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ORIGIN, HISTORY AND DEVELOPMENT OF PHARMACOVIGILANCE THROUGH AGES

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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, in the scientific world everything is rejected or accepted in the light of available clinical data only. Hence, to create pharmacovigilance, program for ASU drugs becomes essential for giving them credibility. Pharmacovigilance lays stress on safe and appropriate use of drugs. Spontaneous reporting of adverse drug reactions (ADRs) is an essential component of pharmacovigilance. However this is significant under reporting of ADR'S. Adverse drug reactions have become a major problem in developing countries. Knowledge of pharmacovigilance could form the basis for interventions aimed at improving reporting rates and decreasing ADRs. 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 its birth.

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Keywords: Pharmacovigilance, adverse drug reaction, Unani system of medicine, Ibn Sina.

INTRODUCTION

Pharmacovigilance is the science of detection, understanding, assessment and prevention of adverse drug reactions and related unfortunate effects. [1] The objective of pharmacovigilance is to identify, analyse 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] In the market, more than 60 to 70% of current medicines are directly or indirectly obtained from plant sources. 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.[3] Other reason

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is misunderstanding regarding herbal medicines 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 notion has led to self-medication by people all over the world in large scale, often leading to unacceptable and un satisfactory end-results, side effects, or unwanted after effects.[4]

History of Pharmacovigilance in modern era: (20th Century):

One of the first pieces of proof of the creation of a system to monitor drug safety was the committee set up by the Lancet to report on mortalities resulting from anaesthesia in Britain and its colonies. The formation of the committee was in response to the death of a 15-year old girl who was given chloroform anaesthesia for the removal of an in grown toe nail in year 1848.[5,6] In the United States of America reportsof cases of aplastic anaemia associated with the use of chloramphenicol were recorded in the 1950.[7] As a result, the Council on Drugs of the American Medical Association setup a Blood Dyscrasia Registry.[8] In1954 thalidomide was synthesized for the first time, to the general public it was introduced in 1956 and was widely prescribed for morning sickness and nausea as a harmless treatment. By November 25, 1961, thalidomide was withdrawn from the market by its manufacturer. It has been estimated that between 6000 and 12000 children had been born with serious congenital malformations as a result of maternal use of thalidomide. [9] By 1961, the Food and Drug Administration (FDA) began the systematic collection of reports of all types of ADRs, chiefly through the Hospital Reporting Program. However, it was a letter from Dr WG Mc Bride that was published in the Lancet suggesting a connection between congenital malformations in new born infants and the drug thalidomide that acted as one of the most significant catalysts for drug safety monitoring. By 1968, ten countries (Australia, Canada, Czechoslovakia, Germany, United Kingdom, and USA), with national drug monitoring centres, collaborated and joined the World Health Organization (WHO) Pilot Research Project for International Drug Monitoring.[6] In 1972, are port was published that formed the basis of the current international system of national centres collaborating in the WHO programme.[6,10] The establishment of a pharmacovigilance system is essential to support public health policy. The study of Olsson *et al* [11], in which data regarding pharmacovigilance activities were collected from 55 low-and middle-income countries, revealed that information gathered through these activities was used in variable ways by the countries to assist regulatory functions, advise consumer groups and develop essential medicine lists and drug therapy guideline.

Back in 1986 Pharmacovigilance was started in India when 12 regional centres were proposed. During this project not a single activity was noted down for about a decade. After this, India then joined the Uppsala, Swedenbased WHO-adverse drug reaction (ADR) monitoring program in 1987. In beginning for ADR monitoring in the country, 8 regional centres were set up in Varanasi, Thiruvananthapuram, Guwahati, Jaipur, Bhopal, New Delhi, Bengaluru, and Chennai. [12] The responsibility to monitor the adverse drug reaction of marketed medicine was assigned to three centers - Jawaharlal Nehru Hospital, Aligarh, All India Institute of Medical Sciences, New Delhi, and King Edward Memorial Hospital, Mumbai. They had to submit the report to the Drug Regulatory Authority of India. However, this too did not yield much. Finally, in the year 2005, the National Pharmacovigilance Program (NPP) was launched which was sponsored by the WHO and it was funded by the World Bank, which was supervised by the National Pharmacovigilance Advisory Committee. [13] However, this program was suspended due to the end of the World Bank funding in mid-2009. As there is a need of improved ADR monitoring required in India, in 2010, under the sponsorship of Health Ministry, a nation-wide revised ADR monitoring program "PV Program of India" was launched.[14,15] The Ministry of AYUSH has introduced new Central Sector scheme for promoting pharmacovigilance of Ayurveda, Siddha, Unani and Homoeopathy (ASU&H) Drugs. Developing the culture of documenting adverse effects and to assure safety monitoring of Ayurveda, Siddha, Unani and Homoeopathy drugs and surveillance of misleading advertisements appearing in the print and electronic media is the main objective of this scheme. 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. [16]

