Pharmacogn. Rev.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogrev.com | www.phcog.net

REVIEW ARTICLE

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

Seyede Nargess Sadati[1], Mohammad Reza Shams Ardekani[1,2], Nastaran Ebadi[1], Maryam Yakhchali[1], Azadeh Raees Dana[1], Fatemeh Masoomi[1], Mahnaz Khanavi[1,2], Farid Ramezany[1]

[1]Department of Traditional Pharmacy, School of Traditional Iranian Medicine, [2]Department of Pharmacognosy and Persian Medicine, Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran

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.

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

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 the use of convoy drugs (*Mobadregh*). According to TPM texts, convoy drugs are a class of modifiers that penetrate well and rapidly into the whole body or into particular organs. Moreover, convoys are substances (or drugs) that facilitate access to the whole body or to specific organs for drugs or food.[1-9]

Recent studies have proven that the simultaneous administration of two medicaments (drug-drug, herb-drug, and herb-herb) can result in clinically significant drug interactions. The medicaments may interact with each other in their absorption and metabolism and so can impact their bioavailability and exhibit synergistic pharmacological activity.[10]

This study reviewed some convoy drugs presented in TPM, their biological effects, and their probable interactions with the main drug considering increased absorption through the inhibition of P-glycoprotein (P-gp) efflux function, the bioavailability enhancement effect, and decreasing the metabolism of the main drug.

Correspondence:
Dr. Farid Ramezany,
Department of Traditional Pharmacy,
School of Traditional Iranian Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: farid.ramezany@gmail.com

Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/0973-7847.176546

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"), *Zakhire Kharazmshahi* ("Kharazmid Reservoir"), *ExirAzam* ("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 P_{450}," "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

Cite this article as: Sadati SN, Ardekani MR, Ebadi N, Yakhchali M, Dana AR, Masoomi F, *et al*. Review of scientific evidence of medicinal convoy plants in traditional Persian medicine. Phcog Rev 2016;10:33-8.

to the target organ. The moment the camphor tablet arrives at the heart, the saffron separates from it and its function is finished.[5]

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.[11] 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 (*Convolvolus scammonia*) and agaric (*Polyporus officinalis*) to convoy them to the brain and its veins where they perform their functions properly.[4] The beneficial influences of saffron extracts and its major component crocin that have been confirmed include treating 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.[15] 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.[16]

(+)-camphor becomes hydroxylated to borneol in the body mediated by cytochrome P450 (CYP450). Borneol, a bicyclic monoterpene, has been used in China for the treatment of cardiovascular and cerebrovascular diseases as a component in multidrug prescriptions.[17] Borneol is principally distributed in abundant blood-supply tissues after intravenous and intranasal administrations in mice. Brain tissue indicated the highest target coefficient and target efficiency after intranasal administration.[18] Distribution indices of borneol in rats with cerebral ischemia-reperfusion (stroke) significantly increased after oral administration in comparison to sham-operated rats.[19] Due to the affinity of saffron and camphor for the heart, they have a more specific effect on the heart in therapeutic doses, while in lower doses they can guide cardiac medicaments toward the heart. In these cases, when saffron and camphor convey the main drug to the heart, their function is finished.[4]

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

Names	Traditional name	Target organ (s)
Saffron (*Crocus sativus*)	*Zafaran*	Heart and brain vessel and other organs
Camphor (*Cinnamommum camphora*)	*Caphoor*	Heart
Hazelwort (*Asarum europaeum*)	*Asaroon*	Brain vessels
Vinegar	*Khell*	Spleen Brain internal
Chicory seed (*Cichorium intybus*)	*Tokhme kasni*	Liver
Celery seed (*Apium graveolens*)	*Tokhme karafs*	Liver
Melon seed (*Cucumis melo*)	*Tokhme batikh*	Liver Urinary tract
Black pepper (*Piper nigrum*)	*Felfel*	Kidney stones
Pennyroyal (*Mentha longifolia*)	*Fodanaj*	Kidney stones
Cinnamon bark (*Cinnamommum zeylanicum*)	*Darchin*	Kidney stones
Anise seed (*Pimpinella anisum*)	*Anisun*	Nonspecific (acceleration)
Wild cinnamon bark (*Cinnamomum iners*)	*Salikheh*	Nonspecific (acceleration)
Sassafras (*Sassafras albidum, Sassafras Hesperia*)	*Sasferas*	Nonspecific (acceleration)
Wine	*Khamr*	Nonspecific (acceleration)
Tea (*Camelia sinensis*)	*Chaye khotaee*	Stomach Body internal
Fennel (*Foeniculum vulgar*)	*Raziyaneh*	Body peripheral
White agaric (*Polyporus officinalis*)	*Gharighoon*	Body peripheral
Long pepper (*Piper longum*)	*Darfelfel*	Nonspecific
Dill (aromatic water) (*Anethum graveolens*)	*Shebet*	Nonspecific
Pine seed (*Pinus* sp.)	*Tokhme Sanobar*	Not specified

