

ORIGINAL ARTICLE

The Concept of the Humoral Theory in Persian Medicine

Abstract

The humoral theory, as a cornerstone of traditional Unani, Chinese, and Persian medical systems, plays a fundamental role in maintaining health. According to this framework, any excess or deficiency in the body fluids disrupts the body's balance and triggers disease. This fundamental understanding underscores the pivotal role of the humoral theory in health and disease. Each humor—, be it sanguis, yellow bile, phlegm, or black bile—possesses distinct qualities, characteristics, properties, and consequences. A comprehensive study of these humors was conducted based on traditional resources to ensure the credibility and depth of our research. We reviewed the main textbooks of Persian Medicine (PM), including Avicenna's *Canon of Medicine*, and searched the databases including Web of Science, Medline, and Scopus from inception to December 31, 2022, to examine the perspectives of contemporary researchers in this regard. Currently, the closest modern scientific concept to humors is that of molecules, although not all molecules correspond to the traditional definitions of humors. However, the potential applications of the humoral theory in modern integrative medicine are extensive and intriguing. Understanding the humoral theory can provide a unique perspective on health and disease, opening new avenues for research and practice in the global shift toward integrative medicine.

The biomolecular and biochemical examples of normal and abnormal humors discussed in Persian Medicine (PM) literature remain unknown. However, many hypotheses can be proposed to open new frontiers in the diagnosis, prevention, and treatment of diseases based on the described characteristics, properties, and consequences of humors. Emerging research in PM over the past two decades supports this claim.

Key words: Humoral theory, Persian Medicine, Traditional Medicine, Integrative Medicine, Temperament

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Introduction

Persian medicine also known as PM has an indispensable role in patients' treatment (Tafazoli, et al., 2022). PM besides other traditional medicine, such Chinese and Indian Ayurvedic medicine, are constructing integrative medicine (Jiang, et al., 2011; Chopra and Doiphode, 2002). This initiative seeks to integrate the finest elements of both traditional and modern medicine to deliver thorough and effective healthcare. Since 2007, the growth of Persian medical schools in Iran has been expected to contribute further to this worldwide effort (Rezaeizadeh, et al., 2009).

This comprehensive medical school is based on a philosophical theory with a structured framework. The extensive knowledge gathered in PM over the centuries has been thoroughly documented and reviewed. (Cragg, and Newman, 2013). The surge in genetic information has enabled new screening methods and the use of combinatorial biosynthetic technology and genome mining. This has led to the identification of unknown molecules, which can be optimized through combinatorial chemistry to create new drug candidates for various diseases.

PM is based on the humoral theory and the temperaments (*Mizaj*), which is the general quality of the individual. It endeavors to maintain the balance between the four humors i.e., sanguis (also named as blood humor), phlegm, yellow bile, and black bile, while considering both the spiritual and physical aspects of human health. Any imbalance in the composition of humors or changes in their quality lead to disease. Therefore, treatment is based on the correction of temperament and humors to achieve an optimum balanced state (Rezaeizadeh, et al., 2009; Shirbeigi, et al., 2017; Ardekani, et al., 2011).

This individualized approach of traditional diagnosis, prevention and treatment is comparable to the recent approach of "*personalized medicine*" and "*precision medicine*" that has gained widespread attention over the past two decades. According to this concept, choosing the appropriate medication is based on personal characteristics and individual differences. In comparison, the inexpensiveness, feasibility and independence of the PM approach from technology should be considered (Moeini, et al., 2017). To understand PM, which is based on the temperaments (*Mizaj*) and the humoral theory, it is necessary to initially examine the concept of the humors.

Jondi-Shapour University, also known as the University of Jundishapur, played a pivotal role in the development and dissemination of the humoral theory. This ancient institution, located in Iran, was a major center of learning and medical knowledge during the Sassanian Empire. The university's scholars were instrumental in preserving and expanding upon the medical theories of Hippocrates and Galen, including the humoral theory, which posits that the balance of bodily fluids—sanguis (blood), phlegm, yellow bile, and black bile—determines health and disease (Bos, 2020). Through translations and original research, Jondi-Shapour University became a bridge between Greek, Persian, and later Islamic medical traditions, ensuring the continuity and evolution of humoral theory in medical practice (NoorMohammadi, 2023).

