# Enhanced Oral Bioavailability of Domperidone with Piperine in Male Wistar Rats: Involvement of CYP3A1 and P-gp Inhibition.

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**ABSTRACT - Purpose:** Domperidone is a commonly used antiemetic drug. The oral bioavailability of domperidone is very low due to its rapid first pass metabolism in the intestine and liver. Piperine, the main alkaloid present in black pepper has been reported to show inhibitory effects on Cytochrome P-450 (CYP-450) enzymes and P-glycoprotein (P-gp). In the present study we investigated the effect of piperine pretreatment on the intestinal transport and oral bioavailability of domperidone in male Wistar rats. **Methods***:* The intestinal transport of domperidone was evaluated by an *in-vitro* non-everted sac method and *in-situ* single pass intestinal perfusion (SPIP) study. The oral pharmacokinetics of domperidone was evaluated by conducting oral bioavailability study in rats. **Results***:* A statistically significant improvement in apparent permeability (Papp) was observed in rats pretreated with piperine compared to the respective control group. The effective permeability (Peff) of domperidone was increased in the ileum of the piperine treated group. Following pretreatment with piperine, the peak plasma concentration ($C_{max}$) and area under the concentration- time curve (AUC) were significantly increased. A significant decrease in time to reach maximum plasma concentration ($T_{max}$), clearance and elimination rate constant ($K_{el}$) was observed in rats pretreated with piperine. **Conclusions:** Piperine enhanced the oral bioavailability of domperidone by inhibiting CYP3A1 and P-gp in rats. This observation suggests the possibility that the combination of piperine with other CYP3A4 and P-gp dual substrates may also improve bioavailability. Further clinical studies are recommended to verify this drug interaction in human volunteers and patients.



## INTRODUCTION

Oral administration has been the most common and convenient route for administration of drugs because of its high patient compliance in combination with a relatively simple and cost efficient manufacturing process. The design of a new dosage form generally depends on the pharmacokinetic and pharmacodynamic parameters of the drug (1). Some drugs remain sub-therapeutic when administered orally if they are poorly bioavailable. This poor oral bioavailability of a drug may be due to metabolism by their corresponding enzymes like CYP450 and efflux from their site of action by P-glycoprotein (P-gp). The major portion of a given dose may never reach the systemic circulation to exert its pharmacological effect until and unless very large doses are given. Lowering the dose and dosing frequency of such drugs can be achieved by significantly improving the oral bioavailability of drugs. Plant-based molecules are most widely used as bioavailability enhancers in combination therapy (2). Following the use of natural bioenhancers, the dose of the drug may be reduced, the risk of drug resistance may be minimized and also the dose-dependent toxicity of the drug, especially with anticancer drugs may be reduced.

The increase in consumption of herbal products as complementary and/ or alternative medicine has been observed during the last decade. Herbal products are generally considered as natural and safe with minimal adverse effects (3, 4). The concomitant use of herbal drugs along with prescription drugs may lead to possible herb - drug interactions.

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The ability of intestinal and hepatic drug transporters to efflux drugs and drug metabolizing enzymes to metabolize drugs is often responsible for poor oral bioavailability. This may lead to herb-drug and food-drug interactions for numerous drugs. The risk of herbal drug interactions possesses two major extreme challenges - adverse toxic reactions and therapeutic failure. Drug toxicity can result from inhibition of drug efflux transporters (P-gp) and metabolic enzymes (CYP-450) responsible for the increase in systemic exposure of drugs. Therapeutic failure can result from induction of efflux transporters and metabolic enzymes leading to faster efflux and metabolism of drugs (5). The close chromosomal location of P - glycoprotein and CYP3A4 (analogous enzyme in rat is CYP3A1) genes, their expression and similar substrate specificities in matured enterocytes suggest that these two proteins may be complementary in nature to form a coordinated intestinal barrier (6).

Black pepper (*Piper nigrum*) is one of the most widely used spices in human diets. Piperine, the main active constituent present in black pepper, is an alkaloid contributing pungency to the pepper. Black pepper is considered as king of spices because of its high volume of international trade (7). Bhardwaj et al., studied the influence of piperine on human CYP450 by human liver microsomes and reported that piperine inhibited the major drug metabolizing enzyme CYP3A4 (8).