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.[4,8] 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.[20] 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, hypocholestrolemic, hypolipidemic, and antiepileptic properties.[21]

Convoying effects of vinegar on the spleen and brain

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 convoy drugs to it.[8,22] For example, the use of vinegar is suggested for convoying and accompanying rose oil to the brain ventricles in treating brain and meninges inflammation.[23]

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.[24-26]

Convoying drugs to the liver

Chicory seeds

Chicory seed is tenuous; it opens obstructions of and convoys drugs to the liver.[8] 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.[27] A new guaianolidese sesquiterpene glycoside, cichotyboside, isolated from the seeds of *Cichorium intybus* L., exhibited significant antihepatotoxic effects similar to those of the standard drug silymarin against CCl_4-induced toxicity in rats.[28] 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.[29,30]

Celery seeds

Celery seed is a potent antiblocking (*mofateh*) agent of liver and spleen obstructions. Because of its antiblocking and discutient (*mohalel*) properties, it can be tenuous and penetrating and can convoy drugs to the liver.[8]

Their hepatoprotective effect,[31] inactivation of toxic metabolites in liver,[32] antihepatocarcinogenesis,[33] antiinflammatory, antioxidant, cyclooxygenase- and topoisomerase-inhibitory activity,[34] and antihypertensive properties[35] have been observed in celery seed extracts.

Convoying drugs to the urinary tract, kidney, and bladder

Melon seed

Melon (*Curcumis melo*) seed can convoy drugs to the liver and the urinary tract.[8] Two species of the genus *Cucumis* (*Curcumis melo* and *Curcumis 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.[36] Isomultiflorenol as a major compound and its isomer Δ7-isomer multiflorenol were identified from triterpene alcohol fractions of the unsaponifiable part of *Curcumis melo* seed lipid.[37] Two pentacyclic triterpenoids, 16α-hydroxy-3-ketoisomultiflorene and 3β- hydroxyl-16-ketoisomultiflorene, isolated from *Antidesma menasu*, showed diuretic activity in experimental animals.[38]

Convoying litholytic drugs

Drug components that allow litholytic main drugs to penetrate to the location of kidney stones faster contain pepper, pennyroyal, and cinnamon.[5] 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.[39]

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.[4,5]

Bioavailability enhancement effects

Several herbal compounds including quercetin, genistein, naringin, sinomenine, borneol, and nitrile glycoside as well as herbal medicines such as *Piper longum* and its active ingredient piperine, *Glycyrrhiza glabra* (glycyrrhizin), *Carum carvi*, and *Cumminum cyminum* have exhibited the capability of enhancing bioavailability.[11,40-43]

Furthermore, curcumin has been reported to have inhibited the activity of breast cancer resistance protein (BCRP1) in mice. Recently, it was reported that monoterpenoids containing the extract of *Zanthoxyli* 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-1(MDR1)–expressing cell lines. It was found that the inhibitory activities of (R)-(+)-citronellal, (S)-(−)-β-citronellol, α-terpinene, terpinolene, (−)-β-pinene, abietic acid, ophiobolin A, cucurbitacin I, and glycyrrhetic acid on the P-gp–mediated efflux of digoxin were greater than 50%.[44-46] In addition, the potential inhibitory effect of glycyrrhetic acid and abietic acid on MRP2- or BCRP-mediated membrane transport has been reported.[47]

Based on the literature reviewed [Table 2], furanocoumarins, including psoralen derivatives in celery seed,[48-50] alkaloids such as piperine in black pepper,[51,52] polyphenolic compounds and catechins in green tea,[53] borneol as a metabolite of camphor and as a component of the essential oil of pennyroyal,[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.[55] 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.[21]

