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Review

Bioavailability enhancing activities of natural compounds from medicinal plants

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There is an increasing interest and medical need for the improvement of bioavailability of a large number of drugs. Of the promising approaches, the co-administration of therapeutic agents with natural compounds possessing absorption improving activities has gained great interest in oral drug delivery. Many natural compounds from medicinal plants have demonstrated capacity to enhance the bioavailability of co-administered drugs by inhibiting efflux pumps or oxidative metabolism, and perturbing the intestinal brush border membrane. These natural compounds include quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside. This article reviews the improvement of drug bioavailabilities exhibited specially by natural compounds from plants mentioned above.

Key words: Bioavailability enhancer, natural compound, absorption, P-glycoprotein.

INTRODUCTION

With rapid advances in drug design technologies, druggable compounds have dramatically been introduced. However, many of these molecules have suffered from low bioavailability upon oral administration due to poor permeation across the gastrointestinal epithelia (Duizer et al., 1998), although they exhibit potential therapeutic effects. Drugs have low membrane permeability, probably because of their low lipophilicity and zwitterionic charac-ter at physiological pH (Raeissi et al., 1999), or because of poor water solubility or efflux by P-glycoprotein (P-gp) (Adachi et al., 2003).

Therefore, improving oral drug absorption and bioavailability of drugs has become an important issue within the pharmaceutical industries. There are numerous approaches to enhance the intestinal absorption (Noach et al., 1994). These approaches include the use of absorption enhancers, prodrugs and permeability-enhancing dosage forms such as liposomes and emulsions. Recently, the application of P-gp inhibitors in improving *peroral* drug delivery has gained special interest (Breedveld et al., 2006).

In Ayurveda, black paper (*Piper nigrum*), long pepper (*Piper longum*) and ginger (*Zingiber officinalis*) are collectively termed '*trikatu'*. The ancient documented *Ayurvedic Material Medica* mentioned these three com-pounds as essential ingredients of many prescriptions and formulations used for a wide range of diseases. Some modern Ayurvedic practitioners have tried to investigate the scientific basis underlying the use of three herbs. It was revealed that *trikatu* has important role to play in increasing drug bioavailability when given orally (Atal et al., 1981) although the mechanisms by which it enhances the bioavailability is not clearly understood.

Some natural compounds have demonstrated to increase the absorption and bioavailability of co-administered drugs. Bioavailability and absorption enhancement through co-administration of drugs with naturally occurring compounds from plants are consider-ed to be very simple and relatively safe.

However, to date bioavailability enhancing activity of

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Abbreviations: EDTA, Ethylenediamine tetraacetic acid; **P-gp,** P-glycoprotein; **BCRP,** breast cancer resistance protein; **AUC,** the area under the plasma concentration-time curve; C_{max} peak concentration.

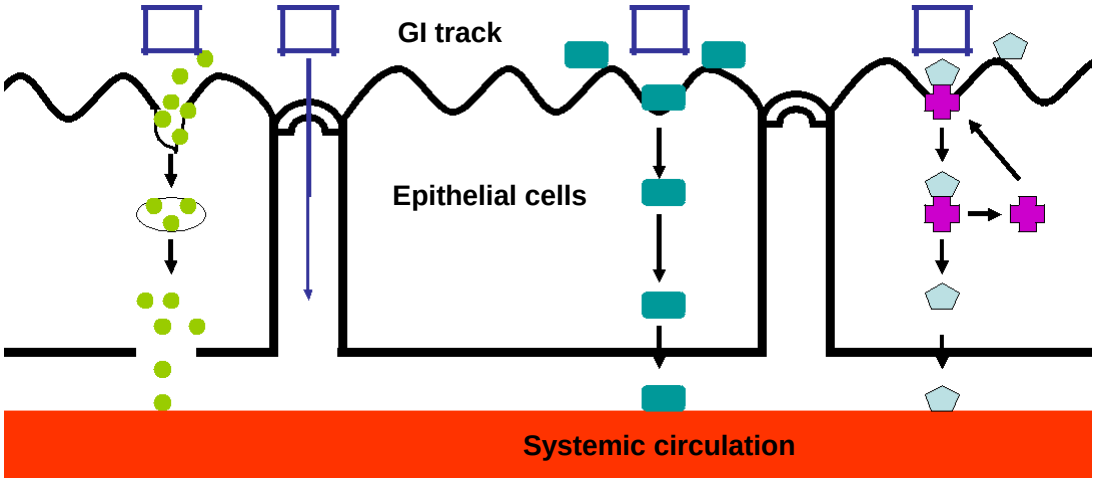

Figure 1. A schematic representation of the absorption pathways. **1)** The paracellular transport and the transcellular transport of drugs or solutes across the epithelial cells of the gastrointestinal tract into the systemic circulation**; 2)** transcellular passive diffusion**; 3)** transcellular endocytosis**; 4)** carrier-mediated transport processes between a specific carrier and a drug (Adapted from Salama et al., 2006).

those compounds seems not to be referred much to yet.

