

REVIEW ARTICLE

The effect of herbal materials on the P-glycoprotein activity and function

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S u m m a r y

P-glycoprotein (P-gp) encoded by the MDR1 (multidrug resistance 1) gene is ATP-dependent transporting protein which is localized in the cell membrane. P-gp is expressed

mainly in organs with the secretory functions and its physiological role concerns tissue protection against xenobiotics. P-glycoprotein is involved in the permeability barriers of the blood-brain, blood-placenta directly protecting these organs. It participates in the transport of many drugs and other xenobiotics affecting their absorption, distribution, metabolism and excretion. The high P-gp activity in the cell membranes of cancer tissue is a major cause of lack of effectiveness of chemotherapy. Hence, the methods which could increase the sensibility of these pathological cells to cytostatics are still being searched. In the experimental studies it was shown that natural plant substances may have an effect on the expression level and activity of P-glycoprotein. *Hypericum perforatum*, *Ginkgo biloba* and *Camellia sinensis* increase P-gp activity while curcumin from *Curcuma longa*, piperine and silymarin inhibit this protein. Taking into account a wide substrate spectrum of P-gp, application of our knowledge on interactions of herbals and synthetic drugs should be considered in order to improve drug impact on different tissues.

Key words: *P-glycoprotein, multidrug resistance, herbal materials, drug transporter*

INTRODUCTION

P-glycoprotein

P-glycoprotein (P-gp) is a protein encoded by multidrug resistance gene (MDR1). It belongs to ATP-binding cassette transporter superfamily (ABC). P-gp is localized in the cell-membrane and plays an important role in the transmembrane efflux of variety substances including drugs and toxins. This transporter has two hydrophobic transmembrane domains (TMDs) and two intracellular hydrophilic nucleotide binding domains (NBDs). The hydrophilic domains hydrolyze ATP while the hydrophobic domains bind the translocated substances [1-3]. P-gp is the first carrier protein of ATP-binding cassette transporter superfamily described in humans. The presence of this protein had been confirmed for the first time on the cancer cells but later it turned out that it occurs also in healthy cells. Physiologically, P-gp is expressed mainly in the cell membrane of secretory organs (kidney, pancreas, bowels) as well as in endothelial capillary of brain, placenta, ovaries and testis [4, 5]. In normal conditions, P-gp pumps definite substrates out of the cells, creating the blood-brain barrier and blood-placenta barrier. According to Schinkel et al. [6], the product of MDR1 gene is a significant element of blood-brain barrier preventing the penetration of drugs and toxins to brain. In the study on mice, they indicated that the lack of P-glycoprotein causes significantly higher drug concentration in the brain. Additionally, Behravan et al. [7] showed a decrease of placental fetoprotection and presence of inborn defects in fetus in the colony of mice CF-1 which were deprived placental activity of P-glycoprotein. Moreover, P-gp takes a part in elimination of many drugs and toxins, but also influences on the absorption and distribution of xenobiotics. In the studies it was shown that increase of P-glycoprotein expression in cancer cells may lead to resistance in AIDS

patients towards protease inhibitors (indinavir, saquinavir) after oral administration. Hence, P-glycoprotein expression may decide about the treatment efficacy of many diseases because many substances can be transported by P-gp (tab.1) [8, 9].

Table 1.

The substrates of P-glycoprotein

Therapeutic group	Example of drugs
Anticancer drugs	Doxorubicin, etoposide, vinblastine, docetaxel, topotecan, colchicine
Antyhypertensive drugs	Diltiazem, losartan, nifedipine
Antiarrhythmic drugs	Amiodarone, digoxin, verapamil
Steroides	Aldosterone, cortisol, hydrocortisone
Antiretroviral drugs	Amprenavir, saquinavir
Immunosuppressive drugs	Cyclosporine, sirolimus, tacrolimus
Antidepressant drugs	Amitriptyline
Antihistamine drugs	Cimetidine, ranitidine
Opioides	Morphine
Antiemetic drugs	Domperidone, ondansetron
Antibiotic drugs	Tetracycline, rifampicin, erythromycin
Antifungal drugs	Itraconazole

