

Review of Scientific Evidence of Medicinal Convoys in Traditional Persian Medicine

Seyede Nargess Sadati¹, Mohammad Reza Shams Ardekani^{1,2}, Nastaran Ebadi¹, Maryam Yakhchali¹, Azadeh Raees Dana¹, Fatemeh Masoomi¹, Mahnaz Khanavi^{1,2}, Farid Ramezany¹

¹Department of Traditional Pharmacy, School of Traditional Iranian Medicine, ²Department 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* (hazelnut), 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), hazelnut, *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.

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 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

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

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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 (*Convolvulus scammonia*) and agaric (*Polyporus officinalis*) to convey 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]

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, hypocholesterolemic, hypolipidemic, and antiepileptic properties.^[21]

Conveying 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 convey drugs to it.^[8,22] For example, the use of vinegar is suggested for conveying 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]

Conveying drugs to the liver

Chicory seeds

Chicory seed is tenuous; it opens obstructions of and conveys 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 guaianolide 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 convey 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.

Conveying drugs to the urinary tract, kidney, and bladder

Melon seed

Melon (*Curcumis melo*) seed can convey 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

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

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

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 Δ^7 -isomer multiflorenol were identified from triterpene alcohol fractions of the unsaponifiable part of *Curcumis melo* seed lipid.^[37] Two pentacyclic triterpenoids, 16 α -hydroxy-3-ketoisomultiflorene and 3 β -hydroxyl-16-ketoisomultiflorene, isolated from *Antidesma menasu*, showed diuretic activity in experimental animals.^[38]

Conveying 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 conveying 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 *Cuminum 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 conveying 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 conveying medicines that exhibited strong to moderate inhibitory effects on CYP450s are (\pm)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] dillapiol 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, saffrol, 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 (<i>b₅</i>)	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)		<i>Trans</i> -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 of: Steroid 5α-reductase	+(BCRP and P-gp)	Flavonoids EGCG	[68, 53, 80]
Fennel	Inhibition: CYP2B1 Inhibition: CYP2D6 and CYP3A4			Fennel extract Dillapiol (in fennel root) 5-methoxyypsoralen (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]
<i>Pennyroyal</i>	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.

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Conflicts of interest

There are no conflicts of interest.

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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 Professor 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.