Review Paper:

Technical Problems, Regulatory and Market Challenges in Bringing Herbal Drug into Mainstream of Modern Medicinal Practices

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Abstract

Awareness of people towards potentiality and lethal effect of modern and synthetic drugs has increased the interest towards herbal drugs. Herbal drugs have always proven their effectiveness in the treatment of severe diseases from the period of ancient civilizations. People believe in herbal drugs as a primary remedy for ailments instead of synthetic drugs. In recent years, the revival of herbal drugs has been observed due to lack of efficient modern therapies, issue of chronic diseases, side effect of chemical drugs, the resistance of microbes against a number of synthetic drugs and a big investment in drug discovery and development. In spite of huge benefit in healing diseases and less side-effect, herbal medicines are not key players in the current medical practices on a wide range as compared to allopathic medicines.

In this review, we have highlighted and discussed the problems in herbal formulation development, regulatory and commercialization of herbal drugs and suggested possible solutions to bring up them into the mainstream of contemporary medical practices and healthcare.

Keywords: Herbal drugs, phytochemicals, side-effects, formulation, drug market, regulatory.

Introduction

Plants contain a number of molecular products having a different level of bioactivities that providing new drugs as well as the new lead for drug development against a range of diseases. The definition "herbal medicine", "traditional herbal medicine", or "phytomedicine" is the utilization of plant part e.g. roots, stems, leaves, bark, fruits, berries, or seeds for therapeutic purposes as described by World Health Organization (WHO) in 2005[114,73]. The world has a flowering plant diversity of 2.5 lakh species and only 1-2% of tropical species have been identified as plants with medicinal value.

Herbal drugs are highly effective with less side-effect, and are compatible with human physiology; still, they are not in the mainstream of the medicinal practices like modern synthetic drugs.[48,53,109]. The total revenue market of the herbal drug is 50.9 billion USD, very less as compared to the synthetic drug which was 934.8 billion USD in the year 2017[3,66].

Countries like Russia, Germany and Britain have separate pharmacopeias indicating medicinal plant with efficient druggability. Each pharmacopeia has its own unique herbal nomenclature system, description and formulation development technique[41]. More than 85 percent of people living in Asia, Africa, America and Middle-East are directly dependent on traditional medicine due its unique value and place in cultural belief and ethnomedicinal aspect. Although many textbooks and manuscripts of traditional medicine have not been accurately translated and their interpretation is not still revealed inherited from one generation to other verbally[22].

It has been reported that approximately 8000 plant species are used as ethnomedicine and 25000 formulations have been developed by such ethnic communities which need to be identified, verified and documented [5,93]. Highly extensive experience of traditional medicine practices can be very much useful in developing new lead for therapeutic purpose. Medical professionals and pharmaceutical companies have shown little interest in herbal medicine development due to technical as well as financial challenges and constraints like complicated process of formulation development, quality control, safety, efficacy, marketing, and regulatory guidelines. This situation becomes financial burden for low economy and underdeveloped countries[88]. In this review, we have addressed the opportunities and challenges associated with herbal drug development and its commercialization together with future scope of research possibilities.

Survey of Literature

A detailed literature survey was done by exploring the databases of PubMed, Mendeley, Springer Nature, Sciencedirect and other reputed websites. Textbooks and other literature sources were also searched for the relevant data and information. The keywords herbal drugs, phytochemicals, side-effects, formulation, drug market were used for the articles published.

Some important medicinal plants with therapeutic values:

After the landmark publication of George Watt[32], the identification and documentation of plant species are

continued with an objective to identify plant of medicinal and economic value. Some of the important plant species having medicinal value are given in the table 1.

Phytochemicals and their biological activities: Biological activity is the significant or side effect of any drug or bio compound on the living. Such activities depend on the amount dose. Phytochemicals are highly efficient in their biological activities and are extracted from plants and examined for a wide range of biological activities against pathogens and diseases. Some of the biological activities of major classes of phytochemicals are given in the table 2.