Cytochrome P450s' inhibitory effects

Herbal medicines such as St. John's wort (*Hypericum perforatum*), garlic (*Allium sativum*), piperine (from *Piper* sp.), ginseng (*Ginseng* sp.), gingko (*Gingko biloba*), soybean (*Glycine max*), alfalfa (*Medicago sativa*), and grapefruit juice display clinical interactions when coadministered with drugs.[56]

Some reports have demonstrated the effects of several components isolated from medicinal herbs on drug metabolizing-enzymes CYP450, uridine 5'-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.[57-60]

A number of flavonoids have been shown to modulate the 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 CYP3A4. Apigenin from among the inhibitors of flavone compounds displayed a significant inhibition on CYP3A4. Accordingly, oral coadministrations of flavonoids can improve the therapeutic effects of drugs with low bioavailability.[59,61,62]

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 CYP450s, with the maximum inhibition being related to CYP3A4, CYP2E1, CYP2D6, and CYP1A2, respectively.[48,63-69] Cytochrome P3A (CYP3A) is the most abundant and clinically significant family of CYP450 enzymes and includes CYP3A3, CYP3A4, CYP3A5, and CYP3A7. CYP3A4 is responsible for the metabolism of 30% of drugs.[70] Recent studies have also shown that baking a medicinal herb with vinegar may change or alter its activity on CYP450s.[71,72]

The natural compounds identified in convoying medicines that exhibited strong to moderate inhibitory effects on CYP450s are (±)camphor found in the essential oils of several useful plants,[73] α-asarone from hazelwort,[74] piperine, and bisalkaloids, dipiperamides from black pepper and long pepper,[51,52,64,75,76] O-methoxycinnamaldehyde (OMCA) from cinnamon,[64] saffrol from sassafras,[77] quercetin and resveratrol from red wine,[78,79] flavonoids from tea,[80] 5-methoxypsoralen (5-MOP) from fennel,[81] dillapiole from root of fennel and dill mature seeds,[81-84] and piperlonguminine from long pepper.[85] As the results mentioned above indicate, CYP3A4 is the most inhibited cytochrome, followed by CYP2D6, CYP2E1, CYP1A2, and 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 (quercetin), 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 monooxygenase enzymes such as GST, uridine diphosphate glycosyltransferase (UGT), and xenobiotic metabolizing enzyme (XME).[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 CYP450s and phase II metabolizing enzymes such as GST. Moreover, vinegar induced CYP2E1, CYP2D6, and CYP3A4.[72,87] Natural compounds from convoy drugs also showed induction effects such as transanethol and eugenol from anise seed, which strongly induced UDP-glucuronyltransferase, DT-diaphorase (DTD), and GST, as well as a small induction effect on CYP1A and CYP2B.[88] Phthalides from celery seeds also exhibited induction activity on GST in target organs.[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

Plant name	Effect on phase I enzymes (CYP 450s)	Effect on phase II enzymes	Inhibition of efflux transporters	Effective component	References
Camphor	Inhibition: CYP2B1 Induction: CYP450 (b_5)	Induction : Aryl hydrocarbon hydroxylase and glutathione S-transferase		(±) - camphor	[73] [87]
Hazelwort	Inhibition: CYP3A4 and CYP2D6		+ (P-gp)	α –asarone α-asarone, β-asarone	[74] [21]
Vinegar	(Baking with vinegar) Alteration in the activity of CYP 450s				[71, 72]
Celery seed	Inhibition: CYP 450s	Induction:glutathion S-transferase	+ (P-gp)	Phthalides(sedanolide) Furanocoumarins (psoralenderivatives)	[89] [48-50]
Black pepper	Inhibition: CYP3A4, CYP2D6	Inhibition: UGT(uridine diphosphate glycosyltransferase) and XME (xenobiotic metabolizing enzyme)	+ (ABC: ATP-binding cassette) ABCB1, P-gp	Piperine, bisalkaloids, dipiperamids	[64, 75, 76, 51, 53]
Cinnamon bark	Inhibition: CYP3A4, CYP2C9 CYP1A2 and CYP2E1			O-methoxycinnamaldehyde	[65]
Anise seed	Small induction: CYP1A and CYP2B	Induction: UDP-glucuronyltransferase (GT), DT-diaphorase (DTD), glutathione S-transferase (GST)		*Trans*-Anethole	[88]
Wild cinnamon bark		Inhibition: GST(Glutathion S-transferase)		Tannic acid and other polyphenols and total flavonoids (methanol extract of leaves)	[86]
Sassafras	Inhibition: CYP1A2, CYP2A6, and CYP2E1,CYP3A4, CYP2D6	Strongly inhibition: 7-ethoxyresorufin O-deethylation, coumarin hydroxylation, and chlorzoxazone hydroxylation		Safrol (4-allyl-1,2-methylenedioxybenzene)in volatile oils of sassafras root bark	[77]
Wine (Red wine)	Reduction: CYP2E1 (liver and kidney)		+ (P-gp)		[66, 67] [78]
Quercetine	Inhibition:CYP3A4				[79]
Resveratrole	Inhibition: CYP2E1				
Tea	Inhibition: CYP3A4 (black and green tea) Inhibition: CYP2B1	Inhibition of: Steroid 5α-reductase	+(BCRP and P-gp)	Flavonoids EGCG	[68, 53, 80]
Fennel	Inhibition: CYP2D6 and CYP3A4			Fennel extract Dillapiol (in fennel root) 5-methoxypsoralen (5-MOP)	[69, 81-83]
Long pepper	Inhibition: CYP1A2			Piperlonguminine (major alkaloid)	[85]
Dill aromatic water	Inhibition: CYP3A4			Dillapiol (in dill mature seeds)	[83, 84]
Pennyroyal	Decrease in CYP450s				[70]

