Effects of *Momordica charantia* and *Tinospora cordifolia* extract on intestinal drug transporter pump: P-glycoprotein

Sir,

P-glycoprotein (Pgp) is a 170-kD plasma membrane glycoprotein, which functions as an ATP-dependent transporter pump occurring in many parts of the body including the apical brush border of the intestinal membrane, (where it functions as a drug transporter). Pgp is major site for pharmacokinetic interaction as the substrates and modulators of Pgp can affect various pharmacokinetic parameters. Pgp substrates include Anthracycles e.g. Doxorubicin, *Vinc* alkaloids e.g. Vinblastine, Steroids e.g. Dexamethasone (DEX), etc. Pgp inhibitors that increase the intestinal permeability are calcium channel blockers e.g. verapamil, calmodulin antagonists, chlorpromazine and steroids. Recently, phytochemicals belonging to the class of aromatic amino residues are also emerging as new modulators of Pgp. Pgp is major target for herb-drug interactions.

*Momordica charantia* (MC), a hypoglycemic agent, is known to reduce the absorption of nutrients and *Tinospora cordifolia* (TC) another hypoglycemic agent has been reported to decrease intestinal hydraulic permeability of nutrients. The findings indicate that these herbal drugs may interact with intestinal permeability of therapeutic medicinal agents. However, the mechanism is not properly understood.

As Pgp is common target of herbs and therapeutic medicinal agents, known to involve in the intestinal transport of nutrients/drugs, the present work aims to study the effect of MC and TC extracts on Pgp mediated intestinal transport of DEX. Male Wistar rats weighing 250 to 300 g were given free access to food and tap water and maintained on 12:12-h light-day cycle. All animal experimental protocols described below were approved by the Institutional Animal Ethical Committee. The animals were divided into six groups of six animals each and were subjected to saline and MC or TC extract (MC fruits and TC stem were procured from local markets, dried in shade and successively extracted with light petroleum ether and cold macerated in hydro alcohol). The treatment groups received extracts suspended in saline solution containing 1% w/v Tween 20 by oral feeding, while the control group rats received saline orally. DEX, the acute and chronic doses at which MC and TC changes the hydraulic permeability were given for 5 days (acute doses: MC 200 mg/kg, 500 mg/kg and TC 150 mg/kg, 400 mg/kg and chronic doses: MC 200 mg/kg and TC 150 mg/kg once daily.

Pre-treatment with Pgp inhibitors verapamil 3 mg/kg, ip and chlorpromazine 5 mg/kg, ip, significantly (P < 0.01, F = 7.03, Df = 6) increased the intestinal absorptive permeability of DEX as compared to the saline-treated group (Table 1). Acute and chronic treatment with MC significantly (P < 0.01, F = 4.58, df = 4) decreased the absorptive permeability of DEX as compared to the saline-treated group and was found even lower than that of verapamil and chlorpromazine pre-treated groups. These findings suggest that MC decreases the DEX absorptive permeability by acting as a Pgp inducer. On the contrary to MC, the absorptive permeability of DEX was significantly (P < 0.01 F = 9.01, df = 6) increased by acute and chronic treatment of TC suggesting an inhibitory effect of TC on Pgp.

In this study, we have investigated the interaction of MC and TC with intestinal transport of DEX by modulation of Pgp. The effect of herbs on Pgp may lead to herb-drug interaction and therefore these herbs can be studied with various therapeutic medicinal drugs.

Acknowledgement

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Table 1

The effect of MC and TC on intestinal absorptive permeability (apical-to-basal) of dexamethazone.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Treatment mg/kg (Route)</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td></td>
<td>6.8 ± 3.7</td>
<td>9.1 ± 3.3</td>
<td>14.3 ± 3.6</td>
<td>12.1 ± 5.7</td>
<td>12.8 ± 3.2</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>(5 mg/kg, i.p.)</td>
<td>9.5 ± 3.5*</td>
<td>12.2 ± 4.5*</td>
<td>13.9 ± 3.5</td>
<td>17.7 ± 2.6*</td>
<td>18.5 ± 4.5*</td>
</tr>
<tr>
<td>Verapamnil</td>
<td>(3 mg/kg, i.p.)</td>
<td>9.3 ± 4.5*</td>
<td>12.5 ± 1.7*</td>
<td>13.3 ± 6.4</td>
<td>18.3 ± 5.7*</td>
<td>19.1 ± 3.6*</td>
</tr>
<tr>
<td>Momordica charantia extract</td>
<td>Acute</td>
<td>2.1 ± 4.1*</td>
<td>2.3 ± 3.3*</td>
<td>2.7 ± 1.3*</td>
<td>1.9 ± 4.4*</td>
<td>1.5 ± 1.7*</td>
</tr>
<tr>
<td></td>
<td>200 mg/kg; p.o.</td>
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<td></td>
<td>500 mg/kg; p.o.</td>
<td>1.5 ± 6.4*</td>
<td>2.5 ± 1.9*</td>
<td>3.2 ± 6.5*</td>
<td>1.4 ± 3.5*</td>
<td>1.2 ± 4.4*</td>
</tr>
<tr>
<td></td>
<td>Chronic (5 days)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>200 mg/kg; p.o.</td>
<td>2.3 ± 2.5*</td>
<td>3.7 ± 1.1*</td>
<td>5.7 ± 6.2*</td>
<td>2.1 ± 2.7*</td>
<td>2.9 ± 4.7*</td>
</tr>
<tr>
<td>Tinospora cordifolia extract</td>
<td>Acute</td>
<td>5.2 ± 1.4</td>
<td>10.6 ± 2.3</td>
<td>15.3 ± 4.7</td>
<td>11.1 ± 3.6</td>
<td>15.2 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>150 mg/kg; p.o.</td>
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<td></td>
<td>400 mg/kg; p.o.</td>
<td>7.3 ± 3.4*</td>
<td>12.4 ± 1.6*</td>
<td>17.3 ± 3.8</td>
<td>12.9 ± 5.9*</td>
<td>18.3 ± 3.7*</td>
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<tr>
<td></td>
<td>Chronic</td>
<td></td>
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<tr>
<td></td>
<td>150 mg/kg; p.o.</td>
<td>6.4 ± 3.4</td>
<td>15.8 ± 1.4*</td>
<td>17.4 ± 2.9</td>
<td>13.1 ± 4.1</td>
<td>12.2 ± 1.6</td>
</tr>
</tbody>
</table>

n = 6 rats in each group, data expressed as mean ± SEM. *P< 0.01 as compared with saline-treated group. ANOVA followed by Tukey multiple comparisons tests.

References