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 Ibn Nafis, 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. [17] As a classical text, Unani does not really use the term "Pharmacovigilance" in its description; but the concept of Pharmacovigilance is vibrant in the Unani system of medicine.

Ibn-i-Sina has done an innovative work in this regard. An elaborated general and systemic pharmacology of 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.[18] He developed general principles for treating patients and then he described them in his first book of al-Qanun under the heading, "On General Means of Treatment". According to him, patients can be treated in three ways: "one among them is regimen and nutrition; the second being the application of drugs; and the third one is the manual treatment, i.e., surgery". While treating with drugs following rules must be taken into consideration: Drugs should be selected as per their quality and quantity, this rule also includes change in weight, potency and properties; and the time of administration of drugs.[19] He then 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 of habitual constipation. The book gives indications for several applications such as ointments; lotions; cupping, leeches; general principles for treatment of inflammation; bloodletting by cupping; cauterization; general principles of wound treatment, ulcers and how to eliminate the sense of pain. 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%).[20] 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.

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 be 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 everlasting 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 have different temperament.[21,22] 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 illustrated that tested drug is better than non-tested and it is of primary concern even in our days when profit-motivated chemists indulge in bogus 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 also described.[20] 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.[20] 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. [20]

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 ancient physicians of Unani system [23]. 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 in certain situations, the required part of the plant might not be available while its other parts are easily available. In such cases physicians can make the use of those parts that are avalaible.[24]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 corrective (Tadbir) to minimize toxicity on the basis of temperament of drugs and its impact in minimizing side effects. In spite of the fact that every drug used in traditional systems of medicine may have some side-effects (Muzarrât), the precautions taken by well-informed and experienced physician, was obviously to avoid any adverse drug reactions. The Unani 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). In other words, there was no random/spontaneous or drug-oriented ADR monitoring.[23] Probably the first work on Unani Pharmacovigilance seems to be complied by Hakim Ulvi Khan of Ulvi family one of the most renowned physicians of his era, his compilation on adverse effects among children in particular published in a Journal named "*Risale Dawaul Atfal*"[25] (Journal of Pediatrics Medicine) and also a series of case reports on ADRs among different age groups published with title Matab Hakim Ulvi Khan. [26]

Avicenna's Death an example of Overdose of medication.

Ibn Sina was suffering from colitis, so as to get free of this he took Enema (Douche) for about 8 times in a single day, but it caused intestinal ulceration without any relief and he further suffered from colonic attack; Then he advised his assistant to include 4 ratti (0.486gms) of *Tukhme Karafs* (Apium graveolens Linn.) in the enema to purge. But mistakenly his assistant exceeded the dosage of *Tukhme Karafs* due to which his condition worsened. Over dose of *Tukhme Karafs* resulted in recurrence of colonic attacks and intestinal disturbance moreover it worsened day by day. He ended up using Mashdaritoos to avoid that condition but tragically, Ibn Sina suffered from severe constipation, that eventually lead to his death.[27, 28]

Need of Pharmacovigilance in Unani System of Medicine:

Since ages, it has been observed that a large portion of population in India is using traditional medicine including Ayurvedic, Siddha and Unani drugs. [29] 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) [19] and manufactured or finished herbal medicinal products

such as tablets, capsules, syrups, linctuses, oils etc. can be easily purchased without prescriptions. One of the common problems with Unani drugs is that a specific medicine is having numerousbenefits 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. 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 complexity of constituents makes it a difficult 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 is 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 scary 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 [30].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; *Dorema ammoniacum* (Renal toxicity), *Plantago ovate* (Breathlessness, Bradycardia), *Datura Stramonium* (Cardiotoxicity), *Melisa Officinalis* (Burning Micturition, headache), *Moschus moschiferus* (Muscular spasm, Tremors), *Viola odorata* (Decrease rate of respiration, Increase contractibility of the heart), *Prunus cerasus* (Diarrhoea), Asparagus officinalis (Vomiting), Crocus sativus (Nausea, vomiting, Headache , Insomnia), Aconitum nepallus (Convulsions).[31]

Other observed and reported ADR in Unani system of Medicine Habbe Shifa (*Tukhm-e-Jauzmasil* (Dhatura stramonium), *Rewand Chini* (Rheum emodi), *Zanjabeel* (Zingiber officinalis roxb.), *Samagh-e-Arabi* (Acacia arabica) a pharmacopoeial preparation manufactured and marketed by Indian Medicines Pharmaceutical Corporation Limited (IMPCL), a

Government of India Enterprises was administered to a female patient who was suffering from of Suda-e-Nazli Muzmin (Headache due to chronic rhino-sinusitis) and reported adverse effect of blurred vision followed by photophobia and difficulty in maintaining the posture (vertigo) in subsequent third dose. The symptoms disappeared after 36 hours of withdrawal of the drug. [32]

The ADR is harmful and unintentional responses of a marketed drug, that is related to dose for diagnosing, treating, or modifying the organ function.[33] The types of adverse reactions are established first for modern medicine and the same can be applied equally to herbal medicine. ADRs are classified as follows:

Type A (acute/augmented): It is dose dependent and explained by pharmacology of the drug. Type B (bizarre/idiosyncratic): It is not dose dependent or expected by pharmacology.

Type C (chronic/cumulative): It generally gives cumulative effect.

Type D (delayed/onset): It is carcinogenic and genotoxic.[34]

CONCLUSION

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. 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. Guidelines for rational use of these traditional medicines are must to be framed such as General Guidelines for methodologies on research. To minimize the bad effects, the drugs are supposed to be used judiciously. Medicinal herbs have already attained a significant role in curing the human welfare not only in the diseased condition but also to maintain the proper health. Moreover, following qualities of Unani drugs are worth to mention. They are affordable and nutritious, which is important for economical countries like India. 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). 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.

REFERENCES

1. **Samal J.** Pharmacovigilance in Ayurveda–Concept and Regulations. Current Pharmacogenomics and Personalized Medicine (Formerly Current Pharmacogenomics) 2018;16(1):4-8.
2. **Wal A, Wal P, Gupta S, Sharma G, Rai AK**. Pharmacovigilance of herbal products in India. *Journal of Young Pharmacists*. 2011;3(3):256-8.
3. **Barnes, J., Anderson, L.A., Phillipson, J.D.,** Herbal medicines: a guide for healthcare professionals. University of London: Pharmaceutical Press. 65, 1963-1964- 2002.
4. **Rajanandh MG, Chamundees wari D**. Perspectives of Pharmacovigilance of AYUSH drugs among healthcare professionals-a cross-sectional survey. *Sri Ramachandra J Med* 2017;9 :1-9.
5. **Routledge P.** 150 years of pharmacovigilance. Lancet 1998; 351:1200– 1.
6. **Van Grootheest K.** The dawn of pharmacovigilance. *Intern J Pharm Med* 2003;17: 195–200.
7. **Rich ML, Ritterhoff RJ, Hoffmann RJ**. A fatal case of aplastic anemia following chloramphenicol (chloromycetin) therapy. *Annals of Internal Medicine*. 1950;33 (6):1459-67.
8. **Wallerstein RO, Condit PK, Kasper CK, Brown JW,** Morrison FR. State wide study of chloramphenicol therapy and fatal aplastic anemia. JAMA 1969; 208:2045–50.
9. **Randall T.** Thalidomide's back in the news, but in more favorable circumstances. JAMA. 1990 Mar 16; 263(11):1467-8.
10. **Olsson S.** The role of the WHO Programme on international drug monitoring in coordinating worldwide drug safety efforts. *Drug Safety*. 1998; 19(1):1-0.
11. **Olsson S., Pal S, Stergachis A., Couper M.** Pharmacovigilance activities in 55 low-and middle-income countries. *Drug Saf* 2010; 33: 689–703.
12. **Gupta YK**. Ensuring patient safety-launching the new pharmacovigilance programme of India. *Pharma Times*. 2010; 42(8):21-6.