Domperidone oral bioavailability is reported to be around 20-25 %. The innate low oral bioavailability of domperidone is due to drug metabolizing enzymes (CYP3A4) and efflux transporters (P-gp) which are located in epithelial cells (enterocytes) lining the small intestine and in the parenchymal cell of the liver (hepatocytes) (9). Consequently, orally administered domperidone can be metabolized twice before reaching the systemic circulation. Thus, oral bioavailability can be markedly attenuated. Significant difference in absorption of domperidone on pretreatment with silymarin was observed due to the inhibition of P-g and CYP3A(10). Domperidone stimulates gastrointestinal motility and is used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies, including that associated with cancer therapy and with levodopa or bromocriptine therapy for Parkinson's disease (11, 12).

The aim of the present study was to observe the influence of piperine pretreatment for 8 days on the intestinal permeation of domperidone in male Wistar rats *in vitro, ex vivo* and to observe the effect of piperine pretreatment for 8 days on the oral bioavailability of domperidone in male Wistar rats.

## MATERIALS AND METHODS

Domperidone was kindly donated by Sun Pharmaceuticals, Baroda, India. Propranolol and verapamil were procured from Lupin Labs Pharmaceuticals Inc, Pune, India). Phenol red was purchased from Himedia (Ghatkopar West, Mumbai, India), and methanol HPLC and acetonitrile HPLC (E. Merck Ltd Vikrolo, East Mumbai, India) were used. All other chemicals used were of AR grade.

Male Wistar rats weighing about 220–240 g were purchased from Mahaveera Enterprises, Ghatkesar road, Hyderabad, India. Rats housed in cages were kept in a room under controlled temperature (20– 22º C) and 12 h day–night cycle. Animals were used for studies after 1-week acclimatization with free access to water and feed. The animal study protocol was reviewed and approved by Institutional Animal Ethics Committee of Kakatiya University (Vidhyaranyapuri, Warangal, IAEC, TS, and India). All the animals were grouped and treated with the following regimens.

The rats were divided into three groups

Group I(control): All the rats in this group were pre-treated orally with 0.25% w/v sodium carboxy methyl cellulose (Sod.CMC) for 7 days and also on the 8$^{th}$ day, 1hr prior to the study (non-everted and perfusion studies). Group II (piperine treated): The rats received piperine (20mg/kg/oral) suspension (0.25%w/v Sod.CMC) for 7 days and also on the 8$^{th}$ day 1hr prior to the study (non- everted and perfusion studies). Group III (verapamil treated): Verapamil (100µM) was co-administered along with buffer containing domperidone (100µg/ml).

**Non-everted sac (normal sac) study**

Male Wistar rats were fasted overnight with free access to water before the experiment. Their intestines were flushed with 50 mL of ice-cold saline with the animal under anesthesia using thiopental sodium (50mg/kg/ip). The rat was exsanguinated, the ileum was isolated and a segment was cut into a length of 10cm for preparation of the sac. One hundred microgram per milliliter (100µg/mL) of domperidone (probe drug) was prepared by dissolving domperidone in pH 7.4

isotonic Dulbecco's Phosphate Buffer Saline (D-PBS) containing 25 mM glucose and 0.5 % of DMSO. The probe drug solution (1mL) was introduced into the non-everted sac (mucosal side), and both ends of the sac were ligated tightly. The sac containing the probe drug solution was immersed into 40 mL of D-PBS containing 25 mM glucose and the same concentration of DMSO was used. The medium was pre-warmed at 37 $^{O}$C and pre-oxygenated with 5% $CO_2$/ 95% $O_2$ for 15 minutes. Under bubbling with a $CO_2/O_2$ mixture gas, the transport of the domperidone from mucosal to serosal surfaces across the intestine was measured by sampling the serosal medium periodically for 120 minutes. Samples of 1 mL were collected at pre-determined time intervals from the serosal medium and replenished with fresh buffer (13). The drug transported was measured using high performance liquid chromatography (HPLC).

**Apparent permeability coefficient ($P_{app}$):**
The apparent permeability coefficient for domperidone was calculated from the equation given below.

$$P_{app} = \frac{dQ}{dt} \cdot \frac{1}{AC0}$$

where, dQ/dt is the rate of drug transport (domperidone) from mucosal to serosal medium, A is the surface area of the intestinal sac used for the study and C0 is the initial concentration of drug present in the intestinal sac (14).

