Review Article

P-Glycoprotein Inhibitors: A Review

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ABSTRACT

Permeability glycoprotein (p-gp) is a very important protein of cytomembrane that pumps several drug substances out of the cell. This ATP-dependent efflux pump with broad substrate specificity is responsible for the development of Multi Drug Resistance (MDR) in various types of cancers. The overexpression of this drug efflux transporter in the tumor cells is responsible for the reduced intracellular concentration of chemotherapeutic agents which fails cancer chemotherapy. P-gp inhibitors, also known as chemosensitizers are the drugs that make the tumor cell more sensitive to the effect of chemotherapy by inhibiting the function of p-gp which is overexpressed on the tumor cell. The present review gives an overview of the structure and function of p-gp. This review provides up-to-date information regarding the various types of natural, synthetic, and polymeric inhibitors of p-gp. Since there is no clinically approved p-gp inhibitor for the reversal of cancer MDR, this review provides the current status of the clinical trials of some major synthetic p-gp inhibitors. This review aimed to stress the discovery and development of novel, inert, non-toxic, more effective, and specific p-gp inhibitors and the use of natural compounds as an alternative to synthetic ones, as the former is associated with less toxicological effects.

Keywords: p-glycoprotein (p-gp), cancer chemotherapy, p-gp inhibitors, multi drug resistance, natural inhibitors, synthetic inhibitors, polymeric inhibitors.

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INTRODUCTION

Cancer is a leading cause of death worldwide accounting for nearly 10 million deaths in 2020 as per WHO report.[1] Multi Drug Resistance (MDR) is the major reason for the failure of cancer chemotherapy. MDR is the phenomenon in which cancer cells exposed to a single chemotherapeutic agent became resistant to other structurally and functionally unrelated chemotherapeutic agents. Different types of mechanisms have been reported to cause MDR. These include disruption of the apoptotic signaling pathway, gene amplification, activation of DNA repair, and overexpression of efflux transporter.[2]

ATP Binding Cassette (ABC) transporters are present in cellular and intracellular membranes and can be responsible for either importing or removing drug substances from cells and tissues. ABC transporters often transport substances against the concentration gradient by using hydrolysis of ATP to drive the transport. There are at least 49 ABC transporter genes which are divided into 7 different families based on sequence similarity. Three of these seven gene families are particularly important for drug transport and MDR in tumor cells. They are, one is ABCB1 gene encoding for Multi-Drug Resistance protein (MDR1) which is also known as p-glycoprotein (p-gp), the second one is ABCG2 gene encoding for Breast Cancer Resistance Protein (BCRP), the third one is ABCC family (C_1 to C_6) encoding for Multi Drug Resistance Protein (MRP).[3] It has been proposed that there is an ATP-dependent conformational change in the protein which causes the substrate to be pumped across the membrane.[4] The ABCB1 gene codes for glycosylated membrane protein. This protein was originally discovered by Ling and co-workers (1976) in the ovary cells of Chinese hamsters that showed resistance to colchicine, also displayed resistance to a wide range of other cytotoxic agents that differ in their chemical structure and mode of cytotoxicity with colchicine.[5] This drug efflux transport protein is commonly referred to as permeability glycoprotein (p-gp) or PGY1 or Multi Drug Resistance protein 1 (MDR1). It has been recently designated as Cluster of Differentiation 243 (CD 243).[6] P-gp confers MDR to tumor cells. Various tumors tend to display low initial levels of p-gp, with level of expression increasing after chemotherapy.[7] The role of p-gp in MDR was further confirmed by Tsuruo and colleagues (1981) who demonstrated that Verapamil (a first-generation p-gp inhibitor) increased the sensitivity of multi drug resistance leukemia cells to anti-cancer drugs. From these studies, there increases considerable interest in the development of p-gp transport inhibitors to combat drug resistance in chemotherapy.[8] Besides, being an important mediator of resistance in cancer chemotherapy p-gp is also found in bacterial cells and can contribute to developing

resistance to multiple antibiotics as well.[9] The following sections of this review give a brief overview of the structure, function, and cellular distribution of p-gp along with the mechanism of drug efflux by p-gp. To date, no p-gp inhibitors have been approved for clinical application. Therefore, this review provides information regarding the various types of natural, synthetic, and polymeric inhibitors of p-gp that are under development. Research has been carried out to develop novel p-gp inhibitors with better safety, efficacy, and specificity to combat cancer MDR.

STRUCTURE OF P-GP

The molecular structure of p-gp in the transport cycle has been investigated using various techniques such as tryptophan fluorescence[10], luminescence[11], anti-body binding[12], double electron resonance (DEER)[13], electron microscopy[14,15], and x-ray crystallography[16,17]. Crystal structure of p-gp has been determined in the mouse[16,17], c.elegans[18], and cyanidioschyzon merolae[19]. All of these p-gp structures exhibit similar conformations. P-gp is ~170 K Da surface glycoprotein with 1280 amino acids, encoded by human MDR1gene.[20] It comprises of two pseudo symmetric halves each containing extracellular Trans Membrane Domain (TMD) to which a wide range of substrates bind and intracellularly confined Nucleotide Binding Domain (NBD) which is also known as ATP Binding Cassettes (ABCs) that provides the energy necessary for the transport of substrate by binding and hydrolyzing two (or sometimes just one) molecule of ATP.[21,22] P-gp-mediated drug resistance depends on ATP hydrolysis, and ATPase activity of p-gp is stimulated by substrate drugs. ATPase is an enzyme that catalyzes the hydrolysis of phosphate bonds in ATP to form ADP and Pi. The energy released from the breakdown of the phosphate bond is utilized to pump the substrate drug out of the cell.[23,24] The current review describes in detail the TMD and NBD of p-gp and various conformations of p-gp.

Trans Membrane Domain (TMD)

P-gp consists of two Trans Membrane Domains (TMD1 and TMD2) that are 43% identical and each of which consists of 6 Trans Membrane helices (TM).[25] TMD1 comprises TM helices 1 to 6, and TMD2 comprises TM helices 7 to 12. The substrate-binding pocket resides in or near the TM6 of TMD1 and TM12 of TMD2.[22] Additionally, TM1, TM4, TM10, and TM11 are also involved in drug binding.[26] In the large and polyspecific drug-binding pocket of p-gp, amino acids in TM1 define the appropriate size of the substrate whereas Gly residue in TM2 and TM3 plays an important role in the assessment of substrate specificity.[25]

Nucleotide Binding Domain (NBD)

P-gp comprises two Nucleotide Binding Domains (NBD1 and NBD2) at the cytoplasmic side. Vanadate trapping and photocleavage experiments have shown that p-gp contains two active ATPase sites but only one ATP is hydrolyzed at a time.[27] Each ATPase comprising of 3 segments. They are walker A/B motif from NBD1 and LSGGQ motif (also known as C motif or signature motif) from NBD2. Walker A motif contains highly conserved Lys residue of histidine permease that has a direct role in the binding of ATP to p-gp.[28] Walker B motif contains highly conserved Asp residue that assists in the binding of Mg^{2+} ions which are essential for stabilizing the ATP binding site.[29] LSGGQ motif is present in ATPase of all ABC transporters but not in other ATPase, and it was thought to be involved in the transduction of energy of ATP hydrolysis to the conformational changes in TMD needed for the efflux of substrate drug.[30] Each ATPase site consists of highly conserved glutamate residue that acts as a catalytic base for ATP hydrolysis.[31] It is unclear why two ATPase domains are present in one transporter complex. Yet in most cases inactivation of one ATPase domain leads to the inactivation of the entire transporter in both humans and bacteria.

