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PHARMACOVIGILANCE OF HERBAL MEDICINES: AN INTANGIBLE APPROACH

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ABSTRACT

Herbal medicines make up an important module of the fashion toward alternative medicine. It is becoming ever more popular in today's world as people seek out for natural remedies. These medicines have been used since the dawn of civilization to maintain health and to treat various diseases. To compete with the growing pharmaceutical market, there is an exigency to develop and scientifically validated more medicinally useful herbal products. This review provides an outline of herbal medicines which is aimed to depict out pharmacovigilance, including standardization of these herbal products.

INTRODUCTION: Herbal medicines consist of plant or its part to treat injuries, disease or illnesses and are used to prevent and treat diseases and ailments or to promote health and healing. It is a drug or preparation made from a plant or plants and used for any of such purposes. Herbal medicines are the oldest form of health care known to mankind [1, 2, 3]. World Health Organization (WHO) has defined herbal medicines as finished, labeled medicinal products that contain active ingredients, aerial or underground parts of the plant or other plant material or combinations. World Health Organization has set specific guidelines for the assessment of the safety, efficacy, and quality of herbal medicines. WHO estimates that approx 81% of the world populations presently use herbal medicine for primary health care [4].

Exceptionally, in some countries herbal medicines may also contain by tradition, natural organic or inorganic active ingredients which are not of plant origin. Herbal medicine is a major component in traditional medicine and a common element in ayurvedic, homeopathic, naturopathic and other medicine systems [5]. These are traditionally considered as harmless since they belong to natural sources [6]. The use of herbal medicine due to toxicity and side effects of allopathic medicines, has led to sudden increase in the number of herbal drug manufacturers.

For the past few decades, herbal medicines have been increasingly consumed by the people without prescription. Seeds, leaves, stems, bark, roots, flowers, and extracts of all of these have been used in herbal medicine over the millennia of their use. Herbal formulations have reached widespread acceptability as therapeutic agents like anti- microbial, anti-diabetic, anti- fertility, anti- ageing, anti- arthritic, sedative, anti- depressant, anti- anxiety, anti-spasmodic, analgesic, anti-inflammatory, anti-HIV, vasodilatory, hepatoprotective, treatment of cirrhosis, asthma, acne, impotence, menopause, migraine, gall stones, chronic fatigue, alzheimer's disease and memory enhancing activities [7]. Herbal medicines have been documented for almost 4000 years. These medicines have survived real world testing and thousands of years of human testing. Some medicines have been discontinued due to their toxicity, while others have been modified or combined with additional herbs to offset side effects. Many herbs have undergone changes in their uses. Studies conducted on the herbs and their effects keep changing their potential uses.

Adverse Drug Reactions: Herbal remedies are not entirely free of adverse drug reactions. Some adverse drug reactions of commonly used herbs are, *Ginkgo biloba* cause spontaneous bleeding, St. John's Wort*(Hypericum perforatum*) cause gastrointestinal disturbances, allergic reactions, fatigue, dizziness, photosensitivity, confusion, *Capsicum annuum* cause hypertension, cardiac arrhythmias, myocardial infarction, *Ephedra* cause anxiety, *Vitex agnus* (Chast tree fruit) cause headache, diarrhea and *Piper methysticum cause* liver toxicity [8].

Drug Interactions: Mostly patients taking drugs with a narrow therapeutic index like Cyclosporine, Digoxin, Phenytoin, Procainamide, Theophylline, Warfarin etc. should be discouraged from using herbal products[9]. All drugs with narrow therapeutic index may either have increased adverse effects or be less effective when used in conjunction with herbal products. Ginkgo is used for Alzheimer's disease and causes increased bleeding with aspirin. Ginseng has multiple uses and causing synergism with monoamine oxidase inhibitors. Kava is used as anxiolytic and shows synergism with benzodiazepines. St. John's Wort is used as

antidepressant and causes reduced plasma levels of warfarin, cyclosporine, oral contraceptives, theophylline etc [10]. Use of heavy metals is permitted in traditional medicines but in definite concentrations, which were mentioned by ancient physicians. There are now many examples of the toxicity caused by the use of heavy metals in the preparations of traditional drugs. Lead, copper, mercury, arsenic, silver and gold that are commonly added to these preparations, have caused toxicity on many occasions. Patients should not use herbal drugs indiscriminately with modern medicines, as there are possibilities of drug interactions and increased risk of adverse drug reactions.

Standardization of Herbal Medicines: Standardization is the code of conduct in order to ensure the consistent efficacy that manufacturers should use to ensure batch-to-batch consistency of their products [11]. Standardization of herbals is a difficult process since the herbal contains complex mixtures of different components or mixtures of herbals are used at times as prevalent in different systems of medicines such as ayurveda. In such cases, the exact component of herbal responsible for claimed effects are unknown.

The most important aspect in standardization is structure elucidation and validation of markers using physicochemical properties such as melting point, boiling point, optical rotation and other pre-formulation data followed by the use of IR, NMR, MS and other highly sophisticated analytical methods [12]. GMP should also be applicable to the quality control of herbal drugs. GMP procedures should be developed for herbal medicine for the safety, identity, strength, purity and quality of herbal drugs [13]. The quality of herbal medicines is based on the assessment of crude plant material, plant preparations and finished products [14]. For imported finished products, confirmation of the regulatory status in the country of origin should be required. The WHO certification scheme on the quality of the pharmaceutical products moving in international commerce should be applied. Internationally several pharmacopoeias have provided monographs stating parameter and standard of many herbs and some product made out of these herbs. Several pharmacopoeias like Pharmacopoeia Committee, Chinese Herbal Pharmacopoeia, British Herbal Pharmacopoeia, British Herbal Compendium, Japanese Standards for Herbal Medicine and The Ayurvedic Pharmacopoeia of India. These pharmacopoeias lay down monograph for herbs and herbal products to maintain their quality in their respective nations.

