Original Article

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Influence of quercetin and chrysin on the intestinal permeability of paclitaxel, a substrate of P-glycoprotein and CYP3A4 using *in vitro* rat gut sac

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Abstract

P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) play a significant role in the disposition and elimination of drugs. The objective of this study was to investigate the mechanism underlying the interaction between paclitaxel (substrate of P-gp and CYP3A4), quercetin and chrysin using everted gut sacs *in vitro* models. Non-everted gut sacs (NEGS) were used to evaluate the transport of paclitaxel from mucosal to serosal (M-to-S) side of the intestine. NEGS were loaded with 1 mL of modified Krebs-Ringer bicarbonate (KRB) buffer containing paclitaxel (50µg/mL) in the presence or absence of known P-gp and CYP3A4 inhibitors. Each sac was placed in individual 50 mL Erlenmeyer flasks containing 30 mL of oxygenated (O_2/CO_2; 95:5) KRB and incubated at 37 ºC for 60 min in a shaker bath. Aliquots (150 µL) of serosal fluid were collected at 10, 20, 30, 40, 50, 60, 70, 80 and 90 min and then replaced by the same volume of buffer. The paclitaxel levels in incubated samples were determined by UV-spectrophotometer at 227 nm. The same experiment was repeated with everted gut sacs (EGS) to study the transport of paclitaxel from serosal to mucosal (S-to-M) side of the intestine. *In vitro* study results showed that the apparent permeability coefficient (P_{app}), net efflux and efflux ratio of paclitaxel were significantly increased by quercetin and chrysin. The present study revealed that quercetin and chrysin enhanced the intestinal absorption of paclitaxel by inhibiting its absorption via P-gp and/or the CYP3A4-mediated biotransformation in intestine.

Keywords: P-glycoprotein, Paclitaxel, Quercetin, Chrysin, Everted Sacs, CYP3A4.

1. Introduction

Paclitaxel is a cytotoxic agent active against various types of malignancies and is used as a single agent or in combination with other agents for advanced gastric cancer. Paclitaxel is a microtubule inhibitor and is metabolized by cytochromes P450 (CYP) CYP3A4 and CYP2C8 isoenzymes to 3' p-hydroxypaclitaxel (3OHP) and 6α-hydroxypaclitaxel (6OHP) respectively (1). Multidrug resistance (MDR) persists as a major problem in the chemotherapeutic treatment of a wide variety of human carcinomas. The mdr1 gene product, P-glycoprotein (P-gp), is the active component involved in the mechanism of many incidences of MDR and acts as an ATP dependent drug efflux pump. Chemotherapeutic agents are actively expelled from MDR tumor cells that over express

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P-gp. This phenomenon limits the effectiveness and inhibits the target cell toxicity of drugs such as doxorubicin, paclitaxel, etoposide and vincristine (2).

Recent evidence suggests that overlapping substrate specificities and tissue distribution exist between drug metabolizing enzymes and P-gp (3). In particular, CYP3A4 has been shown to be one of the major enzymes involved in the metabolism of several anticancer agents and modulators of MDR. Saturation of its capacity to function as a metabolic catalyst in the liver and extrahepatic metabolic tissues is thought to result in drug-drug interactions (4). Predetermination of resulting adverse drug reactions is therefore a crucial step in drug development. In addition, the fundamental mechanism of action of P-gp inhibitors may disrupt pharmacokinetic properties of drugs by inhibiting mechanisms of drug absorption, distribution and elimination (5).

Numerous compounds have been screened / developed for the purpose of MDR modulation and belong to a number of chemical classes ranging from drugs to natural compounds including flavonoids. Quercetin and chrysin are natural flavonoids has been shown to have potent P-gp and CYP3A4 inhibitory activity both *in vitro* and *in vivo*. This report describes an investigation into potential drug interactions between quercetin, chrysin and paclitaxel. Rat gut sacs have been used to investigate the inhibition of paclitaxel transport and by quercetin and chrysin.