This study has endeavored to extract the concept of humors from the sources of PM as well as works of modern researchers in this field, and to eventually identify and introduce the closest concepts of modern medicine that are related to the traditional concept of humors.



Method

This study is a narrative review on the viewpoints of PM scholars, especially Avicenna, regarding humors.

Accordingly, the main sources of PM, Avicenna's *Canon of Medicine*, and electronic databases including Web of science, Medline, and Scopus were searched for related information and articles on humoral theory and humors in traditional medicine from inception to September 3, 2024.

Hence, "*humors*", "*humoral theory*", "*akhlat*", "*Mizaj*", "*temperament*", "*dys temperament*", "*traditional medicine*", "*complementary medicine*", "*alternative medicine*", "*Persian Medicine*", "*integrative medicine*" and "*Unani Medicine*" were searched as keywords.

After the obtained results were reviewed, all notes and documents were gathered to form a comprehensive document file. Subsequently, the findings were reviewed several times, and notes were made about relevant information. Initial codes were created to categorize the data into historical, preventive, and incoherent groups. Subsequently, the recurring codes and items were combined into cohesive themes, which were presented in text and tables. Data were collected, and modern and traditional information were analyzed and compared.

Results

PM is based on the theory of the four elements. These elements are different from those in the chemistry periodic table. Unlike the elements in the periodic table, the four philosophical elements cannot be divided into smaller components (Ardekani, et al., 2011; Moeini, et al., 2017).

According to the philosophical foundations of PM, all composite materials in the world, including human body parts, are made up of a combination of four elements. The diversity of materials arises from the different proportions of these elements. These elements are elemental fire, elemental air, elemental water, and elemental soil (Shirbeigi, et al., 2017; Ardekani, et al., 2011; Naghizadeh, et al., 2021). Also in Chinese medicine the five elements theory is a framework utilized in various traditional Chinese disciplines to interpret a broad range of phenomena, including cosmic cycles and the interactions between internal organs. It is a fundamental aspect of traditional Chinese medicine philosophy and is closely connected to the Yin and Yang theory. These elements consist of wood, fire, earth, metal, and water (Ling, 2020).

Each of these elements has its own qualities. For example, elemental fire is absolutely hot and relatively dry, elemental air is absolutely dry and relatively hot, elemental earth is absolutely dry and relatively cold, and elemental water is absolutely cold and relatively dry.

Therefore, in every being, whether it's a human or a part of the body, a specific quality state prevails on the spectrum of hotness-coldness and wetness-dryness. This state, based on the composition and proportion of the elements, is known as temperament (Shirbeigi, et al., 2017; Ardekani et al., 2011; Avicenna, 2014).

Temperament is a fundamental concept in traditional medicine used to classify individuals as healthy or ill, playing a crucial role in maintaining health and treating diseases. It has gained attention in conventional medicine, shifting the focus towards treating individuals rather than just illnesses. Studies have explored the relationship between tempera-



ment and proteomes in the human body, highlighting its importance in health recognition, disease treatment, and traditional medicine research. (Shirbeigi, et al., 2017, Naghizadeh, et al., 2021, Tabarraei, Eftekhari, and Nazem, 2013).

On the other hand, the elements combine in several stages before entering the body through food. Once inside, they are broken down and digested into components that can build human tissues. These components, derived from the chemical breakdown of food, are called natural or normal humors, or primary moistures (Avicenna, 2014; Fattahi, et al., 2022).

In the digestive system, food undergoes four stages of digestion: gastric, hepatic, vascular, and organ stages. Normal humors are primarily produced from the hepatic stage onwards. Once they leave the blood vessels, these humors are called secondary moistures. After entering the organs, they either become part of the organ or are used by the organ for nutrition or other purposes (Avicenna, 2014; Emtiazy, et al., 2012).

PM scholars have defined humors, which we will refer to in this article to match the closest modern concept. Humors are dispersible, three-dimensional fluid materials that are primarily broken down from food as it enters the body. 'Three-dimensional' means they have measurable length, width, and height. In other words, humors are the result of the initial chemical transformation of food following digestion (Shirbeigi, et al., 2017; Avicenna, 2014).

