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Secondary metabolites from plants inhibiting ABC transporters and reversing resistance of cancer cells and microbes to cytotoxic and antimicrobial agents

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Fungal, bacterial, and cancer cells can develop resistance against antifungal, antibacterial, or anticancer agents. Mechanisms of resistance are complex and often multifactorial. Mechanisms include: (1) Activation of ATP-binding cassette (ABC) transporters, such as P-gp, which pump out lipophilic compounds that have entered a cell, (2) Activation of cytochrome p450 oxidases which can oxidize lipophilic agents to make them more hydrophilic and accessible for conjugation reaction with glucuronic acid, sulfate, or amino acids, and (3) Activation of glutathione transferase, which can conjugate xenobiotics. This review summarizes the evidence that secondary metabolites (SM) of plants, such as alkaloids, phenolics, and terpenoids can interfere with ABC transporters in cancer cells, parasites, bacteria, and fungi. Among the active natural products several lipophilic terpenoids [monoterpenes, diterpenes, triterpenes (including saponins), steroids (including cardiac glycosides), and tetraterpenes] but also some alkaloids (isoquinoline, protoberberine, quinoline, indole, monoterpene indole, and steroidal alkaloids) function probably as competitive inhibitors of P-gp, multiple resistance-associated protein 1, and Breast cancer resistance protein in cancer cells, or efflux pumps in bacteria (NorA) and fungi. More polar phenolics (phenolic acids, flavonoids, catechins, chalcones, xanthones, stilbenes, anthocyanins, tannins, anthraquinones, and naphthoquinones) directly inhibit proteins forming several hydrogen and ionic bonds and thus disturbing the 3D structure of the transporters. The natural products may be interesting in medicine or agriculture as they can enhance the activity of active chemotherapeutics or pesticides or even reverse multidrug resistance, at least partially, of adapted and resistant cells. If these SM are applied in combination with a cytotoxic or antimicrobial agent, they may reverse resistance in a synergistic fashion.

Keywords: ABC transporter, P-gp, MDR, MRP1, secondary metabolites, review

INTRODUCTION

EVOLUTIONARY AND ECOLOGICAL BACKGROUND

Plants are sessile organisms which cannot run away when attacked by an herbivore nor do they have an immune system to combat infesting parasites, bacteria, fungi, or viruses. From early days of the evolution of land plants they had to cope with these environmental challenges. Plants developed a number of mechanical traits, such as resistant epidermal and bark tissues but also spines and thorns as defense tools. In addition, plants evolved a high diversity of defense chemicals, the so-called secondary metabolites (SM; **Table 1**). Besides defense, some SM function as signal compounds or protect against oxidative or UV stress (Wink, 1988, 2003, 2008b, 2010a,b).

The structures of SM have been optimized during evolution in such a way that they can interfere with molecular targets in herbivores and microbes. The main group of targets include (1) proteins, (2) DNA, RNA, and (3) the biomembrane (Wink, 2008a,b; Wink and Schimmer, 2010). Neuronal signal transduction is a central and specific target in animals and many SM, especially alkaloids and amines are directed toward it (Wink, 1993, 2000). SM which interfere with proteins, such as polyphenols, biomembranes (saponins and other lipophilic terpenoids), or DNA (alkylating or intercalating mutagens) affect a wider range of organisms, including animals and microbes. In general, membrane and DNA active SM have cytotoxic properties. Affected cells usually undergo apoptosis (Wink, 2007). Several SM interfere with the neuronal signal transduction in animals and are thus potent neurotoxins (Wink, 1993, 2000).

A large number of SM have lipophilic properties which enable them to readily pass biomembranes in target organisms by simple diffusion. These SM are also dangerous for the producing plants. Therefore, they are usually stored in dead tissue away from living cells, such as resin ducts, oil cells, trichomes, or cuticles (Wink, 2010b). The absorption of polar SM is usually slower or does not

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; MDR, multidrug resistance; MRP1, multidrug resistance-associate protein; P-gp, P-glycoprotein.

Table 1 | Structural types of secondary metabolites and known structures.

Class	Number of structures
WITH NITROGEN	
Alkaloids	21000
Non-protein amino acids (NPAA)	700
Amines	100
Cyanogenic glucosides	60
Glucosinolates	100
Alkamides	150
Lectins, peptides	2000
WITHOUT NITROGEN	
Monoterpenes (incl. iridoids)	2500
Sesquiterpenes	5000
Diterpenes	2500
Triterpenes, steroids, saponins	5000
Tetraterpenes	500
Phenylpropanoids, phenolic acids, coumarins, lignans	2000
Flavonoids, isoflavonoids, anthocyanins, stilbenoids, tannins, xanthones	10000
Polyacetylenes, fatty acids, waxes	1500
Polyketides (quinones, anthraquinones)	750
Carbohydrates, organic acids	400

take place at all, with the exception of SM that can use transporters for sugars or amino acids or endocytosis as a kind of "stowaway." Furthermore, SM usually occur in complex mixtures which may contain SM (such as saponins) that can facilitate the uptake of polar SM (Hebestreit and Melzig, 2003).

