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Awareness of pharmacovigilance in Unani system of medicine: A need of the hour

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Abstract
Unani system of medicine, although originated in Greece, is one of the recognized systems of medicine in India. They are regarded as the safest medical systems. However with the scientific ethos everything is rejected or accepted in the light of available clinical data only. Hence, to create pharmacovigilance, program for ASU drugs become essential for giving them credibility. Pharmacovigilance is an important tool to analyse the drug effect particularly its side effects, if any. To raise awareness among health care professionals about the pharmacovigilance of Unani drugs and to explore different ways of making it operationally better among health care professionals and encourage a culture of reporting regularly to the respective peripheral or higher centers. In order to achieve operational competence in the improvement of pharmacovigilance for Unani medicines and for the best practice model for Unani drugs, a systematic analysis of the areas to be focused upon and the challenges ahead, starting from proper nomenclature of Unani drugs, cultivation, procurement, drying, transportation, processing, labelling and dispensing was undertaken. All the crucial areas were identified and an understanding for the recognition and management of adverse reactions due to Unani drugs was developed. This paper gives brief concept of pharmacovigilance, and reporting of ADR of Unani Drugs.

Keywords: Pharmacovigilance, adverse drug reaction, Unani system of medicine, health care professionals

Introduction
Pharmacovigilance is the science of detection, understanding, assessment and prevention of adverse drug reactions and related untoward effects [1]. Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products and biological [2]. In the world market, more than 60 to 70% of current medicines are directly or indirectly derived from plant sources. The common misconception about herbal medicines is that these medications are absolutely safe and can thus be taken safely by the patient on his or her own without the prescription of a doctor. This assumption has led to large-scale self-medication by people all over the world, often leading to disappointing end-results, side effects, or unwanted after effects [3]. Therefore, in order to establish pharmacovigilance, the ASU drug program is important to give them credibility [4]. The aim of pharmacovigilance is to identify, analyze and understand adverse effects or any other specific drug-related problems that are not limited to chemical drugs, but also to herbal, conventional and complementary medicines, biological medicines, vaccines, blood products and medical devices, and to prevent them. The tradition of herbal use as medicine is as old as history itself. Some scholars state that more than 4000 years ago, the first documented use of herbs for medical treatment started [2]. Adapting internationally acceptable mechanism, in this regards, shall create an impression that these systems are scientific. One of today's essential challenges is the need to show to the world that ASU systems, which have existed for thousands of years, are not only safe, but also scientific [4]. Several recent high-profile herbal safety issues have led to the awareness of the need to control the safety of herbal medicines, such as renal failure and urothelial cancer associated with exposure to Aristolochia species, allergic reactions, skin inflammation with garlic, allergic dermatitis with *Aloe vera* and kava-kava-associated hepatotoxicity [3].
The suspected toxicity and adverse effects has been reported with the increased use of herbal medicine. The untoward reactions can be due to (i) Hypersensitivity, allergic and idiosyncratic reactions (detectable by pharmacovigilance), (ii) Mid-term and long-term toxic effects including liver, renal, cardiac and neurotoxicity also genotoxicity and teratogenicity (detectable by *in vitro* and *in vivo* toxicological studies or by pharmacovigilance), (iii) Side effects (usually detectable by pharmacodynamics and often predictable); (iv) Reactions occurring as a result of overdose, over duration, tolerance, dependence-addiction (detectable

either by pharmacodynamics or pharmacovigilance). The thorough testing of herbal medicine in the market for their pharmacology and toxicology has not been tested; pharmacovigilance has paramount importance in detecting unwanted reactions. Besides that there is a problem regarding unexpected toxicity of herbal medicine due to quality issues including incorrect or misidentified herbs, use of poor quality herbal material, supply of adulterated or contaminated herbs or products, incorrect processing methods. These quality issues should be minimised to some extent by improving regulation i.e. GMP standards for manufacturing. Thus regulation of herbal medicine/ products from many countries with different manufacturing standards remains a problem for poor quality products [5]. Therefore ultimate goal of Pharmacovigilance is to achieve rational and safe use of medical drugs, to assess and communicate the risks, benefits of drugs on the market and to provide education and information to the patient and to be safe from misleading advertisement.

With this context, the purpose of this article is to raise awareness among health care professionals about the pharmacovigilance of Unani drugs and to explore different ways of making it operationally better among health care professionals and encourage a culture of reporting regularly to the respective peripheral or higher centers.

