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AVICENNA'S PERCEPTION OF BLOOD PROPERTIES COMPARED WITH CURRENT BIOMEDICAL KNOWLEDGE

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ABSTRACT

Background and Objective: Blood is one of the most vital fluids in the human body, and is used to diagnose health and disease. Persian scholars especially Avicenna have used four characteristics of color, smell, taste and *qiwam* (viscosity) to define and distinguish between normal and abnormal Blood. Examining these specifications and their equivalents in modern literature, can be an introduction to verifying statements of ancient scholars and reviewing their writings, to better elucidate the pathophysiology of diseases and treatment. Method: The present study is a concept analysis using integrated review of texts based on the Broome 2000 model. Results: According to Persian scholars, aberration of any of the characteristics of normal Blood from the normal range indicates that components have been added to or eliminated from Blood. According to Persian scholars, Blood consists of four components, namely *Dam* (sanguine/Blood), *Balgham* (phlegm), *Safra* (yellow bile) and *Sawda* (black bile) in specific proportions. Any change in terms of quantity or quality of any of the four components leads to abnormality and alterations in normal Blood characteristics. Conclusion: Among the four mentioned characteristics, color and *qiwam* (viscosity) are more conformable to current knowledge. Persian scholars provided precise and thorough explanations about normal and abnormal Blood in discussing physiopathology of diseases, which indicates their mastery of the topic of Blood and Blood diseases. Hence, the holistic and comprehensive approach of Persian Medicine (PM) can be used in dealing with diseases that directly or indirectly affect the physical and biochemical properties of Blood.

Keywords: Blood, Blood color, Blood viscosity, humors (Akhlat), Persian Medicine (PM), Avicenna

INTRODUCTION

Blood is one of the vital fluids of the human body (1) and a colloid that comprises of a dispersion medium in liquid form and a dispersed phase in solid form. Explicitly, Blood cells are the solid phase dispersed in plasma proteins which are in liquid form. Blood has several functions: delivering oxygen from the lungs to tissues and carbon dioxide from the tissues to lungs; delivering essential substances, i.e., nutrients and oxygen to the cells; transporting metabolic wastes to excretory organs such as the kidneys, lungs, skin, and intestines; and controlling the acid-base balance of the body (2). As one of the biological and sensitive body fluids, Blood reflects the health or disease status of individuals, and can help diagnose, treat and even prevent common diseases in humans (3). Hence, via Blood tests, it is possible to diagnose hematological, metabolic, hormonal, inflammatory, and infectious disorders, as well as diseases related to various other organs.

Similarly, PM regards Blood as one of the most important fluids in the body, on which health and illness are dependent (4,5). The role of Blood in growth and nutrition of organs, distribution of energy and spirit of life in the body, as well as the spread of infectious and pathogenic agents has been well-described in PM literature (6). Persian scholars and scientists have used four characteristics including color, taste, smell and *qiwam* (viscosity) to define and distinguish between normal and abnormal Blood (4). Via examining these four characteristics as described in PM literature and modern medicine, it is possible to establish a new bridge between ancient and contemporary medicine and thereby better comprehension of the pathophysiology of diseases to help successful treatment will be made available. Exploring the comprehensive view of Blood in works of Persian scholars, at a time where there were no instrumental technology, such as microscopes and lab-tests, may be an introduction to justifying and re-writing their perspective on pathophysiology and treatment of diseases, especially those diseases with unknown etiology or those with challenging treatment.

MATERIAL AND METHOD

The present study is a concept analysis using integrated review of texts based on the Broome 2000 model (7,8). The research steps included identifying the research question, performing a systematic literature review, selecting appropriate texts, extracting target information from the texts, analyzing and combining the extracted findings, and finally presenting the collective findings.

Authentic PM references, such as Canon of Medicine (Avicenna) and its commentaries, *Kamel al-Sana'a* (Haly Abbas), and *Hedayat al-Muta'alemin* were searched for data on Blood and its properties. Moreover, modern literature including textbooks of basic medical sciences (e.g., Guyton and Hall's Physiology, Rodak's Hematology, Harper's Biochemistry, Junqueira's Basic Histology), and also PubMed, Web of Science, Science Direct, Google Scholar, and Scopus databases were searched with the keywords sanguine, Blood, humors, Blood color, Blood viscosity, and Blood smell. All queries were performed without any time constraints and were carefully studied.

