Review Article

J Babol Univ Med Sci
21; 2019. P: 320-330

Cardiotonic Medicines (Mofarrehs) and Their Mechanism of Action in Persian Medicine

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J Babol Univ Med Sci; 21; 2019; PP: 320-30
Received: Nov 7th 2018, Revised: May 18th 2017, Accepted: June 15th 2019.

ABSTRACT

BACKGROUND AND OBJECTIVE: According to Persian Medicine (PM), heart is one of the main organs that maintain the human health. This medical school has introduced several medicines to maintain the health of the heart or to treat its diseases, such as cardiotonic medicines (Mofarrehs). In this study, Mofarrehs and their function are described from the perspective of PM.

METHODS: In this simple review article, six books from the main sources of PM, including Al-Shamel, Kitab al-Adviyt ol Qalbiye, Qarabadin-e-Kabir, Advieh Ghalbieh, Canon of Medicine and Kholaseh-al-Hekamah were reviewed and Mofarrehs and their function were analyzed. Qualitative content analysis was also performed, and then articles related to the mechanism of action of these drugs were extracted and the name of each Mofarrehs was searched in PubMed, Google Scholar, Scopus, SID, and IranMedex databases.

FINDINGS: Approximately, 30 commonly used Mofarrehs were identified and their characteristics including name, Persian and scientific names, temperament (Mizaj), origin and mode of effect on the heart were concluded and given as follows. In Persian medicine, some foods have been also regarded as Mofarrehs, and in this review, we discuss the mechanisms through which the tonic effects are exerted. Its antidepressant effects due to its antioxidant activity and inhibition of free radical has been proven in recent studies.

CONCLUSION: Administration of Mofarrehs, could initiate the future clinical trials to develop a new and effective natural drugs in the treatment of cardiac and mental illnesses. However, its wide acceptance needs further investigation.

KEY WORDS: *Persian Medicine, Traditional Medicine, Mofarrehs, Mental Disorders, Heart.*

Please cite this article as follows:

Kamaneh SA, Mojahedi M, Mozafari O, Memariani Z, Saravani M. Cardiotonic Medicines (Mofarrehs) and Their Mechanism of Action in Persian Medicine. J Babol Univ Med Sci. 2019;21: 320-30.

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[DOR: 20.1001.1.15614107.1398.21.1.49.4]
[DOI: 10.22088/jbums.21.1.320]

Introduction

In Persian Medicine, Mofarrehs are as medicine that reduces grief, heals the senses, removes boredom and strengthens the brain (1). According to PM, the heart is one of the main organs in determining the state of human health and the origin of the Ruh-e-hayavani (vital spirit; originating from the heart). The heart plays a role in the emergence of various mental states such as fear, sadness and anger, so one of the main focuses of treatment is paying attention to heart condition in patients with mental health problems. Several medicines have been introduced by scholars for the purpose of maintaining health or treating heart disease, and each can be used alone or in combination, and one of these medicines is Mofarrehs (2,3).

Given the tendency of people around the world to use traditional and complementary therapies, being informed about the therapeutic effects and their side effects is an essential principle. Since traditional and complementary medicine gives higher diversity and accessibility to healthcare services, it is an important necessity in achieving health goals. Elements enter the human body through nutrition; after entering the stomach, the food turns into a soup-like compound called chylous ascites and then enters the liver, where it is converted into liver chymus, which is a combination of different substances in four general categories: Safravi (Choleric), Damavi (Sanguine), Balghami (Phlegmatic), and Saudavi (Melancholic) Khelt (humor). These Khelt (humors) form the blood and the rest of the body's moisture, and the body organs act based on the combination of these humors (4). It is believed that, in addition to Khelt, other light objects called "spirit" are also created due to the mild heat of the liver; the spirit is gentle and moving, which changes with the movement of the spirit to the heart and under the influence of the heat of the heart.

