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Importance of pharmacovigilance in Unani system of medicine

Syed Ziaur Rahman, Rahat Ali Khan, Abdul Latif[1]

Department of Pharmacology, Jawaharlal Nehru Medical College, [1]Department of Ilmul Advia, Ajmal Khan Tibbiya College, AMU, Aligarh - 202 002, India

Correspondence to:
Syed Ziaur Rahman

Development of Pharmacology in Unani Medicine

Unani medicine (also called as Greco-Arab medicine) is an ancient system of medicine originated from Greece. It is more commonly practiced in Indian Subcontinent and has an age-old concept and principles of drug management. Some authorities even consider this system of medicine as a holistic loom. It has drugs from natural identity and source. It may pose threat if not prepared, isolated, identified and administered properly.

Greek medicine, roughly speaking, covers the millennium from 500 BC to 500 AD. The inventor of the healing art was Apollo, "who chases away all ills". It is said, that Aesculepius, Hygiea, Panacea, Aphrodite, Pan, Juno, Neptune, Mercury, Pluto, Hippocrates, Dioscoridius, Galen were the successive healers of all ills. Hippocratic materia medica was large. His theory of four humours, Sanguin (*Dam*), Phlegm (*Balgam*), Yellow Choler (*Safrā*) and Melancholia (*Saudā*), is analogous to the three dosas of ayurvedic medicine: Phlegm, Choler and Wind. Dioscoridius (70 AD) was the first person to write a comprehensive illustrated book enlisting the major medicinal plants.[1]

By the tenth century AD, several views in different fields of medicine including those of pharmacology were consolidated. In the time of Ibn Sinâ (980-1037 AD), all knowledge on pharmacology and curative properties of substances were based on clinical observations, i.e., the main feature of pharmacology in the age of Ibn Sinâ was the empirical use of compounds and an accumulation of vast knowledge on clinical pharmacology. Knowledge on curative properties of drugs increased greatly as a result of the consolidation and rapprochement of ancient Greek medicine, Persian-Tajik and Indo-Chinese medicine. Such a rapprochement resulted in the widespread use of the most effective drugs although simultaneously it was also sometimes the cause of discrepancies and even false opinions about curative properties of the same preparations.

It was necessary to systematize different groups of drugs, to establish interconnections and especially to evolve the problems of general pharmacology. Having realized the importance of this problem, Ibn Sinâ paid great attention to general and systemic pharmacology of the then existing drugs. This is confirmed by chapters and even sub-chapters dealing with systemic or general pharmacology of drugs in each of his medical books.[1]

Different works by Ibn Sinâ like the encyclopedic al-Qanun, comprehensive treatises on cardiac drugs, code of recipes and other works contain valuable knowledge on problems of general and systemic pharmacology, pharmacognosy and also of the methods of preparation of more than 2000 simple and complex drugs. He developed general principles for the treatment of patients and described them in the first book of al-Qanun under the heading, "On General Means of Treatment". According to him, treatments are done in three ways: "one of them is regimen and nutrition; the second, application of drugs; and the third, manual treatment, i.e., surgery". Treatment with drugs must take into account the following rules: choice of drugs by their quality, selection of drugs by their quantity and this rule includes change in weight, potency and properties; and the time of administration of drugs.[2] Then he gives detailed descriptions of indications for the use of purgatives and emetics, the administration of which he considers to be a very serious problem, so as not to permit the adaptation and customary constipation. The book gives indications for such applications as ointments; lotions; cupping, leeches; general principles of treatment of inflammation; bloodletting by cupping; cauterization; general principles of wound treatment, ulcers and how to eliminate the sense of pain. An analysis of Ibn Sinâ's general rules of drug therapy and of diseases differing in their etiology reveals his merits in clinical pharmacology, which now is, of course, a separate medical science.[3]

The second book of al-Qanun gives rather detailed pharmacological and pharmacotherapeutic characteristic of 811 drugs, among which those of vegetable kingdom constitute 594 (73.7%), of animal kingdom 118 (14.5%) and of mineral origin 99 (12.2%).[3] To avoid repetition of general properties of the second character of action, Ibn Sinâ at the beginning of the above-mentioned second book deals in detail with questions of general pharmacology, describes more than 60 kinds of pharmacological effects of simple drugs, and combined action of different preparations. He describes local, general, direct, specific, indirect, counter attracting, synergistic, antagonistic, potentiating, cumulative, side-effects and some other kinds of drug action in other ways more than those adopted in modern pharmacology. However, his detailed description made quite clear the effect of the drug.