P-glycoprotein in the pathogenesis and treatment of diseases

The high expression of P-gp in cancer cells leads to multidrug resistance (MDR). Multidrug resistance decreases the sensitivity of cancer cells to a number of cytotoxic agents which is a major clinical problem in modern oncology. Numerous studies about MDR indicate a significant role of ATP-binding cassette transporters especially abnormal high expression of P-glycoprotein in this process. P-gp pumps drugs out of the cells and therefore lethal intracellular concentration cannot be reached. Although cytostatics are delivered, the cancer cells can survive in this way. Probably the expression level of P-gp may be a prognostic factor in leukemia and solid tumors [10, 11]. Cancer originating from tissue with high physiological expression of P-gp may be a source of drug-resistance. It concerns especially the cancer of intestine, kidneys, liver, pancreas and adrenal cortex.

P-gp can also increase drug resistance by the influence on the apoptosis process. In normal conditions, it occurs after stimulation with chemotherapeutic ceramides derived from sphingomyelins activate apoptosis. P-glycoprotein decreases the level of sphingomyelins leading to a reduction in the level of ceramides. Hence, the process of apoptosis is reduced [12, 13].

In addition, the functional polymorphisms of MDR1 gene are also a factor affecting drug resistance. Many studies indicate the relationship between a decreased

level of P-gp and the MDR1 gene polymorphisms with morbidity to some types of cancer. This may be due to weakness of P-gp protective role in xenobiotics [9]. Furthermore, the C3435T polymorphism of MDR1 gene increases the risk of Parkinson's disease, especially after exposition to pesticides. In addition, it was shown that the 3435T allele carriers have lower expression of P-gp in the blood-brain barrier which results in less efficient protection of central nervous system against toxins [14]. It was also stated that most patients with ulcerative colitis have the 3435TT genotype associated with low expression of P-gp. This reduced expression is not sufficient to protect the intestinal epithelium which is damaged by bacterial toxins [15].

Furthermore, P-gp involved in the absorption xenobiotics from gastrointestinal tract determines the treatment efficacy of oral preparations. This situation is complicated by the fact that drugs which are substrates for P-gp are simultaneously its inhibitors. Among these drugs are inter alia antimycotic azoles. These interactions can affect the azole antifungals action and also treatment with the co-administered drugs. Moreover, multidrug therapy can lead to interactions that are difficult to establish [16]. Lower P-gp expression in the intestine is also associated with the C3435T polymorphism of MDR1 gene and it increases bioavailability of some oral drugs e.g. nortriptyline, digoxin. Therefore, lack of modification of nortriptyline dose leads to the risk of hypotension as an adverse effect [17]. Antiretroviral drugs used in HIV therapy are also substrates of P-gp. Among patients infected by this virus which are homozygotes 3435TT, the CD4+ lymphocyte regeneration as the effect of antiretroviral therapy, is faster than in carriers of the 3435C allele. This is also connected with higher bioavailability of drug in case of this polymorphism [18].

P-glycoprotein is an important part of blood-brain barrier and protects sensibility cerebral tissue against toxins. On the other hand, it prevents effective pharmacotherapy in the treatment of brain degenerative diseases (Alzheimer's disease and Parkinson's disease) [19]. Results of studies suggest that the certain synthetic substances at higher doses, for example verapamil, are inhibitors for P-gp. However, their high adverse effects e.g. verapamil's cardiac toxicity prevents the practical application in overcoming the multidrug resistance and the blood-brain barrier [4, 20]. Therefore, the search for safe P-glycoprotein inhibitors of herbal origin is a promising in a view of fewer side effects towards normal tissues in comparison to synthetic drugs.

