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Review Article

# Proactive Pharmacovigilance of Unani drugs; Prospects and Challenges

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## ABSTRACT

**Ethnopharmacological relevance:** Traditionally herbal (Unani) medicines are considered to be safe for therapeutic usage without any major harmful effects. However, besides beneficial therapeutic effects several suspected adverse effects have been reported in the literature as well as clinical practice that *inter alia* include hepatotoxicity, renal failure and allergic reactions. Since the safety of patients remains central to any kind of therapy, it becomes imperative for the relevant regulatory authorities to take appropriate measures required to safeguard the public health by ensuring that all herbal medicines are safe, effective and of standard quality. Therefore, the role of pharmacovigilance in Unani medicine is essential to determine which adverse effects cross the line of a drug"s efficacy and safe therapeutic use. For safe and effective use of Unani drugs, constant vigil and monitoring is required for each medicine throughout its life cycle. This review aims to provide a systematic summary on the importance, gaps, challenges and prospects of pharmacovigilance in the Unani system of medicine.

**Materials and methods:** Relevant literature regarding pharmacovigilance of traditional system of medicine including Unani drugs was retrieved from databases like Web of Science, Google Scholar, Baidu Scholar, Springer, PubMed, SciFinder and ScienceDirect. Information was also collected from classic books of Unani medicine and conference papers on pharmacovigilance of herbal drugs.

**Results:** In order to achieve operational competence in the development of pharmacovigilance for Unani drugs and for the best practice model for Unani medicine, a systematic analysis of the areas to be focussed 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.

**Conclusions:** Pharmacovigilance is a process of identification, documentation and monitoring of adverse drug reaction of selected medicine and reporting to the regulatory body, so that appropriate decisions can be made for the protection of public health. Herbal (Unani) medicines are generally considered as safe medicine, however several case reports of adverse drug reactions have been reported, so they need consistent monitoring for adverse effects. In this regard, this review will provide an insight for the need of the pharmacovigilance and regulation of Unani drugs including their procurement, processing, manufacturing, dispensing and formulation of a comprehensive policy for effective pharmacovigilance of these drugs.

Key words: Unani drugs; Pharmacovigilance; Adverse drug reactions; Toxicity; Safety Monitoring

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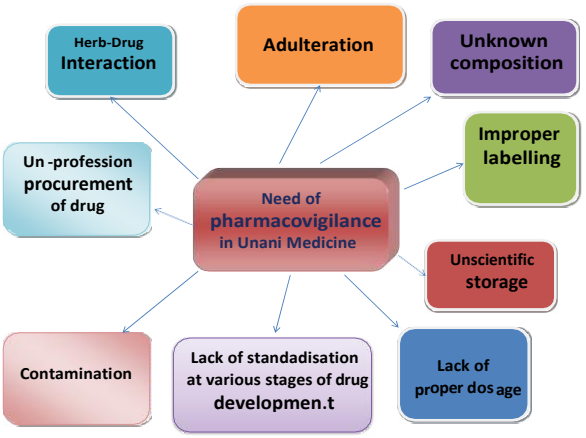


Figure 1: Graphical Abstract

## INTRODUCTION

Unani system of Medicine (also known a Greco-Arab medicine) was developed carefully and systematically from 500 BC till date as an ancient system of medicine. Unani System of medicine not only provides effective treatments for diseases, but its holistic approaches include unique principles of diet, life style and particularly therapeutics, to balance and enrich all aspects of physiology and psychology [1]. For the management of various diseases and ailments affecting patients, Unani system of medicine uses various drugs, majority of whom are from plant origin, followed by animal and mineral origin [2]. Hippocrates, one of the founders of Unani System in his famous book, "MateriaMedica" has proposed the theory of four humours namely sanguine (Dam), Phlegm (Balgum), yellow choler (Safra) and Melancholic (Sauda) whose proportional balance and disturbance are believed to be the main cause of health and disease. Dioscoridous (70 AD) wrote a comprehensive illustrated book, "De MatriaMedica" in which he vividly illustrated the major medicinal plants used in Unani System of medicine for therapeutic uses .Ancient Greek physician Ibn-Sina (980-1037 AD) in his book Encyclopaedia „Al-Qanoon" gave a detailed description of knowledge on pharmacology and therapeutic properties of herbal medicines on clinical observations [3].

As per WHO pharmacovigilance is defined as "Detection, assessment understanding prevention of adverse effects of drugs or any other possible drug related problem at therapeutic concentrations that is used or is intended to be used to modify or explore physiological system or pathological states for the benefit of recipient [4].

