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Discovering Natural Product Modulators to Overcome Multidrug Resistance in Cancer Chemotherapy

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Abstract

Multidrug resistance caused by the overexpression of ABC drug transporters is a major obstacle in clinical cancer chemotherapy. For several years, it appeared that direct inhibition of ABC transporters would be the cheapest and most efficient way to combat this problem. Unfortunately, progress in finding a potent, selective inhibitor to modulate ABC transporters and restore drug sensitivity in multidrug-resistant cancer cells has been slow and challenging. Candidate drugs should ideally be selective, potent and relatively non-toxic. Many researchers in recent years have turned their attention to utilizing natural products as the building blocks for the development of the next generation of inhibitors, especially after the disappointing results obtained from inhibitors of the first three generations at the clinical trial stage. The first step is to discover natural substances (distinct from the first three generation inhibitors) that are potent, selective and relatively non-toxic in order to be used clinically. Here, we present a brief overview of the prospect of using natural products to modulate the function of ABC drug transporters clinically and their impact on human physiology and pharmacology.

Keywords

ATP-binding cassette transporters; Bioavailability; Chemotherapy; Modulators; Multidrug resistance; Natural products

INTRODUCTION

The impact of ATP-binding cassette transporters on cancer chemotherapy

Despite more than two decades of research on the subject, multidrug resistance (MDR) remains one of the major obstacles to successful cancer chemotherapy. This phenomenon occurs when cancer cells spontaneously become insensitive to drugs that are structurally unrelated [1]. A leading cause of MDR in cancer is the overexpression of ATP-Binding Cassette (ABC) transporters that utilize energy derived from ATP hydrolysis to actively transport anticancer drugs across biological membranes, preventing drugs from reaching their targets within a cancer cell [2]. The ABC transporters belong to a superfamily of proteins that are classified into seven subfamilies (ABCA-ABCG) based on their sequence

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homology and domain organization [3]. To date, sixteen members have been identified to be associated with known human diseases. However, only three major ABC drug transporters, including P-glycoprotein (Pgp; ABCB1), multidrug resistance protein 1 (MRP1; ABCC1) and ABCG2 (BCRP; MXR), are believed to seriously affect cancer chemotherapy [2, 4]. The knock-out mouse models lacking these ABC transporters have shown that they have a major impact on the pharmacological behavior of many anticancer drugs (reviewed in [5, 6]). Collectively, they are capable of transporting the majority of anticancer drugs that are administered in the clinic, including, but not limited to, *vinca* alkaloids, anthracyclines, mitoxantrone, paclitaxel, etoposide and tyrosine kinase inhibitors such as gleevec or nilotinib [7–9]. Furthermore, in addition to causing MDR in cancer cells, the physiological functions and the localization of these transporters in human tissues also greatly affects the overall adsorption, distribution, metabolism, elimination and toxicity of almost all classes of drugs [10] (Figure 1). To summarize, the presence of high or over-expression of several ABC drug transporters in mRNA and/or protein level can have a significant impact on overall cancer chemotherapy and lead to the development of MDR and treatment failure [11–15]. Consequently, inhibiting the function or expression of these transporters should restore drug sensitivity in some MDR cancer cells and lead to a substantial improvement in the effectiveness of the anticancer drugs in cancer patients.

Development of inhibitors of ABC drug transporters

Many inventive strategies and ideas have recently been proposed and evaluated in an attempt to overcome MDR in cancer patients [16]. Currently, inhibiting the function (or the expression) of respective ABC drug transporters with potent and low toxicity inhibitors (or modulators) is still considered by many researchers to be the easiest and most direct way to restore drug sensitivity in MDR cancer cells. The fundamental concept underlying the use of an inhibitor (or chemosensitizer) in MDR cancer chemotherapy is to directly block drug efflux mediated by ABC transporters (such as Pgp), to improve drug penetration and distribution, and to elevate drug accumulation in MDR cancer cells, eventually to restore drug sensitivity [2, 17–19]. Substantial efforts have been carried out to develop potent modulators of ABC drug transporters for the past two decades, and some of the major discoveries have been summarized in a recent review [8]. Unfortunately, there is still a lack of irrefutable evidence or clinical trial data to demonstrate that this approach can indisputably improve bioavailability or delivery, or can restore drug sensitivity in MDR cancer patients [2]. The difficulty in finding an ideal inhibitor is often associated with specificity, potency and intrinsic toxicity. Adverse interactions of modulators with drugs administered in parallel or nonspecific side effects are also extremely problematic. To make the matter even worse, there are substantial overlapping substrate specificities among the major ABC drug transporters, which are expressed in vital organs (*e.g.* brain, testes, liver, kidney and intestines) to protect the body from the xenobiotics. There may be some toxicity in these organs associated with the inhibition of these transporters. Furthermore, the variability in expression levels and polymorphisms of ABC transporters among individuals makes clinical trials related to MDR cancer exceptionally challenging [20]. On the other hand, these above mentioned factors are also the reasons why the roles of ABC drug transporters are crucial to advances in personalized medicine [21].

