Review of Scientific Evidence of Medicinal Convoy Plants in Traditional Persian Medicine

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INTRODUCTION

In traditional Persian medicine (TPM), lifestyle modification is more important than treatment. Similarly, single-drug therapy is more desirable than multiple-drug therapy because it has fewer toxic side effects. Based on this theory, medical scientists have tried to interpret the conditions and causes for multiple drug therapy. One concept used in TPM for multidrug therapy is that of the convoy drug (Mobadregh). According to TPM texts, convoy drugs are substances (or drugs), which facilitate the access of drugs or foods to the whole body or to specific organs. This study reviewed some convoy drugs presented in TPM, their biological effects, and their probable interactions with main drugs, considering the increased absorption through inhibition of P-glycoprotein (P-gp) efflux function, bioavailability-enhancing effects, and decreased metabolism of the main drug considering the use of convoy drugs. Convoying drugs to the heart, brain, and other organs is a unique ability of saffron mentioned in TPM texts. It has been noted that when saffron is combined with a camphor tablet, it guides the camphor unique ability of saffron. The effects of vinegar in targeting the liver and brain have also been demonstrated. An evaluation of the results demonstrated that the suggested convoy drugs, including Piper nigrum (black pepper), Piper longum (long pepper), red wine, Camellia sinensis (tea), hazelwort, Mentha longifolia (pennyroyal), Anethum graveolens (dill), Foeniculum vulgare (fennel), and Sassafras albidum (sassafras) can increase the bioavailability of coadministered drugs by inhibition of P-gp or cytochrome P450s (P-gp) or both of them. This evidence could be a good basis for the use of these agents as convoys in TPM.

Key words: Cytochrome P450s, medicinal convoy plant, P-glycoprotein (P-gp), traditional Persian medicine

ABSTRACT

One concept used in traditional Persian medicine (TPM) for multidrug therapy is that of the convoy drug (Mobadregh). According to TPM texts, convoy drugs are substances (or drugs), which facilitate the access of drugs or foods to the whole body or to specific organs. This study reviewed some convoy drugs presented in TPM, their biological effects, and their probable interactions with main drugs, considering the increased absorption through inhibition of P-glycoprotein (P-gp) efflux function, bioavailability-enhancing effects, and decreased metabolism of the main drug using electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar in November and December, 2013. Recent studies have proven the beneficial effects of Crocus sativus L. (saffron) and camphor on the heart and brain, the cerebral therapeutic effects of Asarum europaeum (hazelwort), the hepatoprotective effects of Cichorium intybus (chicory), and Apium graveolens (celery) seeds, and the diuretic effects of Cinnamomum zeylanicum (cinnamon), and Cucumis melo (melon) seeds.

The effects of vinegar in targeting the liver and brain have also been demonstrated. An evaluation of the results demonstrated that the suggested convoy drugs, including Piper nigrum (black pepper), Piper longum (long pepper), red wine, Camellia sinensis (tea), hazelwort, Mentha longifolia (pennyroyal), Anethum graveolens (dill), Foeniculum vulgare (fennel), cinnamon, and Sassafras albidum (sassafras) can increase the bioavailability of coadministered drugs by inhibition of P-gp or cytochrome P450s (CYP450s) or both of them. This evidence could be a good basis for the use of these agents as convoys in TPM.

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INTRODUCTION

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MATERIALS AND METHODS

This paper reviews some medicinal convoy plants mentioned in the most famous TPM books, such as Qanon (“Canon of Medicine”), Kholasatol Hekmah (“Survey of Knowledge”), Zakhere Kharaezmshahi (“Kharaezm Reservoir”), Exir Azam (“Great Panacea”), and Makhzan al Advieh (“Drug Reservoir”). Electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar were searched between November and December, 2013 for each of the plants plus “biological effect,” “interaction,” “herb-herb interaction,” “herb-drug interaction,” “cytochrome P450,” “P-glycoprotein,” and “phase II enzyme” as key words.