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

1. Heravi MY. The Sea of Jewels (Bahr ol Javaher). Qum: Jalal al din Press; 2008. p. 339.
2. Nazem Jahan MA. Grat Panacea (Exir Azam). Tehran: Research Institute for Islamic and Complementary Medicine; Vol. 1., 2008. p. 312.
3. Aghili Khorasani MH. Grand Formulary (Gharabadin kabir). Tehran: Research Institute for Islamic and Complementary Medicine; 2008. p. 511.
4. Aghili Khorasani MH. Survey of Knowledge (Kholasat ol Hekmah). Vol. 2. Qom: Esmailian Press; 2006. p. 287.
5. Avecina H. Canon of Medicine (Qanun). Vol. 5. Tehran: Soroosh Press; 2009. p. 141.
6. Mohammad Arzani MM. Akbari's Medicine (Tebe Akbari). Vol. 2. Qum: Jalal Al Din Press; 2008. p. 1324.
7. Jorjani MH. Kharazmid Reservoir (Zakhire Kharazmshahi). Vol. 3. Qom: Institute of Natural Medicine Resurgence; 2012. p. 368.
8. Aghili Khorasani MH. Drugs Resevoir (Makhzan ol Advieh). Tehran: Tehran University of Medical Sciences Press; 2009. p. 52.
9. Alqarshi (Ibn Nafis) AA. Comprehensive Medical Technology (Al Shamel fi Sana'at). Vol. 17. Tehran: Research Institute for Islamic and Complementary Medicine; 2008. p. 727.