Inhibitors of ABC transporters can be classified into four major categories. The discovery of First Generation Inhibitors involved the screening of drugs or chemicals with known biological activities (such as channel blockers, immunosuppressants and even cardiovascular drugs), to find compounds that also inhibit the function of ABC transporters [8, 22]. In contrast, the Second and Third Generation Inhibitors were specifically designed and synthesized based on structural information from the First Generation Inhibitors [8]. The reasons behind the failure of using inhibitors from the first three generations to restore drug

sensitivity in cancer clinical trials are quite clear. Since most of those inhibitors were not designed to select ABC drug transporters as their primary targets, it is not surprising that they affected other biological targets (unspecific and unfavorable interactions with other targets or drugs). Also, higher concentrations of these drugs are required to reach effective inhibitory effect, thus causing undesirable toxicity (*e.g.* verapamil). In addition, First Generation Inhibitors themselves are often transported substrates of ABC transporters. Mutations in the ABC transporters of interest, the presence of other drug efflux or uptake transporters or channels, and problems with solubility, penetration and distribution, also diminish the effectiveness of these inhibitors [8, 23]. In spite of the lack of effectiveness, it is still crucial to understand the interactions between some of the First Generation Inhibitors and ABC drug transporters, as many are chemotherapeutic drugs used on a daily basis. For instance, the tyrosine kinase inhibitors (TKIs) nilotinib and lapatinib inhibit ABCG2-mediated efflux by competing with the binding of anticancer agents at the ABCG2 substrate binding site. Furthermore, the upregulation of ABCG2 can result in increased efflux of TKIs (gefitinib and vandetanib) after long-term exposure to TKIs [24]. Consequently, their own drug efficacy is also affected by ABCG2-mediated transport [25, 26].

MODULATORS ORIGINATING FROM NATURAL SOURCES: THE FOURTH GENERATION INHIBITORS

Inhibitors or modulators originating from natural sources are sometimes referred to as “Fourth Generation Inhibitors”. In fact, compounds from natural products provide one of the most diverse and novel chemical scaffolds suitable for the development of new inhibitors. It is thus not surprising that many researchers recognize the value of screening for new natural product modulators, because they have the potential to be more successful than many of the modulators already developed. There is a great diversity of materials that can be utilized, as biologically active components are now extracted from plants, fungi and even marine organisms, then purified and characterized. Most importantly, natural extracts are usually low in toxicity and are well tolerated in the human body. For that reason, research groups are actively screening for candidates from natural sources that have a strong modulation effect on the function (or the expression) of disease-linked ABC transporters. Once a lead compound is identified, quantitative structure-activity relationship (QSAR) studies and an optimization process can then be carried out [27, 28]. For instance, the fungal toxin fumitremorgin C (FTC) is an effective ABCG2 inhibitor discovered from natural sources, but has unfavorable neurotoxicity [29]. FTC was therefore optimized into the more potent, specific and less-toxic analog Ko143, which is more appropriate for clinical trials [30]. As a large number of natural product modulators have been discovered over the years, this review will focus on two of the most popular natural products, curcumin and flavonoids, as examples of natural products that modulate ABC drug transporters. A list of key natural product modulators discovered for Pgp, MRP1 and ABCG2 is summarized in Table 1.