As per the report published by WHO, the traditional medicine has widespread acceptance thought-out the world and 70% of the world population depends on traditional health care system for management of various diseases [5]. As the use of herbal medicine has increased, the reports of suspected toxicity and adverse reactions have also increased proportionately. Majority of the adverse events related to the uses of these herbal drugs are attributed either to poor product quality or to improper use (US Report, 2002). Lack of proper regulatory mechanism, weak quality control system and largely uncontrolled distribution channels (e.g., internet sale), is considered to be the main factor for the occurrence of such adverse events [6]. Such adverse reactions can beobserved and categorized as:

a) Side Effects (usually predictable and detectable by pharmacodynamics).

b) Reactions occurring as a result of overdose, over-duration, tolerance, dependence (detected by pharmacodynamics and pharmacovigilance).

c) Allergic, Hypersensitive and idiosyncratic reactions (detected by pharmacovigilance).

d) Mid-term and long-term toxic effects including renal, hepatic, cardiac and neurotoxicity and teratogenicity (detected by in-vitro and in-vivo toxicological studies or by pharmacovigilance).

Pharmacovigilance has taken a centre stage in this whole process, as many Unani herbal products are laden with quality issues, incorrect or misidentified herbs, incorrect processing methods, supply of adulterated or contaminated herbs or products.

WHO has encouraged and welcomed the proactive participation of various stakeholders of the drug regulation across the globe including various Pharmacovigilance Centres to formulate appropriate guidelines for this whole process (http://www.whoindia.org/LinkFiles/Traditional). Taking WHO guidelines into consideration for the safety of herbal medicines and to put Pharmacovigilance systems in place for various traditional systems of herbal medicines includingAyurvedic, Sidda and Unani (ASU), Ministry of AYUSH has taken an initiative in India in this direction [7]. Global initiative led by WHO has provided a common platform for strengthening communication between these alternative systems that will ensure progress towards a common goal i.e., the safety of herbal medicines. The formulated policy has incorporated herbal medicines into the existing National Pharmacovigilance System [8]. National Pharmacovigilance System was aimed at identifying the challenges faced in monitoring the safety of herbal medicines effectively and devising suitable methodology to overcome them. Main thrust was on the reporting of adverse reactions to herbal medicines used in Unani System and to analyze the causes of the reported adverse reactions [9].

## PHARMACOVIGILANCE IN UNANI SYSTEM OF MEDICINE

Although the specific term of Pharmacovigilance does not feature in Unani Classical texts, but the concept of Pharmacovigilance is vibrant in the Unani system of medicine [10]. 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. Ibn-

Sina"s most valuable contribution in Unani medicine is in the form of dissertation on pharmacology and pharmacognosy of various drugs namely, "Al-Qanoon" (the canon of medicine) book of having five volumes, the first volume of which laid out the detailed principles of management of diseases including pharmacotherapy.

As per his versatile experience the selection of a particular drug should be based on the following:

i. Choice of drug by their quality.

ii. Choice of drug by their quantity including changes in weight, potency, and properties.

iii. Time of administration of the drug.

Pharmacological and pharmacotherapeutic characteristics of various drugs used in Unani system of medicine (811) were described in detail by Ibn-i-Sina in „Al-Qanoon" (The Canon of Medicine) which includes 594 drugs from plant origin, 118 from animal origin and 99 from mineral origin. Pharmacological evaluation of a drug by specific tests and comparative analysis where described in detail. He emphasized upon the need to watch constantly action of drugs in most of the cases and the drug being just in proportion to the nature and severity of the disease both in quality and quantity. He indicated that the experiment on humans should be done at last and not on animals as both have a different temperament [3].

Hence, in different Unani formulations the various reasons, rationality and methods for preparation of drugs are based upon:

i) Rationality underlying combination of various medical plants, minerals, animal products etc.

ii) Avoidance of certain diets.

iii) Adverse drug effects.

iv) Complete drug profile.

v) Adverse, drug-drug and food-drug interactions.

vi) Prescribing drugs in senile age, pregnancy, lactation and altered functions of certain organs [2].

Any Adverse or side effects observed and noticed by the Unani Physicians at that period was noted down and communicated to their pupils.

