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EFFECT OF CO-ADMINISTRATION OF QUERCETIN ON GOAT INTESTINAL PERMEABILITY OF BERBERINE CHLORIDE

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ABSTRACT: The purpose of the present study was to explore the effect of co-administration of bioenhancer quercetin on membrane permeability of poorly permeable berberine chloride, on goat intestinal membrane model. The effect of co-administration of quercetin was investigated at 2, 6, and 10 mg concentrations. The study revealed a beneficial effect of low concentration of quercetin on % cumulative drug release (% CDR) of the drug under treatment. The co-administration process resulted in remarkable improvement in the permeability of berberine chloride (% CDR 28.33 ± 1.87) at 2 mg of quercetin. On the contrary, the permeability of berberine chloride was decreased (% CDR 10.46 ± 1.55) at 10 mg concentration of quercetin as compared to berberine chloride alone (% CDR 8.49 ± 1.45 at 10 mg). Apparent permeability coefficient, flux, and enhancement ratio were also found to be increased significantly with decreasing concentration of quercetin as compared with the control. It could be concluded that the use of quercetin will be beneficial for co-administration to enhance the permeability, bioavailability, and reduce the dose, resulting in improved therapeutic outcome of the naturally occurring berberine chloride.

INTRODUCTION: The natural product berberine is an isoquinoline alkaloid most widely used for centuries in Ayurveda and traditional Chinese medicine for the treatment of inflammatory conditions, diarrhea, gastroenteritis and hypertension [1, 2]. Recent research has shown that berberine has diverse promising biological actions against metabolic disorders, microbial infections, as an anti-oxidant, hepatoprotective, anti-arrhythmic, anti-malarial, hypolipidemic, hypoglycemic, anti-proliferative, and antineoplastic activities, *etc.* [3-7]

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As berberine has a variety of activities, low cost, and low toxicity profile, it has gained special interest recently from a therapeutic point of view. However, oral use of berberine has been restricted greatly as it has poor intestinal permeation and very poor bioavailability [8]. It has been reported that berberine is a substrate of multidrug efflux pump P-glycoprotein (P-gp) that acts as an absorption barrier for berberine that leads to poor intestinal absorption that limits its oral use [2].

The pharmacokinetic study of berberine reveals that presence of secretory transporters like P-gp at intestinal epithelium restricts permeation of berberine into systemic circulation by active transport of berberine back into the intestinal lumen and thus it lowers intracellular drug concentration [9]. Thus, the major challenging task to the research scientist lies with improvement in the permeability

as well as bioavailability of berberine to enhance its use in clinical applications. This can be achieved by effectively limiting the activity of P-gp through use of natural, safe, effective herbal bioenhancers that will lead to significant improvement in oral absorption of drugs and has produced a revolutionary shift in the way of therapeutics. Bioenhancers can enhance permeability, bioavailability as well as bioefficacy of drugs with which they are administered. Their mechanistic way of bioenhancement is mainly through the absorption process, drug metabolism, and action on drug target. It has been hypothesized that co-administration of poorly permeable berberine chloride with bioenhancer might improve oral permeability, bioavailability, pharmacological actions as well as reduces its gastrointestinal adverse effects. The use of bioenhancers can make the treatment cost-effective and reduce the toxic effects by reducing the required dose and dosing frequency of drugs [10]. Quercetin is one of the natural and safe herbal bioenhancers which acts as an inhibitor of metabolizing enzymes CYP3A4 and P-gp [11-13].

To the knowledge, several oral formulation techniques such as nanoformulations [1, 14], encapsulation [15, 16], spray drying [17], use of synthetic P-gp inhibitors cyclosporin A, verapamil [18] pretreatment with quercetine [19,] *etc*. have been attempted to overcome poor bioavailability of berberine. However, it was hardly difficult to find out the literature concerning permeability studies of berberine chloride by co-administration process with another molecule. Thus, the beneficial properties of bioenhancers stimulated our interest to examine the effect of co-administration of quercetin on membrane permeability of berberine chloride in goat intestinal model in the present work.

MATERIALS AND METHODS:

Materials: All the chemicals used for all experimental procedures were of analytical grade. Berberine chloride sample was kindly gifted by Indo German Alkaloids, Mumbai, India. Quercetin was purchased from High Media Laboratories Pvt. Ltd. India. Deionized double distilled water was used for the study. Fresh goat intestine was obtained from the local slaughterhouse and used within 1 h of the killing of the goat [19].

