Chapter

P-Glycoprotein Efflux Transporters and Its Resistance Its Inhibitors and Therapeutic Aspects

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Abstract

P-glycoprotein (P-gp) is an active member of the ATP Binding Cassette (ABC) protein subfamily which effluxes a wide range of therapeutic drugs out of the cells commonly known as multidrug resistance. But its protective action towards the normal cells and efflux of the toxic and foreign substances is remarkable. Hence the efflux of the P-gp is a crucial step to overcome for the success of the therapy and in the drug discovery process. Modification of the action of the P-gp through various inducers, inhibitors or the genetic polymorphism is the commonly used methods. When it comes to the inhibitor part the natural inhibitors use is more safe and economical as compared to the synthetic ones. Here we review at the mechanism of action and the pharmacokinetic profile of P-gp, how the P-gp engaged in the Multidrug resistance, the strategy to overcome from its action by using natural inhibitors and formulation perspectives.

Keywords: P-glycoprotein, multidrug resistance, mechanism of action, pharmacokinetics, P-gp inhibitors, natural inhibitors

1. Introduction

Reduce in the remedial rate of most of the diseases and the decline in the therapeutic efficacy of most of the anti-neoplastic and anticancer drugs is due to the phenomena called drug resistance [1]. The main ambiguity to be found out to increase the efficacy of the drugs is to overcome this phenomenon. The drug resistance is not observed to a single chemotherapeutic drug but to a broad range of structurally and functionally different drugs. The exposure to a single therapy for a long time and the recurring use of the medication leads to drug resistance will leads to decrease in the therapeutic efficacy of the drugs. Even if the dose is altered there would not produce any momentous changes in this phenomena [2]. When the human acquired resistance to the drugs it is termed as drug tolerance. This was usually seen of two type's pharmacokinetic drug tolerance and pharmacodynamic drug tolerance.

2. Metabolic or pharmacokinetic tolerance

Followed by the entry of the drug in our body with the time it gets absorbed into the bloodstream, which is then carried out and distributed to various other sites, additionally gets disintegrated into various segments and eventually gets excreted from the body. All these factors determine the potency, side effects and duration of action of the drugs. The major reason for the pharmacokinetic tolerance is when the drug fails to maintain its minimum therapeutic concentration at the target site. Where, in this case the enzymatic action of cytochrome P450 (CYP450) produces the effect. This type of tolerance is mainly determined with the oral dosage form which produces first pass metabolism. Induction of the enzymes are the major reason behind the drug resistance which is further accompanied with various other factors which is further disused in this chapter in detail.

3. Pharmacodynamic tolerance

When the cellular feedback to a substrate is concentrated the development of the pharmacodynamic tolerance eventually occurs. The principle reason behind pharmacodynamic tolerance is when the therapeutic concentration of the substrate to the binding receptors reaches above the maximum therapeutic concentration which eventually results in the desensitisation of the receptors [3]. Other possibilities include the decline in the receptor density which is mainly associated with the receptor agonist and the modification in the action of the possible firing rate. Generally the drug resistance will occur subsequent to the incessant exposure to the drug, but instant tolerances were also observed in rare cases [4].

4. Factors responsible for drug resistance

There are a variety of drug resistance usually seen such as anticancer resistance, anti-human immunodeficiency virus (HIV) drug resistance, antibiotic resistance, anti-tubercular drug resistance, anti-malarial drug resistance and anti-microbial drug resistance. The most part of the drug resistance is caused by MDR proteins, where in this P-gp (P-glycoprotein) involves in producing a major aspect in reducing the drug efficacy in most of the treatment. P-gp, which is a trans-membrane (TM) glycoprotein physiologically, expressed in the parts of the body such as kidney, liver, pancreas, colon and jejunum [5], it also expresses its role eventually in the brain capillary epithelial cells. The core function of P-gp is to safeguard the cells and restrict the entry of xenobiotics and toxic substances. But its action is over-expressed in the diseased cells by restricting the entry of the drugs hence its action should be inhibited in such cases for the success in the therapy.

5. Transporters and its family

P-gp is an efflux protein system associated with the ATP binding cassette (ABC) sub-family B membrane or Multi-drug resistance 1 (MDR1) or cluster of differentiation 243 which belong to ABCB (MDR) super family of ABC transporter [6]. ABC gene indicates the leading family of TM protein, originated mainly in the intercellular membrane or the plasma membrane. By using the energy from the ATP the transport mechanism across the cell membrane is initiated. In humans

around 49 ABC transporters are observed [7], where MDR1A, MDR1B and MDR2 [8] are usually identified in animals and MDR1 and MDR3 [9] which belong to the P-gp gene subfamily is mostly seen in humans. Where MDR1 (P-gp) is widely seen all over the body and efflux a wide range of drugs over the plasma membrane and MDR3 (P-gp) is predominantly observed in the liver, canalicular membrane of the hepatocytes and is accountable for the phosphatidylcholine secretion into the bile [10]. Even though the action of MDR3 or P-gp in the efflux transport mechanism is observed, their direct action in drug resistance is restricted.

The efflux action exhibited by P-gp is having a greater importance since it can protect our body from the entry of the toxins and xenobiotics into the cells mainly to brain, placenta and gonads and eliminating the waste products through the urine [11], by facilitating the energy driven with the ATP hydrolysis the amphipathic drugs are mainly eliminated by the efflux action of the P-gp.

P-gp role is mainly observed in the body parts such as kidney, intestine, liver [12], testis and brain [13]. The entry of the xenobiotics into the blood capillaries are mainly minimised by the localised action of P-gp in the luminal membrane of the epithelial cells [14]. Over-expression of the P-gp is the foremost reason behind the failure of the chemotherapy and other treatment strategies where nowadays the researchers are mainly focussed to overcome with this issue. The studies related to the action exhibited by the P-gp are performed in mice, rats [15] and in humans [16]. The substrates which merge with P-gp have unrelated frameworks. The compounds transported by P-gp are considered as substrates, while the compounds that prohibit the role of P-gp are considered as inhibitors.

P-gp was identified first in 1976 in Chinese hamster ovary cells, where it was obtained to demonstrate anticancer resistance [17]. The research data proved that the P-gp have the ability to acquire resistance to the cytotoxic drugs. They also proved that verapamil was helpful to measure the function of the P-gp by using positron emission tomography [18]. P-gp is used for differentiating the transitional B-cells from the native B-cells. Rhodamine 123 and Mito Tracker Dyes are also used for this purpose [19].

