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Review article

Natural products as multidrug resistance modulators in cancer

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ABSTRACT

Cancer is a prominent cause of death globally. Currently, many drugs that are in clinical practice are having a high prevalence of side effect and multidrug resistance. Risk of tumors acquiring resistance to chemotherapy (multidrug resistance) remains a significant hurdle to the successful treatment of various types of cancer. Membrane-embedded drug transporters, generally overexpressed in cancer, are the leading cause among multiple mechanisms of multidrug resistance (MDR). P-glycoprotein (P-gp) also MDR1/ABCB1, multidrug resistance associated protein 1 (MRP1/ABCC1), MRP2 and breast cancer resistance protein (BCRP/ABCG2) are considered to be a prime factor for induction of MDR. To date, several chemical substances have been tested in a number of clinical trials for their MDR modulatory activity which are not having devoid of any side effects that necessitates to find newer and safer way to tackle the current problem of multidrug resistance in cancer. The present study systematically discusses the various classes of natural products i.e flavonoids, alkaloids, terpenoids, coumarins (from plants, marine, and microorganisms) as potential MDR modulators and/or as a source of promising lead compounds. Recently a bisbenzyl isoquinoline alkaloid namely tetrandrine, isolated from Chinese herb *Stephania tetrandra* (Han-Fang-Chi) is in clinical trials for its MDR reversal activity.

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1. Introduction

Cancer is one of the most devastating and haunting diseases, affecting the lives of millions around the globe [1]. According to World Health Organization (WHO) and International Agency for Cancer Research, there were 18.1 million new cancer cases, 9.6 million cancer deaths, and 43.8 million people living with cancer within five years of diagnosis. The rate of incidence and mortality was higher in men than women, and the overall incidence of lung cancer was marginally higher as compared to breast cancer, also lung cancer was the foremost cause of mortality (or deaths) followed by, colorectal, stomach cancer, liver cancer and breast cancer for both the sexes [2]. In WHO report, by 2050, there will 27 million new cancer cases and 17.1 million deaths per year [3].

Despite the immense research in prevention, detection, and treatment of cancer, these cancer stats are reasonably intimidating. The risk of tumors acquiring resistance to chemotherapy (multidrug resistance) remains a major hurdle to the successful treatment of various types of cancer. Multidrug resistance (MDR) is a phenomenon in which cancer cells that are originally sensitive to a single anti-cancer drug later become resistant to multiple unrelated drugs that are structurally and/or functionally different and may also have different molecular targets [4]. In cancer cells this may be due to explicit nature or various genetic characteristics of cells, also called intrinsic MDR, or may be due to genetic alterations that follow chemotherapy, i.e. acquired MDR which is a more problematic form of MDR as it leads to chemotherapy failure even after the dose escalation up to toxic levels. For intrinsic MDR, cancer cells exhibit resistance to chemotherapy at their initial exposure to the anticancer [3,5]. In this review, we have mainly emphasized the latest insights in the field of multidrug resistance with the main focus being the natural products as multidrug resistance modulators.

2. Multidrug resistance

Multidrug resistance can be due to a number of reasons which may include irregular absorption, metabolism, and distribution to target cells which may differ in the different type of cancer. At times, parts of the body are inaccessible to drugs that can be due to multiple reasons, which includes increased tissue hydrostatic pressure or change in tissue vasculature such that there is no blood flow, and it turns the anticancer drugs, to cancer cells [6–8]. Also, it has been studied that cancer becomes more heterogeneous with its progression (clonal expansion) that further leads to the formation of a group of cancer cells with diverse molecular signatures and distinct levels of sensitivity towards its treatment. This heterogeneity can direct inhomogeneous distribution of genetically different tumor cell subpopulation within the same site or across different disease sites (spatial heterogeneity) or can lead to temporary changes in the molecular makeup of cancer cells (temporal heterogeneity). In terms, it can be said that heterogeneity in tumor cells provides the fuel for resistance [9,10]. Beside these factors, studies have suggested that there are a number of other mechanisms of multidrug resistance in cancer cells, such as reduced uptake of drugs, altered cell cycle checkpoint and cell cycle arrest, altered drug target, increased efflux of drugs by drug transporters, and sequestration of anticancer drugs in lysosomes as well as in intracellular organelles and intercellular vesicles [11–13]. Minko et al. in their review have categorized different mechanisms of MDR into two broader terms, i.e. pump resistance and non-pump resistance. Drug degradation due to lysozymes, drug inactivation metabolism by phase I and phase II enzymes, antiapoptotic and antioxidant defenses, are some of the non-pump resistance mechanisms, among these mechanisms antiapoptotic defense is a major mechanism which prevents transformation of damage caused by anticancer drugs into apoptotic cell death. This system of non-pump drug resistance utilizes the BCL2 protein which is responsible for the release of cytochrome *c* from mitochondria and therefore by breaking the apoptotic signal prevents the caspases activation and apoptosis. The BCL2 protein can be explored for the suppression of non-pump resistance. Beside antiapoptotic defense one more system that can hamper the activity of anticancer drugs is the antioxidant defense system, as most of these drugs induce free radical generation and this oxidative stress results in damage on the level of proteins, nucleic acids, and cell membranes, but some pre-existing systems in the body which normally protects the cells against these free radicals also protects the cancerous cells from the damage by these radicals. These systems include the cytochromes, superoxide dismutase, catalase, glutathione peroxidase, and antioxidants [4,14–18]. As evident from the name the pump resistance is the one which depends on membrane-bound active efflux pumps. The leading cause among various mechanisms of MDR is increased efflux of anti-cancer drugs by membrane embedded drug transporters, which are generally overexpressed in cancer cells and also recently studied that they can be modulated through endogenous cytokines [19]. Most of these transporters belong to ATP-Binding Cassette (ABC) superfamily the largest transmembrane protein family and found in all living beings. Transporters of this family exploit the energy of ATP to actively pump drugs out of cancer cells before they can attain their effective cell concentration and because of their ubiquitous distribution in major organs involved in absorption, distribution, metabolism, excretion, and toxicity (ADMET) of drug they play an important role in drug pharmacokinetics. Till date more than 49 MDR genes from ABC family have been identified and divided into seven subfamilies i.e. A-G, among which P-glycoprotein (P-gp) also MDR1/ABCB1, multidrug resistance associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2) are the most extensively studied and considered as prime factor for induction of MDR (Table 1) (Fig. 1) [5,6,20,21]. There are some other members of ABC transporter family that have been associated with drug resistance, but they also play a highly specialized role in normal physiology, e.g. MRP2 (ABCC2) have an important role in the export of organic acids, unconjugated bile acids, and xenobiotic into bile. Their importance in normal physiology can be assessed from the fact that 33% of human deficient in ABC gene are presented with some disease [22–24]. Typically ABC transporters consist of two transmembrane domains (TMDs) with each domain comprises six alpha helices (also transmembrane helices or TMH) and two

Table 1
Distribution, substrate profile, and inhibitors of selective ABC transporters.

S. No.	Protein	Gene encoding	Tissue distribution	Substrates	Inhibitors	References
1	P-gp	ABCB1	Found apically distributed in the blood-brain barrier, brain parenchyma both astrocytes and microglia, placenta, liver, kidney, small intestine, blood-testis barrier, colon, and pancreas.	**Anticancer drugs**: 5-fluorouracil, actinomycin D, bisantrene, chlorambucil, colchicine, cisplatin, cytarabine, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, gefitinib, hydroxyurea, irinotecan (CPT-11), methotrexate, mitomycin C, mitoxantrone, paclitaxel, tamoxifen, teniposide, topotecan, vinblastine, and vincristine **Antilipidemic:** lovastatin and simvastatin **Calcium channel blockers:** azidopine, bepridil, diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, tiapamil, and verapamil **Immunosuppressive agents**: cyclosporine A, cyclosporine H, sirolimus, tacrolimus, and valspodar (PSC-833) **Natural products**: curcuminoids and flavonoids	Verapamil (**1**), cyclosporine A (**2**), elacridar (**11**) (GF120918), Valspodar (**9**) (PSC-833), zosuquidar (**13**) (LY335979), tariquidar (**17**) (XR9576), and OC144-093.	[21,23,77–80]
2.	MRP1	ABCC1	Found basolaterally in the blood-brain barrier, brain, breasts, colon, heart, kidney, lung, ovary, pancreas, placenta, prostate, skeletal muscle, skin, small intestine, spleen, and testis	Daunorubicin, doxorubicin, imatinib, etoposide, teniposide, camptothecins, vinblastine, vincristine, and methotrexate. Other than drugs it also transports endogenous metabolites, organic anions and conjugated metabolites of drugs	Ibrutinib (**19**), 3-beta-acetyl tormentic acid (**20**) (3ATA), leukotriene C4 (**21**) (LTC4), MK571, S-decyglutathione (**22**), sulfinpyrazone (**23**), Benzbromarone (**24**), and probenecid (**25**)	
3.	MRP2	ABCC2	Found apically in the blood-brain barrier, breasts kidney, liver, lung, pancreas, placenta, and small intestine.	Cisplatin, doxorubicin, epirubicin, etoposide, irinotecan, mitoxantrone, methotrexate, SN-38, vinblastine, vincristine, and oxaliplatin.	Glutathione-conjugated catechol metabolite, LTC4 (**21**), fluorescein (**26**), methotrexate (**27**), cyclosporine A (**2**), benzbromarone (**24**), sulfinpyrazone (**23**), Probenecid (**25**), PSC-833, PAK-104P, thioridazine (**28**), MK571, curcumin (**29**, and myricetin (**30**).	
4.	BCRP	ABCG2	Distributed apically in placenta, blood–brain barrier, seminal vesicle, liver, kidney, small intestine, and blood-testis barrier	**Anticancer drugs:** daunorubicin, doxorubicin, epirubicin, etoposide, irinotecan, mitoxantrone, methotrexate, SN-38, topotecan, and bisantrene **Antivirals:** delavirdine, lopinavir, lamivudine, nelfinavir, and zidovudine	GF120918, fumitremorgin C (**31**) (FTC), Ko143, and tyrosine kinase inhibitors, Gefitinib (**32**),	[73,81]

nucleotide (ATP) binding domains (NBD) on the cytoplasmic side of the membrane. NBDs are highly conserved throughout the family while TMDs are having variable structure and sequences, which in terms describes their specificity towards various substrates which binds to the internal cavity formed by the alpha helices of the TMDs (Fig. 1). The process of drug efflux starts with binding of the substrate to the high-affinity binding site in the inward open cavity formed by TMDs followed by ATP binding and dimerization of NBDs respectively. It is the binding of the ATP which induces conformational changes (outward open) in TMDs which in turns leads to substrate efflux followed by ATP-hydrolysis, NBDs dimer dissolution return of TMDs to its original inward open conformation (Fig. 2). Distribution of ABC transporters at the apical or basolateral membranes of various organs involved in drug absorption and secretion such as liver, blood-brain barrier, kidney, placenta, and intestine suggests their physiological role as protector of these organs from various xenobiotic or toxicants. The physiological role of ABC transporters has been diagrammatically explained by Szackes et al., 2006 [6,21,25–30].

3. Structural characteristics of P-gp, MDR1, MRP2, and BCRP in MDR

3.1. P-glycoprotein (P-gp/ABCB1)

P-gp, also known as MDR1, is a prominent member of ABCB (encoded by ABCB1 gene) subfamilys and can be said as the first ABC transporter which was identified by Dano in 1973, working with multidrug resistant Ehrlich ascites tumor cells. He observed reduced drug permeation which further known to be due to surface glycoprotein, termed P-glycoprotein (P stands for permeation) [31]. It is 170 kDa and 1280 amino acid long plasma membrane protein composed of two homologous TMDs (each contains six transmembrane helices) and two homologous NBDs connected through alpha helix linker (TMD1-NBD1-TMD2-NBD2) (Fig. 3). The linker plays an important role in the function of the protein as suggested by a study in which linker region was deleted, though the protein was expressed but not functional. Structural representation of ATP bound human P-gp recently crystallized by Kim and Chen in 2018 is given in Fig. 3 [32]. NBDs are highly conserved and encompass motifs such as Walkar A (P-loop), Walkar B, ABC signature (C-loop), a glutamine loop (Q-loop), and a switch motif. Together these motifs form a pocket for the binding of ATP (one with each NBD) and its hydrolysis [25,33]. Three isoforms of P-gp have been identified as P-gp I, II, and III, out of them only I and III have been characterized in normal human tissue. P-gp can interact with structurally diverse chemical compounds that can be as tiny as 330 Da–4000 Da owing to its flexible drug binding pocket. This property can confer strongest resistance to a widest variety of chemotherapeutic agents irrespective to their mode of action. The list of chemotherapeutic agents which can act as a substrate for P-gp includes all the major classes of drugs that may be used in chemotherapy such as anthracyclines (e.g. doxorubicin (DOX), daunorubicin), podophyllotoxins (e.g. etoposide, teniposide),

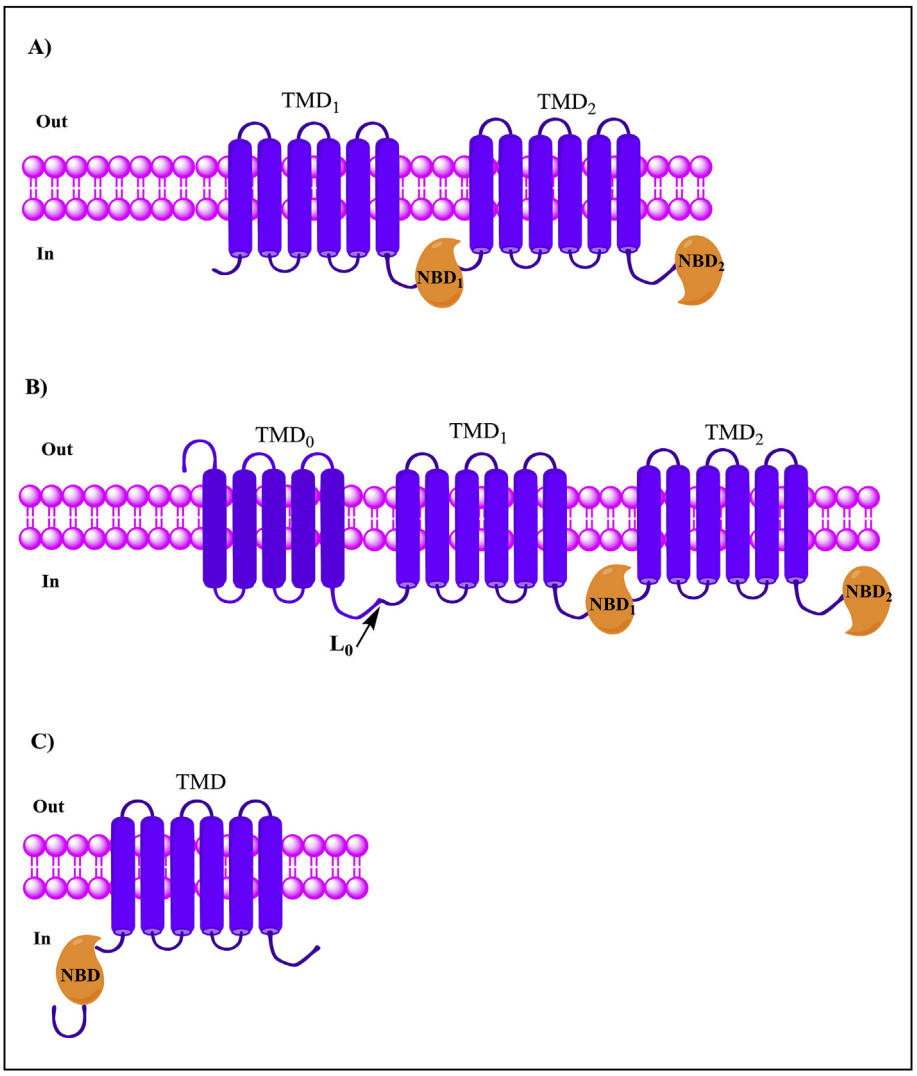

Fig. 1. General topology of **A)** human P-glycoprotein (P-gp), a full transporter belonging to ABCB gene subfamily with two TMDs, consisting of six transmembrane alpha helices each and two NBD, **B)** Multidrug Resistant Protein (MRP1), a full transporter belonging to ABCC subfamily and consisting of three TMD, two six transmembrane helices and one with five helices and two NBDs **C)** Breast Cancer Resistance Protein (BCRP), a half transporters with one TMD comprising six transmembrane helices and one NBD.
TMD = Transmembrane Domain, NBD= Nucleotide Binding Domain

camptothecin (e.g. irinotecan), Actinomycin D, mitomycin C, puromycin, triamterene, chlorambucil, tamoxifen, cisplatin, cytarabine, mitoxantrone etc. [3,6,25,34]. Such diverse substrate variety along with its distinct expression in a range of epithelial cells like kidney, liver, small intestine, pancreas, uterus, placenta brain, and testis render this protein as one of the prime target for developing its modulators for overcoming MDR in cancer.