Permeability Study: Freshly excised goat intestinal tissue was used for permeability study, as goat jejunum is a reliable predictor of oral absorption in humans [20]. It was cut into area 3.2 cm^2 and thickness 500-600 µm and was kept alive by oxygen supply with an aerator and phosphate buffer pH 7.4. As a control sample, 10 mg of berberine chloride was used (Sample code Bo).

For the test sample, a dose of berberine chloride was kept uniform (10 mg), and three different concentrations of quercetin were co-administered along with berberine chloride, as shown in **Table 1**.

TABLE 1: EXPERIMENTAL PLAN FOR STUDY

Composition of Test sample: Berberine + Quercetin		
Sample code	**Berberine chloride (mg)**	**Quercetin (mg)**
Bo	10	--
CoB1	10	2
CoB2	10	6
CoB3	10	10

Co: Co-administration; B: Berberine chloride

The permeability study of pure berberine chloride in the presence (co-administration) and absence (control) of bioenhancer quercetin was performed on excised goat intestine using Franz diffusion cell in phosphate buffer pH 7.4. Goat intestinal membrane with mucosal side orienting upward was tightly clamped between chambers of diffusion cell having 12 ml receptor chamber capacity and 3.14 cm^2 area available for diffusion.

During the study, receptor fluid maintained at 37 ± 1 ºC was stirred at 100 rpm with teflon coated magnetic stirring bead. Berberine chloride in presence and absence of quercetin was loaded on the donor side, and at every 30 min time interval, 2 ml aliquots collected from receptor side were analyzed by UV spectrophotometer at 341 nm maintaining sink condition up to 6 h and cumulative amount permeated was determined (n = 3). Data obtained from permeability study for each test and control sample were used to determine permeability parameters such as % cumulative drug release (%CDR), expressed as mean ± SD, apparent permeability (P_{app}), Flux (J*)* and enhancement ratio (ER) (n=3) by following standard formulae [21, 22].

Permeability coefficient (apparent permeability)-

$$Papp\left(\frac{cm}{s}\right) = \left(\frac{VA}{[area \times time]}\right) \times \left(\frac{[Drug]acceptor}{[Drug]donar}\right)$$

Where,
V_A = volume in acceptor chamber,
Area = intestinal membrane surface area,
Time = total transport time.

$$Flux\ (J)\left(\frac{\frac{mg}{cm2}}{hr}\right) = \frac{mass\ diffusing}{surface\ area \times time}$$

Enhancement Ratio (ER) = Papp of combination / Papp of control

RESULTS AND DISCUSSION: Results of the permeability study of test and control sample are shown in **Table 2**.

TABLE 2: %CDR OF BERBERINE CHLORIDE FROM CONTROL AND COADMINISTRATION STUDY

Time (h)	Bo*	CoB1*	CoB2*	CoB3*
0.5	0.28 ± 0.03	0.96 ± 0.07	1.09 ± 0.19	0.78 ± 0.20
1	0.83 ± 0.20	1.72 ± 0.16	2.39 ± 0.60	1.41 ± 0.43
1.5	1.39 ± 0.38	2.30 ± 0.11	3.05 ± 0.75	2.14 ± 0.45
2	1.97 ± 0.05	2.96 ± 0.14	4.18 ± 0.50	2.78 ± 0.30
2.5	2.34 ± 0.15	10.09 ± 0.94	6.32 ± 1.05	3.32 ± 0.29
3	2.95 ± 0.00	12.50 ± 0.72	7.43 ± 0.99	4.06 ± 0.27
3.5	3.50 ± 0.14	15.96 ± 1.07	8.43 ± 1.05	5.46 ± 0.69
4	4.50 ± 0.41	18.33 ± 1.35	9.49 ± 1.21	6.56 ± 0.98
4.5	5.53 ± 0.30	21.03 ± 1.46	10.48 ± 1.29	7.77 ± 0.96
5	6.95 ± 1.1	23.62 ± 1.52	11.53 ± 1.41	8.72 ± 1.20
5.5	7.7 ± 1.28	26.05 ± 1.60	12.63 ± 1.59	9.55 ± 1.39
6	8.49 ± 1.45	28.33 ± 1.87	13.53 ± 1.60	10.46 ± 1.55

% CDR: % cumulative drug release; *data expressed as mean ± S.D. (n = 3): S.D. standard Deviation; Co: Co-administration; B: berberine chloride; Bo: pure Berberine chloride; CoB1: berberine chloride + quercetin (2 mg); CoB2: berberine chloride + quercetin (6 mg); CoB3: berberine chloride + quercetin (10 mg)

