



Review Paper

Critical assessment of the concept of *Mizaj-e-advia* (Temperament of Drugs) and its role in Drug development

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Abstract

The concept of Mizaj-e-advia (temperament of drugs) in Unani medicine is not only unique in its own way of describing the properties of drug substances but also stands the test of time by proving extremely valuable in predicting the behavior of drugs on administration or topical application to humans. Mizaj-e-advia is a broad concept, which describes the pharmacological properties of crude drugs derived from plant, animal and mineral sources. This classical way of drug development may show promising results as an alternative to the extremely cumbersome and costly experimental phase of the conventional drug development process. However, it needs extensive research to unravel its yet obscure pharmacological correlations and scientific interpretations. This work reviews the concept of Mizaj-e-advia and assesses its role in drug developmental process in Unani Medicine. It also includes a review of some important research works so far undertaken in this field, lays emphasis, and highlights certain preferred and important areas for carrying out further research in this direction.

Key words: *Mizaj-e-advia*, temperament, topical application, Unani medicine.

Introduction

All substances of plant, animal and mineral origin have their individual *Mizaj*, which even the close and related species/forms do not share. Based on closeness of the *Mizaj* of substances with the *Mizaj* of human body, they may serve as food, drug or poison, with decreasing order of similarity. Foods are closely related to *Mizaj* of human body and poisons are just opposite and far away, while drugs may be considered intermediate between the foods and poisons. These substances are categorized into absolute foods, medicinal foods, nutritional drugs, drugs, poisonous drugs, and absolute poisons^{1,2}. Among these substances some act internally (systemic), some externally (topical) and some act both internally and externally. Furthermore, some substances may act quickly while others may act slowly on the body on administration or application¹. The drugs have different effects on different human bodies as per their *Mizaj* (temperament) and conditions of use. The knowledge of *Mizaj* of drugs is very important for a physician for effective treatment. The initial phase of drug development in Unani medicine is carried out through analogy based on certain organoleptic and physical properties of the drugs. This process provides a lead for further drug development through experiment. As the process is simple it may be considered for use as an alternate way of identifying drug leads in conventional medicine too, which may lower the cost and labour of drug development process. The knowledge of *Mizaj* tells about possible actions of drugs in the body, dosage regime and about the duration up to which a drug can be continuously used by the patient. For instance, the drugs of 3rd and 4th degree can't

be used in high doses or for longer duration, while as 1st degree and moderate drugs can be used safely for longer duration without adverse effects on the body^{1,2}.

Mizaj as construct is verifiable as illustrated by Mohammad Immaduddin Shirazi in evaluating *Mizaj of Afiyun*³ and *Beikh Chini*⁴. However *Mizaj* as described in Unani texts especially by Ibn Sina⁵ and others related to the *Ilmul Advia* (Unani pharmacology) amply seems a physical concept stemming out of the very intrinsic theory of the nature of bodies with supra physical connotations⁶. The wholesome objective assessment of the *Mizaj* requires accounting of both the domains. However, physical nature of the concept of *Mizaj-e-advia* warrants its critical evaluation, which is possible only when the physical correlate of the *Mizaj* is made comprehensive and empirical. As the concept of *Mizaj* of drugs is used as a tool to assess the pharmacological, therapeutic and toxicological properties of Unani drugs, it is imperative to evaluate the concept thoroughly from classical literature and then try to interpret it in the light of new scientific developments. Present study was carried out to review the concept of *Mizaj-e-advia* from classical Unani books and include some important research works conducted in this field, lay emphasis on the possible future aspects and need of further research in this field.

Concept of *Mizaj* (temperament) in Unani medicine

The concept of *Mizaj* uniquely belongs to the Unani system of medicine, it is fundamental to the understanding of drug action,

and disease processes as per Unani system. The *Mizaj* not only helps in understanding the status of health and disease of a person but also guides in studying and researching on drugs of both single and compound nature. *Mizaj* has two broad categories, one is concerned about the *Mizaj* of humans and the other type is about *Mizaj* of *advia* (drugs). Classical Unani physicians believed that during the creation or development of a human being or animal, a number of interactions between the basic building elements, which take part in the early development of the creature, and this gives a unique shape and property to them⁷. This property, which emerges after interaction of various building blocks with their properties, is termed as *Mizaj*. This property of *Mizaj* is inseparable from the existence of a human being and so imparts distinctive features for identifying and differentiating a particular body⁷. This particular state (*Mizaj*) of the body is responsible for maintaining health of a human being and disturbances in *Mizaj* lead to pathological states. We will limit its further description in this paper as it is beyond scope of this work and that we are particularly concerned with the *Mizaj* of drugs in here, which need to be, described in detail.