Conformations of p-gp

P-gp consists of two conformations. One is inward-facing conformation and another one is outward-facing conformation. In inward-facing conformation, two NBDs are separated from each other and two TMDs modulate drug-binding pockets, thereby enabling p-gp to recruit substrates of different sizes. In outward-facing conformation, two NBDs dimerizes and open the extracellular end of p-gp as a result of which the drug-binding pocket rearranges so that its affinity for the substrate decreases and the substrate drug is pumped out of the cell. In outward-facing confirmation, two ATP molecules are bound to stabilize the NBD dimer. Subsequent ATP hydrolysis which may occur at only one of the two catalytic sites reset the transporter to the inward-facing state thereby completing one transport cycle. The transition from the inward to the outward-facing conformation involves the global movement of two pseudo symmetric halves of p-gp as well as extensive local rearrangement of TM helices. The two crossing helices in each TMD (TM4 to 5 in TMD1 and TM10 to 11 in TMD2) pivot inward bringing NBDs closer to each other. In addition, the extracellular region of TM7 and 8 pull away from TM9 to 12 resulting in an outward-facing configuration. NBD/TMD interface is important in transmitting conformational changes associated with ATP hydrolysis to substrate binding sites.[32]

FUNCTIONS OF P-GP

P-gp has various physiological functions. Some important physiological functions of p-gp have been discussed in the following sections of the present review. Increased expression of p-gp in the intestinal epithelium can reduce the absorption of drugs that are p-gp substrates, thereby reducing bioavailability. Decreased expression of p-gp in the intestinal epithelium can enhance the plasma drug concentration of p-gp substrate drugs which may result in drug toxicity.[33] The expression of p-gp in the hepatocytes and renal epithelial cells is responsible for the removal of toxic metabolites and xenobiotics from the cells into bile and urine respectively.[34] Expression of p-gp at the luminal

surface of capillary endothelial cells of the brain is responsible for the transport of compounds out of the brain, thereby forming a BBB.[35] The expression of p-gp at the apical surface of foetal epithelial cells is responsible for the protection of the fetus from maternal toxins, thereby forming a blood-placental barrier.[36]

Studies carried out by Paul D.W. Eckford and Frances J.Sharom have concluded that p-gp functions as an outwardly directed flippase for endogenous membrane phospholipids and simple glycosphingolipids. P-gp reconstituted into proteoliposomes can be able to flip glycosphingolipids such as glucosylceramide (Glc Cer), galactosylceramide (Gal Cer), and sphingomyelin (SM) labeled with Nitrobenzo-2-oxa-1,3diazole (NBD) fluorescent label in ATP dependent manner. The rate of flipping of NBD labeled Phosphatidylcholine (PC) is very similar to that of NBD-glc cer and NBD-gal cer. NBD-SM, a phospholipid is also translocated by p-gp. However, NBD-Lactosylceramide (lac cer) shows a low rate of flipping by p-gp when compared to NBD-PC, probably due to increased size and hydrophilicity contributed by the additional sugar residue (Lactose is made up of one molecule of glucose and one molecule of galactose).[37] Sphingomyelinases are the enzymes that convert SM into ceramide. Glucosyl/Galactosyl ceramidases are the enzymes that break down Glc Cer and Gal Cer into ceramide. Rose Nganga et al reported various mechanisms for ceramide-dependent cancer cell death including apoptosis, necroptosis, autophagy, endoplasmic reticular stress, and cell cycle arrest.[38] The translocation of ceramide precursors such as SM and Glc Cer by p-gp from the inner to the outer leaflet of the plasma membrane may inhibit ceramide mediated signaling pathway including apoptosis which may lead to the progression of tumor cell growth. P-gp also inhibits downstream caspases such as caspase 8 and 3 in the apoptotic pathway. This may result in cell resistance to apoptosis. P-gp might inhibit caspase-dependent but not caspase-independent cell death.[39]

Platelet Activating Factor (PAF) is a phospholipid that acts as an inflammatory mediator. Human mesangial cells of the kidney secret PAF in response to glomerular injury and glomerulonephritis. PAF decreases glomerular filtration rate, renal blood flow, and electrolyte excretion in urine which may lead to glomerular damage. PAF is an endogenous p-gp substrate, treatment with a p-gp blocker or pre-incubation with p-gp antisense oligonucleotide inhibited the release of PAF from human mesangial cells that may be useful for reducing glomerular damage occurring in pathological conditions.[40] PAF secreted by the MDR tumor cells stimulates angiogenesis thereby promoting tumor cell growth.[41]

P-gp is also known to play a major role in the translocation of cytokines particularly Interleukin (IL)-1b, IL-2, IL-4, and Interferon-gamma (IFNg) from activated T-lymphocytes. Drach et al reported that IL-2 release was significantly suppressed by p-gp inhibitor verapamil and p-gp specific monoclonal antibodies. The release of IL-4 and IFNg was significantly inhibited by verapamil. However, the release of IL-6 remained unaffected. P-gp is also involved in the transendothelial migration of antigen-presenting dendritic cells and T-lymphocytes during the immune response.[42]

Besides transport function, p-gp also functions as a chloride channel regulator.[43] Drug efflux requires ATP hydrolysis while in contrast activation of chloride channel requires ATP binding only. [44] P-gp is bifunctional, the transport and channel regulatory functions of p-gp have been separated by direct mutations in NBD of p-gp. In Hela cells transfected transiently with cDNA encoding for p-gp has demonstrated that Protein Kinase-C (PK-C) mediated phosphorylation of p-gp regulates the activity of endogenous chloride channel indicating that p-gp is a channel regulator and not a channel itself.[45,46]

NATURAL P-GP INHIBITORS

There are a diverse group of natural substances that can inhibit the function of p-gp. Since the natural compound are associated with less toxicological effects, the use of herbal p-gp inhibitors is an innovative technique for reversing drug resistance in chemotherapy. Various p-gp inhibitors obtained from natural sources including Flavanoids, Alkaloids, Coumarins, Terpenoids, Sterides, Resins, and Saponins are elaborately described in the current review.

Flavonoids

Flavonoids are the polyphenol secondary metabolites of plants. The daily dietary requirement of flavonoids is up to 500mg. Several studies have reported the anti-inflammatory, anti-oxidant, pro-oxidant, anti-diabetic, cardioprotective, anti-viral, anti-bacterial, anti-aging, and anti-cancer effects of flavonoids.[47] They are classified into different sub-classes such as Flavones, Flavonols, Flavanones, Flavan-3-ols, Isoflavones, Chalcones, and anthocyanins. The basic carbon skeleton for all of these flavonoids is the same i.e a 2-phenylcromone with substituent groups attached at positions 2,3 or 4.