Berberine chloride (control) has shown poor membrane permeability of 8.49 ± 1.45% CDR only. The previously reported reasons for poor membrane permeability, low bioavailability and poor stability of berberine were, low apparent oil-water partition coefficient (Ig*Papp* = - 1.08), presence of hydrophobic properties like two methoxy groups and a quaternary ammonium cation in its structure that shows high affinity to the multidrug efflux pump P-gp in gastrointestinal system. Berberine was reported to be a substrate of P-gp efflux pump [23, 24]. In caco-2 cell line study, it was reported that, when synthetic P-gp inhibitors like cyclosporine and verapamil were co-administered with berberine, there was marked enhancement in the absorption of berberine,[18] indicating involvement of P-gp pump in the efflux of berberine into the intestinal lumen, leading to poor absorption and thus low bioavailability [24]. As quercetin act as an inhibitor of P-gp [11-13], co-administration of quercetin has a positive influence on permeability characteristics of berberine chloride. The calculated values of permeability parameters % CDR, Papp, J and ER upto 6 h in cases of all samples has been shown in **Table 3**.

TABLE 3: OBSERVED RESPONSE VALUES WITH *EX-VIVO* PERMEABILITY PROFILES

Samples	%CDR	Papp $\times 10^{-7}$cm/s	*J* mg/cm^2/hr	ER
Bo	8.49	6.37	0.0451	---
CoB1	28.33	19.46	0.1502	3.0549
CoB2	13.53	8.67	0.0716	1.3610
CoB3	10.46	7.43	0.0557	1.1664

Co: Co-administration; B: Berberine chloride; Bo: pure Berberine chloride; CoB1: berberine chloride + quercetin (2 mg); CoB2: berberine chloride + quercetin (6 mg); CoB3: berberine chloride + quercetin (10 mg); %CDR: percentage cumulative drug release; Papp: apparent permeability coefficient; J: flux *i.e.* amount of drug permeated through a unit area in a unit of time; ER-enhancement ratio.

The effect of different concentrations of quercetin on % CDR of berberine chloride has been presented in **Fig. 1**. During co-administration process, it was found that permeability of berberine chloride was remarkably improved (% CDR 28.33 ± 1.87) at 2 mg of quercetin, while minimum value (% CDR 10.46 ± 1.55) was observed at 10 mg quercetin as compared to control sample berberine chloride (% CDR 8.49 ± 1.45 at 10 mg).

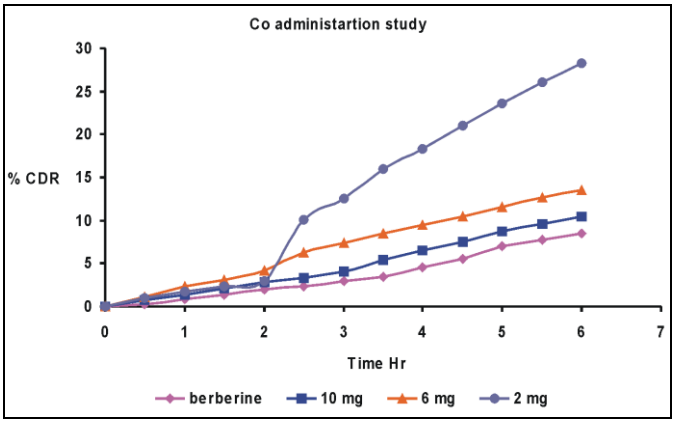

FIG. 1: EFFECT OF CO-ADMINISTRATION OF DIFFERENT CONCENTRATIONS OF QUERCETIN ON % CDR % CDR: CUMULATIVE DRUG RELEASE

It was reported that, during co-administration of a high dose of quercetin (20 mg) with diltiazem in rabbits, the bioavailability of diltiazem was not improved significantly compared with the control. This might be due to the interaction of quercetin with diltiazem in the gastrointestinal lumen to form the complex by co-administration of a high dose of quercetin (20 mg) [25].

Similarly, in the present permeability study on goat intestine, it was found that decrease in the concentration of quercetin has a positive effect of on permeability profile of berberine chloride. Papp, J, and ER were also found to be increased significantly with decreasing concentration of quercetin as compared with the control.

CONCLUSION: In the present investigation, co-administration of quercetin with berberine chloride has a positive influence on membrane permeability of berberine chloride, illustrating 2 mg of quercetin was optimum to increase the permeability of poorly permeable berberine chloride up to a maximum of 28.33 ± 1.87% CDR. It could be concluded that co-administration of quercetin as a bioenhancer would be effective to enhance the membrane permeability and plausibly bioavailability of poorly permeable berberine chloride with improved therapeutic effectiveness.

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COMPETING INTEREST: The authors declare that they have no conflict of interest in this work.

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