6. Cellular localisation

The expression of P-gp is recurrently found predominant in the cancer cells, causing MDR by efflux of lypophilic drug from the cell. P-gp is observed to be over-expressed in renal, colon and adrenal carcinoma, not often in germ cell tumour and lungs even certain in gastric carcinoma, undetectable in breast and endometrial carcinomas. In the normal cells the concentration of the P-gp and its expression is found to be low, but certain cell types like colon, kidney, liver, jejunum and pancreas shows a higher expression of P-gp. While in liver, the broad distribution of P-gp is found on the apical surface of epithelial cells and biliary canalicular front in the small biliary ductules [20]. When it appears in case of pancreas, P-gp exclusively found of the apical surface of epithelial cells of the small ductules. In Kidney the presence of the P-gp is exclusively found on the apical surface of the epithelial cells of the proximal tubules [5]. P-gp expression shows an identical expression in the apical surface of superficial columnar epithelial cells of both jejunum and colon. Where, the expression of P-gp is mostly seen in the surface of cortex and medulla cells in the adrenal glands. Its presence is found out with both secretary and excretory action in the specialised epithelial cells, placental trophoblast [21] and endothelial cells of capillary cells at blood-tissue barrier sites. Its presence is also found in the epithelial cells of bronchi and gastrointestinal tract, prostate gland, salivary glands and sebaceous gland of the skin.

The research reports proved the occurrence of P-gp in the human fetus is with the significance in the regular performance of various organs in the initial stage of embryo development [22]. The evidential reports from the research work conducted in the tissues of rodent and humans [23] came to a conclusion that the expression of the P-gp in the normal tissues are much lower than compared to that at the epithelial cell lining of small Intestine, colon, pancreatic duct, proximal tubules of kidney, bile ducts and adrenal gland [24]. P-gp over-expression is also observed in the secretary epithelial cells in the endothelium of the pregnant woman and also in the placenta for protecting the fetus [25].

7. Kinetics of P-gp

7.1 Absorption

The major reason behind the multidrug resistance in the cancer cells is the action exhibited by P-gp. P-gp transports a wide range of structurally and functionally different cytotoxic compound out of the cell by using the energy driven from ATP. Altering in this property caused by P-gp is a vital approach for overcoming the MDR part and to increase the therapeutic efficacy during the treatment. The incorporation of the P-gp inhibitors with the resistant drugs can be helpful towards suppress the expression of the P-gp. This situation of resistance part not only happens with the chemotherapeutic drugs but also for the treatment strategy used for other conditions also [26]. The over-expression of P-gp in the diseased cells as compared to that of the normal cells is the major reason behind this phenomenon. Research work carried out came with a conclusion that P-gp is the major cause for the antibiotics resistance part also. P-gp trims the overall permeability of the drug to reach the target site by reducing the minimal therapeutic concentration level [27].

7.2 Distribution

P-gp acts as an integral element in the distribution of the drugs. Its action is noticed in the blood brain barrier and also the placental barrier. It can accomplish its effect on the distribution of various therapeutic agents also reduce its activation in the body. The role of P-gp in the brain turned into a point where it resists the entry of the neuro-toxic drugs into the brain and hence sustains the penetration of central nervous system (CNS) agent delivery in the brain [28]. A modulator is in need to inhibit the action of P-gp for improving the efficacy of CNS drugs to the target site including for the Parkinson's and Alzheimer's disease. When it comes towards P-gp inhibition the P-gp also protect the fetus from the entry of the foreign bodies and toxic substances through the placenta [29, 30]. Hence by considering these aspects the inhibition of the P-gp is to be made in a careful manner by not altering the protective mechanism in the normal cells [31].

7.3 Metabolism

The enzymatic activity of CYP3A4 and the efflux mechanism by P-gp together play the role for the decreased therapeutic efficacy and bioavailability of the drugs administered through the oral route. These are major defence system in intestine which acts as a protective barrier from the entry of the toxic substances and the xenobiotics. These proteins are mainly over-expressed in enterocytes and hepatocytes and also establish its role in first pass metabolism of the drugs.

For supporting this statement piperine can be taken as an example. The flavonoid piperine is obtained from black pepper. It have the ability to act as a natural inhibitor of P-gp and CYP34A when and can increase the therapeutic efficacy of the drugs when co-administered [32]. The dose of the piperine administered should be ideal and reaches the minimum therapeutic concentration to produce this effect. Another example is the action exhibited by grape fruit juice. When grape fruit juice and saquinavir is co-administered, the therapeutic concentration of the parent drug can be increased when administered during oral route.

8. Elimination

8.1 Renal excretion

The process of glomerular filtration, tubular secretion and reabsorption involve in the mechanism of renal excretion. P-gp involved in the efflux of the xenobiotics and the waste materials from our body via renal excretion, results in reduced level of the therapeutic drug in the blood plasma. This can also be altered by incorporating the flavonoids with the therapeutic agents. When digoxin a flavonoid and Cyclosporine A is co-administered, Cyclosporine will increase the concentration of digoxin in the plasma by decreasing tubular secretion and glomerular secreation rate [33, 34]. Comparable results are obtained when itraconazole and cimetidine is coadministered [35].

8.2 Biliary excreation

The excretion of the drugs by the influence of the P-gp can also be altered by using the natural P-gp inhibitors. Quercetin, a natural inhibitor of P-gp can add on to the therapeutic concentration of a wide range of drugs in the target site when co-administered. In turn the therapeutic agents such as Azithromycin, erythromycin, cyclosporine A and doxorubicin have an inhibitory action on biliary excretion of drugs mediated by P-gp [36].

8.3 Antimicrobial drug resistant mechanism

The mechanism by which the antimicrobial drugs acquiring resistance to the microorganisms are as follows:

1. Drug inactivation or modification: enzymatic deactivation of pencillin G and the synthesis of β-lactamase in the penicillin resistant bacteria.

2. Verification in target site: the shifting of the pencillin binding site from PBP to MRSA in the bacteria resistant to the penicillin drug.

3. Metabolic pathway modification: For example, the para-aminobenzoic acid path is not necessary for the sulfonamide resistant bacteria which are the extensive predecessor for the combination of nucleic acid and folic acid, as an alternative of like mammalian cells they employ preformed folic acid.

4. Intercellular drug concentration diminution: accumulation of the drugs within the cells is declined by diminishing the drug efflux and drug permeability across the cell surface.