1.1 Introduction to traditional Unani system of medicine

The Unani Medicine System is one of the oldest traditional medicine systems that has existed to prevent and treat different medical problems over the ages. Unani is the Arabic word for Ionian, or Greek, for which Unani medicine is also commonly referred to as Unani Tibb or Graeco-Arab Medicine, since it was developed and refined by Avicenna through systematic experiment [6]. According to Unani medicine, health is considered as a state of body with humors in equilibrium and body functions normal. Health is based on six essential elements: 1. Air 2. Drinks and food 3. Sleep and wakefulness 4. Excretion and retention 5. Physical activity and repose 6. Mental activity and repose. The human body is composed of four fundamental elements as per this conventional system: earth, air, water and fire with cold, hot, wet and dry temperaments, respectively [7]. Human temperament is composed of the dominant humor i.e. Sanguine (*Damawi*), Phlegmatic (*Balghami*), Chloretic (*Safrawi*) and Malancholic (*Sawdawi*), which can be compared with the temperament of Diet, Drugs, Environmental factors etc. as the entities of non-human universe is being made up of directly by elements which are described in terms of qualitative temperament. The loss of equilibrium of humors cause disease and hence the aim of treatment is by restoring the equilibrium of giving factors and by drug with opposite temperament. In addition Unani System of medicine believes that Medicatrix naturae (*Tabiyat Muddabira Badan*) is the supreme power, which controls all the physiological functions of the body, provides resistance against the diseases and helps in healing naturally [8]. Interestingly the definition of health pronounced by WHO is in close approximation with the idea of health described by Unani System of Medicine.

1.2 The concept of treatment in Unani system of medicine

Before comprehending the need of pharmacovigilance in Unani System of Medicine it becomes imperative to briefly understand the concept of treatment in Unani. According to the Avicenna, while treating diseases, at first the *tabeeb* (physician) must know the normal temperament of that patient. Afterwards, physician should assess the pathological temperament based on sign and symptoms, mentioned for respective type of *su-e-mizaj* and then accordingly use his skill to counteract the effect of pathological temperament (tadeel-e-mizaj) existing at the time of the disease [6]. Following modes of treating of disease are available in Unani system of medicine which depends upon the nature of the ailment and its causes. a) *Ilaj-bil-Tadabeer* (Regimental therapy) and *Ilaj-bilGhiza*/*Ilajbi"l-Taghziya* (Dietotherapy) b) *Ilaj-bil-Dawa* (Pharmacotherapy) c) *Ilaj-bil-Yad* (Surgery) [9].

1.3 The concept of Pharmacovigilance in Unani system of medicine

The Unani System of Medicine refers to Graeco-Arabic medicine, based on the teachings of the Greek physician Hippocrates and the Roman physician Galen, and developed by Arab and Persian physicians, such as Rhazes (al Razi), Avicenna (Ibn-e-Sina), Al-Zahrawi, and IbnNafis, into an elaborate medical system in the middle ages. Buqrat (better known as Hippocrates, 460-377 BC) is known as the "father of Unani medicine" and is said to be a descendant of Aesculapius. It originated nearly 2500 years ago in Greece and used drugs of approximately 90% herbal, 4-5% animal and 5-6% mineral origin [6].

As a classical text, Unani does not really use the term “Pharmacovigilance” in its delineation; but the concept of Pharmacovigilance is vibrant in the Unani system of medicine. Ibn-i-Sina has done a pioneering work in this regard. An elaborated general and systemic pharmacology of the then existing drugs includes cardio-active drugs, code of recipes and a valuable knowledge on the methods of preparation of more than 2000 simple & compound drugs [10].

Unani drugs of all origins (plants, animals and minerals) are classified by four degrees on the basis of their temperament, potential (power) and effectiveness (efficacy) which, in their entirety, curb adverse drug reactions. 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. The temperament of a drug may be (*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 [11].

Sometimes it becomes necessary to use a substitute when the drugs are unavailable or when they are unnaturally expensive or when there is a religious prohibition on the use of the drug. Sometimes it so happens that the required part of the plant might not be available while its other parts are easily available. In such cases physicians make do with whatever is available [12].

There are three types of substances that come into contact with the body and respond to it: (a) those that are altered by the body but do not cause any change in the body, (b) those that are altered by the body and create changes in it, (c) those that are not altered by the body but even then produce changes in it. Substances that the body changes (metabolizes) but do not generate any appreciable changes 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 [11].

