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A STUDY OF HERBAL MARKETED FORMULATIONS TOWARDSBACTERIOLOGICAL INFECTION

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ABSTRACT

Herbal formulations play an important role in medicines; however, their suboptimal standardization, in terms of identity, purity, quality, efficacy and safety, has questioned their efficiency in treating various disorders. The present study was conducted to perform quality audit of four herbal formulations, i.e., Ashokarishta (Baidyanath, Dhanwantri, Prabhat, Dabur), Sitopaladichurna (Baidyanath, Dhanwantri, Kashmir, Dabur), Chandraprabhavati(Baidyanath, Dhanwantri, Zandu, Dabur)and Punarnavadimandur(Baidyanath, Unjha, Zandu, Dabur),marketed by various companies. The quality auditing procedures included analysis of moisture content, ash value and pH, presence of heavy metals, pesticidal residue and microbial contamination. The formulations were also pharmacologically evaluated for anti-inflammatory activity (in vivo; rat paw edema model). In Ashokarishta, Dhanvantaribrand did not pass the pH test while all brands failed in total solid contents. Chandraprabhavati (BaidyanathandDabur) passed total ash content. Sitopaladichurna (Dhanvantari) only passed moisture test. In Punarnavadimandur, ash value tests were passed by all brands. All the products passed microbial contamination test. None of the heavy metals was detected withhigher than permissible limits in any of the formulations. Endosulfan I & II was not recovered in all studied samples. Heptachlor, aldrin, 4-DDT were also not found in all the samples in comparison to standard samples. All the samples were free from radioactive substances as detected by Board of Radiation & Isotope Technology. The formulations also possessed anti-inflammatory activity. However, their activity varied among brands. Chandraprabhavati at Dhanwantari, Punarnavadimandoor at Zandu, SitopaladiChurna at Dhanwantari and Ashokarishta at Dabur brand showed better activity as compared to their counterparts. The study concluded that all the formulations were successfully quality audited. The formulations were also found to possess anti-inflammatory activity. However, more research is warranted to explore their anti-inflammatory potential. Most of the antibiotics were originally derived from micro-organisms while the chemotherapeutic agents are from plants.

KEYWORDS: Herbal Marketed Formulations, Bacteriological Infection, medicines, quality, efficacy, safety,micro-organisms.

INTRODUCTION

Nature has always stood as an outstanding benchmark to exemplify symbiotic phenomenon. It has enormous power and is a store house of remedies which can cure every ailment of man. Moreover, it has taken thousands years to accumulate knowledge related to drugs and due to man‟s perpetual quest, we today have natural and effective means to ensure a better health care. The utilization of plant as medicaments has been recognized from ancient time to present day. Despite of the recent major advances in the world of medicines, plants significantly contribute to the health care system. As per

World Health Organization (WHO), the herbal drugs and their associates have been defined in the following ways:

1. Herbal Medicines consist of herbs, finished herbal products and herbal preparations. However, herbal medicinal preparations may also consist of animal & mineral sources in addition to plant sources.
2. Herbs contain basic plant material, i.e. flowers, roots, leaves, fruit, stem, rhizomes, barks, wood, seeds or other parts of plants, which may be a whole plant, or its powdered/fragmented form. In addition to herbs, herbal materials include dry powders, fixed oils, gums, fresh juices, resins, and essential oils. In a few countries, plant materials are processed through various procedures viz. roasting with honey, steaming, processing with alcoholic beverages, etc.
3. Herbal preparation forms the basis for completely finished products. They may consist of tinctures or extracts, powdered herbal materials, or fatty oils obtained from herbal materials. They are processed to obtain the active phytoconstituents through extraction, concentration, purification, fractionation and other biological/physical processes. Herbal preparations also consist of preparations made through heating herbal materials in honey, alcoholic beverages, and other materials.
4. Finished herbal product includes herbal formulations which are made from one or more than one herbs. If they include more than one herb, they can also be called "mixture herbal product". Mixture herbal products and finished herbal products may also consist of excipients.
5. Herbal formulations are the formulation prepared from plant extracts and also contain suitable excipients. As these extracts contain active constituents, they are combined with excipients or a base to prepare a formulation, followed by its standardization using suitable methods. When more than two herbs are used in formulations, they are known as poly-herbal formulations.