8.4 P-gp role in drug resistance

P-gp has a leading aspect in reducing the bioavailability and distribution of the drugs, where P-gp is over-expressed in intestinal region which act as a substrate to P-gp and reduces its absorption pathway. Hence the therapeutic level of the drugs and the bioavailability of the drugs are not accomplished. On the other hand if the P-gp expression is abscessed then the concentration of the drug in the plasma will reach to supra-therapeutic concentration leading to toxicity related issues [9].

The substrate infiltrate into the P-gp all the way through the protein cytoplasmic side or through the inner leaflet of the membrane. ATP attitudes to the cytoplasmic side of P-gp, pursue with its binding, ATP hydrolysis activates which modify the substrate to be efflux form the cell. The substrate excretion occurs followed with the release of the phosphate from the ATP molecule. A novel molecule of ATP attach to the secondary ATP binding site when adenosine diphosphate (ADP) is discharged. This process will proceed with the hydrolysis and discharge of ADP and a phosphate molecule reset the protein.

8.5 Substrate for P-gp

P-gp transports a broad range of substrates which are structurally and functionally different from each other. P-gp substrate mainly appear to be lypophilic and amphipathic in nature [37, 38]. For altering the functions of P-gp its inhibitors are mostly generated. The mechanism of action is either by competition with the drug binding sites without hindering the action of ATP hydrolysis of by blocking the ATP hydrolysis process [39]. Recently allosteric mechanism for P-gp mediated transport also added with the other two mechanisms [40]. P-gp substrates are attached with the protein molecule before getting attached or moved to the extracellular membrane leaflets.

8.6 P-gp inhibitors

The reports from the research work proven that the P-gp has the ability to interact with more than 20 substrates or the modulators. Some of the substrates which are easily transported by P-gp include anthracycline, vinca alkaloids and fluorescent lipids. This binding action of the modulators such as cyclosporine and verapamil are employed for altering the P-gp activity for the chemotherapy. The high flexible and the low specific nature of the P-gp binding pockets could be employed for overcoming the MDR related issues during the chemotherapy [41]. The Classification of the P-gp inhibitors is mainly based on its specificity, affinity and the toxicity. The classification and the division of the inhibitors are mentioned in **Table 1**.

8.7 First generation inhibitors

The inhibitors belonging to this generation are pharmacologically active in nature and are used in specific treatment. Some of them are reserpine, verapamil, cyclosporine A, yohimbine, quinidine, toremifene and tomoxifene. When we are taking the example of leukaemia cells, the resistance could be inverted by using verapamil [42] for producing an effective action high dose of the drug is given to the patient, results in cardiovascular toxicity [43]. Hence these inhibitors are replaced with the second generation inhibitors because of their less therapeutic efficacy.

Generations	Examples
First generation inhibitors	Verapamil, cyclosporine A, reserpine, quinidine, yohimbine, tamoxifen, and toremifene
Second generation inhibitors	Doxverapamil, valspodar, biricodar citrate, dexniguldipine, and dofequidar fumerate
Third generation inhibitors	Tariquidar, zosuquidr, laniquidar, elacridar, mitotane, annamycin, biricodar, ONT-093, R10933, and HM30181
Natural inhibitors	Curcumin, piperine, capsaicin, [6]-gingerol, carnosic acid, limonin, quercetin, β-carotene, leutiolin, and anthocynine

Table 1.
Generation of inhibitors with examples.

8.8 Second generation inhibitor

The substrates coming in this generation inhibitors are pharmacologically inactive in nature but produce its action on P-gp. This generation inhibitors are developed by structurally modifying the first generation inhibitors for obtaining high specificity, low toxicity and potency. Examples for this generation inhibitors include doxverapamil [44], valspodar (PSC 833) [45], biricodar citrate (VX710) [46], dofequidarfumerate and dexniguldipine. Non immunosuppressant analogues of dox verapamil and cyclosporine A are mainly included in this category. PSC 833 which is the most frequently used inhibitor exhibit 5–10 times more potency as compared to that of cyclosporine A [47]. On the other these inhibitors have greater affinity and inhibitory activity towards the ABC transporters and CYPA4 enzymes.

8.9 Third generation inhibitor

To overcome the problems associated with the first and second generation inhibitors, the third generation inhibitors are generally developed. The main advantage of using the third generation inhibitors are their less toxic effect as compared to that of the first two generation inhibitors and their specificity and effectiveness towards the P-gp. They are found with no pharmacological interaction. They do not possess any kind of pharmacological interaction with the chemotherapeutic agents and found to be 200 times more potent than first two generation inhibitors. Examples include Zosuquidar (LY335979), [48] Tariquidar (XR9576), Laniquidar (R101933), [49] Elacridar (F12091), ONT-093, [50] Mitotane (NSC- 38721), [51] annamycin, [52] HM30181,R10933, [53] HM30181, Biricodar. From the 3D QSAR and QSAR activities it is reported that the structure of the inhibitors are mainly responsible to produce the inhibitory activities. Studies reported that the heterocyclic ring of the tariquidar near to the antranilamide ring is responsible to produce the inhibitory activity. But the recent studies reported that tariquidar is having both substrate as well as inhibitory activity on P-gp [54, 55].

8.10 Fourth generation- natural inhibitors

Owing the toxicity issues and the restricted therapeutic caused with the synthetic inhibitors, the natural inhibitors are mainly developed which includes the dietary supplements also. The natural compounds and the food extracts are revealed with an effect on P-gp to reverse MDR and also exhibit anticancer property.

8.11 Spices

From the ancient period itself the use of the spices are predominant as preservative and colouring agents. The phytochemicals constituent in spices are studied for the cure of various ailments and for the management and reversal of MDR caused by P-gp [56].

8.12 Curcumin

Curcumin is used as anti-oxidant, anti-inflammatory agent, anti-infective and anticancer agent [57]. It also exhibits an additional use of reversing the MDR caused by P-gp. It procure this action by acting on P13K/Akt/NF-kB [58] pathway in L1210 MDR leukaemia cells in the mice model. In 2008 Choi et al came with a conclusion that the combination of curcumin and Adriamycin can overcome the MDR effect caused by P-gp by studying with the western blotting results [59]. Mucoadhesive microemulsion loaded with curcumin has the ability for brain targeting through intranasal route [60].

