Potential of natural-based anticancer compounds for P-glycoprotein inhibition

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Abstract: Medicinal value of natural products comes from symbiotic and competitive evolution in Earth's complex biosphere. Billions of years of co-evolutionary interactions among millions of species have produced a large repertoire of defense molecules effective in fighting bacteria, viral, and fungal pathogens. Each species contains millions of different, useful molecules and new research technologies enabled the screening of molecules and complex mixtures from diverse biological sources. Traditional use of plants and other species led to the discovery of many bioactive compounds with various properties. In the last four decades, a large number of them were evaluated for their potential to treat cancer. Penetration of drugs into the cancer cell is necessary for their lethal pharmacological effect through interaction with intracellular target molecules. Increased activity of membrane efflux pumps reduces the intracellular drug accumulation, thereby preventing drug-target interactions. The discovery of the efflux transporter P-glycoprotein (P-gp) in multidrug resistant (MDR) cancer cells prompted the efforts in overcoming drug resistance by P-gp inhibition. The search for nontoxic anticancer agents from natural sources able to overcome MDR has been an imperative in the field of drug design and discovery. Herein, we review various natural compounds from diverse sources emphasizing their potential to inhibit P-gp activity and/or expression.

Keywords: multidrug resistance, anticancer compounds, natural products, ATP-Binding Cassette transporters, P-glycoprotein, traditional medicine

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1. INTRODUCTION

Exploitation of nature for medicine has a long history from ancient times to modern pharmaceutical science. Nowadays, the majority of approved drugs for different health conditions, including cancer, were either isolated from natural sources or designed according to structures found in nature. Although scientific tools (molecular biology, computational chemistry etc.) significantly advanced from the ancient roots, nature will always be the most attractive and the most important source of biologically active compounds.

Anticancer strategies with natural compounds such as anthracyclines (e.g. doxorubicin; DOX), vinca alkaloids (e.g. vincristine), podophyllotoxins (e.g. etoposide) and taxanes (e.g. taxol) sometimes fail to induce optimal therapeutic effect due to the development of multidrug resistance (MDR).

MDR is described as a group of adaptive characteristics, which enable cancer cells to exhibit simultaneous resistance to a number of structurally and functionally unrelated chemotherapeutic agents. Usually, the reduction of intracellular drug concentration leads to the decrease in their cytotoxicity.

The bioavailability of different anticancer drugs depends on the balance between their uptake and efflux. Membrane transporters whose functioning is important for maintaining cellular homeostasis and eliminating toxic substances mediate these processes [1].

ATP-Binding Cassette (ABC) transporters are the most extensively studied efflux transporters involved in the development of MDR. The most characteristic feature of this protein superfamily is the highly conserved ATP-binding domain [2]. The ABC-transporters use energy from ATP hydrolysis to transit their substrates against concentration gradients across the plasma membrane, but also across intracellular membranes of the endoplasmic reticulum, peroxisomes, endosomes and mitochondria [1].

More than 2000 ABC membrane transporters are involved in diverse functions, including the extrusion of toxic compounds, uptake of nutrients, transport of ions and peptides, and cell signaling [3]. They are universally expressed across genera, extending from bacteria and plants to mammals [2]. In physiological conditions, ABC transporters perform the final step of substrates excretion into fluids, such as feces, urine and bile [4].

Members of the ABC superfamily important for anticancer drug efficacy are P-glycoprotein (P-gp/MDR1/ABCB1), Breast Cancer Resistance Protein (BCRP/ABCG2), and Multidrug Resistance Associated Protein (MRP/ABCC) family [1].

P-gp is the best-characterized member of the ABC transporter superfamily due to its important role in the development of MDR. It is involved in both intrinsic and acquired cross-resistance of many aggressive cancers spanning from leukemia to glioblastoma [5].

Herein, we summarize the current knowledge on P-gp structure and function. In addition, we bring a focus on the inhibition of P-gp with natural-based compounds. Comprehensive literature examination for reported P-gp inhibitors was conducted in order to collect information of great interest for the scientists in the field of cancer MDR research and nature inspired chemical synthesis spanning from the last several decades to the latest research reported in 2018. An overview of traditional medicine contribution to the field is also included.

2. P-GLYCOPROTEIN

P-glycoprotein was originally isolated from colchicine-resistant Chinese hamster ovary cells [6]. P-gp synthesis starts in the endoplasmic reticulum. As an intermediate with a molecular weight of 150 kDa, P-gp enters the Golgi apparatus where its carbohydrate moiety is modified before its export to the cellular membrane as functional transporter with a molecular weight of 170 kDa [7]. Two MDR genes, MDR1/ABCB1 and MDR3/ABCB4 (known as MDR2), encode human P-gp, which are located, adjacent to each other, on the chromosome 7q21 [8, 9]. The MDR phenotype of cancer cells is related to the MDR1 isoform [10], while MDR3 isoform functions as a phosphatidylcholine (PC) translocase [11].

2.1. Physiological Role

P-gp tissue localizations suggest that it plays a pivotal role: (i) in the protection of vulnerable organs such as brain, testis, inner ear and placenta from toxic assaults; (ii) secretion of metabolites and xenobiotics into bile, urine, and the lumen of the gastrointestinal tract; and (iii) transport of hormones from the adrenal gland and the uterine epithelium [12]. P-gp was also found to protect hematopoietic progenitor cells of the bone marrow [13].

The highest expression of P-gp is in the apical surface of epithelial cells of the intestine, liver bile ducts, kidney proximal tubules, pancreatic ducts, adrenal gland, placenta, testis and in the apical membrane of endothelial cells lining the capillaries of the brain [9, 14-18].

P-gp expressed on the cellular membrane of the endothelial cells in the blood–brain barrier represents a major guardian of the brain since its transport is oriented towards the blood [18]. P-gp is also present in the blood-inner ear barrier, on the cellular membrane of the capillary endothelial cells of the cochlea and vestibule [19]. Increased levels of P-gp present at the luminal surface of the secretory epithelial cells in the pregnant endometrium and placenta protect the fetus from diverse toxins [20-22]. P-gp in the apical border of fetus-derived epithelial cells towards maternal circulation additionally protects the fetus [19].

2.2. Structure

P-gp consists of 1280 amino acids organized in two tandem repeats of 610 amino acids joined by a linker region of ~60 amino acids [23]. A gene duplication event led to the fusion of two homologous halves, each comprising of six highly hydrophobic α-helices known as transmembrane domains (TMDs) and single nucleotide binding domain (NBD) located in the cytoplasm, which are responsible for the hydrolysis of ATP [10, 12, 24] (Fig. 1). The two halves are joined by a highly charged cytoplasmic “linker region”, which is phosphorylated at several sites by protein kinase C (PKC) [25]. TMDs form the pore through which the substrates are extruded. The first extracellular loop is N-glycosylated [26]. The NH2- and COOH termini are located intracellularly.

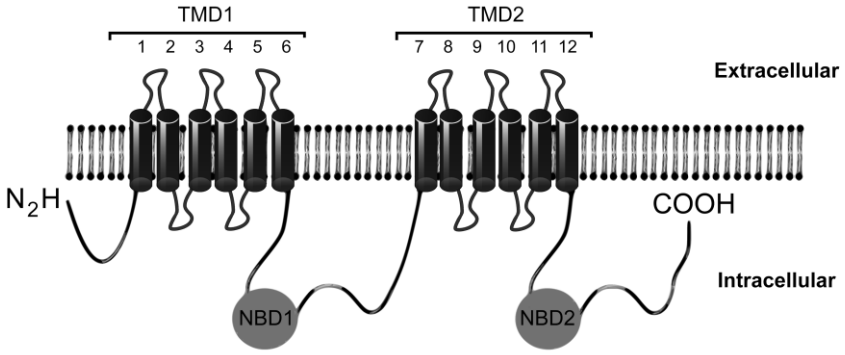


Fig.1. P-glycoprotein structure: NBD - Nucleotide Binding Domain. TMD – Transmembrane Domain.

NBDs consist of two-core consensus Walker A and B motifs, which are characteristic for the proteins with ATP and GTP hydrolyzing activity. LSGGQ signature C motif is unique to the ABC superfamily [27].

Aller et al. described a mouse P-gp crystal structure with a nucleotide-free inward-facing conformation arranged as two "halves" with pseudo two-fold molecular symmetry [28]. The inward facing conformation resulted in a large internal cavity open to both the cytoplasm and the inner leaflet of the membrane. This work gave a new insight enabling the improved structure-based approaches for the modulation of P-gp activity [29].

2.3. Regulation of Expression

P-gp expression is regulated constitutively in a cell- and tissue-specific manner [26]. Interestingly, after application of different drugs, it is also induced in cancer cells originated from tissues that do not express P-gp constitutively [30-36]. Structural diversity among the known inducers suggests the involvement of different signaling pathways in MDR1 transcription. On the other side, MDR1 possesses a great potential to respond to different stimuli including drugs, cytokines, free radicals, heat shock, X- and UV-irradiation [37-43].

Increased MDR1 mRNA level can be the consequence of either gene amplification or increased gene transcription [44-47].

The human MDR1 promoter has multiple response elements that confirm the complexity of the P-gp expression regulation [10, 48]. It also contains an initiator element, which is necessary for the direct basal transcription at the major initiation start point [49]. Several promoter elements that were identified include a GC-box, a Y-box, a p53 element, an inverted mediator-1 element (invMED1), an activator protein 1 (AP-1) element, a heat shock element (HSE), and a steroid xenobiotic receptor (SXR) element, which is the binding site for pregnane xenobiotic/retinoid xenobiotic receptor α (PXR/RXRα) heterodimer [10, 48].

Up-regulation of the MDR1 gene transcription can be activated by several transcription factors: heat-shock transcription factor 1 (HSF-1), specificity protein 1 (Sp1), activator protein 1 (AP-1), CCAAT/enhancer-binding protein β (C/EBPβ) or NF-IL-6 (nuclear factor for IL-6 expression), nuclear factor Y (NF-Y), early growth response protein 1 (EGR-1) and Y-box binding protein 1 (YB-1) [42, 50-54]. On the other hand,

cross coupling of nuclear factor-κB/p65 (NF-κB/p65) and c-fos effectively inhibits transcription of MDR1 gene [55].

2.4. Therapeutic Potential of Inhibition

Mechanisms whose role in the MDR phenomenon is well-recognized include the overexpression of the ABC transporters; altered target proteins (e.g., topoisomerase and tubulin); activity of detoxification pathways; enhanced DNA repair and changes in the apoptotic machinery [56]. Thus, different approaches can be applied to overcome MDR. However, the direct inhibition of P-gp is the most extensively exploited.