REVIEW OF LITERATURE

AnjuDhiman et al. (2011) reported Antibacterial activity of metahnolic extract P. guajava. The methanolic extract exhibited antibacterial activity against E. coli with minimum inhibitory concentration, 0.78 µg/ml, minimum bactericidal concentration of 50 µg/ml, and appreciable antifungal activity with minimum inhibitory concentration of 12.5 µg/ml. Preliminary phytochemical analysis of methanolic extract revealed the presence of antimicrobial compounds such as flavonoids, steroids, and tannins, which may contribute for the antimicrobial action of P. guajava.

NarasimhaRao R et al. (2011) reported in the present work collection of plant material, extraction of the crude drug, Successive solvent extraction, phytochemical tests of plant extract, Thin layer chromatography, HPTLC and In vitro anthelminthic activity.

HetangiRathod et al. (2011) reported efficacy of In situ gelling system. Among oral dosage form, liquid dosage forms are more prone to low bioavailability because of their quick transit from the gastrointestinal tract. Sustained release liquid formulation with efficacy can be produced using approach of In

situ gel. The purpose of the present work was to develop oral in situ gelling system using Galan gum for in situ gelation of ambroxol-HCl. The formulation variables like concentration of polymer and calcium chloride will be optimized using factorial design. Optimized formulations were prepared having desirability and evaluated for various parameter.

Jayvadan K. Patel et al. (2012) reported development of Alginate based floating In situ gelling system of famotidine. It was prepared by dissolving varying concentration of alginate in deionized water containing sodium citrate, to which varying concentration of drug & Calcium chloride was added & dissolved by stirring. Results of preliminary trials indicate that concentration of sodium alginate, calcium chloride & sodium citrate affected the characterization of In situ gel. A 32 full factorial design was developed to study the effect of independent variables, concentration of sodium alginate (X1) & concentration of calcium chloride (X2) as dependent variable ; i.e. viscosity, drug content, drug release at 4 hrs. (Q50)& drug release at 8 hrs (Q80). A subsequent drug release was obtained for more than 8 hrs. In vivo testing of FIGF to albino Wistar rats demonstrated significant antiulcer effect of famotidine.

EhsanMirkamandar et al. (2012) reported evaluation of the invitro antimicrobial activity of a methanolic extract of Salvadorapersica solution on Helicobacter pylori isolated from duodenal ulcer. Minimum inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the extract were determined by the agar dilution method. At concentrations of 10, 100, 200, 500 µg/mL,no zone of inhibition around the ditches was observed while a clear zone of inhibition (12 mm) was detected at 1000 µg/mL concentration for all the isolates. The best antimicrobial activity was observed at MIC 1000 µg/mL ($P \leq 0.05$). The MBC results showed that at a concentration of 1000 µg/mL all cells were dead while at a concentration of 750 µg/mL of S. persica a few H.pylori cells were still able to form colonies on Brucella agar supplemented with sheep red blood cells and antibiotics. From the above results it can be concluded that high concentration of S.persica could inhibit the growth of H. pylori and MIC and MBC were similar at that concentration.

AnanyaChatterjee et al. (2012) presented a Review of the pathophysiology of H.pylori infection and its potential herbal remedy. Natural medicines and plant products, such as tea, resveratrol, curcumin, garlic, cinnamon, etc. can heal H. pylori induced gastric ulcers by scavenging the reactive oxygen and nitrogen species, boosting the host immune system, modulating host-pathogen heat shock proteins interactions. They are nontoxic in nature and hence can be used safely. Therefore, it is concluded that inclusion of natural antioxidants in the normal, daily diet may be the best remedial measure for continued protection from H. pylori infection.

BiplabAdhikary et al. (2011) reported the healing activities of black tea (BT) and the theaflavins (TF) against the indomethacin-induced stomach ulceration were studied in a mouse model. Indomethacin (18mg/kg, p.o.) administration induced maximum ulceration in the glandular portion of the gastric mucosa on the 3rd day, accompanied by increased lipid peroxidation and protein oxidation, depletion of thiol-defense and mucin, as well as reduced expressions of cyclooxygenases (COX) and prostaglandin (PG) E synthesis in the gastric tissues, and plasma total antioxidant status of mice. Treatment with BT (40mg/kg), TF (1 mg/kg), and omeprazole (3 mg/kg) produced similar (74%– 76%) ulcer healing, as revealed

from the histopathological studies. Treatment with all the above samples reversed the adverse oxidative effects of indomethacin significantly. BT and TF also enhanced the PGE synthesis by augmenting the expressions of COX 1 and 2, but did not modulate acid secretion.