RESULTS AND DISCUSSION

Convoying drugs to the heart and brain

Saffron

Some of the convoy medicinal plants and their target organs were shown in Table 1. Convoying drugs to the heart, brain, and other organs is a unique ability of saffron mentioned in TPM texts. It has been noted that when saffron is combined with a camphor tablet, it guides the camphor
to the target organ. The moment the camphor tablet arrives at the heart, the saffron separates from it and its function is finished."[3]

Recent studies have established the effects of saffron aqueous-ethanolic extract in reducing heart rate and the contractility of isolated guinea pig hearts via the inhibition of calcium channels. The role of saffron in protecting ischemic hearts has also been proven by biochemical and histopathological findings.[12]

Saffron and hazelwort can be combined with scammony (Convulvulus scammonia) and agaric (Polyporus officinalis) to convey them to the brain and its veins where they perform their functions properly. The beneficial influences of saffron extracts and its major component crocin have been confirmed including mild to moderate depression; improving learning and memory; radical scavenging; and its anticonvulsant, neuroprotectant, antioxidant, and antitumor properties; it also increases retinal blood flow.[11,13,14]

**Camphor**

Belz et al. (2002) proved the efficacy of camphor and crataegus berry combination (CCC) in the symptomatic therapy of orthostatic hypotension. Moreover, CCC caused an immediate and short-term increase in blood pressure and improved mental performance in aged women. Possible physiological mediating mechanisms are hemodynamic modification, sympathetic stimulation, cerebral metabolism enhancement, and direct influences on neural activation. (+)-camphor becomes hydroxylated to borneol in the body mediated by cytochrome P450 (CYP450). Borneol, a bicyclic monoterpene, has been shown to have antihypertensive, anticoagulant, and antispasmodic properties. Borneol is also used as a CNS stimulant and for the treatment of muscularkeletal conditions.

Table 1: Some medicinal convoy plants and their target organ(s)

<table>
<thead>
<tr>
<th>Names</th>
<th>Traditional name</th>
<th>Target organ(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saffron (Crocus sativus)</td>
<td>Zafaran</td>
<td>Heart and brain vessel and other organs</td>
</tr>
<tr>
<td>Camphor (Cinnamomum camphora)</td>
<td>Caphoor</td>
<td>Heart</td>
</tr>
<tr>
<td>Hazelwort (Asarum europaeum)</td>
<td>Araroon</td>
<td>Brain vessels</td>
</tr>
<tr>
<td>Vinegar</td>
<td>Khell</td>
<td>Spleen</td>
</tr>
<tr>
<td>Chicory seed (Cichorium intybus)</td>
<td>Tokkme kasni</td>
<td>Brain internal</td>
</tr>
<tr>
<td>Celery seed (Apium graveolens)</td>
<td>Tokkme karafs</td>
<td>Liver</td>
</tr>
<tr>
<td>Melon seed (Curcumin melo)</td>
<td>Tokkme batikh</td>
<td>Liver</td>
</tr>
<tr>
<td>Black pepper (Piper nigrum)</td>
<td>Fefel</td>
<td>Urinary tract</td>
</tr>
<tr>
<td>Pennyroyal (Mentha longifolia)</td>
<td>Fodanaj</td>
<td>Kidney stones</td>
</tr>
<tr>
<td>Cinnamon bark (Cinnamomum zeydanicum)</td>
<td>Darchin</td>
<td>Kidney stones</td>
</tr>
<tr>
<td>Anise seed (Pimpinella anisum)</td>
<td>Anisun</td>
<td>Nonspecific (acceleration)</td>
</tr>
<tr>
<td>Wild cinnamon bark (Cinnamomum iners)</td>
<td>Salikheh</td>
<td>Nonspecific (acceleration)</td>
</tr>
<tr>
<td>Sassafras (Sassafras albidum, Sassafras Hesperia)</td>
<td>Sasafras</td>
<td>Nonspecific (acceleration)</td>
</tr>
<tr>
<td>Wine</td>
<td>Khmar</td>
<td>Nonspecific (acceleration)</td>
</tr>
<tr>
<td>Tea (Camelia sinensis)</td>
<td>Chaye khotae</td>
<td>Body internal</td>
</tr>
<tr>
<td>Fennel (Foeniculum vulgare)</td>
<td>Raziyaneh</td>
<td>Body peripheral</td>
</tr>
<tr>
<td>White agaric (Polyporus officinalis)</td>
<td>Gharighoon</td>
<td>Body peripheral</td>
</tr>
<tr>
<td>Long pepper (Piper longum)</td>
<td>Darafel</td>
<td>Body peripheral</td>
</tr>
<tr>
<td>Dill (aromatic water) (Anethum graveolens)</td>
<td>Shebet</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Pine seed (Pinus sp.)</td>
<td>Tokkme Sanobar</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

