PHARMACOKINETIC INTERACTION WITH FEXOFENADINE IN RATS: AN IN SITU AND IN VIVO STUDY

DHANUNIYA SANDOPA1, CHITRA VELLAPANDIAN2*

1Department of Pharmacology, Sri Padmavathi School of Pharmacy, Tiruchanur, Tirupathi-517503, India. 2Department of Pharmacology, SRM College of Pharmacy, SRMIST, Kattankulathur-603203, Tamil Nadu, India

*Corresponding author: Chitra Vellapandian; Email: chitrav@srmist.edu.in

Received: 22 Jun 2023, Revised and Accepted: 22 Jul 2023

ABSTRACT

Objective: The objective of this study was to investigate the influence of Decalepis hamiltonii (D. hamiltonii), a traditional plant used in herbal medicine, on the intestinal absorption and pharmacokinetics of fexofenadine, a substrate of P-glycoprotein (P-gp), in rats.

Methods: In situ intestinal perfusion tests were conducted to assess the intestinal permeability of fexofenadine. P-gp ATPase activity was also evaluated to understand the modulatory effects of D. hamiltonii on P-gp. An in vivo pharmacokinetic investigation was performed by administering oral fexofenadine to rats.

Results: The in situ study results revealed that the effective permeation (Peff) of fexofenadine was significantly diminished (p<0.001**) in aqueous extract of D. hamiltonii (AREDH, 200 mg/kg p. o.) pretreated group compared to normal control indicating modulation in absorption. Further, there was significant augmentation (p<0.001**) of P-gp ATPase activity in AREDH pretreated group (200 mg/kg p. o.) compared normal control indicating P-gp inductive potential of D. hamiltonii. Pharmacokinetic study results revealed that the peak plasma concentration (Cmax) and the area under the concentration-time curve (AUC) of fexofenadine was significantly downregulated (p<0.001**) in AREDH pretreated group (200 mg/kg p. o.) compared to the normal control group indicating the compromised absorption and bioavailability. However, no significant changes were observed in fexofenadine half-life (T1/2) and, time to reach peak plasma concentration (Tmax), or elimination rate constant (k10).

Conclusion: In conclusion, D. hamiltonii significantly reduced the oral bioavailability of fexofenadine by promoting P-gp-mediated drug efflux during intestinal absorption. This suggests that the modulatory characteristics of D. hamiltonii may lead to herb-drug interactions when taken in combination with xenobiotics, emphasizing the importance of considering such interactions in clinical practice and further research.

Keywords: Decalepis hamiltonii, Fexofenadine, P-glycoprotein, Intestinal permeability, Pharmacokinetics

INTRODUCTION

Traditional knowledge of several native local herbs in India led to the preparation of several herbal health drinks, which are only limited to the location from which they originated. Namari sharbat is one such ancient herbal beverage made from the roots of the herb Decalepis hamiltonii, which is native to the southern Indian states of Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu. In the summer, beverages are used to satisfy thirst and function as a hepatoprotective agent, which is beneficial to stomach health. The herb is known as Ananthamulaa in Ayurveda. It belongs to the family Apocynaceae. The roots have high antioxidant activity and are used in the preparation of pickles [1, 2]. Traditional uses of D. hamiltonii root include blood cleansing, the management of intrinsic haemorrhage, fever, Kushtha, wound healing, bronchial asthma, erysipelas and food poisoning. Moreover, numerous pharmacological effects of D. hamiltonii have been reported, including antidiabetic activity, hypolipidemic, antioxidant activity, and antimicrobial activity against food-borne pathogens [3, 4]. Secondary metabolites are abundant in D. hamiltonii tuberous roots, particularly 2-hydroxy-4-methoxybenzaldehyde (HMB) [5]. HMB is a volatile compound that is an isomer of vanillin, the main flavour compound found in the roots of D. hamiltonii, and it has abundant medicinal properties. Moreover, aqueous and methanolic root extracts were identified to possess additional phenolic compounds such as 2-Hydroxy Methyl Benzoic Acid and vanillin are toxic to Hoplochelius panchax, a freshwater fish.