8.13 Piperine

Piperine is the alkaloid constituent present in a larger proportion in black pepper, which is consumed by the population all over the world and added in their diet. Piperine was found with the activity on altering the MDR by inhibiting ABC transporters [61].

8.14 Capsaicin

Capsaicin is found abundant in red chilli, exhibit anticancer and inhibitory activity on P-gp. It potentiates anticancer activity of vinblastine by modulating P-gp. It has the ability to act on β-catanin and NF-KB pathways [62].

8.15 [6]-Gingerol

Ginger is constituted with a major polychemical compound [6]-Gingerol, which add on its spicy taste. It also inhibits β-catanin and NF-KB pathways like the action exhibited by capsaicin, but the actual mechanism of action is still not known [63].

8.16 Carnosic acid

Carnosic acid is the major phenolic constituent found in the leaves of rosemary. Carcinoic acid can act as a substrate to P-gp by stimulating the ATP activity by competitively binding with the ATP binding site [64].

8.17 Procyanidine

This compound composes a major constituent in tea leaves and grape seeds. It exhibits both chemopreventive activity and also antiproliferative effect [65]. It can inhibit NF-KB and translocate YB-1 into the nucleus through dephosphorylation of ERK1/2 and AKT [66].

8.18 Limonin

The citrus fruits are constituted higher with this crystalline compound. It acts as a P-gp inhibitor in leukaemia, melanoma and colon cancer cell lines. It elevates

the accumulation of the Rhodamine 123 and doxorubicin inside the cells. When administered in a concentration of 20 μm it has the ability to increase the anticancer activity of the doxorubicin when studied with CED/ADR5000 Caco-2 and leukaemia cell lines [67].

8.19 Quercetin

Quercetin is the constituent found in higher amount in onion and apple. From the experimental report it is found that Quercetin exhibit chemotherapeutic and P-gp inhibition activity. On the addition of concentration of 0.7 μm, it enhances the anticancer activity of doxorubicin when studies in MCF-07 cell lines [68].

8.20 β- carotene

β- Carotene is abundantly found in vegetables and fruits [69, 70] and is the precursor of Vitamin A [69]. When studied with Caco-2 cell lines it has the ability to efficacy of etoposide, doxorubicin and 5-Fluorouracil and even can manage the P-gp transport activity.

8.21 Strategies to overcome MDR

Various novel approaches were established for the inhibition of MDR in the diseased cell lines, which includes biological, physical and chemical methods as well as ribonucleic acid (RNA), interference, micro RNA and Nanotechologies [71]. MicroRNAs are the undersized non-coding RNAs are normally not synchronised in the cancer cells; with the modification in the miRNA they have the ability to up regulate the MDR part. To alter the expression of P-gp various sequence of miRNAs such as miR-296, miR-27a, miR-298, miR-451 and miR-1253 were resolved, and there were evaluated in esophageal and breast cancer cell lines [72–74].

8.22 Monoclonal antibodies

In the early 1980s two monoclonal antibodies MRK-16 and MRK-17 were discovered to alter the resistance part developed by P-gp in both *in vitro* and *in vivo* studies [75]. MRK-16 was proven with their ability to inhibit the efflux of the drugs actinomycin-D and vincristine where the MRK-17 was proven with their ability to inhibit the MDR cell proliferation. The enhancement in the anticancer activity can be achieved by conjugating the monoclonal antibodies with the P-gp inhibitors. Euhertner Roninson developed a monoclonal antibody UIC2 from the mouse which has the ability to bind with the extracellular parts of the P-gp. In turn it has the ability to decrease the efflux of P-gp substrates which in turn increases the cytotoxicity of P-gp substrates [76].

8.23 Non substrate development

The MDR in cancer cells are towards a broad spectrum of anticancer drugs, hence there is a need to develop a new anticancer drug which have less predictable by the ABC transporter family proteins. Hence a new strategy is followed where the structural modification or the conjugation is made for the discovery of the new molecule which is less familiar to the P-gp as a substrate and which are structurally similar to the compounds which act as P-gp inhibitors.

8.24 MDR and nanotechnology

Nanoparticles are having a broad range of activity in the field for delivery of the anti-infective, anti-cancer and anti-inflammatory drugs. The nanoparticles are usually found in the range from 1 to 100 nm. The categories of nanoparticles include metals, solid lipid, micelles, liposome, polymers, dendrimers, and quantum dots [77–80]. The assembly of the nanoparticles are usually multilayered and the coatings of the nanoparticles are usually done to overcome the problems such as solubility, stability and specificity [81]. The issues related with the macromolecules such as low specificity, cell toxicity, high dose and cellular uptake can be limited by incorporating the drugs in the nanoparticles, even it have the ability to overcome the MDR related issues with P-gp and can enhance the therapeutic value of the parent drug [82].

8.25 Liposomes

Liposomes are extensively used for the delivery of the drugs which are impotent for the diffusion over the membrane layers. These can be modelled in phosphor lipid bi-layer and also in a micelle shapes which helps in encapsulating the soluble drugs and can hold on to their natural action. Thus nanoparticles mediate an appropriate activity in the management of MDR. For instant the activity of the Doxil encapsulated liposomal nanoparticles have the ability to manage the MDR part in the cancer cell lines [83].

8.26 Micelles

Micelles are the polymeric core-shell nanostructures with lypophilic drug core [84]. The lipophobic coating protects the lipophophilic drug from degradation and helps in its solubility. For this reason the lypophilic drugs have long circulation in blood and also mediated the P-gp efflux. The Pharmacokinetic property of the drugs such as fexofenadine could be enhanced when formulated in a self-Nano emulsifying drug delivery system by hampering the CYP450 and P-gp mechanism.

8.27 Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNPS) are having larger pore size and pore volume, biocompatible in nature and are having high surface area. MSNPS have the capacity to load both anticancer drugs and siRNA together at the same time [85]. This combination can alter the resistance caused by P-gp and in turn can enhance the therapeutic efficacy of the drugs [86].

8.28 Polymeric nanoparticles

Polymers employed are usually natural (Gelatine, chitosan and albumin) or synthetic (poly [D, L-lactic acid], poly [D, L-lactic acid] and poly [ε-caprolactone]) in nature. The techniques [87] used for the preparation of polymeric nanoparticles are salting out, dialysis and microemulsion, interfacial polymerisation, supercritical fluid technique and solvent evaporation. Nanoparticles of Human albumin with abraxane and paclitaxel are formulated for improving the efficacy of metastatic breast and pancreatic cancer [88, 89]. This novel formulation is approved for clinical studies by U.S. Food and drug administration.