Government of India recommends quality parameters for various ayurvedic herbal drugs. The physical and chemical stability of the product in the container in which it is to be marketed should be tested under definite storage conditions and the shelf-life should be established. The safety of herbal medicines is based on the toxicological studies [15]. The efficacy of the herbal medicines is based on the pharmacological and clinical effects of the active ingredients. Quantitative and qualitative standardization of a polyherbal product may be done by using the instrumental analysis or by means of chromatography.

Stability Testing of Herbal Medicines: Stability testing of herbal medicines is a challenging risk, because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known [16]. The objective of a stability testing is to provide evidence on how the quality of the herbal products varies with the time under the influence of environmental factors such as temperature, light, oxygen, moisture, other

ingredient or excipient in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container and to establish a recommended storage condition and shelf-life. Stability testing is necessary to ensure that the product is of acceptable quality throughout its entire storage period. Stability studies should be performed on at least three production batches of the herbal products for the proposed shelf-life, which is normally denoted as long term stability and is performed under natural atmospheric conditions.

Stability data can also be generated under accelerated atmospheric conditions of temperature, humidity and light, which is referred to as short term stability and the data so obtained is used for predicting shelf-life of the product. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. With the help of modern analytical techniques like Spectrophotometery, HPLC and by employing proper guidelines it is possible to generate a sound stability data of herbal products and forecast their shelf-life, which will help in improving global acceptability of herbal products [17].

Pharmacovigilance of Herbal Medicines: Pharmacovigilance, a French term referring to identifying side effects of drugs, their treatment, documentation, reportage and regulatory decisions based on them, is a well established science in the developed world [18]. Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from health care providers and patients on the adverse effects of medications, biological products, herbal medicines and traditional medicines. Pharmacovigilance is a discipline involving detection, evaluation and prevention of undesirable effects of medicines. It involves monitoring the safety of drug over a period of time, identification of adverse drug reactions in humans, access risk-benefit ratio [19]. Safety and efficacy are the two major concerns about any drug, while efficacy can be detected with relative ease; the same cannot be said about safety because the adverse effect of a drug may be uncommon but very serious. This gave a birth to a new branch of pharmacology called pharmacovigilance [20]. The aims of pharmacovigilance is to protect patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating pre-disposing factors and quantifying risk in relation to benefits [21].

The purpose of pharmacovigilance is to detect, assess, understand and to prevent the adverse effects or any other possible drug-related problems, related to herbal, traditionally and complementary medicines [22]. Herbal medicines are widely used in both developed and developing countries however, in recent years, there are several high-profile herbal safety concerns having an impact on the public health. Herbal medicines are traditionally considered as harmless but as medicinal products they require drug surveillance in order to identify their risks. Published data shows that the risk is due either to a contaminant or to an added drug.

Extremely limited knowledge about the constituents of herbal medicines and their effects in humans, the lack of stringent quality control and the heterogeneous nature of herbal medicines necessitates the continuous monitoring of the safety of these products. WHO has increased its efforts to promote herbal safety monitoring within the context of the WHO International Drug Monitoring Programme. The WHO guidelines aims to propose the member states of a frame work for facilitating the regulation of herbal medicines used in traditional

medicine covering issues like classification, assessment of safety, assessment of the efficacy, quality assurance, pharmacovigilance and control of advertisements of herbal medicinal products. The pharmacovigilance of herbal medicines exhibits particular challenges because such preparations are available from a wide range of outlets typically where there is no health care professional available, most purchases are in conventional OTC environment.

Various methods in pharmacovigilance are passive surveillance includes spontaneous reporting and stimulated reporting, active surveillance by sentinel sites, drug event monitoring, registries, comparative observational studies by survey study, case control study, targeted clinical investigations by investigate drug-drug interactions and food- drug interactions [23]. The importance of genetic factors in determining an individual susceptibility to adverse drug reactions is well documented and this implies to herbal medicines as well as to conventional drugs. Pharmacovigilance is therefore one of the important post-marketing safety tools in ensuring the safety of pharmaceutical and related health products [24].

Regulatory Status of Herbal Medicines: The legal situation of herbal medicines varies from country to country. Developing countries have folk knowledge of herbs and their use in traditional medicine is wide spread. But, these countries do not have any legislative criteria to include these traditionally used herbal medicines in drug legislation [25]. Approval of herbal medicines in most countries is based on traditional herbal references, provided they are not known to be unsafe when used to treat minor illnesses. But, now-a-days claims are being made to treat more serious illnesses with herbal medicines for which no traditional knowledge is present [26]. Therefore, regulatory requirements for herbal medicines are necessary to ensure the safety, efficacy and quality and to support specific indications; scientific and clinical evidence must be acquired [27]. Depending upon the nature of herbs and market availability, different requirements exist for submission of clinical trial data and toxicity data. The regulatory requirements of herbal medicines is varies from one country to other country [28]. Some countries accept traditional, experience based evidence while some consider herbal remedies as dangerous or of questionable value.

CONCLUSION: Medicinal herbs as potential source of therapeutics aids has attained a significant role in health care system all over the world for human beings not only in the diseased condition but also as potential material for maintaining proper health [29]. It is clear that the herbal industry can make great strides in the world. With the increased use of herbal products, the future worldwide labeling practice should adequately address quality aspects. Standardization of methods and quality control data on safety and efficacy are required for understanding of the use of herbal medicines [30]. A major factor impeding the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants [31]. Further research is required to exploit the compounds responsible for the observed biological activity.

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