The roots of the humoral theory can be traced back to ancient Persian texts from the first three centuries of the Islamic era in Iran. These texts reflect the integration of earlier Greek medical knowledge, particularly the works of Hippocrates and Galen, with Persian and later Islamic medical traditions. They discuss the balance of bodily fluids—blood, phlegm, yellow bile, and black bile—as essential for maintaining health, a concept central to the humoral theory. This synthesis of Greek and Persian medical thought laid the foundation for the humoral theory's influence on subsequent Islamic and medieval European medicine, highlighting the interconnectedness of ancient medical traditions (2012).

The concept of humors in Traditional Persian Medicine (TPM) is deeply rooted in the balance and interaction of four primary fluids: sanguis, phlegm, yellow bile, and black bile. These humors are believed to influence both physical and mental health, with each humor corresponding to specific qualities and temperaments. For instance, sanguis is associated with a sanguis temperament, characterized by warmth and moisture, while phlegm is linked to a phlegmatic temperament, marked by coldness and moisture (Tansaz, et al., 2022). The balance of these humors is crucial for maintaining health, and any imbalance can lead to disease. Recent studies have explored the relevance of these ancient concepts in modern medicine, highlighting the potential for integrating humoral theory with contemporary medical practices (Tansaz, et al., 2021).

Humors are divided into two general categories: normal and abnormal. Normal humors help maintain health by nourishing body tissues and replacing depleted parts. For normal humors to be produced, the food consumed must be suitable and properly digested. To maintain health, both the quantity and quality of each humor must be appropriate, and there must be a balance between them, as the humors influence each other (Emtiazy, et al., 2012; Avicenna, 2014).

This means that both a deficiency and an excess of a humor can be problematic. Sometimes, a lack of a humor can mimic the symptoms of an excess of the opposite humor, leading to misdiagnosis (Movahhed, et al., 2012).



Moreover, the production and regulation of humors are influenced by various factors, including diet, lifestyle, and environmental conditions. TPM emphasizes the importance of personalized treatment plans based on an individual's unique humoral composition and temperament. This approach aligns with modern personalized medicine, which considers genetic, metabolic, and environmental factors in disease prevention and treatment (Kordafshari, et al., 2017). By understanding the intricate relationships between humors and health, TPM provides a holistic framework for addressing both physical and psychological ailments, offering valuable insights for integrative medical approaches (Kordafshari, et al., 2017).

Generally, the quality and quantity of the humors produced depend on various factors, such as lifestyle. For example, the type of food, mood, and behavior can affect humor production. Conversely, the dominant humor in the body can influence mood, behavior, and appetite, as well as the desire for different types of food (Avicenna, 2014).

Tables 1-4 show the temperament, characteristics, properties, and functions of the four types of normal humors: sanguis, phlegm, yellow bile, and black bile. According to PM literature, normal humors like phlegm or black bile are not single substances but categories that include various similar substances. When the quality or quantity of normal humors changes, it leads to the diagnosis of abnormal humors, each with its own symptoms and complications, as detailed in Tables 1-4. There are more types of abnormal humors than normal ones; for instance, there are more varieties of abnormal black bile than normal black bile (Avicenna, 2014; Movahhed, et al., 2012).

Table 1: Normal and abnormal sanguis (blood)

Sanguis			
Normal		Abnormal	
Temperament and characteristics	Properties and functions of normal sanguis	Manifestations of excess quantity or more potent quality	Manifestations of insufficiency
Hot and wet	1. The most excellent of all, which is of a balanced nature and exceeds other humors in quantity. 2. Nourishes and grows the body. 3. Heats and moisturizes the body. 4. It is the most essential humor, and conducive to vitality. 5. Keeps the skin fresh and glowing	Reddish tone of the skin, eyes and tongue	Weakness; slowness or cease in growth
Red in color		Excessive napping	
No unpleasant odor		Great and full pulse	
Sweet in taste,		Reddish concentrated urine	Coldness and dryness of the body
Homogenous brightness		Increased thirst	
		Decreased physical strength with activity due to feeling too hot	
		Decreased appetite	Dullness of facial skin
		Skin stretching	
		Vascular prominence	
		Sluggish movements	
		Slowness of the senses and thinking	
		Feeling of heaviness in the body especially in the head, temporal region, and eyes	
		Yawning	
		Sweet taste in the mouth	
		Fatigue	
		Bleeding from the gums, nose and anus	
		Appearance of boils in the body and rashes and thrush in the mouth	
		Hemoptysis	
		Hematemesis	
		Epistaxis	
		Abscesses	
		Rashes	



