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REVIEW ARTICLE

Treatment of Huntington's disease using medieval Iranian practice

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ABSTRACT

Huntington's disease (HD) is thought to be due to genetically-programmed degeneration of neurons in certain areas of the brain. This degeneration causes uncontrolled movements, loss of intellectual faculties, and emotional disturbances. It is a long time since the disease started tormenting human beings, and to date, conventional medications have failed to slow down the progression of HD. Although, the majority of currently-developed drugs may cure the symptoms of HD, they also trigger several side effects such as fatigue, restlessness, or hyper-excitability. In the present study, investigation was performed widely on medieval Persian prescriptions based on medical plants for treatment of the disease. Over 10 valid medical references of medieval Persian texts were screened to have a complete collection. Naturally-occurring substances derived from plants currently have a particular place in drug discovery. In conclusion, the study presents the clinical approaches that practitioners in medieval Persia used to classify, and deal with HD. The accurate observations of medieval Persian physicians provide a precise and comprehensive description of the HD.

Keywords: *Huntington's disease, Traditional medicine, Herbal medicine, Pharmacology*

The present study tries to shade light on the clinical approaches to Huntington's disease (HD) used by practitioners in medieval Persia medicine. HD is a late-onset neurodegenerative disorder that is caused by a CAG repeat expansion in the *IT15* gene, which results in a long stretch of polyglutamine close to the amino-terminus of the HD protein (huntingtin) [1]. Huntington's disease (HD) is an autosomal-dominant disorder characterized by irrepressible motor dysfunction, cognitive decline and psychiatric disturbances, which lead to progressive dementia and death approximately 15–20 years after disease onset [1,2]. It belongs to a family of neurodegenerative diseases caused by mutations, in which an expanded CAG repeat tract results in long stretches of polyglutamine (polyQ) in the encoded protein [2].

HD has a prevalence of 5–10 cases per 100,000 worldwide, which makes it the most common inherited neurodegenerative disorder [2]. It is a long time since the disease started tormenting human beings and to date, conventional medications have failed to slow down the progression of HD. The disease is always fatal, with an average life span of about 15 years after diagnosis [2,3]. Therapy focuses on supportive cares as well as pharmacological management of the behavioral and neurological problems [1,3]. Although the majority of currently-developed drugs may cure the symptoms of HD, they also trigger several side effects such as fatigue, restlessness, or hyper excitability [1].

In the present study, investigation was performed widely on medieval Persian prescriptions based on medical plants for treatment of the disease. Several documents still exist from which the definitions and treatments of HD in medieval Persia can be ascertained. In addition, these documents give detailed and precise clinical information related to HD. The medieval doctors were listed various signs and symptoms, apparent causes, and hygienic and dietary rules for preventing of HD and other neurodegenerative diseases. The medieval writings are both accurate and vivid, and they provide long lists of substances used in the treatment of neurological diseases. Nowadays, some experimental studies have evaluated medieval Persian natural therapies using modern scientific methods and many of the approaches of physicians in medieval Persia are accepted scientifically.

Al-Razi, who is known as Rhazes in Europe, is one of the greatest names in medieval medicine [4, 5-7]. The largest and most important of al-Razi's medical work is *Liber continents* (The comprehensive book of

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medicine), a collection of medical notes that al-Razi made throughout his life in the form of extracts from everything he had read, as well as observations from his own medical experiences [4,8,9]. Moreover, the other medieval medical texts of Persia such as Qanoon fel-teb (The Canon) by Ebn-e-Sina (Aviccena) (980–1037), and Zakhireh Kharazmshahi by Esmail Jorjani (1042–1136) became the most widely read literatures in medieval Europe [4]. Furthermore, the Persians not only gathered existing medical information, but also added to this knowledge with their own accurate observations and experimentation and introduced many new scientific theories. Therefore, they had brought great contributions to pharmaceutical science [10].

Our major purpose in the present study is isolating and analyzing all of the medical aspects of HD in order to clarify the manner in which medieval Persian practitioners viewed and dealt with the disease. Another purpose of the study is providing appropriate clinical data from centuries of experience in the field of HD in the medieval Persian medicine which may be effective for testing their probable advantages for HD and other neurological disorders.