RESULTS

Blood in PM literature

According to PM literature, Blood is a mixture of four humors, namely *Dam* (sanguine/Blood proper), *Balgham* (phlegm), *Safra* (yellow bile), and *Sawda* (black bile). For an individual to be healthy, each of these humors should be present in a specific proportion, and optimum quality (4). Humors comprise part of body fluids that are produced following digestion and metabolism of food, and preserve function, growth, regeneration, energy production and preservation of the life of the person and the species (9). Any change in the quality or quantity of humors in Blood is abnormal or unhealthy (4). Persian scholars specified four characteristics of color, taste, smell, and *qiwam* (viscosity) to define and identify healthy and unhealthy Blood (4,5,10). Any change in quality or quantity of Blood components, namely the four humors, can alter one or more of these characteristics. Hence, according to PM, Blood abnormalities are associated with changes in these four characteristics (4).

Blood color

One of the main characteristics of Blood described in PM textbooks is color, being red (4). In some sources, normal Blood is divided into two types of arterial and venous Blood, being bright red and dark red respectively (5,11). When other humours are increased in quantity, phlegm gives Blood a whitish tint, yellow bile a yellow tint, and black bile a black tint (10). In the book *Kamel al-Sana'a*, Ali Ibn Abbas Ahwazi writes about the color of menstruation Blood, which may be bright red and clear due to mixing with yellow bile, dark red due to mixing with small amounts of black bile, and thick and black due to mixing with a larger amount of black bile (10).

According to modern literature, "heme" is what gives Blood its red color. This pigment is a precursor for vital molecules and formed from four pyrrole rings, which are heterocyclic aromatic molecules, and a tetrapyrrole ring called porphyrin. This chemical structure and the atom attached to it create a specific color. Binding of iron to porphyrin causes a red-brown color. In plants, binding of magnesium to porphyrin creates the green color in chlorophyll. In marine animals and snails, two copper atoms bonded to porphyrin form hemocyanin, which acts as an oxygen carrier in invertebrates cause a blue-colored Blood (12). This molecule gives Blood a red color and specific odor (12). Hemoglobin and myoglobin are red because they contain "heme" groups. The degree of oxidation of the iron atom in these molecules determines the color of iron. Ferrous iron is red, while ferric iron is brown. Oxygenated Blood and muscle are red, because they contain ferrous iron. In contrast, deoxygenated Blood has a purplish-blue tint, because it contains carbaminohemoglobin. Carboxyhemoglobin (hemoglobin bound to carbon monoxide, which has a greater affinity for hemoglobin than oxygen) gives hemoglobin its cherry-red color. Presence of ferric iron in Blood or muscles gives them a brown color, as is seen in necrotic muscles, methemoglobin and old bruises before "hem" is metabolized (12). Another pigment in Blood is bilirubin. Macrophages metabolize hemoglobin to biliverdin and then bilirubin. Biliverdin is green, while bilirubin is yellow-red. The suffix "*rubin*" comes from the Latin word *rubrum* meaning red. For this reason, the liver has a yellow-red color.

The color change in bruises, hematoma and bleeding is from red to purple-blue, black, green and finally yellow. The red color is due to presence of hemoglobin; then hemoglobin is deoxygenated, and becomes purple. Following decomposition of hemoglobin iron and porphyrin, the color turns black due to presence of iron. Afterwards, porphyrin is converted to biliverdin, a green color change occurs, and finally, when bilirubin is produced, the color changes to yellow (12).

Another pigment that contributes to color of Blood and other tissues is iron. Iron that is not bound to porphyrins or cytochromes and is in the form of trivalent iron in hemosiderin and ferritin, has a gray-black metallic color. When iron is excessively stored in the body, the skin and organs begin to turn gray-black, as seen in hemochromatosis or in Blood recipients such as those with thalassemia major, who receive regular Blood transfusions. Iron in Blood is carried by transferrin and transported to all parts of the body. Transferrin is a glycoprotein that is made in the liver and belongs to the group of plasma beta globulins. Binding of iron to transferrin, is accompanied by binding of one mole of bicarbonate to transferrin, causing transferrin to turn pink. It should be mentioned that plasma is colorless in iron deficiency anemia due to transferrin being devoid of iron (13).