Moreover, research suggests that most of these phenolic acids isolated from plant resources have the potential to interfere with the pharmacokinetics and pharmacodynamics of several xenobiotics, resulting in herb-drug interactions via modulating P-gp function [8]. P-gp (170-kDa) is a protein associated with plasma membrane belonging to the ABC protein family and is present in the blood-brain barrier, liver, kidney, and small intestine of humans and rodents [9]. P-gp, like several other ABC proteins, has a diverse substrate range that includes xenobiotics, hazardous metabolic by-products, and several chemotherapeutic agents used in the treatment of various illnesses (e.g., reverse transcriptase inhibitors, antibiotics, narcotics, antineoplastics, and antidepressant drugs) [10]. P-gp, found on the villus tip of gut enterocytes' apical brush border membrane, actively promotes substrate efflux from gut epithelial cells back into the intestinal lumen. This phenomenon results in modifications in the absorption of several drugs that act as P-gp substrates [11]. Additionally, P-gp also conveys resistance by preventing sufficient accumulation of drugs in the cells, which causes failure in the cytotoxic activity of certain anticancer medications like tamoxifen [12]. All these functions of P-gp attribute their importance to the fate of drugs. Fexofenadine, a non-sedating antihistamine that is used to treat seasonal allergic rhinitis, is one of the known substrates of P-gp [13]. Fexofenadine has a low oral bioavailability (approximately 33%) in humans due to P-gp-driven drug efflux and might be used as a useful probe substrate drug to examine the significance of P-gp-mediated drug interactions [14]. On the contrary, phenolic acids isolated from D. hamiltonii, like caffeic acid and 4-hydroxy isophthalic acid [6, 7]. Furthermore, the volatile oils in D. hamiltonii tuberous roots include 0.17% benzaldehyde, 0.018% salicylaldehyde, 0.081% 2-phenyl ethyl alcohol, 0.044% methyl salicylate, 0.01% p-anisaldehyde, 0.016% benzyl alcohol, 0.45% vanillin and 0.038% ethyl salicylate [3]. Though it has not been proven that D. hamiltonii is toxic to humans, various studies show that micromolar concentrations of phenolic chemical constituents such as 2-Hydroxy Methyl Benzoic Acid and vanillin are toxic to Hoplochelius panchax, a freshwater fish.
acids, vanillin, syringic acid, and ferulic acid, are demonstrated as potential P-gp inhibitors by various studies and are also reported for their ability to attenuate multidrug resistance in various chemotherapy therapies [6, 15-17]. Further, D. hamiltonii is also reported to possess modulating properties towards cytochrome P450 enzymes [18] and human organic anion transporter 1, which result in substantial herb-drug interactions when ingested with xenobiotics. Drug resistance mediated through P-gp is one of the major culprits responsible for chemotherapy failure, and these phenolic acids have been shown to reverse this problem of resistance when administered alongside treatment [15-19]. Though D. Hamiltonii is an important ingredient in the most famous herbal drink of peninsular India, its possible herb-drug interactions are yet to be effectively explored. In the present research, we sought to explore the modulatory property of D. Hamiltonii on the activity of P-gp protein and pharmacokinetic parameters of fexofenadine.

**MATERIALS AND METHODS**

**Experimental chemicals**

Fexofenadine hydrochloride was acquired from TCI Chemicals (India) Pvt. Ltd. HPLC-grade solvents were employed for quantifiable analysis (Merck, India), and all other reagents and chemicals used in the investigation were of analytical quality. Chemicals such as sodium bicarbonate, sodium chloride, potassium chloride, magnesium sulfate, sodium dihydrogen orthophosphate, calcium chloride, di sodium ethylene diamine tetra acetic acid, D-glucose, potassium dihydrogen phosphate, sodium hydroxide, zinc acetate, sodium azide, sodium orthovanadate, magnesium, ATP, EGTA, disodium hydrogen phosphate, potassium.

**Preparation of the plant extracts**

*D. hamiltonii* roots were purchased from a merchant in Kurnool town and gathered in December from Nallamalla woodland, Nandyal district, and confirmed by Dr K. Madhava Chetty, Plant Taxonomist, SV University, Tirupati, with voucher number 0549. The obtained roots were ground into a coarse powder, mixed with nine parts of aqueous alcoholic extract, and filtered to obtain 2 per cent solution of the extract. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

**In situ intestinal perfusion study**

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).

Male albino rats of the strain Wistar, weighing 150-200 gm were chosen. Raghavendra Enterprises Pvt. Ltd. in Bangalore, India, provided the animals. The animals were kept in a conventional environmental laboratory setting and provided laboratory meals and water. Before the trial, all of the animals were adapted to housing conditions for a week. The Sri Padmavathi School of Pharmacy’s institutional animal ethics committee (IAEC) authorised all operations (approval number: SPSP/1016/PO/Re/S/06/CPCSEA/2022/02).
mm ID, particle size 5 μm) was used to examine the samples. Elution was detected at 195 nm at a flow rate of 1.0 ml/min using methanol and 6.8 g of monobasic potassium phosphate in 1000 ml of water as mobile phase, 35:65 (v/v), adjusted to pH 7.4 [14].

