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Review Article

P-glycoprotein efflux pump: Challenges and opportunities

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ABSTRACT

P-glycoprotein (P-gp) is an ATP-dependent membrane transport protein. P-gp, a drug efflux pump, has been reported to play a role in affecting the pharmacokinetics of drugs taken orally. P-gp is widely distributed in the body and is effective at inhibiting cellular absorption as well as the transport of xenobiotics and toxic substances. It functions as a substrate for a wide variety of structurally varied drugs, limiting drug absorption, permeability, and expulsion from cells. This review discusses P-gp and various P-gp inhibitors, such as small molecule compounds, pharmaceutically inert excipients, and active compounds which are often used to counteract P-gp efflux and increase oral absorption and bioavailability of several P-gp substrates, as well as various compositions of intrinsic P-gp inhibition activity. Some examples are micelles, solid lipid nanoparticles, solid dispersions, and nanoparticles. Despite the fact that P-gp-mediated efflux inhibits the absorption and bioavailability of many drugs, this review is useful for developing efficient P-gp substrate formulations to improve oral absorption and bioavailability. It is recognized that inhibiting P-gp has a significant impact on drug pharmacokinetics. This strategy will lead to more cost-effective therapy by lowering the number of drugs required. Furthermore, it will shorten the period of treatment while still delivering effective therapies. As a result, it can cause substantial changes in the field of delivery of a drug.

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INTRODUCTION

P-glycoprotein facilitates the effective transport of a diverse variety of substrates with various structures outside the cells, resulting in poor intestinal permeability and restricted bioavailability after oral treatment. P-gp is specific in its capability to identify substrate molecules and immediately expel them from the gastrointestinal lumen, hence restricting absorption into systemic circulation while actively augmenting elimination from the body via the biliary and urinary systems. Various P-gp inhibitors of commercial and natural origin have shown the capacity to block P-gp transport function, resulting in higher intracellular drug accumulation and better pharmacokinetic and pharmacodynamic profiles of many complex compounds such as erythromycin, clarithromycin, Paclitaxel (PTX), candesartan, and digoxin. As a result, this strategy can be used to increase the bioavailability of a drug that has a low bioavailability.

PREFACE

P-glycoprotein (P-gp)

P-glycoprotein (P-gp) (P-permeability) is an ABC transporter superfamily member that works as a physical barrier by eliminating pathogens & other toxins from

cells. In humans P-gp is a small gene family that has two different isoforms. MDR1/ABCB1 delivers drugs, whereas MDR2/3/ABCB4 exports phosphatidylcholine into the bile (Sharom FJ, 2011). P-gp, a glycosylated membrane-bound protein identified in 1976 in Colchicine-resistant Chinese hamster ovary cells by Juliano and Ling, controlled drug permeability and demonstrated anticancer resistance (Juliano R.L et al, 1976). P-gp may be present in the stomach, kidney, brain, liver, placenta, and pancreas and is involved in the active transport of foreign molecules out of cells (Ferreira R.J. et al, 2015). The main mechanism behind multidrug resistance is usually characterized as active drug transport out of the cell. Moreover, P-gp is widely distributed all through the body and interacts with a wide variety of drugs with varying structural properties, lowering their bioavailability.

One of the most notable features of P-gp is its capability to transport a broader spectrum of substrates with varying configurations. These involve analgesics, anticancer drugs, antidiabetic, antibiotics, corticoids, and antiemetics.

P-gp substrate therapeutic drugs often have low bioavailability or multidrug resistance (MDR) activity (Vaalburg W. et al, 2005). By decreasing permeability across physiological barriers, P-gp can reduce drug therapeutic effectiveness. P-gp influences drug absorption (for example, by discarding drug molecules back further into GI lumen after oral administration of drugs), distribution (for example, by impeding drug permeation further into brain), metabolism (for example, by interacting harmoniously to cytochrome P450 3A), and excretion (for example, by interacting synergistically with cytochrome P450 3A) (for example, by influencing biliary and renal tubular functions) (Akhtar N. et al, 2009).