Market Value of Herbal drug

Herbal medicines have attracted the people globally due to its health benefits, less side effective medicines which are economical in many countries as compared to modern synthetic drugs. Increasing awareness among consumers, guidelines of current Good Manufacturing Practices (GMP) provided by FDA (Food and Drug Administration), the expensive budget of modern medicines and less or no side effect are the market-driven forces that extended the global market for the herbal medicines. China and India are the largest producers of herbal medicinal plants in the world. France is the largest producer of herbal medicines followed by Germany in the European region.

Table 1
Therapeutic activities of some medicinal plants

S.N.	Plants	Therapeutic Effect
1.	Tulsi *(Ocimum sanctum)*	Pyrexia bronchitis, rheumatism, blood-related disorder, epilepsy, asthma, cough, skin, parasitic infection, neuralgia, headache, inflammation, wounds, antipyretic, anti-inflammatory, anti-inflammatory activity, antifungal, antihypoxic and immunomodulatory, metabolic, radioprotective, anticoagulant, anticancerous and anti-diabetic.[1,20,47,50,57,75,86,90,95,102,105,106,108,111]
2.	Aloe Vera *(Aloe barbadensis)*	Abrasion and skin burns, herpes simplex virus (HSV), gingivitis, hemostatic, antiulcer, anti-septic, antibacterial, anti-inflammatory, antioxidant, hypoglycemic and anticancerous.[4,11,19,24,35,39,55,56,77,80,96,115]
3.	Neem (*Azadirachta indica)*	Antibacterial, antifungal, antipyretic, diuretic, antimalarial, immunomodulatory, antiulcer, antidiabetic, anticancer, hypoglycemic, and regeneration of β-cells.[5,8,15,23,32,36,65,69,92,100,112,117]
4.	Haridra *(Curcuma longa)*	Antibacterial, antifungal, antiviral, anti-inflammatory, anticancerous and hypoglycemic.[9,44,52,54,61,109]
5.	Ashwagandha *(Withania somnifera)*	Anti-stress activity, anti-cancerous, Parkinson's diseases, Alzheimer's diseases, Huntington's diseases, neuro atrophy and synaptic loss.[10,103]
6.	Guggulu *(Cammiphora wightii)*	Obesity, gout, rheumatism, inflammation, cardioprotective and restoring fertility.[7,17,101,113]
7.	Brahmi *(Centella asiatica)*	Improving mental power, memory, reduces stress, anxiety, depression, increase mental and social skill in children suffering from autism, anti-ulcer activity, wound healing property, cardio protective and neuro protective activities.[25,84]
8.	Amla *(Emblica offinalis)*	Immunity enhancer, antidiabetic, cardiovascular disorder, eye-defect, hypertension, anemia, improvement of mental disorder, antioxidant, skin diseases, promotes healthier hair, diarrhea and dental problems.[14,34]
9.	Bhringraj (*Eclipta prostrate)*	Hepatic disorders, antidiabetic, anticancer, antioxidant, anti-inflammatory, analgesic, and anti-depressant.[42,59]
10.	Jatamansi (*Nardostachys jatamansi*)	Antifungal, hepatotoxicity, Neurotoxicity, diabetes, Parkinson's diseases, antioxidant, hypertension and diabetes.[91,99]
11.	Bael (*Aegle marmelos*)	Antipyretic, anti-inflammatory, analgesic, antidiabetic, antilipidemic, antiviral, cardioprotective, radioprotective and chemoprotective.[2,13,71]
12.	Sarpgandha (*Rauwolfia serpentine*)	Hypertension, migraine, hypertension, anxiety, autism, acute hallucination, arginine pectoris in coronary heart disease and breast cancer.[63]
14.	Datura *(Datura stramonium)*	Inflammation, wounds, ulcers, rheumatism, bronchitis, gout treating bronchitis, epilepsy, microbial infections and anticancerous.[30]
15.	Black Pepper *(Piper nigram)*	Antioxidant, enzyme stimulation, growth stimulation, immunoregulation, anti-asthmatic, anti-tumor, antibacterial and analgesic.[107]
17.	Sanjeevani (*Selaginellacae bryopteris)*	Heat-stroke, jaundice, irregular menstruation, anti-stress cell death, anti-bacterial, and anti-protozoan, relief from heat stroke and the, memory enhancement, anti-hyperglycemic activity, stomach-ache, anti-depression activity, growth promoter and protective against oxidative stress and UV rays to the cell under apoptosis.[87]