2. Need of pharmacovigilance in Unani medicine [10]

- Adulteration
- Unknown Composition
- Improper Labelling
- Unscientific Storage
- Lack of Proper Dosage
- Lack of Standarisation at Various Stages of drug development
- Contamination
- Un-Profession procurement of drug
- Herb-Drug Interaction

3. Challenges in the pharmacovigilance of Unani medicine

- Ignorance among physicians regarding ADR's.
- Very low reporting of ADR's.
- Too many products and multiple ingredient formulations are difficult to monitor [10].
- False belief about the universal safety of Unani drugs.
- Herbal and allopathic drugs are generally prescribed together.
- False belief that Unani drugs have no expiry date, though this factor has been taken care of by introducing a rule regarding shelf life of all forms of drugs in Drugs and Cosmetics Act, 1945 [13].
- Bulk dispensing. This is one of the most important causes of ADR as some drugs like Kushtaare prescribed in much higher doses than actual dose.
- Concept related to adverse reactions not covered in curriculum.
- Lack of quality control to produce standard medicine.
- Informal pharmacy sector- selling spurious, misbranded and sub-standard drugs.
- A lot of Unani drugs which are available in the market do not have the actual ingredients as are described in Unani literature. This may be due to non-identification/false identification or non-availability of that drug. As such formulation with similar names may have different ingredients thereby and Pharmacovigilance observation of one may not be applicable to other till their content and quality of components are same.
- Also assessment of adverse reactions is difficult because of multi ingredient composition of most drugs [10].
- Practice of Pseudo-allopathy which refers to co-administration of Allopathy drugs along with Unani drugs.
- Poor patient compliance and ignorance, apart from self-medication and home remedies that are practiced by many people.
- Methods to study drug safety problems have not evolved adequately in Unani Medicine.
- Non-availability of compendium of ADR's for Unani medicines

4. National pharmacovigilance programme for ASU drugs (NPP-ASU)

The Ministry of AYUSH has introduced new Central Sector scheme for promoting pharmacovigilance of Ayurveda, Siddha, Unani and Homoeopathy (ASU&H) Drugs. Prime objective of the scheme is to develop the culture of documenting adverse effects and undertake safety monitoring of Ayurveda, Siddha, Unani and Homoeopathy drugs and surveillance of misleading advertisements appearing in the print and electronic media. The scheme intends to facilitate the establishment of three-tier network of National Pharmacovigilance Centre (NPvCC), Intermediary Pharmacovigilance Centres (IPvCCs) and Peripheral Pharmacovigilance Centres (PPvCC). All India Institute of Ayurveda, New Delhi, has been designated as National Pharmacovigilance Centre. In the initial phase of implementation, five National Institutes of AYUSH are designated as the Intermediary Pharmacovigilance Centres and forty-two (42) institutions of AYUSH having clinical facilities as Peripheral Pharmacovigilance Centres. It is intended to have more such centres across the country and achieve the target of 100 peripheral pharmacovigilance centres by 2020. Representatives of Central Drug Standards Control Organisation as the national drug regulatory authority and the Indian Pharmacopoeia Commission being the WHO Collaborating Centre for Pharmacovigilance in the country are associated in the initiative as mentor and guide [14].

4.1 What to report under NPP-ASU [15]

The programme particularly solicits reporting of

- All suspected drug interactions
- All adverse reactions suspected to have been caused by ASU drugs either alone or in conjunction with other drugs
- Death
- Reactions to any other drugs suspected of significantly affecting a patient's management, including reactions suspected for events in the following categories
- Hospitalization (initial or prolonged)
- Life threatening (real risk of dying)
- Disability (significant, persistent, or permanent)
- Required intervention to prevent permanent impairment or damage.
- Congenital anomaly

4.2 Who can report?

Suspected adverse drug effects may be reported by any health care professional. The cases identified by lay public or non-health practitioners shall not be accepted as part of the program. Even so, they can report via the doctor under whom they have undergone treatment.

4.3 Where to report

Reporting should be done in a prescribed format [14]. (Table 1) through a local Pharmacovigilance center. Also e-reporting of ADRs has been launched and report to this website www.ayushsuraksha.com

4.4 Progress of submitted information

The peripheral Pharmacovigilance centers forward the confidential forms to their regional Pharmacovigilance centers where casualty analysis is carried out. The information is then forwarded to the National Pharmacovigilance Resource Centre, where it is consolidated, statistically analysed, and forwarded to the Department of AYUSH [15].

Table 1: Reporting form for suspected ADR of ASU & H Drugs

PHARMACOVIGILANCE OF
AYURVEDA, SIDDHA, UNANI and HOMOEOPATHY (ASU & H) DRUGS
Reporting Form for Suspected Adverse Reactions

Note:

i. Personal in formation of the consumers/patients/ADR reporter's will be kept confidential.
ii. All suspected reactions are to be reported with relevant details.
iii. All completed forms are to be submitted to the program coordinator of nearby Centre.