***In situ*, single-pass intestinal perfusion (SPIP) study**
The *in situ* single-pass intestinal perfusion (SPIP) study was performed according to the previously reported methods (15, 16, 17). Briefly, the rats were divided into three groups: control, standard inhibitor and pretreatment consisting of six animals each. Piperine suspension was administered orally to the pretreated group at a dose of 20 mg/ kg for 8 days and verapamil(100µM) solution was concomitantly administered along with domperidone (100mcg/mL), and the other group was kept as control. The perfusion study was conducted on the 8th day after piperine pretreatment. Rats were anesthetized with thiopental sodium (50 mg/kg, ip) and they were placed on a warm pad to maintain normal body temperature. A midline incision of 3–4 cm was made on the abdomen of rats and an ileum segment of approximately 8–12 cm was isolated using the ileo-caecal junction as a distal marker. Semi-circular incisions were made at each end of the ileum and the lumen was rinsed with normal saline (37 ºC) and both ends were cannulated with polyethylene tubing and ligated using a silk suture. Subsequently, blank perfusion buffer (phosphate buffer saline, pH 7.2) was first infused for 5 min at a flow rate of 1 mL/min using a syringe pump (NE-1600, New Era Syringe Pumps, Inc. NY, USA), followed by perfusion of phosphate buffer saline (pH 7.2) containing domperidone (100µg/ml), propranolol (100 µM) and phenol red (50 mg/mL) at a constant flow rate of 0.2 mL/min for a period of 90 min and the perfusate was collected at 10 min intervals. After completion of cannulation, the ileum segment was covered with isotonic saline-wet gauze (37ºC). At the end of the perfusion, the length of the ileum segment was measured following the last sample collection. Perfusion samples were collected from the control and pretreatment groups at predetermined time points and stored at -80ºC until analysis. Domperidone concentrations in perfusion samples were analyzed by HPLC (10).

**Phenol red water flux correction**
The corrected outlet concentration ($C_{out\ (corr)}$) for domperidone was calculated from the following equation (15).

$$Cout(corr) = Cout \times \frac{\text{Concentration of Phenol red in (CPRin)}}{\text{Concentration of Phenol red out (CPRout)}}$$

where, $C_{out}$ is outlet concentration of the drug, whereas $CPR_{in}$ and $CPR_{out}$ are the concentrations of phenol red entering and exiting the rat intestinal segment, respectively.

**Effective permeability coefficient ($P_{eff}$)**
The effective permeability coefficient of domperidone was calculated from the following equation.

$$Peff = \frac{-Q \times \ln\left(\frac{Cout(corr)}{Cin}\right)}{2\pi rL}$$

Where, Q is the perfusion flow rate, , $C_{in}$ is the inlet drug concentration, r is the radius of the rat small intestine and L is the length of the perfused intestinal segment (13).

Peff was estimated from the steady state concentration of compounds which is considered to be attained when the concentration of phenol red in the perfusate samples is stable. Generally, steady state was reached at 30–40 min after the beginning of the experiment.

***In vivo* bioavailability study in male Wistar rats**

The animal study protocol was reviewed and approved by the institutional animal ethical committee, University College of Pharmaceutical Sciences, Kakatiya University, India. Male Wistar rats weighing 200 to 225g were selected for the study. The bioavailability of domperidone after pretreatment with piperine (dose of 20 mg $Kg^{-1}$ for eight days) was compared with an oral dispersion (domperidone 10 mg $Kg^{-1}$ in 0.25%w/v Sod.CMC suspension). The rats were allowed free access to food and water, until the night prior to dosing and were fasted for 10 h. In the first group, oral domperidone solution (2.5 mg $mL^{-1}$) was administered through a feeding needle, the second group was pretreated with piperine for 8 days and for the third group, verapamil was used. Blood samples (0.5 mL) from a retro-orbital vein were collected at preset intervals of 0, 0.5, 1, 2, 3, 6, 12 and 24 h respectively, after administration of oral solution and after pretreatment with piperine. All blood samples were allowed to clot and centrifuged for 10 min at 4000 rpm. The serum was separated and transferred into clean micro-centrifuge tubes and stored at -20° C until HPLC analysis. The concentration of domperidone in the samples was determined by HPLC.