DHF & DHC

Zuccagnia punctata (family: Fabaceae) is monotypic species widely distributed in western Argentina. The two chemical components of this plant are 3,7-dihydroxy flavone (DHF) and ○2',4'-dihydroxy chalcone (DHC) have been reported to inhibit p-gp at a concentration of 3.2 and 6.0 mg\ml respectively on human proximal tubule cell line (HK-2).[48]

Quercetin

Quercetin isolated from the leaves of *Ginkgo biloba* was able to inhibit p-gp expression in MDR human cervical carcinoma cell line (KB-V1) at the 30mM range.[49] Shapiro and Ling hypothesized thay Quercetin has no direct effect on p-gp of Chinese hamster ovary cells.[49]

Kaempferol

Kaempferol isolated from *Kaempferia galanga* root caused a decrease in p-gp level in several human cancer cell lines. Limtrakul et al reported that treatment with 30mM Kaempferol was able to significantly decrease the p-gp level in the human cervical carcinoma cell line (KB-V1).[50]

Baicalein

Baicalein isolated from the roots of *Scutellaria* was able to inhibit p-gp. It was found that co-administration of Baicalein (0.5,3, and 10mg/kg) with Tamoxifen (10mg/kg) to rats significantly increased the oral bioavailability of Tamoxifen from 47.5 to 89.1%.[51]

Biochanin and Silymarin

Biochanin and Silymarin were isolated from the bark of *Aesculus hippocastanum* and seeds of *Milk thistle* respectively. Zhang and Morris reported that transport of digoxin from the apical-to-basolateral side in Caco-2 cells significantly increased with 50mM Biochanin and Silymarin indicating that these compounds can inhibit p-gp mediated efflux in Caco-2 cells and potentially increase the bioavailability of co-administered drugs that are p-gp substrates.[52]

Wogonin

Wogonin was extracted from the roots of *Scutellaria baicalensi* Georgi. It was reported that Wogonin significantly potentiate the etoposide-induced apoptosis in the human leukemia cell line (HL-60). Consequently, it is suggested that Wogonin may be used to reduce the excretion of anti-cancer agents via p-gp and enhance their pharmacological effect on cancerous cells.[53]

Genistein

Genistein is an important dietary requirement mostly present in vegetables like soybeans. Castro and Altenberg reported that Genistein inhibited the efflux of Rhodamine 123 in human breast cancer cell lines (MCF-7). Genistein also decreased the photo-affinity labeling of p-gp with [^{3}H] azidopine, a p-gp substrate, suggesting that genistein could inhibit p-gp mediated drug efflux by the mechanism that involves a direct interaction of genistein with p-gp. They also suggested that genistein cannot be used reliably to distinguish p-gp and MRP expressing multi drug resistant cells.[54]

Green Tea Polyphenols (GTP)

Jodoin et al suggested that GTPs (30mg/ml) inhibited the photo labeling of p-gp with [^{125}I] iodoarylazidoprazosin (IAAP) by 75% and increases the accumulation of Rhodamine 123 to three folds in CH^{R}C5, MDR cell line, indicating that GTP interacts with p-gp and inhibit its transport activity. Green tea contains many polyphenolic compounds. Flavanols, also called catechins are the major type of polyphenols found in green tea. Among all other catechins present in green tea, (-) epigallocatechin gallate (EGCG) pointedly interacts with p-gp and inhibits its transport activity, and could be used to modulate the functions of p-gp.[55]

Alkaloids

Alkaloids are the secondary plant metabolites containing one or more basic nitrogen atoms. The vast majority of alkaloids are reported to be present in higher plants especially in gymnosperms, angiosperms and few exist in lower plants. Existing literature has reported the ability of alkaloids to interact and prevent p-gp mediated drug efflux. Some important classes of alkaloids with reported p-gp inhibitory activity are discussed in the current review.

Quinoline, Isoquinoline, and Quinazoline alkaloids

Quinine, an isomer of Quinidine showed potent chemosensitization of 8226/DOX6 myeloma cells to doxorubicin at a concentration of 1mg/ml.[56] Quinine dimer showed inhibition of Rhodamine 123 efflux in human breast cancer cell line (MCF-7/DX1) at IC_{50} of 1.7mM and inhibition of [^{125}I] iodoarylprazosin (IAAP) labeling to p-gp.[57]

A benzylisoquinoline alkaloid, Sanguinarine isolated from the bloodroot of *Sanguinaria canadensis* reported inhibiting the p-gp mediated MDR by increasing the bax/bcl 2 ratio and thereby activating caspases.[58] Sanguinarine potentiated the cytotoxicity of Doxorubicin in Caco-2 cells by reducing the IC_{50} value by 18 folds. The IC_{50} value of Doxorubicin in Caco-2 cells was further lowered by 35 folds when Sanguinarine was combined with Digitonine.[59]

Another alkaloid named Chelidonine isolated from the *Chelidonium majus* has potentiated the cytotoxicity of Doxorubicin in p-gp overexpressing Caco-2 cells. Moreover, Chelidonine also inhibited the efflux of p-gp substrate dye, Rhodamine 123 at an IC_{50} value of 9mM.[60]

Similarly, another alkaloid named Berberine, a well-known substrate of p-gp isolated from the root and bark of *Berberis aristata* is reported to significantly enhance the bioavailability of Digoxin due to inhibition of gut p-gp.[61]

Tetrandrine, bisbenzyl isoquinoline alkaloid isolated from *Stephania tetrandra* completely inhibited the [^{3}H] azidopine labeling with p-gp in vincristine resistant KBV200 adenocarcinoma cell line at 2.5mM thus revered the resistance to vincristine in these cells. In-vivo studies confirmed that tetrandrine (also known as CBT-01) cannot inhibit the tumor growth itself but can enhance the cytotoxicity of vincristine in the KBV200 xenograft model in nude mice when given in combination with Vincristine.[62] A derivative of tetrandrine, known as 5-bromo tetrandrine or W198 exhibited cytotoxicity and anti-MDR activity in the KBV200 xenograft model in mice.[63] These two alkaloids i.e., CB-01 and W198 are advanced to clinical stages. Fangchinoline which is also a bisbenzyl isoquinoline alkaloid derived from the roots of *Stephania tetrandra* is known to enhance the cytotoxicity of paclitaxel in p-gp overexpressed colorectal cancer cell line (HCT15).[64]

Another bisbenzyl isoquinoline alkaloid named Cepharanthine is derived from the roots of *Stephania cepharantha.* Ikeda et al showed that cepharanthine enhanced the cytotoxicity induced by doxorubicin and vincristine in p-gp overexpressed human chronic myelogenous leukemia cell line (K562) and thus act as an MDR-reversal agent. Cepharanthine is predicted to interfere with the function of p-gp by interacting with the drug-binding pocket of p-gp.[65]

Indole alkaloids

Indole-3-carbinol and indole-3-carboxaldehyde are present in the cruciferous vegetables of genus *Brassica* and *Illicium simonsii* respectively, have the ability to modulate the overexpression of p-gp induced by vincristine, vinblastine, and doxorubicin as evident by western blotting and immunostaining.[66] Western blot analysis of vinblastine-resistant human leukemia (K562\R10) cells showed that indole-3-carbinol inhibited the level of p-gp expression in resistant cells.[67] So, indole-3-carbinol may be effective as a dietary adjuvant in the treatment of cancer MDR.