2. Materials and methods

2.1. Drugs and chemicals

Paclitaxel and pentobarbitone were obtained as gift samples from Hetero Drugs Limited, Hyderabad, India and KK Chemicals and Pharmaceuticals Private Limited, Pune, India, respectively. Quercetin and chrysin were purchased from Sigma Aldrich Chemicals, St. Louis, MO, USA. All other chemicals and reagents used were of analytical grade.

2.2. Rat gut sac study In vitro

2.2.1. Preparation of gut sac

The everted sac is a simple and useful in vitro model to study the drug absorption as described by Ravindra *et al*., 2013; Venkatesh *et al*., 2013 in our laboratory (6,7). This model provides information on drug absorption mechanisms through testing the drug content in the intestinal and transported through the intestinal tissue. Briefly, Male Wistar rats weighing about 180-220 g were deprived of food for 1 day and provided with only double-distilled water before the experiments. The rats were anesthetized with pentobarbital sodium 40 mg/kg and the small intestine of rats was dissected out. The intestines were rinsed with ice cold saline (0.9 %) in order to discard the intestinal digesta and the distal ileums of the rat intestines (approximately 10 cm each) were taken. Fat and mesenteric attachments were removed and the segments of each rat ileum were everted.

2.3. Influence of quercetin and chrysin on the transport of paclitaxel across everted gut sac

TEverted sacs were filled with modified Krebs–Ringer bicarbonate (KRB) buffer (NaCl 6.9 g, KCl 0.35 g, $MgSO4.7H_2O$ 0.29 g, KH_2PO4 0.16 g, $NaHCO_3$ 2.1 g, $CaCl_2$ 0.28 g, and 0.2% glucose, pH 7.3) containing paclitaxel 50 µg/mL in the presence or absence of quercetin and chrysin (50 µg/mL). Each sac was placed in individual 50 mL Erlenmeyer flasks contain 30 mL of oxygenated (O_2/CO_2; 95:5) KRB and incubated at 37 °C for 90 min in a shaker bath. Transport of paclitaxel from the serosal to the mucosal side was measured by sampling 1 mL of the outer medium (replaced by 1 mL KRB buffer) for every 10 min. Each experiment was triplicate. All the samples collected and centrifuged (Remi, R- 4C Compact model, Mumbai, India) at 6000 rpm for 10 min and the supernatants were analyzed for paclitaxel by UV-Spectrophotometer at 227 nm.

2.4. Influence of quercetin and chrysin on the transport of paclitaxel across non-everted gut sac

Same procedure was repeated with non-everted gut sacs to evaluate the transport of paclitaxel from the mucosal to the serosal side was measured by sampling 1 mL of the outer medium (replaced by 1 mL KRB buffer) for every 10 min. Each experiment was triplicate. All the samples collected and centrifuged (Remi, R- 4C Compact model, Mumbai, India) at 6000 rpm for 10 min and

Table 1. Cumulative amount of paclitaxel (µg/mL) from mucosal to serosal side using rat gut sac model with or without quercetin and chrysin (n=3). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	2.958±0.708	6.208±2.854NS	5.465±1.565 NS
20	4.591±1.025	8.293±5.557 NS	7.148±1.793 NS
30	5.767±0.904	9.538±5.852 NS	8.004±0.648 NS
40	6.827±1.299	12.124±1.027 NS	9.145±1.559 NS
50	7.319±1.601	14.309±1.120**	10.950±2.172 NS
60	7.322±1.428	14.853±0.834**	11.182±2.063 NS
70	7.968±1.833	15.781±2.763***	13.666±1.395*
80	8.263±1.712	16.075±2.121***	14.486±1.774*
90	8.791±1.665	19.382±2.062***	16.174±2.546**

the supernatants were analyzed for paclitaxel by UV-Spectrophotometer at 227 nm.