Curcumin

Curcumin is a common term used for a mixture of curcuminoids that are purified from the Indian spice turmeric powder, mainly comprised of curcumin (curcumin I), demethoxycurcumin (curcumin II) and bisdemothoxycurcumin (curcumin III) [31]. Curcuminoids are known to have many biological activities, including anti-inflammatory [32, 33], anti-cancer [34], and anti-viral properties [35, 36]. In addition, both curcumin and its major metabolite tertrahydrocurcumin were found to restore drug sensitivity in cancer cells overexpressing the MDR-linked ABC transporters Pgp [31, 37], MRP1 [37, 38] and ABCG2 [37, 39] by directly inhibiting their functions. More recently, curcumin was found to be active against MDR tumors in mice as well [40]. Considering its inhibitory effect on multiple ABC drug transporters and its many beneficiary biological properties, it is not

surprising that curcumin has become one of the most exciting natural product modulators in recent years.

Poor bioavailability is the one major problem with using curcumin clinically. The levels of curcumin in plasma and tissues remain low after oral consumption, reported to be in the range of nanomolar and picomolar, respectively [41]. Curcumin is lipophilic and very insoluble in nature, and is also rapidly metabolized in the intestine and excreted in the urine, which means that high doses of curcumin must be consumed for it to be biologically relevant and effective [42]. For instance, in one study, the level of curcumin was only barely detectable in human plasma even after a dose of curcumin as high as 12.0 g [43]. Therefore, several approaches have been investigated to improve the delivery of curcumin in our system [44], including the use of liposomal curcumin [45]; curcumin nanoparticles [46, 47], curcumin phospholipid complex or structural analogues of curcumin [48], or the use of a combination of curcumin and piperine. Piperine has been shown to block the metabolism of curcumin by P450 A3 and by other hepatic and intestinal pathways involved in glucuronidation of this compound [49]. In addition, it was observed that piperine increased the bioavailability of orally given curcumin in both rats and humans with no adverse effect [49]. Thus, it should be useful to test whether the combination of curcumin and piperine improves the bioavailability of coadministered anticancer drugs in cancer patients.

More importantly, both Phase I and II clinical studies with curcumin have been carried out and showed some encouraging results. Despite its poor bioavailability, Phase I studies showed that curcumin is well-tolerated [50] and provided significant improvement in 20–30% of patients with advanced colorectal cancer when treated with 360–500 mg of curcumin [41], with minimal drug-curcumin interactions [51]. Similarly, Phase II studies showed treatment with curcumin clinically can improve the outcome in patients with rheumatoid arthritis [52], chronic anterior uveitis [53], inflammatory bowel disease [54], or psoriasis [55] or in patients with advanced pancreatic cancer [56]. These clinical studies suggest that it would be worthwhile to test curcumin as an adjuvant along with traditional chemotherapy drugs to overcome MDR in cancer patients.

Flavonoids

Among all natural product modulators, the most well-known and well-studied are the flavonoids, which include flavonols, flavones, isoflavones, flavanols, flavanolols, flavanones and chalcones [57]. Typically, each person per day consumes a substantial amount of flavonoids from fruits, vegetables, food supplements, tea and wine. They are known to have many prominent health benefits [58, 59], as well as antitumor [60–62], antimitotic [61], and antiviral [61, 63] properties. They are also able to inhibit kinases [64, 65], and are active in radical scavenging and metal ion chelating [66]. Moreover, it is important to know that many flavonoids are excellent modulators of major ABC drug transporters [67–70]. Collectively, they can change the overall pharmacokinetics, including drug absorption, penetration and elimination by modulating the functions of ABC transporters [71, 72]. The result of such interaction is not at all restricted to inhibition; some flavonoids can stimulate (rather than inhibit) the function of ABC transporters, depending on the substrate of interest [73]. Also, one has to take into account that flavonoids are metabolized into flavonoid conjugates (glucuronide, sulfate or methoxylated) after ingestion, and unlikely to have the exact biological activities or inhibitory effects on ABC transporters as the unmodified forms [74].