Table 2: Normal and abnormal phlegm

Phlegm			
Normal		Abnormal	
Temperament and characteristics	Properties and functions of normal Phlegm	Manifestations of excess quantity or more potent quality	Manifestations of insufficiency
Cold and wet	1. It is immature blood and is capable of transformation into blood whenever required.	Excessive coldness and wetness of the body	Disturbance of the senses (internal and external), movement, and tact and policy
White		Whitish tone of the skin and tongue	
Transparent	2. It may mix up with blood and thus prepare it for nourishment of cold-wet organs such as the brain and spinal cord.	Soft pulse	Joint dryness
Moderate viscosity		Cold and soft skin on tactile examination	Anemia
Tasteless	3. It moistens the joints and the organs involved in frequent movement, so that they do not become dry because of the heat generated by movement and friction.	Decreased thirst	
		Sleepiness and laziness	
		Excessive salivation	
		Delayed digestion	
		Forgetfulness	
		Drowsiness	
		Vertigo	
		Dizziness	
		Nightmares	
		Edema	

Table 3: Normal and abnormal yellow bile

Yellow bile			
Normal		Abnormal	
Temperament and characteristics	Properties and functions of Normal Yellow bile	Manifestations of excess quantity or more potent quality	Manifestations of insufficiency
Hot and wet	1. It is the foamy part of the blood.	Excessive hotness and dryness of the body	Lung weakness
Yellow-colored		With symptoms and diseases that include	Decreased blood perfusion of the organs
Bitter taste	2. It provides nourishment to organs, which deserve a sound part of bile, included in their nourishment, as, for example, the lung and gallbladder.	Yellowness of the eyes and tongue	Constipation
		Coarseness of the tongue	
	3. It attenuates the blood and helps it penetrate narrow canals.	Dryness of the nose	
		Bitter taste in the mouth	
	4. It washes out intestines to remove food residues and viscous phlegm.	Yellow and green vomiting	
		Anorexia	
	5. It irritates the rectal area, inducing the sensation for defecation when appropriate.	Burning diarrhea	
		Rashes	
		Jaundice	



Table 4: Normal and abnormal black bile

Black bile			
Normal		Abnormal	
Temperament and characteristics	Properties and functions of Normal Black bile	Manifestations of excess quantity or more potent quality	Manifestations of insufficiency
Cold and dry Black Sour and astringent in taste	1. Normal black bile is the residue and sediment of good blood, and accounts for its turbidity. 2. It thickens the blood and prevents it from flowing freely through the blood vessels. 3. It bestows stamina, strength, density and consistency to the blood. 4. It needs to mix up with the blood in a required quantity for the nourishment of each of those organs in the nutriment of which there must be a suitable portion of black bile as in the bones, cartilage, ligaments, and spleen. 5. It tonifies the gastroesophageal sphincter.	Excessive coldness and dryness of the body	Decrease in production and formation of bone and cartilage tissues
		Darkness of the color of the body and mucous membranes	Hemodilution
		Thin and emaciated face	Abnormal bleeding
		Obsession	Bidirectional relationship between the gastrointestinal system and the central nervous system, such as post-prandial vertigo and headache; Acid reflux from the stomach to the mouth; muscle spasms
		False appetite	
		Heartburn	
		Dark and concentrated urine	
		Reddish-black urine	Ligament laxity
		Depression	
		Anxiousness	
		Sadness	
		Excess growth of body hair	
		Splenic pain	
		Sleeplessness	
		Dreams of black objects	
		Melancholia	
		Varicose vein	
		Indigestion	
		Insomnia	

Based on the definitions of humors and related diseases in traditional PM literature, and recent articles by PM researchers who have discussed and treated conventional diseases using the humoral theory approach, it has been possible to approximate some traditional medical concepts. These approximations are demonstrated in Table 5.