**Serum and perfusion samples analysis**

Domperidone in serum and perfusion samples were estimated by a reverse phase HPLC method (10).

**Instrumentation**

A Shimadzu HPLC system equipped with a LC-20AT pump and SPD 20 AVP UV visible detector and RP C18 column (250 mm x 4.6 mm ID, particle size 5 µm, (Phenomenex, Kondapur, Hyderabad, India) was used for the HPLC analysis of samples. Mobile phase was 25mM potassium dihydrogen orthophosphate: acetonitrile: triethylamine: O-phosphoric acid: 65:35:0.25:0.30, flow rate of 1mL/min, column at room temperature and a detection λ max at 280 nm. The retention time of domperidone was 5.5 min. and the internal standard used was propranolol with a retention time of 7.4 min.

**Extraction procedure for serum samples**

To 250 µl serum, 20 µl of propranolol (50µg/ml) was added as an internal standard and vortexed for 2 minutes. An equal volume of methanol was added to serum samples for protein precipitation and vortexed on a cyclomixer (Remi Elektrotechnik Limited, Valiv, Thane, India) and centrifuged at 35000 rpm for 8 minutes using a Biofuge Fresco (Buckinghamshire MK169QS, England) centrifuge. Twenty microliters of serum supernatant were taken up into a Hamilton syringe (100µL, Spinco Biotech, Habsiguda, Hyderabad, India) and injected directly into the HPLC.

**Analysis of phenol red by spectroscopy**

The concentration of phenol red in the perfusate was measured using a UV-Visible spectrophotometer (UV-Visible spectrophotometer, Elico, Sanathnagar, Hyderabad, India) at a maximum absorption wavelength of 560nm (15).

**Analysis of pharmacokinetic parameters**

All the pharmacokinetic parameters were analyzed using Phoenix WinNonlin version 6.2 software (Certara, Pharsight Corporation, L.P, USA). The statistical analysis was performed using one-way analysis of variance (ANOVA) and GraphPad Prism version (6.07) (GraphPad Software Inc., San Diego, CA, USA) at a significance level of $p < 0.05$.

## RESULTS

The piperine pretreatment for 8 days resulted in a significant increase in the mean cumulative concentration of domperidone from 0.91±0.02 to 1.88±0.07µg/mL, whereas for the verapamil (standard inhibitor) treated group, the mean cumulative concentration of domperidone was observed to be 2.45±0.14 µg/mL. The transport of domperidone was increased 2.1 and 2.7 times after pretreatment with piperine and verapamil respectively compared to their respective controls in the ileum region (Fig.1). A statistically significant ($P<0.05$) difference was observed in both cases. The piperine pretreatment for 8 days significantly increased the apparent permeability of domperidone. The apparent permeability of domperidone was increased 2.2 and 3.3 times after

pretreatment with piperine and verapamil respectively compared to their respective controls (Table 1). A statistically significant difference was observed in both cases (P<0.05, Fig.2).

**Effect of Piperine and verapamil on intestinal permeability of domperidone**

Domperidone and propranolol intestinal effective permeability (Peff) were determined in the rat ileum segment using a single pass intestinal perfusion technique. Effective permeability values were calculated from the steady-state concentrations of compounds in the perfusate collected from the outlet. As shown in Fig. 3, pretreatment with piperine for 8 days (piperine treated group) and concomitant administration with standard inhibitor verapamil (verapamil treated group) resulted in a significant increase in effective permeability ($p < 0.05$) of domperidone while there was no significant change observed in the effective permeability of propranolol in the control, piperine pretreated and verapamil treated groups, respectively (Table. 1). The increase in effective permeability of domperidone in the ileum was found to be 4.1and 5.9-fold in pretreated and standard inhibitor groups, respectively as compared with that of the control groups (Fig.3). Propranolol was shown to have no interaction with P-gp as it is a highly permeable marker.