In terms of MDR, flavonoids have been studied and characterized extensively by numerous research groups to determine their ability to inhibit Pgp-, MRP1- and ABCG2-mediated efflux and restore drug sensitivity in MDR cancer cells [67–70] (Table 1). A detailed analysis of the structure and inhibitory activity relationships of flavonoids can be found in a

review by Boumendjel *et al.* [75]. Interest in this field developed when one of the earliest reports revealed the potential impact of active components from fruit extracts to affect the outcome of a clinical treatment using Pgp drug substrates [76]. More recently, *in vitro* and *in vivo* experiments using cell lines overexpressing ABC drug transporters and knockout animals have been designed for more detailed studies [70]. *In vitro* biochemical and pharmacological studies have revealed that in most cases, flavonoids modulate ABC drug transporters by competitively binding to the substrate-binding sites of transporters, thus hindering their functions [67, 69, 75, 77]. On the other hand, it appears that some flavonoids also affect ATP binding or hydrolysis at the nucleotide binding domains [75, 78], or alter the surface expression level of ABC transporters [79].

A CLINICAL PERSPECTIVE

Natural products and their derivatives have been investigated clinically for their ability to prevent, inhibit and reverse the progression of cancer. As indicated by surveys, approximately 80% of cancer patients use natural products in combination with classic anti-cancer drugs [80]. This suggests that many cancer patients are quite interested in utilizing natural products either as nutritional supplements or as complementary or alternative medicines. They expect these natural products to significantly reduce the side effects and toxicities caused by anti-cancer drugs, to increase the immune response and enhance the effectiveness of chemoprevention. Some believe they will actually stop or reverse cancer progression. In terms of overcoming ABC transporter-mediated MDR in cancer, many non-toxic natural products or metabolites that inhibit the function of ABC transporters are preferred over the use of First or Second Generation Inhibitors in clinical applications, because the inhibitors from the first two generations can induce undesirable drug-drug interactions or inhibition of physiological functions [72]. Therefore, many researchers are now interested in testing non-toxic natural products to overcome ABC transporter-mediated MDR in clinical settings.

As mentioned earlier, flavonoids are some of the most extensively studied natural products when it comes to their ability to modulate ABC drug transporters [81]. Flavonoids and other natural products usually elevate the level of intracellular concentration of anticancer drugs by directly inhibiting the function of ABC drug transporters that are overexpressed in MDR cancer cells. However, in addition to direct inhibition, many natural products overcome ABC transporter-mediated MDR by altering the bioavailability of various therapeutic drugs upon oral uptake [72]. For instance, Pgp and ABCG2 are both expressed at the apical or luminal membrane of enterocytes in the intestine, which play a role in the elimination of substrate-drugs and food components from the inside to the outside (lumen) of the cells. Although the elimination of substrates is a physiological role of ABC transporters expressed in the intestine, this function limits the absorption of substrate-drugs and food components. A good example is the co-administration of the dietary supplement biochanin A (Table 1) and the anticancer drug paclitaxel. In one report, biochanin A increased the oral bioavailability and peak plasma concentration of the Pgp substrate paclitaxel by 3.7- and 2.0-fold in a rat model [82]. Similarly, other flavonoids such as quercetin and flavone also increased the bioavailability of paclitaxel in male SD rats [83, 84]. Therefore, flavonoids are excellent candidates for modulating ABC drug transporters, as well as reducing the elimination of the co-administered anticancer drugs in *in vivo* systems. The role of flavonoids as ABC transport modulators affecting the bioavailability of drugs and food components has been summarized in recent reports [72, 81]. These studies demonstrate the pharmacological advantages of using natural products to enhance the uptake of co-administered anticancer drugs by cancer cells.

On the other hand, the use of natural product modulators may also increase the risk of unforeseen toxicities mediated by co-administered anticancer drugs, especially in the case when drugs with a narrow therapeutic index are used [85]. Excessive inhibition of ABC transporters by natural products may result in elevation in anticancer drug toxicity throughout the body, leading to unexpected side effects. In the same way, since both Pgp and ABCG2 are expressed at vital organ barriers such as those protecting the brain, the testes, and the fetus (Figure 1), inhibition of these ABC transporters may lead to undesirable toxicity associated with these organs.