Since the first evidence of P-gp inhibition by verapamil [57], the therapeutic potential of P-gp inhibition to improve drug bioavailability has gained a considerable interest in the past four decades. Unfortunately, circumvention of MDR in clinics was not successful as expected [58].

P-gp inhibitors mostly act by: (i) blocking the substrate-binding site [59]; (ii) enhancing the ATP hydrolysis [60]; or (iii) altering the cell membrane composition [61].

Many therapeutic agents in use for clinical indications other than cancer showed P-gp inhibiting activity i.e. verapamil, the calcium channel blocker, as well as cyclosporine A, the immunosuppressant, were found to competitively inhibit P-gp function [57, 62, 63]. However, the presence of multiple binding sites for P-gp substrates complicates the conclusive discrimination between substrates and inhibitors. Therefore, compounds that interfere with ATP hydrolysis, i.e. quercetin, are considered as more valuable P-gp inhibitors [59]. In addition, pharmaceutical surfactants, such as sodium dodecyl sulfate, Tween-20 and Span-80 act by interfering with membrane fluidity consequently changing the conformation of P-gp. It was found that modifications in secondary and tertiary structure were responsible for the loss of P-gp function [59].

P-gp inhibitors are classified into four generations encompassing their affinity, selectivity and drug-drug interaction susceptibility. First-generation inhibitors represent pharmacologically active compounds already in clinical use for other indications [64]. Major representatives are verapamil, a calcium channel blocker; cyclosporin A, an immunosuppressant; reserpine, an anti-hypertensive, quinidine, an anti-arrhythmic; and tamoxifen, an anti-estrogen. These drugs are actually P-gp substrates, which inhibit its activity by competing with other substrates. Clinical application of these compounds for P-gp inhibition is limited due to the high serum concentrations reached with the dose necessary for P-gp inhibition, thus producing severe toxicity and low affinity to P-gp [59].

Second-generation inhibitors were synthetized as analogues of the first-generation inhibitors [64, 65]. These compounds lack the pharmacological activity of the first generation inhibitors, but possess a significantly higher P-gp affinity [59]. Major representatives of second-generation inhibitors are dexverapamil, an R-enantiomer of verapamil, valspodar (PSC-833), a non-immunosuppressive analogue of cyclosporine A and other compounds such as biricodar (VX-710), timcodar (VX-853) and dofequidar (MS-209), are some of the second-generation inhibitors. One of the disadvantages of these compounds is their activity against other ABC transporters [59]. Another important undesirable characteristic is systemic toxicity due to the inhibition of the metabolism and excretion of cytotoxic agents [64]. Many of second-generation inhibitors are substrates for CYP P450, and their competition with chemotherapeutics for CYP P450 leads to unpredictable pharmacokinetic interactions and increased toxicity of chemotherapeutics [64].

To avoid the obstacles observed with the first- and second-generation P-gp inhibitors, third-generation inhibitors were developed. The main goal was to achieve the inhibition of P-gp with high specificity and

potency [64]. Major representatives of the third-generation inhibitors are zosuquidar (LY335979), elacridar (GF120918), laniquidar (R101933), ontogeny (OC144093), tariquidar (XR9576), DP7, PGP-4008 and CBT-1 [64]. They demonstrated a 10-fold higher efficacy against P-gp activity than the first- and second-generation inhibitors by achieving the optimal efficacy in nanomolar range [59].

However, for some of them, tariquidar and elacridar, inhibition of the BCRP was reported [66-69], while zosuquidar and laniquidar, are more specific for P-gp [64]. Importantly, these compounds do not affect CYP3A4 activity [70].

Unfortunately, third-generation inhibitors failed in clinical trials due to the observed systemic toxicity. Thus, tariquidar, in combination either with paclitaxel and carboplatin or with vinorelbine, tested in phase III clinical trials as first line therapy in non-small-cell lung cancer patients, had to be terminated due to the high toxicity [64].

Continuation of efforts in overcoming MDR led to the development of new strategies with new P-gp inhibitors, encompassing: (i) compounds isolated from natural sources and their derivatives; (ii) surfactants and lipids; (iii) peptidomimetics; and (iv) agents capable to inhibit P-gp and exert another anticancer activity (dual ligands). These compounds constitute the fourth-generation of P-gp inhibitors [64].

3. NATURAL PRODUCTS AS P-GLYCOPROTEIN INHIBITORS

Medicinal plants are the most valuable source of bioactive compounds, particularly their secondary metabolites that possess great potential for treatment of different human diseases including cancer. Many natural compounds and phytopharmaceuticals have been investigated as inhibitors of P-gp and MDR modulators [71, 72]. Herein, we describe natural compounds that showed promising anti-P-gp activity achieved on different levels: from transcription and expression regulation to competitive binding and exhausting the ATPase activity of this membrane transporter.

3.1. Flavonoids and Flavones

Plant derived polyphenolic compounds such as flavonoids and flavones (Fig.2) were extensively investigated as MDR modulators and P-gp inhibitors [73]. Thus, a large number of flavonoids (biochanin-A, genistein, quercetin, chalcone, silymarin, phloretin, morin, and kaempferol) were shown to significantly increase the accumulation of both daunomycin and vinblastine in human pancreatic adenocarcinoma Panc-1 cells by inhibiting P-gp [74].

Quercetin is widely distributed dietary flavonoid in different plants (capers, sorrel, radish leaves, carob fiber, dill, cilantro, Hungarian wax pepper, fennel leaves, red onion, radicchio, watercress, kale, chokeberry, cranberry, lingonberry, black plums). It was shown that quercetin induces growth inhibition of many different cancers both *in vitro* and *in vivo* including leukemia, liver, breast, prostate, gastric, colon and lung cancer [75-82]. Importantly, quercetin selectively exerts its activity towards cancer cells by sparing normal cells [83].

Quercetin was able to sensitize a P-gp-positive gastric carcinoma cell line to chemotherapeutics by decreasing P-gp expression and activity probably through down-regulation of MDR1 mRNA expression [84].

This flavonoid can regulate MDR1 gene expression by inhibiting the constitutive as well as induced HSF DNA-binding activity [85]. Quercetin also inhibits heat shock protein (HSP) synthesis [86], and interferes with the formation of the complex between the HSE and HSF by downregulating the level of HSF-1 [87].

In addition, quercetin showed potential to down-regulate MDR1 gene expression by inhibiting YB-1 nuclear translocation in breast cancer cells. Importantly, nontoxic concentrations of quercetin were able to synergize with chemotherapeutic drugs [88]. This evidence implies that quercetin can be used as an MDR reversal agent and P-gp inhibitor.

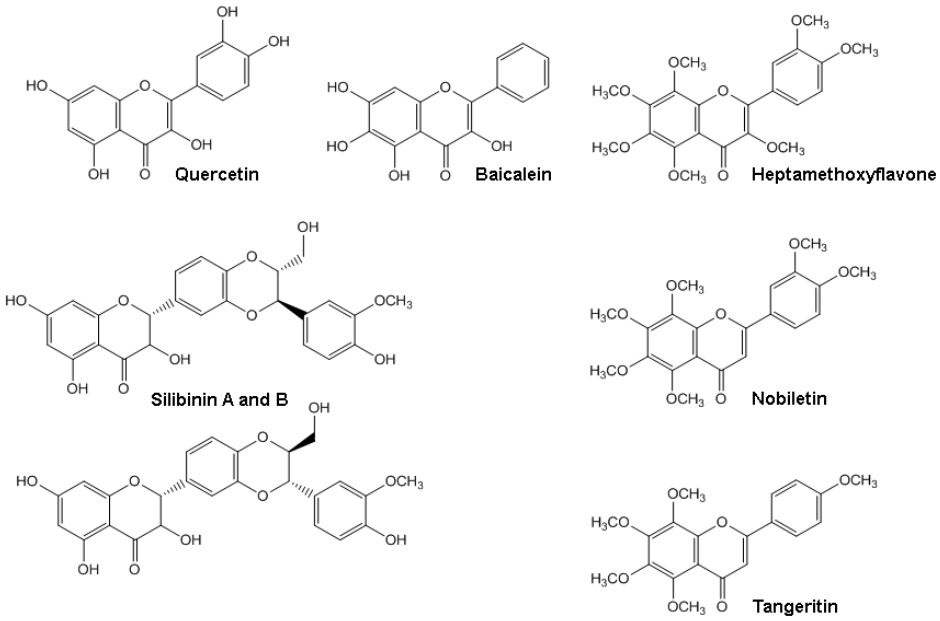


Fig.2. Flavonoids and flavones with anti-P-gp potential

Baicalin and its aglycone, baicalein, are the representative active flavonoids of skullcaps (*Scutellariae Radix*). Their influence on the activity and expression of P-gp was studied in Caco-2 cells and rat gut sacs. Although baicalin did not show any effect on intracellular accumulation of rhodamine123 (a P-gp substrate), and almost had no effect on P-gp expression and verapamil transportation, baicalein significantly increased intracellular accumulation of rhodamine123, down-regulated P-gp expression and increased the transport of verapamil. It seems that the difference in structures of baicalin and baicalein illustrated in the presence of glucosyl group plays a crucial role in influencing the activity and expression of P-gp [89].

In addition, baicalein significantly enhanced the oral bioavailability of tamoxifen, probably due to the inhibition of the CYP3A – mediated metabolism of tamoxifen in the small intestine and/or in the liver and inhibition of the P-gp in the small intestine [72, 90].

Silymarin, a flavonoid complex, is widely used in traditional European medicine. It is extracted from seeds of the milk thistle (*Silybum marianum L.*). Silymarin possesses strong antioxidant activity [91] and exhibits cytoprotective, anti-inflammatory and anticancer effects [92].

Silibinin is the most abundant and the most active component in silymarin [93]. Silibinin is expected to change the bioavailability and pharmacokinetics of drugs that are substrates of P-gp and/or CYP3A4, if they

are applied simultaneously with silibinin. However, recent study showed the opposite suggesting that the presence of silibinin enhances the oral bioavailability of paclitaxel. This can be due to enhanced absorption of paclitaxel in the gastrointestinal tract through the inhibition of P-gp and due to the reduced first-pass metabolism of paclitaxel via the inhibition of the CYP3A subfamily in the small intestine and/or in the liver by silibinin. Therefore, the concomitant use of silibinin may have a therapeutic benefit in the oral delivery of paclitaxel [94].