Influence of herbal materials on P-glycoprotein expression

There are few studies on the effects of inhibitors of herbal origin on the level of expression and activity of transporter genes conditioning the phenomenon of multidrug resistance and the blood brain barrier. These studies mainly concern the impact of synthetic drugs, herbals and their preparations on the expression level and activity of P-gp. One of herbal materials is alcoholic extract of *Hypericum perforatum* (St. John's wort) containing lipophilic constituents such

as naphthodianthrone (hypericin and pseudohypericin), phloroglucinol derivatives (hyperforin) widely used in the treatment of depression. Kasper et al. [21] demonstrated significantly better tolerance of patients to St. John's wort extracts compared with selective serotonin reuptake inhibitors (SSRIs). Simultaneously, the effectiveness of this herb in the treatment of mild and moderate depression is similar to synthetic antidepressants [22]. Studies showed that substances responsible for the activity of alcoholic St. John's wort extract are hyperforin and hypericin. These substances inhibit the reuptake of neurotransmitters such as serotonin and noradrenaline [23-25]. Additionally, many studies confirmed the effect of St. John's wort on the expression level of P-gp and CYP3A4. Changes in concentrations of drugs that are substrates for P-gp under the influence of *Hypericum perforatum* were observed. A single dose of this herb administered with fexofenadine resulted in a significant increase in C_{max} parameter for this synthetic drug. Moreover, the use of the extract for 14 days was associated with decreased plasma concentrations of fexofenadine by 35% [26]. These results suggest that single-dose administration of St. John's wort decreases intestinal P-glycoprotein expression. The opposite effect is observed in long-term administration of this herb. A similar correlation was observed in Rengelshause et al. study. Short-term St. John's wort administration resulted in the increase of voriconazole plasma concentration. The authors also showed that the concentration of this drug in plasma that was administered with the extract for 15 days is lower by 59%, as compared to control group [27]. In other study, long-term use of St. John's wort also caused an increase of P-glycoprotein expression in the intestine and led to reduction in the concentration of digoxin in plasma after oral administration of this glycoside [28]. Cyclosporine which is immunosuppressive drug belongs also to P-gp substrates. Its plasma concentration depends on using St. John's wort. Bauer et al. observed significantly lower level of cyclosporine A in patients who receiving St. John's wort for two weeks. This phenomenon is dangerous because it can lead to organ rejection in transplanted patients by a decrease of immunosuppressants action [29]. These interactions may occur in the case of co-administration of St. John's wort and drugs that are substrates for P-glycoprotein. The mechanism of the effect of St. John's wort on the P-gp expression level depends on activation of pregnane X receptor (PXR) which controls the transcription of the MDR1 gene. Hyperforin is probably PXR ligand, so this St. John's wort's constituent is recognized as a factor increasing P-gp synthesis [30].

Other substance affecting the P-glycoprotein expression and function is curcumin. It is a polyphenolic antioxidant which occurs mainly in the rhizomes of *Curcuma longa* (*Zingiberaceae*). Curcumin is used as a spice, pigment in cosmetics and food products as well as a component of certain drugs [31]. An extensive use of curcumin is the result of its cholagogic, cholepoietic, antioxidant, antimutagenic, anticarcinogenic action. Moreover, it prevents liver against damage and may reduce cholesterol and glucose level [32-35]. Curcumin decreases the expression of MDR1 gene leading to increase the sensibility of resistant human gastric cancer

cells on the vincristine action [36]. It was also shown that the expression of P-gp inhibits apoptosis. It results from changes of lipids composition in the cell membrane, intracellular pH or inhibition of some caspases [37]. Furthermore, it was observed that curcumin may promote caspase-3 activation in SGC7901/VCR cells which stimulates apoptosis. Additionally, curcumin does not cause adverse effect in high doses. Therefore, application of curcumin as specific MDR1 modulator in the treatment of some resistant cancers is possible [36].