Calculation of apparent permeability coefficient (Papp), efflux ratio (ER) and net efflux (NE)

$$Papp = \frac{dQ}{dt} \times \frac{1}{A \times C_0}$$

$$ER = \frac{Papp(S-M)}{Papp\,(M-S)}$$

$$\text{Net Efflux} = P_{app}\,(S-M) - P_{app}\,(M-S)$$

2.5. Data Analysis

All statistics were calculated using Graph Pad Prism 5.0 software (San Diego, CA, USA). Parameter values of various groups were compared using analysis of variance with Tukey's and Dunnett's tests for multiple comparisons. The P value less than 0.05 were considered significant.

3. Results

Intestinal permeability of paclitaxel from mucosal to serosal (M-to-S) and serosal to mucosal (S-to-M) was determined in using rat everted and uneverted gut sacs *in vitro*. The cumulative amount of paclitaxel in the serosal and mucosal sides was calculated from the samples collected from incubation medium (KHB) every 10 min for 90 min shown in Tables 1 & 2. The permeability of paclitaxel form M-to-S was increased significantly from 8.791±1.665 to 19.382±2.062 (P<0.001) and 16.174±2.546 (P<0.01) in presence of quercetin and chrysin respectively at 90 min (Table 3 & 4). Paclitaxel permeability from S-to-M was increased insignificantly with quercetin and chrysin.

The apparent permeability coefficient (Papp), Efflux ratio (ER) and Net efflux (NE) were calculated using standard formulas. The Papp of paclitaxel form M-to-S was increased significantly

Table 2. Cumulative amount of paclitaxel (µg/mL) from serosal to mucosal side using rat gut sac model with or without quercetin and chrysin (n=3). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	2.390±0.568	3.101±0.578	2.976±0.285
20	2.697±0.539	4.822±0.712	4.153± 1.509
30	3.33±0.879	5.338±1.450	5.757±1.523
40	3.991±1.343	6.335±1.744	7.549±1.646
50	5.009 ±1.537	6.624±1.728	8.382±1.001
60	5.314±1.374	8.041±2.631	9.116±1.874
70	5.963±1.288	8.442±1.908	9.739±1.328
80	7.049±1.397	9.220±2.200	10.489±1.992
90	7.924±2.038	11.062±2.551	11.192±1.865

Table 3. Apparent permeability coefficient of paclitaxel ($\times 10^{-4}$ cm/s) from mucosal to serosal side using rat gut sac model with or without quercetin and chrysin (n=3 sacs). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	4.929±1.180	10.346±4.758**	9.109±2.608*
20	3.825±0.854	6.911±4.631*	5.956±1.442NS
30	3.203±0.501	5.298±3.251*	4.446±0.360NS
40	2.844±0.541	5.051±0.428*	3.810±0.649NS
50	2.439±0.534	4.769±0.403*	3.316±0.723NS
60	2.033±0.396	4.125±0.231***	3.105±0.573NS
70	1.897±0.436	3.757±0.657***	3.253±0.331**
80	1.721±0.356	3.384±0.499***	3.107±0.369**
90	1.627±0.308	3.589±0.381***	2.994±0.471**

from 1.627±0.308 to 3.589±0.381 (P<0.001) and 2.994±0.471 (P<0.01) in presence of quercetin and chrysin respectively at 90 min presented in Table 3 & 4. The Papp of paclitaxel form S-to-M was increased significantly from 1.569±0.638 to 2.965±0.805 (quercetin) and 3.198±0.846 (chrysin) at 30 min. The ER of paclitaxel was decreased with quercetin and chrysin when compared to paclitaxel alone but statistically insignificant (Table 5). The net efflux of paclitaxel was decreased significantly from -0.160±0.077 to -1.541±0.689 (quercetin) and decreased insignificantly from -0.160±0.077 to -0.922±0.730 with chrysin (Table 6).