Polymethoxylated flavones are present in grapefruit and orange juices in very low concentrations [95, 96]. These compounds possess numerous biological activities including modification of blood serum lipid profiles [97, 98]. Therefore, they are considered as nutraceuticals with a potential to reduce cholesterol and triglyceride levels. In addition, polymethoxylated flavones significantly inhibited P-gp mediated transport of talinolol in Caco-2 cells. Tangeretin, nobiletin, 3,5,6,7,8,3',4'-heptamethoxyflavone, and sinensetin (5,6,7,3',4'-pentamethoxyflavone) showed similar potential for P-gp inhibition. Their efficacy did not appear to be dependent on the number of methoxy groups [99]. Another study showed that although the number of methoxyl substitutions is not important for the P-gp inhibition, the potency was decreased when both C3' and C5' were substituted [100]. Thus, heptamethoxyflavone and quercetagetin, were as potent as verapamil. Importantly, orange juice-derived polymethoxylated flavones, heptamethoxyflavone, nobiletin and tangeretin, do not inhibit CYP3A4 [101].

Nobiletin, as a non-toxic dietary polymethoxylated flavone, was further investigated in respect to its interaction with P-gp. It shows various biological effects including anti-inflammatory, anticancer, and neuroprotective characteristics [102-104]. Nobiletin inhibited the growth of several prostate cancer cell lines by causing cell cycle arrest in G_0/G_1 phase [105, 106]. In addition, it showed the ability to increase accumulation and uptake of chemotherapeutics [101, 107, 108].

Recent study elucidated the mechanism behind nobiletin interaction with P-gp [109]. It was demonstrated that the activity of ATPase was stimulated by nobiletin in a concentration dependent manner. In addition, verapamil-stimulated ATPase activity was reduced by nobiletin, while docking analysis predicted binding conformation of nobiletin within the large hydrophobic drug-binding cavity of P-gp. Combination of nobiletin and paclitaxel increased the intracellular accumulation of both compounds. Therefore, nobiletin inhibits the activity of P-gp by competitively binding to the substrate-binding site leading to the increased intracellular concentration of both nobiletin and P-gp substrate [109].

3.2. Alkaloids

Alkaloids are basic nitrogenous plants compounds. There are different groups of alkaloids according to amino acid from which they derived. The ability of alkaloids to inhibit P-gp have been widely studied (Fig.3). It was suggested that two structural characteristics present in compounds that modulate P-gp-related MDR are a basic nitrogen atom and two planar aromatic rings.

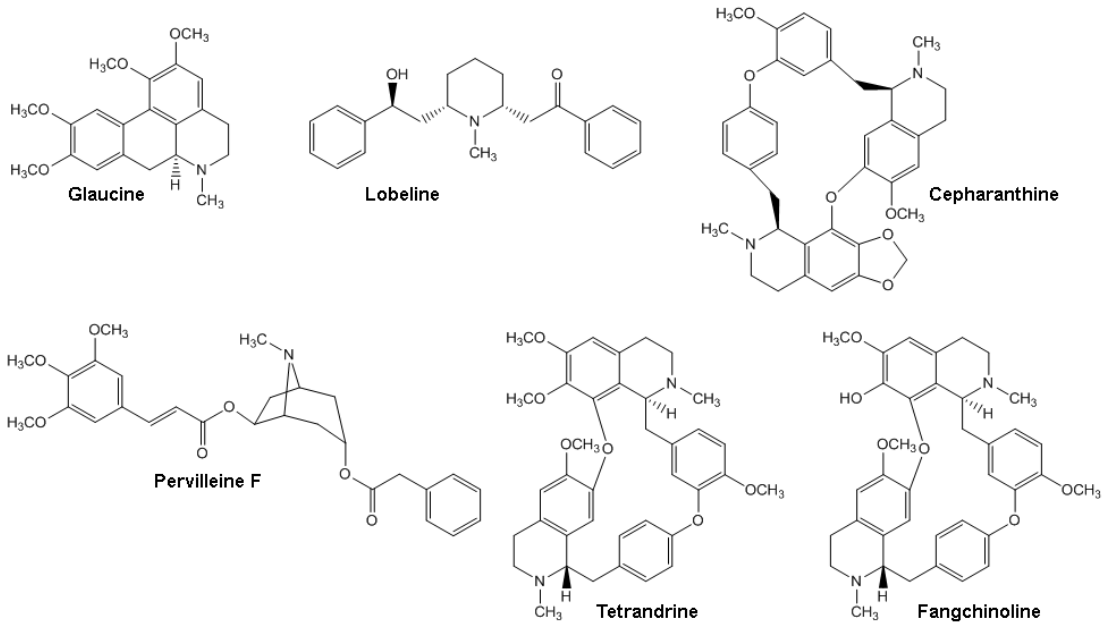


Fig. 3. Alkaloids with anti-P-gp potential

Glaucine is an alkaloid isolated from Chinese herbal plant Yanhusuo that efficiently inhibits P-gp efflux by stimulating its ATPase activity. Furthermore, glaucine suppresses expression of MDR1 gene and reverses the resistance of breast carcinoma cells to adriamycin and mitoxantrone [110].

Lobeline, a piperidine alkaloid isolated from several *Lobelia* species, also inhibits the P-gp activity. Its potential for MDR reversal at non-toxic concentrations was demonstrated in cells treated with doxorubicin [111].

Cepharanthine is a bisbenzylisoquinoline (biscoclaurine) alkaloid, with anti-inflammatory and antineoplastic potential. Cepharanthine derived from *Stephania* genus of flowering plants native to eastern and southern Asia and Australasia. This compound was able to completely overcome the resistance to vincristine, actinomycin D, and daunomycin in oral epidermoid carcinoma cells. Moreover, cepharanthine enhanced sensitivity to adriamycin and vincristine in human chronic myelogenous leukemia by altering the distribution of adriamycin from cytoplasmic vesicles and suppressing the acidification of cytoplasm organelles [112].

Pervilleines A, B, C and F were found in a chloroform extract of the roots of *Erythroxylum pervillei*. Pervilleine A was able to sensitize MDR cancer cells to vinblastine and colchicine. Although transcription of MDR1 gene as well as levels of P-gp were not affected, ATP-dependent binding of [^{3}H]vinblastine in cancer cell membrane vesicles was inhibited by pervilleine A in a dose-dependent manner. In addition, kinetic analysis suggested competitive inhibition mode of pervilleine A action. Model of cancer cells cultured in hollow fibers and implanted into NCr nu/nu mice was then used to confirm pervilleine A potential for MDR reversal *in vivo*. Results showed that cell growth was not significantly inhibited when either vinblastine or pervilleine A were administered alone, but when the combination was applied, cell growth inhibition up to 75% was observed [113]. Pervilleines B and C_were also able to restore the sensitivity to vinblastine by

inhibiting P-gp [114]. Pervilleine F combined with vinblastine induced dose-dependent G_2/M arrest, confirming its ability to restore vinblastine sensitivity [115].

Tetrandrine and fangchinoline are bisbenzylisoquinoline alkaloids present in roots of the creeper *Stephania tetrandra Moore* [82, 116]. In Chinese traditional medicine these alkaloids are usually used to decrease blood pressure [117]. Recently, bisbenzylisoquinoline alkaloids showed anti-inflammatory and anticancer activities [118, 119], inhibiting proliferation and inducing apoptosis of hepatoma, breast cancer, lung cancer and leukaemia cells [120].

Major structural difference between tetrandrine and fangchinoline is in a phenolic hydroxyl group, which is replaced by a methoxy group in tetrandrine. Although tetrandrine is more lipophilic than fangchinoline, fangchinoline displayed stronger MDR reversal activity [121].

3.3. Coumarins

A variety of naturally occurring coumarins including furanocoumarin, pyranocoumarin and sesquiterpenoid coumarins were investigated for their capacity inhibit P-gp activity (Fig.4).

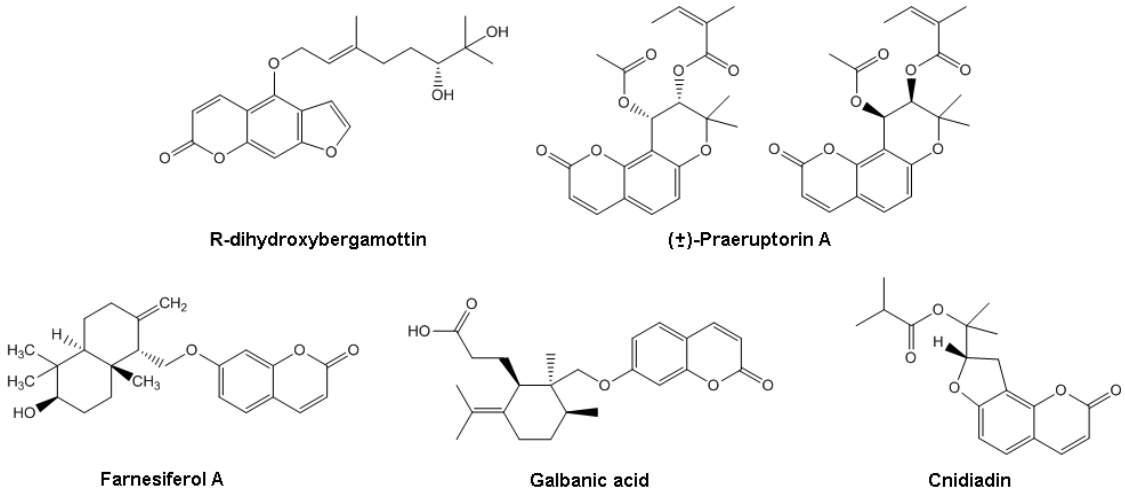


Fig.4. Coumarins with anti-P-gp potential

Structure-activity relation studies suggessted that coumarins substituted by a common α-(hydroxyisopropyl) dihydrofuran moiety, possess considerable anti-P-gp effect. The presence of phenyl group at position C4 in coumarin is extremely important for their activity against P-gp. Moreover, the α-(hydroxyisopropyl-dihydrofuran) group, especially at positions C7–C8 is responsible for the stronger effect on P-gp in comparison with other substitutional groups [122].

Furanocoumarins present in grapefruit juice such as dihydroxybergamottin, bergamottin, FC726, bergaptol and bergapten were able to increase the uptake of [^{3}H]-vinblastine by Caco-2 cells due to inhibition of P-gp [123].

Praeruptorin A is a naturally existing pyranocumarin isolated from the dried root of *Peucedanum praeruptorum Dunn*. It demonstrated the potential to sensitize P-gp overexpressing MDR cancer cells to

other anticancer drugs. Praeruptorin A derivative DCK (3'-*O*,4'-*O*-dicynnamoyl-cis-khellactone) was even more potent than verapamil in the inhibition of P-gp. DCK showed the capacity to increase the intracellular accumulation of doxorubicin without affecting the expression of P-gp. DCK binds simultaneously with substrates to an allosteric site thus affecting P-gp–substrate interactions [124].