Indole alkaloids, reserpine, and yohimbine isolated from *Rauwolfia serpentina* inhibited the efflux of p-gp substrates such as doxorubicin, daunorubicin, vincristine, and teniposide in a human MDR leukemia cell line (CEM/VLB100) at a concentration of 5mM. It is noteworthy that by using pharmacophore modeling of reserpine and yohimbine analogs, the two important characteristics of alkaloids that inhibit p-gp such as basic nitrogen atom and appropriate conformation of the two aromatic rings were mapped for the first time. Pearce et al have demonstrated that for the interaction of reserpine type inhibitors with p-gp, the presence of a pendant aromatic ring represented by the benzoyl moiety is essential.[68] Reserpine also possesses BCRP inhibitory activity.[69]

Aspidofractinine type indole alkaloids such as Kopsiflorine and 11-methoxykopsilongine isolated from Malaysian plant *Kopsia dasyrachis* show good potential to reverse MDR in vincristine resistant KB cells.[70] Kopsiflorine is known to inhibit mRNA expression of the MDR1 gene.[71]

N-methylwelwitindolinone C isothiocyanate is a marine indole alkaloid isolated from *Hapalosiphon welwitschii,* potentiates the cytotoxicity of p-gp substrates such as actinomycin D and daunomycin in Ovarian serous cystadenocarcinoma cells (SKVLB-1). It also potentiates the cytotoxicity of vinblastine, taxol, actinomycin D, daunomycin, and colchicine in MDR breast carcinoma cells (MCF-7/DOX).[72]

Strychnous alkaloids, such as leuconicine A, leuconicine B isolated from *Leuconotis maingayi* and their synthetic analog 3,4,5-trimethoxybenzyl leuconicine A are potent MDR reversal agents and can inhibit the efflux of p-gp substrate drugs such as doxorubicin and vincristine in KBV20C and KB-MDR cell lines.[73]

β-Carboline indole alkaloids tabernines A-C were derived from a methanolic extract of the leaves of Tabernaemontana elegans, showing weak MDR reversal activity in human MDR1 gene-transfected and parental L5178 mouse lymphoma cell lines in Rhodamine123 efflux assay.[74]

Pyrrole alkaloids

Quesada and co-workers isolated a polyaromatic alkaloid, lamellarin from genus *Didemnun* which showed MDR reversal activity. It showed the reversal of p-gp mediated MDR in P388/Schabel cells by increasing the cytotoxicity of p-gp substrate drugs such as doxorubicin, vinblastine, and daunorubicin at a non-cytotoxic dose of 2mM.[75] Similarly, hexamethylated lamellarin (a semi-synthetic derivative of lamellarin) is reported as a potent p-gp inhibitor. Recently lamellarin O was isolated from southern Australian marine sponge, *Lanthella* species which possesses both p-gp and BCRP inhibitory potential. The sensitivity of doxorubicin increases to 5 folds in colon adenocarcinoma cells (SW620 DOX300) by lamellarin O at a concentration of 15mM.[76,77]

Boeger and co-workers reported several permethyl ningalin derivatives as potent MDR reversal agents. Permethyl ningalin B completely reverses the MDR, in comparison to verapamil at a concentration of 1mM. It also reduces the IC_{50} of doxorubicin and vinblastine by around 350 and 35 times respectively. A synthetic analog of permethyl ningalin B exhibited promising MDR reversal activity in p-gp overexpressing breast cancer cell lines by resensitizing them to paclitaxel by 18 folds.[78,79] Another alkaloid named permethyl storniamide A reduces IC_{50} of doxorubicin and vinblastine by 22 and 62 times respectively in the colon carcinoma cell line (HCT116/VM46).[80]

Recently Fu and co-workers isolated a rare alkaloid named cyanogrumide from the marine-derived fermentation broth of the *Actinoalloteichus cyanogriseus.* It is a chemically spirocyclic pyrrolo[1,2-c] imidazole alkaloid. It reverses the doxorubicin-induced resistance in chronic myelogenous leukemia cells (K562/A02) and breast carcinoma cells (MCF-7/DOX), and vincristine-induced resistance in an adenocarcinoma cell line (KB/VCR) at 5μM.[62]

Tropane alkaloids

Other compounds such as pervilleines A, B, and C are novel tropane alkaloid aromatic esters isolated from chloroform extract of the roots of *Erythroxylum pervillei.* These compounds showed p-gp inhibitory activity via inhibition of p-gp gene expression. Pervilleine A resensitizes the MDR adenocarcinoma cell line (KBV1) and lymphoblastic leukemia cell line (CEM/VLB100) to vinblastine with IC_{50} values of 0.36 and 0.02μM respectively. It restores the cytotoxicity of colchicine in human adenocarcinoma cells (KB-8-5) with an IC_{50} value of 0.61μM. Furthermore, pervilleine A does not modulate the p-gp gene expression, rather it inhibits the p-gp efflux pump by a physical mechanism that involves competitive inhibition of ATP-

dependant binding of [^{3}H] vinblastine to MDR KBV1 cell membrane vesicles.[81] Pervilleine B and C were unable to inhibit KBV1 cell growth when vinblastine, pervilleine B, and pervilleine C were administered as single agents. But when they were co-administered with vinblastine, these compounds tumor growth inhibition of up to 77.7% at a dose of 250mg/kg of vinblastine and 0.136mmol/kg of pervilleine B and C. However, when an equimolar dose of verapamil was tested, it was found to be less effective than pervilleine B and C.[82]

Chavez and co-workers isolated three tropane alkaloid esters from stems of *Erythroxylum rotundifolium,* which has been demonstrated to have a significant MDR reversal activity in the human adenocarcinoma cell line (KBV1) via interaction with p-gp. They were 6α-benzoyloxy-3R-(3,4,5-trimethoxycinnamoyloxy) tropane, 6α-benzoyloxy-3R-(E) (3,4,5-trimethoxy cinnamoyloxy) tropane-7α-ol, and 7α-acetoxy-6α-benzoyloxy-3R-(E) -(3,4,5- trimethoxy-cinnamoyloxy) tropane.[83]

Steroidal and indole alkaloids from *Veratrum* species viz…deoxypeganine, verabenzoamine, veratroilzigadenine, veranigrine, 15-O-(2-methylbutyroyl) germine, and veralosinine have been reported to reduce MDR in human MDR-1 gene transfected mouse lymphoma cells.[84]

Coumarins

Coumarins are the derivatives of benzo-a, a phytochemical with vanilla-like flavor. Coumarin is chemically an oxygen heterocycle. Coumarins are a wide class of compounds that are most commonly found in some essential oils such as cinnamon bark oil, cinnamon leaf oil, and cassia leaf oil. The plant families with the richest source of coumarins are Rutaceae, Araliaceae, and Umbelliferae. Coumarins are classified into four main sub-classes based on the position of substitutes and type in a-benzopyrone. They are simple coumarins, furanocoumarins, pyranocoumarins, and the sesquiterpene coumarins. Various types of coumarins were investigated for their ability to reverse MDR by inhibiting p-gp activity, which has been described in the current review. Road et al evaluated a set of 32 natural and synthetic coumarins for their ability to reverse MDR in p-gp overexpressing human leukemia cell line (K562/R7). They proved that the presence of a-(hydroxy isopropyl) dihydrofuran moiety and a phenyl group at C_4 is essential for the p-gp inhibitory activity of coumarins.[85]