This paper describes the efforts to enhance oral bioavailability, especially with cases on absorption or bioavailability enhancement by co-administration of natural compounds.

DRUG ABSORPTION BARRIERS

For a drug to be transported from the lumen of the gut into the systemic circulation and exert its biological actions, it needs to cross the epithelial barrier of the intestinal mucosa. But, unfortunately, oral drug delivery system has many hurdles to penetrate the epithelia membrane due to anatomical and biological barriers (Hayton, 1980). The intestinal epithelium is composed of several structures serving as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. An aqueous stagnant layer that overlies the apical membrane is potential barrier to the absorption of drugs due to its hydrophilic nature. The apical and basolateral membranes are also potential barriers to the absorption of less permeable drugs.

The membranes around cells are lipid bilayers containing proteins (e.g. receptors and carrier molecules). Drugs need to cross the lipid membrane by mainly passive diffusion or carrier-mediated transport involving the spending of energy. There are also aqueous channels within the proteins through which small water-soluble molecules, such as ethanol, can pass. But the nature of the cell membrane makes it impractical for these aqueous channels to be promising enough to admit drug molecules larger than about 0.4 nm. Some large molecules (e.g. insulin) may be transferred across the membrane by endocytosis, in which the cell membrane is invaginated to make a vesicle along the extracellular molecule and uptake it within the cell. Figure 1 represents the absorption pathways across the epithelia (Salama et al., 2006).

It was recently identified that drug efflux pumps like P-gp possess very important role inhibiting efficient drug entry into the systemic circulation (Schinkel and Jonker, 2003). P-gp is a type of ATPase and an energy-dependent transmembrane drug efflux pump belonging to members of ABC transporters. P-gp has 1280 amino acid residues and molecular weight of -170 kDa (Juliano and Ling, 1976). Much work has still been made about the modulation of P-gp, since it is gaining importance in absorption enhancement due to its substrate selectivity and distribution at the site of drug absorption.

APPROACHES FOR ENHANCEMENT OF ABSORPTION OF ORALLY ADMINISTERED DRUGS

There are many approaches to enhance the intestinal absorption of poorly absorbed drugs. These approaches include the use of absorption enhancers, protease inhibitors (which are only effective for peptides and protein drugs), prodrugs and permeability-enhancing dosage forms. Furthermore, the application of P-gp inhibitors in improving *peroral* drug delivery has gained special interest. Here, some trials are summarized as follows.

Absorption enhancers

Many absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers (Lundin

et al., 1990; Aungst et al., 1991). Table 1 summarizes the kinds of various absorption enhancers on the basis of their chemical properties. Surfactants including bile, bile salts and fatty acids exert as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators such as EGTA and EDTA reduce the extracellular calcium concentration, leading to the disruption of cell-cell contacts. Chitosan, particularly trimethylated chitosan, was reported to increase drug absorption via paracellular route by redistribution of the cytoskeletal F -actin, causing the opening of the tight junctions (Schipper et al., 1997).

Table 1. Examples of compounds shown to have intestinal absorption enhancing effects.

Bile salts
Sodium cholate
Sodium deoxycholate
Non-ionic surfactants
Polyoxyethylene alkyl ethers
Polyoxyethylene alkyl esters
Polysorbates
Ionic surfactants
Sodium lauryl sulfate
Dioctyl sodium sulfosuccinate
Fatty acids
Sodium caprate
Oleic acid
Glycerides
Natural oils
Medium-chain glycerides
Phospholipids
Polyoxyethylene glyceryl esters
Acyl carnitines and cholines
Palmitoyl carnitine
Lauroyl choline
Salicylates
Sodium salicylate
Sodium methoxysalicylate
Chelating agents
EGTA
EDTA
Swellable polymers
Starch
Polycarbophil
Chitosan
Others
Citric acid

