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Perspective

Physiological Roles, not Structure will Categorize Placement of Molecules in Humours (*Akhlat*) in Unani Medicine: The Case of Human Haemoglobin

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Abstract: Greeko-Arab medicine or Unani medicine is an ancient system of medicine which is widely practiced in the Indian subcontinent and beyond. This system of medicine is based on the theory of humours, which places body fluids into four classes. This paradigm when considered on the basis of modern sciences, calls for identifying biomolecules which constitute the four humours. Using the example of human haemoglobin, we make the argument that the chemico-biological/physiological roles of the molecules and not their structure will be the rationale for placing molecules in the four humours. The discussion presented here will form the basis of scientifically understanding this ancient system of medicine, and will pave way for further research in this area.

***Keywords*:** human haemoglobin, humours, Unani medicine, chemicobiology

1. Introduction

The Unani system of medicine is an ancient system of medicine which is rapidly gaining attention in modern times. The system classifies body fluids into four *Akhlat* (humours) (singular: *Khilt*). The ratios of these four humours, *Dam* (blood), *Balgham* (phlegm), *Safra* (bile) and *Sauda* (atrabilious bile) form a fundamental basis for defining the *Mizaj* (Unani temperament) of the individuals [1, 2], and the *Mizaj*, in turn, is the basis for drug choice/treatment choice [1, 2]. This idea of identifying *Mizaj* as a basis for the treatment is fairly new to an audience of modern sciences. Similarly, the idea that *Mizaj* is determined by the ratios of humours is fairly complex.

There has been a recent trend of classifying biomolecules, and placing them within the four humours, according to their chemical structure [3, 4]. This basis of classification is inherently flawed. Unani literature provides a descriptive chemico-biological/physiological role and/or attribute of each of the four *Akhlat*. And therefore structure alone cannot be the basis of the classification of molecules in the four *Akhlat*. It may be noted that the *Akhlat* has been described, in Unani literature by attributes which are beyond the scope of this paper.

The purpose of this paper is, in essence, to delineate that physiological role, and not structure should be the basis of placing molecules within the categories of the four humours. This idea has broad, wide spectrum implications for both Unani medicine and the developing correlations between Unani medicine and the modern system of allopathic medicine. Numerous examples can be cited to support this idea. In this paper, we use the example of human haemoglobin to elucidate this concept.

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2. Structural considerations for human haemoglobin

Haemoglobin is a widely studied protein [5]. The detailed structure of which was elucidated by Max Perutz in 1959. In humans, it is coded by HBA1, HBA2 and the HBB genes [6]. The amino acid sequence of haemoglobin is species-specific [7], though certain proteinaceous domains are common to all species which have haemoglobin. The globin protein part of the molecule is synthesised in the cytoplasm by ribosomes. The fully matured haemoglobin molecule is the primary component of the red blood corpuscle. In a healthy individual, the levels range from 12 to 20 g/dl, with the levels in males being slightly higher than the females. The protein is tetrameric [8] in adults, composed of two α and two β subunits, having 141 and 146 amino acids respectively. The subunits are linked to a haeme prosthetic group. The subunits are held together strongly by multiple weak forces which cumulatively exert their effect. These interactions include hydrophobic interactions, hydrogen bonds and some salt bridges [9]. In infants, the tetramer is composed of two α and two ɣ chains, which slowly get replaced by β chains as the person matures [10]. Figure 1 shows the full-length ribbon structure of human haemoglobin.

Figure 1. The full-length structure of human haemoglobin (PDB ID: 1A3N) created on PyMOL

Proteins are primarily classified in *Khilt-e-Balgham* according to the Unani literature. *Balgham* is said to come into existence when *Barid Ratab* (cold/wet) food is taken [1, 2, 11]. *Barid Ratab* food includes curds, yoghurt and buttermilk [3, 11], which are themselves rich sources of protein. However, including haemoglobin in *Khilt-e-Balgham*, because of its proteinaceous nature would be erroneous.

3. Presence of iron in the haeme chemical moiety in human haemoglobin

Human haemoglobin contains the haeme prosthetic group. The haeme prosthetic group is an organic ring-shaped molecule, which by virtue of its structure is capable of hosting an iron molecule [12]. The haeme itself is made of four pyrrole rings. This tetrapyrrole structure has a substitution on the side chain which allows it to hold a metal ion, in this case, iron (Figure 2) [13].

The iron molecule in haeme is articulated by the balanced attractions of the four nitrogen atoms, which point to the inside of a larger ring that they create. The single and double bonds which connect the pyrroles distribute evenly, and this structural feature provides stability to the molecule [14].

Literature from the Unani system of medicine places metal ions in the body in *Khilt-e-Sauda* [1, 2]. The literature reports *Sauda* as being *Barid Yabis* (cold and dry) [1, 2, 11] and metals are specifically placed in *Rasoobi Sauda* (heavier and dense chemical species) [15]. Bones are classified as being *Barid Yabis*, as compared to other organs (heart/liver) in classical Unani literature [1, 2, 11]. It may be noted that bones are also rich in calcium and phosphorus, both of which are metals.

However, despite the presence of iron in the structure of human haemoglobin, it would be erroneous to place human haemoglobin in *Khilt-e-Sauda*.