Furanocoumarins

Cnidiadin, a furanocoumarin, isolated from *Tordylium apulum* belonging to the family Apiaceae. This compound was found to significantly inhibit the extrusion of rhodamine 123 and radiolabeled [^{3}H]-vinblastine, out of MDR1 transfected Madin-Darby Canine kidney cells (MDR1-MDCK) by acting as a chemosensitizer for p-gp and inactivating its transport function. When vinblastine was co-administered with cnidiadin at a 10mM concentration, the proportion of killed MDR1-MDCK cells (normal cell line) reached 93%.[86] Coumarins present in grapefruit juice such as bergamotin, FC726, bergaptol, and bergapten increased the steady-state uptake of [^{3}H]-vinblastine by Caco-2 cells due to inhibition of p-gp efflux. Bergaptol inhibits vinblastine efflux from human MDR1 cDNA transfected LLC-GA5-COL300 cells via inhibition of MRP2 function.[87]

Sesquiterpene coumarins

Galbanic acid isolated from the roots of *Ferula szowitsiana* has been reported to inhibit p-gp via competitive binding with p-gp active sites. Compared to verapamil, galbanic acid at a concentration of 5, 10, and 25mg/ml, significantly inhibited p-gp activity in the doxorubicin-resistant breast cancer cell line (MCF7/ADR).[88]

Farnesiferol A isolated from the roots of *Ferula persica* significantly inhibited p-gp activity in the doxorubicin-resistant breast cancer cell line (MCF7/ADR). Among farnesiferol A, B, and C, farnesiferol A at a concentration of 0.5mg/ml was more potent than verapamil in inhibiting p-gp transporter.[88] Similarly, driportlandin isolated from *Euphorbia portlandica* was more active in the reversal of MDR of mouse lymphoma cells than verapamil.[89]

Tricyclic coumarins

GUT-70, a tricyclic coumarin, derived from the stem bark of *Calophyllum brasiliense* collected in Brazil, acts on p-gp overexpressing the human leukemia cell line and inhibiting its drug efflux mechanism in a concentration and time-dependent manner with IC_{50} values from 2 to 5mM. The study indicated that GUT-70 may be a useful agent for the treatment of leukemia.[90]

Pyranocoumarins

(±)-Praeruptorin A (PA), a naturally existing pyranocumarin derived from the dried root of *Peucedanum praeruptorum* Dunn., re-sensitizes P-gp mediated MDR cancer cells to anticancer drugs. (±)-30 -O,40 -O-dicynnamoyl-cis-khellactone (DCK), which is a derivative of PA was more potent than PA or verapamil in the reversal of P-gp-MDR.[91]

Others

Decursinol, a major coumarin derived from the roots of *Angelica gigas*, showed high permeability in Caco-2 cell monolayers in the absorptive direction. Secretion increased in a concentration-dependent manner, with an efflux ratio of more than 2 at 50mM, indicating that it could be transported through an active efflux transporter such as P-gp, MRP, or BCRP.[92] In another study, bio-guided fractionation from the roots *Citrus Sinensis* (family; Rutaceae) led to the separation of five coumarins namely, clausarin, suberosin, poncitrin, xanthyletin, and thamnosmonin. Among all these compounds, clausarin inhibited p-gp transport activity in K562/R7 cells.[93]

Terpenoids

Terpenoids are derived from isoprene units joined in a head to tail manner. Isoprene is a chemically 5-carbon element known as 2-methyl 1,3-butadiene. Extensive research on the pharmacological activities of terpenoids revealed that terpenoids have an inhibitory effect on p-gp

via several mechanisms. Terpenoids are classified into monoterpenoids (C10), sesquiterpenoids (C15), diterpenoids (C20), sesterterpenoids (C25), triterpenoids (C30), tetraterpenes (C40), and polyterpenes.

Monoterpenoids

Citral is the main product of the lemongrass. Citral is found in various oils extracted from different plant species including *Lemon myrtle, Listea citrate,* etc. Citral can directly inhibit MRP2 but not MRP1 via binding to their active sites in isolated SF9-MRP1 and SF9-MRP2-membrane vesicles.[94] (R)- (+)-citronella, a monoterpenoid found in essential oil from *Zanthoxyli fructus* and also present in some edible plants. Citronella increases the apical-to-basolateral transport and decreases the basolateral-to-apical transport of [^{3}H] digoxin and thereby reduces the efflux ratio of [^{3}H] digoxin in Caco-2 cells, indicating that this compound could inhibit p-gp mediated transport.[30]

Sesquiterpenoids

N.R Perestelo et al isolated sixteen dihydro-b agarofuran sesquiterpenes from the fruits of *Maytenus jelskii* zahlbruchner, and evaluated against mammalian cells with MDR phenotype mediated by p-gp overexpression. Their stereo structures were elucidated by application of 1D and 2D NMR techniques including COSY, HSQC, HMDC, and ROESY experiments. All of these compounds were tested on human MDRI-transfected NIH-3T3 mammalian cells in order to determine their ability to reverse p-gp mediated MDR. All compounds were able to inhibit p-gp transport with low intrinsic cytoloxicity. Eight most efficient sesquiterpenes were able to reverse daunomycin and vinblastine resistance in MDR1 cells with reversal index values similar to or higher than first generation p-gp inhibitor, verapamil. Detailed structural activity relationship revealed that the presence of aromatic ester groups at C6 and C-9 are important for the MDR reversal activity of sesquiterpenes.[95]

Cortes et al reported the p-gp inhibitory activity of a series of 76 dihydro-b-agarofuran sesquiterpenes in his study. The compounds were evaluated for their ability to block efflux pumps on mouse embryo tissue fibroblast (NIH-3T3) cells overexpressing p-gp. The most important pharmacophoric features of these compounds were in the region of the substituents at the C-2, C-3, and C-8 positions. A 3D QSAR study concluded that the presence of two aromatic ester moieties and the size of the molecule are important factors that determine MDR reversal activity of sesquiterpenes.[96,97]

Two derivatives of the anti-malarial artemisinin SM616 and GHP-AJM-3/23 inhibited p-gp function in CCRF-CEM leukemia cells and in MDR CEM/Adr 5000 leukemia cells overexpressing p-gp.[98] Another compound known as b-caryophylene potentiated the anti-cancer activity of paclitaxel on MCF-7 colon adenocarcinoma (DLD-1), and murine fibroblast (L-929) cell line.[99]

Diterpenes

Various types of diterpenes including jatrophanes, lathyranes, uphoractine, pepluane and paraliane were isolated from euphorbia species and evaluated for p-gp inhibitory activity on mouse lymphoma cells by using rhodamine 123 efflux assay. Highly effective compounds can be found among the tetracyclic diterpenes.[100]