Prodrugs

Chemical modification of drugs to produce prodrugs and more permeable analogues has been widely studied as a useful approach to enhance the drug absorption and bioavailability. One of the well-known examples of increasing the lipophilicity of agents to enhance absorption of a polar drug by prodrug strategy is various ampicillin derivatives (Buur et al., 1986). Ampicillin is known to be only 30 - 40% absorbed from the gastrointestinal tract due to its hydrophilic nature. The produgs of ampicillin such as pivampicilline, bacampicilln and talampicillin were synthesized by esterification of carboxyl group of ampicillin. These produgs were more lipophilic than the parent compound and they showed higher bioavailability in comparison with ampicillin following oral administration.

Dosage form and other pharmaceutical approaches

Besides chemical modification approaches, utilization of permeability-enhancing dosage forms is also one of the most practical approaches to improve the intestinal absorption of poorly absorbed drugs. The intestinal absorption of insoluble drugs was enhanced by various dosage formulations such as liposomes (Patel and Ryman, 1976) and emulsions (Engel et al., 1968). Additionally, particle size reduction such as micronization, nanoparticular carriers, complexation and liquid crystalline phases have been investigated to maximize drug absorption (Liversidge and Cundy, 1995; Veiga et al., 2000).

P-glycoprotein inhibitors

Several studies have demonstrated the possible use of P-gp inhibitors that reverse P-gp-mediated efflux in an attempt to improve the efficiency of drug transport across the epithelia, thus resulting in enhanced oral bioavailability. P-gp inhibitors may also influence absorption, distribution, metabolism and elimination of P-gp substrates in the process of modulating pharmacokinetics (Varma et al., 2003).

Early studies on verapamil to reverse P-gp mediated resistance to vincristine and vinblastine (Tsuruo et al., 1981) provided the rationale for its clinical usefulness as P-gp inhibitor. In addition to this, orally administered verapamil has been shown to increase peak plasma level, prolong elimination half-life and increase volume of dis-

Table 2. Inhibitory effect of natural products on P-pg mediated paclitaxel transport in Caco-2 cells. Data are the mean ± S.D (n = 2 – 4) (Reproduced from Hayeshi et al., 2006).

Natural product	Concentration (µM)	P_0 [a]	P_1 [b]	K_{iapp} [c] (µM)	% Inhibition
Flavone	33	44±4	29±4	66	33
	100		16±8	56	64
Quercetin	33	40±2	37±5	NI	NI
	100		28±2	233	30
Genistein	33	40±2	38±2	NI	NI
	100		32±3	412	20
Caffeic acid	33	40	44	NI	NI
	100		39	NI	NI
Catechin	33	40	39	NI	NI
	100		42	NI	NI
Daidzein	33	40	38	NI	NI
	100		40	NI	NI
Diospyrin	33	40	43	NI	NI
	100		42	NI	NI
Ellagic acid	33	47	41	NI	NI
	100		42	NI	NI
Epicatechin	33	40	38	NI	NI
	100		35	NI	NI
Etoposide	33	47	44	NI	NI
	100		41	NI	NI
Ferulic acid	33	40	40	NI	NI
	100		38	NI	NI
Geshoidin	33	53	55	NI	NI
	100		53	NI	NI

NI: no inhibition.
[a] P_0 = Permeability of paclitaxel − Permeability of paclitaxel in presence of verapamil.
[b] P_1 = Permeability of paclitaxel in presence of test compound−Permeability of paclitaxel in presence of verapamil.
[c] The K_{iapp} is the extracellular concentration of test compound, [I], bringing about 50% inhibition of active paclitaxel transport and $K_{iapp} = [(P_1/P_0)/(1-P_1/P_0)][I]$.

tribution of doxorubicin, another P-gp substrate, after oral administration (Kerr et al., 1986).