Genetic polymorphisms in drug metabolizing enzymes and ABC transporters may also alter the activity of the anti-cancer drugs, affect the bioavailability and disposition of anticancer drugs, and result in lower therapeutic efficacy or greater toxicity [86]. For example, the natural product biochanin A, mentioned earlier, alters the bioavailability of paclitaxel, a drug substrate of both Pgp and CYP3A. This elevation in systemic paclitaxel exposure is attributed to the synergistic inhibition of both Pgp and CYP3A by biochanin A in the intestine [82]. Moreover, some of the SNPs in the *MDR1* (*ABCB1*) gene appear to be associated with altered transporter function and expression, thereby affecting the metabolism and disposition of drugs [87, 88]. It is essential to know what concentrations of natural products are realistically able to inhibit or chemosensitize MDR cancer cells effectively. For instance, flavonoids in foods are often present as B-glycosides of aglycones and methoxylated forms. After ingestion, flavonoids are metabolized into glucuronide and sulfate and methoxylated conjugates. However, the main metabolites, such as glucuronides and sulfate conjugates may not even interact with Pgp [81]. For that reason, *in vivo* studies must be carried out in order to identify the active component(s), inhibitory concentrations, and the quantity of natural products needed to be ingested in order to achieve beneficial effects.

In principle, non-toxic natural products can be used as potent candidates to overcome ABC transporter-mediated MDR in cancer, to improve the oral bioavailability of anticancer drugs and provide significant health benefit to cancer patients. However, the altered bioavailability of natural products may result in unexpected side effects of anticancer drugs (or other co-administered drugs). Furthermore, genetic polymorphisms, the variability in metabolic enzymes and the expression of ABC transporters make it difficult to predict the effect of a natural product on the pharmacokinetics of the co-administered anticancer drugs clinically. In other words, when both the inhibitor (a natural product) and the drug substrate (an anticancer drug) of an ABC transporter are administered together, one should assess the potential risk resulting from altered bioavailability. Further *in vivo* studies and clinical data are required to elucidate the mechanisms of herb-drug and food-drug interactions mediated by ABC transporters, and to understand the pharmacokinetic profile and potential usage of natural products as chemosensitizers in MDR cancer chemotherapy.

CONCLUSIONS AND PERSPECTIVE

Multidrug resistance in cancer caused by the overexpression of ABC drug transporters is a major obstacle in modern chemotherapy. Even though many innovative approaches are available to us, finding a selective, low toxicity inhibitor/ modulator of ABC drug transporters still appears to be the most likely way to resolve this problem. However, finding such a modulator is a complex challenge due to the properties of these modulators themselves, as well as the important physiological and pharmacological roles of these ABC transporters. As a result of some unfavorable clinical outcomes from the first three generations of inhibitors, we are now at a stage of searching for alternative and novel scaffolds from natural sources. The progress of discovering Fourth Generation/ Natural Product Inhibitors is still in the early stages of exploring various extracts/ active components

ranging from plants and fungi to marine organisms (Table 1). In addition to those listed in Table 1, many more herbal extracts or traditional Chinese medicines also have great potential to be developed into potent chemosensitizers, since they appear to be biologically active. For instance, traditional herbal medicines are known to have a therapeutic effect on rheumatoid arthritis [89], diabetic nephropathy [90, 91], liver fibrosis and cirrhosis [92–94], heart disease [95, 96] and many other medical conditions. Further effort must be invested in discovering more active compounds from these natural sources.

In summary, natural sources provide us with a multitude of choices ranging from yeast and plants to marine organisms, but the right approach is needed in order to be successful. In our opinion, systematic high-throughput screening of traditional Chinese and South Asian medicines or herbal extract libraries should be the first step in the discovery of non-toxic, potent and selective inhibitors. QSAR studies and manipulations utilizing combinatorial chemistry must then follow if we are to see any success in using modulators to overcome ABC drug transporter-associated multidrug resistance in clinical settings. In addition, we also need to consider the use of natural product modulators as adjuvants to traditional chemotherapy drugs to improve cancer patient treatment.