Ibn Sinâ describes in detail means of pharmacological evaluation of a drug by tests and by comparison. The test must be performed under the following conditions: The drug must be free from physico-chemical influence and other factors as well

as changing its activity; the disease for which the drug is tested must be simple, i.e., without complications; The drug should be tested for two opposite diseases, since sometimes it cures one disease directly (direct action) and the other indirectly. The drug should, both in quality and quantity, be in just proportion to the nature and severity of the disease. The initial effectivity of drug is rather more natural to the drug than its perpetual action. The action of drug should be watched constantly in all or in most of the cases. If it is not so, the action may be regarded as temporary and accidental. The last experiment should be conducted on human bodies and not on animals as both keep different temperament.[4]

Ibn Sinâ believes that negative effect of the drug can be relieved only at patient's bedside, by continuous observation of its action. His thesis, that tested drug is better than non-tested, is of primary concern even in our days when profit-motivated chemists indulge in spurious practices.

In the second book of al-Qanun, the drugs are presented in alphabetic order. Each drug is characterized not only by its pharmacological, but also by its pharmacognostic properties. Doses, scheme of treatment, indications and contraindications are described also.[3]

The third as well as fourth book of al-Qanun deals with questions of particular toxicology, pharmacotherapy with minerals, vegetables and poisonous insects as well as the toxicity of snake poison. These books also contain pharmacological characteristics of cosmetics.[3] The fifth book deals entirely with compound drugs and their preparation, and serves as pharmacopoeia for the al-Qanun. There are only two chapters in this book. The first chapter "On complex Drugs included in Pharmacopoeia" is one of the biggest chapters and consists of 12 independent sections, characterizing the composition and preparation of 508 complex drugs that were used up to the tenth century. The second chapter, entitled "Test of Drug for such Separate Disease" consists of 18 sections and represents a sort of reference book on "Symptoms and their Treatment", wherein preparations, and indications for 186 complex drugs are described. Ibn Sinâ investigated principles of combination of different substances included in the complex drugs.[3]

Rationality in the Use of Unani Drugs for the Prevention of ADRs

According to WHO, "Pharmacovigilance activities are done to monitor detection, assessment, understanding and prevention of any obnoxious adverse reactions to drugs at therapeutic concentration that is used or is intended to be used to modify or explore physiological system or pathological states for the benefit of recipient." These drugs may be any substance or product including herbs, minerals, etc. for animals and human beings and can even be that prescribed by practitioners of Unani or ayurvedic system of medicine.

In Unani medicine, proper reasoning in the method of preparation of drugs, including a rationality underlying combination of various medicinal plants, minerals, animals products etc.; method of administration; various preservatives; indications and contraindications in different situations; restriction, avoidance and abstinence of certain diet (*Parhez*); adverse drug effect; complete drug profile; adverse drug–drug or food–drug interaction; guidelines for prescribing in extremes of age or in the presence of altered organ function or in the presence of pregnancy or lactation, etc., are given in various Unani Formularies. Moreover, correctives (*Muslehat*) to drugs are used since a long time to minimize some undesirable effects, which the basic and the adjuvant constituents may produce in a normally prescribed combination of with both single and compound drugs. Drugs that are toxic in crude form are processed and purified in many ways before use (*Tadbir*). In spite of the fact that every drug used in traditional systems of medicine may have some side-effects (*Muzarrât*), the aim of the above precautions, taken by well-informed and experienced physician, was obviously to avoid any adverse drug reactions.[1]

The physicians after noticing any unknown side-effect in patients either used to write those adverse reactions in their *Bayaz* (Notebooks) or communicate their experiences to their pupils (in modern terminology prescription auditing and monitoring). There was then no association of physicians worldwide as prevalent nowadays under different names and different governmental patronage, in order to interact or exchange experiences. The Indian physicians used to practice in their own region or community. In other words, there was no random/spontaneous or drug-oriented ADR monitoring.[1]

Co-relation of Pharmacovigilance and the Theory of Temperament

The concept of temperament (*Mizaj*) and pulse examination (*Moain-e Nabdh*) in diagnosis and therapy, selection of drugs according to their potency into four degrees (*Darjat-e Advia*) or pharmacotherapy (*Ilaj bil advia*) according to their temperamental potency into four degrees (*Darjat-e Advia*), use of correctives (*Tadbir*) to minimize toxicity on the basis of temperament of drugs and its impact in minimizing side-effects and use of substitutes (*Abdal al Advia*) for better efficacy and cost-effectiveness are the main concern for rational drug management in Unani medicine.