Some molecules serve as structural humors, acting as fundamental building blocks for the formation of tissues and, subsequently, organs. They contribute to the architecture of cells, enabling the construction of complex biological structures. Table 6 contrasts the traditional definitions and characteristics of humors with the modern concepts of molecules.



Table 5: Examples of conventional medicine concepts mentioned to be close and correlated to the definition, excess and deficiency of the four traditional humors based on Persian Medicine expert opinions

PM humor		Examples of near conventional medicine concepts	References
Sanguis	Definition	Carbohydrates, hemoglobin	(Akhtar, Chaudhary, and Khan, 2018)
	Excess	hemorrhagic stroke, migraine, varicose veins, cystitis,	(Movahhed, et al., 2012; Alorizi, and Nimruzi, 2016; Zargaran, et al., 2016; Ghafari, and Ghobadi, 2018; Tabarraei, et al., 2018)
	Deficiency	Anemia; growth disorders; failure to thrive (FTT), cachexia, types of hypothermia, dermatological disorders, epithelial tissue disorders, Anemia	(Movahhed, et al., 2012; Yarzou, et al., 2015; Farsani, and Movahhed, 2016; Shirbeigi, et al., 2016a)
Phlegm	Definition	Cholesterol, integral proteins, peripheral proteins, phospholipids, synovial fluid, saliva, gastric mucosa, body secretions	(Akhtar, Chaudhary, and Khan, 2018)
	Excess	ischemic stroke, atherosclerosis, coronary heart disease (CHD), depression, asthma, gastroesophageal reflux disorder (GERD), Polycystic ovary syndrome disease (PCOD), fatty liver disease, hypothyroidism, Alzheimer's disease and dementia, sinusitis	(Alorizi, and Nimruzi, 2016; Zargaran, et al., 2013; Choopani, et al., 2012; Fallahi, et al., 2013; Anushiravani, et al., 2018b; Amini, et al., 2019; Adel Mehraban, et al., 2021; Naghizadeh, Zareian, and Tabarraei, 2020; Zamani, et al., 2018; Ebrahimpour, Khazaneha, and Tajadini, 2021; Shirbeigi, et al., 2018; Anushiravani, et al., 2018a; Faryabi, et al., 2022)
	Deficiency	Osteoarthritis, sensory and motor disorders	(Movahhed, et al., 2012; Yarzou, et al., 2015; Karami, et al., 2021)
Yellow bile	Definition	Blood flow velocity, blood dilution, surfactant, bilirubin, biliverdin, urobilin	(Movahhed, et al., 2012; Akhtar, Chaudhary, and Khan, 2018)
	Excess	Bleeding disorders, hepatitis, urticaria, gallstones, stroke, stomach inflammation	(Movahhed, et al., 2012; Zargaran, et al., 2013; Alizadeh, Khadem, and Aliasl, 2017; Shirazi, Kenari, and Eghbalian, 2022)
	Deficiency	Asthma, dyspnea, acute respiratory distress syndrome, Raynaud syndrome, hyperviscosity syndrome, ileus	(Movahhed, et al., 2012; Amini, et al., 2019)
Black bile	Definition	Viscosity, Fibrinogens, bone hydroxyapatite, gastric secretions, gastric acid, immunoglobulins, phospholipids	(Movahhed, et al., 2012; Akhtar, Chaudhary, and Khan, 2018)
	Excess	Hyper-pigmented skin disorders, osteoarthritis, coagulation disorders, cancer, types of hypothermia, depression	(Movahhed, et al., 2012; Faryabi, et al., 2022; Shirbeigi, Zareie, and Ranjbar, 2016b)
	Deficiency	Gastroesophageal reflux disorder (GERD)	(Alizadeh, Khadem, and Aliasl, 2017; Adel Mehraban, et al., 2021)



Table 6: Comparison between traditional definition and characteristics of humors and modern concept of molecules