P-glycoprotein inhibitors

The ability of P-glycoprotein to detect substrate compounds and rapidly eliminate them from the gastrointestinal lumen limits absorption into systemic circulation while actively enhancing removal from the body via the biliary and urine systems. Study has supported efforts to lower P-gp activity to improve therapeutic delivery and avoid resistance to antibiotics. Several synthetic and natural substances have been shown to block P-gp transport activity, leading to increased intracellular drug accumulation, MDR reversal (Shukla S. et al, 2008), and improved pharmacokinetic and pharmacodynamic profiles of many complex molecules, which could be useful in developing possibly effective oral formulations of drugs that, due to low oral absorption, should only be administered through parenteral routes, which also affect absorption, distribution, and metabolism.

Mechanism of P-glycoprotein inhibition-

The efflux pump is inhibited predominantly to increase therapeutic drug delivery. P-gp, in particular, can be inhibited by: i) competitively, noncompetitively, or allosterically inhibiting drug-binding sites; ii) interfering with ATP hydrolysis; and iii) altering the lipid integrity of cell membranes (Ashokraj Y. et al, 2003). The goal is to improve drug bioavailability and absorption in the targeted organ.

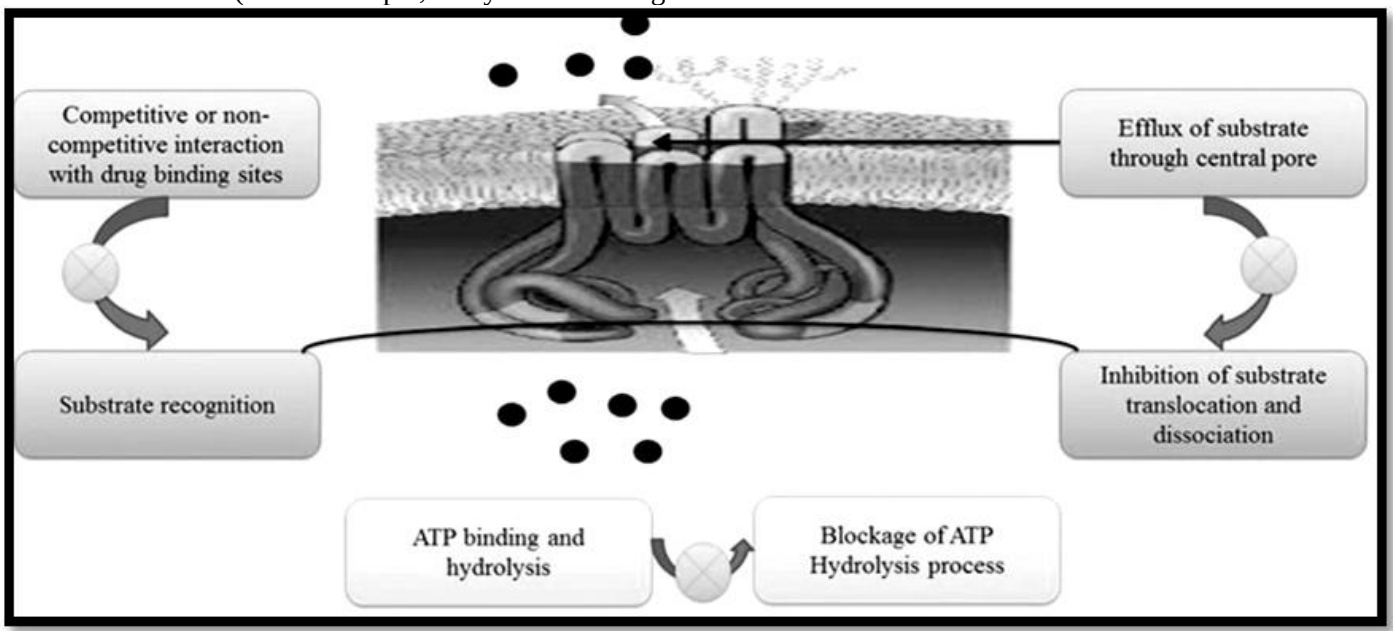

Fig. 1: Mechanism of P-glycoprotein Inhibition

Classification of p-glycoprotein inhibitors-

P-glycoprotein inhibitors of three generations have been developed to reverse MDR by interfering directly or indirectly with P-glycoprotein. Specificity, toxicity, and affinity are used to classify them (Palmeira A. et. al, 2012). First-generation inhibitors have shown intrinsic pharmacological activity in clinical trials. Verapamil, nifedipine, cyclosporin A, ibuprofen, reserpine, and tamoxifen are among them. Their use, however, is restricted due to their toxicity as a consequence of the