**Statistical analysis**

The standard deviation (SD) of each mean value is shown along with it (mean±SD). With a significance level of p<0.05, statistical analysis was carried out using the student’s unpaired t-test and analysis of variance (ANOVA) in version 9.0 GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA).

**RESULTS**

**Effect of AREDH on intestinal permeability of fexofenadine**

The modulatory property of AREDH on intestinal permeability of fexofenadine was assessed through an in-situ technique. The results of the in-situ rat gut technique involving AREDH in two dosage administrations along with a P-gp inducer (rifampicin) and inhibitor (ketoconazole) are demonstrated in fig. 1. According to the graphical representation, it reveals that the effective intestinal permeability (Peff) of fexofenadine was effectively diminished by inducer and AREDH when given orally at 200 mg/kg when compared to the normal control. Further, there was a significant augmentation in Peff of fexofenadine in animals administered with an inhibitor. On the contrary, when AREDH was given through perfusate at 1 mg/kg, it failed to exhibit any alterations in Peff fexofenadine when compared to the normal control group.

![Fig. 1: Effect of AREDH on intestinal permeability of fexofenadine](image1)

**Effect of AREDH on P-gp ATPase activity of fexofenadine**

The measurement of P-gp ATPase activity was measured as the amount of inorganic phosphate produced. Fig. 2 depicts the outcomes of AREDH’s P-gp ATPase modulatory activity, as well as the inducer and inhibitor. The graphical representation indicates that administration of AREDH (200 mg/kg; p. o.) and the inducer resulted in significant upregulation of P-gp ATPase activity when compared to normal control. While AREDH administered via perfusate was ineffective in inducing P-gp ATPase activity, the inhibitor group presented a significant diminution in the activity of P-gp ATPase compared to the normal control group.

![Fig. 2: Estimation of P-gp activity in different groups, all the values were expressed as mean±SEM n=6 *p<0.01, ** statistically significant difference in the AREDH group when compared to normal control. *p<0.01, ** statistically significant difference in inducer when compared to normal control. ns no significant difference in inhibitor and AREDH in perfusate when compared to normal control](image2)

**Effect of AREDH on pharmacokinetic parameters of fexofenadine**

Fig. 3 depicts the plasma concentration-time plots of fexofenadine following fexofenadine (10 mg/kg; p. o) administration in control and pre-treated groups (AREDH 200 mg/kg). While table 1 summarises the mean values of parameters associated with the pharmacokinetics of fexofenadine in both the absence and presence of pretreatment with AREDH, the oral pharmacokinetics of fexofenadine were shown to be substantially changed by AREDH (200 mg/kg) pre-treatment for 7 d when related to the control group (fexofenadine alone). When fexofenadine was pre-treated with AREDH, the Cmax, AUC0-t, and AUC0-∞ of fexofenadine decreased significantly when compared to the control group. Furthermore, the CL and Vd of fexofenadine were higher in the pre-treatment group compared to the control group, whereas there was no significant difference in Tmax, T1/2, and K10.

![Fig. 3](image3)

**Table 1: Effect of AREDH on pharmacokinetic parameters of fexofenadine**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean values±standard error (n=6) (control)</th>
<th>Mean values±standard error (n=6) (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ka (h)</td>
<td>1.32±0.021</td>
<td>1.12±0.028</td>
</tr>
<tr>
<td>k10/h</td>
<td>0.229±0.003</td>
<td>0.231±0.005</td>
</tr>
<tr>
<td>t1/2 ka (h)</td>
<td>0.52±0.008</td>
<td>0.62±0.016</td>
</tr>
<tr>
<td>t1/2 k10 (h)</td>
<td>3.02±0.034</td>
<td>3.00±0.064</td>
</tr>
<tr>
<td>Vd (ml/kg)</td>
<td>2.29±0.040</td>
<td>2.71±0.044**</td>
</tr>
<tr>
<td>CL (ml/kg/min)</td>
<td>0.52±0.004</td>
<td>0.62±0.006</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.68±0.010</td>
<td>1.77±0.017</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>3.02±0.035</td>
<td>2.44±0.021**</td>
</tr>
<tr>
<td>AUC0-0 (µg/ml/min)</td>
<td>17.58±0.171</td>
<td>14.71±0.108**</td>
</tr>
<tr>
<td>AUC0-∞ (µg/ml/min)</td>
<td>19.05±0.162</td>
<td>15.97±0.154**</td>
</tr>
</tbody>
</table>

Significant deviation from the control group (p<0.001).