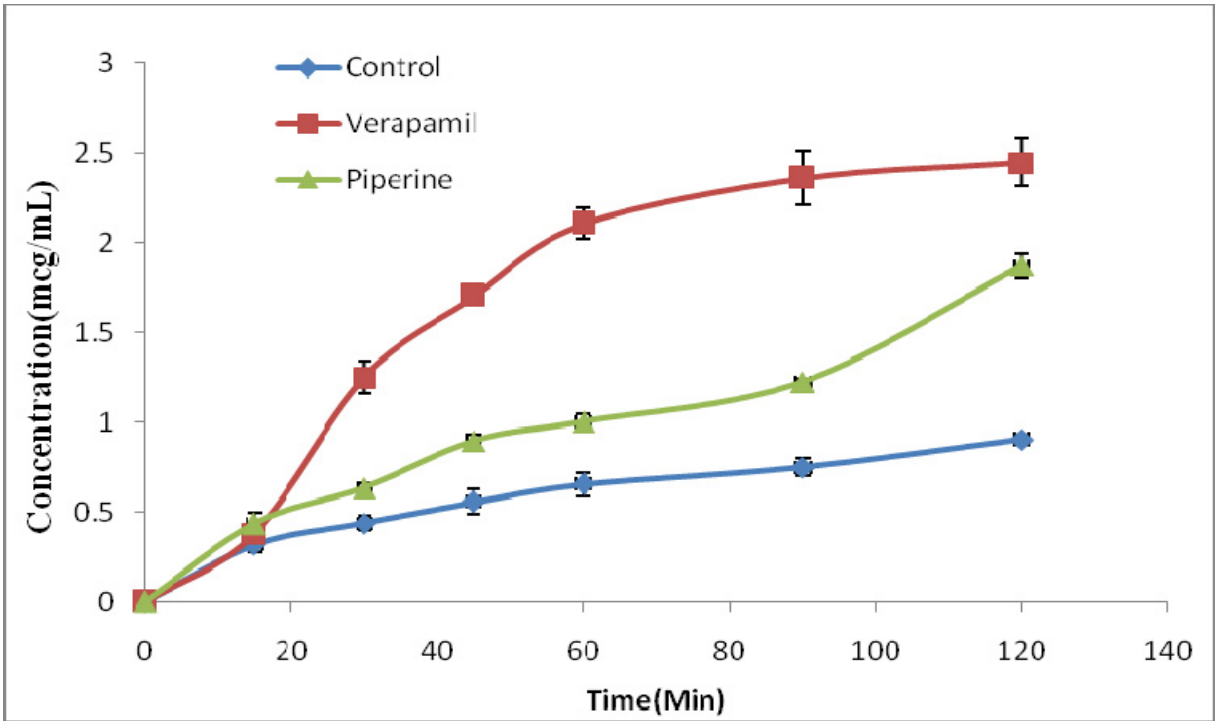


**Figure 1.** Effect of piperine pre-treatment on intestinal transport of domperidone in Male Wistar Rats. Data represents Mean ±SD cumulative transport of domperidone in ileal non-everted sacs.

**Table.1.** Apparent and effective permeability values for control, pierine treated and verapamil treated groups.

| | Control (cm/s) | Piperine Treated (cm/s) | Verapamil Treated (cm/s) |
|---|---|---|---|
| **Apparent Permeability (Domperidone)×$10^{-6}$** | 0.13±0.01 | 0.28±0.01 | 0.44±0.03 |
| **Effective Permeability (Domperidone) ×$10^{-4}$** | 0.68±0.1 | 2.78±0.3 | 4.0±0.2 |
| **Effective Permeability (Propranolol)×$10^{-4}$** | 0.93±0.1 | 0.94±0.02 | 0.93±0.01 |

Data represent Meam±SD.