THE RESPONSE OF HERBIVORES AND PATHOGENS AGAINST PLANT DEFENSE CHEMICALS

In the evolutionary arms race herbivores and microbes evolved mechanisms to avoid or inactivate the defense chemistry of plants. Mechanisms of resistance in animals and humans are complex and often multifactorial. Mechanisms include: (1) Activation of ATP-binding cassette (ABC) transporters, such as p-gp, which pump out lipophilic compounds that have entered a cell, (2) activation of cytochrome p450 oxidases (CYP) which can oxidize lipophilic agents to make them more hydrophilic and accessible for conjugation reaction with glucuronic acid, sulfate, or amino acids, and (3) activation of glutathione transferase (GST), which can conjugate xenobiotics with glutathione. The reactions of CYP, GST, and conjugation are well known in pharmacology and categorized as phase I and phase II reactions. These reactions are important in the metabolism of medicinal drugs and toxins. This evolutionary history also applies for humans which enables us to metabolize a large number of xenobiotics.

In phase I, a lipophilic SM is made more hydrophilic by introducing hydroxyl groups. This reaction is catalyzed by CYP and CYP1A1, CYP1A2, CYP3A4, and CYP2D6 are the most important enzymes. Furthermore, these CYP can cleave *N*-methyl, *O*-methyl, or methylene groups in order to obtain a more hydrophilic or better accessible substrate (Guengerich, 2001). In the human genome, about 57 active CYP genes are known (Ingelman-Sundberg and Gomez, 2010). A substantial polymorphism of CYPs exists which enables them to metabolize a wide range of xenobiotics. The regulation of the corresponding genes is only partly known. The genes encoding these enzymes, which occur in intestinal epithelia and in the liver, are inducible by SM that have entered the body. In phase II, the hydroxylated xenobiotics are conjugated with polar molecules, such as glutathione, sulfate, or glucuronic acid. These conjugates are eliminated via the kidneys and urine. That means, on exposure to lipophilic SM, genes which encode these enzymes are often induced and that activation can inactivate the toxins. Several SM carry methylenedioxy groups on their phenolic rings, such as in the isoquinoline alkaloids berberine and hydrastine, which are assumed to be inhibitors of CYP (Wink, 2007). Alkaloids which can inhibit CYP have been summarized by Wink (2007).

Resistance mechanisms in bacterial pathogens are even more evident because several pathogens already have evolved resistance against medicinally used antibiotics. The main mechanisms include:

- Direct inactivation of the antibiotic, e.g., by cleavage of the beta-lactam ring of penicillin by beta-lactams or acetylation, methylation of other antibiotics
- Target site modification: molecular change of the target molecule (proteins, rRNA) in such a way that the antibiotic cannot bind any longer
- Bypass or alteration of metabolic pathways in cases where an antibiotic blocks a pathway (e.g., as for sulfonamides)
- Prevention of drug uptake
- Export out of the cell by ABC transporters so that the intracellular concentration of an antibiotic (e.g., tetracycline) are reduced. In Bacteria, this is one of several factors responsible for multidrug resistance (MDR).

ABC TRANSPORTER

Resistance against defense chemicals can be obtained through the expression of ABC transporters that are present in most cells and organisms. They are especially active in epithelia of intestinal, liver, kidney, and endothelia (Twentyman and Bleehen, 1991; Nielsen and Skovsgaard, 1992; Nooter and Stoter, 1996; Steinbach et al., 2002; You and Morris, 2007).

Three types of ABC transporters have been studied in detail:

1. P-glycoprotein (P-gp; molecular weight 170 kD) or MDR1 protein (multiple drug resistance protein) was the first cloned ABC transporter. It is encoded by the *ABCB1* gene. P-gp is composed of two similar moieties and each half contains one transmembrane and one ATP-binding domain. P-gp is an efflux pump directed to the gut lumen. The substrate molecules bind to transmembrane domains and then are exported to extracellular space, driven by the energy of ATP hydrolysis. A wide range of lipophilic chemotherapeutical agents, such as anthracenes, anthracyclines, epipodophyllotoxins, taxanes, and Vinca alkaloids, which can enter tumor cells by free diffusion, are substrates of P-gp and can be extruded by the transporter (Loo and Clarke, 2005).

2. Multiple resistance-associated protein 1 (MRP1; 190 kD) is encoded by the *ABCC1* gene. MRP1 transports drugs conjugated to glutathione (GSH), and also unmodified therapeutics in the presence of GSH (van der Kolk et al., 1999). MRP1 is structurally similar to P-gp, and can expel anthracenedione, anthracycline, epipodophyllotoxin, Vinca alkaloids, etc. (Wijnholds et al., 2000).
3. Breast cancer resistance protein (BCRP; 72 kD) is the product of the *ABCG2* gene. It has one transmembrane domain and one ATP-binding domain and only functions after dimerization. BCRP confers resistance to doxorubicin, camptothecin, and mitoxantrone (Ambudkar et al., 1999; Schinkel and Jonker, 2003; Mao and Unadkat, 2005; Krishnamurthy and Schuetz, 2006).

Breast cancer resistance protein and P-gp are highly expressed at the apical membrane of blood–brain barrier (BBB), placenta, liver, intestine, and other organs (Schinkel and Jonker, 2003). These ATP-driven transporters can pump lipophilic compounds out of the cell, either back to the gut lumen or into the blood system, thus reducing the intracellular concentration of potentially toxic compounds.

ATP-binding cassette transporters are also important at the BBB. The BBB only allows the entry of small lipophilic substances by passive diffusion. However, the uptake of lipophilic compounds in the brain is relatively low due to the high activity of P-gp, MRP, and organic anion transporting polypeptides (OATPs). These transporters catalyze a rapid efflux of lipophilic xenobiotics from the CNS (Elsinga et al., 2004; Mahringer and Fricker, 2010).