10. Posadzki P, Watson L, Ernst E. Herb-drug interactions: An overview of systematic reviews. Br J Clin Pharmacol 2013;75:603-18.
11. Boskabady MH, Shafei MN, Shakiba A, Sefidi HS. Effect of aqueous-ethanol extract from *Crocus sativus* (saffron) on guinea-pig isolated heart. Phytother Res 2008;22:330-4.
12. Joukar S, Najafipour H, Khaksari M, Sepehri G, Shahrokhi N, Dabiri S, *et al*. The effect of saffron consumption on biochemical and histopathological heart indices of rats with myocardial infarction.Cardiovasc Toxicol 2010;10:66-71.
13. Javadi B, Sahebkar A, Emami SA. A survey on saffron in major islamic traditional medicine books. Iran J Basic Med Sci 2013;16:1-11.
14. Xuan B, Zhou YH, Li N, Min ZD, Chiou GC. Effects of crocin analogs on ocular blood flow and retinal function. J Ocul Pharmacol Ther 1999;15:143-52.
15. Belz GG, Butzer R, Gaus W, Loew D. Camphor-crataegus berry extract combination dose-dependently reduces tilt induced fall in blood pressure in orthostatic hypotension. Phytomedicine 2002;9:581-8.
16. Werner NS, Duschek S, Schandry R. D-camphor-crataegus berry extract combination increases blood pressure and cognitive functioning in the elderly - a randomized, placebo controlled double blind study. Phytomedicine 2009;16:1077-82.
17. Zuccarini P. Camphor: Risks and benefits of a widely used natural product. J Appl Sci Environ Manage 2009;13:69-74.
18. Zhao JY, Du SY, LU Y, Wu HC, Li HY. Study on tissue distribution of borneol in mice by intravenous and intranasal administrations. Zhongguo Zhong Yao Za Zhi 2013;38:1071-4.
19. Xu P, Li Y, Du SY, Lu Y, Bai J, Guo QL. Comparative pharmacokinetics of borneol in cerebralischemia-reperfusion and sham-operated rats. J Zhejiang Univ Sci B 2014;15:84-91.
20. Oprean R, Tamas M, Roman L. Comparison of GC-MS and TLC techniques for asarone isomers determination. J Pharm Biomed Anal 1998;18:227-34.
21. Meng X, Liao S, Wang X, Wang S, Zhao X, Jia P, *et al*. Reversing P-glycoprotein-mediated multidrug resistance *in vitro* by α-asarone and β-asarone, bioactive cis-trans isomers from *Acorus tatarinowii*. Biotechnol Lett 2014;36:685-91.
22. Jorjani MH. Kharazmid Reservoir (Zakhire Kharazmshahi). Qom: Institute of Natural Medicine Resurgence; 2012. p. 409.
23. Nazem Jahan MA. Great Panacea (Exir Azam). Tehran: Research Institute for Islamic and Complementary Medicine; Vol. 1. 2008. p. 111.
24. Zhao RZ, Yuana D, Liub SJ, Chena YJ, Liua LJ, Zhaoa Y. Liver targeting effect of vinegar-baked Radix Bupleuri on rhein in rats. J Ethnopharmacol 2010;132:421-8.
25. Zhao R, Liu S, Mao S, Wang Y. Study on liver targeting effect of vinegar-baked Radix Bupleurion resveratrol in mice. J Ethnopharmacol 2009;126:415-20.
26. Dou Z, Li K, Wang P, Cao L. Effect of wine and vinegar processing of rhizoma corydalis on the tissue distribution of tetrahydropalmatine, protopine and dehydrocorydaline in rats. Molecules 2012;17:951-70.
27. Ahmeda B, Al-Howiriny TA, Siddiqui AB. Antihepatotoxic activity of seeds of cichorium intybus. J Ethnopharmacol 2003;87:237-40.
28. Ahmed B, Khan S, Masood MH, Siddique AH. Anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*. J Asian Nat Prod Res 2008;10:223-31.
29. Ghamarian A, Abdollahi M, Su X, Amiri A, Ahadi A, Nowrouzi A. Effect of chicory seed extract on glucosetolerance test (GTT) and metabolic profile in early and late stage diabetic rats. Daru 2012;20:56.
30. Ziamajidi N, Khaghani S, Hassanzadeh G, Vardasbi S, Ahmadian S, Nowrouzi A, *et al*. Amelioration by chicory seed extract of diabetes- and oleic acid-induced non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) via modulation of PPARα and SREBP-1. Food Chem Toxicol 2013;58:198-209.
31. Ahmed B, Alam T, Varshney M, Khan SA. Hepatoprotective activity of two plants belonging to the Apiaceaeand the Euphorbiaceae family. J Ethnopharmacol 2002;79:313-6.
32. El-Shinnawy NA. The therapeutic applications of celery oil seed extract on the plasticizer di(2-ethylhexyl) phthalate toxicity. Toxicol Ind Health 2015;31:355-66.