Characterizing pharmacological activity of the drugs, Ibn Sinâ, unlike many other ancient physicians, paid special attention to the individual sensitivity of the organism itself about which he wrote: "Saying that the drug is hot or cold, it does not mean that the drug by its substance is maximally hot or cold or that it is by its substance hotter or colder than human body. No, it means that this drug induces heat or cold in the body, exceeding heat or cold of the human body. Thus the drug may be cold when compared to the human body and hot in comparison with scorpion body; hot comparing with human body and cold, in comparison with snake. Moreover, the drug may be hot for one body and cold for another body. So the patient is not advised to use one and the same drug for change of nature, it is useless. In other words, stress is laid on the particular temperament of the individual,[4] the medicines administered go well with the temperament of the patient, thus accelerating the process of recovery and also eliminating the risk of drug reaction. Ibn Sinâ's thesis that only one drug should not be used to treat "one and the same patient" shows that, basing on his daily observations at patients bedside, Ibn Sinâ clearly realized that the body could adapt itself to the drug.

Likewise, Unani drugs of every origin (plant, animal and mineral) are categorized in four degrees on the basis of their

temperament, potentiality (potency) and power of effectiveness (efficacy), which in its entirety curb adverse drug reactions. Higher the degree, higher the adverse effects. A drug used in Unani system has a documented temperament (hot, dry and moist). The temperament of the drug is measured on a scale of one to three degrees. A drug may have temperament (*Har* as Hot and Cold, Hot and Dry, Hot and Moist; *Barid* as Cold and Hot, Cold and Dry, Cold and Moist; *Yabis* as Dry and Hot, Dry and Cold, Dry and Moist). This classification of herbs seems to be based on the clinical observations of the yesteryear physicians of Unani system.

All substances which come in contact with the body and react upon it are of three types: (a) those that are altered by the body but do not produce any change in the body, (b) those that are altered by the body and produce changes in it, (c) those that are not altered by the body but even then produce changes in it. Substances that are altered (metabolized) by the body but do not produce any appreciable change are: (i) nutritive food articles in general which become a part of the body, and (ii) non-nutritive substances which are the balanced medicines. Substances that are altered by the body and also produce changes in it are: (i) the action of which ceases after digestion and are (a) assimilable as the medicinal foods, and (b) non-assimilable as the actual medicines; (ii) those, which continue to act even after digestion until they produce destructive changes in the body. These are poisonous medicines.

The concept of the use of substitutes (*Abdal al Advia*) is based on well laid down principles described by Unani medicine authors. Substitute should only be used when the original drug meant for use is not available. No drug can be a complete substitute for another drug. If a drug is substituted by some other drug having same property, the second should be a substitute for the original drug for that very specific activity. The second drug may be replaced by a third for some different action. It is essential that the substituted drug should match the original drug in temperament. A hot and dry drug of first degree should be replaced by a hot and dry drug of first degree. Hot and dry drug should not be replaced by a cold and moist temperament drug.[5]

Thus after determining the temperament of substitutes of drugs, its usefulness on a particular temperament of patient and disease condition is taken into consideration. This is the way of natural treatment with natural drugs. Each patient is receiving drugs according to their nature. So this pattern of treatment produces lesser adverse reactions. For example, a herb with cold temperament could only be replaced by a herb with cold temperament and a drug with moist temperament can only be replaced by a drug with moist temperament and not otherwise. Further, the drug should match in temperament with the person to whom the drug has been prescribed. According to Unani system of medicine, each individual has either cold, hot, dry or moist temperament. Jadwar (Delphinium denudatum Wall) as a whole has one specific temperament. It has 21-22 known alkaloids. The temperament of its active principle (Delphinine or Methyllycaconitine) will not be the same. Inactive principles may in addition change the balance of body temperament.[5]

Unani medicine is said to have a holistic approach; refers to the whole knowledge as a total recognition of the patient's condition. Is there any rationality? Looking at the concept and principles of Unani medicine, it does not interfere with physiologically inherent forces of *viz*. *medicatrix naturae*, that is, of self-preservation. The purpose of Unani medicine is to assist natural recuperative power and thus eradicate the disease from the human body. Nature of the body, *Tabciyat* (equivalent term for Greek - *Physicis* from where "Physician" derived, also cf. *Tabaêy* and *Tabeeb*), spontaneously removes the morbid matter through the process of sweating, urination or defecation. Otherwise, munzij (maturation) is done to make the body to remove the morbid matter followed by Muz'hil via diaphoretic, diuretics and purgatives.