As a result, the animal spirit or vital spirit (Ruh-e-hayavani) is created. In PM, it is believed that whenever the vital spirit reaches an organ, it prepares the organ for acceptance of vital sense, movement and acts, and since it is also the source of psychological spirit, the mental and psychological states such as fear, sadness, and anger are also attributed to the heart in addition to the brain. Nowadays, the use of natural methods in the prevention and treatment of diseases has been associated with public acceptance worldwide, and the World Health Organization has designed a ten-year strategy for all countries to revise their traditional medicine and move towards using the capacity of traditional schools. The school of PM, which is based on the knowledge, observations and experiences of Iran scholars over the generations, has a wide range of measures and recommendations for the prevention, diagnosis and treatment of diseases (5–7), and Iranian scholars have had simple insights and recommendations in their approach to human health that can still be addressed (8, 9). Therefore, to find new drugs in the treatment of heart disease, we can search the sources of PM for this purpose. In this study, Mofarrehs and their function are described from the perspective of PM.

Methods

In this study, six references from the most authentic written sources of PM were reviewed. The most important Persian medical and pharmaceutical sources that are considered as sample study in PM were gathered, which included Al-Shamel, Makhzan ol Advieh, Qarabadin-e-Kabir, Kitab al-Adviyt ol Qalbiye, Canon of Medicine and Kholaseh-al-Hekamah. The material related to the Mofarreh in these books were reviewed and notes were taken. The contents of each note were summarized under the general heading of the name of the Mofradehs (mono-ingredient medicaments) and under the heading of the Persian name and scientific name, temperament (Mizaj), origin (plant, animal, and mineral) and how it affects the heart.

Then, the contents of each title were extracted from the notes without any interference. The texts with difficult prose were simplified and Arabic texts were translated, and finally, by summarizing these titles, the general conclusion was extracted. Adherence to the principle of trustworthiness in expressing the material and mentioning the source for all material was taken into account as ethical consideration. After extracting their scientific names from sources such as "A Dictionary of Iranian Plant Names" (10), "Dictionary of Medicinal Plants" (11) and "Matching the Old Medicinal Plant Names with Scientific Terminology" (12), they were listed in a table. Finally, we searched online databases including PubMed, Google Scholar, Scopus, SID, IranMedex for human, animal and laboratory studies from 2012 onwards regarding the effect of Mofradehs on the heart using the keywords "CNS depressant effect", "anxiolytic efficacy", "decline in mood", "antidepressant", "anti-stress effect", "cardio protective", and "improves cardiac function".

[DOR: 20.1001.1.15614107.1398.21.1.49.4]
[DOI: 10.22088/jbums.21.1.320]

Results

By definition, in Dehkhoda dictionary, the literal sense of "Mofarreh" is cheerful, refreshing, joyful, enjoyable, and comforting. In PM, Mofarreh is a medication that enlarges the heart and removes the grief and sorrow, improves the senses, removes boredom and strengthens the brain (1). Overall, Mofarreh is anything that reduces grief, refines one's mind and causes happiness (13). Mofarrehs are applied (*mono-ingredient*) as a single medicine or combined with other drugs (*multi-ingredients*) as a compound medicine that will remove sadness from the human being and make the thought and organs of thought clear and happy (14). Tonekaboni considers everything that causes external and sensory pleasures as Mofarrehs, and in people with temperate Mizaj, listening to gentle sounds, seeing beautiful scenery, eating and drinking pleasant foods and drinks, smelling good odors, or touching things with good material make them joyful (15). Ibn Sina in "Kitab al-Adviyt ol Qalbiye" considers Mofarrehs as the enjoyment that results from understanding and perceiving things that are understood by the five senses or caused by inner satisfaction, such as a sweet feeling for a sense of taste, a good smell for a sense of smell and feeling of vengeance for strong anger (16). Considering the differences in individual characteristics as well as the influence of factors on individuals, Mofarrehs has many different types.

Mechanisms that cause Farah (joy): There are two factors involved in the creation of joy: first, reinforcing the triple strengths of body, and second, the expansion of the vital spirit. First: To reinforce the body's strengths, one must produce more spirit, especially the Ruh-e-hayavani (vital spirit; originating from the heart) and Ruh-e-nafsani (psychological spirit; originating from the brain), and on the other hand, one must maintain the Mizaj of these spirits as well as the general Mizaj of the body temperate (temperate Mizaj). Second: moderating the humor and the spirit expands them and facilitates the movement of spirit to the organs, but it should be noted that although high concentration impedes the expansion and relaxation of the spirit, its excessive tenderness and dilation can accelerate the erosion (dispersion) of the spirit and thereby weaken the body (1).