33. Sultana S, Ahmed S, Jahangir T, Sharma S. Inhibitory effect of celery seeds extract on chemically inducedhepatocarcinogenesis: Modulation of cell proliferation, metabolismand altered hepatic foci development. Cancer Lett 2005;221:11-20.
34. Momin RA, Nair MG. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from *Apium graveolens* Linn. seeds. Phytomedicine 2002;9:312-8.
35. Moghadam MH, Imenshahidi M, Mohajeri SA. Antihypertensive effect of celery seed on rat blood pressure in chronic administration. J Med Food 2013;16:558-63.
36. Wright CI, Van-Buren L, Kroner CI, Koning MM. Herbal medicines as diuretics: A review of the scientific evidence. J Ethnopharmacol 2007;114:1-31.
37. Itoh T, Shigemoto T, Shimizu N, Tamura T, Matsumoto T. Triterpene alcobols in the seeds of two cucumis species of cucurbitaceae. Phytochemistry 1982;21:2414-5.
38. Rizvi SH, Shoeb A, Kapil RS, Popli SP. Two new diuretic triterpenoids from *Antidesma menasu*. Phytochemistry 1980;19:2409-10.
39. Afzal M, Khan NA, Ghufran A, Iqbal A, Inamuddin M. Diuretic and nephroprotective effect of Jawarish Zarooni Sada-a polyherbal unani formulation. J Ethnopharmacol 2004;91:219-23.
40. Kesarwani K, Gupta R, Mukerjee A. Bioavailability enhancers of herbal origin: An overview. Asian Pac J Trop Biomed 2013;3:253-66.
41. Patil S, Dash RP, Anandjiwala S, Nivsarkar M. Simultaneous quantification of berberine and lysergol by HPLC-UV: Evidence that lysergol enhances the oral bioavailability of berberine in rats. Biomed Chromatogr 2012;26:1170-5.
42. Lai XJ, Zhang L, Li JS, Liu HQ, Liu XH, Di LQ, *et al*. Comparative pharmacokinetic and bioavailability studies of three salvianolic acids after the administration of *Salvia miltiorrhizae* alone or with synthetical borneol in rats. Fitoterapia 2011;82:883-8.
43. Yang S, Zhang K, Lin X, Miao Y, Meng L, Chen W, *et al*. Pharmacokinetic comparisons of single herb extract of Fufang Danshen preparation with different combinations of its constituent herbs in rats. J Pharm Biomed Anal 2012;67-68:77-85.
44. Liu JY, Lee KF, Sze CW, Tong Y, Tang SC, Ng TB, *et al*. Intestinal absorption and bioavailability of traditional Chinese medicines: A review of recent experimental progress and implication for quality control. J Pharm Pharmacol 2013;65:621-33.
45. Yoshida N, Koizumi M, Adachi I, Kawakami J. Inhibition of P-glycoprotein-mediated transport by terpenoids contained in herbal medicines and natural products. Food Chem Toxicol 2006;44: 2033-9.
46. Lee CA, O'Connor MA, Ritchie TK, Galetin A, Cook JA, Ragueneau-Majlessi I, *et al*. Breast cancer resistance protein (ABCG2) in clinical pharmacokinetics and drug interactions: Practical recommendations for clinical victim and perpetrator drug-drug interaction study design. Drug Metab Dispos 2015;43:490-509.
47. Yoshida N,Takada T, Yamamura Y, Adachi I, Suzuki H, Kawakami J. Inhibitory effects of terpenoids on multidrug resistance-associated protein 2- and breast cancer resistance protein-mediated transport. Drug Metab Dispos 2008;36:1206-11.
48. Jakovljevic V, Raskovic A, Popovic M, Sabo J. The effect of celery and parsley juices on pharmacodynamic activity of drugs involving cytochrome P450 in their metabolism. Eur J Drug Metab Pharmacokinet 2002;27:153-6.
49. Ahluwalia VK, Boyd DR, Jain KA, Sharma ND. Furanocoumarin glucosides from the seeds of *Apium graveolens*. Phytochemistry 1988;27:1181.
50. Dahan A, Altman H. Food-drug interaction: Grapefruit juice augments drug bioavailability-mechanism, extent and relevance. Eur J Clin Nutr 2004;58:1-9.
51. Nowack R. Review Article: Cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: Grapefruit juice, St John's Wort - and beyond! Nephrology (Carlton) 2008;13:337-47.
52. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther 2002;302:645-50.
53. Farabegoli F, Papi A, Bartolini G, Ostan R, Orlandi M. (-)-Epigallocatechin-3-gallate downregulates Pg-P and BCRP in a tamoxifen resistant MCF-7 cell line. Phytomedicine 2010;17:356-62.