Shanthi A. et al. (2011) reported the anti-ulcer activity of the polyherbal formulation. It was investigated by ethanol induced gastric ulcer model in wistar rats. In this evaluation the ulcer index was measured using histopathological sections. The formulation with 500mg/kg per oral produced significant inhibition of the gastric lesions in ethanol induced ulcer model with respect to standard 20mg/kg of Omeprazole (P.O) administration. And the dose fixation was made with the help of acute toxicity studies with varying doses in wistar rats. And the result shows that the formulation might be useful in severe gastric ulcer, antiulcerogenic and as well as ulcer healing properties, which might be due to its antisecretory activity. The formulation is non-toxic even at relatively high concentration.

Ramachandran S, et al. (2010) reported development of floating drug delivery system for improving the drug bioavailability by prolongation of gastric residence time of famotidine in stomach. The floating micro balloons were prepared using polymer Eudragit L-100 by solvent evaporation and diffusion technique. The prepared famotidine loaded microspheres were characterized for drug loading, entrapment, encapsulation efficiency, particle size distribution, surface morphology, differential scanning calorimetric, test for buoyancy, in-vitro release and in-vivo antiulcer studies. The results showed an increased drug loading, encapsulation and entrapment efficiency. The thermo gram of the DSC showed that the drug was encapsulated in amorphous form and SEM studies revealed the discrete, spherical shaped spheres with rough surface and presence of holes on floating microspheres due high entrapment of PEG which are responsible for drug release and floating ability. The sizes of spheres were found between 20-120 micron which exhibited prolonged release (In-vitro > 8 h) and remained buoyant for > 10 h. The mean particle size increased and the drug release rate decreased at higher Eudragit L-100 polymer concentration. The in-vivo results showed significant antiulcer property of famotidine loaded microspheres when compared to control and standard group of rats by using pyloric ligation method. The mean volume of gastric secretion, mean pH and mean total acid for formulation treated group was calculated as 3.45+/-0.88 ml, 5.65+/-0.74, and 114.15+/-1.80 mEq/L respectively.

Dr. SoumendraDarbar et al. (2010) reported evaluation of the gastro protective effect of Livina, a polyherbal formulation on ethanol (50%) induced gastric ulcers in mice. Forty young white male Swiss albino mice were divided to five groups (8mice/group). Three case groups received Livina (50, 100, 200 mg/kg) and control negative and positive groups received distilled water and ranitidine respectively. Animals were killed and their stomachs were removed and macroscopic and microscopic ulcer index were determined. Data were subjected to one-way ANOVA followed by Dennett‟s t-test. The results indicated that polyherbal formulation, Livina (50,100,150 mg/kg) significantly decreased the ulcer index ($p< 0.05$) showed an antiulcer effect characterized by reduction of acid volume (AV), free acidity (FA), total acidity (TA), and increasing rate of pH, when compared to the control group. The present findings demonstrate that, Livina has gastro protective effect on ethanol induced gastric ulcer in mice model.

Ch. SanthoshKumari et al. (2010) reported antimicrobial and antiulcer activities of Aloe vera plant extract were evaluated against H. pylori strains. According to several studies, oral consumption of Aloe Vera works effectively to soothe conditions like heartburn, arthritis and rheumatism pain and asthma. Therefore the current study is aimed to evaluate the anti-H. pylori and antiulcer properties of Aloe vera. The antimicrobial activity was detected by using disc diffusion method. In vivo activities were also studied in albino rats by ethanol induced ulcers and the treatment regimens. The results showed that Aloe vera exhibited strong antimicrobial activity against H. pylori at two different concentrations of 250, 500mg/mL in comparison with standard Clarithromycin. In vivo studies showed a very good response in ulcer healing properties. Study found that use of Aloe vera may act as complementary and alternative medicine for gastrointestinal diseases.