The macrocyclic cathyrane diterpene, latilagasceneB isolated from *Euphorbia lagascae* showed a very strong p-gp inhibitory activity in human MDR1 gene-transfected and parental L5178 mouse lymphoma cell lines.[101] Similarly, latilagasceneD-F and jolkinol B, isolated from the methanolic extract of same plant displayed a potent p-gp inhibitory activity on mouse lymphoma cells compared to verapamil.[102] The macrocyclic lathyrane polyester *Euphorbia* factor L_{10} derived from the seeds of the *Euphorbia lathyris* has a p-gp inhibitory activity.[103]

The Jatrophane diterpenes, Euphodendroidin D and Pepluanin A were the most powerful inhibitors of daunomycin efflux activity. Their activity was found to be atleast two folds higher than conventional p-gp inhibitor, cyclosporin A. Additionally other macrocyclic jatrophane diterpenes named, euphomelliferine and euphomelliferine A isolated from the methanolic extract of *Euphorbia mellifera* showed a significant MDR reversal activity on human MDR1-gene transfected mouse cells (L5178Y MDR) and on human colon adenocarcinoma cells (COLO 320). They did not induce apoptosis in COLO 320 cells.[104]

The tetracyclic diterpenes polyesters, euphoportlandols A and B were isolated from the acetone extract of *Euphorbia portlandica.* The compounds were evaluated for their p-gp inhibitory activity on MDR1-gene transfected L5178Y mouse T-lymphoma parentral cells, by using rhodamine 123 efflux assay. Both the compounds were found to have inhibitory activity on p-gp at a concentration of 40mg/ml.[105]

Helioscopinolides A, B, E, and F ent-abietane lactones, isolated from the *Euphorbia* species displayed p-gp inhibitory activity on human MDR1-gene transfected mouse lymphoma cells at a sub-cytotoxic concentration in a concentration-dependent manner.[106]

Limonoid

Obacunone, a limonoid isolated from *Phellodendron amurense* (family Rutaceae) displayed significant p-gp mediated MDR reversal activity on human colorectal cancer call line (HCT15) and human MDR uterine sarcoma cell line (MES-SA/DX5) with an ED_{50} value of 0.0011mg/ml respectively.[107]

Steroids

The basic chemical structure of steroids contains cyclopentanoperhydrophenanthrene with many substituents, which includes a hydroxy group at the C-3 position, methyl at the C-10 and C-13 positions, and different side chains at the C-17 position. They are

generally found on higher plants and have been used against various diseases, such as inflammation and cancer. Based on the type of substituent present at the C-17 position, sterides are classified into cardiac glycosides, steroid saponins, steroid hormones, and others. Some important plant-derived sterides with p-gp modulatory activities were described in this review.

Paris saponin VII(CS7) was isolated from *Trillium tschonoskii* maxim, modulated drug resistance of ovarian serous adenocarcinoma cell line (MCF-7/ADR) in a dose-dependent manner. PS VII treatment in MCF-7/ADR cells led to increased Tumor Necrosis Factor Receptor1 (TNFR1), TNF-related apoptosis-inducing ligand (TRAIL), Fas-associated death domain (FADD) expression, and activation of polymerase caspase-8 and 3. It also reduced the expression and activity of p-gp in MCF-7/ADR cells.[108] In another study, bio-guided fractionation of the roots of *Paris polyphylla* (family: rilliaceae) led to the isolation and identification of three steroidal saponins, namely 3-O0Rha (1→2) [Ara (1→4)] Glc-pennogenine, gracillin, and polyphyllinD. These three compounds showed strong inhibition of p-gp mediated daunorubicin efflux in the human leukemia cell line (K562/R7) when compared to cyclosporin A.[109]

Ginsenoside Rg3, isolated from *Panax ginseng* displayed MDR reversal activity in drug-resistant human oral squamous cell carcinoma cell line (KBV20C) by promoting the accumulation of rhodamine 123 in these cells. Photo-affinity labeling study with [^{3}H] azidopine revealed that Rg3 is a competitive p-gp inhibitor that can compete with anti-cancer drugs for binding to p-gp, thereby blocking drug efflux.[110] Another steride, known as protopanaxatriol ginsenosides (PTG), isolated from the same plant species showed MDR reversal activity on daunorubicin-resistant acute myelogenous leukemia cell line (AML-2/D100) overexpressing p-gp in a concentration-dependent manner. Moreover, PTG at a concentration of 200mg/ml or more completely inhibited the [^{3}H] azidopine photo-labeling of p-gp indicating that PTG has a chemosensitizing effect on p-gp mediated MDR cells.[111]

Tenacissimoside A and 11R-O-benzoyl-12-O-acetyltenacigenin B, two derivatives of tenacigenin B, isolated from the plant *Marsdenia tenacissima*, has been reported to reverse the MDR in p-gp overexpressing doxorubicin-resistant human liver cancer cell line (HepG2/DOX). This compound increases the sensitivity of HepG2/DOX cells to the anti-cancer drugs doxorubicin, vinblastin, puromycin, and paclitaxel.[112]

Astragaloside II, isolated from the plant *Astragalus membranaceus* (family: Fabaceae) which is widely used in traditional Chinese medicine. It showed a strong potency to increase 5-fluorouracil (5-FU) cytotoxicity towards 5-FU resistant human hepatic cancer cells (Bel-7402/FU), by downregulating the expression of p-gp and MDR1 genes. It can significantly increase the intracellular accumulation of rhodamine123 via inhibition of p-gp transport function.[113]

Taccalonolides isolated from *Tacca chantrieri* is a microtubule-stabilizing agent. Taccalonolide A and E showed potent p-gp inhibitory activity on paclitaxel and doxorubicin-resistant p-gp overexpressing syngenic murine mammary adenocarcinoma model (Mam17/ADR). Taccalonolide A and E at a dose of 38mg/kg and 86mg/kg respectively, showed excellent anti-tumor activity with 91% tumor growth inhibition. Taccalonolides have advantages over the taxanes (conventional microtubule-stabilizing agents) in their ability to circumvent MDR mechanisms including overexpression of p-gp, MRP7, and b III isotypes of tubulin.[114]

Resins

Resins are amorphous products of complex nature derived from various plants exudates. Some resins have been reported for their p-gp inhibitory activity. Gambogic acid is a xanthonoid that is derived from the brownish or orange resin *Garcinia hanburyi.* Gambogic acid can inhibit ABCB1 activity. The co-incubation of gambogic acid with cytotoxic drugs such as vincristine, Adriamycin, and docetaxel resulted in lower IC_{50} values than a single chemotherapeutic agent in the MDR breast cancer cell line (MCF-7/ADM) and human oral squamous cell carcinoma cell line (KB/VCR). Xu Wang et al suggested that gambogic acid functions as a non-competitive inhibitor of ABCB1 by directly inhibiting and reducing its expression levels by promoting protein degradation through the post-translational proteasome pathway.[115]

SYNTHETIC P-GP INHIBITORS

Synthetic p-gp inhibitors (also known as small molecule inhibitors) are synthesized by using various approaches. All of these compounds do not share any properties in common, except that they are p-gp inhibitors. Concurrent administration of p-gp substrate therapeutics with these p-gp inhibitors can prevent the substrate expulsion by p-gp thereby increasing the intracellular concentration of the substrate drug. Synthetic p-gp inhibitors are mainly classified into first, second, and third-generation inhibitors based on their affinity, specificity, and toxicity. The two major limitations of these p-gp inhibitors are their unwanted immunosuppressive and cardiovascular effect, which halts their clinical development.