In Middle-East, Saudi Arab and UAE are the global leaders in herbal medicines production. Due to the poor economy and unstable political situation, Africa still lags behind in herbal medicine production globally[13]. It has been estimated that the global market of herbal medicine will reach up to 5 trillion US dollar in 2050 from 60 billion US dollar in 2010[109].

The global herbal pharmaceutical companies leading in this sector and growing vastly are Himalaya Drug Company, India, Shen Chang Pharmaceutical Company, China, Schwabe, Germany, Arkopharman, France, Madaus, Spain, Zandu Pharma, India, Dabur, India, Hamdard Laboratories, India, Blackmores, Australia, Tsumara, Japan, Patanjali Ayurveda, India, Nutraceutical International, USA and China Herbs Company, USA. The global herbal market is governed by big pharmaceutical firms and small pharma industry and the market becomes highly competitive and fragmented. The multinational big firms are extending their business into developing countries and continuously making pressure on regional or indigenous herbal companies on the issue of product portfolios, quality and price.

There is huge competition and in the future this will become more intense. Big firms are focusing on the quality of the product and advancement in the technology such as extraction techniques and purification protocols to ensure the better quality needed for the growth of herbal medicine in the market. Some challenges like fragile regulatory and authorities regarding quality control and patent laws, lack of institutes that provide a high quality and therapeutic knowledge which arises due to lack of high level of research evidence that inhibit the growth of herbal medicine market[26,78,97].

Problem and Challenges in herbal drug development

Formulation Development: Formulation development is a methodological approach to combine the active ingredients and inactive parts known as excipient, filler or matrix. The formulation in the herbal drug is divided into two categories, pure herbal formulations and another composed of minerals, bio compounds, metallic with the herbal drug. Minerals are added in drug formulations to show their therapeutic effect. In Ayurveda, herbal formulation is prepared into two ways-use of a single drug for developing formulations or more than one drug constituents which are also known as a polyherbal formulation (PHF). It is important to note that the bio compound present in minute quantity is not much sufficient to show the desired therapeutic effect and single drugs are less effective compared to a combination of drugs obtained from different plant species.

The drug when combined with other drug constituents shows a better therapeutic effect. This is known as synergism. This positive drug-drug interaction is predominant in polyherbal formulations and works in two synergistic approaches-pharmacokinetic and pharmacodynamic mechanism. The pharmacokinetic synergistic approach is the capacity of the herbal drug to promote ADME (absorption, distribution, metabolism, and excretion) of another drug while pharmacodynamics approaches deal with the therapeutic effect of active ingredients in polyherbal drugs on similar cell receptor[49,94].