HERBAL MEDICINE: MARKET POTENTIAL IN INDIA

In recent times there has been a change in worldwide trend from man-made to herbal medicine, which is also known as „Return to Nature". Medicinal plants have been acknowledged for millennia and are greatly esteemed worldwide as an extreme source of potent medicinal agents for the cure & prevention of diseases. Nature has blessed our motherland with ample treasure of medicinal plants; that is why it has been called as Medicinal Garden of the Earth. Ancient civilizations such as India, South America, and Egypt, China etc. are still using many herbal remedies for the treatment of many ailments. India, in this regard, has a unique and important position in the globe, where numerous recognized and traditional systems of medicine such as Siddha, Ayurveda, Homeopathy, Unani, Naturopathy and Yoga are practiced for the better health care of community. There is no doubt that the herbal medicinal drugs are very much popular among urban and rural Indian community. The basis for their acceptability and popularity results from the minimal/ no adverse effect associated with these natural products. Demand for plant based food supplements, pharmaceuticals, health products, medicines, cosmetics, etc. is growing in developing as well as in developed countries. This is happening because of this increasing recognition that the herbal products have less/ no adverse effects, are non-toxic and easily accessible at reasonable price. Nowadays, interest with plant based medicine is revived due to the increasing awareness of the health risks linked with the reckless use of current allopathic medicines. Moreover, the herbal drug industry is also developing very quickly in the global market. Unfortunately, India is still behind to mark its footprints in international business of herbal industry because lack of scientific approach in herbal drugs. Therefore, in order to open the floodgate for the growth of potential market in India, it is essential to focus on the market potential of herbal medicines.

HERBAL MEDICINE: INDIAN HERBAL TRADE IN WORLD SCENARIO

The consumption of herbal medicines is in vogue and the market is also developing gradually. Indian herbal industry earns about Rs. 2,300 crores as adjacent to the pharmaceutical industry"s yield of Rs. 14,500 crores at a growth rate of 15%. In the last few years, India has been a substantial exporter of herbs and medicinal plants. Moreover, India is the second main manufacturer of castor seeds in the entire world, which produces approximately 125000 tonnes per year.

Standardization of herbal formulations

In general, standardization is defined as a process of developing and implementing standards, based on some consensus, so as to maintain consistency. In other words, it can be said that herbal medicine‟s standardization is the process of setting some standards and parameters for inherent characteristics, to attain an assurance of quality, efficacy, safety and reproducibility. Standardization is used to describe and standardize all the measures which are important to be controlled during manufacturing followed by quality control resulting in a reproducible quality. It also includes the entire field of study from birth of a plant to its clinical application. Furthermore, “evaluation” of a drug refers to its identification followed by its quality and purity determination. It also includes determination of any adulteration. Standardization is undertaken by considering all the important aspects of a plant material, from its collection to its evaluation, including pharmacognostical, phytochemical, qualitative as well as quantitative. It also takes care of microbial load, toxicity, and biological activity.

NEED FOR QUALITY AUDIT AND STANDARDIZATION OF HERBAL FORMULATIONS

1. The standardization techniques and the concept of quality control used earlier were quite different from the techniques developed and used in today‟s scenario.
2. Despite of the previous standardization methods, the evolution in the plants through the dynamic years may have led to changes in the methods of standardization.
3. The availability and supply of authentic raw material has become a big challenge which is mainly due to the high demands as compared to production.
4. Besides evolution, the physical and chemical properties of plants may have undergone change over time and due to changes in environmental factors.
5. Moreover, the variations can occur due to seasonal variation, ecotypic, genotypic and chemotypic variations. Moreover, drying and storage\conditions and the presence of xenobiotic also lead to variations.

Commercialization of plants and their associated products has increased the urgency to standardize them. Moreover, the herbs-associated adverse events observed and reported in developed countries have warranted the requirement for herbal standardization and evaluation of safety and efficacy of medicinal plants and herbal products. Internationally, there has been a revolution in the herbal medicine industry where more utilization of herbal medicines has been observed. It is mainly because of the shortcoming and the dangers associated with the modern medicines. The regulatory authorities must take the responsibility to ensure medication‟s safety, purity, efficacy and potency. The regulatory authorities should strictly follow all standard parameters of quality as prescribed not only for raw materials, but for final products also in formularies, pharmacopoeias and good manufacturing practices imposed by statutory. These measures would reasonably apply to every type of preparation. Although medicinal products are gaining popularity all over the world, the major hurdles in its acceptance are due to absence of a standard profile in terms of quality control. The herbal medicine‟s quality can be ensured by the profile of its constituents, which further ensures its safety and efficacy in the form of final product.