3.2. Multidrug resistance associated protein 1 (MRP1/ABCC1)

The second most effective transporter, whose range of substrate is as diverse as that of P-gp, is MRP1. Belonging to ABCC (encoded by ABCC1 gene) subfamily this protein was first identified in 1992 by Cole et al. from drug resistant human small-cell lung cancer cell line (H69). Cells of this cell line were showing resistance to doxorubicin without increase expression of P-gp [6,35]. Despite many similarities in their biochemical and pharmacological properties P-gp and MRP1 have only 23% similarity in their sequence. This protein is 190 kDa and 1580 amino acids long with slight modification in structure, i.e. having an additional TMD (TMD_0) containing five extra transmembrane helices connected by a cytoplasmic linker (L_0) and has only one functional site for ATP hydrolysis (Fig. 4). According to some studies, TMD_0 deletion does not make cell functionally incompetent to transport and binding of substrates, while removal of L_0 peptide results in abnormal transport [36]. Chemical nature of their substrates also differs as P-gp transports mostly hydrophobic chemicals while substrates of MRP1 are structurally more diverse and typically amphipathic organic acids (most of them are Phase II metabolic products of the drugs) with large hydrophobic groups. Unlike P-gp, MRP1 also exports endobiotics such as pro-inflammatory molecules (e.g., leukotrienes C_4), hormones (e.g., estrogens and prostaglandins), and antioxidants (e.g., oxidized and reduced glutathione). It has been studied that MRP1 play a role in acute myeloblastic and lymphoblastic leukemia, non small cell lung cancer, neuroblastoma, prostate cancer, breast cancer [33,36–39].

3.3. Multidrug resistance associated protein 2 (MRP2/ABCC2)

MRP2 is also known as hepatocellular canalicular multiple

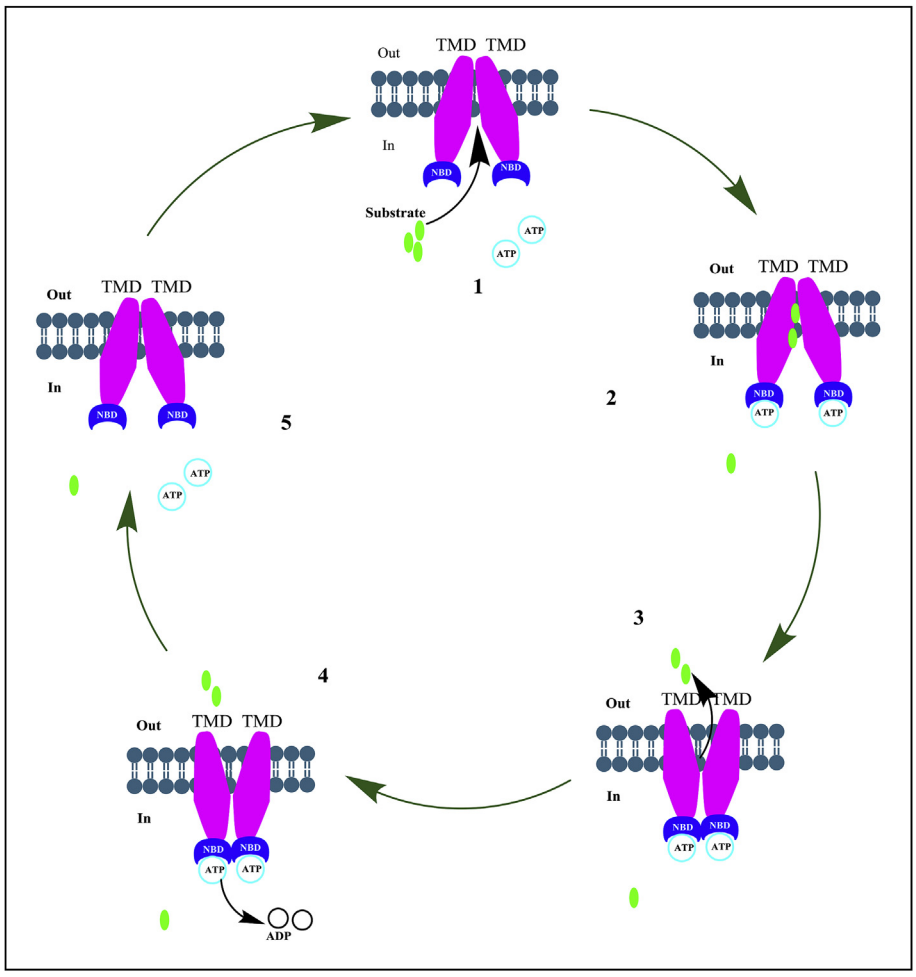

Fig. 2. Working of ATP switch model of ABC transporters. 1) ABC transporter inward open position at rest. 2) Substrate binding to TMDs followed by ATP binding to NBDs. 3) ATP binding causing conformational changes in NBD and in turn, TMD changes to outward open conformation which leads to efflux of bound substrate. 4) ATP hydrolysis to ADP which further causes conformational changes in NBDs and TMDs. 5) ABC transporter back to its open inward conformation. TMD = Transmembrane Domain. NBD = Nucleotide Binding Domain.

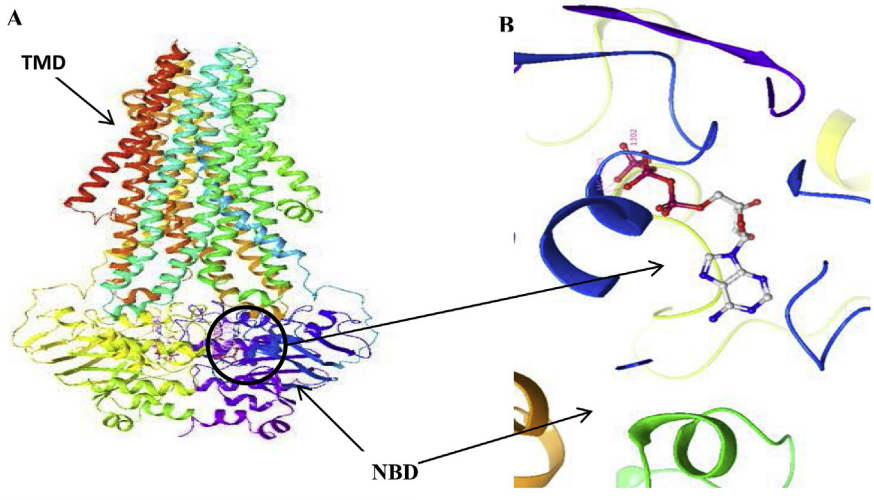

Fig. 3. A) Structural representation of human P-gp protein (PDB ID: 6C0V) in outward facing conformation with an ATP bound (in stick representation) to each Nucleotide Binding Domains. **B)** Close-up view of ATP bound to NBD motifs.

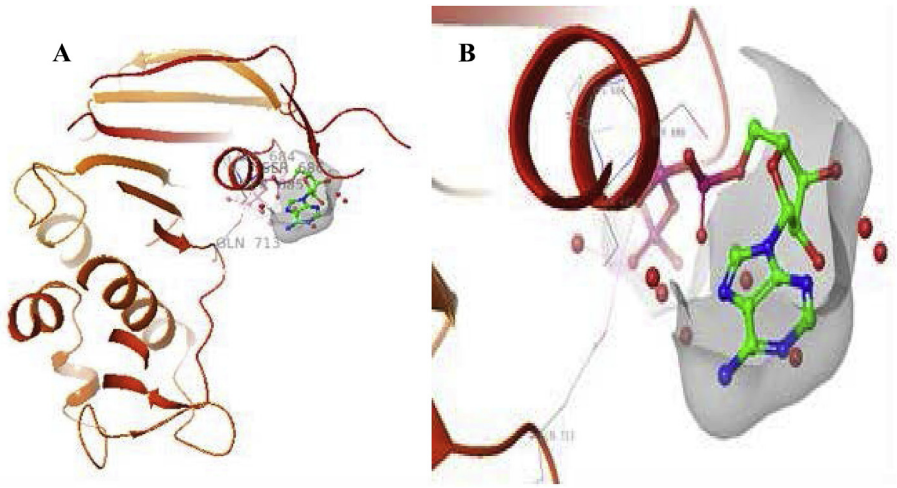

Fig. 4. A) Structural representation of human multidrug resistance protein (MRP1/ABCC1) (PDB ID: 2CBZ) in its bound open form of nucleotide binding domain (NBD). **B)** MRP1 with ATP bound (in stick representation) in NBD.

organic anion transporters (cMOAT), as it was first identified from rat liver by Buchtler et al., in 1996 [40,41]. Unlike MRP1, MRP2 expression can primarily be noted in the apical plasma membrane of hepatocytes, the brush-border membrane of kidney proximal tubules and the intestine, though MRP2 expressed mostly on the apical side of the lumen but their expression is not restricted only to the apical side as they can also be found on basolateral side [42,43]. MRP2 transporters can also be detected in $CD4^{+}$ lymphoblasts, gallbladder, peripheral nerves, and placental trophoblasts. Analogous to its structural similarities with MRP1 i.e three transmembrane domains (TMD1, TMD2, TMD0) and two nucleotide binding domains with six alpha-helices in TMD1 and TMD2, while 5 alpha helices in TMD0; MRP2 can transport xenobiotics and their metabolites, unconjugated bile acids, organic anions, GSH conjugates, glucuronides, and sulfates, much like MRP1. Basic residues in TM helices especially in TM6, TM9, TM16, and TM17 are proven to be essential for substrates recognition and binding [6,30,44]. The physiological function of MRP2 was backed by knockout studies in mice ($Mrp2^{-/-}$) which showed decreased clearance of endogenous metabolites and metabolites of drugs. Absence of MRP2 significantly hampers excretion of bilirubin glucuronide and total GSH, which is why mutation in the gene encoding amino acids involved in transport of non bile salts leads to Dubin-Johnson syndrome, an autosomal recessive disorder characterized by conjugated hyperbilirubinemia, a chronic condition of liver in which there is deposition of brown pigments in liver due to compromised excretion of anionic conjugates from hepatocytes into bile [45]. *In vitro* studies confirmed the expression of MRP2 associated with increase in efflux of many anticancer drugs, like methotrexate, cisplatin, irinotecan, paclitaxel and vincristine, along with its increased expression in lung, gastric, renal and colorectal tumor cell lines, similarly MRP2 has been observed to increase efflux of sorafenib approved to be used in renal and hepatocellular carcinomas. It has also been found to be highly expressed in some tumors originating from the kidney, colon, breast, lung, and ovary, and in cells from patients with acute myelogenous leukemia. Recently its participation in oesophageal squamous cell carcinomas has also been noted by Yamasaki et al., 2011. Since its involvement in various types of cancer, researcher have also tried to develop its modulators, e.g. montelukast has been shown to inhibit the efflux of paclitaxel and saquinavir from MRP2- overexpressing cells, azithromycin, cyclosporin A, glibenclamide, indomethacin, rifampicin, fusidate, gatifloxacin are some of the other examples which inhibit MRP2 mediated efflux [45–48].

3.4. Breast cancer resistance protein (BCRP/ABCG2)

First identified in 1998 by Doyle et al. this protein got its name from the drug selected breast cancer cell line, i.e. MCF-7. ABCG2 gene encoded BCRP also named as mitoxantrone resistance protein (MXR) and ABCP because of its presence in mitoxantrone resistant cell line and human placenta cells. Expressing highly in drug challenged cancer cell lines BCRP likewise to its partners, P-gp and MRP1, and MRP2, is strong transporter with broad substrate specificity including most of the anticancer drug such as methotrexate, 7-ethyl-10-hydroxy camptothecin, doxorubicin, bisantrene, irinotecan, etoposide, tyrosine kinase inhibitor (imatinib, flavopiridol), both positively and negatively charged molecules as well as water soluble molecules (Table 1) [3,5,33,49,50]. In comparison to full transporters (P-gp and MRP1), BCRP is a half transporter comprising of one TMD (having six TMH) one NBD having a molecular weight of only 75 kDa and just 655 amino acids long, also the shortest ABC transporter. For BCRP to be fully functional, it needs to flock either via homodimerization or heterodimerization by a disulfide bridge at Cys 603 (Fig. 5) [51]. Its function in physiology, pathophysiology, and pharmacokinetics can be assessed from their high levels of expression in liver, central nervous system, testes, placenta, prostate, uterus, and ovary. Other than these sites, ABCG2 has also been found to express in the small intestine and large intestine, kidney, lung, stomach, pancreas, but in low level [52]. Physiologically BCRP serves a major protective role in most of the distributed tissues except mammary gland, where it concentrates the toxins in milk. In placenta, knockout studies in mice and explorative studies in perfused human placenta have confirmed its protective role for the fetus, while in blood-brain barrier it limits the brain penetration of most of the drugs and in the intestine, it limits the oral bioavailability of its substrate drugs [29,37].