8.29 Expression and its over-expression, advantage and drawback

The expression of the P-gp is mainly found in all parts of the body by acting as a protective shield from the entry of the toxins and the xenobiotics. Their action is unavoidable in the Blood brain barrier, blood placental barrier and blood testes barrier but when concentration on the therapeutic aspect of the drugs the absorption of the drugs through the intestinal is retarded due to the expression of the P-gp in the intestinal lumen, not only in the lumen part though their presence are predicted all over the body but their expression is more in the diseased cells mainly the cancer cells. The plasma membrane of the intestinal epithelial cells pumps back the drug which enters into it and which are recognised as the substrate and are excreted [90–92]. Higher levels are seen in the biliary epithelium, proximal tubules of the kidney and the drugs are seen in the bile and the urine. For inhibiting the role of the P-gp the P-gp inhibitors are developed. Though the inhibitors shows the action when checked in preclinical studies but their action retards when come into the clinical trials. The progress report of the inhibitors are explained in **Figure 1**. The failure in the therapeutic efficacy with the cancer treatment is mainly due to the over-expression of P-gp.

8.30 Cancer and drug resistance

In 1940s: first cancer chemotherapy trails begin.

In 1970s: Mammalian cells showed resistance to the anticancer agents recurrently exhibited cross-resistance to drugs which are structurally and functionally dissimilar.

Multidrug resistance was a foremost problem in the cancer chemotherapy because it involved resistance to some of the commonly used and the first line anticancer drugs.

In 982s: Multidrug resistance was shown in most of the cases which results in decline in the intercellular drug accumulation, apparently as a result of altering in the plasma membrane. In many multidrug resistant cell lines, the resistance was found to correlate with over expression of a 170-kDa membrane protein (P-gp) [93, 94].

Why to study Multidrug resistance?

- Important role in the cancer multidrug resistance and its pathogenesis.
- Important role in Drug pharmacokinetics (Uptake distribution and excretion).

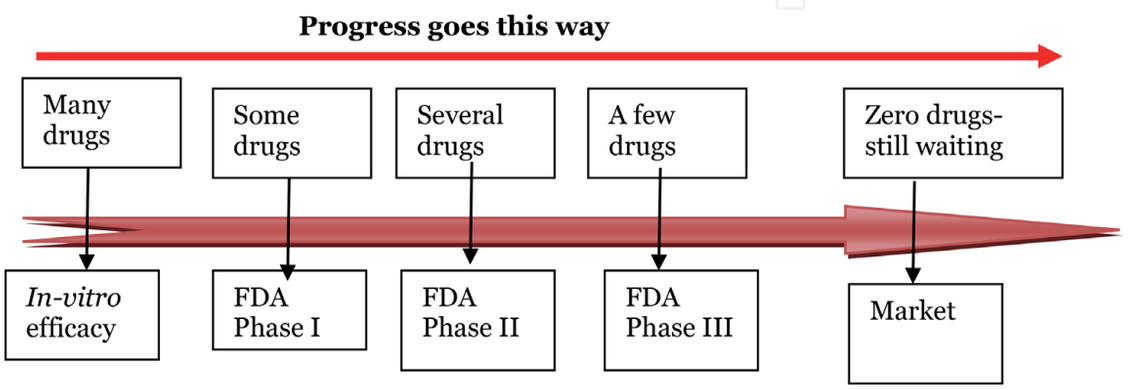

Figure 1.
P-gp inhibitor development timeline. The progress report of the inhibitors.

- Important role in removing toxins.
- Key role in development of inhibitors.
- To learn about the biology of the transport system.

9. Conclusion

P-gp is the protein belonging to the ABC family protein transporters with the aspect of protecting the cells and vital organs from the entry of the xenobiotics, toxins and drugs. The over-expression of the P-gp in the diseased cells leads to the therapeutic failure during the treatment regimen but the role of the P-gp for producing protective action in the brain and fetal cells are also unavoidable. Hence for an effective therapeutic aspect, the action of the P-gp and its role should be studied. For overcoming the unwanted action of the P-gp the inhibitors of the P-gp are mainly developed and the strategies for overcoming the MDR by using natural inhibitors and the formulation aspects and caused are mentioned in this chapter.

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References

[1] Lowe HJ, Barnett GO. Understanding and using the medical subject headings (MeSH) vocabulary to perform literature searches. JAMA. 1994;**271**:1103-1108

[2] Miller NS, Dackis CA, Gold MS. The relationship of addiction, tolerance, and dependence to alcohol and drugs: A neurochemical approach. Journal of Substance Abuse Treatment. 1987;**4**:197-207

[3] Bespalov A, Müller R, Relo AL, Hudzik T. Drug tolerance: A known unknown in translational neuroscience. Trends in Pharmacological Sciences. 2016;**37**:364-378

[4] Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, et al. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. Clinical Pharmacology and Therapeutics. 1999;**66**:295-305

[5] Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC, et al. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. Proceedings of the National Academy of Sciences of the United States of America. 1987;**84**:7735-7738

[6] Vishal R, Tandon B, Kapoor G, Bano S, Gupta Z, Gillani S, et al. P-glycoprotein pharmacological relivance. Indian Journal of Pharmacology. 2006;**38**:13-24

[7] Dean M, Rzhetsky A, Allikmets R. The human ATP-binding cassette (ABC) transporter superfamily. Genome Research. 2001;**11**:1156-1166

[8] Fischer V, Einolf HJ, Cohen D. Efflux transporters and their clinical relevance. Mini Reviews in Medicinal Chemistry. 2005;**5**:183-195

[9] Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: Clinical implications. Clinical Pharmacokinetics. 2003;**42**:59-98

[10] van Helvoort A, Smith AJ, Sprong H, Fritzsche I, Schinkel AH, Borst P, et al. MDR1 P-glycoprotein is a lipid translocase of broad specificity, while MDR3 P-glycoprotein specifically translocates phosphatidylcholine. Cell. 1996;**87**:507-517

[11] Colabufo NA, Berardi F, Contino M, Niso M, Perrone R. ABC pumps and their role in active drug transport. Current Topics in Medicinal Chemistry. 2009;**9**:119-129

[12] Pérez-Tomás R. Multidrug resistance: Retrospect and prospects in anti-cancer drug treatment. Current Medicinal Chemistry. 2006;**13**:1859-1876