Similar effect has a piperine – an alkaloid present in *Piper nigrum* and *Piper longum* (*Piperaceae*). Piperine has antidiarrhoeal and immunostimulatory properties [38, 39]. It also decreases the activity of P-glycoprotein and CYP3A4 enzyme. Hence, the use of this alkaloid significantly increases the concentration of rifampicin, phenytoin, propranolol and theophylline [40, 41]. Studies on the use of piperine in order to increase the sensitivity of tumor cells to cytotoxic drugs are promising. At a concentration of 50 μ alkaloid decreases the resistance to doxorubicin by 32.16-fold in MCF-7/DOX cell line and 14.14-fold in A-549/DDP cell line [42].

Silymarin as a mixture of flavonolignans such as silybin (60-70%), silidianin and silychristine may also influence the P-glycoprotein activity [43]. These unique phytochemicals are derived from seeds of milk thistle (*Silybum marianum*; *Asteraceae*). Silymarin is known because of its hepatoprotective property. These flavonolignans are widely used in the treatment of liver disorders e.g. cirrhosis, viral hepatitis as well as prevention of liver cancer. It was shown that silymarin protects the hepatocyte membrane, stimulates the synthesis of proteins and has antioxidant activity which lead to hepatocytes regeneration [44]. In *in vitro* study it was observed that silymarin inhibits P-gp activity in Caco-2 cells while Gurley et al. *in vivo* did not find significant changes in digoxin pharmacokinetics postulating a lack of effect of milk thistle supplementation on P-gp activity [45, 46]. This may be connected with low bioavailability of silymarin because its oral absorption is only 23-47% [44].

Ginkgo biloba (*Ginkgogaceae*) extract containing two groups of active substances: flavonoids (24%) such as quercetin, kaempferol, tamarixetin and terpenoids (6%): ginkgolides A, B, C, J, M, bilobalide may influence the P-glycoprotein activity. Its neuroprotective property and improving the cerebral circulation are useful in the treatment of dementia. Li et al. showed that ginkgolide A and B induce hepatic P-gp while flavonoids and bilobalide do not influence P-gp activity [47]. In another study it was shown that long-term use of *Ginkgo biloba* extracts in rats decrease bioavailability of cyclosporine which may affect the modulation of P-gp activity [48].

Green tea leaf (*Camellia sinensis*, *Theaceae*) has beneficial properties connected with presence of polyphenols, mainly catechins. Its chemopreventive, anticarcinogenic, antiatherogenic and antioxidant actions may influence the P-glycoproteins activity because (-)-epicatechin may increase the P-gp level and its protective action against various toxins [49].

The increase of P-gp expression may be also caused by *Coptis chinensis* (*Ranunculaceae*) which is used against symptoms of inflammatory. Its compound berberine reduces rhodamine 123 accumulation in human and murine hepatoma cells [50].

According to Li et al., tetrandrine from *Stephania tetrandra* (*Menispermaceae*) inhibits P-glycoprotein expression of multi-drug resistance of mouse S180 tumor cell [51]. Glabridin, which is a compound of *Glycyrrhiza glabra* (*Glycyrrhizaceae*), increases the absorption of rhodamine 123 seven-day after oral administration [52]. *Panax ginseng* (*Araliaceae*) due to its adaptogens property may lead to the reversion of daunorubicin resistance by interaction with azidopine binding site of P-glycoprotein [53]. Vauqueline and ephedrine from *Angelica sinensis* (*Apiaceae*) down-regulated MDR1 expression. Strychnine, which comes from the same plant, is free of this feature [54]. Some examples concerning the influence of plants and herbal substances on the function and expression of P-gp were shown in table 2 and 3.

Table 2.