4. Recent trends in MDR modulation

It has been recognized that ABC transporters have profound engrossment in the pharmacokinetics of various chemotherapeutic drugs and their modulation through various modes can be useful in the treatment and prognosis of various cancer types. The key transporters which are discussing in the present review are P-gp, MRP1, MRP2, and BCRP. To date, several chemical substances have

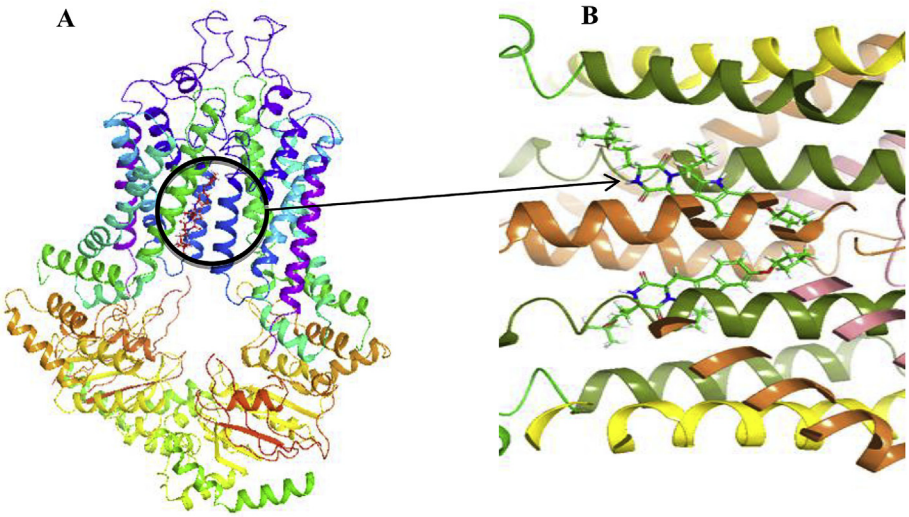

Fig. 5. A) Structural representation of human breast cancer resistance protein (BCRP) (PDB ID: 6FFC) in its dimeric form and an inhibitor bound (in stick representation) to its binding site. **B)** Close-up view of the binding site cavity in an inward conformation of the transmembrane domains (TMDs).

been tested in a number of clinical trials for their MDR modulatory activity. All these can be classified as first, second and third generation modulators broadly based on their affinity for transporters and magnitude of side effects [25,53,54]. However, to date, no compound has shown a significant reversal of MDR without any major toxicity [55]. Most of these inhibitors/modulators are inhibitors of P-gp. The first generation modulators include verapamil (**1**) (calcium channel blocker) [53], cyclosporine A (**2**) (immunosuppressant), and quinine (**3**) (antimalarial), quinidine (**4**) (antiarrhythmics), reserpine (**5**) (anti-hypertensives), tamoxifen (**6**) and toremifene (**7**) (antiestrogens), despite promising results in preclinical trials these drugs showed major toxicities in clinical trials, most of them were related to their primary pharmacological activities, e.g. verapamil (**1**) showed cardiac failure and hypotension [53]. Beside their toxicities, these compounds also failed to prove effective against tested cancer like lung, ovarian and multiple myeloma. Non-specific ABC transporter inhibition in multiple tissues (liver, kidney, bone marrow), nephrotoxicity, myelosuppression, hyperbilirubinemia, and neurotoxicity are some other factors which lead to discontinuation of these drugs as ABC transport modulator [23,56]. Majority of second generation drugs are analogs of first generation drugs with more affinity, efficacy, low toxicity and without intrinsic pharmacological activity shown by first generation drugs. These include dexverapamil (**8**) [57], valspodar (**9**) [58] and biricodar (**10**) (tacrolimus derivative) [59]. These compounds were showing improved toxicity, potency and their effectiveness in clinical trials were not at par when used with chemotherapeutic drugs. Most of the second generation compounds interact with cytochrome P450 enzymes family involved in the pharmacokinetics of drugs including chemotherapeutic drugs. Through interaction with cytochrome P450 enzymes these modulators decrease the clearance of other drugs, which leads to their toxicity and this was one of the reasons for failure of valspodar (**9**) in the clinical trials, when co-administered with anticancer drugs its interaction with pharmacokinetics of drugs leads to their toxicity which in turn leads to its treatment failure [25,54,60]. QSAR approach has opted in the development of third generation drugs to overcome the limitations of both first and second generation modulators [61]. Elacridar (**11**), laniquidar (**12**) [62], zosuquidar (**13**) [63], dofequidar (**14**), mitotane (**15**) [64], annamycin (**16**), and tariquidar (**17**) [65], are the members of third generation modulators category. In contrast to first and second generation modulators, these are more specific and potent with diminutive pharmacokinetic interactions [66–68]. Oral elacridar (**11**) given in combination with topotecan to the breast cancer patients results in improved bioavailability of topotecan [69], similarly zosuquidar (**13**), when given along with paclitaxel in human non-small-cell lung cancer (NSCLC) xenografts, showed some interesting results, also observed 75% response rate of 16 AML (Acute Myeloid Leukemia) patients who were given zosuquidar (**13**) along with daunorubicin and cytarabine [70,71]. Tariquidar (**17**) also have shown significant improvement in the sensitivity of paclitaxel and vinblastine in mice small-cell lung cancer, but fail to perform in advanced breast cancer phase II study [72]. Since, P-gp is one the most studied human transporters as it has broad substrate specificity and wide distribution in human body, so many efforts have been made to modulate its activity in multidrug resistant cancer and some of its modulators were also found active against BCRP [(tariquidar (**17**), elacridar (**11**)], and MRP1 [(tariquidar (**17**), biricodar (**10**), dofequidar (**14**)]. There are some inhibitors reported in the literature which are specific inhibitors of BCRP examples [73] of such inhibitors are included in Table 1 along with the inhibitors of MRP1, MRP2 and P-gp. Recently, two drugs (Bicalutamide and enzalutamide) which were previously being used in docetaxel resistant prostate cancer as anti-androgens were found to inhibit P-gp via decreasing ATPase activity (tested via rho123 assay and P-gp-Glo assay) by 40% and 60% respectively at a concentration of 40 μM. These drugs significantly increased the cytotoxicity in presence of docetaxel both *in vitro* in docetaxel resistant cell lines (C4-2B-TaxR and DU145-DTXR) and *in vivo* in SCID mouse injected tumor cells [74]. Though some of these inhibitors have shown noteworthy success in increasing sensitivity of anticancer drugs in preclinical and some clinical trials, most of these inhibitors either underperformed in clinical trials or showed high toxicity [75]. The chemical structures of some these modulators are given in Fig. 6.

Despite the continuous efforts in the field of multidrug resistance the field is yet to taste the success. There are multiple reasons discussed in literature for the timely failure of the various drugs, e.g. 1) Toxicities due to primary pharmacological actions of the drug; 2) Lack of strong preclinical data and choice of appropriate animal model; 3) Interference with pharmacokinetics of chemotherapeutic drugs which further leads to various toxicities; 4) Non-specificity of the inhibitors towards ABC transporters. Although there are some success stories such as a recent study published by

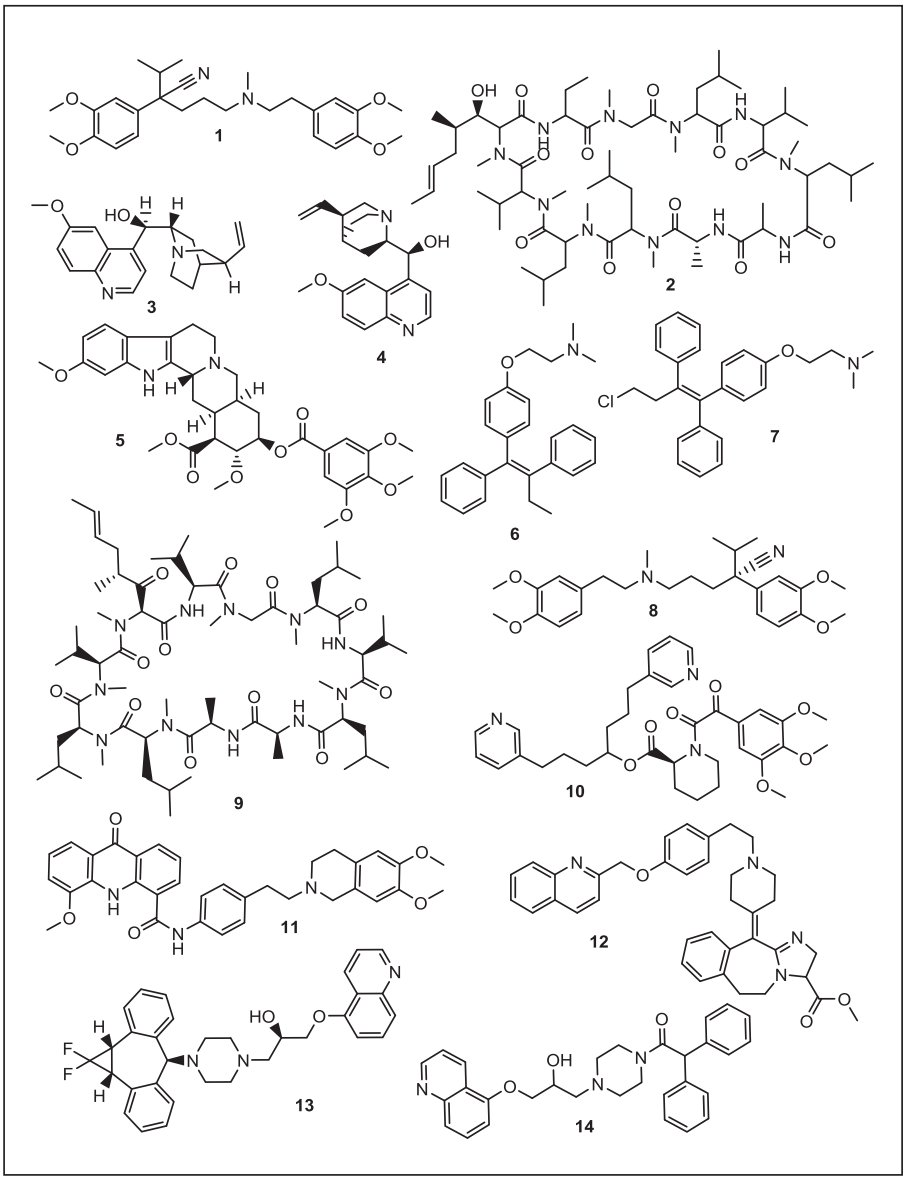

Fig. 6. Structure of selected MDR modulators.

Chang et al., in which they have systematically discovered a non-toxic chemical compound [1,2,4]triazolo[1,5-*a*]pyrimidin-7-one [(WS-10), (**18**)] from their in-house library. They tested the compound for its MDR reversal activity and thereby increasing sensitivity of paclitaxel and doxorubicin in SW620/Ad300. It was further tested through cellular thermal shift assay for its binding to ABCB1 [76]. Due to lack of non-toxic and specific compounds scientists are now exploring natural products for the solution of current problems in the field of multidrug resistance. In this review, we will discuss different classes of chemicals which are of natural origin and act as MDR modulators.

5. MDR modulators of natural origin

Nature has always answered many of the complex clinical problems, and pharmaceutical industries have always looked forward to providing starting material for drug discovery. Much work has been done in the area of natural product as MDR modulators [82–84]. In this review, we will discuss compounds of natural origin which have been explored as modulators of MDR through inhibiting or otherwise ceasing the activity of three major ABC transporters (P-gp or MDR1, MRP1 or ABCC1, MRP2, and BCRP or ABCG2).

5.1. Modulators from plants

5.1.1. Flavonoids

Flavonoids belong to an important class of secondary metabolites named polyphenols and distributed widely in various parts of plants. Flavonoids are characterized by 2-phenylchromane ring system and can be divided into different sub-classes based on the substitution at ring B, and oxidation status of ring C. Chalcones,

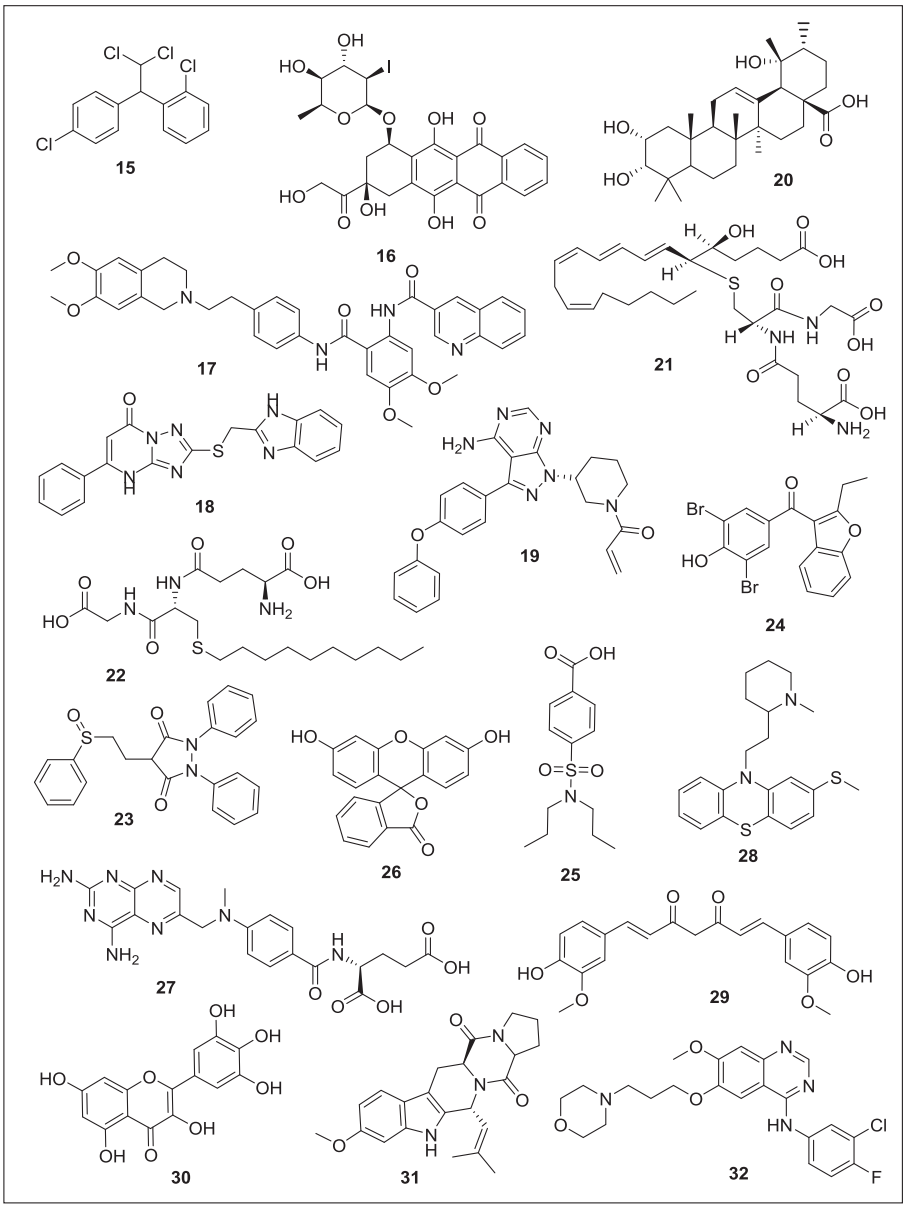

Fig. 6. (*continued*).