**Hazelwort**

According to TPM texts, hazelwort can transfer the power of scammony and agaric to the brain and its veins, where they do their function correctly. Asarone is a compound in the rhizome of Asarum europaeum L. and Acorus calamus L. that is responsible for the therapeutic effects and specific odor of these herbs. Asarum is used in phytotherapy and the food and beverage industries. The roots of these plants contain two isomers, α-asarone and β-asarone. β-asarone easily passes through the blood-brain-barrier (BBB) and shows significant pharmacological effects on the cardiovascular and central nervous systems, while α-asarone shows neuroprotective, hypcholesterolemic, hypolipidemic, and antiplatelet properties.

**Vinegar**

Vinegar is a tenuous, rapidly penetrating supplier of the power and faculties of medicines to the spleen and brain. It has an affinity for the spleen, so it is able to convey drugs to it. For example, the use of vinegar is suggested for conveying and accompanying rose oil to the brain ventricles in treating brain and meninges inflammation. Recent studies showed that vinegar can induce a liver- and brain-targeting effect by increasing the distribution of the main drug in the liver and brain while simultaneously reducing its distribution in other organs.

**Convoying drugs to the liver**

**Chicory seeds**

Chicory seed is tenuous; it opens obstructions of and convoys drugs to the liver. Recent studies have confirmed the benefits of chicory and celery seeds in preventing toxic effects in the liver. In a study by Ahmed et al. (2003), different fractions of ethanol extract of chicory seeds showed antihepatotoxic effects, while the methanol fraction containing phenolic compounds was more effective than other fractions. A new guainiolide sesquiterpene glycoside, cichotyboside, isolated from the seeds of Cichorium intybus L., exhibited significant antihepatotoxic effects similar to those of the standard drug silymarin against CCl4-induced toxicity in rats. The aqueous extract of chicory seeds showed beneficial short-term and long-term effects in diabetic rats. Furthermore, the seed extract improved fatty liver caused by diabetes, oleic acid, and steatohepatitis.

**Celery seeds**

Celery seed is a potent antioxidant agent of liver and spleen obstructions. Because of its antioxidant and discutient (mohalel) properties, it can be tenuous and penetrating and can convey drugs to the liver.[8] Their hepatoprotective effect,[21] inactivation of toxic metabolites in liver,[20] antihepatocarcinogenesis,[20] antiinflammatory, antioxidant, cyclooxygenase- and topoisoenzyme-inhibitory activity,[20] and antihypertensive properties[25] have been observed in celery seed extracts.

**Convoying drugs to the urinary tract, kidney, and bladder**

**Melon seed**

Melon (Curcumin melo) seed can convey drugs to the liver and the urinary tract. Two species of the genus Curcumin (Curcumin melo and Curcumin trigonus) were shown to significantly increase urinary volume (UV). They...
also displayed increases in urinary chloride excretion due to the extract interfering with absorption in the renal tubule.\textsuperscript{[80]} Isomultiflorenol as a major compound and its isomer $\Delta^7$-isomer multiflorenol were identified from triterpene alcohol fractions of the unsaponifiable part of \textit{Curcarmel melo} seed lipid.\textsuperscript{[87]} Two pentacyclic triterpenoids, 16c-hydroxy-3-ketoisomultiflorene and 3$\beta$-hydroxy-16-ketoisomultiflorene, isolated from \textit{Antidesma menasii}, showed diuretic activity in experimental animals.\textsuperscript{[94]}

Convoying litholytic drugs

Drug components that allow litholytic main drugs to penetrate to the location of kidney stones faster contain pepper, p carsa, and cinnamon.\textsuperscript{[80]} In addition to their convoying abilities, these drugs are effective in moving stones. Some studies have proven the diuretic and nephroprotective properties of cinnamon bark.\textsuperscript{[89]}