Despite the development of latest analytical techniques to assess the quality of the herbal formulation, it is very difficult to define parameters to control their quality and safety parameters. It is because of the inherent variability and complex nature of the constituents of plant-based preparations. In addition, the constituents responsible for the so-called therapeutic effects are not properly defined. Moreover, they are either unknown or just partially explained. The use of combination of several herbal ingredients commonly used in traditional practices has further complicated it. The variation among batches occurs right from the harvesting/ collection of plant as raw material itself due to lack of any reference/ standard which may help in their identification. These variations are more likely to multiply at the time of storage and processing. Therefore, standardization must include the complete area of study for herbal drugs and their products, i.e. from the cultivation of crude drugs to its clinical application. As plant preparations and herbal remedies obtained from them substantially represent a portion of international market, there is a need to develop nationally as well as internationally recognized guidelines for their quality assessment and quality control.

MICROBIOLOGICAL CONTAMINATION AND ANTI-BACTERIAL TRAITS

Herbal medicines play an important role in healthcare throughout the world and are known to possess antiulcer, antipyretic, anti-diabetic, and even the anti-cancerous activity including the combating potential against an array of clinical complications [1-9]. Besides the advancement in antibiotics, medicinal herbs have long been in use with an objective of managing public health especially in Asia [10]. Together with adverse side effects and toxicity, the emergence of drug-resistant bacteria appears to be a major limitation of using antibiotics. In this context, herbal medicines appeared as alternative source of healthcare management throughout the world, with 21,000 plants currently being used for medication purposes [4]. Indeed, the anti-bacterial features of natural medicines made them as a suitable swap of the synthetic drugs. However, even being advantageous over antibiotics in the aspect of combating against drug-resistant pathogens, conversely herbs may harbor an array of microorganisms, aerobic spores, and the fungal population, which are likely to originate from the soil or may gain access from the manure used in the plantation fields. Also, the method of harvesting herbs, processing and handling, transportation and improper storage and distribution may also impart microbial flaw. Moreover, while a number of study of microbial contamination of the pharmaceutical products have been conducted, the microbiological study on the medicinal herbal products is still in its infancy. Besides, the knowledge on anti-microbial potential of the herbal medicines is needed to correctly interpret the efficacy of the herbal products. Another important aspect of using the herbal medicines underlies on the strategies for the safe application of these products. The evidence-based knowledge on microbiological and pharmacological aspects on herbal medicine may help the operative management of herbs. Being a developing country, availability, cost effectiveness and accuracy of medication are largely required for the overall public health management. Based on these facts, current investigation attempted to measure the prevalence of pathogenic bacteria and fungi in the commonly used products with a time course motif, and further to determine the anti-bacterial traits of the tested herbal medicines.

Estimation of Specific Pathogenic Microorganisms

From the dilutions 10-3 and 10-5, 0.1ml of each sample was spread onto the membrane fecal coliform agar and MacConkey agar (Hi-Media Laboratories Pvt. Ltd., India) for the triplicate enumeration of total fecal coliform (TFC), and coliforms (especially, Escherichia coli and Klebsiella spp.), respectively. Plates were incubated for 24 hours at 44.5°C and 37°C for fecal coliform and coliforms, correspondingly. Likewise, Staphylococcus spp. and actinomycetes were isolated onto Mannitol Salt Agar and Actinomycetes agar (Hi-Media Laboratories Pvt. Ltd., India), respectively by adding 0.1ml of diluted sample each, and all the plates were then incubated at 37°C for 24 hours. Ten (10) ml of sample was transferred into 90ml of selenite cysteine broth (SCB) and alkaline peptone water (APW) for the enrichment of Salmonella, Shigella, and Vibrio spp., respectively and incubated at 37°C for 6 hours. After incubation, the samples were diluted up to 10-6 and then 0.1ml of samples from 10-3 and 10-5 dilutions were spread onto Salmonella-Shigella agar (Hi-Media Laboratories Pvt. Ltd., India) and thiosulfate citrate bile salt sucrose agar (Hi-Media Laboratories Pvt. Ltd., India) for the isolation of Salmonella spp. and Shigella spp., and Vibrio spp., respectively. The plates were incubated at 37°C for 48 hours for the detection of typical colonies. Finally, all the isolates were biochemically examined following standard procedures. All the experiments were done in triplicate.