flavones, flavanones, flavonols, flavanols, anthocyanins, and isoflavones are the subclasses of the flavonoids [85]. Flavonoids serve various protective functions in plants, whereas they have profound medicinal and nutritional value for humans as well [86]. Flavonoids, due to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties along with their capacity to modulate key cellular enzyme, are associated with a broad spectrum of health-promoting effects. They are being used in the treatment of cancer, Alzheimer's disease (AD), atherosclerosis, multidrug resistance as they have a strong affinity for P-glycoprotein [87,88]. Moreover, structural features of flavonoids (Fig. 7) are found to contribute positively to inhibition of P-gp, MRP1, MRP2 and BCRP [89]. It has been reported that a hydroxyl group at position 5, double bond across 2 and 3, and a methoxyl group at position 3 are required for their P-gp and BCRP inhibitory activities and the exchange of a 3-methoxy group by an OH group can decrease their activity [90,91]. This structural-activity relationship of flavonoids have also been studied by other researchers and found that 3-prenylchalcone binds to NBD2 with 20-fold higher affinity compared to the unprenylated chalcone [88]. Quercetin (**33**) has been tested both *in vitro* and *in vivo* for their anticancer and chemosensitizing activity (Refer table Chen et al., 2010). It is multi-targeted and multi-pump category chemosensitizer which can act through substrate binding site or ATP binding site of various transporters. It has shown interaction with P-gp, MRP1 and BCRP [92]. Isolated from leaves of *Ginkgo biloba*, quercetin (**33**) has shown to strongly inhibit transport of Hoechst 33342, a fluorescent probe and substrate of P-gp, by inhibiting ATPase activity to one third at a concentration of 25 μM [80,93]. Also, Limtrakul et al. testified that when given at a concentration of 30 μM quercetin (**33**) significantly decreases the level of P-gp in MDR human cervical carcinoma cell line (KB-V1) [94]. Borska et al. reported that quercetin (**33**) synergistically increases the cytotoxicity in the sensitive parent cell line (EPG85-257P) and chemosensitizes the doxorubicin resistant gastric cell carcinoma cell line (EPG85-257RDB) along with downregulation of ABCB1 gene at an IC_{50} value of 12 μM after 72 h

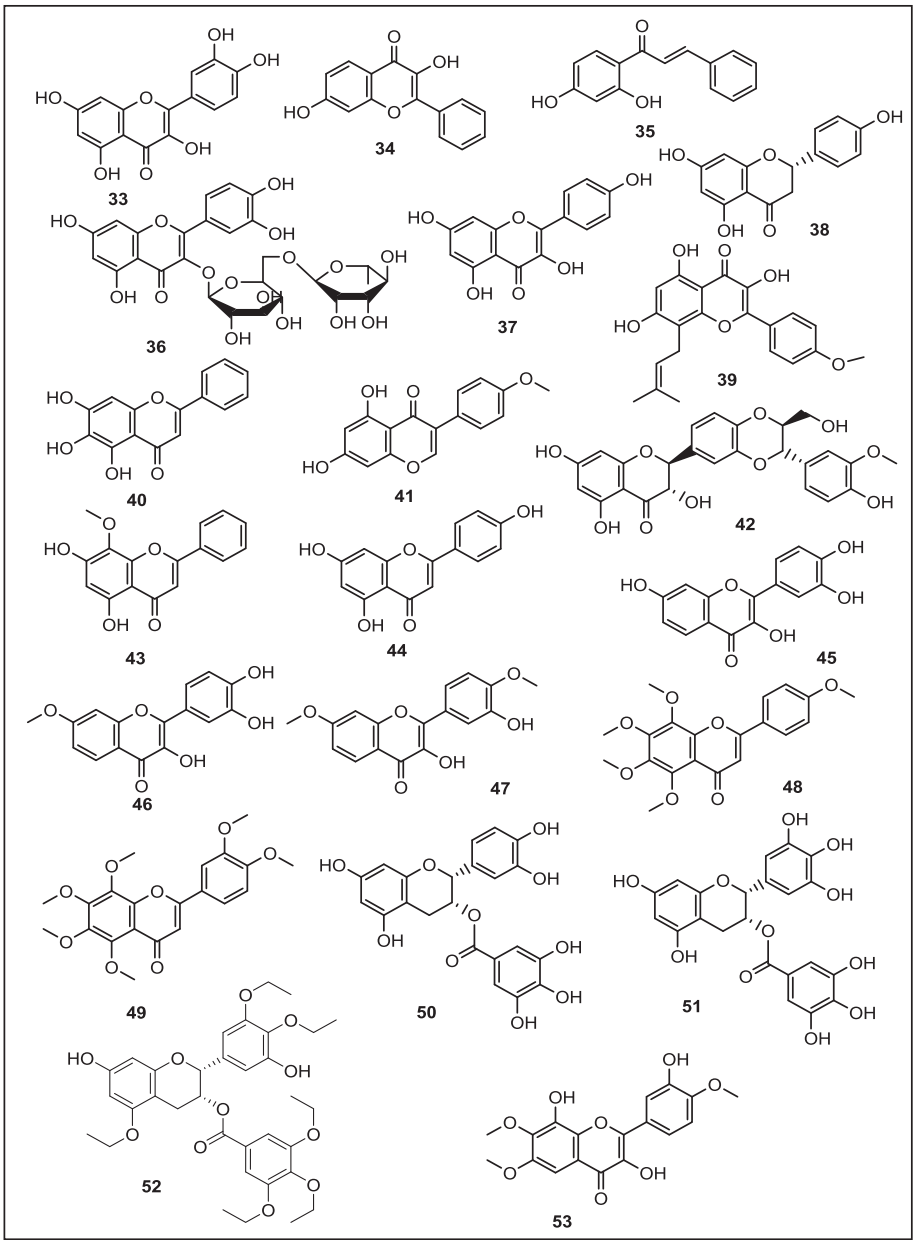

Fig. 7. Structures of flavonoids having MDR modulatory activity.

[95]. Quercetin (**33**) could be a potential modulator of ABCB1 as suggested by experiments conducted in oral resistant cancer cell lines (KB/VCR) and resistant leukemia cell lines (K562) in which it has been reported to decrease the expression of ABCB1 [96,97]. Another group of scientists has used quercetin (**33**) conjugated with glutamic acid as a P-gp inhibitor. After synthesizing hydrolyzable conjugation, they synthesize two non-hydrolysable conjugates. They were tested in human uterine sarcoma MES-SA and doxorubicin resistant, P-gp overexpressed cell line MES-SA/Dx5. P-gp inhibition activity was studied by flow cytometric analysis of intracellular doxorubicin in the presence and absence of these conjugates and found to inhibit P-gp. ATPase activity of both conjugates increases at a concentration of 100 μM like verapamil which indicates their binding to the drug-binding site in TMD. Both the conjugates outperformed when compared with verapamil and quercetin (**33**) for their MDR-reversal activity, as they have many folds increased the reversal effect of chemotherapeutic drugs like doxorubicin, actinomycin D, vinblastine, and paclitaxel [98,99]. Recently in an interesting study conducted by Chen et al. found that quercetin (**33**) increases the accumulation of rhodamine123 (Rh123), doxorubicin (ADR) and also increase the chemosensitivity of resistant phenotype of human hepatocellular carcinoma (BE/5-FU) towards cytotoxic drugs in a dose-dependent manner. It also down-regulate the expression of ABCB1, ABCC1, and ABCG2 and thus decreases the activity of their respective proteins. They also concluded that this suppression was executed via FZD7/β-catenin pathway [100].

In 2012 Chieli et al., reported that ZpE and two of its components: 3,7-dihydroxyflavone (**34**) (DHF) and 2′,4′-dihydroxychalcone (**35**) (DHC) found in *Zuccagnia punctata* (ZpE) Cav. (Fabaceae), have modulatory activity on both the expression and activity of P-gp. In a simple Rh123 assay, DHF and DHC have shown significant dose dependent increase of intracellular fluorescence with IC_{50} values of 3.2 and 6.0 mg/mL respectively for the inhibitory

effects of P-gp on the human proximal tubule cell line (HK-2) [101].

Rutin (**36**) isolated from *Ruta graveolens* grass having much similar structure with quercetin (**33**) significantly decreased the accumulation of rhodamine 123 (P-gp substrate) in LS 180, a human colon adenocarcinoma cell line, indicating a possible activation of P-gp [102]. Zhang et al. reported that rutin leads to activation of P-gp and hence decreases the bioavailability of cyclosporine. Thus, P-gp is involved in transmembrane transport and intracellular accumulation of rutin (**36**) in human colonic cancer cells (Caco-2) [103].

Another flavanol type flavonoids kaempferol (**37**) and naringenin (**38**) have been reported to inhibit P-gp activity. Isolated from *Kaempferia galanga* L. root kaempferol (**37**) causes a decrease in P-gp levels in the human glioblastoma cell line (T98G) [104]. Naringenin (**38**) in a study conducted by Surya Sandeep et al. significantly increases the concentration of felodipine by inhibiting P-gp [105] and Limtrakul et al. reported significant decrease in the P-gp level KB-V1 cells when treated with 30 μM kaempferol (**37**) [94].

Similarly, icaritin (**39**), a hydrolytic product of icariin, was isolated from *Herba epimediu* and baicalein (**40**) isolated from roots of *Scutellaria* found to inhibit P-gp. Icaritin (**39**) significantly decreases the expression of MRD1 gene and increases the intracellular accumulation of Adriamycin (ADR) in HepG2 (a human hepatocellular carcinoma (HCC) cell line)/ADR cell line at concentrations of 1, 15 and 30 μM, while baicalein (**40**) significantly increases the oral bioavailability of tamoxifen in small intestine from 47.5 to 89.1% through its P-gp inhibitory activity at concentration 0.5, 3 and 10 mg/kg [106,107]. In a recent study icaritin (**39**) have shown excellent activity in MG-63/DOX, a doxorubicin resistant human osteosarcoma cell line. It showed a dose dependent increase in accumulation of Rh123, 6-carboxyfluorescein diacetate, and doxorubicin and significantly cut down the expression of MRD1 and MRP1 with no effect on BCRP as checked by mRNA and proteins analysis. Apoptosis assay confirmed its role in increasing sensitivity of resistant cancer cells to doxorubicin and western blot assay indicated the involvement of icaritin (**39**) in inhibition of phosphorylation of STAT3 in a dose-dependent manner, which further suggested the participation of Jak/STAT signal pathway in the reversal of MDR [108]. In another review by Gupta et al. the usability of flavonoids as MDR modulators have been reported on the basis of structure activity relationship Structural characteristics of flavonoids including hydroxyl group at 5th position in A ring of phenylpropanoid ring system double bond between 2 and 3 position and methoxy group at 3 position is essential for its P-gp inhibitory activity [89].

Biochanin A (**41**) and silymarin (**42**) isolated from the bark of *Aesculus hippocastanum* L. and seeds of Milk Thistle, both can inhibit P-gp mediated drug efflux as tested in Caco-2 cells where they significantly increased the accumulation of digoxin and vinblastine at a concentration of 50 μM. In another study, wogonin (**43**) extracted from the roots of *Scutellaria baicalensi* Georgi has been reported to augment the apoptosis by raising the concentration of etoposide in the human leukemia cell line (HL-60) through P-gp inhibition suggesting their potential use in chemotherapy as P-gp inhibitor for increasing the bioavailability of anti-cancer drugs [109].

Flavonoids such as apigenin (**44**) and fisetin (**45**), also known as natural sedatives were also tested for their MDR modulatory activity in doxorubicin resistant human uterine sarcoma cells (MES-SA/Dx5) and were found to increase the doxorubicin accumulation inside the cells significantly. At a concentration of 10 μM, apigenin (**44**) increase the intracellular concentration of the drug by 29% as compared to 20% of fisetin (**45**) [110]. In another study on flavonoids from citrus fruits, such as naringenin (**38**), methylated derivatives of naringenin and tangeretin were tested by rho123 accumulation assay as MDR modulator and apoptosis inducer; it was observed that all the tested compounds were active inhibitors of P-gp in doxorubicin resistant human colon adenocarcinoma cell line (LoVo/Dx). . Out of four tested compounds (naringenin (**38**), naringenin 7-methyl ether (**46**), naringenin 7,4′-dimethyl ether (**47**) and tangeretin (**48**) was found to be the most active modulator and inducer of apoptosis [111]. Similar to tangeretin (**48**) another polymethoxyflavonoid nobiletin (**49**) has been found to inhibit P-gp and MRP1 when tested in P-glycoprotein overexpressing human carcinoma KB-C2 cells and human MRP1 gene-transfected KB/MRP cells. It was found to interfere with the ATPase activity in bot P-gp and MRP1. It increases the accumulation of daunorubicin in KB-C2 cells and calcein in KB/MRP cells at a concentration of 50 μM comparable to their respective standards (Verapamil (**1**) and MK-571) [112]. Green tea polyphenols Epicatechin gallate (**50**) and epigallocatechin gallate (EGCG) (**51**) were also evaluated for their role in cancer treatment and was found to have antiproliferative activity at a high dose. These polyphenols were also tested along with doxorubicin in resistant human hepatocellular carcinoma cell line and found to inhibit cell growth *in vitro* and halted the growth of hepatoma in mouse grafted with tumor at nontoxic doses. They also increased accumulation of rhodamine 123 inside the cells which suggests their chemosensitizing action might be due P-gp inhibitory activity which is also supported by the deceased MDR1 expression after treatment with the green tea polyphenols along with doxorubicin [113]. In most recent studies an ethylated epigallocatechin gallate derivative Y_6 (5,3′,4′,3″,4″,5″-6-*O*-ethyl-EGCG) (**52**), which is more stable than EGCG, was tested in doxorubicin resistant hepatocellular cancer cells (BEL-7404/DOX). It reverses multidrug resistance by decreasing expression of ABCB1. It was further confirmed through both *in vivo* (in BALB-c mice with BEL-7404/DOX xenograft model) and *in vitro* (in HEK293 cells transfected with ABCB1 gene) experiments that Y_6 act as MDR modulator via inhibiting P-gp. It significantly reduces the IC_{50} (from 8.80 to 1.05 to 0.62 and 0.92) values of doxorubicin and cisplatin at concentration of 1 and 2 μM [114]. One more phytopolyphenol, curcumin (**29**) which do not belong to the class of flavonoids but has significant P-gp inhibitory activity when tested in vinblastine selected Caco-2 cell line as suggested by increased cellular accumulation of rhodamine 123 and Calcein-AM uptake assays. Calcein AM is a P-gp substrate which undergoes hydrolysis by endogenous oxygenases and converted into calcein (fluorescent) which is not P-gp substrate and got accumulated inside the cell [115].