Recent studies have proven the beneficial effects of saffron and camphor in the heart and brain, cerebral therapeutic effects of hazelwort, hepatoprotective effects of chicory and celery seeds, and diuretic effects of cinnamon and melon seed. This evidence could explain the use of these agents as convoy agents in TPM. Based on TPM sources, a convoy agent must have a therapeutic effect on the target organ(s). If it is used in an amount lower than its therapeutic dose and lower than the amount of other components in a formulation, it can direct the main drug to the target organ without showing any therapeutic effect. However, the pharmacokinetic interactions and tissue-targeting effects of these agents need further investigation.\textsuperscript{[83,84]}

Bioavailability enhancement effects

Several herbal compounds including quercitin, genistein, naringin, sinomenine, borneol, and nitrite glycoside as well as herbal medicines such as \textit{Piper longum} and its active ingredient piperine, \textit{Glycyrrhiza glabra} (glycyrrhizin), \textit{Carum carvi}, and \textit{Cumminum cyanum} have exhibited the capability of enhancing bioavailability.\textsuperscript{[11,40-45]}

Furthermore, curcumin has been reported to have initiated the activity of breast cancer resistance protein (BCRP1) in mice. Recently, it was reported that monoterpenoids containing the extract of \textit{Zanthoxly Fructus} can inhibit the P-gp-mediated efflux of digoxin. Another study screened the inhibitory activities of different terpenoids on P-gp-mediated efflux in human multidrug resistance-associated protein (MDR1)–expressing cell lines. It was found that the inhibitory activities of (R)-(+)citrconelol, (S)-(−)β-citronellol, α-terpineine, terpinolene, (−)β-pinene, abietic acid, ophiolobin A, cucurbacin I, and glycyrrhetic acid on the P-gp-mediated efflux of digoxin were greater than 50%.\textsuperscript{[144-146] In addition, the potential inhibitory effect of glycyrrhetic acid and abietic acid on MRP2- or BCRP-mediated membrane transport has been reported.\textsuperscript{[87]}

Based on the literature reviewed [Table 2], furanocoumarins, including psoralen derivatives in celery seed,\textsuperscript{[48-50]} alkaloids such as piperine in black pepper,\textsuperscript{[51,52]} polyphenolic compounds and catechins in green tea,\textsuperscript{[53,54]} borneol as a metabolite of camphor and as a component of the essential oil of pennyroyal,\textsuperscript{[17,54] are responsible for inhibiting P-gp and increasing the bioavailability of the coadministered main drug. P-gp is a well-known transporter that acts as a gatekeeper protein for xenobiotics at the luminal membrane of brain capillary endothelial cells (BCEC). Additionally, it has been proven that active efflux mechanisms at the BBB limit the brain penetration of xenobiotics. P-gp–restricted penetration into the brain has led to several assays to eliminate this barrier by using specific P-gp inhibitors.\textsuperscript{[59] Among the introduced convoying drugs for the brain, α-asarone and β-asarone existing in hazelwort may increase the permeability of drugs into the brain by inhibiting P-gp at the BCEC, thereby increasing the drug concentration in the brain.\textsuperscript{[21]}

Cytochrome P450s’ inhibitory effects

Herbal medicines such as St. John’s wort (\textit{Hypericum perforatum}), garlic (\textit{Allium sativum}), piperine (from \textit{Piper sp.}), ginseng (\textit{Ginseng sp.}), gingko (\textit{Gingko biloba}), soybean (\textit{Glycine max}), alfalfa (\textit{Medicago sativa}), and grapefruit juice display clinical interactions when coadministered with drugs.\textsuperscript{[84]}

Some reports have demonstrated the effects of several components isolated from medicinal herbs on drug metabolizing-enzymes \textit{CYP450}, uridine S’-diphospho (UDP)-glucuronosyltransferase, and glutathione S-transferase (GST). Some natural compounds, such as flavonoids, anthocyanins and their metabolites, furanocoumarins, pipermethystine from kava, and some dietary polyphenols, can inhibit or induce these metabolic enzymes and alter the therapeutic effects of coadministered drugs.\textsuperscript{[50-60]}

A number of flavonoids have been shown to modulate the \textit{CYP450} system, including the inhibition or induction of these enzymes by various mechanisms. Among the inhibitors, five polyphenols (quercetin, phloretin, chrysin, apigenin, and acacetin) exhibited strong inhibitory activity (100% inhibition) against \textit{CYP3A4}. Apigenin from among the inhibitors of flavone compounds displayed a significant inhibition on \textit{CYP3A4}. Accordingly, oral coadministrations of flavonoids can improve the therapeutic effects of drugs with low bioavailability.\textsuperscript{[59,81,82]}