Etiology of HD

Medieval Persian physicians observed that HD could be related to environmental or biological events [11-13]. Various substances were also known to provoke single episodes of HD as well as recurrent HD, especially in susceptible individuals. Patients were advised to avoid anything that has a negative impact on the brain activity [12-14]. Persian medicine emphasizes the concept that many causes of HD result from a dynamic interactions between endogenous factors and precipitating factors [12,15]. It is supposed that the potential role of each needs to be considered in order to determine the appropriate management of a patient with HD.

Management of HD

Medieval Persian medical literatures encouraged the treatment of HD by tackling the conditions such as nutritional therapy, and prescription of medicaments that contribute to HD [12-14]. In addition, they strongly believed that proper nutrition played a critical role in the brain activity [4,12,15]. Also, Persian practitioners asserted that most disorders generate solely from long continued errors of diet and regimen; they placed special emphasis on food and diet in their therapeutic management [13,16]. Furthermore, they accented the importance of the dose and defined a schedule for drug administration. Also, drugs were taken via oral or topical routes, as well as through the skin of trembly organs [14,16] and based on the underlying conditions, drug therapy plan was individualized. Finally, they recommended different single or combined drug prescriptions to patients suffering from HD that will be discussed later.

Combined drug therapy

Amongst the medicinal herbs advised for treatment of HD, Avicenna recommended several prescriptions (combined drugs) for HD treatment. He believed that the mixture of *Wild Rue* (*Ruta graveolens)* and *Harts tangue* (*Phyllitis scolopendrium*) are an excellent antidystaxia drugs treatment of HD [12]. It is worth to mention that *Wild Rue* was recommended by many Persian practitioners for treatment of HD [4,12-14]. Furthermore, it has been shown that the ethanol extract of *Rue* has ecbolic, anthelmintic and antispasmodic properties [17]. *Rue* was also recommended in medieval Persian medicine as an anti-aphrodisiac plant, which has been confirmed in our previous study too [18]. Avicenna also advised individuals suffering from HD to devour the mixture of *Marsh mallow* and leaves of *Cardamom* (*Elettaria cardamomum)* with honey. Moreover, in another place, he prescribed the oral administration of the mixture of *Aloe vera (Aloe)* and *Lavandula officinialis (lavender)* with honey [12]. Furthermore, medieval practitioners in Persia advised the oral use of mixture of *Marguerite* (*Anthemis pyrethrum*), *Preyn (Cinnamomum zeylanicum), Citrullus colocynth* and *Aloe vera (Aloe)* with honey three times a day in order to treatment of tremor and neurological disorders [12-14].

In severe case of HD, Avicenna strongly believed that it would be very beneficial for HD individual to take the oral administration of mixture of *Elove tree (Caryophyllue aromaticus), Strychnus nux vomica, Myristica fragrans (houtt), Alpinia officinarum (lesser galangal), Citrus aurantium amara (sour orange), Ocimum basilicum (basil seen), Myrabalani nigrae (black myrobalan), Aloexylon agallochum (lour)(agallochum), Calamintha graveolens (Calamint)* and *Lavandula officinialis (lavender)* with honey three times a day [12]. Also Razi in Al-hawi (Continents) advised patients suffering from HD with severe dystaxia, to eat a magic electuary which is the mixture of *Pimpinella anisum L (Anise), Pistacia lenticus L (lentisk), Illicium verum (hook F), Star anise* and *Aloexylon agallochum (lour) (agallochum)* with oxymel (a mixture of honey and vinegar) three times a day[13].