A/U/S/H	
Code	**Un-NIUM/Code of Peripheral Centre/ADR Number/Year**

1. Patient/consumer identification (Please complete or tick boxes below as appropriate)

Name		Patient Record Number (PRN)
Place of Birth	IPD/OPD	
Address Village/ Town Post/Via District/State		Age: Sex: Male/Female
Diagnosis:	Constitution and Temperament:	

2. Description of the suspected Adverse Reactions

Date and time of initial observation	
Description of reaction	

3. Whether the patient is suffering with any chronic disorders?
Hepatic Renal Cardiac Diabetes Any others

4. Addictions, if any? If yes, please specify:

5. H/Oprevious allergies/Drug reactions, if any: If yes, please specify:

6. List of all ASU & H drugs used by the patient during the period of one month:

Name of the drug	**Manufacturer /Batchno.**	**Dose**	**Form/Route of administration**	**Date of**		**Reason for use**	**Any unwanted occurrences**
				Starting	**Stopped /Continued**		

7. List of other drugs used by the patient during the period of one month:

Name of the drug	**Manufacturer /Batchno.**	**Dose**	**Form/Route of administration**	**Date of**		**Reason for use**	**Any unwanted occurrences**
				Starting	**Stopped/ Continued**		

8. Details of the drug suspected to cause ADR:

a. Name of the drug:

b. Manufacturing date and Expiry date (if available):

c. Remaining pack/label (if available):

d. Consumed orally along with (water /milk/honey/or any other)

e. Whether any dietary precautions have been prescribed? If yes, please specify:

f. Whether the drug is consumed under medical supervision or used as self-medication.

g. Any other relevant information associated with drug use:

9. Management provided/taken for suspected adverse reaction

10. Please indicate outcome of the suspected adverse reaction (tick appropriate)

Recovered:	Not recovered:	Unknown:	Fatal:	If Fatal Date of death:
Severe: Yes/No.	Reaction abated after drug stopped or dose reduced:			
	Reaction reappeared after re-administration of drug:			
Was the patient admitted to hospital? If yes, give name and address of hospital				

11. Any abnormal findings of relevant laboratory investigations related to the episode done pre and post episode of ADR:

12. Particulars of ADR Reporter:

Please tick:	Patient /Attendant/Nurse/Doctor /Pharmacist /Health worker/Drug Manufacturer/Any others (please specify)
Name:	
Address:	
Telephone/E-mail:	

Signature of the reporter: Date:

Please send the completed form to: The centre from where the form is received or
To The Coordinator
Intermediary Pharmacovigilance Centre for Unani Drugs
(IPvCC) National Institute of Unani Medicine
Kottigepalya, Magadi Main Road, Bangalore - 560 091
Email: ipvcnium@gmail.com

5. Discussion

A common misconception that prevails among the mainstream Unani medicines are always safe for people. It is important to change this mind set. It has to be understood that use of all sorts of medicines are associated with some degree of risk, and it totally lies with the treating physicians to trade-off between the benefits and the potential risk. This risk can be considerably reduced by use of good quality medications and following various guidelines and instructions mentioned in Unani classics related to administration of drugs. To achieve this it is very important to understand and study the principles of drug safety mentioned in Unani System of Medicine. The Department of AYUSH has gone a long way in creating infrastructure for pharmacovigilance reporting. The clinicians of Unani should be given training regarding assessment of adverse reactions and must be taught the procedure for reporting of such reactions. The forms for assessing and reporting should be simplified to facilitate easy reporting. Close monitoring of all drug prescriptions should be done. Adequate inclusion of pharmacovigilance may be done in the undergraduate curriculum of Unani. Bulk dispensing of drugs is a major issue and it steps should be taken to monitor it. Dispensing of *safoof* (powders) in sachets can be done to provide fixed dose. Pharmaceutical houses need to share the burden and as well as responsibility for proper implementation of pharmacovigilance program. Data generated from various studies like clinical or pharmacological trials should be regularly updated in the textbooks. Experts of Unani may also be reoriented and trained as experts in pharmaco-vigilance. The drug information should be easily available and should be completely digitalised so that the knowledge is available instantly. Though, the Traditional Knowledge Digital Libraryis a positive step in this direction [15]. Moreinstitutes should be involved in the process so as to create a deeper penetration of the concept. Students should be educated and the institutes may serve as satellite areas for data collection for any ADR and AE. As a part of promotional activities, brochures on pharmacovigilance for ASU drugs were prepared and being distributed at stall at Arogya/CME etc., Guest lecturers were delivered during scientific sessions of different National and International seminars and research scholars and public were informed by putting advertisement related to NPP ASU drugs in different journals and souvenirs.

It is high time that different stake holders dealing with traditional systems like Ayurveda, Siddha and Unani should come forward and actively participate to make pharmacovigilance program for ASU drugs a successful one.

6. Conclusion

The need of the hour is to educate the physicians and encourage them to analyse and report any adverse effects that occur in a patient, no matter how petty or irrelevant they may seem. Quality drugs are one of the main pillars of effective therapy. The onus of providing quality drugs lies with the pharmaceutical houses. This article recommends for more sensitizing programs, advertisement about ADR reporting at grass root health care system. This step will not only promote ADR reporting, but also will be helpful in reducing overall economic burden of health care cost, morbidity & mortality.

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