Moderating the Mizaj by reinforcing the natural strengths causes Farah (joy) and in this regard, some of Mofarrehs cause joy by heating, and some Mofarrehs such as rose water and camphor cause joy by cooling; echium amoenum and lapis lazuli act by removing melancholic substances, while fragrant and delicious agate reinforces the nature gently. Terminalia chebula, amber, and coral cause joy by reducing the rate of spirit erosion. Fragrance is one of the Mofradeh that cause Farah (joy) (1). Mofradeh such as Melissa officinalis, Salix aegyptiaca, Cinnamon, Red roses, Saffron, Coriandrum sativum, Coriandrum sativum, Pyrus communis, Echium amoenum, Musk, Nimphea alba, jonquil, Iris spp., Hyacinthus, Cyperus rotondus, Aquiloria agallocha roxb, Acacia farnesiana, Santalum sp., Elletaria cardamom, Malus domestica, Croton sp., Zingiber zerumbet, Elettaria cardamomum cause Farah with their fragrance. Another mechanism for the Farah of heart is antidote property. Among the spices that act with antidote property, cinnamon, Curcuma zedoaria and pistachio can be mentioned (16).

Another mechanism for the Farah of heart is astringency (1). Mofarrehs such as Myrtus communis, phyllanthus emblica, Albizia lebbeck, saffron, Pistachio vera, Elletaria cardamom, Coriandrum sativum, and myrobalan act with this mechanism. Another mechanism for the Farah of heart is exsiccation property. This type of Mofarrehs exsiccates the moisture of spirit and makes the spirit luminous and prone to Farah. Mofarrehs such as Albizia lebbeck, phyllanthus emblica, Citrus medica, and Frankincense act with this mechanism (1). Symphoricarpos and Albizia lebbeck cause Farah through diffusion and dispersion. Some Mofarrehs cause Farah based on their character. Albizia lebbeck, phyllanthus emblica, lavender, Stipa capensis, and Dracocephalum act based on their character (16).

Sapphire also acts the same way (17). In many cases, a combination of several Mofradeh are involved in the creation of the Farah, such as the combination of Corallium vulgare, Dronicum sp, Echium amoenum, and lapis lazuli. Some of the Mofradeh act based on character and fragrance, such as Ambergris and Musk, whose Farah is a combination of character and fragrance. Malus domestica causes Farah based on its character and when its Mizaj is warm, it causes Farah by moderating the Mizaj of spirit. The mechanism of action of Dronicum sp is also based on its character and moderating the Mizaj of spirit (17). Table 1 summarizes some of Mofarrehs and their mechanism of action based on PM. Jam is made with some Mofarrehs, such as pears, roses, and quince, while some other can be used as spices for food, such as saffron, cinnamon, and Coriandrum sativum. Some of the Mofarrehs are basically foodstuff, so they can be incorporated into the daily diet to benefit from their preventive and therapeutic properties.

[DOR: 20.1001.1.15614107.1398.21.1.49.4]
[DOI: 10.22088/jbums.21.1.320]

Table 1. Mofarreh – e – ghalb in PM in alphabetical order and their mechanism of action

Name	Fragrance	Exsiccation	Contraction	Character	Antidote	Other
Albizia lebbeck		+	+	+		
Citrus medica var. cedrata		+		+		
Punica granatum			+			Softening
Croton sp.	+		+	+		
Nepeta mentoides or lavender	+		+	+	+	
Muscus arboreus	+		+			
Cuscuta epithymum		Dependent property				Separation of Sauda from spirit
Myrtus communis	+		+	+	+	
phyllanthus emblica		+	+	+		
Melissa officinalis	+			+		
Corallium vulgare			+	+		
Polypodium vulgare						Dependent property
Salix aegyptiaca	+					
Centaurea behen	+		+	+		
Citrusmedicava.cedrata		+		+	+	
Malus domestica	+			+		
Curcuma zedoaria					+	
Cinnamumum verum j.presl	+			+	+	
Dronicum sp			+	+	+	
Musk medication					+	
Aurum				+		
Taxus baccata	+		+			
Zingiber zrumbet	+			+	+	
Crocus sativus	+		+			
Cinnamomum tamla	+		+	+		
Cyperus rotondus	+			+		
Cinnamomum iners	+					
Iris spp.	+					
Polygonatum orientale	+					
Santalum sp.	+		+	+		
Bambusa arundinace			+	+		Strong compound
Tiea Sigillata					+	Absolute antidote
Liquidambar orientalis	+	*				More temperate than musk
Aquiloria agallocha roxb	+					
Polyporus officinalis Erics				+		
Pistachio vera	+		+		+	
Argentum				+		
Elletaria cardamomu	+		+	+		
Cinnamomum cassia	+		+			
eugenia caryophyllata	+			+		
Cinnamomum camphora	+			+	+	
Coriandrum sativum	+			+		
Pyrus communis	+		+	+		
Boswellia carterii	+	+			+	