Eupatin (**53**), a flavonol has found to have anticancer activity through anti-mitotic activity and moderately potent BCRP inhibitory activity ($IC_{50} = 2.2$ μM). ABCG2 has been reported to involve in the resistance to several anticancer agents, and eupatin (**51**) and its derivatives are quite promising in synergistically reversing the drug resistance of cancer cells [116]. Beside eupatin (**53**), flavonoids apigenin (**44**), biochanin A (**41**), kaempferol (**37**), naringenin (**38**), and silymarin (**42**) all significantly increased mitoxantrone accumulation in BCRP overexpressing human lung carcinoma NCI-H460 MX20 and human breast cancer MCF-7 MX100 cells line, as compared to BCRP-negative counterparts (NCI-H460 cells and MCF-7/ADR) [117].

There is no doubt that flavonoids got the potential to be used in combination with suitable anticancer agents to improve their therapeutic index by increasing their bioavailability and thus reducing lethal side effects by lowering dose of chemotherapeutic drugs [118]. But to reconnoiter their pharmacological activities these we must overcome some challenges these includes herb-drug interactions when co-administered with other drugs, then the bioavailability of flavonoids which can be influenced by factors such as pH, first pass mechanism [119], low hydrophobicity [120] and interaction with CYP enzymes [121].

5.1.2. Alkaloids

First isolated in the early nineteenth century (1806) by Friedrich Wilhelm Serturner and got its name from Meissner in 1819, alkaloids are secondary metabolites occurring diversely around the globe in plants, fungi, and bacteria. The prime requirement to be classified as alkaloid is one or more basic nitrogen usually in a heterocyclic ring and marked physiological activity on human or animals. One of these prime requirement i.e. basic nitrogen atom is also helpful in their P-gp inhibitory activity along with small alkyl lipophilic molecule with two planner ring system can serve as beneficial for MDR modulatory activity of various alkaloids. Derived from amino acids alkaloids are reported to be present in higher plants especially in gymnosperms and angiosperms, and a few exist in lower plants [122,123].

5.1.2.1. Quinoline, isoquinoline and quinazoline alkaloids. Quinoline alkaloids (Fig. 8) have been discussed under the category of first generation inhibitors which includes quinine (**3**) and quinidine (**4**) from Cinchona bark. Interestingly compounds derived by their structural modification e.g. a homodimer of quinine (**3**) Q2 cross-linked via FDA-approved agents with biodegradable spacer, showed accumulation of Rh123 ($IC_{50} = 1.7\ \mu M$), inhibition of [^{125}I] iodoarylprazosin (IAAP) labelling to P-gp indicating the interaction with drug binding site of the protein, and also decreased the transport of radiolabeled paclitaxel ($IC_{50} = 2.0\ \mu M$) in resistant MCF-7/DOX cell line thus increasing sensitivity of the drug. An isoquinoline alkaloid chelidonine (**54**) isolated from *Chelidonium majus*, inhibited the efflux of P-gp substrates dyes Rh123 and calcein AM (CAM) at concentration 9 and 11 μM respectively in Caco-2 (said to be an ideal cell line to study MDR as it highly express ABC transporter proteins) and resistant human T cell leukemia cell line CEM/DOX5000 cells, thus rendering the cells more sensitive to doxorubicin. It also lowers the expression of MDR1, MRP1, BCRP, increases the caspase-3, and caspase-8 mRNA levels at 50 μM. Another isoquinoline alkaloid Glaucine (**55**) isolated from stems of Chinese medicinal plant *Corydalis yanhusuo*. Glaucine (**55**) inhibited P-gp and MRP1-mediated efflux in resistant breast cancer cell line MCF-7/ADR and also increased ATPase activities of the transporter pumps suggesting its probable interaction with P-gp [124].

Tetrandrine (**56**) a bisbenzyl isoquinoline alkaloid isolated from Chinese herb *Stephania tetrandra* (Han-Fang-Chi) has been known to exert an antitumor effect through its anti-proliferative and apoptosis inducing properties [125]. When tested in human epidermoid carcinoma cell lines (KBv200 cells) it completely inhibited [^{3}H] azidopine labeling of P-gp at 2.5 μM and consequently reversed the resistance to vincristine. Despite outstanding *in-vitro* activity against KBv200 in combination with vincristine, tetrandrine (**56**) failed to inhibit the growth of tumor *in-vivo* [126]. Even derivatives of tetrandrine (**56**) such as 5-Bromo tetrandrine (**57**) exerted cytotoxicity in KBv200 cells ($IC_{50} = 2\ \mu M$) [127]. One more study conducted by Wang et al. has reported dose dependent decrease in expression of MRP1 and increase in CMFDA in the human oesophageal squamous carcinoma cisplatin-resistant cell line (YES-2/DDP) when treated with tetrandrine (**56**) [128]. In a recent study by Jiang et al. they found synergistic action of tetrandrine (**56**) and paclitaxel on resistant breast cancer cell line MCF-7/ADR when given as self-assembled nanoparticles [129]. In a study conducted by Wei et al., they tested berbamine (**58**) which is a bizbenzylisoquinoline alkaloid isolated from *Mahonia fortune*, both *in vitro* and *in vivo* (in imatinib-resistant BCR-ABL-positive human leukemia K562 (K562-r) cells). They identified a decrease in mRNA for MDR1 and expression of P-gp protein in treated cell line as compared to untreated. It has also shown anti-proliferative activity both *in vitro* and *in vivo* and causes to increase apoptosis (through down regulation of anti-apoptotic proteins Bcl-2 and Bcl-x_L) [130]. Another isotetrandrine (**59**), isoquinoline alkaloid isolated from *Caulis mahoniae*, was tested and found to sensitize MCF-7/DOX cells to DOX in a dose-dependent manner [131].

Another bisbenzylisoquinoline alkaloid hernandezine (**60**) was found to be a selective inhibitor of ABCB1 or P-gp as suggested by Rh123 assay. It is a biologically active alkaloid isolated from *Thalictrum flavum* (Ranunculaceae). Hernandezine (**60**) raises the resistance reversal factor (RRF) (Comparative sensitivities of anticancer drug in sensitive and resistant cell line) for doxorubicin and vincristine to 34 and 356 fold in resistant KB-V-1 cells in

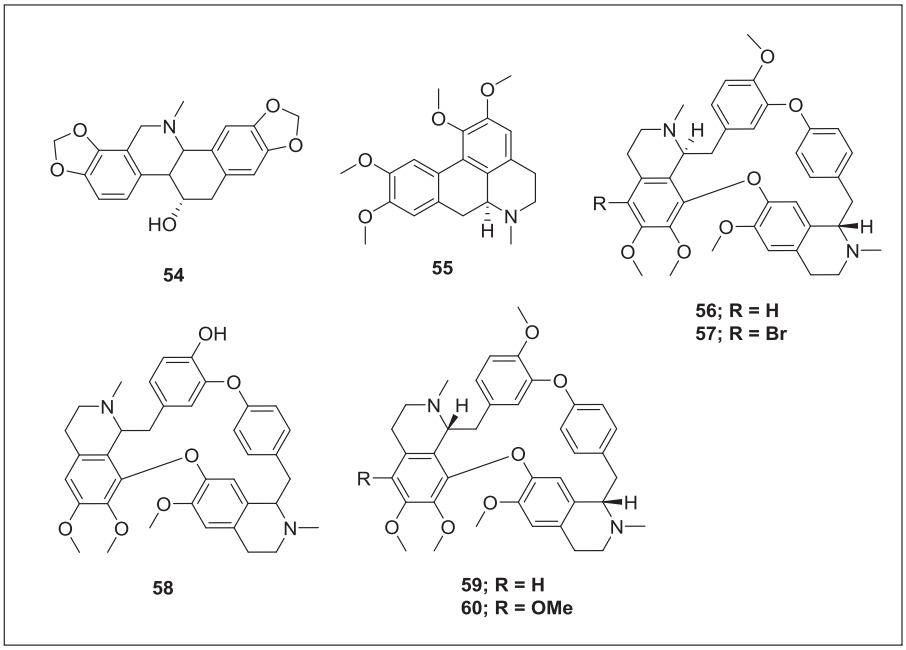

Fig. 8. Structure of MDR modulatory quinoline, isoquinoline and quinazoline alkaloids.

comparison to wild KB-3-1 cells and 46 and 435 fold for doxorubicin and vincristine respectively in resistant ABCB1 overexpressing variant NCI-ADRRES cells in comparison to wild ovarian carcinoma cell line OVCAR-8 cells. Recently hernandezine (**60**) an isoquinoline alkaloid was recognized as an effective to inducer autophagic cell death via direct activation of AMP-activated protein kinase (AMPK) and recent studies reports that autophagy may catalyze the development of MDR [132,133].

5.1.2.2. Indole alkaloids. Reserpine (**5**) and yohimbine (**61**) are indole type alkaloids which were isolated from roots of *Rauwolfia serpentine*, These alkaloids and their analogs inhibit P-gp mediated efflux of substrate drugs such as doxorubicin, daunorubicin, and vincristine in multidrug resistant human leukemia cells line CEM/VLB100 at 5 μM, that results in chemosensitization of MDR cells. Its anti-P-gp activity can be evidenced by the competitive inhibition of ^{125}I-NASV (a photoactive analog of vinblastine). Structure of these alkaloids was the mainstay behind pharmacophore modeling and mapping basic structural characteristics (such as basic nitrogen atom and conformations of aromatic rings) of P-gp inhibitors, and interestingly reserpine is also found to be an inhibitor of BCRP [134,135]. Indole-3-carbinol (**62**) and indole-3-carbaldehyde (**63**) are two indole alkaloids present in many cruciferous vegetables and fruits of *Illicium simonsii*, found to downregulate the overexpressed P-gp protein in K562/R10 a resistant human leukemia cell line. You et al., 1994, tested three indole alkaloids from *Peschiera latea* (Apocynaceae), conoduramine (**64**), coronaridine (**65**) and voacamine (**66**) on human oral epidermal carcinoma cells (KB-V1) and found promising results with two bisindole alkaloids voacamine (**66**) and conoduramine (**64**) as a chemosensitizer in presence of vinblastine ($ED_{50} = 1.7$ μg/ml). Voacamine (**67**) was tested again in two different tumor cell lines: the sensitive lymphoblastoid cell line CEM-WT and its resistant derivative CEM-R, the sensitive osteosarcoma cell line U-2 OS-WT and its resistant counterpart U-2 OS-R; voacamine showed drug accumulation in both the cell lines. Recently voacamine (**66**) was again tested in osteosarcoma cell line sensitive, resistant and P-gp negative cell line (SAOS-2-WT, SAOS-2-DX, and Me30966SAOS-2-WT, SAOS-2-DX, and Me30966). The study with rational testing confirmed the P-gp mediated drug accumulation in resistant cell line and chemosensitization of the anticancer drug doxorubicin even in nontoxic concentration by the compound voacamine (**66**) [136–138]. In 2009, seven strychnan alkaloids (leuconicine A-G) was isolated from stem-bark extract of *Leuconotis griffithii* and *Leuconotis maingayi* and tested on human oral epidermoid carcinoma cell lines KB/S and KB/VJ300 (vincristine-sensitive and vincristine resistant) and out of seven leuconicine A (**67**) and B (**68**) were promising candidates [139]. Later Munagala et al. tested leuconicine A, (**67**) B (**68**) and a synthetic derivative 3,4,5- trimethoxybenzyl leuconicine A (**69**) in sensitive and resistant cell line (KB-V20C and KB-MDR) and observed that out of three 3,4,5- trimethoxybenzyl leuconicine A (**69**) is a potent inhibitor of P-gp as it lowers the dose of vincristine in resistant cell line by 10 fold at concentration of 70 nM and 90 fold at a concentration of 1 μM [140].

Ergoline derivative bromocriptine (**70**) semi-synthesized by bromination of ergocriptine, is a potent P-gp inhibitor and have significant MDR reversal activity (measured as RRF) as observed at concentration of 10 μM in K562, K562-DOX, K562-VCR and in A549 cells for DOX, VCR, VBT, vinorelbine, and etoposide was in the range of 1.6–3000. It was also observed that bromocriptine (**70**) was able to inhibit CAM efflux in P-gp overexpressing cell line [141].

Interestingly, harmine (**71**) a β-carboline type alkaloid selectively inhibit BCRP instead of P-gp (ADR500 cell line) when tested in BCRP over expressive breast cancer cell line MDA-MB-231 [142]. It was tested in mitoxantrone efflux assay at a concentration of 10 μM it was found to inhibit BCRP as effectively as 20 μM of Fumitremorgin C, a well known inhibitor of BCRP [138]. Weak MDR reversal activity was observed in β-Carboline indole alkaloids tabernines A-C (**72**–**74**) isolated from *Tabernaemontana elegans*, tested in Rh123 assay and parental L5178 mouse lymphoma cell lines [143]. Similarly, arboloscine A (**75**) isolated from *Kopsia pauciflora* showed moderate activity in vincristine resistant KB-VCR cell line [144]. The chemical structures of indole type of alkaloids having MDR modulatory activity are given Fig. 9.

5.1.2.3. Steroidal alkaloids. In vivo study in L5178 mouse T-cell lymphoma cells transfected with pHaMDR1/A retrovirus, six alkaloids from *Veratrum lobelianum*, one from *Veratrum nigrum* and three from *Peganum nigellastrum* were tested for their MDR modulatory activity. But only two steroidal alkaloids veralosinine (**76**) (Fig. 10) and veranigrine (**77**), displayed potent MDR reversal activity by resensitizing resistant cells in a synergistic manner with DOX [145].

5.1.2.4. Piperidine, piperazine and diketopiperazine alkaloids. Piperine (**78**) (piperidine), lobeline (**79**) (piperidine), stemocurtisine (**80**), oxystemkerrine (**81**), stemofoline (**82**), are some of the notable examples of this class of alkaloids (Fig. 11) as an active MDR modulators. Starting with piperine (**78**), a well-known bioavailability enhancer in Indian system of medicine, i.e. Ayurveda, obtained from *Piper nigrum* (black pepper) [146]. When tested in doxorubicin resistant breast cancer cell line MCF-7/DOX and colon cancer cell line A-549/DDP found to inhibit non-selectively inhibit efflux of doxorubicin and mitoxantrone mediated by P-gp, BCRP, and MRPs and hence decreases their IC_{50} values. Although, their effect on BCRP was not up to the level of standard FTC, whereas piperine (**78**) has got higher inhibition as compared to verapamil (**1**) and MK-571, known inhibitors of P-gp and MRP1 respectively [147]. Second in the category is lobeline (**79**), a piperidine alkaloid from *Lobelia inflata*, which has successfully reduced the IC_{50} of DOX in Caco-2 cells by 3.5 times by inhibiting P-gp in Rho123 accumulation assay at a dose of 20 μM [148]. Interestingly tertiary alkaloids, i.e. stemocurtisine (**80**) and oxystemokerrine (**81**) obtained from *Stemona aphylla* and Stemofoline (**82**) obtained from *Stemona burkillii*, were found to inhibit P-gp to some extent. While out three stemofoline (**82**), when tested in human cervical carcinoma cell line (KB-V1), dose and time dependently inhibited P-gp activity and significantly reduced the IC_{50} values of VBT, PTX, and DOX [149].