NATURAL COMPOUNDS FROM MEDICINAL PLANTS AS DRUG BIOAVAILABILITY ENHANCERS

Bioavailability enhancing activity of natural compounds from medicinal plants may mainly be attributed to various mechanisms such as P-gp inhibition activity, non-specific mechanisms promoting rapid absorption of drugs such as increased blood supply to the gastrointestinal tract, decreased hydrochloric acid secretion preventing break-down of some drugs, non-specific mechanisms inhibiting enzymes participating in metabolism of drugs. In many cases, bioavailability and absorption-enhancing effect of natural compounds from medicinal plants were reported to be attributed to inhibition of P-gp. Inhibitory effects of natural products on P-gp mediated paclitaxel transport in Caco-2 cells were shown in Table 2 (Hayeshi et al., 2006). In that study, flavone, quercetin and genistein showed a considerable P-gp inhibition activities compared to other natural compounds tested. Additionally, naringin and sinomenine were also reported to be inhibitors for efflux transporters such as P-gp and breast cancer resistance protein (BCRP) (Tsai et al., 2001; Chan et al., 2006) . Also, attenuation of physical barrier such as an increase in intestinal brush border membrane fluidity and inhibition of metabolic enzymes participating in biotransformation of drugs were reported to be absorption enhancing mechanisms of natural compounds (Khajuria et al., 2002) . In this section, experimental cases on bioavailability enhancement through co-administration of drugs with natural compounds are introduced.

Quercetin

Quercetin (2-(3,4-dihydroxyphenyl)- 3,5,7-trihydroxy-4*H*-chromen-4-one) is a flavonoid, an aglycone form of a number of other flavonoid glycosides found in citrus fruits. Quercetin has exhibited a wide range of beneficial biolo-

gical activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumoral and anti-viral effects (Nijveldt et al., 2001). Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem (Choi and Li, 2005), digoxin (Dupuy et al., 2003; Wang et al., 2004) and epigallocatechin gallate (Anup et al., 2005).

The plasma concentrations, the area under the plasma concentration-time curve (AUC) and peak concentration (C_{max}) of diltiazem in the rabbits pretreated with quercetin were significantly higher than those obtained from untreated group. It was reported that diltiazem is metabolized by CYP3A4 both in the liver and small intestine (Pichard et al., 1990; Molden et al., 2002) and the absorption of diltiazem in the intestinal mucosa was inhibited by P-gp efflux pump (Yusa and Tsuruo, 1989; Saeki et al., 1993). The increased AUCs and C_{max} of diltiazem by pretreatment of quercetin might have been resulted from the inhibition of the P-gp efflux pump and the metabolizing enzyme, CYP3A4 in the intestinal mucosa. There were reports on its inhibition ability of the P-gp efflux pump (Scambia et al., 1994; Shapiro and Ling, 1997) and restraint of the metabolizing enzyme, CYP3A4 (Dupuy et al., 2003; Miniscalco et al., 1992).

The absorption of epigallocatechin gallate was also reported to be enhanced with red onion supplementation, abundant source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1323 to 1814 ng h/ml, when co-administered with quercetin. Moreover, it was demonstrated that increased amount of quercetin administered along with epigallocatechin gallate could increase absorption of epigallocatechin gallate from the intestine (Anup et al., 2005).

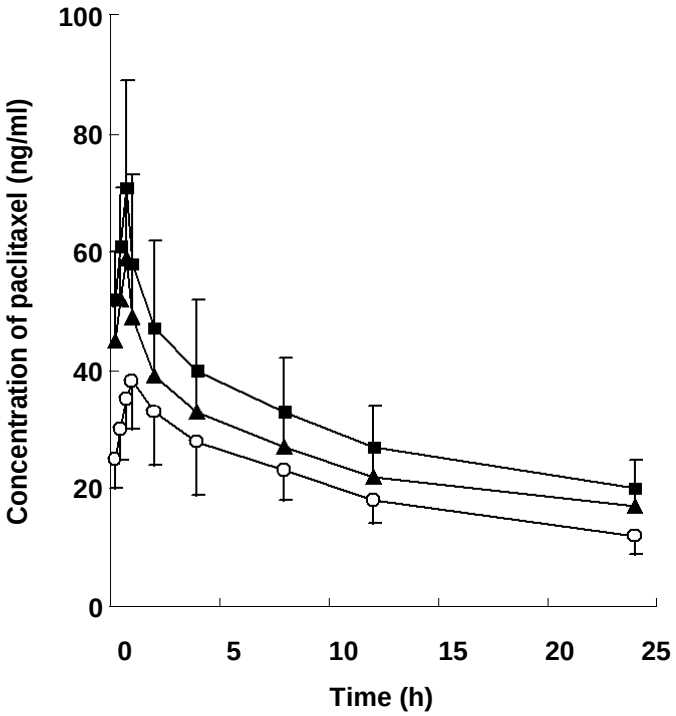

Figure 2. Mean plasma concentration–time curves of paclitaxel after oral administration of paclitaxel (30 mg/kg) to rats in the presence or absence of genistein (3.3 and 10 mg/kg). Bars represent the standard deviation (n = 6). ( ), oral administration of paclitaxel at a dose of 30 mg/kg; ( ), in the presence of genistein at a dose of 3.3 mg/kg; ( ), in the presence of genistein at a dose of 10 mg/kg) (Adapted from Li and Choi, 2007).