13. **Ajanal MN, Nayak SU, Kadam AP, Prasad BS**. Pharmacovigilance study of Ayurvedic medicine in Ayurvedic Teaching Hospital: A prospective survey study. Ayurveda. 2015; 36 (2):130.
14. **Kalaiselvan V, Prasad T, Bisht A, Singh S, Singh GN.** Adverse drug reactions reporting culture in Pharmacovigilance Programme of India. T*he Indian journal of medical research*. 2014; 140(4):563.
15. **Kalaiselvan V, Sharma S, Singh GN.** Adverse reactions to contrast media: An analysis of spontaneous reports in the database of the pharmacovigilance programme of India. *Drug Saf* 2014;37:703-10.
16. Protocol for National Pharmacovigilance programme for ASU drugs 2021. https://www.ayushsuraksha.com/glossary/#NPvCC.
17. **Ansari S, Khan QA, Anjum R, Siddiqui A, Sultana K.** Fundamentals of Unani system of medicine-a review. *European Journal of Biomedical and Pharmaceutical Science*. 2017;4:219-23.
18. **Pervaiz AD, Nahida R, Shameem AR, Farooq AD, Shabir AP**, Hussain IM. Proactive Pharmacovigilance of Unani drugs. Prospects and Challenges. *J Pharamacovigilance*. 2020;8:285
19. **Sina I.** Kulliyat Qanoon fit Tib. Urdu Urdu Trans: Kantoori GH.) New Delhi: Idarae Kitabus Shifa:YNM
20. **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.
21. **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.
22. **Ibn Sina**. vol. 2, Cairo; 1294/1877. p. 224-225.
23. **Rahman SZ, Khan RA, Latif A.** Importance of pharmacovigilance in Unani system of medicine. *Indian Journal of pharmacology*. 2008;40(S1):S17.
24. **Azmi HWA**. Kulliyat-e-Advia. New Delhi: Ejaz Publishing House 1997.
25. **K Hakeem Ulvi**. Risale Dawaul Atfal. Idare Kitab us Shifa: New Delhi; YNM.
26. **K Hakeem Ulvi**. Matab Hakim Ulvi Khan. Idare Kitabus Shifa: New Delhi, YNM.
27. **Moosavi J**. The place of Avicenna in the history of medicine. *Avicenna journal of medical biotechnology*. 2009;1(1):3.
28. **Sina I**. Al Qanoon Fit Tibb. Urdu Trans: Kantoori GH.) New Delhi: Idarae Kitab us Shifa. 2010:19-20.
29. **Singhal, K.C., Rahman, S.Z.,** 2004. Abdal al Advia (substitution of drugs) - a challenge to pharmacovigilance (chapter 3) In: Arunabha R, Kavita G, editors. Pharmacovigilance: an update. Vallabh bhai Patel Chest Institute: New Delhi, 22-44
30. **Loew D, Kaszkin M.** Approaching the problem of bioequivalence of herbal medicinal products. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2002 Dec;16(8):705-11
31. **Ansari AP, Ahmed NZ, Wadud A, Anwar N, Sheeraz M, Ahmed H.** A concept of Muzir and Muslah of Unani drugs with scientific evidences: an overview. *Journal of Research in Unani medicine*. 2018;7(1):70-7.
32. **Azhar M.** Adverse Effect of Unani Pharmacopeial Formulation Habb-e-Shifa. *Journal of Pharmacovigilance*. 2018; 6(5):269.
33. **Trikramji AJ**, editor. Charak Samhita. 8th Adhyaya. 5th ed. Varanasi: Chaukhambha Sanskrit Sansthan; 2001. p. 275
34. **Edwards IR**, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000; 356: 1255-9.