5.1.2.5. Miscellaneous alkaloids. Acridone alkaloids 2- methoxycitpressine I (**83**) and (−) acrimarine E (**84**) showed found in *Citrus sinensis* family Rutaceae, showed to inhibit P-gp mediated efflux of its substrate drug in K562/R7 human leukemic cells, a P-gp overexpressing cell line. A furanoacridone alkaloid gravacridonediol (**85**) exhibited MDR reversing activity by increasing substrate accumulation in Rh123 assay and showed synergistic cytotoxic effect with DOX in resistant L5178 mouse lymphoma cells [150,151].

A phenanthroindolizidine alkaloid, (−) antofine (**86**) from *Cynanchum vincetoxicum* found to have MDR reversing capacity when tested in PTX resistant human lung cancer cells A549-PA. At a concentration of 5 nM with 1.25 μM PTX, (−) antofine (**86**) shows a synergistic effect in its activity. Also, confirmed by western blotting and RT-PCR that it has an effect on transcription and translation of P-gp which was further confirmed by Rh123 assay [152].

Some peptides, e.g. tyroservatide (**87**) (Tyr-Ser-Val) and cationic peptide NK-2 have displayed MDR modulatory activity. Tyroservatide reduces the intracellular accumulation of Rh123 and DOX in BEL-7402/5-FU by 1–2 folds and Rh123 by 2- to 3 fold. It also reduces the expression of the MDR1 gene. Interestingly, NK-2 due

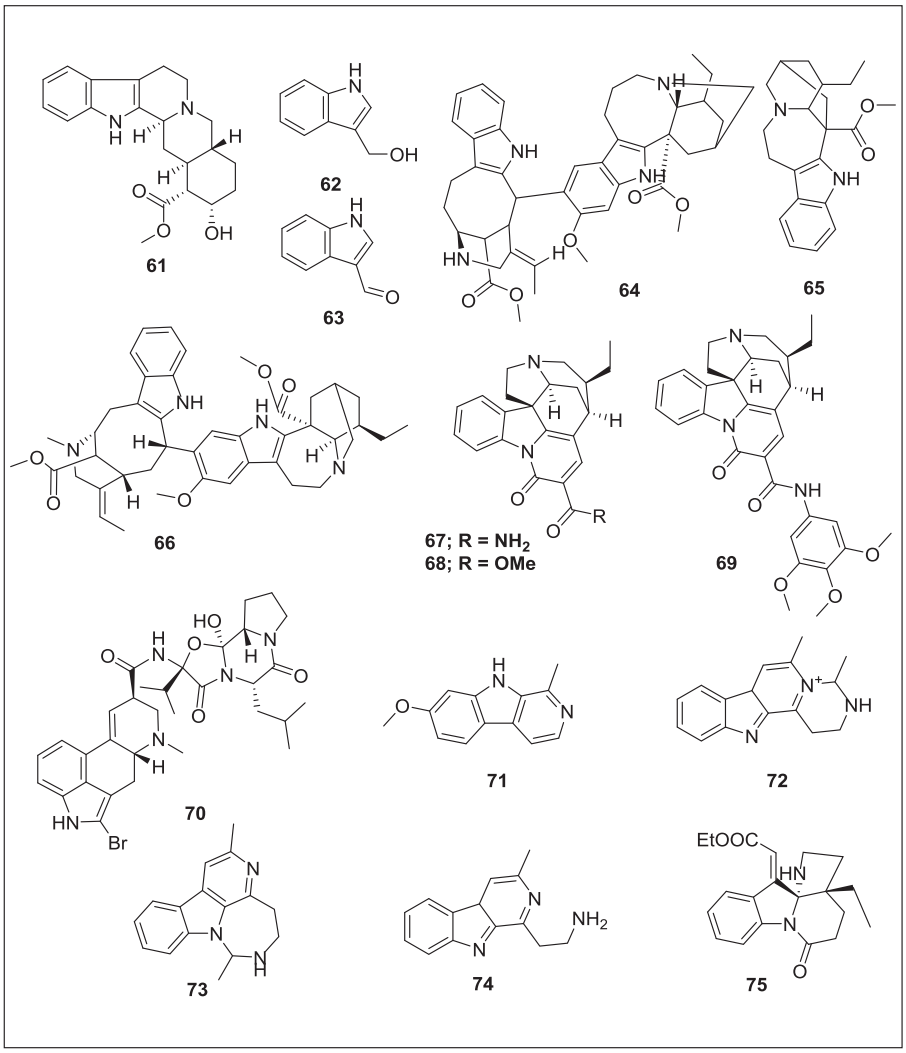

Fig. 9. Structure of Indole alkaloids having MDR modulatory activity.

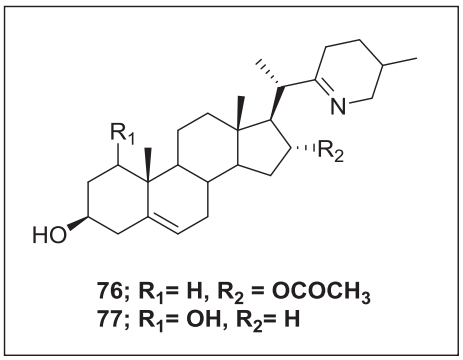

Fig. 10. Structure of steroidal alkaloid having MDR modulatory activity.

to its cationic nature act as a P-gp anchor and leads to its down-regulation which is evident by decreased IC_{50} of DOX from 3.5 μM to 0.7 μM in NCI-H460/R cell line [153,154].

A category of nucleosides which includes clitocine (**88**) obtained from *Leucopaxillus giganteus* which significantly reduces the P-gp expression in human doxorubicin selected P-gp over expressive human hepatocellular carcinoma (R-HepG2) and human uterine carcinoma (MES-SA/Dx5) cell lines thus reversing MDR activity [155]. Similarly, sulfinosine (**89**) displayed MDR reversal activity by decreasing the expression of the MDR1 gene and thus increasing the concentration of DOX in glioblastoma and non-small cell lung carcinoma [156].

In a study by Cihalova et al. purine alkaloids such as Purvalanol A (**90**), olomucine (**91**) and roscovitine (**92**), known inhibitors of cyclin dependent kinases were tested for their MDR modulatory activity in human ileocecal adenocarcinoma HCT-8 and human liver carcinoma HepG2 cell lines expressing P-gp (Fig. 12). Compounds were found to inhibit efflux of Hoechst 33342 and daunorubicin, known substrates of P-gp and also found inhibit ATPase activity [157].

5.1.3. Cardiotonic steroids

First isolated from the toad venom of Bufo species, cardiotonic steroids have been used in the treatment of heart failure, and some Arab physicians have used them for the treatment of cancer. They can be classified into bufadienolides and cardenolides based on the ring system present at 17β-position [158]. In a study, 69 cardenolides were investigated for their P-gp inhibitory activity using ATPase, resazurin reduction assay and molecular docking. Out of 69 tested compounds six were, namely (3β,5β,12β,17β)-3,12-

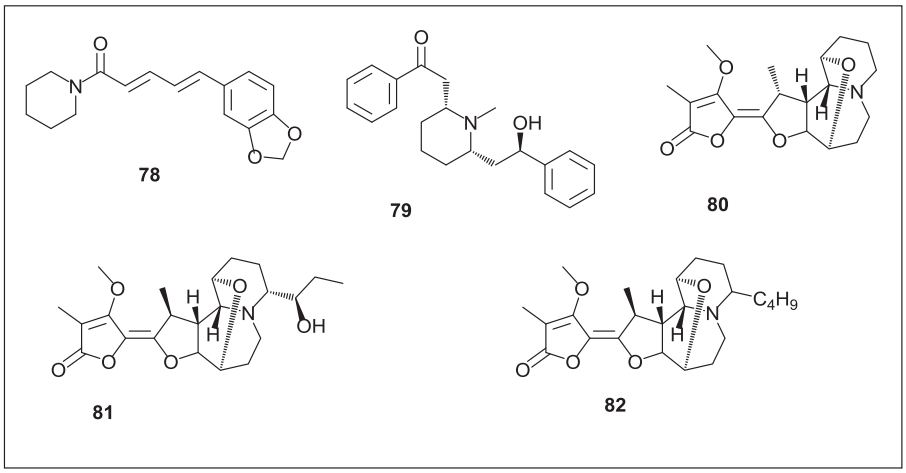

Fig. 11. Structure of Piperidine, piperazine and diketopiperazine alkaloids having MDR modulatory activity.

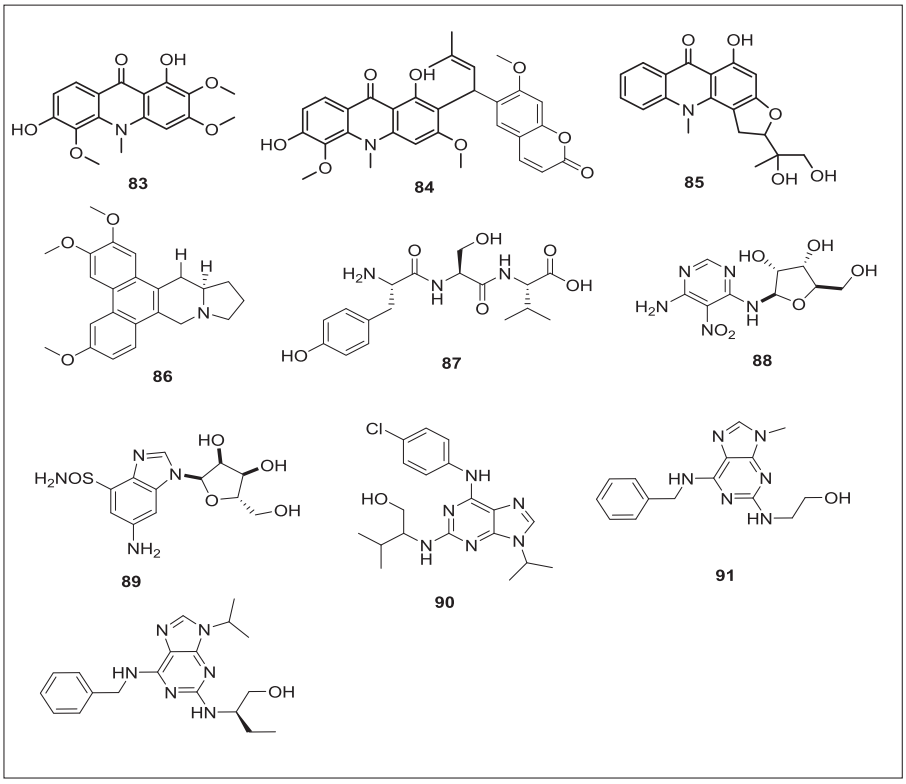

Fig. 12. Structures of miscellaneous alkaloids having MDR modulatory activity.

Bis(acetyloxy)-11-oxoandrostane-17-hydroxymethyl-α-acetate (**93**), (3β,5β,11α,12α,14β,17β)-3,11-bis(acetyloxy)-12,14-dihydroxybufa-20,22-dienolide (**94**), (3β,5β,11α,12β,14β,17β)-3,11,12-tris(acetyloxy)-14-hydroxy-androstane-17-carboxylic acid methyl ester (**95**), (3β,5β,14β,15α)-3-acetyloxy-14,15-dihydroxy-androst-16-ene-17-carboxylic acid methyl ester (**96**), (3β,5β,14β,15β,17α)-3-acetyloxy-14,15-epoxy-androstane-17-carboxylic acid methyl ester (**97**), 2-[7-(Acetyloxy)tetradecahydro-2,4b-di-methyl-1-oxo-2-phenanthrenyl]-succinic acid dimethyl ester (**98**) (Fig. 13), found out to be promising P-gp inhibitors and lead to DOX accumulation in CEM/ADR5000 cells. The molecular docking studies were showing compound interacting with the amino acids of modulator (M-site) site and thus supporting *in vitro* studies [34].

5.1.4. Coumarins

Coumarins (Fig. 14) belonging to the benzopyrone family of natural compounds, found mostly in oils and occur in higher plants. They can be classified as simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins based on the position of the substituents [159]. P-gp inhibitory activity of coumarins has been reported in a number of studies. Cnidiadin (**99**), furanocoumarin from *Tordylium apulum* (Apiaceae) significantly inhibited efflux of the rhodamine123 and the radiolabeled anti-

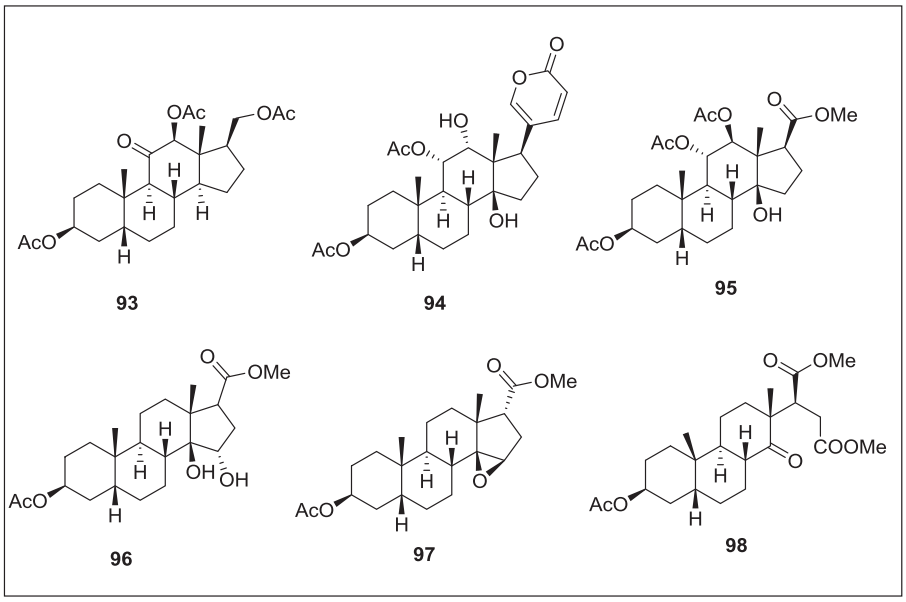

Fig. 13. Structure of cardenolides having MDR modulatory activity.