***Mizaj-e-advia* (Temperament of drugs)**

Drugs used in Unani medicine, are of plant, animal or mineral origin, all of which are composed of four basic *arkan* (basic elements) and that these elements possess the property of heat, cold, moisture and dryness^{1,8}. The interaction of elements gives rise to different *Mizaj* and pharmacological properties to different drugs, which get manifested on administration to human body. The *Mizaj* is formed of two parts, one-part results from interaction of heat and cold and the other part from interaction of moisture and dryness. Sometimes it happens that the interaction of two opposite *qualities* i.e. heat with cold and moisture with dryness, takes place in such a way that none of the two dominates but both of them are equal in effect. This type of interaction will result in formation of *motadil* (balanced/moderate) *Mizaj*. The *Mizaj* of this kind of drug is neither hot or cold nor wet or dry, but its effect is imperceptible in terms of these properties⁸. The moderate drugs as per Unani medicine are considered safe and presumed to be least toxic. These presumptions also stand verified through a long history of clinical practice of the classical physicians. The potency and toxicity of other categories of Unani drugs is defined in comparison with the moderate drug. Depending upon the interaction of different elements and the nature of their effect on human body, nine categories of drugs have been defined.

Motadil: This type of drug does not produce any perceptible effect on the body in therapeutic doses even if consumed repeatedly⁸.

Ha'ar and *motadil* drug: This drug when consumed makes the body feel hot.

Barid and *motadil*: These drugs make the body feel cold after consumption.

Yaabis and *motadil*: These drugs induce dryness in the body.

Ratab and *motadil*: These induce moisture in the body.

The patient may not always perceive the hot or cold effect as such; in that case, the effect is assessed indirectly through the nature of the action of drug. The other four types of drugs are compound *Mizaj* in nature, these are; *Ha'ar* and *Ratab*, *Ha'ar* and *Yaabis*, *Barid* and *Ratab*, and *Barid* and *Yaabis*^{1,2,8}.

The practical implementation of Unani Tibb (medicine), depends upon; identification of drugs, knowledge of their *Quwa* (forces) and general and specific actions, knowledge of dosage of drugs and identification of less efficacious and more efficacious drugs. Some drugs are single and some compound and before knowing the compound forms, we ought to know the single forms of drugs. The plant origin drugs include; roots, barks, branches, leaves, fruits, seeds, gums, flowers etc. The knowledge of them was gained through keen observation, experiment, testing and serendipity. We know this fact that like all other objects in this universe the drugs also are composed of elements on the principle of interaction, mixing and interaction of their *kafiyat*. Therefore, the different genus of drugs is also different based on pattern of interaction of elements, *Mizaj* and *Quwa* (driving forces)¹. Some drugs are hot, others hotter, some cold and others colder, some wet and others more wet, and in the same way some may be dry while others are drier in *Mizaj*, in the same manner their primary and secondary *Mizaj* and other dependent functions are different among the drugs¹.

***Darjaate Mizaj-e-advia* (Degrees of drug temperament)**

The drugs of same *Mizaj* do not possess *Mizaj* in exactly the same limits. In one, it may be towards the upper limit, in another it may be in between and yet in another it may be towards the lower limit of the *Mizaj*. In the same way physicians thought that, every disease has different stages in terms of *Mizaj*, just like that of the drugs⁸. In the initial stage, a disease may be mild and its symptoms intensify with time gradually in such a way that every next stage is more intense than its previous stage. In this course of the disease, they found four prominent stages in the course of the disease as on these stages the symptoms were somewhat clear and distinctive. Thus four distinct stages as per severity were thought to occur in the course of the disease in such a manner that every next stage is /severe and every previous stage was less harmful than the follower was. So in order to exactly treat these different stages of a disease with proper and specific drugs corresponding to the stage of disease, the physicians differentiated the drugs in four degrees of *Mizaj* as per the intensity of their effect. Therefore, the four degrees of the drugs correspond to the four stages of *Su'ie Mizaj* (derangement of body temperament)⁸. The degree of derangement induced in the body by a particular degree of *Su'ie Mizaj*, equals the derangement that could be produced by the same degree of the drug on a healthy individual⁸. In the description of the stages of *Mizaj* of drugs, the stages in the *Su'ie Mizaj* have been taken into consideration.