Pharmacovigilance and Dietotherapy (*Ilaj bil Ghiza*)

Dietotherapy aim is to treat certain ailments by administration of specific diets or by regulating the quantity and quality of food. This system attaches great importance to diet and digestion, both in health and disease. A physician while prescribing medicine stipulates regimen and directs on the foodstuffs to be avoided. Correct diet and digestion are assumed to produce correct balance of humours and maintain progress of health, whereas faulty diet and digestion derange the balance and produce disease. Obviously, the humoural imbalance can be corrected by medication, coupled with proper diet and digestion because improper diet and digestion can aggravate the disease or interfere with the healing effect of medicine.

Pharmacoenvironmentology and Unani Medicine

The Unani medicine system recognizes the influence of surroundings and ecological conditions on the state of health of human beings. The aim is to restore the equilibrium of various elements, humours and faculties of the human body. Six essentials for the prevention of health and maintenance of proper ecological balance by keeping water, food and air free from pollution: (a) atmospheric air; (b) food and drink; (c) rest and activity of body; (d) psychological activity; (e) sleep and wakefulness; (f) elimination and retention. On the other hand, there is also a growing focus among scientists, herbalists and environmentalists about the impact of drugs and herbs on environment and surroundings apart from its impact on animals and human beings. Pharmacoenvironmentology is a branch of pharmacology that deals with entry of chemicals or drugs into the environment after elimination from humans and animals, post-therapy. Thus, there is also a need of monitoring Unani drugs and its impact on environment.[6-8]

Modern Trends of Indigenous Drugs Monitoring including Unani Medicine

Modern medicine rests largely only on the concept of disease and suffering to be treated by administering something, a drug or potion, to the individual. However, evidence is accumulating that a wide range of apparently unconnected ailments can be due to abnormal reactions to ingested materials (like food) and that a cure can be affected by simply withholding those materials. A difficulty also arises because symptoms are often vague rather than specific, and chronic rather than acute. Complaints of irritability, depression, fatigue, headache, joint and muscle pain or gastro-intestinal disturbances may well be dismissed as being of psychological or emotional origin. Diagnosis is often difficult and time consuming, and may well

require skills, which can be provided only by one who has taken a special interest. Although indigenous drugs, which are commonly known as herbal remedies in the United States and Europe, continue to be widely used in the community and there is a perception among consumers that these preparations are "natural", and therefore have no ill-effects and are safe. Adverse reactions are a cost of modern therapy.

Reasons for adverse drug reactions in herbal medicine may be varied, like risks associated with parenteral use are greater because all drugs are prepared for internal purpose or for external application. Adulteration of herbals with pharmaceutical drugs is a problem in many countries. In the present scenario, when ADR Monitoring is being done on wide scale and in a well-maintained way, there is still a very low reporting of adverse drug reactions of herbs. The legal status and approval mechanism of herbal medicine also varies from country to country and risks associated with its irrational use are also greater. An exclusive drug reaction monitor centre for herbal drugs should be set-up by WHO or other Organization. However, the project of WHO Collaborating Centre for International Drug Monitoring on safety monitoring of herbal medicines is under way. Herbal ATC classification for medicinal purposes into a logical hierarchical structure compatible with the WHO Drug Dictionary is one step ahead in this direction.