4. Discussion

The primary objective of this study was to evaluate intestinal transport of paclitaxel in with or without quercetin and chrysin using rat gut sacs in vitro to predict pharmacokinetic drug-drug interactions (DDI). The results demonstrated that quercetin and chrysin significantly enhanced the absorption of paclitaxel. As paclitaxel is mainly metabolized by hepatic cytochrome P450 enzymes and transported by P-gp. In DDI studies with other drugs/compounds, similar results were shown. Previous investigations suggested that interactions between inhibitors of CYP3A4, P-gp and anticancer agents may result from saturation of the capacity of drug metabolizing enzymes that function as metabolic catalysts in the liver and extrahepatic metabolic tissues. The P-gp modulator, OCI44-093, is a potential candidate for use in cancer therapy enhanced oral bioavailability of paclitaxel (P-gp substrate) in study conducted with human liver microsomes in vitro due to inhibition of P-gp (8). In another study, the absorption of paclitaxel was increased in the presence of apigenin, rutin, and verapamil, a typical P-gp and CYP3A4 inhibitor

Table 4. Apparent permeability coefficient of Paclitaxel ($\times 10^{-4}$ cm/s) from serosal to mucosal side using rat gut sac model with or without quercetin and chrysin (n=3 sacs). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	3.983±0.947	5.168±0.963NS	4.955±0.475NS
20	2.247±0.449	3.993±0.568*	3.461±1.257NS
30	1.569±0.638	2.965±0.805*	3.198±0.846**
40	1.542±0.559	2.639±0.726NS	3.145±0.686**
50	1.669±0.512	2.208±0.576NS	2.793±0.333*
60	1.476±0.382	2.233±0.731NS	2.532±0.520NS
70	1.419±0.306	1.771±0.454NS	2.318±0.316NS
80	1.467±0.291	1.754±0.458NS	2.184±0.415NS
90	1.467±0.377	2.048±0.472NS	2.072±0.345NS

Table 5. Efflux ratio of paclitaxel from serosal to mucosal side using rat gut sac model with or without quercetin and chrysin (n=3 sacs). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	0.808±0.006	0.603±0.382NS	0.569±0.138NS
20	0.599±0.129	0.862±0.677NS	0.585±0.152NS
30	0.579±0.141	0.721±0.465NS	0.714±0.148NS
40	0.583±0.156	0.516±0.098NS	0.822±0.072NS
50	0.694±0.205	0.471±0.617NS	0.853±0.084NS
60	0.730±0.164	0.542±0.181NS	0.813±0.016NS
70	0.750±0.025	0.477±0.134NS	0.719±0.139NS
80	0.855±0.064	0.509±0.141NS	0.734±0.179NS
90	0.891±0.073	0.577±0.169NS	0.709±0.185NS

(9).

Similarly, Choi *et al*., 2005 conducted a study to investigate the effect of verapamil on the pharmacokinetic parameters of paclitaxel (50 mg/kg) when paclitaxel is co-administered with verapamil (1, 5, and 15 mg/kg) orally in rats. The results suggested that the bioavailability of paclitaxel was increased with verapamil in the dose dependent manner due to inhibition of CYP3A4 in the intestinal mucosa and liver, and the P-gp efflux pump in the intestinal mucosa (10). In another study, the effect of morin on the pharmacokinetics of orally and intravenously administered paclitaxel was evaluated in rats. The results suggest that the enhanced oral exposure of paclitaxel should be mainly due to the inhibition effect of morin on P-gp mediated gastrointestinal transport of paclitaxel during the intestinal absorption (11).

Silibinin, a flavonoid, is an inhibitor of P-glycoprotein (P-gp)-mediated efflux transporters, and its oxidative metabolism is catalyzed by CYP3A4. The effect of oral silibinin on the bioavailability and pharmacokinetics of orally and intravenously administered paclitaxel was investigated in rats. The effect of silibinin on the P-gp as well as CYP3A4 activity was also evaluated. Compared to the control group, silibinin significantly increased increased intestinal absorption, peak plasma concentration and absolute bioavailability of paclitaxel due to P-gp inhibition (12).