Some examples concerning the influence of medicinal plants on the P-gp function and expression [4]

Plant	Medicinal uses	Study model	Effect	References
<i>Alisma orientalis</i>	Anti-hepatitis B, antiplatelet	<i>In vitro</i>	Inhibition of P-gp	[55]
		<i>In vitro</i>	Induction of P-gp expression	[56]
		<i>In vitro</i>	Increase of P-gp expression	[50]
<i>Coptis chinensis</i>	Inflammatory symptoms	<i>In vitro</i>	Up-regulation of <i>mdr1</i> and <i>mdr1b</i> mRNA expression after coptisine	[57]
		<i>In vivo</i> (rats)	Inhibition of intestinal P-gp (increased bioavailability of drugs such as digoxin and cyclosporine)	[58]
<i>Camelia sinensis</i>	Puritis, fatigues, urine retention	<i>In vitro</i>	Inhibition of P-gp efflux function	[59]
		<i>In vitro</i> and <i>in vivo</i>	Down-regulation of MDR1 expression	[60]
		<i>In vitro</i>	Inhibition of P-gp efflux function (some catechins)	[49]
<i>Curcuma longa</i>	Anti-inflammatory agent for gastrointestinal discomfort	<i>In vitro</i>	Increase sensitivity to anticancer drugs by inhibition of MDR1 expression	[61]
		<i>In vitro</i>	Inhibition of P-gp function	[62]
<i>Marsdenia tenacissima</i>	Cancer, asthma	<i>In vitro</i>	Inhibition of P-gp function	[63]
<i>Paeonia alba</i>	Menstrual disorders, heat rashes, stops bleeding	<i>In vitro</i>	Induction of intestinal P-gp expression	[64]
<i>Paeonia lactiflora</i>	Reduces fever and pain, prevents infection	<i>In vitro</i>	Inhibition of P-gp efflux function	[65]
<i>Peucedanum praeruptorum</i>	Antispasmodic, antibacterial and anti-platelet aggregation effects	<i>In vitro</i>	Down-regulation of P-gp expression	[66]
<i>Phellodendron wilsonii</i>	Anti-bacterial and anti-tumor effects, relieves itching	<i>In vivo</i> (rats)	Inhibition of intestinal P-gp	[67]

Plant	Medicinal uses	Study model	Effect	References
<i>Panax ginseng</i>	Adaptogens, nourishing stimulants, type II diabetes	<i>In vivo</i> (rats)	Induction of intestinal and brain P-gp expression	[68]
		<i>In vivo</i> (rats)	Induction of P-gp expression	[69]
<i>Pseudolarix kaempferi</i>	Anti-bacterial, anti-tumor, kills parasites and relieves itching	<i>In vitro</i>	Induction of P-gp expression	[70]
<i>Stephania tetrandra</i>	Diuretic, antirheumatic and analgesic	<i>In vitro</i>	Reduction of P-gp expression	[51]
		<i>In vitro</i>	Inhibition of MDR1 expression	[71]
<i>Triterogium wilfordii</i>	Autoimmune disorders, cancer	<i>In vitro</i> and <i>in vivo</i> (rats)	Down-regulation of MDR1 expression	[72]

Table 3.

The effect of herbal substances on the P-glycoprotein activity and function

Substances	Source of substance	Effect
Hyperforin, hypericin	St. John's wort (<i>Hipericaceae</i>)	Induction
Curcumin	<i>Curcuma longa</i> (<i>Zingiberaceae</i>)	Inhibition
Piperine	<i>Piper nigrum</i> ; <i>Piper longum</i> (<i>Piperaceae</i>)	Inhibition
Silymarin	<i>Silybum marianum</i> (<i>Asteraceae</i>)	Inhibition
Ginkgolide A, B	<i>Ginkgo biloba</i> (<i>Ginkgogaceae</i>)	Induction
Polyphenols	Green tea leaf (<i>Theaceae</i>)	Induction
Tetrandrine	<i>Stephania tetrandra</i> (<i>Menispermaceae</i>)	Inhibition
5-Schisandrins	<i>Schisandrae fructus</i> (<i>Schisandraceae</i>)	Inhibition
Glabridin	<i>Glycyrrhiza glabra</i> (<i>Glycyrrhizaceae</i>)	Inhibition
Protopanaxatriol ginsenosides	<i>Panax ginseng</i> (<i>Araliaceae</i>)	Induction
Phellamurin	<i>Phellodendron wilsonii</i> (<i>Rutaceae</i>)	Inhibition
Pyranocoumarins	<i>Peucedanum praeruptorum</i> (<i>Apiaceae</i>)	Inhibition
Honokiol	<i>Pseudolarix kaempferi</i> (<i>Pinaceae</i>)	Inhibition
Coraria lactone	<i>Alisma orientalis</i> (<i>Alismataceae</i>)	Induction
Vauqueline	<i>Angelica sinensis</i> (<i>Apiaceae</i>)	Inhibition
Ephedrine	<i>Angelica sinensis</i> (<i>Apiaceae</i>)	Inhibition
Tenacissimoside A	<i>Marsdenia tenacissima</i> (<i>Asclepiadaceae</i>)	Inhibition
Paeoniflorin	<i>Paeonia alba</i> (<i>Paeoniaceae</i>)	Induction