Table 2
Biological Activities of Phytocompounds

S.N.	Phytochemicals	Classification	Biological Activity
1.	Carotenoids, Polyphenols, Curcumin, Flavonoids	Anticancerous	Inhibitors of the tumor inhibited the development of lung cancer, anti-metastatic activity[97]
2.	Polyphenol compounds, flavonoids, carotenoids, tocopherols, ascorbic acid	Antioxidants	Inhibition of lipid peroxidation oxygen free radical quenching[121]
3.	Reductive acids, tocopherols, phenols, indoles, aromatic isothiocyanates, coumarins, flavones, carotenoids, retinoids, cyanates, phytosterols	Detoxifiers	Inhibitors of pro-carcinogen activation, inducers of drug binding of carcinogens, inhibitors of tumorigenesis[81]
4.	Terpenoids, alkaloids, phenolics	Antibacterial & Antifungal	Inhibitors of microorganisms, reduce the risk of fungal infection[28,81]
5.	Alkaloids, terpenoids, volatile flavour compounds, biogenic amines	Neuroprotective and chemo preventive	Brain disorder and Neuropharmacological agents anti- oxidants, cancer chemoprevention[12,79,85]
6.	Cellulose, hemicellulose, gums, mucilages, pectins, lignins	NSA (Non-starch polysaccharides.)	Water holding capacity, delay in nutrient absorption, binding toxins, and bile acids[43,64]
7.	Terpenoids, alkaloids, phenolics	Antidiabetic	Inhibition of α-glycosidase, inhibition of pancreatic α-amylase, inhibition of PTT1B[7,8,26,70,83,94,118]

Research reports suggested that polyherbal formulations based drugs like diabetes, diabrid, diasulin are much effective as compared to allopathic drugs like tolbutamide, gliclazide which have a narrow therapeutic window. Such polyherbal drugs like diakyur showed no toxic effect even at a high dose of 12800mg/kg. Hence, the polyherbal drugs are effective, safe, eco-friendly as well as economical as compared to modern allopathic medicines specially in rural areas and people belong to low economy countries[17,46,86].

Polyherbal drugs have high efficacy but they are not safe at all time. In recent years polyherbal drugs are taken concurrently with allopathic drugs sometimes resulting in organ toxicity as their safety studies are not done and the drug was thoroughly administered[121]. Even after implementing the standardization, enhancement in reproducibility of the drug in each batch is still a big issue to solve. Batch to batch difference in quality of the formulations is highly affected by a number of factors like geographical locations, climate, habitat, soil types, techniques of cultivation, harvesting, collection of raw material and storage, processing, manufacturing and packaging of drugs leads to variations in quality and poor reproducibility of the formulations[112].

Presence of heavy metals in the formulations and its control is another big challenge[24]. Failure in implementations of WHO guidelines in developing formulations creates loop-hole to adulteration, contamination and poor formulation practices. Hence, for a simple, efficient and economical dosage that is free from all these problems, it is necessary to know appropriate knowledge of proprietaries. Selection of suitable excipients and other ingredients in definite proportions is much essential based on their chemical, physical and mechanical properties to overcome this problem and challenges.

As per WHO guidelines, ingredients of a respective drug formulation must protect, support and enhance stability, bioavailability or patient acceptability [46]. The role of excipient in drug development is also crucial as the excipient provides a successful pathway for ease of administration via providing suitable volume, weight, and consistency. In Ayurveda, an excipient in the formulation not only acts as inert material but also takes part in successful pharmacological action of the drug. Lethal effects of synthetic excipient industries have focused on natural polymers due to their non-toxic behavior, economical, potentiality, biodegradable and biocompatible nature.

Herbal formulations include the main ingredients, bio enhancer, supportive ingredients, binders, synergistic, sweeteners, colouring and flavoring agents. Bio enhancers are the components that are responsible for the increase in the bioavailability and absorption of the drug. Cow urine, water, honey, shunthi, marich, pippali are established bioehnacers while agar, starch, guar gums, xanthan gum, gelatin, acacia and cellulose are widely used as binders, colloidal, gelling agents. In current herbal drug manufacturing practices, dosage manufactured are divided into the categories- solid dosage form (Gutika or churna), semi-solid dosage form (Avleha and ghrita) and liquid dosage from (Asava, arista, and Taila)[46].

Stability of Herbal Drug: Stability studies are essential for the herbal drug compound. This is carried out to evaluate the effect of oxidation, temperature, humidity, radiations on the natural products[90]. Herbal drugs are prone to degradation if stored for a long time under the influence of all these factors. Hence, a drug is invalidated in a clinical trial when it is unstable or its ingredients are degraded. During the manufacturing process, the active components are under the exposure of hydrolysis, oxidation, a bacterial or fungal attack which causes severe problem to the stability of the products[8]. The variation in the shelf life of herbal drug formulation should not increase more than ± 5 % of the primary assay value[61].