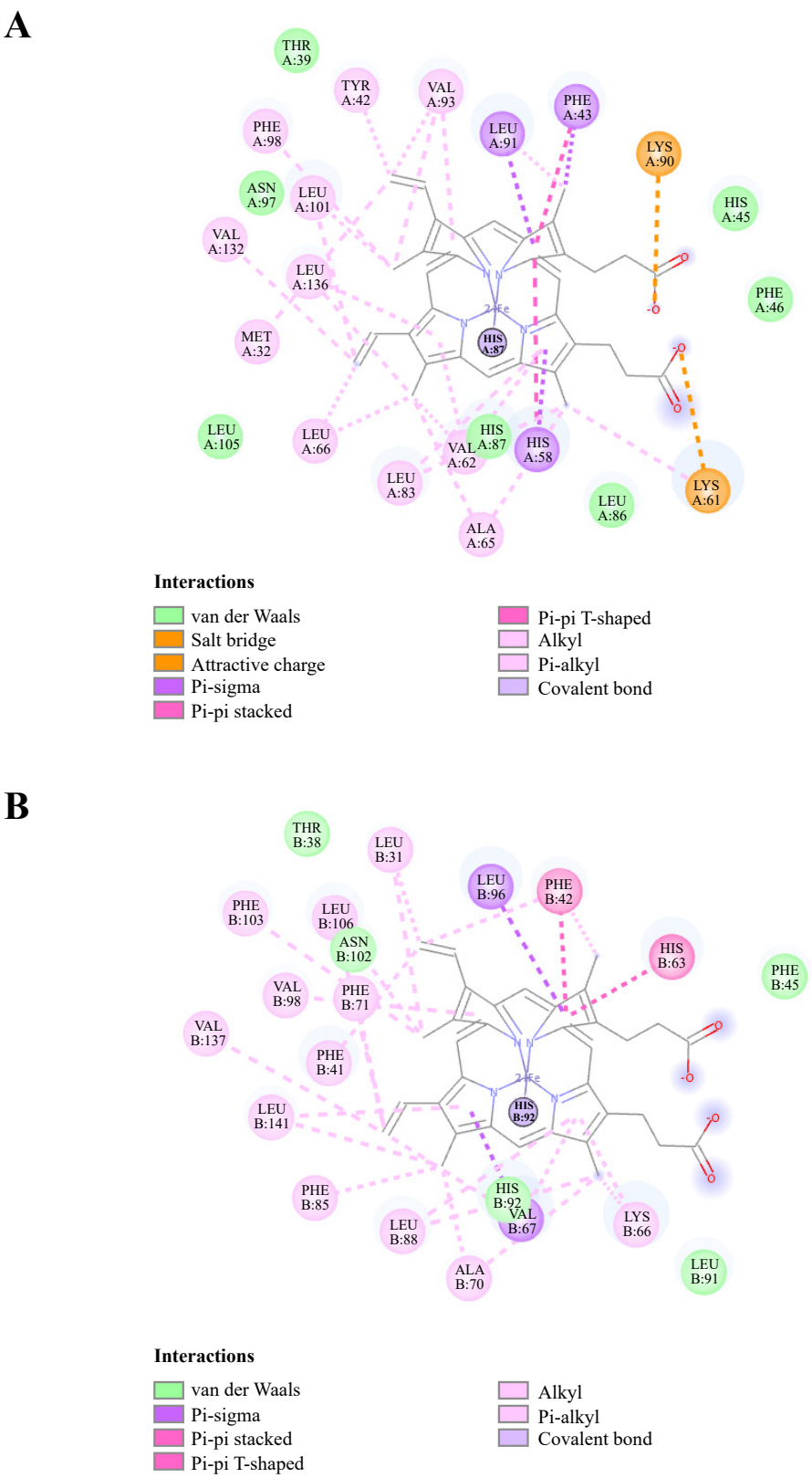

Figure 2. Interaction of the amino acids of the α and β subunit of human haemoglobin (A and B) with the tetrapyrrole ring of the haeme. The interactions and forces responsible for the articulation are also shown. Images are drawn with Discovery Studio

4. Chemico-biological/physiological role of human haemoglobin

The physiological role of haemoglobin is the transportation of oxygen. In classical Unani literature, one of the functions of *Dam* (Blood) is that it is *Hamil-e-Rooh* (transporter of oxygen) [1, 2, 11, 15]. At the molecular level, this function is carried out by haemoglobin.

Further, *Dam* is largely composed of *Khilt-e-Ahmar* (the red fluid) [1, 2, 11, 15]. Haemoglobin is what gives oxygenated blood its bright red colour. Thus haemoglobin, despite being largely proteinaceous (an attribute of K*hilt-e-Balgham*) and harbouring an iron ion (an attribute of *Khit-e-Sauda*), must be placed in *Khilt-e-Dam*.

5. Conclusion

The concept of placing biomolecules in the categories of *Akhlat* on the basis of their chemical structure is flawed. The basis of placement, we feel, should be on the chemico-biological/physiological role that the molecule/chemical species plays in that physiological state. For instance, placing calcium and phosphorus of bones in *Sauda* can be defended in the light of Unani literature. However, placing haemoglobin in *Sauda*, because of the presence of iron in the haeme moiety, cannot be justified. We feel that our classification scheme for molecules/chemical species and their placement in *Akhlat* provides a more logically sound and scientifically defendable argument. The paradigm discussed here will provide a basis for the scientific revalidation of the classical literature of Unani medicine. It will further pave way for providing a greater intellectual depth to the understanding of the existing Unani literature in terms of modern sciences.

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Conflict of interest

There is no conflict of interest for this study.

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