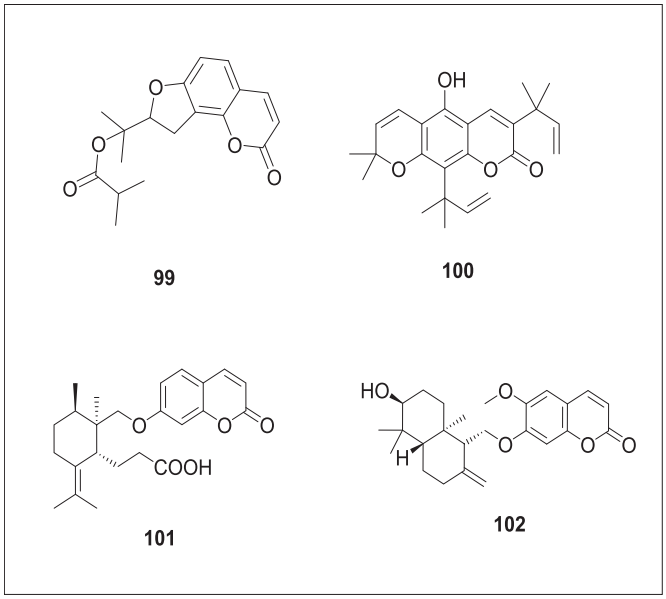

Fig. 14. Coumarin having MDR modulatory activity.

cancer agent [^{3}H]- vinblastine out of MDR1 transfected Madin–Darby canine kidney (MDCK-MDR1) cells, via competitive inhibition of P-gp transport activity. At 100 μM concentration, cnidiadin in combination with vinblastine killed 93% of cells [160]. In another systematic study from roots of *Citrus sinensis* (Rutaceae) led to the isolation of five coumarins, namely, clausarin (**100**), suberosin, poncitrin, xanthyletinand thamnosmonin. Among these compounds, clausarin (**100**) inhibited P-gp-mediated drug efflux in human leukemic cells, (K562/R7), which in daunorubicin accumulation assay showed a significant activity of about 45%, compared with cyclosporin A.

Further, two compounds from the roots of different species of *Ferula*, galbanic acid (**101**) (*Ferula szowitsiana*) and farnesiferol A (**102**) (*Ferula persica*) were evaluated for their P-gp inhibitory activity using a rhodamine123 efflux assay in MCF7/ADR cells. Both farnesiferol A (**102**) and galbanic acid (**101**) was found to be more potent than verapamil in terms of P-gp inhibition [161].

5.1.5. Terpenoids

Terpenoid is one of the most extensively studied and structurally diverse classes of natural compounds. Terpenoids can be classified based on the number of isoprene units in the parent structure such as monoterpenoids (C10), sesquiterpenoids (C15), diterpenoids (C20), sesterterpenoids (C25), triterpenoids (C30), tetraterpenes (C40) and polyterpenes. Terpenoids show a wide array of pharmacological activities including anticancer and inhibitory effects on primary ABC transporters (Fig. 15).

Lage et al. evaluated nineteen terpenoids from *Euphorbia* spp, for their antineoplastic and MDR modulatory activity. The group tested the compounds on gastric (EPG85-257), pancreatic (EPP85-181) and colon (HT-29) carcinomas and their resistant phenotypes (EPG85-257/RDB). Interestingly it was found that most of the compounds were more active in resistant cell lines as compared to parental sensitive cell lines. Lathyrane diterpene such as latilagascenes C (**103**) and D (**104**), diterpene lactone 3β-acetoxy helioscopinolide B (**105**) and helioscopinolide E (**106**) was found to be most active in resistant cell lines [162].

Hu et al. studied tanshinones isolated from Chinese herb *Salvia miltorrhiza* and tested their P-gp reversal activity by testing them in Caco-2 cell lines using digoxin bi-directional transport assay, doxorubicin efflux assay and western blot analysis for checking the expression of mRNA for P-gp. Out of five tanshinones, only cryptotanshinone (**107**) and dihydrotanshinone (**108**) was able to decrease digoxin efflux ratio in dose dependent manner as well as increase the substrate concentration in cancer cells. They were also found to downregulate the expression of P-gp which further supported their candidature to be developed as P-gp reversal agent in colon cancer [163].

Paris saponin VII (**109**) (PSVII), a saponin extracted from *Trillium tschonoskii* Maxim was assessed for their MDR modulatory potential by P-gp inhibitory activity and antineoplastic activity through induction of apoptosis in MCF-7/ADR breast cancer cell line. PSVII was found to exhibit P-gp inhibitory (tested by Rh123 accumulation assay) activity and reduced the expression of P-gp along with

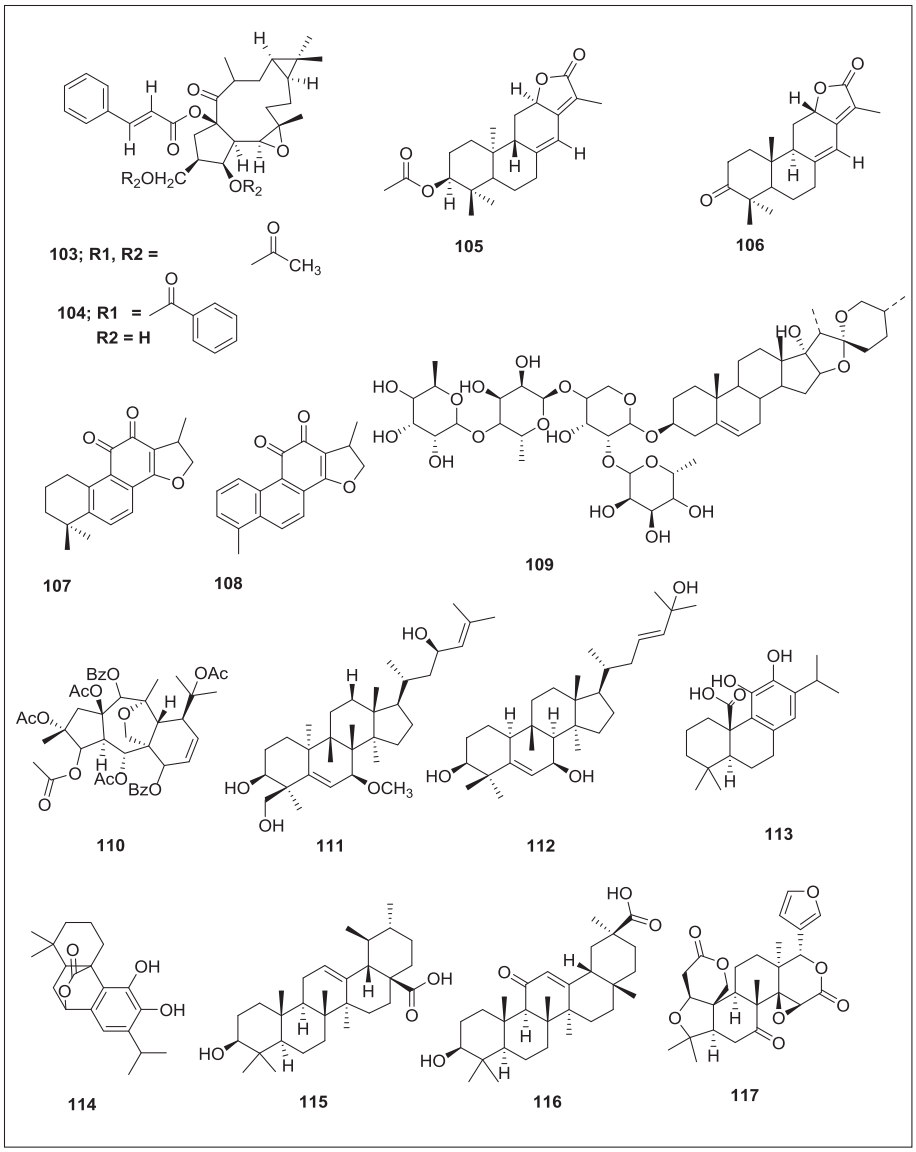

Fig. 15. Structures of plant terpenoids having MDR modulatory activity.

suppression of cell viability and sensitizing cells for apoptosis [164].

Recently a myrsinol diterpene J196-10-1 (**110**) isolated from traditional Chinese herb LANGDU, (dried roots of *Euphorbia prolifera* Buch-Ham) which was used in folklore medicine as an anticancer and anti-inflammatory activity, was evaluated for its MDR reversal activity using Rh123 accumulation assay, P-gp expression, and ATPase activity. The results suggested that it competitively inhibit (increase ATPase activity) the P-gp transporter and increase the substrate (Rh123) accumulation, but do not significantly alter mdr1 gene expression [165]. The crude extract of *Marsdenia tenacissima,* a traditional Chinese medicinal herb has been clinically used for the treatment of cancer. This herb was mainly used in combination with anticancer drugs and was found to inhibit P-gp mediated drug efflux. Later b11 polyoxypregnanes isolated from the herb as tenacigenin B derivatives with an oligosaccharide chain at C-3, acylated groups such as acetyl, benzoyl, 2-methylbutyryl, and tigloyl esters at C-11 and/or C-12, 12–14 and an epoxide ring at C-8 and C-14 out of which three were found to be active against MRP1, BCRP along with P-gp mediated drug efflux [166–168]. Besides the terpenoid compounds discussed above literature on terpenoids as active MDR modulators can be assessed form the review done by Yu et al. which also describes various structural characteristics required in terpenoids for their P-gp inhibitory activity e.g. the carbonyl group at C2, C3, C8 positions and a lipophilic substituent at C6 position is required for desired activity [80].

In a recent study by Ramalhete et al. on 30 cucurbitane type of triterpenoids of which 15 were isolated from *Momordica balsamina,* a plant native of Africa (also known as African pumpkin), and 15 were their molecular derivatives. These compounds were investigated for their MDR modulatory activity in human L5178 mouse T-lymphoma cell line transfected with the human MDR1 gene. Although all the isolated compounds have shown significant activity in rhodamine exclusion assay, compounds Balsaminol B (**111**) and Balsaminagenin C (**112**) were the most active at the lowest concentration tested and displayed strong MDR reversing activity in a dose-dependent manner as compared to their derivative [169]. Three terpenoids from rosemary namely carnosic acid (**113**), carnosol (**114**) and ursolic acid (**115**) were found to inhibit P-gp in KB-C2 cells and increases the cellular accumulation of daunorubicin and rhodamine 123 with increasing concentrations hence when

tested for their chemosensitization (at a concentration of 10 μM) in presence of vinblastine they significantly reduce the growth of cells. The compounds were also tested for their ATPase activity against verapamil as a standard and found to have comparable ATPase stimulatory activity at a concentration of 100 μM (as compared to 200 μM of verapamil) [170].

Similarly, one more dietary triterpenoid, glycyrrhetinic acid (**116**) from roots and stem of *Glycyrrhiza glabra* commonly known as licorice, was evaluated for its inhibitory activity on P-gp overexpressing KB-C2 cell and MRP1 expressing KB/MRP cell line using accumulation studies of daunorubicin (for P-gp) and calcein (for MRP1).

Limonin (**117**), a triterpenoid and well known constituent of citrus plants, exhibited potent P-gp inhibitory activity at concentration of 20 μM, when tested for its substrate accumulation by rhodamine 123 assay, cell cytotoxicity and cell proliferation by MTT assay and MDR reversal activity by chemosensitization of doxorubicin in parental leukemia cell line (CCRR-CEM), daughter adriamycin resistant leukemia cell line (CEM/ADR5000) and drug resistant human colon adenocarcinoma cell line (Caco-2). It decreases the IC_{50} value of doxorubicin from 42.13 to 19.14 μM a 2.2 fold enhancement in cytotoxicity. Similarly, it dose-dependently increases the intracellular rhodamine accumulation by inhibiting P-gp efflux [171].

5.2. Modulators from marine sources

Other than plants, the ocean is a vast source of natural products as 70% of the earth is covered by water and contains diverse life varieties nearly 80% of all life varieties. Marine natural products with various activities ranging from antiviral to anticancer have been isolated [172]. Drugs like Ziconotide, from a tropical cone snail for the treatment of pain, Cytarabine, from sponge for cancer, and vidarabine from sponge for the treatment of viral infections have been approved by US-FDA, and many are in various phases of clinical trials [173]. Marine-derived drugs such as macrolide eribulin mesylate and the peptide soblidotin are currently in phase III clinical trials for cancer and drugs like synthadotin, dolatostatin, bryostatin, and aplidin are some other drugs which are in phase I/II clinical trials [174–176].

5.2.1. Terpenoids

Isolated from *Callyspongia siphonella*, a red sea sponge, sipholane triterpenoids [(Sipholenol A (**118**), Sipholenone E (**119**), Sipholenol L (**120**) and Siphonellinol D (**121**)] (Fig. 15) possess modulatory activity against P-gp. They consist of two halves; one of them is a perhydrobenzoxepine, and another one is *cis*-decalin system linked together through an ethylene bridge [177,178]. Sipholenol A (**118**) was tested for its P-gp inhibitory and chemosensitizing activity along with vinblastine, colchicine, and paclitaxel in KB-C2 and KB-V1 cells, it was found to act by stimulating ATPase and inhibiting substrate binding to P-gp, and no change on P-gp expression was observed. Also, sipholenol A (**118**) is a specific inhibitor of P-gp and has no effect on MRP1 and BCRP. In one study 10 new sipholane triterpenoids were investigated for their P-gp modulatory activity in KB-3-1 (parent cell line) and KB-C2 cell line (P-gp overexpressing). Three out of ten compounds were found to interact with P-gp, namely sipholenone E (**119**), sipholenol L (**120**) and siphonellinol D (**121**) were able to reverse the colchicine resistance in cancer cells at a concentration of 10 μM. P-gp inhibitory activity of Sipholenone E (**119**) was better than that of sipholenol A (**118**), while two other were showing activity comparable to that of sipholenol A (**118**) and similarly showing no interaction with other ABC transporters. Sipholenol L (**120**) and siphonellinol D (**121**), like sipholenol A, also interact directly with P-gp, stimulate ATPase activity [174,177]. The ester derivatives (SWJ226 and SWJ32) of these compounds were found even stronger P-gp inhibitor in both *in vitro* (paclitaxel accumulation), and *in silico* studies than that of sipholenol A. The studies with ester derivatives were carried out in parental human colon cancer cell line SW620 and P-gp overexpressing SW620/Ad300 cell line resistant for doxorubicin and there reversal activities was determined by calculating fold-of-resistance (FR) (calculated by dividing the IC_{50} value for doxorubicin of SW620/Ad300 with or without reversal agent, or of SW620 in the presence of reversal agent by the IC_{50} value for doxorubicin of SW620 in the absence of reversal agent). Sipholenol A-4-*O*- acetate (**122**) and sipholenol A-4-*O*-isonicotinate (**123**) at a concentration of 5 μM reduce the FR to the extent of verapamil. These derivatives were also not active against MRP and BCRPs [179].