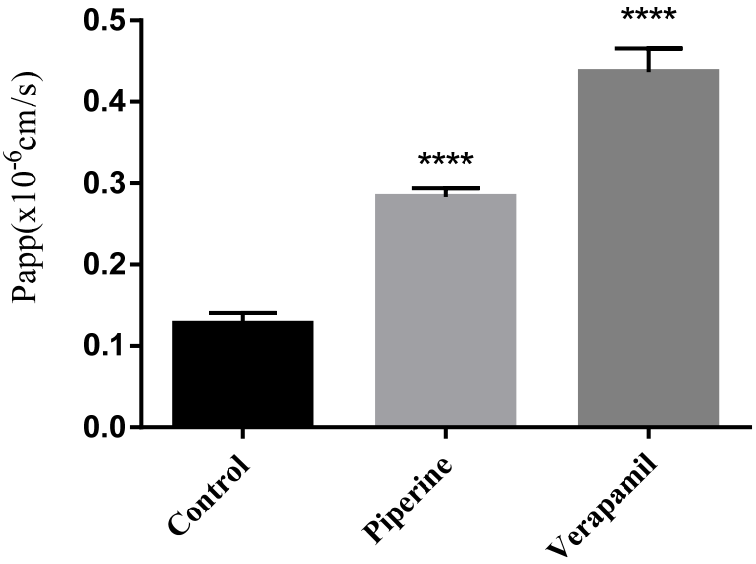


**Figure 2.** Effect of Piperine pretreatment on apparent permeability of Domperidone in male Wistar rats. Control (domperidine alone); Piperine (pretreatment with piperine for 8 days followed by domperidone on the 8th day) and Verapamil (standard inhibitor). Data represents Mean ±SD. (n=6).****Significant difference ($p<0.0001$) compared to control group.

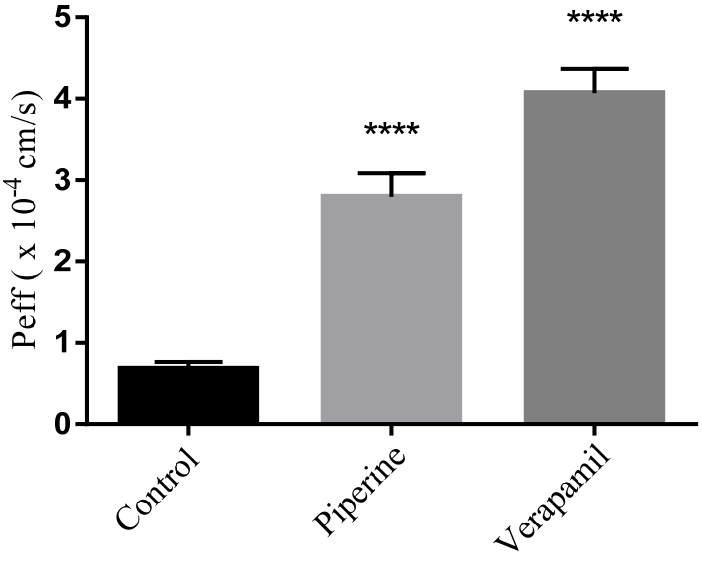


**Fig.3.** Effect of Piperine pretreatment on effective permeability of Domperidone in male Wistar rats. Control (domperidone alone); Piperine (pretreatment with piperine for 8 days followed by domperidone on the 8th day); Verapamil(standard inhibitor). Data represents Mean ±SD. (n=6).****Significant difference ($p<0.0001$) compared to control group.

***In vivo* Study**

All the rats tolerated the treatments well and there were no cases of severe adverse effects during the study period. The serum concentration-time profile of domperidone after oral administration of domperidone (10 mg/kg) in the control, piperine (20mg/kg) pretreated and verapamil treated groups were characterized and are depicted in Fig. 4. The mean pharmacokinetic parameters of domperidone are summarized in Table 2. Domperidone oral pharmacokinetics were found to be significantly ($p < 0.05$) altered with piperine pretreatment for 8 days compared to the control group. The increases in $C_{max}$,

$AUC_{0–24}$ and $AUC_{0-\infty}$ of domperidone were found to be 1.6, 1.3 and 1.5 - fold respectively in the piperine pretreated group compared to that of the control group. $T_{max}$ decreased from 2 to 1 hrs (Fig.4). There was a statistically significant difference observed in the pharmacokinetic parameters, $C_{max}$, $T_{max}$, $AUC_{0-\infty}$, $AUC_{0-24}$, $k_{el}$, and clearance.

## DISCUSSION

Dietary supplements and foods, including fruits, vegetables, herbs, spices and teas that contain complex mixtures of phytochemicals have the greatest potential to induce or inhibit the expression and activity of drug-metabolizing enzymes. CYP450 enzymes may be particularly vulnerable to modulation by the multiple active constituents of foods, including dietary supplements (18). CYP3A4 is known to be involved in the most common food–drug interactions, as demonstrated by reports of clinically important interactions involving orally administered drugs that are substrates of this enzyme (19).