Stability testing guidelines were also drafted by the FDA in suitable analytical methods and protocol must be applied to check impurities in the formulations. It is essential to execute non-biased identification and quantitative analysis of all the active compounds in the herbal drug formulations. Spectroscopic technique such as FTIR integrated with chemometric data can provide a total metabolic finger point profile of herbal formulations[123,124].

Insufficient pharmacokinetic information of herbal drugs: Pharmacokinetic and pharmacodynamics studies of herbal drug are not fully studied and only few of them were reported for their ADME including curcumin, ginseng, gingko, ginger etc.[83] Most of the phytocompounds undergo phase I and or/ phase II metabolism under *in-vivo* study.

The limited knowledge of ADME and pharmacokinetics of the herbal drug is due to the lack of information about the active compound and very little concentration in systemic circulation which is much difficult to measure. As the herbal drugs are highly effective in chronic disease and other ailments, a better understanding of their pharmacokinetic is necessary to control the amount of dose and ADME to control the concentration at the targeted site and a therapeutic effect is achieved [63].

Efficacy, Bioavailability, Toxicity, and Safety of Herbal drug: Efficacy of herbal drug is defined as the ability to produce a therapeutic effect. Herbal drugs have been reported to be highly efficacious for certain notable conditions. Due to lack of studies and research by scientific communities, efficacy of most of the herbal drug is not reported. This may be due to the poor pharmacokinetic window, lack of commercial interest and patent production. As per law, herbal medicines do not come under any formal obligation to test the efficacy. There is no such generalization made on available data of the therapeutic value of herbal drugs.

Hence, as the proper efficacy of the herbal drug is unknown, medical professionals do not prefer to write herbal remedies for the disease[30]. While discussing the toxicity, it is a common perception that natural drug has no adverse effect but based on the clinical evidence, it has been reported that natural drugs have the lethal effect. Chamomile tea has shown an adverse effect which was used to treat colic. Infant deaths were reported on ingestion of pyrrolizidine, an alkaloid obtained from *Symphytum officinale*. *Tripterygium wilfordii* contains highly toxic diterpenoids epoxide that causes apoptosis leading to kidney damage[16].

The problem of acute neuropathy arises when *Averrhoa carambola* is ingested that contains a high amount of oxalate. Plants like *Guaiacum officinale* and *Arctostaphylos uva-ursi* may cause stone formation. Inhibition of mitochondrial ATP synthesis is caused by *Cellilpis laureola* while *Ephedra sinica* causes renin-angiotensin-aldosterone system abonarmalities.

One of the important anti-diabetic medicinal plants *Glycyrrhiza glabra* and *Harpaphytum procumbens* affects renal fluid transport. Medicinal plants such as liquorice, isapghul, ginseng, gingko, St. John;s wort, *Senna, Silybum marianum, Sassafras, Ephedra, Aloe vera, Alfa-Alfa, aconite* which are widely used as plant medicine contain toxic ingredients and have adverse effect on the human body and side effect increases as the production and sale of drugs are uncontrolled or unregulated and consumers have not been informed properly about their adverse effects[75]. Advocating issues for the herbal medicine with false slogan and propaganda that herbal medicine has no side effect, can mislead people from the actual information and knowledge as herbal medicines are not completely safe at all[30,112].

Clinical trial and ethics with herbal drugs: Due to this surge in the global market, it has become mandatory to prove their efficacy, toxicity level, and safety before entering into the market [77]. According to WHO, 'herbal drug' should be regarded as "finished, labeled, medicinal products that contain an active ingredient aerial or underground part of the plant material, or combinations thereof whether in the crude state or as plant preparations" which also strictly advocates the importance of clinical trials to ensure its efficacy and safety before entering into market. For the large scale endorsement as well as survival at the international market and obey WHO guidelines, a clinical trial is much essential to compete with modern medicines[123].