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Abbreviations

ABC	ATP-binding cassette
FTC	Fumitremorgin C
MDR	multidrug resistance
MRP	multidrug-resistance protein
Pgp	P-glycoprotein

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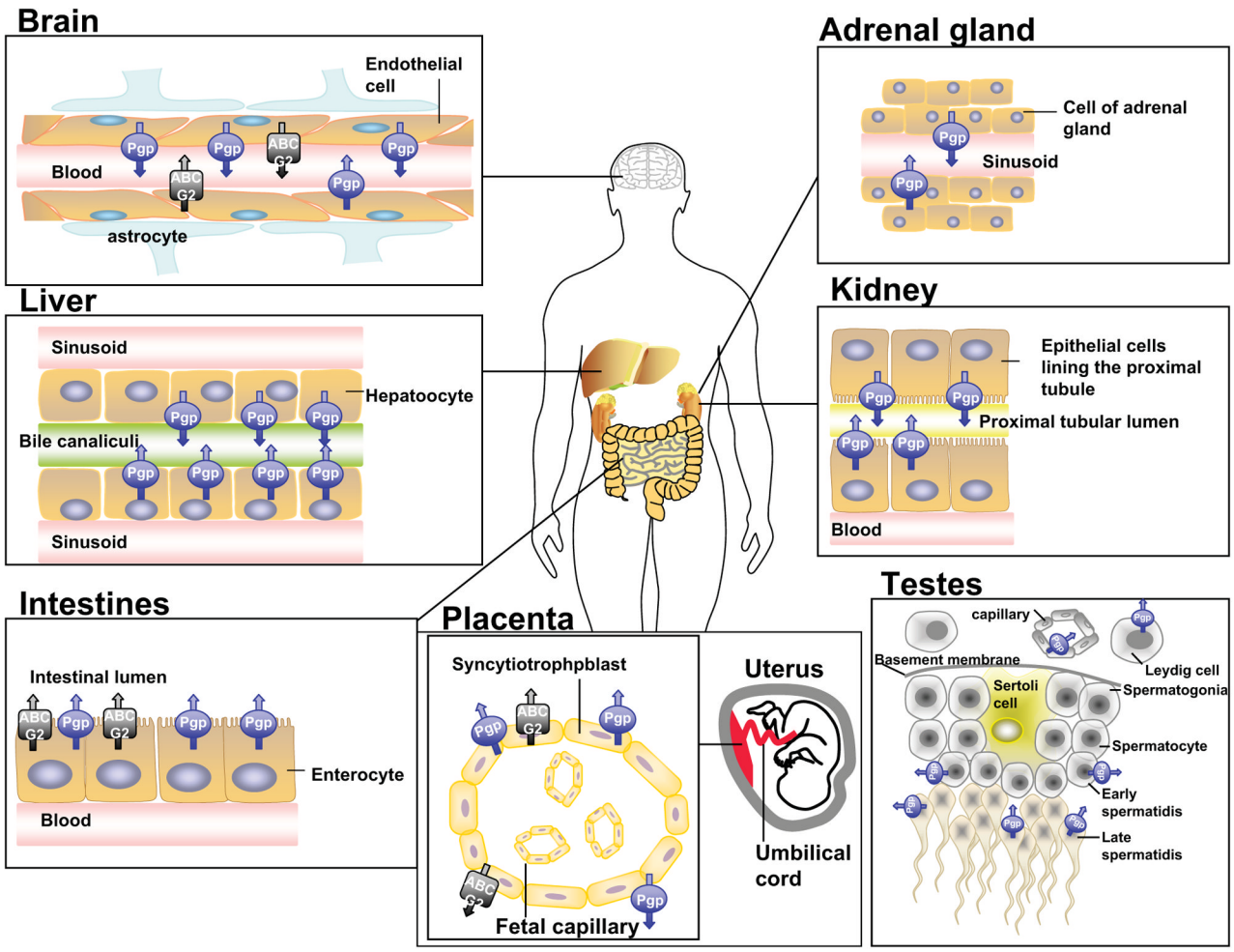

Figure 1.

Tissue localization of P-glycoprotein and ABCG2 in human organs. These transporters are present on apical or luminal surface of epithelial or endothelial cells.