high blood concentrations necessary to block P-gp at the appropriate dosage. To address the toxicity difficulties associated with first-generation inhibitors, the second generation of P-gp inhibitors was developed; second-generation agents exhibit lower therapeutic characteristics but improved affinity than first-generation inhibitors (Rodrigues F. et al, 2011). Blocking two or more ABC transporters, on the other hand, results in complicated drug-drug interactions for this family of drugs. Such inhibitors comprise non-immunosuppressive cyclosporin A, Valspodar, and dexverapamil derivatives. Third-generation inhibitors were developed to avoid the problems observed with second-generation inhibitors. This class of P-gp inhibitors has been shown to be more selective to Pgp, avoiding interactions with the pharmacokinetics of other drugs (bioavailability, excretion, and so on) (Palmeira A. et. al, 2012). Laniquidar (R101933), Zosuquidar (LY335979), and Elacridar (GF120918) are P-gp inhibitors of this generation.

Table 1: Examples of enhanced pharmacokinetics of P-gp substrates with P-gp inhibitor co administration

P-gp substrates	P-gp inhibitor	Pharmacokinetic effect	References
	First-generation		(Sababi M. et al, 2001)
Digoxin	Verapamil	Increase in absorption rate	
Doxorubicin	Cyclosporine	Inhibitor dose-dependent permeability enhancement	(Erlichman C. et al, 1993)
	Second-generation		(Giaccone G. et al, 1997)
Doxorubicin	Valspodar (PSC 833)	~50% increase in AUC	
Paclitaxel	R-verapamil	Delayed mean paclitaxel clearance and increased peak concentration	(Tolcher AW. et al, 1996)
	Third-generation		
Docetaxel	Laniquidar (R101933)	~1.5-fold increase in AUC and ~2-fold increase in Cmax	(Van Zuylen L. et al, 2002)
Doxorubicin	Zosuquidar (LY335979)	~25% increase in BA at doxorubicin dose of 60 mg/m2 and ~15% increase at a dose of 75 mg/m^2	(Callies S. et al, 2003)

Natural P-glycoprotein inhibitors-

Because of the high serum concentrations produced by the dose necessary to block P-gp, the utilization of synthetic inhibitors is found to induce substantial toxicity. As a result, more effective natural P gp inhibitors are utilized. Inhibitors derived from natural sources are frequently called "Fourth Generation Inhibitors." Natural sources of P-gp inhibitors include alkaloids, flavonoids, coumarins, resins, saponins, terpenoids, and others (Foster B.C. et al, 2001).

Significance of P-gp Inhibitors in the treatment of various diseases

P-gp increases MDR by affecting drug absorption, distribution, metabolism, and excretion lowering the effectiveness of specific drugs such as anticancer, antidepressants, antibiotics, calcium channel blockers, antiarrhythmics, and HIV protease inhibitors, and cardiac glycosides. P-gp inhibitors are employed to address a wide range of ailments including cancer, parasite infection, diabetes, schizophrenia, HIV, and others.

Cancer Chemotherapy-

P-gp is a drug efflux pump present on the periphery of cancer cells that inhibits drug absorption within the tumor. It causes anticancer agents to be expelled before they reach their intended target. It also usually leads to the emergence of anticancer drug resistance in cells. As a result, the drugs used are ineffective or fail to provide the expected results. Several techniques have been studied to circumvent P-gp-mediated resistance mechanisms (Raub TJ., 2005). P-gp recognizes drugs that are primarily found in the plasma membrane. Cytotoxic medicines combined with inhibitors such as verapamil or cyclosporine may diminish P-gp-mediated efflux and improve drug delivery to the targeted area. To circumvent P-gp complications, the carrier system contains both a chemotherapeutic medication and an inhibitory agent (Bentolila D. et al, 2000). (Gruber A. et al, 2000) Valspodar enhanced cellular absorption of daunorubicin in leukemic blasts in vivo by interacting with P-gp.