Humor	Molecule
3D matter	3D matter in various sizes
Fluid	Usually dissolved in the aqueous environment of the body
Dispersible	Usually dispersed in the aqueous environment of the body
First metamorphosis from food	Usually enters the body with food and is a breakdown product of food
Structural humors are building blocks of simple tissues and thereby, organs	Some molecules participate in the structure of cells and tissues and thereby in the structure of organs
Warm humors, i.e., yellow bile and sanguis	Some molecules have a stimulating effect on the body and, for example, increase tissue blood perfusion or excite or enhance metabolism
Cold humors, i.e., phlegm and black bile	Some molecules have an inhibitory effect in the body and reduce tissue blood perfusion or reduce body metabolism
Abnormal humors	Some biological molecules go out of their natural state and normal function due to inappropriate branch substitutions or abnormal spatial configuration

Discussion

As previously mentioned, humors are defined as dispersible three-dimensional (3D) fluid materials that are primarily decomposed from food as it enters the body. On the other hand, biomolecules also usually enter the body through food in the form of larger heterochain polymer molecules such as fat, carbohydrates and proteins following many types of digestion and decomposition processes that exist in the body. Subsequently, these macromolecules gradually degrade into simpler, smaller, and mostly bioactive molecules. Thus, it can be deduced that the closest modern scientific and biological concept that can be comparable to this definition is the concept of molecule. (Shirbeigi, et al., 2017; Avicenna, 2014; Akhtar, Chaudhary, and Khan, 2018; Vaghasloo, Naghizadeh, and Babashahi, 2017)

The Unani system of Medicine integrates anatomy and physiology under seven basic principles, including Aa 'za (organs), which are considered materialistic causes for the body. Despite modern rejection of ancient theories on organ formation, literature explores the role of body fluids in cell formation. Lack of molecular biology evidence has marginalized CAM's clinical success. These studies use proteomic tools to analyze proteins in Iranian traditional medicine, revealing distinct protein networks in different temperaments. Haar-e Gharizi, the natural heat, is distributed by the heart and can be balanced through SINA therapy, a personalized heat treatment to enhance health (Rezadoost, Karimi, and Jafari, 2016; Akhtar, Chaudhary, and Khan, 2018; Vaghasloo, Naghizadeh, and Babashahi, 2017).

According to various functions noted in PM manuscripts for humors, it seems that the nomenclature of humors such as black bile or phlegm refers to categories of various kinds of molecules instead of indicating a single substance. Regarding this point of view, the numerous physiological functions related to hormones or mediators may be considered as the normal properties and functions of humors discussed in the humoral theory.

Recent studies have further elucidated the molecular underpinnings of these traditional concepts. For instance, proteomic analyses have identified specific protein networks that



correlate with different temperaments, providing a modern scientific basis for the humoral theory. These findings suggest that traditional Persian Medicine's categorization of humors may align with contemporary understandings of molecular biology and personalized medicine (Rezadoost, Karimi, and Jafari, 2016; Akhtar, Chaudhary, and Khan, 2018; Shirbeigi, et al., 2017). This integration of ancient wisdom with modern science could pave the way for novel therapeutic approaches that are both effective and culturally resonant.

Furthermore, it seems that warm humors, namely, yellow bile or sanguis, can be compared to some molecules including mediators or cytokines involved in excitatory biological processes, while cold humors, such as phlegm and some types of black bile, can be compared to some molecules including mediators or cytokines involved in inhibitory biological processes (Movahhed, et al., 2012; Akhtar, Chaudhary, and Khan, 2018; Rezadoost, Karimi, and Jafari, 2016).

Conclusion

While the biomolecular and biochemical examples of normal and abnormal humors in PM literature remain unknown, their described characteristics suggest potential new frontiers in disease diagnosis, prevention, and treatment. Emerging research in personalized medicine (PM) over the past two decades supports the idea that the humoral theory could offer valuable insights, particularly for newly identified diseases like diabetes. Although direct evidence is limited, the holistic approach of balancing bodily fluids might complement modern biomedical models, providing a unique perspective on disease mechanisms and therapeutic strategies. Integrating traditional concepts with contemporary scientific approaches could enhance patient care.

Authors' Contribution

All authors contributed to the conception, design of the work, acquisition, analysis and interpretation of data for the work. All authors read and approved the final version of the work.

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Conflict of Interest

The authors declare that they have no competing interests.

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