The results presented in Table 2 show that from among the medicinal plants introduced as convoys in TPM, extracts from celery, black pepper, cinnamon, red wine, tea, fennel, and pennyroyal have inhibitory effects on \textit{CYP450}s, with the maximum inhibition being related to \textit{CYP3A4}, \textit{CYP2E1}, \textit{CYP2D6}, and \textit{CYP1A2}, respectively.\textsuperscript{[83-85,87-89] Cytochrome \textit{P3A} (\textit{CYP3A}) is the most abundant and clinically significant family of \textit{CYP450} enzymes and includes \textit{CYP3A3}, \textit{CYP3A4}, \textit{CYP3A5}, and \textit{CYP3A7}. \textit{CYP3A4} is responsible for the metabolism of 30% of drugs.\textsuperscript{[70] Recent studies have also shown that baking a medicinal herb with vinegar may change or alter its activity on \textit{CYP450}s.\textsuperscript{[71,72]}

The natural compounds identified in convoying medicines that exhibited strong to moderate inhibitory effects on \textit{CYP450}s are (±)camphor found in the essential oils of several useful plants,\textsuperscript{[71]} α-asarone from hazelwort,\textsuperscript{[74]} piperine, and bisalkaloids, dipiperamides from black pepper and long pepper;\textsuperscript{[51,52,64,75,76]} O-methoxycinnamaldehyde (OMCA) from cinnamon,\textsuperscript{[84] safrol from sassafras,\textsuperscript{[77]} quercetin and resveratrol from red wine,\textsuperscript{[86] flavonoids from tea,\textsuperscript{[80]} 5-methoxysoralen (5-MOP) from fennel,\textsuperscript{[81]} dillapiole from root of fennel and dill mature seeds,\textsuperscript{[84-86]} and piperlongumimine from long pepper.\textsuperscript{[87] As the results mentioned above indicate, \textit{CYP3A4} is the most inhibited cytochrome, followed by \textit{CYP2D6}, \textit{CYP2E1}, \textit{CYP1A2}, and \textit{CYP2B1}. These natural compounds belong to phenylpropanoid compounds (dillapiol, safrol, OMCA, α-asarone), furanocoumarins, especially psoralen derivatives (O-MOP), which are characteristically natural components for the Umbelliferae family, flavonoids (quercitin), piper alkaloids and their derivatives, and monoterpenoids (camphor).

The results also indicated that the tannic acid-rich extract of wild cinnamon leaves, flavonoids from tea, and piperine from black and long pepper can inhibit phase II conjugation and monoxygenase enzymes such as GST, uridine diphosphate glycosyltransferase (UGT), and xenobiotic metabolizing enzyme (XME).\textsuperscript{[77,80,86]}

Among the mentioned convoy drugs, some exhibited induction effects on phase I and II metabolic enzymes. The oral administration of camphor increased the activity of \textit{CYP450}s and phase II metabolizing enzymes such as GST. Moreover, vinegar induced \textit{CYP2E1}, \textit{CYP2D6}, and \textit{CYP3A4}.\textsuperscript{[82,87] Natural compounds from convoy drugs also showed induction effects such as transanethol and eugenol from anise seed, which strongly induced UDP-glucuronosyltransferase, DT-diaphorase (DTD), and GST, as well as a small induction effect on \textit{CYP1A1} and \textit{CYP2B1}.\textsuperscript{[80] Phthalides from celery seeds also exhibited induction activity on GST in target organs.\textsuperscript{[89]}

CONCLUSION

According to the beneficial effects of saffron and camphor on the heart and brain, cerebral therapeutic effects of hazelwort, hepatoprotective effects of...
Table 2: Effects of some medicinal convoy plants on CYP450s, phase II enzymes, and efflux transporters