CNS disorders-

Natural gums are polysaccharides composed of several sugar groups which are connected to form considerably large compounds; these are sustainable, biodegradable, and physiologically safe; and they have been found to produce gels with significant network formation. Gums can be grafted and cross-linked, resulting in the formation of hydrogels, xerogels, and nanoparticles that are significant in inhibiting the Pglycoprotein (P-gp) efflux transporter (Choo E. F. et al, 2006). Chitosan which is a cationic polysaccharide that may be combined with nucleotides to produce nanosystems may improve drug permeability through the CNS by bypassing tight junctions & the development of nanoparticles comprising chitosan and nucleotides may contribute to this (Bemkop-Schnürch A. et al, 2008). Natural polymers such as anionic gums such as gellan gum, alginates, and xanthan have been reported to inhibit the P-glycoprotein efflux pump at 0.05 and 0.5 mg/ml (Hunter R. L. et al, 1994). P-gp substrate concentrations such as vinblastine and doxorubicin are elevated in the presence of xanthan gum. In everted gut sac cells, alginate flavicam elevated the intracellular concentration of doxorubicin (Werle M., 2008). Polymeric P-gp inhibitors as excipients in drug delivery systems are a beneficial method because they have high inhibitory efficacy and are not absorbed through the gastrointestinal tract and eliminate any potential systemic effects.

Table 2: Examples of Natural P-gp inhibitors with their major constituents and mechanism of action

Source	Chemical constituent	Mechanism of action	References
Alkaloids			
Piper nigrum (Family: Piperaceae)	Piperine	In low dose, it inhibits P-gp expression and function	(Han Y. et al, 2008)
Cinchona pubescens (Family: Rubiaceae)	Cinchonine, Hydrocinchonine, Quinidine	Inhibits mRNA expression of P-gp	(Caillot D et al, 2000)
Lobelia inflata (Family: Campanulaceae)	Lobeline	Inhibits P-gp function probably by substrate competition.	(Ma Y. et al, 2008)
Flavonoids and Phenolics			
Camellia sinensis (Family: Theaceae)	Epigallocatechin gallate, Epicatechin gallate, Catechin gallate, Epicatechin	Interact with P-gp and inhibit its transport activity, could be used to modulate the function of P-gp	(BeÂliveay R et al, 2002)
Cicer pinnatifidum (Family: Fabaceae)	Biochanin A	Modulates P-gp by interacting bi-functionally with the vicinal ATP-binding site and the steroid binding sites as well as inhibition of P-gp ATPase by binding to the ATP-binding site.	(Morris M.E et al, 2003)
Terpenoids			
Euphorbia dendroides (Family: Euphorbiaceae)	Euphodendroidin D	Inhibits P-gp activity via binding with its active sites.	(Corea G. et al, 2009)
Glycyrrhiza glabra (Family: Fabaceae)	Glycyrrhizin	Inhibit P-gp ATPase activity	(Li X. et al, 2014)

Coumarins			
Citrus paradisi (Family: Rutaceae)	Bergaptol	Specific inhibitor of P-gp and/or MRP2 function.	(Morimoto S. et al, 2000)
Ferula szowitsiana (Family: Umbelliferae)	Galbanic acid	Inhibits P-gp via competitive binding with P-gp active sites	(Hanafi-Bojd M.Y et al, 2011)
Saponins			
Panax ginseng (Family: Araliaceae)	20(S)-ginsenoside F1	inhibits P-gp ATPase activity	(Choi C.-H. et al, 2003)
Dioscorea opposite (Family: Dioscoreaceae)	Gracillin	Inhibits P-gp via direct interaction with active binding sites.	(Bayet C. et al, 2009)

Antimicrobial therapy-

Antimicrobial drugs are prevented from entering microorganisms by P-gp molecules. The lower intracellular drug concentrations result in decreased drug permeability to their desired site of action and, as a result, it causes resistance. Many infectious infections may fail to respond to therapy as a result of this transport mechanism (Wright GD., 2003). P-gp inhibition might be a useful strategy for lowering transporter-mediated bacterial multidrug resistance. These could be used with antibiotics to increase their duration and thereby therapeutic efficacy. They have the potential to inhibit the formation of resistant variations that may occur while therapy. Microorganisms become more susceptible to antimicrobial drugs when such inhibitors are present (Pagès JM, Lee VJ., et al, 2006). (Seral et al, 2003) evaluated how P-gp inhibitors (verapamil, cyclosporine, and GF120918) affected the antibacterial activity of macrolides (erythromycin, azithromycin, and clarithromycin) in J774 murine macrophagesP-gp increased azithromycin, erythromycin, telithromycin, and roxithromycin expulsion, leading to decreased drug deposition. As a result, inhibitors could increase their concentration within cells and, their antimicrobial activity. Tariquidar, a third-generation P-gp inhibitor, was examined by (Leitner et al, 2011) for its efficacy in lowering ciprofloxacin resistance in bacteria. Tariquidar's efficacy was tested on Staphylococcus aureus strains. Tariquidar decreased the MIC of ciprofloxacin by 10-fold. The outcomes indicated that tariquidar substantially improved S. aureus sensitivity to ciprofloxacin.