54. Mkaddem M, Bouajila J, Ennajar M, Lebrihi A, Mathieu F, Romdhane A. Chemical composition and antimicrobial and antioxidant activities of *Mentha* (*longifolia* L. and *viridis*) essential oils. J Food Sci 2009;74:M358-63.
55. Kusuhara H, Sugiyama Y. Active efflux across the blood-brain barrier: Role of the solute carrier family. NeuroRX 2005;2:73-85.
56. Saxena A, Tripathi KP, Roy S, Khan F, Sharma A. Pharmacovigilance: Effects of herbal components on human drugs interactions involving cytochrome P450. Bioinformation 2008;3:198-204.
57. Dreiseitel A, Schreier P, Oehme A, Locher S, Hajak G, Sand PG. Anthocyanins and their metabolites are weak inhibitors of cytochrome P450 3A4. Mol Nutr Food Res 2008;52:1428-33.
58. Manthey JA, Myung K, Merten-Talcott SU, Butterweck V, Derendorf H, Widmer W. The isolation of minor-occurring furanocoumarins in grapefruit and analysis of their inhibition of CYP3A4 and p-glycoprotein transport of talinolol from caco-2 cells. Proc Fla State Hort Soc 2006;119:361-6.
59. Kimura Y, Ito H, Ohnishi R, Hatano T. Inhibitory effects of polyphenols on human cytochrome P450 3A4 and 2C9 activity. Food Chem Toxicol 2010;48:429-35.
60. Lim ST, Dragull K, Tang CS, Bittenbender HC, Efird JT, Nerurkar PV. Effects of kava alkaloid, pipermethystine, and kavalactones on oxidative stress and cytochrome P450 in F-344 rats. Toxicol Sci 2007;97:214-21.
61. Zheng J, Zhou HH. Effects of the flavonoids on cytochrome P-450 CYP1, 2E1, 3A4 and 19. Yao Xue Xue Bao 2007;42:8-12.
62. Wang HJ, Pao LH, Hsiong CH, Shih TY, Lee MS, Hu OY. Dietary flavonoids modulate CYP2c to improve drug oral bioavailability and their qualitative/quantitative structure-activity relationship. AAPS J 2014;16:258-68.
63. Tsukamoto S, Cha BC, Ohta T. Dipiperamides A, B, and C: Bisalkaloids from the white pepper Piper nigrum inhibiting CYP3A4 activity. Tetrahedron 2002;58:1667-71.
64. Hasegawa A, Yoshino M, Nakamura H, Ishii I, Watanabe T, Kiuchi M, *et al*. Identification of inhibitory component in--Cinnamon--o-methylcinnamaldehyde inhibits CYP1A2 and CYP2E1-. Drug Metab Pharmacokinet 2003;17:229-36.
65. Orellana M, Varela N, Guajardo V, Araya J, Rodrigo R. Modulation of rat liver cytochrome P450 activity by prolonged red wine consumption. Comp Biochem Physiol C Toxicol Pharmacol 2002;131:161-6.
66. Orellana M, Araya J, Guajardo V, Rodrigo R. Modulation of cytochrome P450 activity in the kidney of rats following long-term red wine exposure. Comp Biochem Physiol C Toxicol Pharmacol 2002;132:399-405.
67. Nishikawa M, Ariyoshi N, Kotani A, Ishii I, Nakamura H, Nakasa H, *et al*. Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam. Drug Metab Pharmakokinet 2004;19:280-9.
68. Langhammer AJ, Nilsen OG. *In vitro* inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy. Phytother Res 2014;28:603-10.
69. Mimica-Dukic N, Popovic M, Jakovljevic V, Szabo A, Gašic O. Pharmacological studies of *Mentha longifolia* phenolic extracts. ii. hepatoprotective activity. Pharm Biol 1999;37:221-4.
70. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology and Therapeutics 2013;138(1):103-41.
71. Cheng Y, Huang Y, Tian Y, Xu L, Liu GQ, Zahng ZJ. Assessment of the effects of Radix bupleuri and vinegar-baked Radix Bupleuri on cytochrome 450 activity by a six-drug cocktail approach. Chin J Nat Med 2013;11:302-8.
72. Su T, Mao C, Yin F, Yu Z, Lin Y, Song Y, *et al*. Effects of unprocessed versus vinegar-processed *Schisandra chinensis* on the activity and mRNA expression of CYP1A2, CYP2E1 and CYP3A4 enzymes in rats. J Ethnopharmacol 2013;146:734-43.
73. De-Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR. *In vitro* inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. Toxicol Lett 1997;92:39-46.
74. Pandit S, Mukherjee PK, Ponnusankar S, Venkatesh M, Srikanth N. Metabolism mediated interaction of α-asarone and *Acorus calamus* with CYP3A4 and CYP2D6. Fitoterapia 2011;82:369-74.