In Unani System of medicine the various classical books of drugs (Plant Origin, Animal Origin and Mineral Origin) provide a detailed knowledge about the temperament (Hot, Dry and Moist) based on the years of clinical observation of Unani physicians [1] and use of single or compound drugs for the management of various ailments is governed by various factors such as:

a) Temperament (Mizaj) and pulse examination (Moina-e-Nabdh) of the patient.

b) Potency/temperamental potency of drugs into four degrees (Darjat-e-Advia).

c) Toxicity minimization of drugs by the use of various correctives (Tadabir) on the basis of temperament of drug and its effects in minimizing side effects.

d) Use of substitutes (Abdale-Advia) in case of non-availability and cost effectiveness of original drug [11].

According to Ibn-Sina, principle motive of the Pharmacotherapy is that stress must be laid on the particular temperament of the individual [12] and the drug administrated, so that it goes well with the temperament, enhancing the recovery of the patient and also elimination of the risk of adverse drug reactions. Under Unani system, drugs (Plant, Animal and Mineral origin) are assigned a particular degree out of four degrees, based on temperament, potency and efficacy. Higher the degree, higher the chances of adverse effects [13].

- Har as Hot & Cold, Hot & Dry, Hot & Moist
- Barid as Cold & Hot, Cold and Dry, Cold and Moist
- Yabis as Dry and Hot, Dry and Cold, Dry and Moist

## CHALLENGES IN THEPHARMACOVIGILANCE OF UNANI MEDICINE

Following WHO guidelines for the safety monitoring of herbal medicines and putting Pharmacovigilance programme for Unani drugs in its right perspective, the Department of AYUSH, Ministry of Health and Family Welfare, Government of India, New Delhi took an initiative to start Pharmacovigilance for various traditional systems of medicine like ASU (Ayurvedic, Siddha and Unani) in the year 2008 so that there is proper review and analysis of the ADR reports at different levels and to suggest proper remedial measures. An estimated 65-80% of the world population uses traditional medicine for their primary health care [14]. In India it has been observed that a large chunk of population uses traditional medicine including Ayurvedic, Siddha and Unani drugs from centuries [15]. They are generally regarded as the safest medical systems. However the distinct features of Unani medicines and the way in which they are named, prescribed, sourced, utilized and regulated, raises important issues and challenges for Pharmacovigilance of Unani medicine. Easy procurement of these medicines from not only pharmacies, but various groceries and business outlets without proper prescription has raised many issues and challenges for their safety. Unani drug formulations contain substances of varied origins like plant, animal and mineral source in varied proportions. They include both relatively crude preparations, such as herbal tinctures, Joshanda (decoction), Khaisanda (infusion) [3] and manufactured or finished herbal medicinal products such as tablets, capsules, syrups, linctuses, oils etc. and are also available for purchase without prescriptions.

One of the common problems with Unani drugs is that a specific medicine is having multiple uses and may be taken by healthy individuals for "general well-being" as well as by patients with chronic diseases. The problem can further be compounded if the procedures for preparation of the same Unani drug vary. In contrast with conventional medicines, Unani medicines are chemically rich complex mixtures comprising of hundreds of constituents. In majority of the Unani Drugs the chemical constituents are unknown though some drugs have documented phytochemistry. There are only few Unani drugs for which the specific constituents responsible for Pharmacological activity are fully understood. Besides difficulties in assuring quality due to the variation in chemical composition, unlicensed Unani products poses big problem that includes intentional or accidental substitution of species, contamination with restricted or toxic substances including prescription medicines and differences between labelled and actual contents commonly seen in practical field.

It is a well known fact that different, parts of plants (roots, rhizomes, shoots, leaves, flowers, seeds, bark etc.) have different active constituent profile and from various Unani herbs only specific

plant part or parts such as shoots or leaves have medicinal value. In addition to this, the quantity and quality of active constituents can also get changed between different batches of herbal material due to the following factors: -

a) Environmental factors such as rainfall, sunlight, wind, altitude, soil quality etc

b) Inter- or intra-species variations

c) Time of harvesting and the course of day

d) Post harvesting factors such as drying, transportation and storage [16]

Processing techniques of the crude Unani drugs can also affect the quality and quantity of various chemical constituents. Majority of the Unani drugs contain multiple herbal ingredients and a Unani practitioner usually prescribes combination of different herbal compound formulations, further adding to the chemical complexity of the Unani medicines taken by patient. This enormous convolution of constituents makes it an uphill task in determining their clinical pharmacokinetics, clinical pharmacodynamics and toxicology. Hence the pharmacovigilance, safety monitoring and causality assessment of the adverse reactions due to a particular Unani drug is not as simple as in case of allopathic drugs since establishing which constituent or herbal ingredient(s) in a formulation is responsible for the ADR is difficult.