---

D. Sandopa & C. Vellapandian

Mean data of Pharmacokinetic Parameters (k10 = Elimination rate constant, ka = Absorption rate constant, t1/2 k10 = Elimination half-life, t1/2 ka = Absorption half-life, CL = Clearance, Vd = Volume of distribution, Cmax = Maximum Concentration in the Plasma, Tmax = Time taken to reach Maximum Concentration, AUC 0-∞ = Area under the curve from 0 to infinity, AUC 0-t = Area under the curve from 0 to time t) of Fexofenadine and its standard error was calculated when administered via oral route in control and test groups.

DISCUSSION

In a country like India, the general populace extensively utilizes several herbal products on their own or in conjunction with prescription and non-prescription treatments, thinking that they are safe since they are derived from natural rather than synthetic sources. Certain herbal products are consumed daily, such as basil, blueberries, garlic, and ginger, and are used as ingredients in cooking. Nannari sharbat is one such ancient herbal beverage made from the roots of the herb D. hamiltonii, which is widely consumed in southern India. In the summer, beverages are used to satisfy thirst, and they also function as hepatoprotective agents, which are beneficial to stomach health. Herbs, like any other synthetic medication, have a dose-dependent impact. A precise dose of an herbal substance may have a medicinal effect, but going above or below the amount may have negative consequences. Though most herbs are not used for life-threatening disorders, they may be used intentionally or unintentionally by the general population to enhance bioavailability, minimise toxicity, or activate other functions through synergistic action. Herbal medications, like synthetic medicines, interact with pharmaceuticals in two ways: pharmacokinetically and pharmacodynamically. Pharmacokinetic interactions affect medication or herbal medicine absorption, distribution, metabolism, or excretion. These interactions impact pharmacological action by either increasing or decreasing the free drug accessible to have a therapeutic effect. Pharmacodynamic interactions have a qualitative influence on a drug’s activity, either by increasing (synergistic or additive activities) or antagonising it. Before oral drugs get to the capillaries that lead to the portal vein, they have to navigate through the mucosal layer of the gut wall. The multidrug resistance-glycoprotein (P-gp) transporters have all been reported to interact with a variety of phenolic acids, which has led to their involvement in drug-herb interactions.

D. hamiltonii roots are used in many ayurvedic remedies and have been traditionally consumed by tribal people as pickles and to preserve food grains (as a bio-insecticide). The main ingredient in the famous herbal drink Nannari is the aqueous root extract of D. hamiltonii. It has been reported that D. hamiltonii contains several phenolic acids like caffeic acid, vanillin, syringic acid, and ferulic acid, which have been demonstrated as potential P-gp modulators by various research studies. Due to their modulating property, the goal is to investigate the interaction of P-gp substrates (many prescription and non-prescription drugs) and modulators (phenolic compounds of AREDH) to recognize the possible consequences in pharmacokinetics and to predict the clinical outcome. Therefore, in the present study, the drug fexofenadine has been used as a presumed substrate of P-gp to investigate the herb-drug interactions of AREDH due to its possible modulatory effect on the ABC protein P-gp, which predominantly orchestrates the pharmacokinetic fate of fexofenadine. Previous research evidenced that there is a significant expression of P-gp (mdr1a) mRNA from the duodenum to the ileum, implying that P-gp plays a crucial role in the transport of fexofenadine from the intestine [24]. Additionally, research shows that the rat model for permeation investigations is suitable for human prediction since MDRI in rats expresses P-gp with a similar level of affinity and expression [25]. Furthermore, it has been demonstrated that oral xenobiotic absorption in rats and humans is similar [26]. Thus, rat gut permeability studies would be more useful for forecasting in vivo P-gp substrate absorption. Studies suggested computing the passive permeability of actively transported molecules using a non-everted gut sac model [27, 28]. As a result, in the current study, an in-situ perfusion assessment was performed to investigate the role of P-gp in fexofenadine intestinal transport [29].