Sesquiterpene coumarin representatives farnesiferol A, isolated from the roots of *Ferula persica*, and galbanic acid isolated from the roots of *Ferula szowitsiana*, significantly inhibited the P-gp activity in doxorubicin resistant breast cancer cells [125].

Cnidiadin derived from *Tordylium apulum* is an antineoplastic agent with a capacity to competitively inhibit binding and efflux of P-gp substrates thus enhancing the cytotoxicity of vinca alkaloids in P-gp overexpressing MDR cancer cells [126].

3.4. Taccalonolides

Taccalonolides encompass structurally and mechanistically distinct microtubule-stabilizing agents isolated from *Tacca chantrieri*. Taccalonolides A, E, B, and N showed anti-P-gp activity *in vitro*, while taccalonolides A and E (Fig.5) were also efficient *in vivo* in suppressing the growth of doxorubicin and paclitaxel resistant P-gp overexpressing tumor. Taccalonolides' advantage over the other microtubule stabilizers such as taxanes is their potential to evade different mechanisms of MDR [127].

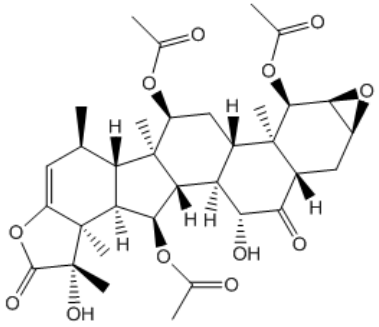


Fig.5. An example of taccalonolide with anti-P-gp potential

3.5. Diterpenes

Euphorbia species (*Euphorbiaceae*) has been used in ethnopharmacology since ancient times [128]. Plants of the *Euphorbia* species are considered as one of the most common elements of Mediterranean landscape. *Euphorbia* contains a unique profile of diterpene polyesters (ingenane, lathyrane, jatrophane, tigliane and daphnane) often found in the complex mixture. Some of these compounds showed significant biological activities such as antibacterial, antiviral, antiproliferative, cytotoxic, platelet aggregation-inhibiting, and vasoconstrictor activities [129]. Because of their biological actions diterpenes, especially jatrophanes, became the subject of intensive studies. The most important result of these studies is the finding that jatrophanes are inhibitors of P-gp and potential MDR modulators (Fig.6).

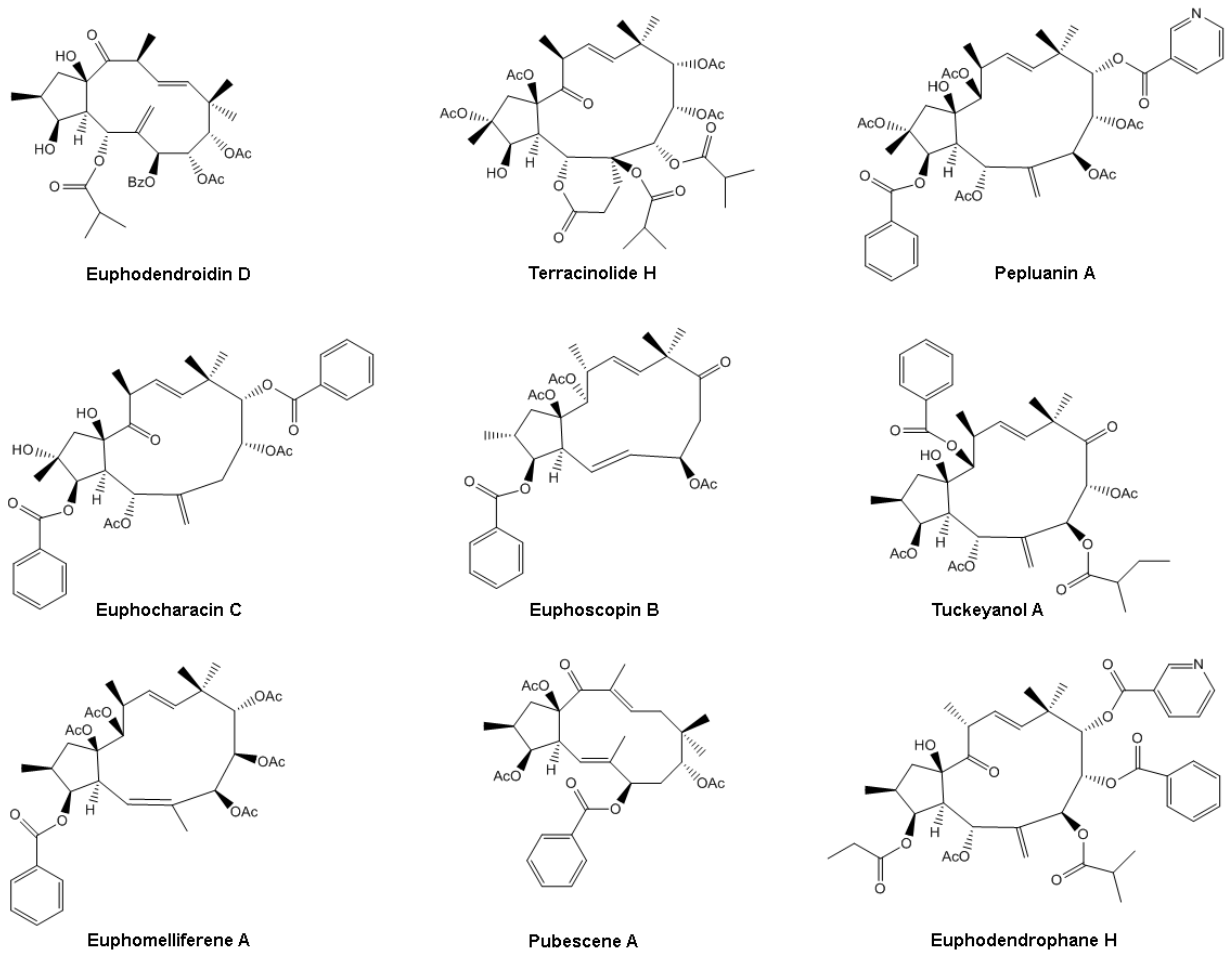


Fig.6. Diterpenes with anti-P-gp potential

The first study that showed jatrophanes' P-gp inhibiting activity was on resistant mouse lymphoma cells [130]. Some jatrophane diterpenes isolated from *Euphorbia serrulata* and *Euphorbia peplus* strongly inhibited the activity of P-gp in the MDR human colon carcinoma cells [130, 131]. The P-gp-inhibiting potential of euphodendroidin A-I, terracinolide B, C, F, H, J- L and 13α-OH terracinolide B and G, isolated from *Euphorbia dendroides*, then pepluanins isolated from *Euphorbia peplus* and euphocharacins from *Euphorbia characias* was investigated by monitoring intracellular accumulation of daunomycin [132-135]. Euphodendroidin D and pepluanin A were the most powerful P-gp inhibitors, at least two-fold more efficient than the conventional modulator cyclosporine A. P-gp modulators more efficient than cyclosporin A were also terracinolide H and euphocharacins C and I. Euphodendroidins A, B and G, terracinolide J, 13α-OH terracinolide G, pepluanine E and euphocharacine E inhibited P-gp to the same extent as cyclosporin A. Other compounds were less effective, and terracinolides C and L did not inhibit P-gp.

The biological evaluation of euphodendroidins' activities has shown the involvement of ring A in P-gp binding and the importance of free hydroxyl group at position 3. Substitution at the proximal C-5 with a large group and hydroxyl group at position 2 decreased the activity of euphodendroidins. The analysis of modified jatrophanes revealed the effect of substitution at positions 3, 6 and 15 and the relevance of relative configuration of hydroxyl groups. Benzoyl (Bz) group at C-9, propionyl group at C-3, and hydroxyl group at C-15 had a positive role on euphocharacins' activities, , while hydroxyl group at C-2 had a negative contribution. Pepluanin A has been reported as the most powerful inhibitor of P-gp with acetyl (Ac) at C-8 and nicotinoyl (Nc) at C-9 [136]. Taken together, these studies indicated that jatrophanes and modified jatrophanes share a common pharmacophore, whose activity is dramatically affected by the position and type of substituents in the jatrophane skeleton [133, 135].

Pubescenes A-D, isolated from *Euphorbia pubescens*, inhibited the activity of P-gp in MDR mouse lymphoma cell line [137]. However, these compounds, as well as euphopubescenol, euphopubescene and pubescenol, isolated from the same species, did not inhibit P-gp in the MDR breast cancer cell line [128].

Euphoscopin B from *Euphorbia helioscopia* was two times more efficient than cyclosporin A in inhibiting excretion of mitoxantrone, which is a P-gp substrate. Other examined jatrophanes isolated from this species were as active as cyclosporin A (euphoscopins C, M and N) or less active (euphornin) [138].

Tuckeyanols A and B, and euphotuckeyanol isolated from *Euphorbia tuckeyana* displayed a very strong P-gp inhibiting activity in MDR mouse lymphoma cell line. They were more active than conventional P-gp inhibitor verapamil [139].

Euphomelliferine and euphomelliferines A and B isolated from the methanolic extract of *Euphorbia mellifera* inhibited P-gp in a dose-dependent manner in MDR mouse lymphoma and human colon carcinoma cell lines [140]. In addition, the ent-abietane lactones, helioscopinolides A, B, E and F isolated from *Euphorbia* species showed a significant MDR reversing activity in a concentration-dependent manner in MDR mouse lymphoma cells [141].

Besides P-gp inhibiting activity jatrophane diterpenes also displayed antiproliferative and tubulin polymerizing activities. Pubescenes A-C isolated from *Euphorbia pubescens* moderately inhibited the growth of human non-small cell lung carcinoma cells in a concentration-dependent manner, but did not inhibit the growth of human breast adenocarcinoma and human glioblastoma cells [142]. Pubescenol and pubescenes D isolated from the same species moderately inhibited the growth of all three human cancers cell lines [143]. Euphopubescenol and euphopubescene also isolated from *Euphorbia pubescens* showed antiproliferative effect in human breast adenocarcinoma and non-small cell lung carcinoma cell lines, with GI_{50} values between 40.9-75 μM, but they did not inhibit the growth of human glioblastoma cells [137]. Some jatrophic diterpenes isolated from *Euphorbia esula*, *Euphorbia peplus* and *Euphorbia serrulata* had moderate to severe antiproliferative effect in human colon carcinoma cell line [131]. Moreover, macrocyclic jatrophane diterpenes isolated from *Euphorbia semiperfoliata* interacted with microtubules in the same way as paclitaxel (stimulated purified tubulin polymerization *in vitro*), but without inducing cell cycle arrest in the G_2/M phase [144].