First-generation inhibitors

The first-generation inhibitors are developed based on screening among the available compounds that already have some proven clinical use but were later observed to be p-gp substrate cum inhibitors. They include verapamil[116,117](calcium channel blocker), cyclosporine A[117,118] (an immune suppressant), a calmodulin antagonist[119] (trifluoperazine, clopenthixol, trifluopromazine, and flupenthixol), chlorpromazine, prochlorperazine, anti-malarial quinine, anti-arrhythmic quinidine, reserpine, yohimbine, anti-neoplastic vincristine, tamoxifen, and toremifene reported to possess p-gp inhibitory activity.[120] Verapamil was found to increase the intracellular concentration of many cytotoxic drugs

including doxorubicin in numerous cancer cell lines.[116] Further studies found that other calcium channel blockers such as diltiazem, bepridil, nicardipine, nifedipine, felodipine, and isradipine also possess p-gp inhibitory activity.[119,121,122] Many of these drugs are competitive p-gp inhibitors. However, these drugs require high serum concentration to inhibit p-gp above the approved therapeutic range due to which many of these inhibitors failed in clinical trials. Cyclosporin A is considered a golden first-generation inhibitor.

Second-generation inhibitors

Second-generation inhibitors are developed by the structural modifications of first-generation inhibitors. Their chirality was altered to reduce the toxicity of the parent compound and to achieve the better p-gp inhibitory activity. These inhibitors include dexverapamil[123](R-enantiomer of verapamil), valspodar, or PSC 833 (a non-immunosuppressive analog of cyclosporin A), emopamil, gallopamil, and roll-2933 inhibited p-gp activity in-vitro.[124,125] However, these inhibitors are inevitable cytochrome P450 3A4 substrates for metabolism, thereby altering the pharmacokinetic profile of the concurrently administered anti-cancer p-gp substrate which are metabolized by the same enzyme system. As a result, there occurs difficulty in adjusting the chemotherapeutic dose in cancer patients.[126,127]

Third-generation inhibitors

Third-generation inhibitors are synthesized by using combinatorial chemistry and Quantitative Structural Activity Relationship(QSAR) approaches. These approaches led to the discovery of compounds with high specificity and low toxicity and they are 10 times more potent than previous generation inhibitors. Since these agents are not the substrates for CYP3A4, they do not show any alterations in the pharmacokinetics of co-administered anti-cancer agents. Third-generation inhibitors include zosuquidar (LY335979)[128], elacridar (GF120918)[129], XR9051[130], OC144-093[131], biricodar(VX-710)[132], timcodar (VX-853)[132], tariquidar(XR9576)[133] and others. VX-710 and VX-853 are known to possess both p-gp and MRP inhibitory activity. Moreover, XR9576 showed unacceptable adverse events in the phase-II clinical trials which halt its clinical development. Due to serious toxic effects associated with these synthetic inhibitors, there is a need to develop more effective, highly specific, and less toxic p-gp inhibitors.

POLYMERIC P-GP INHIBITORS

Pharmacologically inert, polymeric pharmaceutical excipients have been reported to inhibit p-gp efflux pumps. Several types of natural and synthetic polymeric p-gp inhibitors are discussed in the current review. They inhibit p-gp efflux pump by acting on the lipid membrane and are associated with fewer adverse effects.

Natural polymeric p-gp inhibitors

Several natural polymers such as Anionis gums, sodium alginate, and dextran has been reported to possess efflux pump inhibitory activity.

Anionic gums

Among the anionic gums, Xanthan gum and gellan gum has reported possessing p-gp inhibitory activity. They both are used as food additives. Xanthan gum is produced by a process involving the fermentation of glucose or sucrose by the *Xanthomonas campestris* bacterium. The p-gp inhibitory activity of xanthan gum at a concentration of 0.5mg/ml was evaluated by using everted gut sac model. It increases the accumulation of p-gp substrate drugs vinblastine and doxorubicin in gut cells. Similarly, gellan gum synthesized by the bacterium *Sphingomonas elodea* at a concentration of 0.5mg/ml improved the serosal transport of vinblastine and doxorubicin.[134]

Sodium alginate

Alginates are natural linear co-polymers that consist of b-(1-4)-linked D-mannuronic acid and b-(1-4)-linked L-guluronic acid units. Alginates such as flavicam and Ascophyllum have been evaluated for their efflux pump inhibitory activity, using everted gut sac model. Flavicam is derived from *Lessonia flavicam.* Flavicam at a concentration of 0.5mg/ml increased the accumulation of doxorubicin but no effect is observed on vinblastine accumulation. Ascophyllum derived from *Ascophyllum nodosum,* enhanced the vinblastine and doxorubicin accumulation in everted gut sac cells at a concentration of 0.5mg/ml. Furthermore, the serosal transport of vinblastine was enhanced but not of doxorubicin. Ascophyllum also increased the blood levels of vinblastine to 1.7 folds in comparison to control, when administered at a concentration of 250mg/kg through oral gavage in rats.[134]

Synthetic polymeric p-gp inhibitors

A wide variety of synthetic polymers are used in pharmaceutical applications that contribute to an improved action of drug formulation. For example, a naturally derived polymer (chitosan) enhances drug permeation through biological membranes via the opening of tight junctions.[135] It has been reported that various synthetic polymers can inhibit efflux pumps. They are polyethylene glycol(PEG), PEG-based detergents, poloxamers, dendritic polymers, and thiolated polymers.

Polyethylene glycol (PEG)

PEGs such as polyethylene oxide (PEO) glycol and polyoxyethylene (POE) glycol are the polymers produced via the polymerization of ethylene oxide molecules. Johnson et al reported that PEG 400 at a concentration of 1-20% markedly reduced the basolateral to apical transport of digoxin when tested using stripped rat jejunal mucosa indicating that PEG 400 is an efflux pump inhibitor.[136] Shen et al showed that different

concentrations of PEGs (0.1-20% v/v or w/w) inhibited the secretory transport of rhodamine 123 in isolated rat intestine.[137] Hugger et al demonstrated that the permeation of doxorubicin and paclitaxel through Caco-2 monolayer was improved in the presence of PEG 300. The mechanism by which PEG 300 inhibits the efflux pump was mediated by changes in the microenvironment of Caco-2 cell membranes. PEG 300 at a concentration of 20% v/v caused complete inhibition of p-gp in Caco-2 and MDR1-MDCK cell lines.[138] Whereas, cremophor® EL(0.1%) and Tween® 80 (0.05% w/v) only partially inhibited p-gp activity in Caco-2 cells and not at all inhibited p-gp activity in MDR1-MDCK cell monolayers.[139]

PEG-based detergents

It has been reported that various polymeric surfactants including D-alpha-tocopheryl polyethylene glycol succinate 1000, polysorbates as well as POE stearates, and alkyl-PEO surfactants can inhibit efflux pumps.[140]

D-alpha-tocopheryl polyethylene glycol succinate 1000(TPGS 1000):