Single drug therapy

Having discussed the combined drug prescriptions, which were advised by medieval Persian physicians, we now turn to some medicinal plants that were recommended by them as single drug (not combined with other plants or substances). Firstly, *Marshmallow* or *Hock (Althaea officinalis),* which the effective part of this plant for HD treatment in medieval Persian medicine is its leaves [12-14]. The leaves contain chemicals such as anthocyanin, altheine, dioxybenzoic acid and cyaniding [19]. This plant was strongly utilized in ancient medicine of Persia in order to ease tremor and cause nerve calmative. Another plant is the *Guava, Psidium guajava,* which belongs to the family of Myrtaceae and it has been used as health tea [20]. Its leaves contain copious amounts of phenolic phytochemicals which inhibit peroxidation reaction in the living body, and therefore could prevent various neurological diseases [20-22]. The fruits and leaves of *Guava* have therapeutic effects that are used as nerve calmative and in some countries like Peru, it is used as an antidystaxia

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Table 1. Natural remedies for Huntington's disease in medieval Persian medicine

Origin of drugs	Family	Scientific Name	Common Name	Administration
Plant-derived drugs	*Myrtacea*	*Psidium guajava*	Guava	Oral
	Lamiaceae	*Lavandula stoechas*	Lavender	Oral
	Lamiaceae	*Hyssopus officinalis*	Hyssop	Oral
	Brassicaceae	*Brassica rapa*	Cabbage	Oral
	Euphorbiaceae	*Ricinu communis*	Castoroll plant	Oral
	Umbelliferae	*Trachyspermum.copticum*	Zniun	Oral/Topical
	Fabaceae	*Medicago sativa*	Alfalfa	Oral
	Malvaceae	*Althaea officinalis*	Marshmallow	Oral
	Rutaceae	*Citrus aurantium*	Sour orange	Oral/Topical
	Fabaceae	*Trifolium pratenes*	Red cover	Oral
	Lamiaceae	*Mentha mozaffarianii*	Wild mint	Oral/Topical
	Fabaceae	*Mucuna pruiens*	Velvet bean	Oral
	Rhamnaceae	*Ziziphus jujube*	Jujube	Oral
Animal-derived drugs		Brain of rabish		Topical
		EFAs rich foods		Oral
Other Origins		Water of rain		Topical
		Water of sea		Topical
		Sulfur water		Topical
		Galipot		Oral

drug [20,23]. Moreover, due to the astringency properties of the plant, it is commonly employed to halt gastroenteritis, diarrhea and dysentery [21,23]. *Sour orange* or *Citrus aurantium* that belongs to the *Rutaceae* family was also recommended in order to cure neurological diseases [24-25]. The peel, flower, leaf, and fruit of this plant are used in both traditional medicine and modern medicine [26]. The plant is native to Iranian flora; it usually grows in regions with moderate climate [25]. Also, orange leaves have calmative, anti-dystaxia and digestive effects [26,27]. In addition, orange flowers have antispasmodic effects in neurological diseases [26,28].

Alfalfa or *lucerne*, which is highly valued legume forage, grows extensively in tropical and cool subtropical regions [25]. Its Seeds contain the alkaloids, stachydrine and 1-homostachydrine, and are considered as emmenagogue and lactigenic [29,30]. It is also considered as antiscorbutic, aperient, diuretic, ecbolic, antidystaxia, estrogenic, stimulant, and tonic, and is said to aid peptic ulcers, as well as urinary and bowel problems [30-32]. In ancient Persian medicine, it was believed that the topical administration of baked *Lucerne* on the trembling organs would be efficient and curative [10,14]. They also believed that eating the *Lucerne* bean with *olive* oil and rubbing them on trembly organs, lead to health recovery [12,14]. Finally, *Mucuna pruriens* var *or Velvet bean*, which is a magic plant in ancient medicine, generally grows in equatorial regions, especially in Africa, India and Iran [33,34]. It is used as an accompany drug in treatment of dystaxia and Parkinson's disease [35,36]. It is also utilized for gastric ulcer in recent centuries [33,34]. Moreover, this plant is naturally enriched with lipids, essential fatty acids (EFAs) and minerals at high levels [33,34]. It has been recently shown that EFAs have an essential role in health recovery in HD patients [37,38].

Other treatments

In ancient medieval Persian medicine, an endless series of ointments, powders, and mixtures of various substances were prescribed in order to treat and cure neurological diseases. Some drugs were listed in medieval Persian writings including plants, various animal products, and minerals are briefly shown in Table1.