The increased bioavailability is due to reduced metabolism which in turn may be due to a combined effect of inhibition of metabolizing enzymes belonging to CYP group and inhibition of the efflux transporter P-gp. Such enhanced absorption has been reported earlier by many researchers for different drugs with pretreatment with plant products containing anthocyanins, polyphenols and flavonoids (20).

From the last decade, the use of phytochemicals along with drugs as complementary and alternative medicine is increasing enormously considering that they are safe with minimal adverse effects. These phytochemicals can modulate various drug transporter systems and drug metabolizing enzymes which lead to possible herbal- drug interactions (3, 21). Piperine, the main alkaloid present in black pepper and long pepper shows inhibitory effects on drug efflux transporter (P-gp) and one of the major drug metabolizing enzymes CYP3A4. Piperine has been reported to show an inhibitory effect on P-gp mediated efflux of digoxin and cyclosporine in Caco-2 cells and CYP3A4 mediated metabolism of verapamil in human liver microsomes (8). In the present study, the influence of piperine pretreatment on the intestinal transport and oral bioavailability of domperidone was observed.

The interaction between domperidone and piperine has been studied using *in-vitro*, *in-situ* and *in-vivo* models. The *in-vitro* non-everted rat intestinal sac model is the most direct method of identifying the transport of drug from apical to basolateral direction. A significantly lower permeability in the apical to basolateral direction provides evidence that some form of efflux transporter such as P-gp may be inhibiting the transport of test component (21).

**Table.2.** Pharmacokinetic parameters of Domperidone (10mg/kg) in Control, Piperine and Verapamil treated groups. ****significant at p<0.0001, ***significant at p<0.001, ** significant at p<0.01, * significant at P<0.05 in comparison to respective control.

| **Pharmacokinetic parameters** | **Domperidone** | | |
|---|---|---|---|
| | Control | Piperine | Verapamil |
| $K_{el}$ ($h^{-1}$) | 0.049±0.008 | 0.037±0.004** | 0.034±0.002*** |
| $T_{max}$ (h) | 2 | 1 | 1 |
| $C_{max}$ (ng/ml) | 114.4±15.36 | 178.22±13.87**** | 248.91±23.42**** |
| $AUC_0^t$ (h. ng/ml) | 1122.94±114.9 | 1489±72.00**** | 1677.75±87.38**** |
| $AUC_0^\infty$(h. ng/ml) | 1641.23±93.90 | 2493.44±381.8**** | 2819.39±116.5**** |
| CL/F (L/h/kg) | 6.11±0.33 | 4.08±0.58**** | 3.55±0.15**** |
| Data represent Mean±SD, | | | |

The results from a non-inverted sac study revealed that the transport of domperidone across the rat intestine is very much affected by piperine. In the present study, the mean± SD cumulative concentration of domperidone and apparent permeability were shown to increase after pretreatment with piperine for 8 days. Piperine showed a significant increase in oral bioavailability of fexofenadine by inhibiting P-gp mediated drug efflux in the rat intestine (22). This observation indicated the role of P-gp, an efflux pump, on domperidone absorption.

*In situ* intestinal perfusion studies were carried out on live animals to study the transport of compounds in a physiologically relevant environment in which the integrity of the organ is preserved (21). From this technique, we can study the actual extent of P-gp efflux that can be expected *in-vivo*. In the present study, the effective permeability of domperidone was significantly increased after pretreatment with piperine. Phenol red, a non-absorbable marker and propranolol, a highly passive permeable marker were used to provide information on the integrity of the intestinal membrane (13,15,17). Statistically significant differences were not observed in the permeability of propranolol for the control, verapamil and piperine treated groups which indicates that there was no change in membrane integrity during the perfusion study.