There will be significant variation in the chemical composition of Unani drug formulations containing same herbal ingredients but produced by different manufactures. This phenomenon is observed in both licensed and unlicensed Unani drugs manufactures. Maintaining uniformity in the active constituents of Unani is quite a daunting and challenging task owing to the fact that specific active ingredients are known only for few Unani medicines. Considerable variation in the products of the same herbs and their parts manufactured by different companies is another challenge in the safety and efficacy to be focused upon; hence the monitoring strategy should be product specific and extrapolated only to those products or extracts that have been shown to be pharmaceutically equivalent as well as bioequivalent [17].

As a result of the limited data available about Unani drugs and due to the apparent differences between different preparations of herbal formulations though it is difficult to attribute causality of adverse reactions to any single active ingredient of a Unani formulation yet the overall safety monitoring of the whole formulation is possible and since pharmacovigilance allows reporting of even suspected ADRs with probable or possible causality, a pool of signals could be generated about the safety of entire formulations available in the market. Since Unani formulations utilize a group of several herbs for the management of a particular disease, different preparations and products containing the same herbal ingredients could be grouped together in order to detect signals and to investigate “class effects” as observed in conventional medicine. Furthermore safety of well-known single active ingredients used in Unani formulations can be established separately through controlled clinical trials in humans after standardizing them for their dose, toxicity, frequency and duration of therapy following acute, sub-acute and chronic toxicity studies and pre-clinical studies related to their safety and efficacy.

Identifying a particular herb used in Unani medicine by common or vernacular names varies widely and various names used represent more than one species in different areas, making it difficult to be accomplished with accuracy. Popular belief heard and propagated through generations that the herbal medicines are safe as they are obtained from natural sources, needs to be revisited as many plants or their parts are highly poisonous or have inherently toxic constituents eg; Doremaammoniacum (Renal toxicity), Plantago ovate (Breathlessness, Bradycardia), Datura Stramonium (Cardiotoxicity), Melisa Officinalis (Burning Micturition, headache),Moschusmoschiferus (Muscular spasm, Tremors), Viola odorata (Decrease rate of respiration, Increase contractibility of the heart), Prunuscerasus (Diarrhea), Asparagus officinalis (Vomiting), Crocus sativus (Nausea, vomiting, Headache , Insomnia), Aconitum nepallus (Convulsions) [18].

From the Indian perspective, a minimal number of patients use herbal products including Unani medicine after seeking proper consultation from qualified practitioners. Large number of patients procures it from such practitioners who do not have proper training, certification or qualification. Concerned regulatory bodies of the government too have failed to implement the relevant laws required to curb such a menace. It has also come to fore that sometimes patients do not disclose that they are already taking some herbal or conventional medicines [19] and also some doctors practising the traditional medicine (ASU) hardly bother to document a drug history from the patient even if some sought of ADRs are reported. It is of utmost importance that a patient should disclose the use of herbal products (A.S.U) to a healthcare professional including the start date/stop date or ongoing use of these drugs (both herbal and conventional) since there could be a potential for drug-herb interactions. Concurrent use of Unani drugs with conventional medicines is rampant too.

In nutshell it can be said that the way in which Unani drugs are described (named), perceived and obtained; issues relating to the healthcare professionals and Unani drug practitioners; patient"s/ user"s behaviour towards Unani drugs; present opportunities for Unani drugs to be used inappropriately or even unsafely, are largely responsible for the suspected ADRs to go undetected and unreported.

## REMEDIAL MEASURES REQUIRED FOR PROACTIVE PHARMACOVIGILANCE OF UNANI DRUGS

To achieve operational efficiencies that would make proactive Pharmacovigilance for the Unani drugs a benchmark for drug monitoring programme, the following measures need to be taken by the governments, regulatory authorities, academicians, prescribers and patients:

1. A separate subject of Pharmacovigilance must be included in the curriculum of graduate & post-graduate level studies in Unani Medicine.
2. Clinical Research units of different pharmacies including institutions conducting postgraduate/doctoral level research should include Pharmacovigilance as one of the criteria in their research projects.
3. Drug licensing authorities of Unani medicines shouldinclude Pharmacovigilance as one of the pre-requisites for giving marketing permission for new drugs.
4. Regularity framework governing the manufacturing and licensing of the Unani drugs should be revisited.
5. Manufacturers of Unani drugs should demonstrate the quality, safety and efficacy of their products before marketing.