Being one of the largest pharmaceutical markets in the world, clinical trial in India is one of the most challenging and problematic parts of the drug development process. There are certain drawbacks in rules and regulations for clinical trials which create a major problem for new drug formulations entering into the herbal drug market. Clinical trials are one of the highly ordered and regulated enterprises that comply with the ethical code of conduct and requirements[77,114].

Quality Control, Laws and Regulatory Affairs: Impurities, degradation of active ingredients, moisture and temperature affect the quality of the drugs and its efficacy. Hence, it is mandatory to ensure control over the quality of the product in the market. The well-structured, well-maintained specifications ensure the qualities of the products. Official pharmacopeias, monographs, handbooks, and guidelines by the drug control authorities ensure the quality control of the herbal. Various analytical techniques can be used to check the quality of the herbal drug by determining the identification and percentage of ingredients, their efficacy, safety and toxicity level time to time[119].

As per the WHO information, 80% of the people in the world depend on the herbal drug for their primary healthcare and the herbal drugs are not completely regulated and controlled by the states. There is a huge difference between people living in developed countries and developing countries in terms of herbal drug consumption. Such a vast difference leads to the regulation of herbal drug with consolidation and objectives of good manufacturing practices (GMP) and good clinical practices (GCP) [124]. For this, there is an equal weightage given to the modern system of medicine and traditional system of medicine and they have been included in national health schemes by the respective governments in developing countries having rich biodiversity of herbal medicinal plants.

For herbal drug manufacturers and industries and marketer, it becomes mandatory to be certified by the local drug regulatory authority. In 1997, WHO declared that it is the duty of manufacturer as well as the regulatory authority to check the quality standard of the drugs. Regulatory authorities should be responsible for quality assurance, evaluation of experimental, dossiers and post-marketing compliances of the products as per GMP standards. Hence, it is the regulatory to ensure good agriculture and collection practices (GACP)[123].

Indian drug manufacturers have their market in the USA, European Union, Middle-East, Africa and South-East Asia. In USA drug market Indian herbal drugs are sold and marketed as per dietary supplement herb and education act 1994 and this act states that there is no need for efficacy and safety data for market approval. Also, manufacturers do not need to get from food and drug (FDA) the power to take action again any harmful herbal drug. Indian manufacturers prefer to sell their drug under the dietary supplementary act which does not require any scientific evidence.

But in European Union, as per the traditional herbal medicinal product directive (2004/24/EC) manufacture has to submit the preclinical safety data, bibliographic evidence including quantitative and qualitative data of ingredients, amount of ingredients, therapeutic indications, adverse reaction, posology, route of administration and contraindications as per article (8(3) a to h, i, j and k) for marketing authorization[100]. An insufficient regulatory

guideline is crucial for the development of the quality product for herbal drug manufacturers.

Most of the herbal drug manufacturers are not aware of the National Medicinal Plant Board Guidelines regarding good agricultural and collection practices (GACP) together with good storage practices in accordance with WHO guidelines. Industries and associations who know the guidelines, consider these impractical to implement, hence show no interest due to lack of education and awareness among the growers and also subsequent operational cost and other financial issues. Supply of standardized and certified raw material for a quality product is also a big issue and there is always a need for more expanded and elaborated guidelines for raw materials. Good manufacturing practices always advocate that the raw material must be free from adulteration, contamination, personnel, and role of an independent body for quality assurance and forge documentation.

Problem and challenges in marketing and commercialization of herbal drugs

Standardization of raw materials: As far as the quality of the herbal drug is concerned, standardization is a major problem for the Indian herbal industry. Most of the herbal drug industries have complained about the problem in the collection and authentication of raw material and facing the problem of adulteration in it. It is a common fact that herbal plants are prone to contamination during harvesting, collection, and processing. Heavy metal contamination is another problem which is identified in each step from collection to manufacturing[100].