[13] Ohtsuki S, Terasaki T. Contribution of carrier-mediated transport systems to the blood-brain barrier as a supporting and protecting interface for the brain; importance for CNS drug discovery and development. Pharmaceutical Research. 2007;**24**:1745-1758

[14] Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, D'Giano C, et al. ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. Epilepsia. 2007;**48**(Suppl 5):140-149

[15] Syvänen S, Hooker A, Rahman O, Wilking H, Blomquist G, Långström B, et al. Pharmacokinetics of P-glycoprotein inhibition in the rat blood-brain barrier. Journal of Pharmaceutical Sciences. 2008;**97**:5386-5400

[16] Ikoma Y, Takano A, Ito H, Kusuhara H, Sugiyama Y, Arakawa R, et al. Quantitative analysis of

11C-verapamil transfer at the human blood-brain barrier for evaluation of P-glycoprotein function. Journal of Nuclear Medicine. 2006;**47**:1531-1537

[17] Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochimica et Biophysica Acta. 1976;**455**:152-162

[18] Luurtsema G, Windhorst AD, Mooijer MP, Herscheid JD, Lammertsma AA, Franssen EJ. Fully automated high yield synthesis of (R)-and (S)-[11C] verapamil for measuring P-glycoprotein function with positron emission tomography. Journal of Labelled Compounds and Radiopharmaceuticals. 2002;**45**:1199-1207

[19] Wirths S, Lanzavecchia A. ABCB1 transporter discriminates human resting naive B cells from cycling transitional and memory B cells. European Journal of Immunology. 2005;**35**:3433-3441

[20] Croop JM, Raymond M, Haber D, Devault A, Arceci RJ, Gros P, et al. The three mouse multidrug resistance (mdr) genes are expressed in a tissue-specific manner in normal mouse tissues. Molecular and Cellular Biology. 1989;**9**:1346-1350

[21] Arceci RJ, Croop JM, Horwitz SB, Housman D. The gene encoding multidrug resistance is induced and expressed at high levels during pregnancy in the secretory epithelium of the uterus. Proceedings of the National Academy of Sciences of the United States of America. 1988;**85**:4350-4354

[22] Marzolini C, Kim RB. Placental transfer of antiretroviral drugs. Clinical Pharmacology and Therapeutics. 2005;**78**:118-122

[23] Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR, et al. Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. The Journal of Histochemistry and Cytochemistry. 1990;**38**:1277-1287

[24] van der Valk P, van Kalken CK, Ketelaars H, Broxterman HJ, Scheffer G, Kuiper CM, et al. Distribution of multi-drug resistance-associated P-glycoprotein in normal and neoplastic human tissues. Analysis with 3 monoclonal antibodies recognizing different epitopes of the P-glycoprotein molecule. Annals of Oncology. 1990;**1**:56-64

[25] van Kalken CK, Giaccone G, van der Valk P, Kuiper CM, Hadisaputro MM, Bosma SA, et al. Multidrug resistance gene (P-glycoprotein) expression in the human fetus. The American Journal of Pathology. 1992;**141**:1063-1072

[26] Breedveld P, Pluim D, Cipriani G, Wielinga P, van Tellingen O, Schinkel AH, et al. The effect of bcrp1 (Abcg2) on the *in vivo* pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): Implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. Cancer Research. 2005;**65**:2577-2582

[27] Mullin S, Mani N, Grossman TH. Inhibition of antibiotic efflux in bacteria by the novel multidrug resistance inhibitors biricodar (VX-710) and timcodar (VX-853). Antimicrobial Agents and Chemotherapy. 2004;**48**:4171-4176

[28] Löscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cas sette gene family. NeuroRx. 2005;**2**:86-98

[29] Kwan P, Brodie MJ. Potential role of drug transporters in the pathogenesis

of medically intractable epilepsy. Epilepsia. 2005;**46**:224-235

[30] Kortekaas R, Leenders KL, van Oostrom JC, Vaalburg W, Bart J, Willemsen AT, et al. Blood-brain barrier dysfunction in parkinsonian midbrain *in vivo*. Annals of Neurology. 2005;**57**:176-179

[31] Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. Clinical Pharmacokinetics. 2004;**43**:487-514

[32] Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF, et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. The Journal of Pharmacology and Experimental Therapeutics. 2002;**302**:645-650

[33] Fanos V, Cataldi L. Renal transport of antibiotics and nephrotoxicity: A review. The Journal of Antimicrobial Chemotherapy. 2001;**13**:461-472

[34] Rengelshausen J, Göggelmann C, Burhenne J, Riedel KD, Ludwig J, Weiss J, et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. British Journal of Clinical Pharmacology. 2003;**56**:32-38

[35] Karyekar CS, Eddington ND, Briglia A, Gubbins PO, Dowling TC. Renal interaction between itraconazole and cimetidine. Journal of Clinical Pharmacology. 2004;**44**:919-927

[36] Zhao YL, Cai SH, Wang L, Kitaichi K, Tatsumi Y, Nadai M, et al. Possible involvement of P-glycoprotein in the biliary excretion of grepafloxacin. Clinical and Experimental Pharmacology & Physiology. 2002;**29**:167-172

[37] Schwab M, Eichelbaum M, Fromm MF. Genetic polymorphisms of the human MDR1 drug transporter. Annual Review of Pharmacology and Toxicology. 2003;**43**:285-307

[38] Sauna ZE, Ambudkar SV. Evidence for a requirement for ATP hydrolysis at two distinct steps during a single turnover of the catalytic cycle of human P-glycoprotein. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**:2515-2520

[39] Sauna ZE, Smith MM, Müller M, Kerr KM, Ambudkar SV. The mechanism of action of multidrug-resistance-linked P-glycoprotein. Journal of Bioenergetics and Biomembranes. 2001;**33**:481-491

[40] Maki N, Hafkemeyer P, Dey S. Allosteric modulation of human P-glycoprotein. Inhibition of transport by preventing substrate translocation and dissociation. The Journal of Biological Chemistry. 2003;**278**:18132-18139

[41] Lee KS, Park JH, Lee HJ, Rhie S. Preclinical study of a potent P-glycoprotein and cytochrome P450 enzyme inducer rifampicin changing pharmacokinetic parameters of risperidone and its metabolite, 9-hydroxyrisperidone, using a rat model. Journal of Pharmaceutical Investigation. 2012;**42**:345-351