Conclusion and Recommendations

If Unani drugs or any other systems of medicine can provide cure of at least few diseases, then it should be guided that they are used judiciously. Guidelines for rational use of these TM are must to be framed such as General Guidelines for methodologies on research and evaluation of TM, WHO, 2000. Following qualities of Unani drugs are worth mention. They are economical and nutritious, which is important for economical countries; they are no foreign body and hence match with human body physiology. They have lesser side-effects. However, following steps toward quality control methods for Unani drugs are needed to be taken up: publication of Unani Pharmacopoeias, Formularies, Standardization of Unani Drugs and Traditional Knowledge Digital Library (TKDL). Evidence generation for Unani medicine needs balance between scientific skepticism and spiritual sensitivity. The concepts of evidence in Unani may be built with meta-analysis, individual RCT, opinion of expert (authority), statement of credible persons, perception through senses or mind, inference based on reasoning, planning (based on the basis of clinical experience), descriptive studies, applicability to general population and other populations and reports of expert committees. Following shortcomings with regard to evidence in Unani medicine are to be taken care of: complex, individualized treatments including pharmacogenetic,[9] lack of standardization, appropriate placebo interventions, ethical limitations on type of comparisons, maintenance of blinding, devaluation of information from other sources.

The number and type of drugs is constantly increasing, while the financial resources for health care services in general remain limited. Therefore, rational drug management has become an increasingly important topic in order to make optimal use of the drug budget and to offer health services of the highest possible standard, safe and devoid of adverse drug reactions. Study of indigenous medicine including Unani in relation with drug safety and quality assurance is thus imperative. There is no systematic data on the incidence of traditional medicine-associated adverse effects. One of the difficulties has been that there are many complex issues relating to adverse event detection with traditional products. These include the problems of products with multiple ingredients, drugs of multiple systems of medicine,[10] misclassification of names, poor standardization of products, lack of clinical trials,[11] variation in manufacturing processes, contamination, adulteration and misidentification of herbs.[12] In particular, rare adverse events and delayed effects may not be readily identified despite traditional use, countering the argument that many herbal remedies are safe because of previous traditional use.[13]

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References

1. Rahman HSZ. Historical perspective of traditional medicine with special reference to ADRs. National Symposium on Relevance of Pharmacovigilance for Indian System of Medicine. Department of AYUSH, Ministry of Health and Family Welfare, Government of India and Society of Pharmacovigilance, India; 4th November 2006. p. 53-61.
2. Ibn Sina. vol 1, Cairo, 1294/1877, p. 187 and English translation, In: Mazhar H. Shah, editor. Karachi, 1966. p. 359, 25, 185, 188, 361, 194, 372.
3. Denisenko PP. Development of pharmacology and toxicology in the medicine of India and Middle Asia, interaction between Indian and Central Asian science and technology in Mediaeval times, vol. 2. New Delhi: INSA; 1990. p. 1-7.
4. Ibn Sina. vol. 2, Cairo; 1294/1877. p. 224-225.
5. Singhal KC, Rahman SZ. Abdal al Advia (substitution of drugs) - a challenge to pharmacovigilance (chapter 3). In: Arunabha R, Kavita G, editors. Pharmacovigilance: an update. New Delhi: Vallabhbhai Patel Chest Institute; 2004. p. 22-44.
6. Rahman SZ, Khan RA, Gupta V, Uddin M. Pharmacoenvironmentology: A component of pharmacovigilance. Environ Health 2007;6:20 (Online) http://www.ehjournal.net/content/6/1/20.
7. Rahman SZ. Impact of human medicines on environment - a new emerging problem. Popul ENVIS 2006;3:3-4.
8. Rahman SZ, Khan RA. Environmental pharmacology - a new discipline (Editorial). Indian J Pharmacol 2006;34:1-2.
9. Rahman SZ, Kumar A, Singhal KC. Pharmacogenetic and pharmacogenomic in the sphere of pharmacovigilance - a review (chapter 3). In: Mathur GP, Mathur S, editors. Current trends in pediatrics, vol. 1. New Delhi: Academa Publishers; 2005. p. 20-32.
10. Latif A, Rahman SZ. A serious adverse drug interaction of two traditional medicines - a case report. J Pharmacovigilance Drug Saf 2005;2:26-29.
11. Jabin Farkhunda, Singhal KC, Bhargava R, Latif A, Rahman SZ. Clinical trial of an herbal formulation and associated adverse drug reactions in patients of bronchial asthma. J Pharmacovigilance Drug Saf 2005;2:16-19.
12. Rahman SZ, Latif A, Singhal KC. Adverse drug reactions of an herbal drug due to mis-identification: a case report. Pharmacoepidemiol Drug Saf 2002;11 Suppl 2: 241.
13. Rahman SZ, Singhal KC. Problems in pharmacovigilance of medicinal products of herbal origin & means to minimize them. Uppsala Reports 2002;17 Suppl:1-4.