Microbial contamination is also a serious issue as they degrade the active ingredients and reduce the quality of the herbal product. To resolve these problems, marker-based analysis such as taxonomic, genomic, chemical and proteomics is applied but these processes are too much expensive and time-consuming and most of the herbal manufacturers in India are small and middle scale industries and they cannot afford such expensive techniques. Also, GMP-based regulations in India have no guidelines for marker-based identification for standardization of raw materials [8,123].

Insufficient Regulatory Guidance: The herbal industry is also facing a lack of sufficient regulatory guidance regarding quality issues, good agricultural and collection practices as well as good and storage practices. In 2009 GACP was developed that complied with WHO standard but most of the manufacturers are not well aware of these guidelines. Herbal firms have advocated for an elaborated explanation of these guidelines [39].

Implementation of Drug and Cosmetic act (DCA) regulations, clinical trials and ethics: Since its formation drug and cosmetic act has not been implemented successfully and strictly for herbal drug production and marketing. According to the survey report, only 107 out of 150 companies have good manufacturing (GMP) compliances although DCA has made it compulsory since 2006. Due to some contradiction between State Food and Drug Administration (SFDA) and DCA drug which is not permitted in one State, allowed manufacturing in another State. Also, the difference in the timeline for drug registration across the States creates a problem for the herbal drug manufacturer. It has been noticed that most of the herbal drug company have not to deal with safety concern of herbal drug and only a few of them have conducted a clinical trial in various medical colleges and research centers across the country. There are no compliances and harmonization between different regulatory authorities and this creates a problem for the market expansion and capital investment due to the difference in their regulations[34,118].

Awareness for Government schemes and supports: Small and medium scale industries have an important share in the herbal drug market and these industries and entrepreneurs are not aware of the schemes and support of Government to promote herbal drug industries in the country. India is lacking in quality control and good agricultural and collection practices due to lack of education and awareness. Growers are not well educated and aware of GACP. Also, industries and associations are not interested to provide education and necessary information as this needs operational cost, proper management and time. Proper branding and broadcasting of herbal drug via print and electronic media to medical professionals and common people are also challenging tasks to increase the sales of the goods and generation of revenue [100,123].

Discussion

The popularity of herbal drugs is increasing day by day due to its high efficacy, safety, and synergistic effect. Dealing with stability of herbal formulation is a key challenge to the herbal drug as stability decides its quality and efficacy. Novel methods like the use of suspension, biodegradable cellulose, therapeutic proteins, nanoparticles and emulsifiers to stabilize the drug formulation can be highly efficient for instability of drugs. Prevention of drug from degradation due to environmental factor is also a major concern while dealing with drug stability. For stability of drug, proper guidelines must be followed that include packaging and container. Study of pharmacokinetics and ADME is essential to ensure the efficacy, toxicity and safety profile of herbal drug as side effect and toxicity of the herbal drug is reported including kidney damage, stone formation, acute neuropathy, and infant deaths. Together with clinical trials and ethics, the major part of herbal drug development that validates its efficacy, safety, and toxicity level. Such validation is mandatory to survive in the international drug market and to compete with modern allopathic medicines.

Objectives of a clinical trial, protocol, and procedure must be known to the subject and investigator and informed consent must be generated in this respect. Regulations for

the herbal drug quality and safety standards by competent authority are much essential for the herbal drug manufacturer to maintain the quality of their products. Due to insufficient guidelines in regulations, herbal manufacturer and industries and growers are unaware of good agriculture and collection practices (GACP) as well as good storage practices.

It is important to note that only those herbal drugs who comply with international guidelines and GACP standards can get the opportunity of growth and establishment in the international market. Commercialization and marketing of the herbal drug in this modern drug era are the most challenging and difficult tasks due to loopholes and drawbacks in quality production, standardization, and business law and regulatory.