The 1st degree drug is that if a healthy person takes its therapeutic dose, only once, he does not feel any effect in the body. If the same drug is taken a few times (2-3 times) then a slightly increased effect is felt. If the drug does not show any effect even after taking the drug few times and in increased dose, then it is said to be moderate in nature⁸.

The 2nd degree drug is that which shows some effect even on first dose, and this effect is equal to that of the first degree drug when given few times and in higher dosage.

The 3rd degree drug is that which produces an unhealthy feeling and troubling situation in the body just at the first proper dose⁸.

If on administration of the first selected dose of a drug produces a severe effect in the body, which may result in death of the person, it is a 4th degree drug. Therefore, these drugs are called as poisonous drugs⁸.

The four degrees of the drugs are dose dependent; therefore, any change in the dose may increase or decrease the *Mizaj*. Degrees of *Mizaj* are not discrete, but every degree is further divisible into three levels, i.e. initial, intermediate and the last level, with increasing intensity of *Mizaj* from first to last level. If by increasing the actual dose in very low quantity (one and half), the subsequent effect in the body is comparable to that of the next degree, the drug is said to be in the last level of that *Darjae Mizaj*. If the amount of the effect is produced only by doubling the dose, it is the second level. Similarly, if that effect is obtained by giving the drug three times or four times than its actual dosage, it is said to be in the first level of the corresponding *Darjae Mizaj*. There is no degree of *Mizaj* above the 4th degree. The three levels of the 4th degree *Mizaj* can be marked out by comparing the time span in producing the serious hazard - if the time of death decreases by increasing, the dose of the drug to one and a half times, it is said to be in the last level of the 4th degree. If that much time is taken by doubling the dose it is the second level, or if that much of time until death is taken by giving the drug three to four times than the actual dose, it is said to be the first level of the 4th *Darjae Mizaj*⁸.

Unani drug development and assessment of *Mizaj* of drugs

Unani medicine has its own method of establishing action of drugs. A priori drug is subjected to *Mizaj* assessment by the method of analogy and then it recommends experimentation in humans. Pre assessment of *Mizaj* by analogy is carried out based on organoleptic characters of drug and by its physicochemical properties. However, the assessment of these characters have greater component of subjectivity. The methods for knowing the *Mizaj* of drugs are of two types; experiment and analogy.

Methodology

There are certain conditions for assessment through experiment^{2,5,8,9,10} these are – i. At the time of experiment, the

drug should be free from new and temporary effects like heat and cold. ii. The disease for which the drug is tested should be single/ isolated in naturally because we cannot otherwise reach to a proper conclusion. iii. If a drug produces benefit in two opposite diseases, we cannot conclude that its action is opposite to either of the two diseases, because a drug may have acted in two different ways in the two conditions, either against the cause or against the symptom. iv. The strength of the temperament of the drug and the disease should be equal, otherwise a less cold drug cannot benefit in a comparatively more warm disease. v. The nature of action of the drug in relation to the time should be taken into account to rule out any transient action of the drug. vi. Beneficial effects on long use depict the actual action of the drug most of the times. vii. The temperament of the drug should be tested in human being only but not in other animals, because the *Mizaj* of humans may be different from the animals. viii. The tester should know the difference of way of action of a food and a drug. The drugs are considered as acting through their *kafiyaat* while the food acts by its *Maada* (matter) to replace the molecules of the body for maintenance of growth. These principles need to be obeyed on testing the action and temperament of drugs on moderate bodies. Sometimes drugs are discovered accidentally, which are later confirmed through experiment. In spite of all these experiments done by the classical physicians, it is permissible that in the later ages we try to know about those drugs, which they could not. Although enough experiments have been conducted by them on whatever the drugs were known to them, still the significance and scope of further research is pertinent¹⁰.

Analogy: This process helps in identification of drugs by organoleptic and physicochemical properties, such as Taste, Smell, Colour, *Istihallah* (burning property), *Anjumaad* (freezing property) and a few more such properties¹⁰.

Taste: Nine different types of tastes have been described that include; *Dasmi* (greasy), *Hullu* (sweet), *Maleh* (salty), *Hareef* (pungent), *Hamiz* (sour), *Kabiz* (astringent), *Murr* (bitter), *Iffs* (acid), *Tuffa* (tasteless)^{1,2,9,10}. Things that can be taken orally may be hot, cold or moderate. On the bases of different combinations of these situations many types of tastes are formed. The tastes indicating hotness of a drug in decreasing order are; *Hareef* > *Murr* > *Maleh* > *Hullu* > *Dasmi*. The tastes indicating coldness in increasing order are as; *Kabiz* < *Hamiz* < *Iffs*¹⁰.