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Succinum	+		+		
lazuli			+		
Echium amoenum	+		+		
garnet			+		
Margarita			+		
Musk	+			+	
Shilajit			+		
Sedum spurium	+				
Mentha sp.	+	+	+		
Ocimum basilicum	+				
Nimphea alba	+				
Rosa damascena	+	+			
Terminalia chebula		+	+		With dependent and independent property
Ruby			+		

Here we investigate the Mofarrehs with wider therapeutic use.

Albizia lebbeck: It is one of the Mofarrehs, its nature is warm, and because it has the softening and exsiccation property, it cleanses the heart and body from Sauda and Balgham and strengthens the heart. Albizia lebbeckfun causes Farah through its character and strengthens all the three natural, vital and psychological spirits, Albizia lebbeck makes the spirit luminous and leads to complete Farah. It also has fattening properties, which increase Farah (1, 14, 16, 18 – 20).

Phyllanthus emblica: It has cold and dry Mizaj, so by removing inappropriate Sauda from the blood it purifies the spirit and blood from the Sauda and strengthens the mind and improves thinking. In addition, the Phyllanthus emblica particularly causes Farah in the heart, brain, and it exsiccates moisture (1, 14, 18 – 20).

Crocus sativus (Saffron): It has warm Mizaj-e-ektesabi (Acquired Mizaj) and dry Mizaj-e-jebelli (Innate Mizaj) and acts better when it is fresh. Crocus sativus, due to its aromatic properties and its power of contraction, strengthens the spirit, and expands, freshens and brightens it and has a great effect on the movement of the spirit, but it should be noted that its consumption in large quantities leads to spirit erosion due to high levels of Farah and expansion (1, 14, 16, 18–20).

Zingiber zrumbet: It is the root of a plant, whose nature is warm and dry in Mizaj-e-ektesabi, and creates Farah and strength in the heart and brain. Its Farah is based on character and its power of contraction and elegance also help a lot. In addition, Zingiber zrumbet is somewhat Saudavi laxative and helpful in the treatment of Saudavi diseases such as asphyxia, sadness and phobia (1, 16, 18 – 20).

Echium amoenum: It has a great effect on the Farah and strengthening of the heart. This Saudavi laxative plant is dilute and it's the cleanser of blood in the heart. In this plant, Farah is caused by its character and temperate Mizaj and therefore no drug is preferred over this (1, 14, 16, 18 – 20). Echium amoenum is used exclusively in the treatment of heart disease, regardless of the coldness or the warmness of the heart. Therefore, despite its warmness, Echium amoenum is used as Mofarrehs in warm cardiac disease.

Minerals: Some minerals have also been introduced as Mofarrehs, most notably Usnea barbata, Corallium rubraum, Aurum, Bole, Ambergris, Argentum, Lapis lazuli, Garnet, pearl, Shilajit and ruby. Scholars of PM also used some potions, extracts, digestive medicines and syrups as Mofarrehs. For example, the extract of parsnip (Pastinaca sativa), which is Mofarrehs and strengthens the heart, is a combination of parsnip extract, Echium amoenum, Centaurea behen, Santalum, that is made with Pussy Willow, rock candy, and Melissa officinalis. Another extract that is very effective in Farah of the heart is parsnip extract with rose water and Pussy Willow (14). The method of preparation of various types of Mofarrehs such as galenical Mofarrehs and the great Mofarrehs is available in Gharabaddin Book (21).