Assessment of Antibacterial Activity of Herbal Medicine

The antibacterial activity of the samples was detected employing agar well diffusion method. Suspensions (with standard turbidity compared to that of the McFarland standard of 0.5) of each of the test bacteria; i.e., the laboratory strains of Pseudomonas spp., Listeria spp., Bacillus spp., Vibrio spp., Salmonella spp., Klebsiella spp., Staphylococcus spp., E. coli was spread evenly over the Muller Hinton Agar (Hi-Media Laboratories Pvt. Ltd., India) which in turn resulted in the uniform lawns. Wells were made in the Muller Hinton Agar, and 100 µl of each of the samples was then introduced (with a concentration of around 11 mg/ml) separately in the specified well along with a positive control (Gentamicin, 10µg) and a negative control (normal saline). Presence of clear zone around the sample solution (if any) was indicative of the presence of antibacterial activity of the samples tested and the diameter of inhibition zone was recorded.

QUALITY AUDIT/ STANDARDIZATION OF HERBAL FORMULATIONS

Quality control of plant and their materials for efficacy and safety of herbal products is of high importance. Definition of quality is the status of a drug‟s purity, identity, content, or also by the manufacturing process and other physical, chemical, or biological properties. Quality control means a procedure involved to ensure validity as well as quality of a raw material or a finished product. For traditional medicines, the information related to quality control is procured and studied. They are then transformed into assessment strategy under two headings, i.e., quality and identity. According to the guidelines, all the medicines of either origin, i.e., plant or synthetic, need to fulfill the criteria set for safety, quality, identity and efficacy. This can be achieved through suitable clinical trials which are conducted by following a randomized study or a double-blind placebo-controlled, multi-center study. In medicine, natural products consist of a wide variety of raw materials which make definitions important clear.

Quality criteria are formed on the basis of clear scientific definitions of raw material. For example herbal drugs mean plants or parts of the plants that are converted into phyto-pharmaceuticals through simple processes which involve harvesting, drying, and storage. They are therefore capable of any variation. This quality of variability is due to differences in time of harvesting, geographical location, and growth. In addition, this definition includes some other crude plant based products with no properties of plant, i.e., no organic structure, such as fatty oils, essential oils, gums, and resins. Isolated or derived constituents obtained after processing the crude material such as extracts or isolated purified compounds obtained after fractionation of extracts are not included in this definition. Combinations with chemically isolated constituents or synthesized active substances are not considered as herbal medicines.

Quality control mainly focuses on the following:

► Identity: Can we identify the herb?

► Purity: Is there any contaminant?

► Assay: Is the quantity of phytoconstituents present in the plant within the defined limits?

Assessment of the content is one of the most tedious tasks, especially when the phyto constituency of plant is not revealed. It has been reported that phyto-markers are sometimes considered to be important for assessment of quality control. Such an assessment does not involve the assessment of any therapeutic activity. Criteria such as physicochemical parameters, type of extraction, organoleptic properties, presence of adulteration, presence of moisture content, solvent residues and soluble as well as insoluble ash content is required to be checked to prove purity as well to identify the plant. The accurate identity of the botanical quality or crude herbal material is of major importance to standardize a herbal drug. Macroscopic and histological examinations help to achieve identity. Voucher specimens are the reference sources which are reliable. Outbreak of diseases in plants may change the morphology of the plant which can be a reason of incorrect identification. This can be followed by an incorrect botanical quality determination which subsequently affects the labeling. A well-known example of Paraguay Tea which is a New York (South American) product is attributed to such change. 24 Purity is said to be closely attached to the safe use of drugs. It also deals with such factors as contaminants, ash values and heavy metals. By application of improved analytical methods, the plant or its material can be evaluated in terms of purity and can assess whether the plant consists of microbial aflatoxins, adulteration, pesticide residues, and radioactivity. Analytical methods viz. gas chromatography (GC), high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and photometric analysis can also be used for establishing constant composition of herbal preparations. It depends on if the active constituents of the preparation are known or unknown, various concepts like normalization versus standardization must be applied to establish relevant criteria to attain uniformity.