Diabetes treatment-

P-gp is well-known for its role in the efflux of therapeutic medicines from the systemic circulation into the intestinal lumen, which results in multidrug resistance (Aller SG et al, 2009). Efflux of oral anti-diabetic agents may affect bioavailability and interfere with therapeutic efficacy in Type 2 Diabetes Mellitus (T2DM). One strategy for increasing drug systemic availability is to inhibit Pgp with a substance that interferes with antidiabetic drug binding to the efflux transporter. (Sama et al., 2012) stated, that nateglinide has a notable antihyperglycemic effect when given in conjunction with piperine. As per the aforementioned study results, Piperine could be utilized as a natural P-gp inhibitor to block this efflux transporter from eliminating active molecules, therefore enhancing the bioavailability of antidiabetic drugs.

Schizophrenia treatment-

Schizophrenia is a serious mental illness. Because individuals with schizophrenia require extensive treatment, antipsychotic management therapy is essential (Ceraso, A. et al., 2020). The availability of a psychotropic substance in the target organ, most notably the brain, determines its pharmacological action. As a consequence, they investigated the changes in drug concentrations in brain tissue and CSF after receiving Risperidone in combination of Clozapine (CLZ) or probenecid and verapamil. Verapamil and CLZ, according to Mahar Doan et al., significantly raised RIS exposure (Mahar Doan. et al., 2002). When given with verapamil (5 mg/kg), the absolute oral bioavailability of RIS (at a dose of 4 mg/kg) in rats was 3.18 times greater than the absolute oral bioavailability of RIS alone (Cousein, E. et al., 2007). As a result, CLZ significantly increased RIS absorption in this trial, owing largely to P-glycoprotein (P-gp) inhibition in the intestinal mucosa, because CLZ amounts in the GIT are projected to increase if adminsitered orally.

HIV treatment-

P-gp transports all HIV protease inhibitors in the following order: ritonavir > nelfinavir > indinavir > saquinavir. According to the findings, plasma levels of saquinavir, nelfinavir, and, indinavir in MDR-1

knockout mice were 2–5 times higher than in control animals. P-gp inhibition may enhance protease inhibitor absorption, bioavailability, and penetration into HIV sanctuary locations while limiting elimination. Increased protease inhibitor concentrations at these sites may lead to higher viral replication inhibition. P-gp inhibitors such as cyclosporine and verapamil hindered HIV protease inhibitor transport.

Formulation Approaches

Some drug delivery systems are leading the way with strategies to avoid and inhibit P-gp efflux. Solid lipid nanoparticles (SLNs), SNEDDS, micelles, nanoparticles, microspheres, and solid dispersions are a few examples. These drugs can have both P-gp inhibitory properties as well as the capacity to withstand P-gp efflux. Because P-gp inhibitors are included in their composition, this leading to improved intestinal absorption and BA of P-glycoprotein substrates, as well as P-gp inhibitory characteristics.

Solid lipid nanoparticles (SLNs)-

Linagliptin (LGP), a potent DPP-4 inhibitor, is used to treat type II diabetes. LGP formulations are marketed as instant and prolonged-release tablets for oral administration as standalone and in predefined co-treatment with other anti-diabetic drugs. However, owing to first-pass metabolism, limited permeability, and P-gp efflux, the medication has only 29.5 % oral bioavailability (Shaik M. et al, 2019). Researchers have been interested in solid lipid nanoparticles (SLNs) as potential nanoparticulate drug carriers due to their ability to include hydrophobic/hydrophilic components, therapeutic targeting, avoidance of organic solvents, high tolerance & stability, and scaling-up capability (Han C. et al, 2008). The combination of P-gp inhibitors such as poloxamer 188 and Tween 80 in LGP-SLNs boosted absorptive transport of LGP, as per in situ single-pass perfusion, and Caco-2 permeability, rat everted sac experiments. In-vivo pharmacokinetics and pharmacodynamic investigations on rats, LGP-SLNs showed greater bioavailability and therapeutic efficacy than LGP-SOL. Increased bioabsorption would result in lower dosage, dose-related adverse effects, and dosing frequency, and also improved patient satisfaction. As a result, SLNs are appropriate carriers for the oral administration of LGP, a novel anti-diabetic agent (Kejal Chavda. et al, 2021).