Leukocytes, or white Blood cells (WBCs), are so named because they are colorless compared to red Blood cells (RBCs). Leukemia is derived from the Greek word *leukos*, meaning white, and *haima*, which means Blood (14).
Leukemia was first described by Virchow and means white Blood.

Abnormal color of Blood and Blood compounds have been attributed to several causes. Yellow plasma is due to high levels of bilirubin (15). A green-colored plasma indicates increased ceruloplasmin levels following OCP use. Also, sulfonamides cause attachment of a sulfur atom to the porphyrin ring of the "heme" group, which forms sulfohemoglobin and gives plasma a green color. Among other factors that cause green plasma, is the gram-negative pseudomonas that induces production of pyocyanin and pyoverdine pigments. Plasma is cloudy and milky-colored in individuals who donate Blood after eating a fatty breakfast (15). A lipemic Blood sample is the color of strawberry milkshake, and the plasma is milky white due to the presence of fat particles (16,17). A cherry-colored plasma indicates hemolysis (15).

A cherry-colored Blood has been attributed to megaloblastic anemia, hemolytic anemias, low hematocrit, high carbon monoxide levels in smokers, and carbon monoxide poisoning. This is due to the fact that hemoglobin that carries carbon monoxide has a cherry-red color. In bacterial infections, the color of Blood changes to dark crimson or black (15,17). When dealing with abnormal Blood color in a critically-ill patient, differential diagnoses include cyanide poisoning, dyshemoglobinemias (e.g., methemoglobinemia and carboxyhemoglobin), lipemia and drug overdose should be considered (16). The color of menstruation Blood can be black, red-brown/black, light red, pink, orange or gray. Black Blood is usually seen at the end of menstruation, and typically indicates that Blood has remained in the uterus for a long enough time to oxidize. Menstruation Blood is red, black or brown before it turns black. Bright red Blood is seen at the beginning of menstruation and indicates fresh Blood with a constant flow that gradually turns dark red and then black, but in some women Blood remains bright red throughout menstruation. When mixed with cervical secretions, menstruation Blood turns pink. Use of hormonal contraceptives that lower body's estrogen levels can give menstruation Blood a pinkish color. This color is also seen in anemic women. In cases of bacterial vaginosis or trichomoniasis, menstruation Blood turns orange when mixed with cervical secretions. A gray color is also indicative of bacterial vaginosis (18).

The taste of Blood

According to PM literature, Blood has a sweet taste, (4) like that of sugar or honey (19). Abnormal Blood tends to be bitter when mixed with bile (5,11); tasteless, sour or salty when mixed with phlegm; and sour when mixed with black bile (11).

In modern physiology, tastes are divided into five groups: sour, salty, sweet, bitter and yumami (pleasant). Acids have a sour taste due to containing hydrogen ions, and also ions and sodium ionized salts. The sweet taste is not caused by one group of substances, but several, most of which are organic and including sugars, glycols, alcohols, aldehydes, ketones, amides, esters, some types of amino acids, some small proteins, sulfonic acids, halogen acids and mineral salts of lead and Beryllium. Like sweetness, bitterness is not caused by one type of chemical substance. All bitter substances are organic, and include long-chain organic substances that contain nitrogen, and also alkaloids, which are present in many medical drugs such as quinine, caffeine, strychnine and nicotine. Yumami taste is a Japanese word meaning delicious, and used to describe a desirable taste that is qualitatively different from the other four tastes. Foods containing L-glutamate such as meat extract and leftover cheese have this taste (20).

The smell of Blood

Another property of Blood mentioned in PM sources is smell. Normal Blood is not foul-smelling (4). Normal Blood does have an odor, but it is not like the smell of infection nor with sourness (21). In contrast, infections give Blood a bad, stinky, and sour odor (11). Reduced or lack of Blood odor indicates increased levels of phlegm or watery substances. Pungent-smelling Blood is a sign of mixing with yellow bile, whereas one of the causes of sour-smelling Blood is mixing with black bile (10).