Multidrug resistance was discovered during chemotherapy of cancer patients who developed resistance against a cytotoxic drug. It transpired that the tumor cells were able to pump out the lipophilic alkaloids (such as Vinca alkaloids, taxanes, and anthracycline derivatives) at almost the same speed as they were entering the tumor cells. Activated cells became resistant to vincristine but also to several other lipophilic drugs. This means that a cross-resistance or MDR had occurred. As a consequence, a major obstacle to the successful chemotherapy of tumors is MDR. Upon exposure to xenobiotics MDR genes can become upregulated. Overexpressed ABC transporters (P-gp, MRP1, or BCRP) can mediate resistance of tumor cells against a variety of anticancer drugs (Schinkel and Jonker, 2003). This phenomenon is called MDR, which is one of the most important reasons of chemotherapy failure (Gottesman, 2002).

Several of human protozoal parasites (*Plasmodium*, *Leishmania*, *Trypanosoma*) can develop resistance against prophylactic and therapeutic agents, such as quinolines, naphthoquinones, sesquiterpene lactones, and others. The underlying mechanism includes membrane glycoproteins that are orthologous to human P-gp. These ABC transporters can also be induced and activated.

ATP-binding cassette transporters are also present in bacteria and fungi in which they confer resistance to antibiotics and fungicidal compounds (Steffens et al., 1996). A medicinally important issue is the increasing resistance of bacteria toward antibiotics, and ABC transporters can be involved in bacterial MDR (besides other mechanisms discussed above). Apparently, ABC transporters are an old invention of nature, which occur from *E. coli* to *Homo sapiens*.

OVERCOMING RESISTANCE CAUSED BY ABC TRANSPORTERS

Multidrug resistance reversal agents are also called chemosensitizers or modulators. They can inhibit the efflux activity of transporters and other relevant MDR targets (see above); in consequence they can potentiate cytotoxicity, and are therefore important alternatives to overcome MDR (Watanabe et al., 1995; Dantzig et al., 1996; Robert and Jarry, 2003).

Multi-resistant tumor cells frequently express different ABC transporters simultaneously, e.g., P-gp, MRP1, BCRP, and others (Annereau et al., 2004; Gillet et al., 2004). Because the substrate spectra of ABC transporters only partly overlap, co-expression of transporters might produce more diverse resistance profiles than those of any one member alone. Thus broad-spectrum reversal agents are needed and some compounds exhibit this property (Hyafil et al., 1993; Maliepaard et al., 2001; Brooks et al., 2003).

A number of natural or synthetic compounds have been discovered that can inhibit P-gp and re-sensitize resistant tumor cells *in vitro* (Chauffert et al., 1990; Genne et al., 1992; He and Liu, 2002; Wink, 2007). Although these agents work successfully in some patients, most results of clinical trials were disappointing (Solary et al., 2000; Dantzig et al., 2001). Some of these reversal agents did not work *in vivo* or some had too severe side effects. Therefore, new and better reversal agents are still needed.

Most modulators of ABC transporters act by binding to membrane transport proteins (especially P-gp, MRP1, and BCRP) as competitive inhibitors, or by indirect mechanisms related to phosphorylation of the transport proteins, or the expression of the mdr1 and mrp1 genes. Other inhibitors not only act at the level of the transporter gene but influence their expression; for example, the alkaloid piperine lowered the expression levels of *ABCB1*, *ABCC1*, and *ABCG2* genes which encode P-gp, MRP1, and BCRP (Li et al., 2011b).

INHIBITORS OF ABC TRANSPORTERS FROM PLANTS

For this review we carried out a comprehensive literature research. **Table 2** summarizes the search results for SM from plants, which can serve as ABC transporter substrates and might be useful in strategies to reverse drug resistance in cancer cells, fungi, and parasites. Compounds affecting other resistance mechanisms, which are important and which were discussed above, were not considered in this review.

Lipophilic SM, such as monoterpenes, diterpenes, triterpenes (including saponins), steroids (including cardiac glycosides), and tetraterpenes (carotenoids; **Table 2**) function as substrates for P-gp in cancer cells. The ABC transporter from fungi, AtrB (Andrade et al., 2000), or the NorA efflux pump in *Staphylococcus aureus* can also be affected (Smith et al., 2007). Because of their lipophilicity, these terpenoids most likely are substrates for P-gp and other ABC transporter. If administered as a chemosensitizer in combination with a cytotoxic agent they function as inhibitors competing for binding to the active side of the transporters.

Table 2 | Secondary metabolites from plants that can inhibit P-gp, MRP1, BCRP, bacterial, and fungal ABC transporters.