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Effect on phase I enzymes (CYP 450s)</th>
<th>Effect on phase II enzymes</th>
<th>Inhibition of efflux transporters</th>
<th>Effective component</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camphor</td>
<td>Inhibition: CYP2B1</td>
<td>Induction: Aryl hydrocarbon hydroxylase and glutathione S-transferase</td>
<td>+ (P-gp)</td>
<td>(±) - camphor</td>
<td>[73]</td>
</tr>
<tr>
<td>Hazelwort</td>
<td>Inhibition: CYP3A4</td>
<td></td>
<td>a- asarone</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>Vinegar</td>
<td>(Baking with vinegar)</td>
<td></td>
<td>a-asarone, β-asarone</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>Celery seed</td>
<td>Inhibition: CYP 450s</td>
<td>Induction:glutathion S-transferase</td>
<td>+ (P-gp)</td>
<td>Phthalides(sedanolide)</td>
<td>[89]</td>
</tr>
<tr>
<td>Black pepper</td>
<td>Inhibition: CYP3A4, CYP2D6</td>
<td>Inhibition: UGT(uridine diphasate glycosyltransferase) and XME (xenobiotic metabolizing enzyme)</td>
<td>+ (ABC: ATP-binding cassette) ABCB1, P-gp</td>
<td>Furanoconutamin (psoralen derivatives)</td>
<td>[48-50]</td>
</tr>
<tr>
<td>Cinnamon bark</td>
<td>Inhibition: CYP3A4, CYP2C9</td>
<td></td>
<td>Tannic acid and other polyphenols and total flavonoids (methanol extract of leaves)</td>
<td>[86]</td>
<td></td>
</tr>
<tr>
<td>Anise seed</td>
<td>Small induction: CYP1A and CYP2B</td>
<td></td>
<td>Safrol (4-allyl-1,2- methylenedioxybenzene) in volatile oils of sassafras root bark</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>Wild cinnamon bark</td>
<td>Inhibition: CYP1A2, CYP2A6, CYP2E1, CYP3A4, CYP2D6</td>
<td>Inhibition: GST(Glutathion S-transferase)</td>
<td>Strongly inhibition: 7-ethoxyresorufin O-deethylation, coumarin hydroxylation, and chlorozoxazone hydroxylation</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>Sassafras</td>
<td>Inhibition: CYP1A2, CYP2A6, CYP2E1, CYP3A4, CYP2D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine (Red wine)</td>
<td>Reduction: CYP2E1</td>
<td>(liver and kidney)</td>
<td>+ (P-gp)</td>
<td>O-methoxycinnamaldehyde</td>
<td>[65]</td>
</tr>
<tr>
<td>Quercetine Resveratrole</td>
<td>Inhibition: CYP3A4</td>
<td></td>
<td></td>
<td>Trans-Anethole</td>
<td>[88]</td>
</tr>
<tr>
<td>Tea (black and green tea)</td>
<td>Inhibition: CYP3A4</td>
<td>Inhibition: of: Steroid 5α-reductase</td>
<td>+ (BCRP and P-gp)</td>
<td>Flavonoids</td>
<td>[68, 53, 80]</td>
</tr>
<tr>
<td>Fennel</td>
<td>Inhibition: CYP2B1</td>
<td></td>
<td>Flavonoids</td>
<td>[69, 81-83]</td>
<td></td>
</tr>
<tr>
<td>Long pepper</td>
<td>Inhibition: CYP1A2</td>
<td></td>
<td>Dipinol (in fennel root)</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>Dill aromatic water</td>
<td>Inhibition: CYP3A4</td>
<td></td>
<td></td>
<td>Dipinol (in dill mature seeds)</td>
<td>[70]</td>
</tr>
<tr>
<td>Pennyroyal</td>
<td>Decrease in CYP450s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

chicory and celery seeds, and diuretic effects of cinnamon and melon seed, we can clarify the use of these herbs as convoy agents to the specific organs based on TPM experiences. In addition, vinegar can induce a liver- and brain-targeting effect by increasing the distribution of the main drug in the liver and the brain. The evaluation of the results demonstrated that the suggested convoy drugs, including black and long pepper, red wine, tea, hazelwort, pennyroyal, and dill, can increase the bioavailability of coadministered drugs by two mechanisms, the inhibition of P-gp and CYP450s. Fennel, cinnamon, sassafras, and camphor can increase the bioavailability of other drugs when orally consumed by inhibiting their metabolism. Although camphor, vinegar, celery, and anise seed have inductive effects on the metabolism of orally coadministered drugs, they may accompany other drugs to the site of action with different mechanisms such as targeting or synergistic effects or other unknown mechanisms that need to be studied.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES


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