Mechanism of action of some Mofarrehs from the perspective of conventional medicine: Now we examine the substances and mechanisms of action of some herbal Mofarreh and the protective effects they have on the heart, and how they affect the spiritual states, especially the sedative and antidepressant effects they exert on the body from the perspective of conventional medicine (Table 2).

[DOR: 20.1001.1.15614107.1398.21.1.49.4]
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Table 2. Mechanism of action of some Mofarreh – e – ghalb medicines and their effect on heart and mood from the perspective of conventional medicine

Name	Indicative substance (essential oil - extract - product) or mechanism of action of the plant	Evidence of effect on mood	Evidence of effect on the heart
Croton sp.	caryophyllene oxide, β-caryophyllene, α-copaene, linalool and β-pinene, limonene and alfa-pinene.	Inhibitory effect on central nervous system (22)	-
Nepeta mentoides or lavender	Linalool, Gamma aminobutyric acid	Anxiolytic and Depressive Effects (23), Effects on Nervous System (24)	Lowering systolic blood pressure in mice and substantially sedating in humans (25).
Cuscuta epithymum	g-aminobutyric acid Polyphenols, flavonoids	Anxiolytic and Antidepressant Effects (23)	Protective effect on the heart (26)
Myrtus communis	The effect of M. communis extract on REM sleep inhibition The effect of oxidative stress and lipid peroxidation on atherosclerosis The effect of M. communis extract on REM sleep inhibition The effect of oxidative stress and lipid peroxidation on atherosclerosis	Treatment of anxiety disorders in humans (27)	Protective effect on the heart with effect on atherosclerosis (28)
phyllanthus emblica	GABA (B) agonist, and p-CPA (tryptophan hydroxylase inhibitor with effect on depression) And effect of upregulating the PI3K / Akt / GSK3 beta / beta-catenin cardioprotective pathway on the heart	Its extract has antidepressant properties (29)	Protective effect on the heart (30)
Melissa officinalis	Volatile compounds, triterpenoids, phenolic acids and flavonoids	Antidepressant effect (31)	Crude extracts and pure compounds. Also with the antagonistic effect of β-adrenergic on the heart, Antiarrhythmic and Anxiolytic Effects (31)
Polypodium vulgare	Aqueous extract of rhizome	Inhibitory effect on central nervous system and adrenoreceptors (32)	-
Salix aegyptiaca	Extract	Anxiolytic effect on mice (33)	-
Centaurea behen	Phenolic and flavonoid compounds	Antidepressant effect (34)	-
Malus domestica	-	-	Protective effect on mice heart disease (35)
Curcuma zedoaria	malondialdehyde (MDA) levels, superoxide dismutase (SOD), and glutathione peroxidase (GPX)	-	The most effective treatment for heart failure (36)
Cinnamomum zeylanicum	Improving resistance of organs to insulin	Protective effect on the central nervous system (37)	-
Dronicum sp.	Antioxidant effects and free radicals		Impact on heart and lung diseases (38)
Zingiber zrumbet	terpinen-4-ol	-	Effects on reducing blood pressure (39)
Crocus sativus	safranal	Impact on Depression and Anxiety Disorders (27)	Protective effect on the heart (40)

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Cinnamomum tamla	phytoconstituents, antioxidants, reduced calcium and nitric acid accumulation in the heart	Anxiolytic, antidepressant and anti-stress (41)	Cardioprotection in an animal model mediated by eugenol (42)
Cyperus rotondus	oligomeric flavonoids	Protective effect on the nervous system (43)	Protective effect on the heart (44)
Pistachio vera	Hydro-alcoholic extract	Hypnotic, Anxiolytic and Muscle Relaxing Effects (45)	-
Elletaria cardamomu	terpenes	-	Protective effect on the heart (46)
Cinnamomum cassia	5-HT(1A) receptor	Anxiolytic effect (47)	-
eugenia caryophyllata	clove oil	Reducing depression and increasing locomotor activity (48)	-
Coriandrum sativum	hydro-methanolic extract	-	Protective effect on the heart (49)
Succinum	of radix ginseng, radix notoginseng and succinum	-	Treatment of angina pectoris (50)
Echium amoenum	E. amoenum	Antioxidant and Free Radical Inhibition (51) Anxiolytic effect (52)	-
Musk	cytokines IL-6 and TNF-alpha	-	Improving cardiac function and correction of cardiac remodeling (53)
Sedum spurium	EtOAC extract	Impact on hemolysis and erythrocyte defense (54)	
Mentha sp.	methanolic extract, L possesses	-	Hypertension in normal people, Hypertension in animal models (55)
Ocimum basilicum	basil essential oils	Anti-Anxiety and Anti-Depression in Alzheimer's disease (56)	-
Nimphea alba	hydrolysable tannins, mainly ellagitannins, flavonoid	Antioxidant and anti-inflammatory (57)	-
Rosa damascena	Rosa damascena oil on depression Hydro-alcoholic extract on the heart	Improvement of sexual disorders in depressed men (58)	Protective effect on the heart, and lowering blood pressure (59)
Terminalia chebula	Ethanol extract	-	Protective effect on the heart (60)