The results from the *in-vivo* oral pharmacokinetic study showed a significant increase in AUC, $C_{max}$ and volume of distribution. The higher plasma levels in the absorption phase and earlier $T_{max}$ of domperidone may be due to inhibition of P-gp and Cyp3A1 across the rat intestine and liver. A significant decrease in clearance and elimination rate constant indicates that piperine could inhibit the hepatic elimination of domperidone. Piperine has been reported to decrease the clearance of midazolam due to an inhibitory effect of piperine on CYP3A4 (23). Pretreatment with piperine significantly enhanced the AUC and $C_{max}$ of domperidone which may be due to increased intestinal absorption of domperidone via the inhibition of P-gp mediated drug efflux, and CYP3A4 mediated drug metabolism. Piperine has been reported to decrease the metabolism of pioglitazone as a result of CYP3A4 and CYP 2C8 inhibition (24).

The issue of cardiotoxicity of oral domperidone has arisen recently. Domperidone has been reported to prolong the QTc interval and result in a predisposition to ventricular arrhythmias similar to that of class III anti-arrhythmic agents (25).

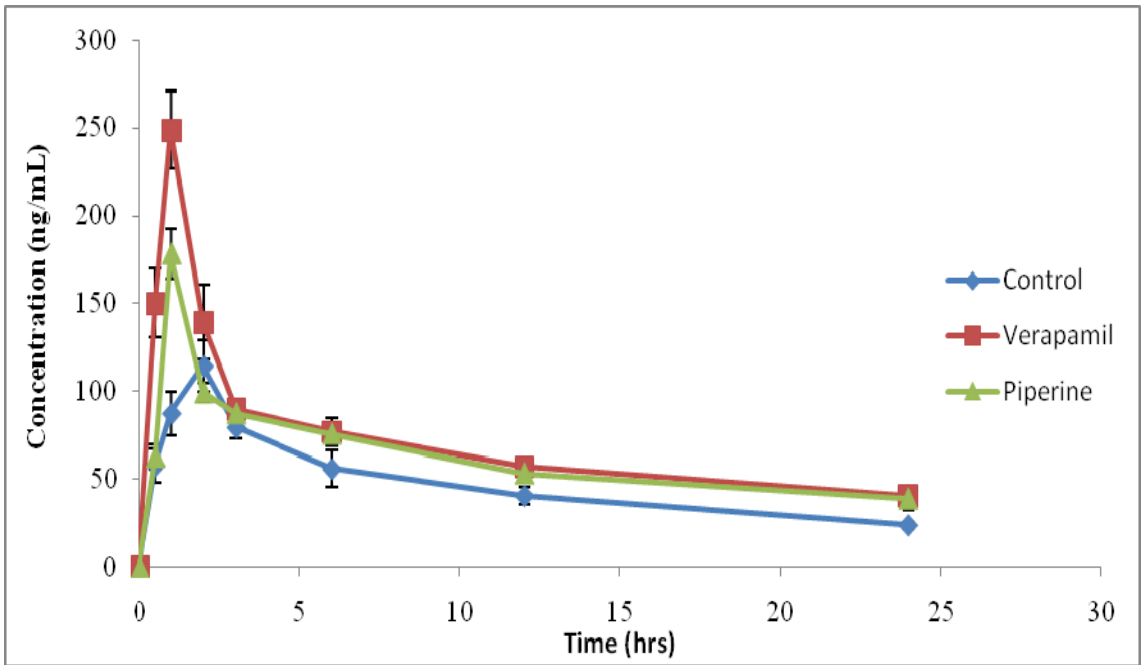


**Figure 4.** Effect of Piperine pretreatment on oral bioavailability of Domperidone in Male Wistar rats. Control(domperidone alone), Piperine (pretreatment with piperine for 8 days followed by domperidone on the 8th day, Verapamil (standard inhibitor). Data represents Mean±SD.

Domperidone was found to be the drug of choice for treating gastrointestinal symptoms in patients with Parkinson's disease because there is a minimal risk of developing extrapyramidal side effects compared to other drugs. They reported that patients receiving a daily dose of above 30mg should be treated with special caution, considering its potential cardiac effects (26).

## CONCLUSION

The improvement in absorption of domperidone may be due to the inhibition of P-gp and Cyp3A1 in the intestine and liver by piperine. Piperine enhanced the oral pharmacokinetics of domperidone, suggesting that combined use of piperine and domperidone may be useful in reducing the dose of domperidone and require close monitoring of potential drug interactions in cardiac patients. The combination of piperine with any other CYP3A4 and P-gp dual substrate may improve absorption of drugs which have poor oral bioavailability. Further studies are recommended to verify their influence in humans.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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