Natural product	Occurrence	Activities	Reference
TERPENOIDS			
Monoterpenes			
Citronellal, citronellol	*Zanthoxylum piperitum* (Rutaceae)	1	Yoshida et al. (2005)
Diterpenes			
Andrographolide	*Andrographis paniculata* (Acanthaceae)	2 (biphasic action)	Najar et al. (2010)
Jatrophane diterpene polyesters	*Euphorbia serrulata*, *E. esula*, *E. salicifolia*, *E. peplus* (Euphorbiaceae)	3 in mouse lymphoma cells	Hohmann et al. (2002)
Latilagascene A, latilagascene B, latilagascene C (lathyrane diterpenes)	*Euphorbia lagascae* (Euphorbiaceae)	4, 5	Duarte et al. (2006)
Totarol	*Podocarpus totara* (Podocarpaceae)	Inhibits *Staphylococcus aureus* NorA efflux pump	Smith et al. (2007)
Triterpenes			
Aegicerin	*Clavija procera* (Theophrastaceae)	Reverses MDR in resistant *Mycobacterium tuberculosis* strains	Rojas et al. (2006)
Betulinic acid, pomolic acid	*Licania tomentosa*, *Chrysobalanus icaco*, (Chrysobalanaceae)	3 in leukemia cells	Fernandes et al. (2003)
Limonin, deacetylnomilin	*Citrus jambhiri*, *Citrus pyriformis*, *Phellodendron amurense* (Rutaceae)	6	Min et al. (2007), El-Readi et al. (2010)
Dyscusin A, cumingianol A–F, cumingianoside R	*Dysoxylum cumingianum* (Meliaceae)	3 in cancer cells; 7	Kurimoto et al. (2011a,b)
Euscaphic acid, tormentic acid, 2 α -acetyl tormentic acid, 3β-acetyl tormentic acid	*Cecropia lyratiloba* (Moraceae)	3 in leukemia cell line	Rocha Gda et al. (2007)
Glycyrrhizin	*Glycyrrhiza glabra* (Fabaceae)	2 (biphasic action)	Najar et al. (2010)
21α-Hydroxytaraxasterol and related triterpenes	*Euphorbia lagascae* (Euphorbiaceae)	6, 7	Duarte et al. (2009)
Obacunone, 12-alpha-hydroxylimonin	*Phellodendron amurense* (Rutaceae)	1 in MDR cancer cells	Min et al. (2007)
Phytolacca saponins N-1–N-5	*Phytolacca americana* (Phytolaccaceae)	3 in 2780 AD cells	Wang et al. (2008)
Sinocalycanchinensin E	*Sinocalycanthus chinensis* (Calycanthaceae)	Enhances colchicine-induced cytotoxicity in MDR KB cells	Kashiwada et al. (2011)
β-Amyrin, uvaol, oleanolic acid	*Carpobrotus edulis* (Aizoaceae)	3 in mouse lymphoma cell line and Gram-positive bacteria	Martins et al. (2010), Ordway et al. (2003)
Steroids			
Cardenolides	*Nerium oleander* (Apocynaceae)	3 ovarian cancer 2780AD cells	Zhao et al. (2007)
Cycloartanes (9,19-cyclopropyl-triterpenes)	*Euphorbia species* (Euphorbiaceae)	8	Madureira et al. (2004)
Digoxin, digitoxin	*Digitalis* spp. (Plantaginaceae)	2	de Lannoy and Silverman (1992), Cavet et al. (1996)
Ginsenoside Rc, ginsenosides Rd, parishin C	*Panax* spp. (Araliaceae)	4 in lymphoma cells	Berek et al. (2001)
Methylprototribestin	*Tribulus terrestris* (Zygophyllaceae)	4 (doxorubicin)	Ivanova et al. (2009)
Protopanaxatriol (ginsenoside)	*Panax ginseng* (Araliaceae)	2, 4 in AML-2/D100 cells	Choi et al. (2003)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Stigmasterol, β-sitosterol-*O*-glucoside	*Citrus jambhiri*, *Citrus pyriformis* (Rutaceae)	1 in Caco2 and leukemia cells	El-Readi et al. (2010)
Withaferin A	*Withania somnifera* (Solanaceae)	4 in K562/Adr cells	Suttana et al. (2010)
Tetraterpenes			
Carotenoids (lycopene, violaxanthin, and related compounds)	*Capsicum annuum* (Solanaceae); *Daucus carota* spp. *sativus* (Apiaceae)	1, 9	Molnar et al. (2004), Kars et al. (2008), Gyemant et al. (2006)
PHENOLICS			
Phenyl propanoids			
Chlorogenic acid	*Coffea arabica* (Rubiaceae) and many plants	1	Najar et al. (2010)
Curcumin, tetrahydrocurcumin	*Curcuma longa* (Zingiberaceae)	1, 5	Zhou et al. (2004), Limtrakul et al. (2007), Hou et al. (2008), Lu et al. (2012)
Flavonoids, catechins, chalcones, xanthones, stilbenes, anthocyanins, and related polyphenols			
Acacetin	Several families	1, 10 in human erythrocytes and breast cancer cells	Wesolowska et al. (2009)
Afrormosin, robinin, amorphigenin	Several Fabaceae	1, 10	Gyemant et al. (2005)
Ampelopsin	*Hovenia dulcis* (Rhamnaceae)	1, 5 in K562/ADR cells	Ye et al. (2009)
Apigenin,	Several plants	1, 4, 9, 10 in MES-SA/DX5 cells; substrate for multidrug transporter in *Plasmodium falciparum*	Zhang et al. (2004), Leslie et al. (2001), Perez-Victoria et al. (1999), Wesolowska et al. (2009), Angelini et al. (2010)
Baicalein	*Scutellaria baicalensis* (Lamiaceae)	Substrate for Yorlp and Pdr5p transporters in yeast *Saccharomyces cerevisiae*	Kolaczkowski et al. (1998)
Biochanin A	Several families	1, 9	Chung et al. (2005), Zhang et al. (2004)