Crocus sativus (saffron) has a protective effect on the heart, which works by strengthening the antioxidant system and reducing heart rate, and leads to the reduction of serum troponin levels and prevents heart damage (61). Recent studies have shown that the risk of cancer in the body is reduced by the consumption of Malus domestica (apple) (62). Apple contains antioxidants that protect the body's cells, and it has protective effect on the brain and heart (63). Bergamot with its antioxidant properties affects the cardiac muscle and improves the metabolic functions of the heart by lowering plasma lipid (64, 65). Pomegranate is one of the most useful and available fruits in our country that decrease systolic blood pressure by inhibiting angiotensin – converting enzyme (66). Pomegranates reduce atherosclerosis and cardiovascular disease by inhibiting low-density lipoprotein (67, 68). Tamarind (Tamarindus indica) also exerts its protective effects on the body with its antioxidant properties (69, 70). Other medicines such as astragalus (71, 72), Ginkgo biloba (73, 74), Rheum officinale (Chinese rhubarb) (75), and Ambergris (76) are herbs that have been shown to have protective effects on the heart through various mechanisms. Cinnamon and garlic have antioxidant properties that have beneficial effects on the heart, kidney and liver (77).

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Discussion

Cardiotonic medicines are a wide range of medicines used in PM that cause Farah in the heart and cure heart-related psychological illnesses by various mechanisms. Considering that many of these medicines, in addition to their Mofarrehs and tonic properties, have different mechanisms in the treatment of diseases in other organs, choosing the appropriate medication to treat each disease according to their mechanism of Farah to simultaneously cover several medical needs of patients is a key point in PM.

Each Mofarrehs (single drug) in PM has its own characteristic and features that are common in several Mofarrehs. For example, in a person who suffers from asphyxia associated with gastric Balghami disease, it is more appropriate to use Mofarrehs with power of contraction. Therefore, each Mofradeh falls into its own group according to its different properties in PM.

Jam is made with some Mofarrehs, such as pears, roses, and quince, while some other can be used as spices for food, such as saffron, cinnamon, and Coriandrum sativum. Some of the Mofarrehs are basically foodstuff, so they can be incorporated into the daily diet to benefit from their preventive and therapeutic properties. Therefore, we can reduce the use and dosage of chemical drugs and reduce their side effects. On the other hand, it seems that using Mofarrehs in patients with cardiovascular disorders who suffer from mental disorders such as depression can be mutually beneficial in the recovery of both diseases.

Suggestions: Although using the materials recommended in the books of PM scholars backed by hundreds of years of valuable experience can be helpful, the results of recent studies provide clear evidence of the myriad benefits of these herbs to human health. However, it is necessary to evaluate their efficacy in clinical trials in cases where there is no documentation, while it is possible to assess whether there are clinically and pharmacologically common chemicals in these products or not? How much of this Farah is related to the heart and how much to the brain? What is the connection between the new findings of cardiac drugs and the psychological findings? And many other questions that could be a good platform for researchers interested in this field.

Acknowledgment

Hereby, we would like to thank the Deputy of Research and Technology of Golestan University of Medical Sciences for the financial support of this research as well as the members of the Health Services Research (HSR) Council in the East of Golestan Province.

[DOR: 20.1001.1.15614107.1398.21.1.49.4]
[DOI: 10.22088/jbums.21.1.320]

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