Modern literature state that Blood has a metallic odor due to presence of iron (22). Likewise, menstruation Blood in healthy women has a metallic smell due to the presence of iron in Blood. However, presence of pathogenic bacteria and microorganisms, bring about an unpleasant and sometimes fishy smell (23).

The qiwam (viscosity) of Blood

One of Blood characteristics Persian scholars have used to describe normal and abnormal Blood is *qiwam* (viscosity) (19). The definition of Blood *qiwam* according to PM sources is equivalent to viscosity in modern medicine (24). Normal Blood is neither thin or thick, and is medium in consistency. Any deviation from this moderation towards dilution or thickening, is considered abnormal. An increase in the water, thin phlegm, or yellow bile proportions of Blood, cause dilution. In contrast, increased black bile or thick phlegm, Blood will become thick (21,25,26). A reduction in temperature increases Blood *qiwam*, whereas a rise in temperature as in fevers, causes Blood to dilute (4). According to PM, one of the important reasons for abnormal uterine bleeding is low Blood viscosity due to an increase in Blood temperature or addition of watery components to Blood (27).

According to modern literature, the internal resistance of fluids to flow is called viscosity (28). Viscosity is an important feature of Blood and plays a key role in vascular homeostasis. This property is mainly determined via measuring hematocrit, plasma viscosity, RBC deformability and aggregation, and shear rate (29). The viscosity of whole Blood with normal hematocrit is three to four times that of water. When hematocrit rises to 60-70%, in conditions like polycythemia, the viscosity of Blood can rise up to 10 times the viscosity of water, significantly slowing Blood flow in the vessels. Other factors that influence Blood viscosity include types and concentration of proteins in plasma. The viscosity of plasma is 1.5 times the viscosity of water (20). Blood is a non-Newtonian fluid, because its viscosity increases with decreasing Blood flow. The low flow allows the resistance between the molecules to increase, and the RBCs aggregate (rouleaux formation), and viscosity increases. At high shear rates, such as during exercise, Blood flow increases, and concentration or viscosity decrease (30).

Another important factor in Blood viscosity is temperature. Plasma has a viscosity of 1.8 at 37 degrees Celsius. A decrease in Blood temperature, causes thickening and deceleration of flow. Therefore, there is an inverse relationship between temperature and viscosity. Viscosity increases by about 2% for each degree of temperature decrease, so Blood viscosity increases at low temperatures. Triggering coagulation mechanisms result in platelet aggregation and interaction with plasma proteins. Consequently, RBCs are trapped and form a clot, which dramatically increases Blood viscosity (31).

Any pathological increase in cellular components (RBCs, leukocytes, or platelets) or non-cellular components (proteins) can cause hyper viscosity syndrome (28). In marginal lymphoma of the spleen, the plasma viscosity reaches 11 due to the increase in immunoglobulins, while its normal value is 1.5-1.9 (32). The increase in the viscosity of whole Blood is related with an increase in plasma fibrinogen concentration and a decrease in the ratio of albumin to Globulin (33)(33). As an important functional protein, albumin preserves the normal permeability of the microvascular wall, reduces Blood viscosity, and decreases platelet adhesion (34). The relationship between some nutrition-related diseases such as hypertriglyceridemia, hypoalbuminemia, and diabetes with Blood/plasma viscosity has been well-established (34). Cholesterol and triglyceride levels are positively related to Blood viscosity (30). In some diseases, such as chronic anemia and liver disease, the viscosity of plasma and Blood shows a long-term decrease due to decreased concentration of plasma proteins (30). Blood viscosity is increased in inflammatory and infectious diseases, following an increase in the concentration of acute phase proteins (AFR) and hypergammaglobulinemia, that increase adhesion of erythrocytes. Any molecule that is large enough to fill the intercellular space and join two RBCs can promote RBC adhesion. These "bridging" molecules include acute phase reactants such as fibrinogen, CRP, haptoglobin, and ceruloplasmin, as well as immunoglobulin M (IgM) and low-density lipoprotein (LDL). An example of RBC aggregation caused by bridging molecules is increased ESR in hyperfibrinogenemia (35). In COVID-19, Blood viscosity increases significantly. This infection is associated with significant inflammatory response and increased levels of interleukin-6 (IL-6) that initiates the acute phase response and can result in a cytokine storm. In such conditions, fibrinogen synthesis increases, while albumin levels decrease. Fibrinogen concentration reaches 14 g/L (normal range 2-4 g/L), which is higher than any other disease in the authors' experience. Plasma viscosity increases to 4.2 in COVID-19. Hyperfibrinogenemia in COVID-19 increases RBC aggregation and therefore ESR, which can even rise to 140 (36). Experimentally, a change in viscosity causes a threefold decrease in Blood flow. Therefore, Blood viscosity is a chief factor (35). Blood hyperviscosity increases the risk of cardiovascular diseases such as myocardial infarction, deep vein thrombosis, and stroke (35).