As a part of a study on spurges from the southeastern Balkan region, six new jatrophanes (euphodendrophanes A-F) and a new tigliane (euphodendriane A) were isolated from the whole plant *Euphorbia dendroides* [145]. The new jatrophanes showed moderate inhibitory effect against four cancer cell lines: non-small cell lung carcinoma and its resistant counterpart, colorectal carcinoma, and glioblastoma. The most effective compounds were jatrophane euphodendrophane B and tigliane

euphodendriane A. Importantly, the presence of MDR phenotype in non-small cell lung carcinoma cell line did not change the inhibitory potential of tested compounds. However, the effectiveness of euphodendrophane B was significantly higher in comparison to its structurally closely related derivative euphodendrophane A. The presence of isobutyl group at position 3 likely increased the inhibitory ability of euphodendrophane B in comparison with euphodendrophane A which possesses propyl group at the same position [145].

Euphodendrophane A and B were nontoxic for normal cells (peripheral blood mononuclear cells), showing selectivity towards cancer cells [146]. Both compounds demonstrated stronger P-gp inhibition than standard P-gp inhibitor Dex-verapamil. Furthermore, both jatrophanes reversed resistance to paclitaxel and doxorubicin thus behaving as potent MDR modulators [146]. In combination with paclitaxel, euphodendrophane A/B induced cell cycle arrest in the G_2/M phase leading to cell death. Euphodendrophane A stimulated purified tubulin assembly *in vitro* in the same way as paclitaxel. Therefore, disturbance of cell cycle after combined treatment of jatrophanes with paclitaxel could be partly explained by their mutual effect on microtubule assembly [146]. Euphodendrophane A/B significantly reduced the level of *mdr1* gene expression in sensitive non-small cell lung carcinoma cells suggesting that they could not contribute to the development of resistance. Both jatrophanes also exerted an anti-angiogenic effect by decreasing the vascular endothelial growth factor (VEGF) secretion [146].

Thirteen new jatrophane diterpenoids (euphodendrophane G–P, Q-S) were isolated from the latex of *Euphorbia dendroides* [147]. New jatrophane diterpenoids G-L and Q-S were tested for their P-gp inhibiting activity in three different human MDR cancer cell lines: non-small cell lung carcinoma, colorectal carcinoma and glioblastoma. Among the investigated jatrophanes, euphodendrophane H and K were found to be the most powerful inhibitors of P-gp in MDR non-small cell lung carcinoma cell line. Their efficacy was significantly higher than Dex-VER. Euphodendrophane J, L, and S showed considerably high anti-MDR potency, R was moderately active, I was almost, while G and Q were completely ineffective in MDR non-small cell lung carcinoma cells [147]. Complete blockade of P-gp pump was observed in DLD1-TxR cells treated with euphodendrophane H, J, K, L and S. Moderate P-gp inhibition was observed with euphodendrophane G, I, and R, while euphodendrophane Q was also ineffective in DLD1-TxR cells. Almost all tested compounds (euphodendrophane H–P, Q-S) along with Dex-VER were moderately active against P-gp pump in U87-TxR cell line. Only euphodendrophane G was ineffective [147].

Structure-activity relationship did not show clear difference in the activity of jatrophanes with 6,17 *exo*-(G-L), and those with 5,6 *endo* double bond (Q-S). The lack of substituents at C-7, C-8 and C-9 in euphodendrophane G decreased its MDR-modulatory activity in comparison with other assessed jatrophanes. Within jatrophanes with 6,17 *exo* double bond, the presence of OBz instead of OAc or ONic group at C-8 had a positive role in the modulation of P-gp, as demonstrated by the efficacy of euphodendrophane H and K. Furthermore, the presence of OBz instead of OAc group at C-9 within jatrophanes with 5,6 *endo* double bond also influenced the P-gp-inhibiting ability, as shown by the activity of euphodendrophane S compared to euphodendrophane Q and R [147].

In addition, euphodendrophane H significantly sensitized MDR non-small cell lung carcinoma and colorectal carcinoma cells to paclitaxel, similar to well-known P-gp inhibitors Dex-verapamil and tariqudar, while euphodendrophane S demonstrated moderate chemo-sensitizing effect [148]. Moreover,

nanomolar concentration of paclitaxel exerted anti-mitotic effect by leading to cell cycle arrest at G_2/M phase in combination with euphodendrophane H or S in MDR non-small cell lung carcinoma cells [148].

Recently, seven new jatrophane diterpenoids, nicaeenin A-G, with eight known jatrophane diterpenoids, namely euphodendrophanes A-C, F, N, O, Q, S, were isolated from latex of *Euphorbia nicaeensis* collected in Serbia [149]. Almost all new jatrophanes showed significant potential to inhibit P-gp activity in two MDR cancer cell lines (non-small cell lung carcinoma and colorectal carcinoma). The most powerful were nicaeenin F and nicaeenin G. Moreover, nicaeenin G significantly sensitized MDR non-small cell lung carcinoma cells to doxorubicin [149].

3.6. Sesquiterpenes

Dihydro-β-agarofuran sesquiterpenes were isolated from *Celastraceae* plants known for their efficacy against MDR phenotype in *Leishmania* [150]. Having in mind that ABC transporters responsible for the development of classic MDR phenotype are highly conserved among species dihydro-β-agarofuran sesquiterpenes were also tested against human P-gp (Fig.7).

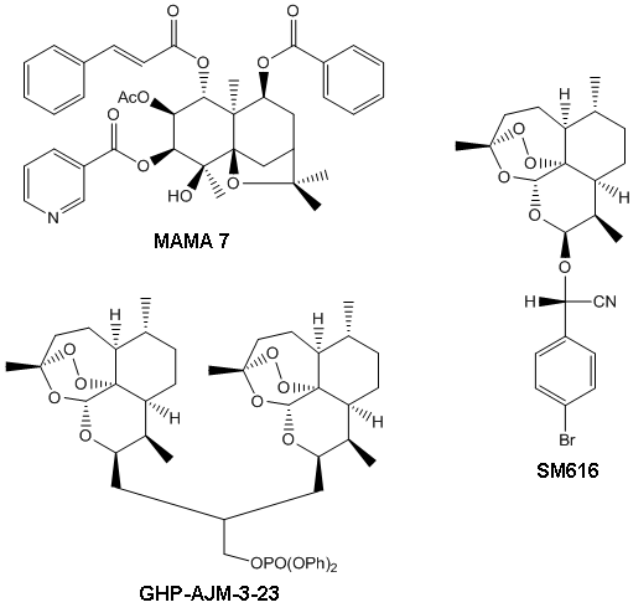


Fig.7. Sesquiterpenes with anti-P-gp potential

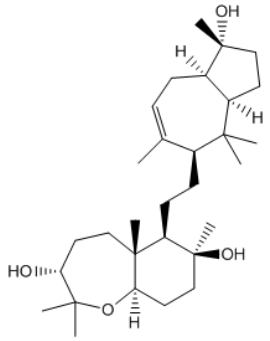
Quantitative structure-activity relationship study performed in mouse embryo tissue fibroblasts with P-gp expression revealed that the most important pharmacophoric features of these compounds were in the region of the substituents at the C-2, C-3 and C-8 positions [151]. In addition, the esterification level, the presence of two aromatic ester moieties and the size of the molecule are important factors for their anti-P-gp activity. These compounds possess low toxicity and many of them are able to overcome the MDR by modulating drug accumulation [151]. Among dihydro-β-agarofuran sesquiterpenes MAMA 7, MAMA 10, MACHU 4, MACU 5, MACU 7 and MACU 8 were the most active against P-gp.

Although anti-malarial compound artemisinin was found to significantly increase MDR1 mRNA levels and P-gp protein expression in colorectal carcinoma cells, its two derivatives [152], SM616 and GHP-AJM-3/23, inhibited P-gp activity in both sensitive and P-gp overexpressing leukemia cells as well as in porcine brain capillary endothelial cells [153].

3.7. Triterpenes

Although marine-derived compounds showed promising results as new anticancer agents, only a few marine compounds were identified as MDR reversal agents. Among them, the anti-P-gp activity of sipholane triterpenoid sipholenol A isolated from colonial tube-sponge (*Callyspongia siphonella*), is particularly interesting [154].

Sipholenol A potentiated the efficacy P-gp substrate drugs such as colchicine, vinblastine and paclitaxel in P-gp-overexpressing MDR cancer cells (Fig.8). In addition, it increased the intracellular accumulation of [^{3}H]-paclitaxel and stimulated the activity of P-gp ATPase [154].



Sipholenol A

Fig.8. An example of triterpenes with anti-P-gp potential

A series of related sipholane triterpenoids have been also isolated from the same sponge [155], while three of them, sipholenone E, sipholenol L and siphonellinol D, were investigated in respect to P-gp inhibition [156]. It was shown that sipholenone E, sipholenol L and siphonellinol D potently reverse MDR in cancer cells by directly inhibiting the P-gp efflux which results in an increase in the accumulation of both [^{3}H]-paclitaxel and calcein. All three compounds stimulated P-gp ATPase activity suggesting that these triterpenoids directly interact with P-gp. Moreover, molecular docking study suggested the ability of sipholanes to interact with a binding site of co-crystallized ligand QZ59-RRR at the crystallographic structure of P-gp [156].

3.8. Steroidal Saponins

Saponins are widely present in different plants and classified into two major groups: steroidal and triterpenoidal.

Steroidal saponins isolated from *Paris polyphylla* abundant in Asia, 3-O-Rha(1→2)[Ara(1→4)]Glc-pennogenine, gracillin and polyphyllin D, and ecdysteroids (20-hydroxyecdysone and pinnatasterone, Fig.9) decreased P-gp-mediated daunorubicin efflux in human leukemia cells [157].

Representatives of cucurbitacins, balsaminagenin B (Fig.9), balsaminoside A and karavelagenin C were also able to reverse MDR in cancer cells. Moreover, these compounds synergistically enhanced the effect of doxorubicin in daunorubicin acute myelogenous leukemia subline, which overexpress P-gp [158].