Self-nano emulsifying drug delivery systems (SNEDDS)-

(Cui. et al, 2019) integrated docetaxel and cyclosporine A with Capryol 90, Cremophor EL, and Transcutol HP using SNEDDS. Docetaxel is a taxane-based anticancer drug that is commonly utilized in the management of several malignancies. It has very low oral bioavailability. Cyclosporine is a medication. In an SPIP investigation using rat intestine, a co-loaded SNEDDS had the highest absorption rate (Ka) and apparent permeability (Papp), following the drug-loaded SNEDDS as well as the drug solution in 4 intestinal segments (duodenum, jejunum, ileum, and colon). Docetaxel-cyclosporine A co-loaded SNEDDS had 9.2 and 3.4-fold higher oral bioavailability than the drug solution and drug-loaded SNEDDS, respectively. The co-encapsulation in SNEDDS of a particular P-gp inhibitor (cyclosporine A) and a P-gp substrate (docetaxel) enhances drug absorption and bioavailability, allowing for oral chemotherapy.

Micelle-

Paclitaxel (PTX), derived from the bark of the western Taxus brevifolia, is a commonly utilized chemopreventive drug in the treatment of a wide range of cancers (H. Li. 2016). Due to its limited water solubility, it is administered by i.v infusion of a cremophor EL-containing formulation, which has substantial side effects. Low oral bioavailability is a critical issue in the development of oral formulations. Moreover, P-glycoprotein mediated mdr limits its therapeutic usage in a variety of resistant cancers. A new super-antiresistant PTX micelle formulation for oral administration was produced in this investigation. The micelle also contained bromotetrandrine (W198), a P-gp inhibitor. To prevent Cremophor EL-induced toxicity, the micelles were made using Solutol HS 15 and D-a-tocopheryl polyethylene glycol succinate. PTX micelles improved absorption after oral intake in rats and reduced tumor development in multidrug-resistant MCF-7/Adr nude mice. Co-administration of PTX with P-gp inhibitors including cyclosporin A, PEG 400 (F. Zhang. et al, 2016) significantly enhanced PTX oral bioavailability.

Nanoparticles (NPs)-

Rapamycin, a macrolide derived from Streptomyces hygroscopicus, was administered to patients with breast cancer using PLGA-NPs (Katiyar S.S. et al, 2016). The medication is a P-gp substrate having limited oral bioavailability as well as water solubility. Piperine was similarly administered alongside rapamycin for such P-gp inhibitory and anticancer activities. A study of gut sac permeability found that rapamycin-loaded NPs containing piperine were more permeable than rapamycin suspension. Furthermore, co-loading piperine in the NPs enhanced permeability 5-fold, indicating piperine's P-gp inhibitory activity.

Solid dispersion (SD)-

Solid dispersions (SD) are drug dispersions in polymer or small molecule solid matrices. Dispersed states include eutectic mixture, amorphous or crystalline suspensions, and crystalline or glass solutions (Dai W.-G. et al, 2014). (Gurunath. et al, 2015) utilized

kneading, spray drying, and freeze-drying to form the solid dispersion of candesartan with PVP K30 and naringin, a natural flavonoid P-glycoprotein inhibitor. Mixing naringin with candesartan solid dispersions boosted oral bioavailability by 1.3 to 1.6 times when matched to candesartan solid dispersions alone in rabbit pharmacokinetic studies. When compared to candesartan solution alone, freeze-dried solid dispersions containing naringin increased oral bioavailability by 3.7-fold. P-gp inhibitor naringin significantly enhanced intestinal permeability as well as oral bioavailability of a P-gp substrate.

CONCLUSION

One of the most major inconveniences to the efficient administration of drugs is P-gp. We highlighted in the first section of this review article that P-gp is abundantly distributed in a range of tissues, and it is evident that blocking P-gp has a considerable influence on the pharmacokinetics of a drug. Effective inhibition would enable not only improved cellular uptake, transport, and half-lives of pharmaceuticals, and precise prediction of their pharmacokinetics and adjustments for particular site targeting. These developments will lead to more cost-effective therapy by lowering the number of drugs required. Furthermore, it will shorten the period of treatment while still delivering effective therapies. As a result, it can cause substantial changes in the field of delivery of a drug.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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