To perform assay or content is one of the most complicated areas of quality control. Since the active constituents in most herbal drugs are not known. Markers can sometimes be used. The cases, where no marker or active constituent can be defined the percentage of extractable matter along with a solvent can be used in the form of assay which is an approach that is often observed in pharmacopeias. The nature and type of the compounds which are involved

affects the choice of extracting solvent. Such information can be extracted from the traditional guides. A hot tea is a suitable example for this. In such cases, the extraction is carried out in hot water so as to obtain the extract. By steam distillation a special form of assay can determine essential oils. When the markers, for example alkylamides in Echinacea or active constituents for examples sennosides in Senna plant, are known, there are a number of modern chemical analytical techniques such as TLC, UV/VIS, GC, HPLC, a combination of GC, mass spectrometry (MS) and MS (GC/MS), which can be used.

There are numerous problems which do not apply to synthetic drugs, but still influence the quality of herbal drugs:

- Herbal drugs mainly consist of mixtures of several phyto-constituents.
- In many cases the novel phyto-active principles are unknown.
- Reference compounds or selective analytical methods are not accessible commercially to all researchers.
- Chemical nature of plants and their materials are variable.
- Chemically, the variuous cultivars and varieties of plant are available or do exist.
- The quality and source of the raw material also exhibit variation.
- The harvesting, drying, storing, transporting, and processing techniques such as mode of extraction, use of solvent, instability of constituents and polarity of the extracting solvent etc. also affect the amount of phyto constituents.

There should be some strict guidelines which must be followed to produce a quality herbal drug successfully. Proper botanical identification, standardization, and phytochemical screening are among them. The standardization and quality control of herbal medicines consists of many steps. The raw materials, in terms of quality and source, the manufacturing processes and the quality of agricultural practices are the essential steps to be taken to assess and determine quality control of herbs and their finished products such as medicines. They play a vital role in authenticating a plant in terms of its stability and quality. The quality of a plant material is confirmed by the existing conditions during growth. Accepted Good Agricultural Practices (GAP) can too have a control on it. These consist of seed selection, use of fertilizers, harvesting and growth conditions. Moreover, drying and storage also play an important role. GAP procedures have been considered as a vital component of control quality. There are many important factors such the plant part used, collected, the plant‟s age, time of harvesting and method of collection, the plant‟s exposure to light, temperature at which plant was processed, irrigation facilities, drying processes, quality and quantity of nutrients expected in plants, packing methods, storage conditions and transportation mediums of raw materials. All these factors highly influence the therapeutic value, purity and quality of herbal medicines. Besides, there are many other factors such as microbial contamination, extraction procedure, and use of pesticides and presence of heavy metals. All these factors are responsible for changing efficacy, quality, and safety of herbal drugs. In place, the plant/ plant material of interest is obtained from wild source and hence are cultivated in controlled conditions; many of such factors are avoidable and can be omitted from assessment. The active principles are sometimes destroyed by enzymatic processes which persist for long periods starting from collection till marketing and results in a variation of the composition. Therefore proper quality control and standardization of herbal

preparations & raw material should be done. Standardization includes adjustment of the herbal drug preparation with a defined content of a constituent or with a group of substances having already known therapeutic activity by mixing herbal drugs or by adding excipients to it or herbal drug preparations. Botanical extracts that are directly derived from crude plant material depict substantial variation in quality, therapeutic effects, and composition. The standardized extracts are those high-quality extracts which contain stable level of specified compounds. These compounds are subjected to strict quality controls during every phase whether its growth, harvesting, or manufacturing processes. Standardization as a result may have many different meanings; no regulatory definition do exists in order to standardize dietary supplements. Some of the manufacturers may use this term standardization in a wrong way to refer to manufacturing practices that are uniform. If a recipe is followed, a product cannot be termed as standardized. Hence, if the term "standardized" is present on the label of a supplement, one cannot be assured product‟s quality. For standardization and analytical purposes, marker substances need to be established, if the active principles are known. Marker substances can be defined as the constituents with defined chemicals thus helps in ensuring purity, and quality of the finished product.