Calodenin B, dihydrocalodenin B, and other dimeric proanthocyanidins	*Ochna macrocalyx* (Ochnaceae)	Inhibit MDR in *Staphylococcus aureus* (RN4220, XU212, and SA-1199-B)	Tang et al. (2003)
Chrysin	Several species	1, 2 (biphasic action), 9	Molnár et al. (2008), Gyemant et al. (2005), Zhou et al. (2004), Zhang et al. (2004), Critchfield et al. (1994), de Wet et al. (2001)
Chrysosplenol-D, chrysoplenetin	*Artemisia annua* L. (Asteraceae)	Synergistic inhibition of MDR in *Staphylococcus aureus*	Stermitz et al. (2002)
Cyanidin, callistephin, pelargonin, ideanin, cyanin, pelargonidin, and related anthocyanidins	*Glycine max* L. Merr. (Fabaceae), *Aronia melanocarpa* L. (Rosaceae)	1	Molnár et al. (2008)
Daidzein	Several species of Fabaceae	1, 9, 10	Chung et al. (2005), Zhang et al. (2004), Cooray et al. (2004)
5,7-Dimethoxyflavone, kaempferide	*Kaempferia parviflora* (Zingiberaceae)	9 (*in vitro* and *in vivo*)	An et al. (2011)
Diosmin	*Citrus* spp. (Rutaceae)	2	Yoo et al. (2007)
Ellagic acid, tannic acid	Several species	Inhibit an efflux pump in *Acinetobacter baumannii* and enhances antibiotic activity	Chusri et al. (2009)
Epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate (EGCG)	*Camellia sinensis* (Theaceae); *Carpobrotus edulis* (Aizoaceae)	1 in MCF-7/Adr and mouse lymphoma cell line; 9, 10; 3 in Gram-positive bacteria	Martins et al. (2010), Zhang et al. (2004), Zhu et al. (2001), Gyemant et al. (2005), Mei et al. (2004), Wei et al. (2003)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Fisetin	Several species	2, 9 in breast cancer cells; 4 in MES-SA/DX5 cells; substrate for Yorlp transporters in yeast *Saccharomyces cerevisiae*	Chung et al. (2005), Kolaczkowski et al. (1998), Angelini et al. (2010)
Formononetin and other isoflavones	Several species of Fabaceae	1, 2, 10	Molnár et al. (2008), Gyemant et al. (2005)
Galangin	Several plant families	2 (biphasic action); 10	Zhou et al. (2004), Critchfield et al. (1994), de Wet et al. (2001)
Genistein and derivatives	Several species of Fabaceae	1, 2, 9, 10	Zhang et al. (2004), Taur and Rodriguez-Proteau (2008), Leslie et al. (2001), Versantvoort et al. (1994, 1996)
Hesperidin, neohesperidin, nobiletin, Tangeretin	*Citrus jambhiri*, *Citrus pyriformis* (Rutaceae)	1, 9	El-Readi et al. (2010), Zhang et al. (2004), Ofer et al. (2005)
Icariin	*Epimedium grandiflorum* (Berberidaceae)	1, 5	Liu et al. (2009)
Isobavachalcone	*Dorstenia barteri* (Moraceae)	Inhibits efflux pump in Gram-negative bacteria	Kuete et al. (2010)
Kaempferol, morin, taxifolin, spiraeoside, and related flavonoids	Several plants	2 (biphasic action); 1 and OCT, 9, 10	Zhou et al. (2004), Zhang et al. (2004), de Wet et al. (2001), Gyemant et al. (2005)
Luteolin and its glycosides	Several plants	1, 9, 10	Zhang et al. (2004), Nissler et al. (2004)
Mangiferin, norathyriol, and other xanthones	*Mangifera indica* (Anacardiaceae)	Modulate the function of MDR1/P-glycoprotein (P-gp ABCB1) multidrug transporter. (biphasic action)	[8, 34, 35] Najar et al. (2010), Chieli et al. (2010)
Naringin, naringenin, and derivatives	*Euphorbia lagascae*, *Euphorbia tuckeyana* (Euphorbiaceae); *Citrus* hybrids (Rutaceae)	1, 9, 10; substrate for MDR1 in *Plasmodium falciparum*	Chung et al. (2005), Zhang et al. (2004), Ofer et al. (2006), Leslie et al. (2001), Perez-Victoria et al. (1999), de Castro et al. (2007, 2008), Wesolowska et al. (2007), Duarte et al. (2010)
Pentagalloylglucose (gallotannin)	Several species	1 in MDR KB-C2 cells	Kitagawa et al. (2007)
Phloretin, phloridzin	Several species	1, 9	Molnár et al. (2008), Zhang and Morris (2003), Zhang et al. (2004), Gyemant et al. (2005)
Plagiochin E	*Marchantia polymorpha* (Marchantiaceae)	Reverses the efflux pump in *Candida albicans*	Guo et al. (2008)
Quercetin, 3′,4′,7-trimethoxyquercetin, quercetagetin, hesperetin, isoquercitrin, myricetin, and derivatives	Several species	1 and OCT in MDR cancer cells; 9, 10; substrate for Yorlp in yeast *Saccharomyces cerevisiae* substrate for MDR1 in *Plasmodium falciparum*.	Scambia et al. (1994), Kolaczkowski et al. (1998), Shapiro and Ling (1997), Conseil et al. (1998), Cooray et al. (2004), Ofer et al. (2005), Ohtani et al. (2007), Leslie et al. (2001), Zhang et al. (2004)
Resveratrol	Several plants	7, 9	Cooray et al. (2004)
Rotenone	*Derris* spp., *Tephrosia* spp., *Lonchocarpus* spp. (Fabaceae)	1	Molnár et al. (2008), Gyemant et al. (2005)