75. Subehan, Usia T, Kadota S, Tezuka Y. Mechanism-based inhibition of human liver microsomal cytochrome P450 2D6 (CYP2D6) by alkamides of *Piper nigrum*. Planta Med 2006;72:527-32.
76. Gurley BJ, Fifer Ek, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): Drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta Med 2012;78:1490-514.
77. Ueng YF, Hsieh CH, Don MJ. Inhibition of human cytochrome P450 enzymes by the natural hepatotoxin safrole. Food Chem Toxicol 2005;43:707-12.
78. Randhawa GK, Kullar JS, Rajkumar. Bioenhancers from mother nature and their applicability in modern medicine. Int J Appl Basic Med Res 2011;1:5-10.
79. Chan WK, Delucchi AB. Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4. Life Sci 2000;67:3103-12.
80. Donovan JL, Chavin KD, Devane CI, Taylor RM, Wang JS, Ruan Y, *et al.* Green tea (*Camellia sinensis*) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers. Drug Metab Dispos 2004;32:906-8.
81. Subehan, Zaidi SF, Kadota S, Tezuka Y. Inhibition on Human Liver Cytochrome P450 3A4 by Constituents of Fennel (Foeniculum vulgare): Identification and characterization of a mechanism-based inactivator. J Agric Food Chem 2007;55:10162-7.
82. Nowack R, Andrassy J, Fischereder M, Unger M. Effects of dietary factors on drug transportand metabolism: The impact on dosage guidelines in transplant patients. Clin Pharmacol Ther 2009;85:439-43.
83. Budzinski JW, Foster BC, Vandenhoek S, Amason JT. An *in vitro* evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 2000;7:273-82.
84. Jianu C, Misca C, Pop G, Rusu LC, Ardelean L, Teodora Gruia AT. Chemical composition and antimicrobial activity of essential oils obtained from dill (*Anethum graveolens* L.) grown in western Romania. Rev Chim 2012;63:641-5.
85. Song M, Hwang JY, Lee MY, Jee JG, Lee YM, Bae JS, *et al. In vitro* inhibitory effect of piperlonguminine isolated from Piper longum on human cytochrome P450 1A2. Arch Pharm Res 2014;37:1063-8.
86. Tan MS, Ab Halim MR, Ismail S, Mustaffa F, Ali NI, Mahmud R. Inhibitory effect of selected Malaysian herbal plants on Glutathione S-transferase activity. Int J Pharm 2011;7:349-55.
87. Banerjee S, Welsch CW, Rao AR. Modulatory influence of camphor on the activities of hepatic carcinogen metabolizing enzymes and the levels of hepatic and extrahepatic reduced glutathione in mice. Cancer Lett 1995;88:163-9.
88. Rompelberg CJ, Verhagen H, van Bladeren PJ. Effects of the naturally occurring alkenylbenzenes eugenol and trans-anetholeon drug-metabolizing enzymes in the rat liver. Food Chem Toxicol 1993;31:637-45.
89. Zheng G, Kenney P, Zhang J, Lam LK. Chemoprevention of benzo[a]pyrene-induced forestomach cancer in mice by natural phthalides from celery seed oil. Nutr Cancer 1993;19:77-86.


Seyede Nargess Sadati


Mohammad Reza Shams Ardekani


Nastaran Ebadi


Maryam Yakhchali


Azadeh Raees Dana


Fatemeh Masoomi


Mahnaz Khanavi


Farid Ramezany

ABOUT AUTHORS

Seyede Nargess Sadati, Assistant Professor of Pharmacognosy, Department of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.

Mohammad Reza Shams Ardekani, Professor of Pharmacognosy, Department of Pharmacognosy and Persian Medicine and Pharmacy Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences.

Nastaran Ebadi, Pharm D., Ph.D candidate of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.

Maryam Yakhchali, Pharm D., Ph.D candidate of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.

Azadeh Raees Dana, Pharm D., Ph.D candidate of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.

Fatemeh Masoomi, Ph.D of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.

Mahnaz Khanavi, Associate Profesor of Pharmacognosy, Department of Pharmacognosy and Persian Medicine and Pharmacy Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences.

Farid Ramezany, Ph.D of Traditional Pharmacy, School of Traditional Iranian Medicine, Tehran University of Medical Sciences.