6. The importance of pharmaceutical quality standards for the safety and efficacy of Unani drugs should be a prerequisite. (At present manufacturers are required only to demonstrate pharmaceutical quality standards for their licensed herbal medicinal products.)
7. Manufacturers should have appropriate quality control and quality assurance procedures for their products.
8. If ADR association with a particular unlicensed Unani drug is suspected, it is essential to establish whether the herbal ingredients shown are what the product actually contains and whether the products could be adulterated or contaminated.
9. A sample of the suspected Unani drug should be retained for pharmaceutical analysis if needed.
10. Preclinical and clinical trials of the Unani products should be made mandatory.
11. Post marketing surveillance of studies should be a routine for each product.
12. Information regarding adverse effects, including interactions with other medicine, food, alcohol, disease and so forth, active constituents pharmacokinetics, pharmacodynamics should be brought into the notice of scientific community [20].
13. Information regarding use among special patient groups like children, elderly people, and individuals with renal or hepatic disease, pregnant and breast-feeding women and effects of long term use should be notified.
14. In case of Unani drugs, it is said that, since they are being used from centuries hence are safe without any toxicity. It is acceptable to some extent "that the test of time" may have pointed out some inherently toxic plants but delayed adverse effects cannot be ruled out. Also, effects that arise from the use in patients with modern illnesses, such as HIV/ AIDS and safety issues when Unani drugs are used concomitantly with conventional medicines should be thoroughly studied [21].
15. The drug regulatory system should provide consumers and patients with adequate protection against poor-quality and unsafe unlicensed herbal medicinal products including Unani Drugs.
16. There should be National Registration Scheme for (all the herbal drugs including Unani meeting certain quality and safety parameters).
17. Manufacture of Unani drugs should be directed to comply with the information and labelling requirements.
18. A designated qualified and experienced person should have a constant access to the manufacturing process for quality assurance.
19. The identity crisis in Unani herbs used in different formulations can be sought by the proper identification and can be ensured by the binomial botanical names (genus and species) in addition, the specific plant part used should also be stated since one or more plants may be used medicinally with considerable variation in phytochemical composition.
20. Information regarding method of processing the crude herbal material (e.g., type and extract), that can influence the precise chemical composition and hence the potential toxicity of a herbal product should be provided [22].
21. Drug Extract Ratio indicating the strength and the formulation of the product e.g., tablets, syrups, linctuses, tincture) etc. should be standardized.
22. As the current research on Unani drugs is mainly aimed at discovering the pharmacological activities and clinical efficacies, the aspect of safety has taken a backseat. More and more emphasis should be laid upon the safety and toxicological aspect of the drugs.
23. Methods and strategies which are suitable to the Unani drugs should be developed.
24. National Pharmacovigilance Programme should be closely linked to the National Drugs Regulatory System.
25. National Drug Regulatory System should incorporate the national safety monitoring programme for Unani drugs.
26. At state and national level, the capacity for reporting adverse events on Unani drugs, analyzing their causes and learning from past experiences should be encouraged.
27. The gap between the Unani drug"s potential and reality should be eliminated. The flowery language used to describe the potential of the drug; when there is high gap between purported effects and reality; should be assessed.
28. The Unani medicine practitioners are potential and useful source of information on ADRs. Hence regular training programs about need, identification and reporting should be organized both at state and national level.

## CONCLUSION

Herbal (including Unani) medicines are being used widely for therapeutic purpose both in developed and developing countries. In recent years several safety concerns relating to the use of traditional drugs that have had an impact on the public health have led to an increasing recognition of the need to develop Pharmacovigilance (safety monitoring) systems for Herbal (including Unani) drugs. Pharmacovigilance programme for these traditional drugs is in its infancy, hence various challenges are confronted in monitoring the safety of these Drugs. Synergism between the ideas and co-operation among conventional physicians and traditional practitioners of Unani drugs (Hakeems) is needed to bring a positive change in this direction. A balance between scientific scepticism and spiritual sensitivity should be taken into consideration while analyzing Unani drugs. While developing a robust Pharmacovigilance system for the safety of Unani drugs, systematic review of literature, scientific data on their safety, effective use, opinion of experts, statements of credible persons, perceptions gained through practice, inferences based on clinical experiences, individual RCTs, should be taken in consideration. Through these measures one can explore in-depth challenges that Pharmacovigilance of Unani drugs faces and what steps need to be taken to improve the safety monitoring of Unani Medicine in future.

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## Author's contribution

All the authors designed the study, carried out the literature survey and wrote the paper.

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