, but there have been reports concerning the induction of CYP3A4 [65]. In addition, diallyl disulfide induced *in vivo* CYP2B1 / 2 activity in rats and *in vitro* inhibited CYP2E1 activity in rat and human recombinant CYP isozyme system. Allicin also inhibited CYP1A2 activity in recombinant human CYP isozyme system. The effect on P-gp is not clear [58].

*Camellia sinensis* is used worldwide as a medicinal and dietetic herbs and typically contains catechins as the principal pharmacologically active phytochemicals, including EGCG. Among the interactions is mentioned lowering the absorption of alkaloids such as morphine, antidepressants and neuroleptics as a result of the impact of tannin tea [72]. There is also a risk of modulation of cytochrome P450 activity. Green tea extract may increase CYP1A, 2B and 3A activity in rats, while in humans reduces CYP2C9, 2D6, and 3A4 in human liver microsomes [73]. Our results suggest that green tea extract may decrease mainly the expression of CYP2C6 in rat liver (homologue to human CYP2C9) and may participate in clinically significant interactions with drugs metabolized by these enzymes [74]. In addition, EGCG may inhibit CYP1A2 and CYP3A4 in human cells [75]. Green tea polyphenols including EGCG also appears to inhibit the activity of P-gp [58].

Rosemary extract increased the protein expression of hepatic CYP2B1 / 2, but did not change hepatic CYP1A1 /2 in rats [76]. Further, rosmarinic acid induced the *in vitro* activity of CYP1A, 2B and 3A in both human and rat hepatoma cells but inhibits human recombinant CYP3A4 activity, not CYP2C9 and 2D6 [77]. In addition, rosemary extract inhibited P-gp-mediated efflux of doxorubicin and vinblastine in P-gp-overexpressing human breast cancer cells [78], mRNA and protein expression of P-gp and efflux of doxorubicin and rhodamine 123 used as a dye in human gastric cancer cells resistant to Adriamycin [58, 79].

The protein expression of intestinal CYP3A and P-gp was significantly reduced by treatment with curcumin (60 mg / kg / day) for 4 days [80]. Curcumin decreases the expression of MDR1 gene (P-gp) leading to increase the sensibility of resistant human gastric cancer cells on the vincristine action [64, 81]. In addition, curcumin inhibited the activity of CYP1A1, 1A2, and 2B1 in rat liver microsomes [58].

Numerous authors claim that *Panax ginseng* may interact with oral anticoagulants, hypoglycemic agents, corticosteroids and antiplatelet agents [60, 82]. The interaction was observed of ginseng with monoamine oxidase inhibitor- of phenelzine. In addition, ginseng may increase the effect of warfarin, heparin, aspirin and other anticoagulants. In animals, ginseng induces alcohol and aldehyde dehydrogenases activity increasing the clearance of alcohol. Ginseng taken with stimulants can cause tachycardia or hypertension. The suggested daily dose is 80-350 mg of the extract or 1–2 grams of powdered raw material [72]. Studies have shown that interactions are the result, among others, of changes in the activity of drug metabolizing enzymes. Ginseng extract inhibited the *in vitro* activity of CYP1A1 / 2, 1B1, and 2E1 in rat liver microsomes [83], while it did not modify the mRNA expression of rat hepatic CYP1A2, 2B1, and 3A23 [84]. It was also shown that ginseng extract inhibited CYP1A1, 1A2, 1B1 and activities in recombinant human CYP isozyme system [58].

Products containing *Echinacea purpurea* are commonly used in phytotherapy of colds, coughs, bronchitis, influenza, inflammation of the mouth and throat. It is one of the most commonly used therapeutic agents in adults and children and its application declare for 10–20% of herbs consumers. Although *E. purpurea* appear to be tolerated in short (8–10 days) and long-term (2 months), uncontrolled consumption can generate a multiple drug interaction [85]. Therefore, *E. purpurea* should not be administered with drugs that affect liver function: anabolic steroids, amiodarone, methotrexate, and ketoconazole as well as with immu-

nosuppressive drugs such as cyclosporin. Prolonged stimulation of the immune system can lead to immunosuppression. There are also studies *in vivo* indicating the possibility of interaction between *E. purpurea* and other therapeutic agents including antibiotics, and substrates of CYP enzymes such as anticoagulants, benzodiazepines and calcium channel blockers [86].

Alcoholic extracts of valerian root are used as a sedative in nervous tension, anxiety, sleep disorders and vegetative neurosis. It has been shown that isolated valepotriates, as used in the treatment of geriatric have affinity for benzodiazepine receptors in the brain, which explains their sedative and little anxiolytic effect. Valerian should not be used with benzodiazepines and alcohol. Based on presented studies, it is claimed that valepotriates may prolong the action of barbiturates whereas intraperitoneal administration of valerenic acid may cause an increase of the anesthetic effect of pentobarbital [72]. Many studies indicated that *V. officinalis* with drugs can lead to the potential herb-drug interactions, mainly by CYP3A4, CYP2C9 and CYP2C19 enzymes modification. Our results suggest that standardized *V. officinalis* extract can decrease the CYP3A4 activity *in vivo* and may participate in clinically significant interactions with drugs metabolized by this enzyme. Inhibition of the CYP3A4 enzyme causes a decrease of drug metabolism leading to an undesirable pharmacological effect and the appearance of toxic symptoms of overdose [87].

It is known that the active substances of alcoholic extract of *Hypericum perforatum* are hyperforin and hypercin which inhibit the reuptake of neurotransmitters such as serotonin and noradrenaline. Moreover, many studies confirmed the effect of St. John's wort on the expression level of P-gp and CYP3A4 [64]. Clinical studies indicate that St. John's wort (SJW) may interact with antidepressants, antiepileptics, immunosuppressants (cyclosporine, tacrolimus), oral contraceptives, anticoagulant (warfarin), calcium blockers (nifedipine, verapamil), digoxin, anti-HIV, anticonvulsants, anesthetics, drugs used in addicted patients (e.g., methadone), muscle relaxing agents, drugs acting on the respiratory system, hypoglycemic, antimicrobic, and antimigraine medicines as well as cytostatics [88]. Most of these interactions are the result of induction of CYP3A4 and P-glycoprotein (P-gp) by St. John's wort extract. For example SJW can reduce the serum concentration of selected antineoplastic agents such as imatinib, irinotecan and docetaxel and reduce the clinical efficacy of these drugs [89]. Furthermore, the clinical studies shown that extract of St. John's

wort induces CYP2E1 and CYP2C19 but not CYP1A2, CYP2D6, or CYP2C9 [88].

The study highlighted only the selected aspects of the herb-drug interaction. This subject is inexhaustible and the underlying mechanisms of interaction are still the topic of many research. Due to the possible occurrence of herb-drug interactions, safely is to consult the use of herbal products in high doses. In addition, consumers/patients should describe the use of herbal remedies or supplements in medical interviews.

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**Correspondence address:**
Monika Karasiewicz
Department of Stem Cell and Regenerative Medicine
Institute of Natural Fibres and Medicinal Plants
2 Kolejowa Street, 62-064 Plewiska, Poland
phone: +48 616659550
fax: +48 616517192
email: monika.karasiewicz@iwnirz.pl