Genistein

Genistein (5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) belongs to the isoflavone class of flavonoids. It is also well known as a phytoestrogen (Kurzer and Xu, 2003). Since genistein was reported that it was able to inhibit P-gp, BCRP and MRP2 efflux function, the intestinal absorption of paclitaxel, a substrate for efflux transports such as P-gp (Sparreboom et al., 1997), BCRP (Doyle and Ross, 2003) and MRP2 (Huisman et al., 2005) was dramatically increased, co-administered with genistein. The inhibition of the efflux transporters by genistein also contributed the improvement of systemic exposure of paclitaxel (Li and Choi, 2007). The presence of genistein (10 mg/kg) caused an increase in AUC (54.7%) and a decrease in the total plasma clearance (35.2%) after oral administration of paclitaxel at a dose of 30 mg/kg in rats (Figure 2).

Naringin

Naringin (7-[[2-O-(6-Deoxy- -L-mannopyranosyl)- -D-glucopyranosyl]]oxy]-2,3-dihydro-5-hydroxy-2-(4 hydroxyphenyl)-4H-1-benzopyran-4-one) is the major flavonoid glycoside found in grapefruit and makes grapefruit juice taste bitter. Narinigin exerts a variety of pharmacological effects such as antioxidant, blood lipid-lowering and anticarcinogenic activities.

Also, naringin was reported to inhibit P-gp (Tsai et al., 2001) and CYP3A1/2 in rats (Zhang et al., 2000). Oral naringin (3.3 and 10 mg/kg) was pretreated 30 min before intravenous administration of paclitaxel (3 mg/kg) and after intravenous administration of paclitaxel, the AUC was significantly improved (40.8 and 49.1% for naringin doses of 3.3 and 10 mg/kg, respectively) (Lim and Choi, 2006).

Sinomenine

Paeoniflorin is a bioactive monoterpene glucoside, which has been widely used to treat inflammation and arthritic conditions. Paeoniflorin has a poor absorption rate and thus a very low bioavailability (3 – 4%) when administered orally (Takeda et al., 1995). Co-administrated sinomenine (7,8-didehydro-4- hydroxy-3,7-dimethoxy-17-methylmor phinan-6-one, an alkaloid extracted from *Sinomenium acutum* Thunb.) (Cheng et al., 1964), dra-

Table 3. Effect of piperine on the fluidity of intestinal brush border membrane- *In vitro* study (Reproduced from Khajuria et al., 2002).

Assay System	Fluidity Measured as excimer/monomer ratio
Buffer + Pyrene	0.072± 0.002
Buffer + Pyrene + Piperine (2 M)	0.076± 0.001
Buffer + Pyrene + BBMV	0.147± 0.002
Buffer + Pyrene + BBMV + Piperine (2 M)	9.25± .025
Buffer + Pyrene + BBMV + Piperine (5 M)	11.5± 0.45
Buffer + Pyrene + BBMV + Piperine (10 M)	13.1± 0.25
Buffer + Pyrene + BBMV + Piperine (20 M)	15.4 ± 0.30*
Buffer + Pyrene + BBMV + Piperine (50 M)	19.1 ± 0.60*

*p < 0.01 as compared to the control group (1% carboxymethyl cellulose in 0.9% saline).
Values are represented as Mean ± SEM for five experiments.
Excimer/Monomer ratio was measured at 470/372 nm.
BBMN means Brush border membrane vesicles.

Table 4. Effect of piperine on glycyl-glycine dipeptidase and leucine amino peptidase activation in rat jejunum (Reproduced from Khajuria et al., 2002).

Treatment groups (mg/kg body wt.)	Glycyl-glycine dipeptidase (moles of substrate hydrolyzed/min/mg protein)	Leucine amino peptidase (moles -naphthyl-amine released/min/mg protein)
Control	239 ± 37	12 ± 1.2
5.0	260 ± 9.0*	19 ± 2.9*
10.0	260 ± 10*	20 ± 2.0*
20.0	261 ± 11*	19 ± 3.5*

*p < 0.01 as compared to the control group (1% carboxymethyl cellulose in 0.9% saline).
Values are represented as Mean ± SEM for five rats.

matically altered the pharmacokinetic behaviors of paeoniflorin in rats (Liu et al., 2005). The results of AUC obtained in the study demonstrated that oral bioavailability of paeoniflorin was enhanced by more than 12 times in rats treated with sinomenine. The mechanism underlying this improvement of bioavailability of paeoniflorin may be explained by that sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine (Chan et al., 2006).