Rutin	Several species	1 and OCT; substrate of MDR in *Plasmodium falciparum*	Ofer et al. (2005, 2006), Foster et al. (2001), Perez-Victoria et al. (1999)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Silymarin (isosilybin, silychristin, silydianin, silybin)	*Silybum marianum* (Asteraceae)	1, 4, 5, 9 in cancer cells	Zhou et al. (2004), Agarwal et al. (2006), Zhang and Morris (2003), Zhang et al. (2004), Trompier et al. (2003)
Tiliroside	*Platanus orientalis* (Platanaceae), *Herissantia tiubae* (Malvaceae)	5; inhibits (NorA) efflux protein in *Staphylococcus aureus*	Falcao-Silva et al. (2009)
Tricin	*Sasa borealis* (Gramineae)	3 in adriamycin-resistant MCF-7/ADR cells	Jeong et al. (2007)
3′,4′,6-Trihydroxy-2,4-dimethoxy-3-(3″,4″-dihydroxybenzyl) chalcone, and derivatives	*Onychium japonicum* (Sinopteridaceae)	3 in MCF-7/ADR and Bel-7402/5-Fu cells	Li et al. (2011a)
3,5,4′-Trimethoxy-trans-stilbene	*Dalea versicolor* (Fabaceae)	Enhances the antimicrobial effect of berberine against NorA *S. aureus* mutant strain	Belofsky et al. (2004)
Quinones, anthraquinones, naphthoquinones			
Aloe-emodin	*Rheum palmatum* (Polygonaceae); *Aloe* spp. (Asphodelaceae)	2	Cui et al. (2008)
Diospyrone (a naphthoquinone)	*Diospyros canaliculata* (Ebenaceae)	Inhibits efflux pump in Gram-negative bacteria	Kuete et al. (2010)
Emodin	*Rheum palmatum* (Polygonaceae)	2; synergistic antimicrobial effect with ampicillin or oxacillin in MRSA	Lee et al. (2010), Cui et al. (2008)
Rhein	*Rheum palmatum* (Polygonaceae)	2, 4	Cui et al. (2008), van Gorkom et al. (2002)
Lignans			
Syringaresinol	*Sasa borealis* (Gramineae)	1 in adriamycin-resistant MCF-7/ADR cells	Jeong et al. (2007)
Coumarins and furanocoumarins			
Bergamottin, 6′,7′-dihydroxybergamottin, 6′,7′-epoxybergamottin	*Citrus* hybrids (Rutaceae)	1	de Castro et al. (2007, 2008)
Alkaloids			
Acronycine	*Bauerella australiana*	2	Dorr et al. (1989)
Arborinine, evoxanthine	*Ruta graveolens* (Rutaceae)	1, 5 in cancer cells	Rethy et al. (2008)
Berbamine	*Berberis* sp. (Berberidaceae)	2 in BBB and in Caco2 cells	He and Liu (2002)
Berberine	*Hydrastis canadensis* (Ranunculaceae)	1, 2, 2 in BBB; 8 (bacteria) 2 in vascular smooth muscle cells (VSMCs)	Severina et al. (2001), He and Liu (2002), Efferth et al. (2005), Suzuki et al. (2010)
Camptothecin	*Camptotheca acuminata* (Nyssaceae)	Substrate for ABC2 transporter in *Botrytis cinerea*; for PMR5 in *Penicillium digitatum*, AtrBp in *Aspergillus nidulans*; 11	Mattern et al. (1993), Lee et al. (2005), Nakaune et al. (2002), Andrade et al. (2000)
Canthin-6-one, 8-hydroxy-canthin-6-one, 5(zeta)-hydroxy-octadeca-6(E)-8(Z)-dienoic acid	*Allium neapolitanum* (Amaryllidaceae), (Simaroubaceae), (Rutaceae)	Inhibits *Mycobacterium*, methicillin-resistant *Staphylococcus aureus* (MRSA); and a MDR strain of *S. aureus*	O'Donnell and Gibbons (2007)
Capsaicin	*Capsicum frutescens* (Solanaceae)	2, 4	Okura et al. (2010)
Catharanthine		2, 4 (vinblastine) in CEM/VLB1K cells	Beck et al. (1988), Zamora et al. (1988)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Cepharanthine	*Stephania cepharantha* (Menispermaceae)	4 (doxorubicin and vincristine)	Ikeda et al. (2005), Katsui et al. (2004), Nakajima et al. (2004)
Chelerythrine	*Zanthoxylum clava-herculis* (Rutaceae)	Reversal of drug resistance in methicillin-resistant *Staphylococcus aureus* (MRSA)	Gibbons et al. (2003)
Cinchonine, hydrocinchonine, quinidine	*Cinchona pubescens* (Rubiaceae)	4	Solary et al. (2000), Genne et al. (1994), Lee et al. (2011)
Colcemid, colchicine	*Colchicum autumnale* (Colchicaceae)	2	Elsinga et al. (2004)
Conoduramine	*Peschiera laeta* (Apocynaceae)	2, 4 in KB cells	You et al. (1994)
Coptisine	Several species of Ranunculaceae; Berberidaceae	2 in vascular smooth muscle cells (VSMCs)	Suzuki et al. (2010)
8-Oxocoptisine	*Coptis japonica* (Ranunculaceae)	1 in MES-SA/DX5 and HCT15 cells	Min et al. (2006b)
Coronaridine, heyneanine dippinine B and C	*Tabernanthe iboga* (Apocynaceae)	4 in vincristine-resistant KB cells	Kam et al. (2004)
Cycleanine	*Synclisia scabrida* (Menispermaceae)	6 in MCF-7/Adr and KBv200 cells	Tian and Pan (1997)
Cyclopamine	*Veratrum* spp. (Melanthiaceae)	1, 3	Lavie et al. (2001)
Dauriporphine	*Sinomenium acutum* (Menispermaceae)	1 in MES-SA/DX5 and HCT15 cells	Min et al. (2006a)
Emetine	*Psychotria ipecacuanha* (Rubiaceae)	2, 11	Möller et al. (2006)
Ergotamine	*Claviceps purpurea* (Clavicipitaceae)	1 in MDR cells	Yasuda et al. (2002)