Discussion

The human Blood is a complex colloidal biological fluid including cellular components (RBCs, WBCs, and platelets) and plasma (37). Approximately 92% of the plasma is water and the remaining 8% comprises proteins, electrolytes, enzymes, hormones, dissolved gases, micronutrients, and waste material. The physical properties of Blood include density and viscosity, which are higher than water. The color of Blood lies in a range of red colors that mostly depends on oxygen content. In this article, the chemical composition of Blood is not discussed. Among the mentioned properties of Blood in PM, the most comparable to the new findings is, primarily, viscosity and then, color.

Blood viscosity is one of the main factors in determining hemorheological properties. An increase in cellular components of Blood (RBCs, WBCs, and platelets) especially RBCs, increased plasma components (fibrinogen, immunoglobulins), and impaired adhesion and deformability of RBCs result in increased Blood viscosity. Therefore, in various diseases, including hematological and oncological (polycythemia, leukemia, thrombocytosis, multiple myeloma, spherocytosis, sickle cell anemia), metabolic (diabetes, hypertriglyceridemia, hypoalbuminemia), infectious (pneumonia, malaria, COVID-19), and rheumatological (rheumatoid arthritis, lupus erythematosus) disorders, Blood viscosity is increased, resulting in serious complications such as myocardial infarction (MI), cerebrovascular accident (CVA), deep venous thrombosis (DVT), and microvascular angiopathies such as retinopathy, nephropathy, and neuropathy. Among the causes of low Blood viscosity, are anemia, increased Blood water content, and high albumin.

One of the interesting points that was brought up more than a thousand years ago by Ibn Sina, one of the greatest sages of Iran, was the etiologies of Blood thickening state that is mentioned in the book, Canon of Medicine. The three main causes include cooling, coagulation, and extracomponents added to Blood, all of which are compatible with contemporary medicine. Modern literature indicates that there is an inverse relationship between temperature and viscosity; specifically, the lower is Blood temperature, the higher is the viscosity and the slower Blood flow. Also, initiation of coagulation pathways results in increased Blood viscosity. Most importantly, is added components that is regarded as added impurities to Blood in PM and an increase in components including Blood cells, fibrinogen, immunoglobulins, and triglyceride in conventional medicine. Generally, Blood components that are effective in increasing or decreasing Blood viscosity, can be regarded as equivalent to humors as described in PM literature. According to Persian scholars, one of the etiologies of Blood thickening is addition of black bile or thick phlegm to Blood. In contrast, addition of watery substances, thin phlegm, and yellow bile, results in dilution of Blood.

Thus, fibrinogen, immunoglobulins, and triglyceride can be considered as components of thick humors, including black bile or thick phlegm. In contrast, albumin can be regarded as a component of thin phlegm, because an increase in albumin reduces Blood viscosity, just as thin phlegm dilutes Blood. Indeed, another reason why albumin is considered as a component of thin phlegm is that PM sources refer to the phlegm in Blood as "*Bayaz al-bayzi*", meaning similar to egg white (which albumin is a main component of) (4,21) Regarding the most common cause of increased Blood viscosity, being an increase in RBCs, these cells are rich in sanguine and black bile. As Hakim Jilani has mentioned in his commentary on Ibn Sina's Canon of Medicine, the best way to identify Blood impurities is observation. He also mentions that if Blood is poured over hot water, the dark sediment at the bottom of the tube is black bile, and the white part is phlegm. Reconciling these statements with modern findings, suggests that the heat of water causes lysis of RBCs, and thereby entry of hemoglobin into plasma that creates a cherry-colored appearance, and the residue of RBCs, which is equivalent to black bile, settles at the bottom of the container.