Similarly, the effect of orally administered genistein (isoflavonoid), an inhibitor of P-gp, CYP3A4 and 2C8 on the pharmacokinetics of paclitaxel was investigated in rats. The presence of 10 mg/kg genistein significantly (P<0.05) increased the area under the plasma concentration-time curve (AUC, 54.7% greater) of orally administered paclitaxel, which was due to the significantly (P<0.05) decreased total plasma clearance (CL/F) of paclitaxel (35.2% lower). Genistein also in-

Table 1. Net Efflux of paclitaxel ($\times 10^{-4}$ cm/s) from serosal to mucosal side using rat gut sac model with or without quercetin and chrysin (n=3 sacs). Data expressed as Mean±SD.

Time (Min)	Paclitaxel	Paclitaxel+quercetin	Paclitaxel+chrysin
10	-0.946±0.234	-5.161±5.436*	-4.154±2.398NS
20	-1.578±0.822	-2.917±5.144NS	-2.495±1.266NS
30	-1.354±0.569	-2.333±2.680NS	-1.248±0.635NS
40	-1.181±0.539	-2.352±0.230NS	-0.665±0.273NS
50	-0.770±0.628	-2.561±0.977**	-0.522±0.394NS
60	-0.557±0.405	-1.892±0.772NS	-0.573±0.053NS
70	-0.477±0.140	-1.985±0.746*	-0.935±0.557NS
80	-0.253±0.147	-1.672±0.619*	-0.833±0.654NS
90	-0.160±0.077	-1.541±0.689*	-0.922±0.730NS

creased the peak concentration (Cmax) of paclitaxel significantly (P<0.05 by 3.3mg/kg, 66.8% higher; P<0.01 by 10mg/kg, 91.8% higher). The presence of genistein improved the systemic exposure of paclitaxel in this study due to inhibition of P-gp and CYP3A4 (13).

Schisandrol B (Sch B), one of the active components in Schisandra, has been reported to be able to inhibit the activity of P-gp and CYP3A. It might be possible that Sch B would alter the pharmacokinetic behavior of paclitaxel, a substrate of P-gp and CYP3A4. Therefore, the effect of Sch B on the pharmacokinetics of paclitaxel administered orally and intravenously was investigated in rats. Paclitaxel were administered to rats orally (30 mg/kg) or intravenously (0.5 mg/kg) with or without the concomitant administration of Sch B (10 or 25 mg/kg). Oral pharmacokinetic parameters of paclitaxel were significantly altered when pretreated with Sch B. There were significant increases in oral bioavailability, AUC and Cmax in the presence of Sch B (25 mg/kg) due to P-gp and CYP3A4 inhibition (14).

The effects of silymarin, an inhibitor of the P-glycoprotein efflux pump, on oral bioavailability of paclitaxel were evaluated in rats. The result revealed that oral bioavailability of paclitaxel is significantly improved by co-administration with silymarin (10 and 20 mg/kg), an inhibitor of the P-gp efflux pump (15). Similarly, the effect of naringin on the bioavailability and pharmacokinetics of paclitaxel after oral administration of paclitaxel or its prodrug co-administered with naringin was investigated in rats. This study results revealed that the absolute bioavailability (AB, %) of paclitaxel with naringin was significantly higher (3.5-6.8%, P<0.01) than the control (2.2%) due to inhibition of P-gp and CYP3A4 (16).

The activities of P-gp and drug-metabolizing enzymes can be inhibited by several flavonoids or drugs in rats. Chrysin as a model flavonoid because it possesses anti-inflammatory and antioxidative properties and is used as a dietary supplement. The pharmacokinetics of nitrofurantoin, a specific Bcrp substrate, after oral or intravenous administration in rats and mice treated with chrysin. Oral chrysin increased plasma concentrations of nitrofurantoin in rats due to inhibition of Bcrp in the small intestine in rats (17, 18).

5. Conclusion

The present study results revealed that quercetin and chrysin significantly increased the absorption of paclitaxel may be due to the inhibition of P-gp and CYP3A4.

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Conflict of Interest

None declared.

5. References

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