Parguerene I (15-bromoparguer-9(11)-ene-2,7,16,19-tetrol-2,7,16-triacetate)(**124**) and parguerene II (15-bromoparguer-9 (11)-ene-2,7,16,19-tetrol-2,7,16,19-tetraacetate)(**125**) (Fig. 16) are bromoterpenoids isolated in 1996 from *Laurencia filiformis*, a red alga from Australia. In a systematic study including a battery of tests (including calcein AM accumulation assay, Hoescht 33342 efflux assay, cytotoxicity assay, MDR reversal assay using vinblastine, paclitaxel, and doxorubicin) for evaluating MDR modulatory effect of these compounds was carried out by Huang et al., in 2013. In this study, approximately 1200 compounds from different marine sources were tested for their MDR reversal activity and came up with these two compounds. Perguerenes were further evaluated in human colon cancer cell line SW620 and its P-gp overexpressing daughter cell line SW620 Ad300 selected with doxorubicin (for P-gp), and the human lung cancer cell line NCI-H460 and BCRP overexpressing, mitoxantrone selected daughter cell line H460-MX20 (for BCRP). MRP1 modulatory activity was evaluated using HEK293/pcDNA3.1 and HEK293/ABCB1 transfected with either empty pcDNA3.1 vector or pcDNA3.1 vector containing ABCB1. At a concentration of 20 μM, these compounds have similar or activity as that of verapamil in calcein AM accumulation assay, Hoescht 33342 efflux assay, paclitaxel accumulation assay. Both compounds were active against P-gp and MRP1 but not for BCRP. Due to their differential interaction, compared to known inhibitors (verapamil and cyclosporine A), with extracellular antibody binding epitopes for P-gp, it was prosed that perguerenes interact with P-gp and induce conformational changes [180].

5.2.2. Alkaloids

Isolated from marine organisms such as a prosobranch mollusk (*Lamellaria* sp.), an ascidian (*Daphniphyllum chartaceum*), a sponge (*Dendrilla cactos*), and unidentified ascidians and belonging to polycyclic pyrrole-containing alkaloid; possessing chromenoindoles I scaffold, Lamellarins is another class of alkaloids from a marine source. Lamellarin such as lamellarin L, D, I, K and N were reported to have anticancer properties through various mechanisms. A lamellarin, i.e. lamellarin O **(126)** (Fig. 17) was tested in parent human colon cancer cell line (SW620) and P-gp overexpressing cell line SW620/Ad300 for their modulatory activity through calcein-AM accumulation assay, Hoescht 33342 efflux assay and MDR reversal assay in the presence of doxorubicin. At a concentration of 20 μM it increases calcein fluorescence by 85% of standard inhibitor (verapamil at 100 μM) and increases intracellular Hoescht 33342 2.5 fold as compared to 2.3 fold of positive control verapamil. IT also increases the sensitivity of resistant cell line by 4.8 fold at 15 μM as compared to 8.8 fold increase by positive control at 2.5 μM. Lamellarin O **(126)** was also an inhibitor of BCRP as suggested by its effect on mitoxantrone accumulation in parental NCI-H460 and BCRP overexpressing H460/MX20 cell lines where it increases mitoxantrone accumulation 94.5% that of FTC (100%) at 20 μM and reverses accumulation of radiolabeled mitoxantrone in

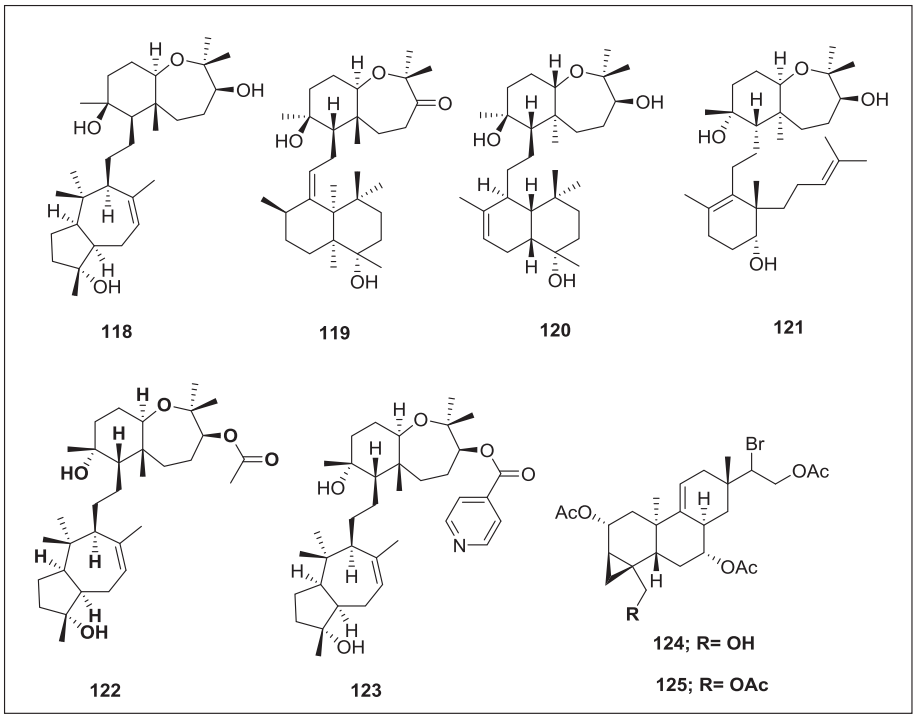

Fig. 16. Structures of marine terpenoids having MDR modulatory activity.

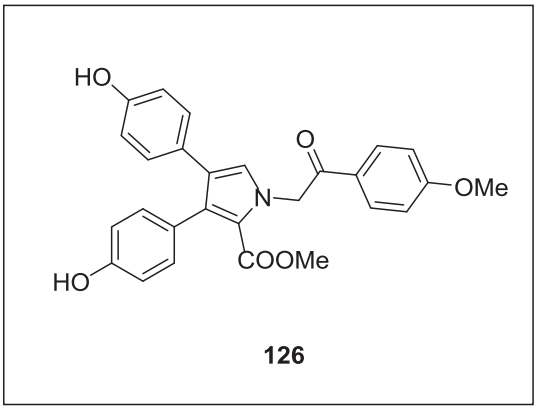

Fig. 17. Structure of marine alkaloids having MDR modulatory activity.

resistant cell line [181,182].

5.2.3. Peptides

Bioactivity-guided fractionation of the marine ascidian *Botryllus tyreus* collected along the coast of Papua New Guinea leads to a class of naturally occurring peptides, i.e. botryllamides; which are a group of dehydrotyrosine derivatives. In a study by Henrich et al. ten botryllamides was tested as inhibitor of BCRP in NCI-H460/MX20, BCRP over-expressing cell line. The activity was assessed against cellular accumulation of Pheophorbide A (PhA) a BCRP substrate withFTC as a positive control inhibition of BODIPY-prazosin efflux from ABCG2 transfected HEK293 cells, stimulation of ATPase activity and competitive inhibition of [^{125}I- iodoarylazidoprazosin (IAAP) labelling of BCRP. Among ten botryllamides tested for BCRP inhibitory activity botryllamide G (**127**) was found out be most active followed by botryllamide I (**128**) and J (**129**) (Fig. 18) [182,183].

5.3. Modulators from microorganisms

A new family of secondary metabolites obtained from the fermentation of a fungus isolated from soil of Brazil, i.e. *Asperagillus fischeri*. The fungus pathogens, 5-*N*- acetylardeemin (**130**) have MDR reversal activity, which was later confirmed by an extensive study by Chou and co-worker who reported non-toxic hexacyclic alkaloids, i.e. 5-*N*-acetylardeemin (**130**) and 5-*N*-acetyl-8-demethylardeemin (**131**) as potent reversal agents *in vitro* as well as *in vivo* (Fig. 19). Tested in four cell lines, they have increased the chemo sensitivity of anticancer drugs such as VCT, VBL, DOX, and PTX by interacting with P-gp as suggested by inhibition of the photo affinity labeling with [^{3}H] azidopine, a photoactivatable substrate of P-gp. In nude mice bearing MX-1 human mammary carcinoma xenografts 5-*N*- acetylardeemin (**130**) have reduced the tumor size by 75% in comparison to control group [143,144]. Studies conducted in P-gp, MRP and LRP (BCRP) positive and P-gp negative cell line suggests that these compounds can interact with MRP but not with LRP. Moreover, in some recent studies these compounds plus more isolates (5-*N*-acetyl-15β-hydroxyardeemin (**132**)) from fermentation broth of *Asperagillus fumigatus* have been found to posses MDR reversing activities in three cancer cell lines, doxorubicin resistant leukemia cell (K562/DOX), human cisplatin-resistant lung adenocarcinoma cell (A549/DDP), and cisplatin-resistant ovarian cancer cell (SK-OV-S/DDP) [184].

Nocardioazine A (**133**), a diketopiperazines alkaloid obtained from saline liquid cultures of *Nocardiopsis* sp. of bacteria isolated from Australian marine sediments, has emerged as a new class of natural compounds active against ABC transporters. Precisely it is prenylated diketopiperazines extracted from the liquid saline culture by fractionation with ethyl acetate. The compound was tested in P-gp overexpressing human colon cancer cell line (SE620/Ad300) by calcein-AM accumulation assay; nocardioazine A was found active in calcein-AM accumulation assay and MDR reversal assay with doxorubicin at a concentration of 20 μM [185].

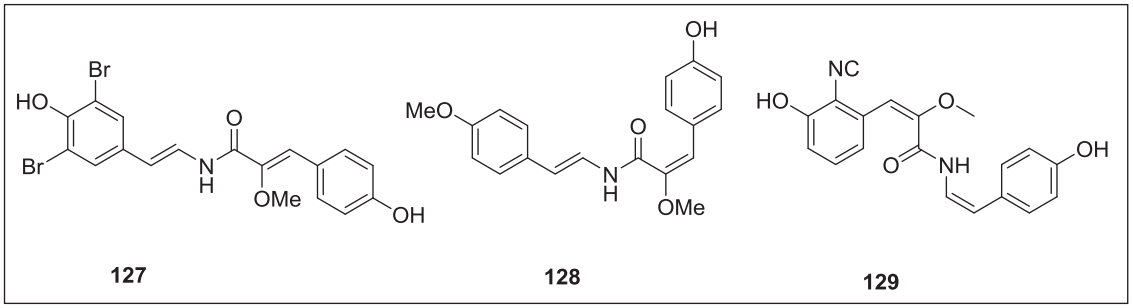

Fig. 18. Structures of marine peptides having MDR modulatory activity.

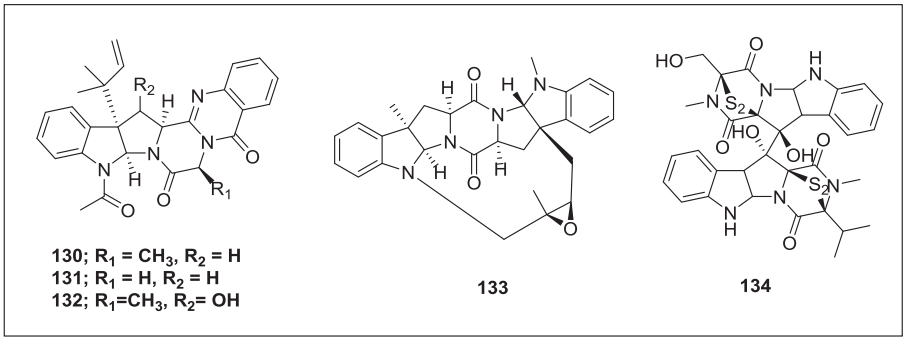

Fig. 19. Structure of compounds of microbial origin having MDR modulatory activity.

Recently, Du et al. isolated an epipolythiodiketopiperazine preussiadin A (**134**) from ascomycetous fungus *Preussia typharum* which was found to actively inhibit P-gp in isogenic cell line pair, the parental SK-OV-3 line and the P-gp-expressing clone SK-OV-3/MDR-1-M6/6 (M6/6) [186].

6. Challenges and future perspective

Nature has always been an important source of new drugs, new drug leads as well as new chemical entities which can be very well asserted from the figure that currently 60–70% of drugs in the market are directly or indirectly from natural products. Though the natural product drug discovery requires a lot of time and effort which starts right from collection of plant then its authentication and continuing with isolation of novel compounds and its targeted activity but, this process can be fasten by generating a library of previously isolated natural compound and using combinatorial chemistry, *in silico* approaches to have an idea about the binding and affinity of compounds towards a particular target as done by Chang et al., with WS-10 [76]. Another thing with natural product is quality and quantity of isolated compound which might not be sufficient for all the drug discovery process and poses a major challenge. However, this problem can be dealt through synthesis/semi-synthesis or by using tissue culture techniques. Also, screening methods for isolated compounds are very slow and time consuming where technologies like proteomics, which can detect or predict the activity of particular compounds for their desired outcome based on the analysis of different biomarkers, will be very helpful. Proteomics generates huge amount of multidimensional data such as protein structure, protein binding (both to other proteins, drugs and/or enzymes), its localization and expression. In a disease like cancer which involves an ocean of proteins involved in various pathways techniques like 2D-PAGE for identification of various biomarkers, MS, MS/MS, LC-MS/MS for identification and accurate quantification, protein microarray techniques for calculating protein-protein, protein-drug and protein enzyme interactions and lastly using bioinformatics for analysis the vast amount of data generated through these techniques. These techniques can be used in predicting the response of particular molecule in multidrug resistant cancer. As through these techniques we can have an accurate idea about the involvement of a particular ABC transporter protein and its interaction with drug in question, by using proteomics we can accurately quantify ABC transporters and which can serve as a basis for the success or failure of certain chemotherapies [187–189].

7. Conclusion

In summary, the MDR is a complex problem and need a multi-targeted approach. The studies discussed in this review shows that fourth generation of the MDR modulators will be of compounds of natural origin and success stories like that of tetrandrine/CBT-01® and its 5-bromo derivative has proven this by advancing to the stage of clinical trials. Similar to tetrandrine alkaloids there are quite promising leads from other class of natural products also. The need is to carefully and systematically scrutinize these active *in-vitro* leads which can be further synthesized (fully of partially) by medicinal chemists to avoid the shortage of supply which is one of major drawback of natural product related drug discovery. Also, chemists can also play a crucial role in fine tuning of the promising leads which can be developed into effective MDR modulators in the future. The modern methods such as QSARs will be beneficial for the researcher in designing highly selective and potent modulators with improved toxicity profiles. Also, modern techniques such as proteome based analysis of various biomarkers involved in drug action will greatly influence the drug development. As these techniques can help in predicting the response of natural as well as naturally derived drugs on various protein biomarkers involved in

cancer prognosis.

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Abbreviations

MDR	Multidrug Resistance
ABC	ATP Binding Cassette
P-gp	Permeability glycoprotein
BCRP	Breast Cancer Resistance Protein
MRP	Multidrug Resistance associated Protein
TMD'	Transmembrane Domain
NBD	Nucleotide Binding Domain
TMH	Transmembrane Helix
RRF	Resistance Reversal Factor
JAK/STAT	Janus Kinase/Signal Transducer and Activator of Transcription
US-FDA	United States Food and Drug Administration
QSAR	Quantitative Structure Activity Relationship
2D-PAGE	Two dimensional Polyacrylamide Gel Electrophoresis
ATP	Adenosine Triphosphate
DOX	Doxorubicin
Rh123	Rhodamine 123
ADR	Adriamycin
IAAP	Iodoarylprazosin
CAM	calcein AM
CMFDA	5-chloromethylfluorescein diacetate
IC_{50}	Inhibitory Concentration
PTX	Paclitaxel
VBT	Vinblastine
VCT	Vincristine
FTC	Fumitremorgin C
MS	Mass spectrometry

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