CONCLUSIONS

In summary, both synthetic drugs and compounds from natural products may inhibit P-glycoprotein by the interference with efflux activity of the drug pump or reduced P-glycoprotein expression. However, synthetic substances are too toxic at the required doses and can lead to adverse events e.g. neurotoxic

side-effects, cardiac toxicity. Therefore, the search for novel inhibitors from herbal products for transporters involved in the function of the blood-brain barrier and the phenomenon of multidrug resistance may be more promising in overcoming these problems by the reduction of side effects as compared to synthetic drugs.

Moreover, the effect of the commonly used herbal medicines on the level of P-gp expression should be considered due to the participation of this protein in the processes of absorption and elimination of various drugs from the organism. It is important in case of drugs with a narrow therapeutic index because it can lead to extension of a therapeutic dose and achievement of the concentration of toxins. Therefore, in such situations it may be necessary to start an individualized pharmacotherapy based on the level of P-gp expression, because presented herbal substances can be used as potential modulators of the level of P-glycoprotein expression. Additionally, the possibility of use of phytotherapy as a sample of elimination of multidrug resistance and the prevention of diseases, especially CNS disorders, should be also considered.

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WPLYW SUROWCÓW ROŚLINNYCH NA AKTYWNOŚĆ I FUNKCJE GLIKOPROTEINY P

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Streszczenie

Glikoproteina P (P-gp) kodowana przez gen oporności wielolekowej MDR1 to ATP-zależne białko transportowe zlokalizowane w błonach komórkowych. P-gp ulega ekspresji głównie w obrębie narządów pełniących funkcje wydzielnicze, a jej fizjologiczna rola polega na ochronie tkanek przed ksenobiotykami. Glikoproteina P bierze udział w barierach przepuszczalności krew-mózg, krew-łożysko, chroniąc bezpośrednio te organy. Uczestniczy w transporcie leków i innych ksenobiotyków, wpływając na ich absorpcję, dystrybucję, metabolizm i wydalanie. Wysoka aktywność P-gp w błonach komórek nowotworowych jest główną przyczyną braku skuteczności chemioterapii. Poszukiwane są więc sposoby zwiększenia wrażliwości tych patologicznych komórek na cytostatyki. Badane są w tym kierunku naturalne substancje roślinne, ponieważ zaobserwowano ich wpływ na stopień ekspresji oraz aktywność glikoproteiny P. *Hypericum perforatum*, *Ginkgo biloba* i *Camellia sinensis* to surowce zwiększające aktywność P-gp, natomiast kurkumina z korzenia ostryża długiego, piperyna oraz sylimaryna hamują działanie tego białka. Ze względu na tak wielokierunkowe oddziaływanie fitoterapii oraz szerokie spektrum substratowe P-gp, stosując wiedzę na temat interakcji surowców roślinnych z lekami syntetycznymi należy zawsze mieć na uwadze zwiększenie biodostępności stosowanych leków.

Słowa kluczowe: glikoproteina P, oporność wielolekowa, surowce roślinne, transporter leku