Table 1

List of key natural products that modulate function of P-glycoprotein, multidrug resistant protein 1 and ABCG2

Name	Targeted ABC transporter	Source	Reference
3′-4′-7-Trimethoxyflavone	ABCG2	Plant	[97]
5-Bromotetrandrine	Pgp	Plant	[98]
6-Prenylchrysin	ABCG2	Plant	[99]
Abietane diterpene	Pgp	Plant	[100]
Acacetin	ABCG2	Plant	[101]
Agosterol A and derivatives	Pgp	Marine organisms	[102]
Alisol B 23-acetate	Pgp	Plant	[103]
Amooranin	Pgp	Plant	[104]
Asarum heteropoides var. mandshuricum	Pgp	Plant	[105]
Baicalein and derivatives	Pgp	Plant	[106]
Biochanin A	Pgp	Plant	[77]
	ABCG2	Plant	[68]
Bitter melon extract	Pgp	Plant	[107]
Cantharidin	Pgp	Insect	[108]
Cannabinoids	MRP1	Plant	[109]
	Pgp	Plant	[110, 111]
	ABCG2	Plant	[112]
Catechins	Pgp	Plant	[113]
Cepharanthine	Pgp	Plant	[114]
	MRP1	Plant	[115]
Chrysin	ABCG2	Plant	[68]
Coumarins	Pgp	Plant	[116]
Curcumin	Pgp	Plant	[31, 117]
	MRP1	Plant	[38]
	ABCG2	Plant	[39]
Cycloartanes	Pgp	Plant	[118]
Daizein	ABCG2	Plant	[119]
Deoxyschizandrin	Pgp	Plant	[120]
Eudesmin	Pgp	Plant	[121]
Eupatin	ABCG2	Plant	[122]
Euphocharacins A-L	Pgp	Plant	[123]
Fumitremorgin C	ABCG2	Fungus	[29, 124]
Genistein	ABCG2	Plant	[101]
Ginkgo biloba extract	Pgp	Plant	[125, 126]
	MRP1	Plant	[125]
Ginsenoside Rg	Pgp	Plant	[127]
Ginsenosides	ABCG2	Plant	[128]
Grapefruit juice extracts	Pgp	Plant	[129]

Name	Targeted ABC transporter	Source	Reference
Hapalosin	Pgp	Plant	[130]
Harmine	ABCG2	Plant	[131]
Hesperetin	ABCG2	Plant	[119]
Hypericin and hyperforin	Pgp	Plant	[132]
Isoquinoline alkaloid, isotetrandrine	Pgp	Plant	[133]
Jatrophanes	Pgp	Plant	[134]
Kaempferol	ABCG2	Plant	[101]
Kaempferia parviflora extracts	Pgp	Plant	[135]
	MRP1	Plant	[136]
Kavalactones	Pgp	Plant	[137]
Kendarimide A	Pgp	Marine organisms	[138]
Morin	Pgp	Plant	[77]
Myricetin	MRP1	Plant	[139]
Naringenin	ABCG2	Plant	[101]
Ningalin B and derivatives	Pgp	Plant	[140, 141]
Opiates	Pgp	Plant	[142]
Phloretin	Pgp	Plant	[77]
Piperine	Pgp	Plant	[143]
Plumbagin	ABCG2	Plant	[144]
Polyoxygenated steroids	Pgp	Marine organisms	[145]
Protopanaxatriol ginsenosides	Pgp	Plant	[146]
Pyranocoumarins	Pgp	Plant	[147]
Quercetin	ABCG2	Plant	[119]
	Pgp	Plant	[148, 149]
	MRP1	Plant	[67, 69]
Resveratrol	ABCG2	Plant	[119]
Rotenoids	ABCG2	Plant	[150]
Schisandrol A	Pgp	Plant	[151]
Sesquiterpenes	Pgp	Plant	[152]
Silymarin	Pgp	Plant	[77]
	ABCG2	Plant	[119]
Sinensetin	Pgp	Plant	[153]
Stemona curtisii root extract	Pgp	Plant	[154]
	MRP1	Plant	[154]
Stilbenoids	ABCG2	Plant	[155]
Taxane derivatives	Pgp	Plant	[156, 157]
Tectochrysin	ABCG2	Plant	[99]
Terpenoids	ABCG2	Plant	[158]
	Pgp	Plant	[159]
Tetrahydrocurcumin	ABCG2	plant	[37]
Tetrandine	Pgp	Plant	[160]
Tryprostatin A	Pgp	Fungus	[161]

Name	Targeted ABC transporter	Source	Reference
Tryptanthrin	Pgp	Fungus	[162]
Vitamin E TPGS	Pgp	Plant	[163]