Piperine

Piperine (1-piperoyl piperidine) is a major alkaloidal component of *Piper nigrum* Linn. or *Piper longum* Linn. Piperine, or mixtures containing piperine, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs including ingredients of vasaka leaves, vasicine, sparteine, sulfadiazine, rifampicin, phenytoin and propranolol (Atal et al., 1981; Bano et al., 1987; Bano et al., 1991).

The mechanism of enhancing the drug bioavailability may be explained by following possible explanations: a) increased blood supply to the gastrointestinal tract, b) increased enzymatic activities like gamma- glutamyl trans-peptidase which participates in active transport of nutrients across the intestinal cells and c) non-specific mechanisms inhibiting enzymes involving in biotransformation of drugs, preventing their inactivation and elimination (Goldstein, 1984; Esposito, 1984).

It was recently proposed that absorption- enhancing ability exhibited by piperine may strongly be related to alteration of the lipid fluidity of the cell membrane (Table 3). Piperine caused the increased brush border membrane fluidity with concentration dependency. Piperine also can interact with proteins embedded in the cell membrane by stimulating leucine amino peptidase and glycyl-glycine dipeptidase activity (Table 4). This suggests that piperine could modulate the cell membrane dynamics related to passive transport mechanism due to its apolar nature by interacting with surrounding lipids and hydrophobic domain of cellular proteins (Khajuria et al., 2002).

Glycyrrhizin

Glycyrrhizin [(3 ,18)-30-hydroxy-11,30-dioxoolean-12-

en-3-yl 2-*O*- -D-glucopyranuronosyl- -D-glucopyranosiduronic acid] is a triterpenoid saponin found in *Glycyrrhiza glabra* Linn. Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested (Imai et al., 2005). The absorption-enhancing activity obtained from the simultaneous treatment of sodium deoxycholate and dipotassium-glycyrrhizin was much greater than sodium deoxycholate alone in Caco-2 cell monolayers (Sakai et al., 1999). The absorption enhancing activity of glycyrrhizin was increased by presence of the other absorption enhancers (Imai et al., 2005).

Nitrile glycosides

Nitrile glycosides and its derivatives are components derived from the pods of *Moringa oleifera* Lam. They do not possess drug activity of their own but reported to promote and augment the biological activity, bioavailability or the uptake of drugs in combination therapy. The nitrile glycoside (e.g. niaziridin) has enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients (Khanuja et al., 2005). In bioactivity test, niaziridin-rich fraction of *Moringa oleifera* Lam. remarkably enhanced activity of rifampicin, ampicillin and nalidixic acid by 1.2 – 19 folds against both the Gram (+) and (-) strains by enhancing drug absorption in culture model (Khanuja et al., 2005).

Cuminum cyminum Linn.

Cuminum cyminum Linn. is a small and thin annual herb, grown extensively in South-East Europe and North Africa bordering the Mediterranean sea. It is an effective gastric stimulant, beneficial in abdominal lump and flatulence. It has therapeutically been used as an anti-diarrheal, galactagogue, diuretic and also beneficial in hoarseness of voice (Zargari, 1989).

Bioavailability/bioefficacy enhancing activity of *Cuminum cyminum* Linn. was revealed toward a number of drugs (Qazi et al., 2009). Various volatile oils and luteolin and other flavonoids were seemed to attribute the bioavailability/bioefficacy enhancing activity. Especially luteolin has demonstrated to be a potent P-gp inhibitor in the literature (Boumendjel et al., 2002).

CONCLUSION

In this paper, bioavailability and absorption enhancing effects of natural products were introduced. Many compounds were reported that these compounds contribute the enhancing of co-administered drugs with significant enhancing therapeutic activities. In many cases, bioavailability enhancing effect of natural compounds could be attributed to inhibition of P-gp and oxidative metabolism with minimal toxic effects. Therefore, co-administration of natural compounds is expected to be one of the promising approaches to enhance the absorption and bioavailability of drugs.

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