Fangchinoline	*Stephania tetrandra* (Menispermaceae)	Reduces resistance to paclitaxel and actinomycin D in HCT15 cells	Choi et al. (1998), Wang et al. (2005)
Galanthamine	*Galanthus nivalis* (Amaryllidaceae)	1 at the BBB	Namanja et al. (2009)
Gamma-fagarine	*Phellodendron amurense* (Rutaceae)	1 MDR cancer cells	Min et al. (2007)
Glaucine	*Glaucium flavum* (Papaveraceae)	1, 2	Ma and Wink (2009)
Harmine	*Peganum harmala* (Zygophyllaceae)	9	Ma and Wink (2010)
Homoharringtonine, cephalotaxine	*Cephalotaxus harringtonia* (Cephalotaxaceae)	2, 11	Zhou et al. (1995), Efferth et al. (2003)
Hydrastine	*Hydrastis canadensis* (Ranunculaceae)	2	Etheridge et al. (2007)
Ibogaine	*Tabernanthe iboga* (Apocynaceae)	5, 9	Tournier et al. (2010)
Indole-3-carbinol	Many species of Brassicaceae	Downregulation of upregulated P-gp; dietary adjuvant in MDR cancer treatment	Arora and Shukla (2003)
Insularine, insulanoline	*Antizoma miersiana* (Menispermaceae)	9 in MCF-7/Adr and KBv200 cells	Tian and Pan (1997)
Kopsamine, pleiocarpine, lahadinine A, kopsiflorine	*Kopsia dasyrachis* (Apocynaceae)	4	Kam et al. (1998)
Lobeline	*Lobelia inflata* (Campanulaceae)	4 in tumor cells	Ma and Wink (2008)
5-Methoxyhydnocarpine, pheophorbide A	*Hydnocarpus kurzii* (Flacourtiaceae), *Berberis* spp. (Berberidaceae)	Inhibitor of NorA MDR pump in *Staphylococcus aureus*	Stermitz et al. (2000a,b, 2001), Guz et al. (2001)
N-trans-feruloyl 4′-*O*-methyldopamine	*Mirabilis jalapa* (Nyctaginaceae)	Inhibits growth of *Staphylococcus aureus* overexpressing the multidrug efflux transporter NorA	Michalet et al. (2007)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Oxyberberine, canthin-6-one, 4-methoxy-*N*-methyl-2-quinolone, oxypalmatine	*Phellodendron amurense* (Rutaceae)	1 in MDR cancer cells	Min et al. (2007)
Paclitaxel	*Taxus* spp. (Taxaceae)	2	Distefano et al. (1997)
Palmatine	Several species of Ranunculaceae; Berberidaceae	2 in vascular smooth muscle cells (VSMCs); 8 (bacteria)	Severina et al. (2001), Suzuki et al. (2010)
Piperine	*Piper nigrum* (Piperaceae)	1, 2, 3, 9 in cancer cells; inhibition of overexpressed mycobacterial putative efflux protein (Rv1258c)	Han et al. (2008), Bhardwaj et al. (2002), Li et al. (2011b), Sharma et al. (2010)
Quinine	*Cinchona pubescens* (Rubiaceae)	2; 4	Genne et al. (1994), Zamora et al. (1988)
Rescinnamine	*Rauvolfia serpentina* (Apocynaceae)	3 of vinblastine; induces MDR1 and p-gp expression	Bhat et al. (1995)
Reserpine	*Rauvolfia serpentina* (Apocynaceae)	8 in bacteria; 3 in methicillin-resistant *Staphylococcus aureus* (MRSA) strains (NorA MDR pump); 2; 3 of vinblastine in CEM/VLB1K cells	Beck et al. (1988), Gibbons and Udo (2000), Markham et al. (1999)
Roemerine	*Annona senegalensis* (Annonaceae)	2; 4	You et al. (1995)
Rutaecarpine	*Evodia rutaecarpa* (Rutaceae)	6 in p-gp overexpressing CEM/ADR5000 cells	Lee et al. (1995), Adams et al. (2007)
Sanguinarine	*Sanguinaria canadensis* (Papaveraceae)	4	Ding et al. (2002), Weerasinghe et al. (2006)
Stemocurtisine, oxystemokerrine	*Stemona aphylla* and *S. burkillii* (Stemonaceae)	P-gp modulator, enhance the cytotoxicity of vinblastine, paclitaxel, and doxorubicin in KB-V1 cells	Chanmahasathien et al. (2011)
Tetrandrine	*Stephania tetrandra* (Menispermaceae)	1; reduces resistance to paclitaxel and actinomycin D in HCT15 cells; 4 in MDR mice; 6 (*in vitro* and *in vivo*); 4in cancer patients treated with doxorubicin, etoposide, and cytarabine	Choi et al. (1998), Xu et al. (2006), Zhu et al. (2005), Fu et al. (2002, 2004)
Thaliblastine	*Thalictrum* spp. (Ranunculaceae)	Reverses MDR by decreasing the overexpression of P-gp in MCF-7/Adr cells	Chen and Waxman (1995), Chen et al. (1993, 1996)
Tomatidine	*Solanum lycopersicum* (Solanaceae)	1,2	Lavie et al. (2001)
Trisphaeridine, pretazettine, 2-*O*-acetyllycorine, risperidone	Several species of Amaryllidaceae	1 and 3 in L5178 MDR mouse lymphoma cells	Zupko et al. (2009)
Vasicine acetate, 2-acetyl benzylamine	*Adhatoda vasica*. (Acanthaceae)	Inhibit *Mycobacterium tuberculosis* and a MDR strain	Ignacimuthu and Shanmugam (2010)
Veralosinine, veranigrine	*Veratrum lobelianum*, *Veratrum nigrum* (Melanthiaceae)	1 and 3 against doxorubicin	Ivanova et al. (2011)
Vincristine, Vinblastine	*Catharanthus roseus* (Apocynaceae)	2; 2 in BBB; 11	He and Liu (2002), Hu et al. (1995)
Vindoline		2; reversal of vinblastine resistance in a MDR human leukemic cell line and CEM/VLB1K cells	Beck et al. (1988)