In situ perfusion assessment in the rat jejunum was executed to confirm the role of P-gp activity modulation in fexofenadine intestinal transport. One of the key biopharmaceutical processes used to measure the rate and degree of gastrointestinal (GI) medication absorption is intestinal Peff, which was estimated through this in situ study in rats that were pre-treated with AREDH along with an inducer and inhibitor of P-gp for comparison. The effective permeability of fexofenadine was considerably downregulated in the AREDH (200 mg/kg) and inducer (rifampicin) (13.5 mg/kg) pre-treated groups when compared to the normal control group. This was also supported by the results of the P-gp ATPase activity assessment. AREDH 200 mg/kg, like the inducer (rifampicin), increased P-gp ATPase activity compared to normal controls, indicating a direct relationship to altered Peff of fexofenadine in pre-treated groups. On the contrary, when AREDH was given through perfusate, Peff fexofenadine showed no significant modulation and was comparable to normal control. Thus, the decrease in fexofenadine intestinal permeability observed in AREDH 200 mg/kg pre-treated rats is attributable to AREDH-induced P-gp ATPase activity. These findings also revealed how fexofenadine was effluxed back to the gut via P-gp. Furthermore, in groups where AREDH (Test-2) and an inhibitor (ketoconazole) are given through perfusate, the permeability values of the AREDH group couldn’t display any statistically significant difference when compared to the control. This effect was in direct relation to P-gp ATPase activity modulation in the AREDH group. In contrast, activity of P-gp ATPase was like that of the normal control group. However, the inhibitor group exhibited significantly augmented Peff of fexofenadine when compared to the normal control, which slightly correlated with its respective P-gp ATPase activity modulation, albeit the downregulation of the activity was not statistically significant. There, it indicates that AREDH possessed substantial inducing properties towards P-gp ATPase rather than inhibition, which resulted in altered absorption of fexofenadine in vitro and in situ studies.

To further comprehend the impact of AREDH on the pharmacokinetic characteristics of fexofenadine, an in vivo pharmacokinetic study of fexofenadine was carried out in rats pretreated with AREDH for 14 d. Though the in vitro and in situ studies
proposed the probable influence of AREDH pre-treatment on the transport and permeation of fexofenadine, there was no significant change in the pharmacokinetics of fexofenadine except for a few parameters. AUC and Cmax were significantly repressed in the AREDH pre-treated group when compared to the control group, likely indicating diminished absorption of fexofenadine due to AREDH pre-treatment via induction of P-gp ATPase. The absorption half-life was also slightly repressed. It also indicates that the systemic exposure to fexofenadine was also slightly restricted with AREDH pre-treatment. Furthermore, the CL and Vd of fexofenadine were slightly higher in the AREDH pre-treated group compared to the control group, whereas parameters like Ka, k10, and T1/2 k10 were almost similar in both groups. Furthermore, these findings show that AREDH pre-treatment had a limited effect on hepatic drug elimination as well as an effect on absorption.

Finally, herbal products contain several active ingredients with varied or comparable pharmacological effects. Previous studies indicate that the occurrence of phenolic acids and various other chemical constituents in herbs are capable of binding to nuclear receptors like the constitutive androstane receptor (CAR), the vitamin D-binding receptor (VDR) and pregnancy and xenobiotic receptor (PXR), which influence the expression of enzymes associated with drug metabolism and drug transporters [30]. Any of these receptors can be activated or inhibited by the binding of an herbal constituent as a ligand. This increases or decreases the metabolism or transport of the co-administered conventional drugs(s), which can result in diminished therapeutic efficacy or augmented toxicity of the drugs. The present study suggests that the chemical constituents of D. hamiltonii modulating the receptors responsible for influencing and inducing P-gp ATPase activity is the possible mechanism for alterations in the pharmacokinetic properties of fexofenadine, indicating a potential herb-drug interaction. To assess the likelihood that these products will interfere when used along with prescription medication, patients should be questioned about any usage of herbal remedies or natural product(s) and other medications.

CONCLUSION

In essence, the current investigation demonstrates that D. hamiltonii is a possible P-gp inducer, which may result in medication ineffectiveness, resistance, or even tolerance development. As a result, caution should be exercised while co-administering D. hamiltonii medicines that are efficiently transported by P-gp. It is highly advised that herbal remedies be assessed, monitored, and tested when taken in conjunction with other pharmaceuticals to avoid potential interactions. Further studies are required to isolate specific constituents responsible for P-gp induction and elucidate the underlying mechanism orchestrating this interaction. A comprehensive approach and understanding will help combat undesirable clinical difficulties.

FUNDING

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES