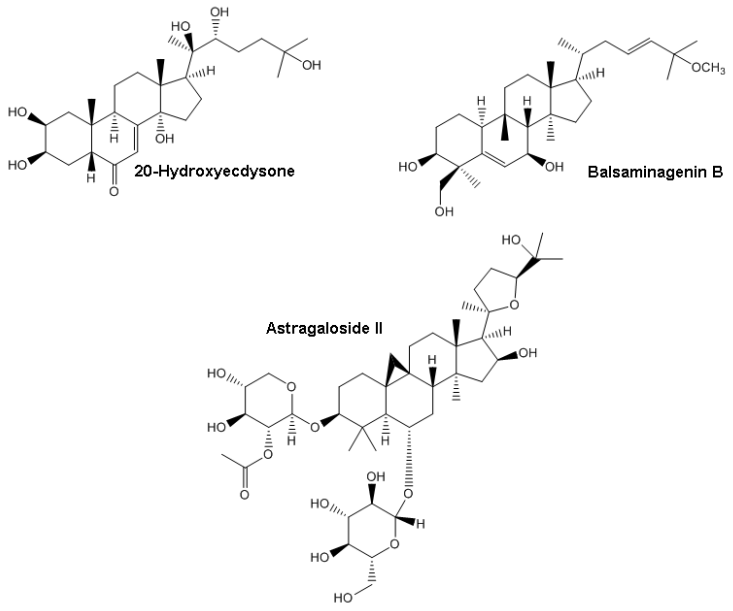


Fig.9. Saponins with anti-P-gp potential

Besides the chemosensitizing effect, protopanaxatriol ginsenosides can be considered as a valuable chemotherapy tool due to their ability for long-term use without the concern of P-gp activation [159].

Astragaloside II (Fig.9) is a saponin widely used in Chinese traditional medicine. Besides its anticancer effect *in vitro* and *in vivo*, astragaloside II showed chemosensitizing effect towards 5-fluorouracil-resistant hepatocellular carcinoma cells. Astragaloside II directly inhibits P-gp function and decreases the expression of P-gp and corresponding MDR1 gene [160].

3.9. Polyenes

Polyenes contain at least three alternating double and single carbon–carbon bonds that interact by conjugation resulting in some unique optical properties. Thus, many natural dyes contain linear polyenes, e.g. β-carotene, which is responsible for the color of carrots.

β-carotene (Fig.10) is present in various fruits and vegetables. It possesses antioxidant properties, while recent studies reported its anticancer and cancer preventive activities.

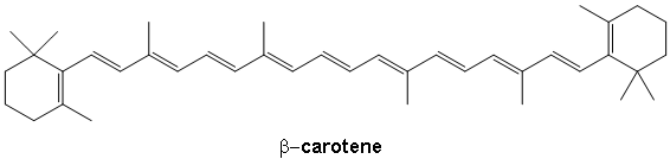


Fig.10. An example of polyene with anti-P-gp potential

Some prospective studies showed that supplementation with β-carotene has a preventive effect on the development of breast, head, and neck cancer [161, 162]. It was also demonstrated that β-carotene can induce differentiation, suppression of stemness and exert antimetastatic effect in cancer cells [163, 164].

In addition, β-carotene showed the ability to inhibit P-gp function [165].

A recent study revealed that β-carotene-P-gp interaction kinetics differed between rhodamine 123 and doxorubicin (both P-gp substrates). High concentrations of β-carotene resulted in different conformation change patterns of P-gp by influencing the epitope levels (the effect was detected by the conformational sensitive UIC2 antibody), while lower concentrations of β-carotene stimulated both P-gp basal ATPase activity and verapamil-stimulated P-gp ATPase activity. Thus, β-carotene significantly inhibited human P-gp efflux function without altering MDR1 mRNA expression [166].

3.10. Lignans

Lignans are present in more than seven families of plants as secondary metabolites. Their major bioactive representatives are abundant in *Phyllanthus* genus from *Euphorbiaceae* family [167]. Lignans (Fig.11) possess a wide spectrum of pharmacological properties, which encompasses immunosuppressive, vasoactive, antioxidant, antiviral, anti-inflamatory and anticancer activities.

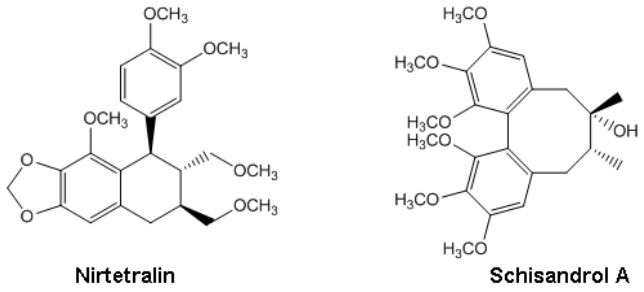


Fig.11. Lignans with anti-P-gp potential

A recent study revealed anti-P-gp potential of several lignans (nirtretalin, niranthin, phyltetralin and phyllanthin) isolated from *Phyllanthus amarus* hexane extract. In addition, these compounds demonstrated synergism with doxorubicin against leukemia cells [168].

Another study showed the potential of a schisandrol A isolated from *Schisandra chinesis* for P-gp inhibition. This lignan with low cytotoxicity interferes with formation and function of P-gp-substrate complex [169].

3.11. Marine Natural Products

Oceans and seas cover almost 70% of the Earth and own nearly 80% of the biological diversity on our planet. Therefore, marine water represents the largest source for natural product chemistry. Thousands of new compounds from marine sources discovered in last several decades have displayed a wide range of biological activities [170, 171].

Several marine compounds or analogs inspired by marine natural products have been approved for clinical use in different indications including cancer treatment (cytarabine, trabectedin and halaven) [170, 171].

Several marine products showed ability to inhibit P-gp activity and overcome the MDR phenotype in cancer (Fig.12).

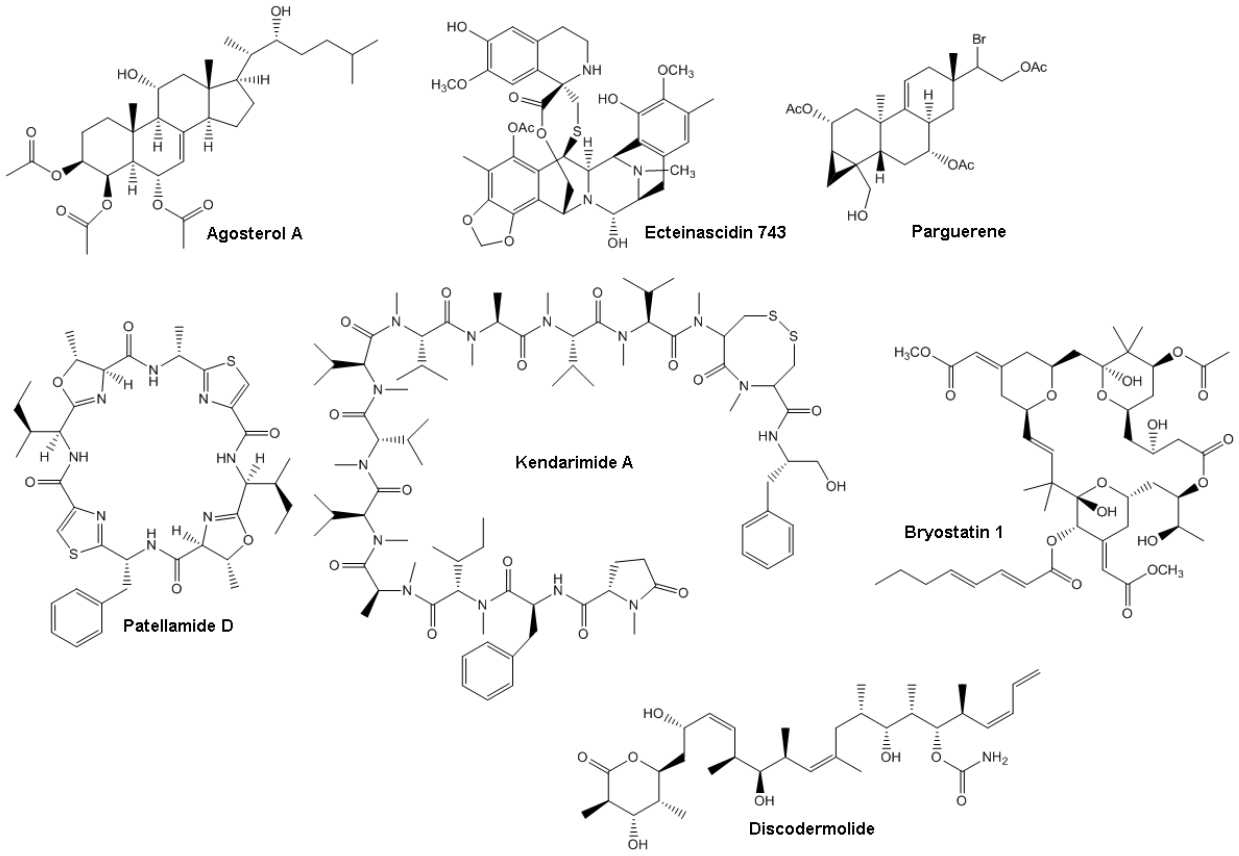


Fig.12. Marine natural products with anti-P-gp potential

Among them, lamellarins are a group of polyaromatic alkaloids originally isolated from *Lamellaria* species [172], the ascidian, *Didemnum chartaceum* [173, 174] and the sponge, *Dendrilla cactos* [175]. Besides anticancer and anti-P-gp activity [176], lamellarins showed immunomodulating activity [174] and inhibition of human immunodeficiency virus (HIV) integrase [177].

Agosterol A is novel polyhydroxylated sterol acetate isolated from the marine sponge with the potential to completely reverse MDR in human epidermoid carcinoma cells [178]. Moreover, it inhibited the [^{3}H] azidopine photolabeling of P-gp suggesting that agosterol A can act as P-gp inhibitor [179].

Ecteinascidin 743 isolated from the Caribbean tunicate - *Ecteinascidia turbinata* [180, 181], showed partially reversed resistance to doxorubicin and vincristine in MDR epidermoid carcinoma comprising P-gp overexpressing cancer cells. Photoaffinity labeling experiments revealed that ecteinascidin 743 does not interact directly with P-gp [182]. Due to its efficacy in cancer treatment, ecteinascidin 743 received orphan drug status specifically for soft tissue sarcoma treatment as monotherapy, and in combination with pegylated liposomal doxorubicin in the United States and for the treatment of patients with relapsed platinum-sensitive ovarian cancer in the United States and Europe [183]. However, CYP3A4 has an important role in the metabolism of ecteinascidin 743, suggesting a risk of drug-drug interactions. It has a favorable safety and tolerability profile and is not associated with the cumulative and/or irreversible end organ toxicities [184]. It is also known under the commercial name trabectedin (Yondelis®).

Two brominated diterpenes, parguerenes I and II, isolated from the Australian marine red alga - *Laurencia filiformis*, were shown to be non-cytotoxic inhibitors of P-gp mediated drug efflux. These compounds exhibited a dose-dependent reversal of resistance to vinblastine, doxorubicin and paclitaxel without affecting the expression of P-gp. The interaction of parguerenes I and II with an extracellular antibody binding epitope of P-gp was demonstrated, while the structure-activity relationship between these two brominated diterpenes indicated possible manipulation and optimization of the core pharmacophore in order to increase their anti-P-gp activity [185].

The patellamides are thiazole- and oxazoline-containing cyclic octapeptides isolated from *Lissoclinum patella* sowing cytotoxic and drug resistance reversing potential in the MDR human leukemia cells [186, 187]. Patellamide D demonstrated strong sensitization effect (similar to verapamil) in combination with vinblastine, adriamycin and colchicine [188].

Kendarimide A isolated from the sponge, *Haliclona* species, reversed MDR in a human carcinoma cell line with the overexpression of P-gp [189]. Importantly, kendarimide A is composed of a similar number of amino acid residues as cyclosporin A suggesting that peptides with analogous amino acid length share the same ability to reverse MDR [189].

Bryostatins are macrolide lactones found in bryozoan, *Bugula neritina*. These compounds are potent modulators of protein kinase C acting as anticancer and memory enhancing agents [190]. Bryostatin 1 possesses the ability to modulate the P-gp activity and bind to G185 and V185 mutant P-gp thus showing the unique potential to inhibit mutant P-gp [191].

Discodermolide is a polyketide discovered in the marine sponge, *Discodermia dissoluta* that displays immunosuppressive and anticancer activities [192-194]. Although discodermolide shares it mechanism of action with paclitaxel by blocking the cell cycle at the G_2/M checkpoint and by inducing induces apoptosis, it is more potent against several types of cancers including those resistant to paclitaxel [195].

3.12. Natural Products Clinically Approved for Indications Other than Cancer

Prostratin (Fig.13) is a small molecule found in the bark of the mamala tree of Samoa, *Homalanthus nutans* that belongs to the family of Euphorbiaceae. The antiviral activity of prostratin was discovered

during research on the traditional knowledge of Samoan healers who use the mamala tree to treat hepatitis. Prostratin is a protein kinase C activator with a potential to inhibit HIV reactivation in CD4+ T-lymphocytes [196].

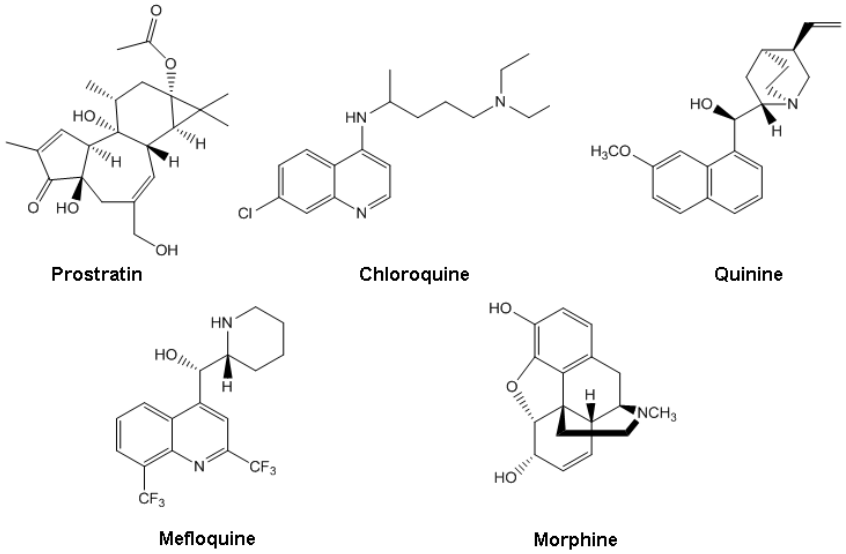


Fig.13. Different bioactive compounds with anti-P-gp activity

It also exhibits promising a therapeutic potential against cancer. Recent study showed that orally administrated prostratin is able to suppress human pancreatic carcinoma [197].

New interesting findings showed that prostratin is specifically efficient against high salt pre-treated breast cancer cells due to the inhibition of salt inducible kinase 3. This led to the inhibition of P-gp expression and activity. Namely, high salt treatment induces expression of P-gp and resistance to paclitaxel due to the enhanced the Ca^{2+} influx [198].

An investigation of anti-malarial drugs interaction with ABC transporters revealed that chloroquine, quinine and mefloquine (Fig.13) act as P-gp inhibitors [199]. Co-administration of anti-malarial compounds with other drug types is highly anticipated particularly when co-infections with HIV might occur due to the overlap in geographical dissemination [200]. Therefore, prediction of drug-drug interactions due to the interaction with P-gp is necessary.

Morphine (Fig.13) is a benzylisoquinoline alkaloid with two additional ring closures, which is the most abundant opiate found in opium extracted from the latex of poppy, *Papaver somniferum*. Morphine is the most frequently administrated analgesic in pain therapy particularly during anticancer therapy [201]. It is known that morphine (as well as other psychostimulants) is able to alter the neuronal and glial microenvironment, leading to the stroke of the blood-brain-barrier [202]. Recent preclinical studies showed significant increase of doxorubicin levels in brain when it was administrated in the presence of therapeutic plasma levels of morphine [203]. New evidences revealed that morphine enhances the effect of doxorubicin through the inhibition of P-gp, which is the major constituent of the blood-brain-barrier [204]. Another study showed that morphine is able to reduce the ATPase activity of P-gp thus increasing temozolomide efficacy in glioblastoma treatment. In addition, combination of temozolomide with

morphine showed increased tumor growth inhibition *in vivo* and long-term response in a glioblastoma xenograft model [205].

4. TRADITIONAL MEDICINE

Herbal medicines have been traditionally used for thousands of years in treatment of numerous diseases, and are still commonly used as complementary or alternative medical aid [206].

4.1. Traditional Chinese Medicine

Traditional Chinese medicine represents a substantial resource for natural products. Many compounds isolated from plants used in traditional Chinese medicine have an important role in inhibiting cancer progression through apoptosis induction, immune system modulation and/or overcoming MDR.

Salvia miltiorrhiza Bunge has been a well-known traditional Chinese medicinal herb for over a thousand years. Traditionally, the dried root of *S. miltiorrhiza* has been used as a hemorrheologic agent to promote circulation in treatment of cardiovascular and cerebrovascular diseases [207], but also as dietary supplement [208]. Herbal plants that promote circulation are traditionally prescribed for cancer patients [209]. During recent decades over 70 compounds were isolated from *S. miltiorrhiza*. Most of its bioactive constituents, which can be found mainly in the root, belong to hydrophilic phenolic acids (e.g. rosmarinic acid, salvianolic acid A, salvianolic acid B, danshensu, etc., Fig.14) and lipophilic tanshinones (e.g. tanshinone I, tanshinone IIA, miltirone, cryptotanshinone, etc.) [210-212]. These secondary metabolites are known to possess anti-oxidative, anti-inflammatory, as well as anti-neurodegenerative activities without causing major side effects [213-215]. Numerous studies have revealed that these lipophobic and lipophilic compounds also possessed substantial anticancer activities including overcoming MDR [216].

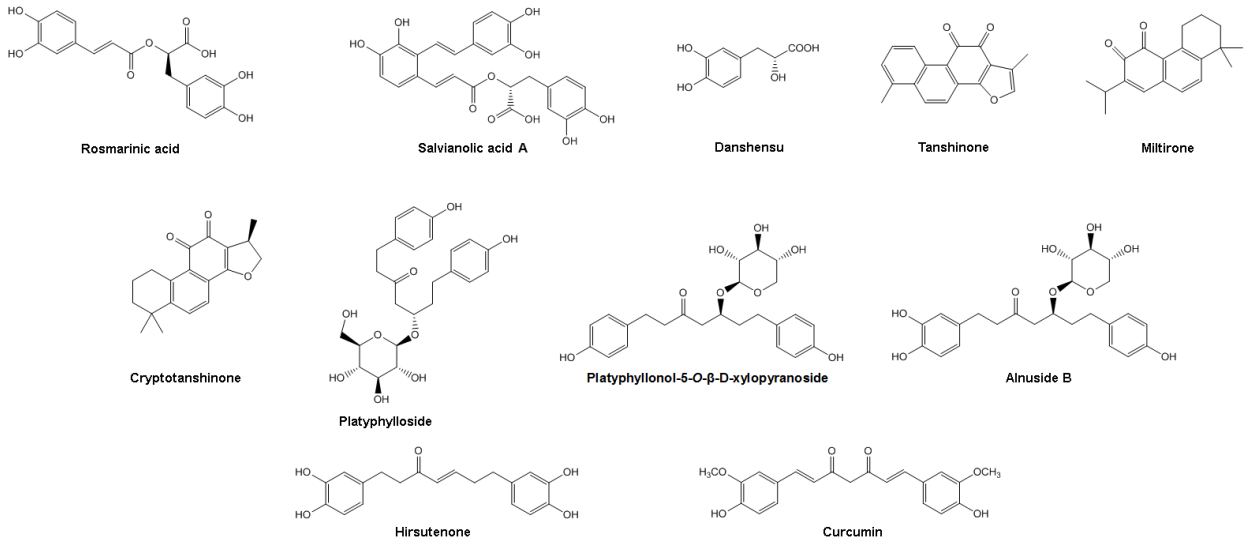


Fig.14. Compounds isolated from medicinal plants with anti-P-gp potential

Tanshinones are the main lipid-soluble compounds of *S. miltiorrhiza* and belong to a group of abietane diterpenes [217]. Their chemical structure is composed of naphthalene or tetrahydronaphthalene ring A and B, ortho- or para-quinone or lactone ring C, and a furan or dihydrofuran ring D [218]. The most common tanshinones are the ortho-quinones including tanshinone IIA, tanshinone I (Fig.14) and cryptotanshinone.

Cryptotanshinone (Fig.14) showed strong cytotoxicity towards both parental and P-gp-overexpressing adriamycin resistant lymphoblastoma cells [219]. This compound also decreased P-gp mRNA and protein levels, and inhibited ATPase activity of P-gp in colon cancer cells [220]. Moreover, cryptotanshinone suppressed doxorubicin efflux in P-gp-overexpressing human hepatocyte carcinoma cells [221]. Cryptotanshinone modulated cell death and survival, cell proliferation, reactive oxygen species (ROS) production, cell cycle arrest, DNA damage and cellular movement in lymphoblastoma cells [219]. Cryptotanshinone triggered the mitochondria-mediated intrinsic apoptotic pathway through ROS production, loss of mitochondrial membrane potential and DNA damage, and activated caspases 3, 7 and 9.

Miltirone, (Fig.14) another lipophilic tanshinone, was shown to be cytotoxic towards both sensitive and MDR lymphoblastic cells [222]. A recent study reported that miltirone interacted with P-gp and inhibited its activity in doxorubicin-resistant hepatocyte carcinoma cells [223]. Miltirone also promoted ROS-mediated MAPK signaling and apoptosis [223].