TPGS 1000 has been used as a solubilizing agent, an emulsifier, and lipid-based drug delivery. Varma and Panchnagula reported that TPGS 1000 can improve the oral bioavailability of p-gp substrate paclitaxel by inhibiting p-gp. A formulation containing 25 mg/kg paclitaxel and 50 mg/kg TPGS 1000 improved the oral bioavailability in rats to about 6 folds.[141] collnot et al investigated the relationship between the length of the alkyl chain of various TPGS derivatives and their efflux pump inhibitory activity. Results have shown that TPGS 1000 is the most potent p-gp inhibitor among other TPGS derivatives ranging from TPGS 200 to 6000.[142]

Polysorbates:

Polysorbates are PEGylated sorbitanes esterified with fatty acid. They are commonly known under the brand name tween®. Different types of tween® 20 (polyoxyethylene sorbitan monolaurates), tween®40 (polyoxyethylene sorbitan monopalmitate), tween® 80 (polyoxyethylene sorbitan monooleate). Friche et al (1990) demonstrated that 0.01% v/v of tween® 80 increased the accumulation of daunorubicin in resistant Ehrlich ascites tumor cells.[143] In another study, it has been reported that the efflux ratio of rhodamine 123 was reduced in the presence of tween® 80 with excised rat intestinal mucosa.[144]

POE stearates and alkyl-PEO surfactants:

According to some studies, POE stearates commonly known as (Myrj®) and alkyl PEO surfactants (commonly known as Brij®) can inhibit efflux pump. Lo demonstrated an improved intracellular accumulation of epirubicin in the presence of POE 40 stearate using Laco-2 cells. The results indicate POE 40 stearate mediated efflux pump inhibition.[145] Foger et al reported that POE 40 stearate increases the oral bioavailability of p-gp substrate Rhodamine 123 in rats to about 2.4 folds.[146]

Poloxamers

Poloxamers are block co-polymers consisting of ethylene oxide (EO) and propylene oxide (PO) segments. Poloxamers are commonly known under the brand name Pluronics®. They are the functional excipients that can affect the immune response and wound healing.[147,148] The efflux pump inhibitory activity of Pluronics® is used in the following areas. (1) Blood-Brain Barrier drug delivery and (2) Cancer chemotherapy. Pluronics® can inhibit efflux pumps through any of the two mechanisms. (a) Pluronics® mediated ATPase inhibition and ATP depletion (b) Effect of Pluronics® on membrane fluidization.[149] Pluronics®P85 has a molar mass of about 4,600 Da and is known for its efflux pump inhibitory activity. Apart from Pluronics®, another copolymer CRL-1605 has already been used successfully to improve the oral bioavailability of tobramycin and amikacin via p-gp inhibition.[150]

Dendrimers

Dendrimers (also known as dendritic polymers) are completely synthetic macromolecules with a defined structure. Dendrimers are used in anti-cancer drug delivery systems[151], gene delivery, and imaging[152]. Various studies have reported the efflux pump inhibitory activity of dendrimers. D'Ëmanuele et al showed that the conjugation of p-gp substrate propranolol to generation-3(G3) and lauroyl-G3 polyamidoamine dendrimers improved apical to basolateral transport and decreased basolateral-to-apical transport through Caco-2 cell monolayer. The mechanism probably involves circumvention of p-gp transporter rather than p-gp inhibition. The accumulation of vinblastine and doxorubicin increased with everted gut sac model to about 3-4 folds in the presence of G3 dendrimers, indicating a possible efflux pump inhibition.[153]

Thiomers

Thiomers (also known as thiolated polymers) are multifunctional polymers used in buccal, nasal, ocular, oral, and vaginal delivery. Studies demonstrated that the thiomer chitosan thiobutyl amidine (chito-TBA) improves the apical-to-basolateral transport of p-gp substrate Rhodamine 123 through excised guinea pig ileal mucosa and decreases basolateral-to-apical transport of substrate.[154] Foger et al showed that oral administration of tablets containing a combination of chito-TBA and glutathione led to improved bioavailability of rhodamine 123 in rats, in comparison to tablets based on either poloxamer or Myrj®.[155]

CLINICAL TRAILS CONDUCTED ON P-GP INHIBITORS

Chico et al conducted a phase-I study of 7-day oral administration of PSC-833 (valspodar) in combination with paclitaxel, administered as a 96-hour continuous infusion. The results obtained from these studies revealed a similar mean steady-state concentration and area under the concentration vs time curve (AUC) when patients received paclitaxel at a dose of 13.1 or 17.5 mg/m(2)/day for 4 days with PSC833 as when they received a paclitaxel dose of

35mg/m(2)/day for 4 days without PSC833. Surrogate assay with CD56+ cells suggested that the maximum tolerated dose for PSC833 gives serum levels much higher than those required to block p-gp.[156] Fracasso et al conducted a phase-I study of paclitaxel in combination with a second-generation p-gp inhibitor, PSC 833, in refractory malignancies to determine the maximum tolerated dose (MTD), dose-limiting toxicity, and pharmacokinetics of paclitaxel when given with PSC 833 to patients with refractory solid tumors. Treatment with paclitaxel 122.5 mg/m(2) as 3 hours of continuous intravenous infusion along with 29 hours of continuous intravenous infusion of PSC 833 increases the peak plasma concentration and AUC of paclitaxel.[157] Similarly, another phase-I study was conducted to determine the MTD of doxorubicin and paclitaxel when co-administered with valspoder. 33 patients with various refractory malignancies were enrolled and received doxorubicin as 15 min infusion followed by paclitaxel as a 1-hour infusion for the first cycle. And for the second cycle patients received reduced doses of doxorubicin and paclitaxel with PSC 833 at 5 mg/kg p.o four times a day for 12 doses. PSC 833 significantly altered the pharmacokinetic profile of these two drugs, requiring approximately 60% dose reduction for an equivalent degree of myelosuppression.[158] Bates et al conducted a phase-I study of orally administered PSC 833 in combination with vinblastine administered as a 5-days continuous infusion.[159]

CONCLUSION AND FUTURE PROSPECTIVE

A combination of a chemotherapeutic agent with a p-gp inhibitor might provide an interesting approach to overcoming MDR in cancer patients. Over the past few years, significant progress has been made in understanding the pharmacological and physiological role of P-gp. However, many questions about P-glycoprotein remain unanswered, including its physiological role in the cell and the mechanism by which it effluxes a wide variety of molecules out of the cell. An understanding of the structure, cellular distribution, functional features, and mechanism of drug efflux by p-gp will facilitate the development of potential p-gp inhibitors or modulators. This review also summarizes the various types of natural, synthetic, and polymeric p-gp inhibitors. Among all other types of p-gp inhibitors, plant-based inhibitors mentioned in this review could provide insights into a wide range of possibilities of using different methods to develop effective P-gp inhibitors. The safe, non-toxic nature of herbs makes them stand out and are unique forever. Though the upcoming research identifies and develops countless candidates from these classes, only the clinical trial reports can establish them as perfect rational P-gp inhibitors. Hopefully, future research will provide more data to unwind the mystery behind this complex protein to investigate the physiological function and pharmacological role of P-gp/MDR1, and considerable efforts will focus on attempts to reverse MDR and increase the bioavailability of chemotherapeutic agents.

Conflict of Interest: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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