Topically-applied drugs were usually mixed with vinegar; in order to reduce the side effects and to dilute the dose of potent substances. Also the drugs were mixed with flour, egg white, honey, or milk. In addition, administration of *myrrh (*C*ommiphera myrrha*) to patients suffering from HD was believed to ease tremor [12,39]. Both Avicenna and Razi believed that bathing the body and trembly organs in the rain water, sulfur water, desert water and sea water cause a remarkable recovering effect on HD patients [12,13]. In medieval Persian medical texts, rain water was strongly recommended for improvement of all neurological diseases [12-14]. Furthermore, medieval Persian physicians described the treatment of HD using many substances with variable modes of action. They developed many substances that were supposed to have antidystaxia properties. Moreover, they advised substances such as galipot and dietary regime which contained high levels of essential fatty acids (EFAs) for health recovery of HD

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[12-14]. It is noteworthy that EFAs are the mixture of eicosapentaenoic acid (EPA), docosohexaenoic acid (DHA), gamma-linolenic acid (GLA), vitamin E and lipoic acid. GLA, EPA, and DHA are found in relatively-high amounts in the brain and are believed to play a role in controlling movement regulation by brain [3]. Lipoic acid and vitamin E are antioxidants that may help to reduce further degeneration in the brain [3,37,40]. Also, EFAs are components of cell membranes that may affect cell death and movement disorders, because it has been shown that EFAs can improve certain movement disorders [37,38].

Moreover, bloodletting was recommended as an effective method in order to improve a severe case of HD. Phlebotomy from the first vertebra was thought beneficial because it was believed that it eliminated the vapors that produce the illness to rise to the brain [12,13]. However, how and why it can be leaded to ease tremor is unclear.

CONCLUSION

Here, we put special emphasis on the review of clinical aspects of HD throughout Persian medical history in Middle Ages. The medieval Persian practitioners believed that dietary factors play a key role in the development of various human diseases. Across cultures, there are many different dietary patterns which are believed to promote human health. Despite cultural differences, there are some shared characteristics of healthy dietary pattern. In fact perceiving plant foods as beneficial diet is advised by the folklore of many cultures over centuries.

Clearly, there are many possible targets and available strategies that might permit the development of new and effective treatments for HD from plants and their naturally-occurring secondary metabolites. Although research into herbal remedies is increasing in line with usage, the majority of these investigations are preliminary and few studies focus on the clinical trials of such compounds. It is worth to mention that in medieval Persian medicine, diets and herbs that contain high level of EFAs are strongly recommended for health recovery of HD patients [12- 14]. Recently, some studies have been conducted to examine EFAs effects on transgenic HD mice. In one research, 60 mice were fed either a mixture of EFAs or a placebo, every other day from birth through adulthood. The results showed that EFAs completely protected the mice from HD-related locomotion problems and improved other abnormal behaviors. Additionally, only 15% of the EFAs-treated mice died during the 43-week study, compared to 42% of the placebo-treated mice [3]. Another research carried out a similar six-month study on seven patients with advanced HD. The patients in this study received a placebo or ethyl-eicosapentaenoic acid (ethyl-EPA), a highly unsaturated fatty acid. This study confirmed that ethyl-EPA caused a significant improvement in the cerebral structure and function of HD patients. They hypothesized that ethyl-EPA would be particularly effective against HD; because it had been shown to inhibit a neurodegenerative enzyme and reverse brain atrophy in schizophrenic patients [37]. Also, diets supplemented with foods that have a high oxygen radical absorbance (antioxidant substances) capacity, have been shown to reduce the levels of tumor necrosis factor A and B in neuronal tissues. These pro-inflammatory cytokines are implicated as crucial neuronal mediators in some types of neurological disorders such as HD [40].

Despite progress in the development of HD therapy in recent years, effective and potent drugs are still required for the treatment of HD. The attempt to find new pharmacologically active analgesics obtained from plants has led to the discovery of some clinically-useful drugs that, during the past two centuries, have played a major role in the treatment of human diseases. However, most medicinal plants prescribed by Persian physicians remain largely unexamined. In recent years, medieval Persian natural therapies for HD have been evaluated using modern scientific methods in order to revive traditional treatments. Furthermore, future accurate experimental and clinical research trials should focus on the identification of effective and safe anti-dystaxia drugs, from plants or plant derivatives, with special emphasis on their probable toxicity and adverse effects.

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