Smell: Smell is weak evidence as compared to the taste. All substances with smell are hot in nature with the rule that light smelling substances are less hot and this heat is dispersed in the whole of the matter of that substance¹⁰. However, the substances, which have smell that is soothing in nature, do not contain heat, e.g. camphor, Neelofer etc. Bad smelling substances contain lot of heat and *Ufoonat* but the odour of a substance is not sufficient to judge its qualities as odour is a weak parameter^{1,10}.

Colour: The analogy and evidence through colour assessment is the weakest of all. It only helps in differentiating between different forms of a single genus^{1,2}.

Istihallah: If the drug is easily influenced by the heat then it is presumed that it will also be easily acted upon by the innate heat of the body and as such, a hotter drug will be more easily influenced by the fire. However, sometimes this happens due to loose structure of the substance and not due to its hot nature.

Anjumaad: if two drugs are similar with respect to viscosity and fluidity, lightness and heaviness, and if the new drug freezes more easily than the known one, it means the new drug is colder and if it freezes slowly compared to known drug, it is treated to be hotter in nature¹⁰.

Research in the field of Mizaj and Mizaj-e-advia

Knowledge and thorough understanding of the concept of *Mizaje Insaani* (temperament of humans)^{11,12} as well as *Mizaj* of drugs is undoubtedly fundamental and a prerequisite for efficient treatment and understanding of the disease process and drug actions. Many people have tried to assimilate the philosophy based *Mizaj* theory into latest scientific developments for better understanding in response to the ever-increasing scientific knowledge and due to lot of thrust on evidence based medicine in present era. The fact although bitter, has to be accepted that still a very limited research work has been conducted in this field for better understanding of the theory of *Mizaj* on scientific parameters. Evaluation of the concept of *Mizaj* is essential for understanding the pharmacological basis of Unani drugs. The new trend for understanding the concept of *Mizaj* is based on the knowledge of chemistry, physics, Phytochemistry, pharmacology etc. *Mizaj* is a broad concept, which forms after complex chemical reactions between the constituents, so it would be reasonable to correlate and interpret it in terms of chemical bonding and physical properties of drugs¹³. *Mizaj* of drugs may also share some association with the important chemical constituents like alkaloids, glycosides, essential oils, terpenes, tannins, flavinoids etc, present in the crude drugs. According to Salimuzaman Saddiqui¹⁴, plant drugs with alkaloids are generally bitter in taste and indicate hot temperament while drugs with tannins are considered cold. Similarly, pathophysiology, prevalence and occurrence of specific diseases in individuals or specific populations may also be related to the nature and *Mizaj* of particular individuals, this may help in locating the high risk groups in the population so that timely preventive measures can be employed¹⁵. There have been attempts in describing the concept of *Mizaj-e-advia* in the light of modern pharmacology¹⁶. The concept human temperament may explain disease process like ageing¹⁷ and lay basis for proper management and prevention of diseases. The concept of four degrees of *Mizaj* is based on relative potency and toxicity of drugs² and both properties are believed to increase from 1st to 4th degree of *Mizaj*. The drugs of 4th degree *Mizaj* are highly potent

and can be toxic if due care is not taken while prescribing them to patients. Thus, correlation of degree of drug temperament and toxicity may assist and simplify the toxicity studies of drugs.

Conclusion

The success of Unani medicine and its travel through the ages amply indicates and proves the credibility of the basic theories like *Mizaj* on which this system is based. Research in the field *Mizaj-e-advia* may be expected to have promising implications in the direction of Unani drug pharmacology. The concept of *Darjae Mizaj* need to be evaluated, which may enlighten the toxicological aspect of Unani drugs and of, be of help in cost effective Unani drug development and formation of a reliable test for assessment of *Mizaj*. The major difficulties faced in establishing the mechanism of pharmacological actions of Unani drugs can simply be owed to their complex and multiple component nature. These drugs are believed to be acting on multiple targets in the body in association and in holistic approach, which makes it difficult to explore their pharmacological pathways. Exploration of the pharmacological and toxicological implications of *Mizaj-e-advia* by measuring its physical correlates may provide a simple and cost effective method for selecting leads for drug development. The novel approach, network pharmacology takes into account the multidisciplinary and cross-disciplinary fields to optimize the efficacy and safety of drug discovery. The theory of *Mizaj* may be expected to reveal promising facts in the light of the new concept of network pharmacology, as proposed by Hopkins (2007), wherein emphasis is laid down on the holistic approach of treatment or what we call multiple targets of the drug, which affect the disease process in combined manner.

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