Plant phenolic acids have been shown to possess significant preventive and treatment potential in cancers, both *in vitro* and *in vivo*, through scavenging free radicals, metabolism of xenobiotics, gene expression regulation, DNA repair signaling pathways modulation, cell survival, apoptosis, angiogenesis and invasion [224, 225]. Additionally to anticancer action, phenolic acids from *S. miltiorrhiza* showed significant cardiovascular protective properties [226], as well as neuroprotective [227, 228], antidiabetic [229, 230], and anti-microbial effects [231, 232]. Their combination with classic chemotherapeutics improved anticancer properties and showed potential for overcoming MDR resistance in tumor cells.

Hydrophilic phenolic acid, 3,4-dihydroxyphenyllactic acid (also known as rosmarinic acid), is an ester derivative of caffeic acid found in various medicinal and culinary plants, including *S. miltiorrhiza*, oregano and basil [233]. Rosmarinic acid (Fig.14) has extensively been studied regarding its anticancer properties and ability to modulate MDR. This phenolic acid showed substantial cytotoxicity towards both sensitive and doxorubicin-resistant leukemia cells [234]. Rosmarinic acid also reversed the MDR in human gastric cancer cell line as well as breast cancer cells via downregulation of *mdr1* and P-gp expression [235, 236]. Rosmarinic acid also increased the P-gp efflux activity which was accompanied by increased intracellular ATP levels in hepatocyte carcinoma cells [237].

Another hydrophilic phenolic acid, salvianolic acid A (Fig.14), reversed paclitaxel resistance through modulation of the PI3K/AKT pathway and suppressed proliferation in paclitaxel-resistant breast cancer cells [238]. Furthermore, combined treatment with salvianolic acid A and paclitaxel inhibited migration and invasion, and suppressed the expression of transgelin 2 in human breast cancer cells [239]. Adriamycin resistant breast cancer cells displayed collateral sensitivity towards salvianolic acid A, which triggered S phase cell cycle arrest, mitochondrial-mediated apoptosis, caspase-3 activation, Bcl-2 down-regulation, P-gp expression modulation. Salvianolic acid A also showed stronger antitumor activity *in vivo* and reduced body weight loss compared to doxorubicin in MDR xenograft studies [240]. This compound inhibited arginine methyltransferase 1, a protein with a key role in maintenance of P-gp expression.

Additionally, salvianolic acid A enhanced doxorubicin action in nude mice with drug-resistant tumors [241].

4.2. Universal Traditional Medicine

Numerous other universally used traditional medicines have been reported to interfere with P-gp [242]. Alcoholic extract of *Hypericum perforatum* (St. John's wort) contains lipophilic components such as naphthodianthrones (hypericin and pseudohypericin), and phloroglucinol derivative hyperforin. It was shown that hyperforin and hypericin, which inhibit the reuptake of neurotransmitters, are mainly responsible for the extract's biological activities [243-245]. Various studies confirmed the effect of St. John's wort on the expression level of P-gp and CYP3A4. Namely, St John's wort components were shown to increase the duodenal P-gp expression after oral administration by 1.4-fold [246]. In addition, the activity of P-gp substrate fexofenadine was altered under the influence of *Hypericum perforatum* and a single-dose application of this extract decreased fexofenadine plasma concentration by 35% suggesting a decrease in intestinal P-glycoprotein expression [247]. In another study, short-term administration of St. John's wort increased plasma concentration of voriconazole [248]. However, long-term application seems to have the opposite effect and cause an increase of P-glycoprotein expression in the intestine [246, 248]. The activation of the pregnane X receptor that controls the transcription of the MDR1 gene, is behind the observed effect of St John's wort extracts on the P-gp expression levels. Hyperforin, the active component from St John's wort, likely binds to pregnane X receptor and is believed to trigger increased P-gp synthesis [249].

Piperine is an alkaloid found in *Piper nigrum* and *Piper longum* (*Piperaceae*) with antidiarrhoeal and immunostimulatory properties [250, 251]. It was also reported to decrease the activity of P-glycoprotein and CYP3A4 enzyme, and significantly increase the plasma concentrations of rifampicyn, phenytoin, propranolol and theophylline [252, 253]. Piperine also decreases the resistance to doxorubicin by 32.16-fold in breast resistant cancer cells and 14.14-fold in cisplatin-resistant lung adenocarcinoma cells [254].

Silymarin is an extract from the seeds of milk thistle (*Silybum marianum*) that contains a standardized mixture of flavonolignans: silybin, silidianin and silychristin. It is known for its hepatoprotective properties and may also influence the activity of P-glycoprotein [255]. Besides being widely used in the treatment of cirrhosis and viral hepatitis, the phytochemicals from this extract are also linked to prevention of liver cancer. For example, it was reported that silymarin has protective effect on the hepatocyte membrane, triggers proteins synthesis and possesses antioxidant properties which aid hepatocytes regeneration [256]. Silymarin inhibited P-gp activity *in vitro* in colorectal carcinoma cells but did not significantly influence digoxin pharmacokinetics *in vivo* [257, 258] which could linked to its low bioavailability [256].

The bioactive substances of the *Ginkgo biloba* extract include flavonoids (quercetin, kaempferol, tamarixetin) and terpenoids (ginkgolides A, B, C, J, M, bilobalide) and may have an impact on the P-gp activity [82]. A study showed that ginkgolides A and B induce P-gp expression in human primary hepatocytes, while flavonoids and bilobalide do not affect P-gp activity [259]. *In vivo*, quercetin significantly decreased the bioavailability of cyclosporine (CYP3A4 and P-gp substrate) in rats after long-term use, which implies modulation of P-gp activity [260].

The licorice plant, *Glycyrrhiza glabra*, is a legume native to southern Europe and parts of Asia and well-known for the sweet flavor extracted from its root. Glabridin, a compound isolated from licorice, inhibited P-gp-mediated transport of digoxin in rats. [261]. However, glabridin is a P-gp substrate and P-gp-mediated efflux is likely responsible for its low oral bioavailability.

Green tea leaf, *Camellia sinensis* (*Theaceae*), contains bioactive polyphenols, primarily catechins, that possess chemopreventive, anticarcinogenic, antiatherogenic and antioxidant properties [262]. (-)epicatechin was suggested to bind to and activate an allosteric site that enhances P-gp overall function or efficiency. This mechanism of heterotropic allosteric enhancement of P-gp could be behind the reported chemoprotection and anticarcinogenic effect of green tea consumption [262].

The Chinese goldthread (*Coptis chinensis*) was also linked to the increased P-gp expression. Its bioactive constituent berberine was reported to reduce rhodamine 123 accumulation in human and murine hepatoma cells [263].

Ginsenosides Rg1, Re, Rc, and Rd found in the ginseng root (*Panax* genus) inhibited P-gp function in MDR mouse lymphoma cells [264]. Protopanaxatriol ginsenosides from *Panax ginseng* (*Araliaceae*) were shown have a chemosensitizing effect on Pgp-mediated MDR cells by increasing the intracellular accumulation of drugs through direct interaction with P-glycoprotein at the azidopine site [159].

Plants of the *Alnus* genus are also well known for their vast traditional medical values which are recognized through antioxidative, anti-inflammatory, antiviral, anticancer, hepatoprotective, and neuroprotective properties [265-272]. Most investigated species of this genus include *A. japonica*, *A. hirsute* and *A. rubra* [273-276]. A large number of natural products have been isolated from this genus including diarylheptanoids, terpenes, flavonoids, phenols, sterols, and others [265]. In addition to *Alnus*, diarylheptanoids are also found in abundance in *Zingiber*, *Curcuma*, *Alpinia*, *Betula* and *Myrica* genera [277]. Diarylheptanoids isolated from the bark of black alder (*Alnus glutinosa*), namely platyphylloside, platyphyllonol- 5-O--D-xylopyranoside, alnuside B, hirsutenone, (Fig.14) and two new diarylheptanoids with a p-coumaroyl group, exerted significant cytotoxicity against non-small cell lung carcinoma cells and their P-gp overexpressing MDR counterparts [278]. Alnuside A and methylhirsutanonol suppressed P-gp function, and their ability to increase the accumulation of the P-gp substrate doxorubicin was comparable with that of curcumin [278].

Curcumin (Fig.14) is a well-known diarylheptanoid isolated from the rhizomes of *Curcuma longa* (Zingiberaceae) and one of the most studied anticancer compounds isolated from natural sources [279]. Curcumin is traditionally used as a spice and a pigment in food products or cosmetics, as well as a constituent of specific drugs [280]. It was shown to inhibit numerous ABC drug transporters and possess anti-inflammatory [281], antiviral [282] and anticancer [283] properties as well as potential medicinal value in neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases [284, 285]. Moreover, it can prevent liver damage and reduce glucose levels and cholesterol [286-289]. Curcumin was shown to directly inhibit P-gp, MRP1 and BCRP activity and overcome MDR phenotype in cancer cells [290-293] and tumors in mice [293]. Curcumin also suppressed P-gp function in human epidermoid cancer cells and showed chemosensitizing properties [294]. Curcumin decreased *MDR1* gene expression and sensitized resistant human gastric cancer cells to vincristine [295]. Moreover, it was detected that curcumin promoted the activation of caspase-3 in vincristine-resistant human gastric cancer cells and triggered apoptosis. In addition to inhibition of ABC transporters, curcumin was shown to regulate cancer cell growth and survival by inhibiting the mTOR signaling pathway through a protein

phosphatase-dependent dephosphorylation mechanism [296, 297]. Since curcumin is lipophilic and rapidly metabolized, high doses are needed to reach biological activity. However, this compound is well tolerated and does not reduce the efficacy of other drugs [298]. Since it does not produce adverse effect in high doses, the application of curcumin as a P-gp modulator exhibits potential for treatment of resistant cancers [295]. The delivery of curcumin has been improved through various methods including nanoparticles [299, 300], liposome encapsulated curcumin [301], the curcumin-piperine combination [302], as well as curcumin-phospholipid complex and structural analogs [303].

5. CONCLUSION

Recent stagnation in interest of modern pharmacology for natural products prompted us to review the extraordinary potential of natural-based compounds in respect to their activity against P-gp, an efflux transporter principally responsible for the inefficacy of chemotherapy.

Many natural products possess the ability to interact with P-gp by inhibiting its activity and affinity for substrates. Continuous identification of new P-gp inhibitors from natural sources significantly contributes to the development of new approaches for overcoming MDR.

Considering the availability and diversity of natural sources, it is likely that novel anticancer as well as cancer preventive drugs will be mainly developed according to naturally occurring structures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors acknowledge the support from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No III41031) and COST Actions CM1106 (Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells) and CM1407 (Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery).

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