[42] Koski A, Raki M, Nokisalmi P, Liikanen I, Kangasniemi L, Joensuu T, et al. Verapamil results in increased blood levels of oncolytic adenovirus in treatment of patients with advanced cancer. Molecular Therapy. 2012;**20**:221-229

[43] Thomas H, Coley HM. Overcoming multidrug resistance in cancer: An update on the clinical strategy of inhibiting p-glycoprotein. Cancer Control. 2003;**10**:159-165

[44] Wilson WH, Jamis-Dow C, Bryant G, Balis FM, Klecker RW,

Bates SE, et al. Phase I and pharmacokinetic study of the multidrug resistance modulator dexverapamil with EPOCH chemotherapy. Journal of Clinical Oncology. 1995;**13**:1985-1994

[45] Tidefelt U, Liliemark J, Gruber A, Liliemark E, Sundman-Engberg B, Juliusson G, et al. P-glycoprotein inhibitor valspodar (PSC 833) increases the intracellular concentrations of daunorubicin *in vivo* in patients with P-glycoprotein-positive acute myeloid leukemia. Journal of Clinical Oncology. 2000;**18**:1837-1844

[46] Minderman H, O'Loughlin KL, Pendyala L, Baer MR. VX-710 (biricodar) increases drug retention and enhances chemosensitivity in resistant cells overexpressing P-glycoprotein, multidrug resistance protein, and breast cancer resistance protein. Clinical Cancer Research. 2004;**10**:1826-1834

[47] Friche E, Jensen PB, Nissen NI. Comparison of cyclosporin a and SDZ PSC833 as multidrug-resistance modulators in a daunorubicin-resistant Ehrlich ascites tumor. Cancer Chemotherapy and Pharmacology. 1992;**30**:235-237

[48] Kemper EM, Cleypool C, Boogerd W, Beijnen JH, van Tellingen O. The influence of the P-glycoprotein inhibitor zosuquidar trihydrochloride (LY335979) on the brain penetration of paclitaxel in mice. Cancer Chemotherapy and Pharmacology. 2004;**53**:173-178

[49] Luurtsema G, Schuit RC, Klok RP, Verbeek J, Leysen JE, Lammertsma AA, et al. Evaluation of [11C]laniquidar as a tracer of P-glycoprotein: Radiosynthesis and biodistribution in rats. Nuclear Medicine and Biology. 2009;**36**:643-649

[50] Dörner B, Kuntner C, Bankstahl JP, Bankstahl M, Stanek J, Wanek T, et al. Synthesis and small-animal positron emission tomography evaluation of [11C]-elacridar as a radiotracer to assess the distribution of P-glycoprotein at the blood-brain barrier. Journal of Medicinal Chemistry. 2009;**52**:6073-6082

[51] Bates SE, Shieh CY, Mickley LA, Dichek HL, Gazdar A, Loriaux DL, et al. Mitotane enhances cytotoxicity of chemotherapy in cell lines expressing a multidrug resistance gene (mdr-1/P-glycoprotein) which is also expressed by adrenocortical carcinomas. The Journal of Clinical Endocrinology and Metabolism. 1991;**73**:18-29

[52] Consoli U, Priebe W, Ling YH, Mahadevia R, Griffin M, Zhao S, et al. The novel anthracycline annamycin is not affected by P-glycoprotein-related multidrug resistance: Comparison with idarubicin and doxorubicin in HL-60 leukemia cell lines. Blood. 1996;**88**:633-644

[53] van Zuylen L, Sparreboom A, van der Gaast A, van der Burg ME, van Beurden V, Bol CJ, et al. The orally administered P-glycoprotein inhibitor R101933 does not alter the plasma pharmacokinetics of docetaxel. Clinical Cancer Research. 2000;**6**:1365-1371

[54] Pajeva IK, Wiese M. Structure-activity relationships of tariquidar analogs as multidrug resistance modulators. The AAPS Journal. 2009;**11**:435-444

[55] Kannan P, Telu S, Shukla S, Ambudkar SV, Pike VW, Halldin C, et al. The "specific" P-glycoprotein inhibitor tariquidar is also a substrate and an inhibitor for breast cancer resistance protein (BCRP/ABCG2). ACS Chemical Neuroscience. 2011;**2**:82-89

[56] Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P, et al. Potential of spice-derived phytochemicals for cancer prevention. Planta Medica. 2008;**74**:1560-1569

[57] Anuchapreeda S, Leechanachai P, Smith MM, Ambudkar SV, Limtrakul PN. Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells. Biochemical Pharmacology. 2002;**64**:573-582

[58] Choi BH, Kim CG, Lim Y, Shin SY, Lee YH. Curcumin down-regulates the multidrug-resistance mdr1b gene by inhibiting the PI3K/Akt/NF kappa B pathway. Cancer Letters. 2008;**259**:111-118

[59] Zhang W, Han Y, Lim SL, Lim LY. Dietary regulation of P-gp function and expression. Expert Opinion on Drug Metabolism & Toxicology. 2009;**5**:789-801

[60] Mandal SD, Mandal S, Patel J. Brain targeting efficiency of curcumin loaded mucoadhesive microemulsion through intranasal route. Drug Delivery. 2016;**46**:179-188

[61] Bezerra DP, de Castro FO, Alves AP, Pessoa C, de Moraes MO, Silveira ER, et al. *In vitro* and *in vivo* antitumor effect of 5-FU combined with piplartine and piperine. Journal of Applied Toxicology. 2008;**28**:156-163

[62] Nabekura T, Kamiyama S, Kitagawa S. Effects of dietary chemopreventive phytochemicals on P-glycoprotein function. Biochemical and Biophysical Research Communications. 2005;**327**:866-870

[63] Nabekura T. Overcoming multidrug resistance in human cancer cells by natural compounds. Toxins. 2010;**2**:1207-1224

[64] Nabekura T, Yamaki T, Hiroi T, Ueno K, Kitagawa S. Inhibition of anticancer drug efflux transporter P-glycoprotein by rosemary phytochemicals. Pharmacological Research. 2010;**61**:259-263

[65] Chen Q, Zhang R, Li WM, Niu YJ, Guo HC, Liu XH, et al. The protective effect of grape seed procyanidin extract against cadmium-induced renal oxidative damage in mice. Environmental Toxicology and Pharmacology. 2013;**36**:759-768