Ginkgo is a classic example having 6% terpenes and 26% ginkgo flavones. These products are no longer represents the whole herb and highly concentrated. Now they considered as phyto-pharmaceuticals. They are in many cases for more effective than the whole herb. The process however may cause loss of efficacy and adverse effects, in some cases herb–drug interactions may also rise. The second type of standardization depends on a specific percentage of markers present in compounds and guaranteed for manufacturers. These do not indicate quality or therapeutic activity of the plant. In preparation of herb based drug, the primary processing as well as production of the herbal drug or medicinal plant has a big impact on the quality of the active pharmaceutical ingredients. Since naturally growing medicinal plants are inherently complex and simple analytical techniques which are used to identify and characterize the active constituents individually by biological or chemical means are available in a limit an adequate quality assurance system is the need of the hour. Such assurance is also necessary during cultivation, primary processing, harvesting, handling, storage, packaging, and distribution. Contamination and deterioration through adulteration, particularly through microbial contamination, may occur at of these stages. Therefore, for herbal starting materials, it is very important to set up manufacturing, harvesting, and good agricultural practices to reduce such undesirable factors to the maximum. Therefore the processors, producers, and the traders of herbal drugs or medicinal plants have a role to play. Adequate manufacturing practices and strict standards to control the quality should be adhered to by the manufacturers and the suppliers of the herbal drugs. Lately, only a few manufacturers follow complete good manufacturing and quality control procedures through physical, microscopic, biological and chemical analysis. The organization like Health Canada has helped to safeguard health of Canada by conducting premarket reviews of every drug only after that may be authorized for sale. Also the products which are available in the market are regularly analyzed to ensure that they do not have any unsafe ingredients. It also ensures that the products must really possess the ingredients which are indicated on the labels. The quality and potency of an individual herbal product may not be clear due

to lack of regulation. For a given plant product it is obvious that the conditions prevailing during the growth cycle of the plant also determine its quality. For cultivated plants therefore, the GAP system has been introduced, in which at every step, a set of criteria has to be adhered. These steps include selection of seeds, conditions of growth, use of fertilizers, optimization time of harvesting, harvesting, and drying. GAP procedures are likely to become an inseparable part of quality control in future.

CONCLUSION

The herbal plants are being used as medicines since ages. Due to advancements and keep interest of scientists in exploring the therapeutic potential of herbals, the plants have been combined so as to impart synergistic effects or multiple effects. Since then, the herbal formulations have gained importance. The major positive point associated with such formulations is their high efficacy as well as the minimal adverse effects associated with their use. However, the variation associated with the growth and development of the plants, with respect to their geographical, climatic, harvesting, irrigation variations, also affect the quality, efficacy and safety related to plants. Therefore, there is a need to standardize the plants as well as the formulations prepared by using their combinations. Standardization of plant material involves comprehensive quality audit of the plant from its collection to its pharmacological evaluation. The present study was an initiative to standardize four commonly used herbal formulations (Ashokarishta, Sitopaladichurna, Chandraprabhavati and Punarnavadimandur). The present study is the first study conducted to standardize these marketed preparations. It may be used as a standardizing tool for the future prospective as well as by researchers willing to work on the same formulations. This study also forms the basis for the niche researchers to extend the work on these formulations and work to explore their pharmacological potential. Our study concludes the all the formulations were safe as there was no radioactive agents found in them. Moreover, the formulations contained heavy metals, but were found within limits. The pesticidal residue was also found within permissible limits. All the herbal formulations did not show any microbial contamination. The formulations also possessed anti-inflammatory activity as shown by Chandraprabhavati at Dhanwantari brand, Punarnavadimandoor at Zandu, SitopaladiChurna at Dhanwantari and Ashokarishta at Dabur brand. The Indian herbal industry is growing in a tremendous rate. With the tremendous increase in traditional herbal therapy several concerns regarding the safety and quality of herbal medicines have also been observed. There is need for more advanced techniques of standardization. The advancement of analytical techniques will serve as a rapid and specific tool in the herbal research, thereby, allowing the manufacturers to set quality standards and specifications so as to seek marketing approval from regulatory authorities for therapeutic efficacy, safety and shelf- life of herbal drugs.

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