Regarding Blood color in modern literature, the main pigment of Blood is hemoglobin, which is red. Factors that cause changes in the normal red color are molecules such as oxygen, carbon dioxide, or carbon monoxide that can attach to hemoglobin. Oxygenated hemoglobin is bright red, deoxygenated hemoglobin is dark red, carboxyhemoglobin is cherry red, and sulfa hemoglobin has a green tint. Another factor is the ferrous iron in hemoglobin, because if the iron is in ferric form, like methemoglobinemia, Blood will turn brown. Changes in Blood color can provide clues for underlying etiologies, especially in critically-ill patients. Abnormal Blood color in such patients may indicate cyanide poisoning, drug overdose, dyshemoglobinemia such as carboxyhemoglobin and methemoglobinemia, and hyperlipidemia. Bilirubin and carotene pigments are other factors that can alter Blood color. Since hemoglobin is abundantly present in RBCs that make up almost half of Blood volume, the predominant color of Blood is red. Changes in other pigments in Blood have a small effect on this predominant redness, and are hardly visible. Therefore, changes related to other pigments are generally discussed considering Blood plasma. Specifically, a range of red colors can be seen at the level of whole Blood. For example, Blood color of a person with high levels of bilirubin, has a yellow tint. In contrast, high triglycerides, turn Blood color into a dull pinkish red, due to the presence of fat particles that prevent passage of light. Accordingly, one of the differential diagnoses of pink Blood is severe hypertriglyceridemia. In leukemia, the red Blood becomes white due to the high levels of leukocytes, as is clear from the name "leukemia" which means white Blood.

According to PM, sanguine is red; yellow bile is yellowish saffron or bright red; phlegm is white; and black bile is black. Hence "hem", which is abundant in RBCs, can be regarded as a component of sanguine and bilirubin, which is yellow-red, a component of yellow bile. Iron is one of the components of black bile and triglyceride is one of the components of phlegm. Based on color characteristics and their hyper viscosity inducing property, WBCs are rich in phlegm. Comparing the color of menstruation Blood in PM and conventional medicine, it can be concluded that aging and oxidation cause production of abnormal black bile in Blood.

Most of the diseases that are accompanied by abnormal Blood color are hematological diseases such as polycythemia, leukemia, methemoglobinemia.

Reconciling information related to the taste of Blood in PM sources and modern science, it can be concluded that tastes outside of the sweet range, indicate Blood abnormality. In other words, an increase in substances such as acids, salts, and drugs and poisons (alkaloids) that create salty, sour, and bitter tastes respectively, indicate an abnormal Blood. Since salty and sour tastes are among the abnormal tastes of humors, and considering that they are the tastes of acids and salts, it can be stated that abnormal Blood taste is generally associated with metabolic diseases and acid-base changes.

According to PM literature, Blood should not smell unpleasant, in which case it is abnormal and infected. Similarly, modern medicine regards the bad smell of menstruation Blood as a sign of infection. Therefore, diseases accompanied by unpleasant smell of Blood are generally associated with infections and septicemia.

CONCLUSION

Centuries ago, at a time when there were no instruments such as microscopes and laboratory tests, Persian scholars especially Avicenna specified Blood properties, by which they described physical and chemical conditions of Blood and the compounds added or eliminated from normal Blood. Recognizing this knowledge and correlating it with modern science is a big step towards verifying writings of the sages on pathophysiology and treatment of diseases. The precise and thorough explanation of Persian scholars about normal and abnormal Blood in fundamentals of medicine (physiopathology) and diseases indicated their mastery of the topic of Blood and Blood diseases. Collectivel y, the holistic and comprehensive approach of PM can be used in dealing with diseases that directly or indirectly affect the physical and biochemical properties of Blood.

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