(Continued)

Table 2 | Continued

Natural product	Occurrence	Activities	Reference
Voacamine	*Peschiera laeta*, *Peschiera fuchsiaefolia* (Apocynaceae)	1, 2; 2 in BBB; reversal of vinblastine; and doxorubicin resistance in MDR cancer cells by binding to P-glycoprotein	You et al. (1994), Meschini et al. (2003, 2005)
Yohimbine	*Rauwolfia serpentina* (Apocynaceae)	Reversal of vinblastine resistance in a MDR human leukemic cell line and CEM/VLB 100 cells	Zamora et al. (1988), Bhat et al. (1995)

Activities: 1: inhibits p-gp; 2: p-gp substrate; 3: reversal of MDR; 4: reversal of p-gp mediated MDR; 5: inhibition of MDR1 gene. 6: p-gp modulation in cancer cells; 7: induction of apoptosis; 8: substrate for ABC transporter; 9: blocks BCRP and increases in mitoxantrone accumulation; 10: MRP1 inhibitor; 11: induction of MDR overexpression.

Among the structurally heterogenous group of alkaloids, a large number of the more lipophilic substances from the classes of isoquinoline, protoberberine, quinoline, indole, monoterpene indole, and steroidal alkaloids (**Table 2**) can serve as substrates whereas the more polar alkaloids with a tropane, quinolizidine, piperidine, and pyrrolizidine skeleton do not bind to ABC transporters (Wink, 2007). Similar to the situation of terpenoids, the active alkaloids probably function as competitive inhibitors of P-gp and BCRP in cancer cells, and NorA in bacteria and fungi (**Table 2**).

It is remarkable on the first sight that also quite a large number of more polar phenolic SM (phenolic acids, flavonoids, catechins, chalcones, xanthones, stilbenes, anthocyanins, tannins, anthraquinones, and naphthoquinones) inhibit P-gp, MRP1, BCRP, and OATP in cancer cells with MDR. Some of them can reverse MDR when given in combination with cytotoxic agents (**Table 2**). Bacteria and fungi appear to be sensitive as well (Guz et al., 2001; Falcao-Silva et al., 2009). Some of these phenolics are lipophilic enough to be competitive inhibitors of ABC transporters.

Polyphenols are exciting tethering compounds of proteins. They can effectively interact directly with proteins by forming hydrogen and ionic bonds with amino acid side chains. They can thus interfere with the 3D structure of proteins (conformation) and inhibit their activities (details in Wink, 2008b; Wink and Schimmer, 2010). We speculate therefore, that the inhibition seen in polyphenols is caused by a direct binding and complex formation (not necessarily the active side) of ABC transporters. Since many polyphenols have no or very low toxicity (e.g., many of them are ingredients of our food, such as flavonoids or tannins), they might be excellent candidates as reversal agents, both in chemotherapy and in agriculture.

We have focused on ABC transporters in this review. But as mentioned above, resistance can be due to other mechanisms as well and is often multifactorial. Faria et al. (2011) and Kim et al. (2007, 2010) have successfully employed thymol (a phenolic monoterpene), salicyl aldehyde, and the alkaloid berberine to enhance the activity of fungicides in *Candida*, *Aspergillus*, *Penicillium*, and *Cryptococcus*. These experimental data can be regarded as a proof of concept that plant secondary products can be interesting candidates for chemosensitization (even if they not interfere with ABC transporters) of pathogenic fungi in agriculture and food technology to improve the fungicidal activity of certain fungicides.

CONCLUSION

This review summarizes the evidence that selected SM of plants can be interesting candidates to inhibit ABC transporters in MDR cancer cells or to chemosensitize pathogenic fungi and other microbes for treatment with antimicrobial agents. Whereas lipophilic terpenoids and alkaloids appear to be substrates of P-gp, MRP1, or BCRP and thus competitive inhibitors, the more polar phenolic compounds (flavonoids, tannins, quinones) can bind to the transporter proteins and inhibit their activity by disturbing protein conformation. A combination of a cytotoxic agent, antibiotic, or fungicide with a natural chemosensitizer (not necessarily an inhibitor of ABC transporters) might provide an interesting strategy to overcome MDR in cancer patients and to improve antibiotic or antifungal efficacy in medicine, agriculture, or food industry.

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