[66] Hsu CP, Lin YH, Chou CC, Zhou SP, Hsu YC, Liu CL, et al. Mechanisms of grape seed procyanidin-induced apoptosis in colorectal carcinoma cells. Anticancer Research. 2009;**29**:283-289

[67] Han YL, Yu HL, Li D, Meng XL, Zhou ZY, Yu Q, et al. Inhibitory effects of limonin on six human cytochrome P450 enzymes and P-glycoprotein *in vitro*. Toxicology in vitro. 2011;**25**:1828-1833

[68] Borska S, Chmielewska M, Wysocka T, Drag- Zalesinska M, Zabel M, Dziegiel P, et al. *In vitro* effect of quercetin on human gastric carcinoma: Targeting cancer cells death and MDR. Food and Chemical Toxicology. 2012;**50**:3375-3383

[69] Chieli E, Romiti N, Rodeiro I, Garrido G. *In vitro* modulation of ABCB1/P-glycoprotein expression by polyphenols from *Mangifera indica*. Chemico-Biological Interactions. 2010;**186**:287-294

[70] Nile SH, Park SW. Edible berries: Bioactive components and their effect on human health. Nutrition. 2014;**30**:134-144

[71] Livney YD, Assaraf YG. Rationally designed nanovehicles to overcome cancer chemoresistance. Advanced Drug Delivery Reviews. 2013;**65**:1716-1730

[72] Bao L, Hazari S, Mehra S, Kaushal D, Moroz K, Dash S, et al. Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated

by miR-298. The American Journal of Pathology. 2012;**180**:2490-2503

[73] Hong L, Han Y, Zhang H, Li M, Gong T, Sun L, et al. The prognostic and chemotherapeutic value of miR- 296 in esophageal squamous cell carcinoma. Annals of Surgery. 2010;**251**:1056-1063

[74] Perez J, Bardin C, Rigal C, Anthony B, Rousseau R, Dutour A, et al. Anti-MDR1 siRNA restores chemosensitivity in chemoresistant breast carcinoma and osteosarcoma cell lines. Anticancer Research. 2011;**31**:2813-2820

[75] Broxterman HJ, Kuiper CM, Schuurhuis GJ, Tsuruo T, Pinedo HM, Lankelma J, et al. Increase of daunorubicin and vincristine accumulation in multidrug resistant human ovarian carcinoma cells by a monoclonal antibody reacting with P-glycoprotein. Biochemical Pharmacology. 1988;**37**:2389-2393

[76] Mechetner EB, Roninson IB. Efficient inhibition of P-glycoprotein-mediated multidrug resistance with a monoclonal antibody. Proceedings of the National Academy of Sciences of the United States of America. 1992;**89**:5824-5828

[77] Altstadt TJ, Fairchild CR, Golik J, Johnston KA, Kadow JF, Lee FY, et al. Synthesis and antitumor activity of novel C-7 paclitaxel ethers: Discovery of BMS-184476. Journal of Medicinal Chemistry. 2001;**44**:4577-4583

[78] Cassinelli G, Lanzi C, Supino R, Pratesi G, Zuco V, Laccabue D, et al. Cellular bases of the antitumor activity of the novel taxane IDN 5109 (BAY59-8862) on hormone-refractory prostate cancer. Clinical Cancer Research. 2002;**8**:2647-2654

[79] Bar-Zeev M, Assaraf YG. Livney YD. B-casein nanovehicles for oral delivery of chemotherapeutic drug combinations overcoming P-glycoprotein-mediated multidrug resistance in human gastric cancer cells. Oncotarget. 2016;**7**:23322-23334

[80] Yang L, Li W, Kirberger M, Liao W, Ren J. Design of nanomaterial based systems for novel vaccine development. Biomaterials Science. 2016;**4**:785-802

[81] Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clinical Cancer Research. 2008;**14**:1310-1316

[82] Wen Y, Meng WS. Recent *in vivo* evidences of particle-based delivery of small-interfering RNA (siRNA) into solid tumors. Journal of Pharmaceutical Innovation. 2014;**9**:158-173

[83] Ogawara K, Un K, Tanaka K, Higaki K, Kimura T. *In vivo* anti-tumor effect of PEG liposomal doxorubicin (DOX) in DOX-resistant tumor-bearing mice: Involvement of cytotoxic effect on vascular endothelial cells. Journal of Controlled Release. 2009;**133**:4-10

[84] Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: Design, characterization and biological significance. Advanced Drug Delivery Reviews. 2001;**47**:113-131

[85] Chen AM, Zhang M, Wei D, Stueber D, Taratula O, Minko T, et al. Co-delivery of doxorubicin and bcl-2 siRNA by mesoporous silica nanoparticles enhances the efficacy of chemotherapy in multidrug-resistant cancer cells. Small. 2009;**5**:2673-2677

[86] Sheng J, Li F, Wong ST. Optimal drug prediction from personal genomics profiles. IEEE Journal of Biomedical and Health Informatics. 2015;**19**:1264-1270

[87] Devulapally R, Paulmurugan R. Polymer nanoparticles for drug and small silencing RNA delivery to treat cancers of different phenotypes. Wiley Interdisciplinary Reviews.

Nanomedicine and Nanobiotechnology. 2014;**6**:40-60

[88] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. The New England Journal of Medicine. 2013;**369**:1691-1703

[89] Dhar S, Gu FX, Langer R, Farokhzad OC, Lippard SJ. Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized pt(IV) prodrug-PLGA-PEG nanoparticles. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**:17356-17361

[90] Sureshkumar R. Plasma glycoprotein efflux induced resistance: Implications, mechanism, inhibitors, and novel strategies to overcome. Asian Journal of Pharmaceutics. 2018;**12**(04):261-271

[91] Karthika C, Sureshkumar R. Can curcumin along with chemotherapeutic drug and lipid provide an effective treatment of metastatic colon cancer and alter multidrug resistance? Medical Hypotheses. 2019;**132**:109325

[92] Hamed AR, Abdel-Azim NS, Shams KA, Hammouda FM. Targeting multidrug resistance in cancer by natural chemosensitizers. Bulletin of the National Research Centre. 2019;**43**(1):8

[93] Falasca M, Linton KJ. Investigational ABC transporter inhibitors. Expert Opinion on Investigational Drugs. 2012;**21**(5):657-666

[94] Sharom FJ. Complex interplay between the P-glycoprotein multidrug efflux pump and the membrane: Its role in modulating protein function. Frontiers in Oncology. 2014;**4**:41