Indian herbal drug market is facing the problem of poor quality of raw material, microbial contamination and heavy metal accumulation in each step from its cultivation to manufacturing. Such problems hinder the growth of the herbal market and poor quality and contaminated drugs are restricted by the FDA from the international market. There is a continuous process of herbal drug manufacturing as per WHO guidelines to implement GACP and GMP to ensure the standard and quality of herbal medicines.

Proper implementation of drug controlled authorities regulations by establishment harmonization is prerequisite to avoid any delay in new drug registration. Herbal companies, manufacturers and entrepreneurs should be aware of the scheme and support provided by the Government from time to time to promote business and market growth with high-quality safe drugs.

At present, modern healthcare has reached its market in billions of dollar and herbal medicine has a very small contribution in that. This is due to ignorance, technical and regulatory issues, lack of research interest and very small market participation of pharma companies and industries.

Conclusion

At present, modern healthcare has reached its market in billions of dollar and herbal medicine has a very small contribution in that. In this review we have discussed the scope and opportunities associated with herbal drug together with problem and challenges that herbal pharma manufacturing companies are facing currently.

Modern and standard cultivation methods, procurement of authenticated raw materials and manufacturing of herbal drugs as per quality control standards are necessary to compete with global market and good manufacturing practices. Concerning safety profile of the drug also promotes its reliance among customers. Awareness among the medical professionals and common people can bring the herbal drug into the mainstream of modern healthcare practices.

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References

1. Agarwal V., Anti-fungal properties of Ocimum sanctum Linn : A short review, *J Med Plants Stud.,* **3(5),** 74-75 **(2015)**

2. Agrawal A., Verma P. and Goyal P.K., Chemomodulatory effects of Aegle marmelos against DMBA-induced skin tumorigenesis in Swiss albino mice, *Asian Pac J Cancer Prev.*, **11(5),** 1311-4 **(2010)**

3. Agtmael M.A., Van Eggelte T.A. and Van Boxtel C.J., Artemisinin drugs in the treatment of malaria: From medicinal herb to registered medication, *Trends Pharmacol. Science*, **20**, 199–205 **(1999)**

4. Ajmera N., Chatterjee A. and Goyal V., Aloe vera: It′s effect on gingivitis, *J Indian Soc Periodontol*., **17(4),** 435 **(2013)**

5. Alfa Abou- et al, Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer, *Journal of Clinical Oncology,* **24**, 4441-4447 **(2018)**

6. Ali H., Houghton P.J. and Soumyanath A., α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus, *J Ethnopharmacol*., **107(3),** 449-455 **(2006)**

7. Ansari A.S., Sevliya K., Mohammad I., Badar A. and Lohiya N.K., Plants for Female Fertility Regulation: A Review, *J Pharmacol Toxicol*., **12(2),** 57-75 **(2017)**

8. Archana A. and Bele A.K., Standardization of herbal drugs: an overview, *Int Res J Pharm.,* **2(12),** 56-60 **(2011)**

9. Arun N. and Nalini N., Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats, *Plant Foods Hum Nutr*., **57(1),** 41-52 **(2002)**

10. Ashwini S., Jyoti P., Pradnya R., Ghadage M. and Sagar T., Ashwagandha: Nature's boon for healthy life, *World J Pharm Res.*, **3(2),** 1961-1967 **(2014)**

11. Avijgan M., Kamran A. and Abedini A., Effectiveness of Aloe Vera Gel in Chronic Ulcers in Comparison with Conventional Treatments, *Iran J Med Sci.,* **41(3),** S30 **(2016)**

12. Babii C. et al, A novel synthetic flavonoid with potent antibacterial properties: In vitro activity and proposed mode of action, *PLoS One,* **13(4),** 1-15 **(2018)**

13. Baliga M.S., Bhat H.P., Joseph N. and Fazal F., Phytochemistry and medicinal uses of the bael fruit (Aegle marmelos Correa): A concise review, *Food Res. Int*, **44**, 1768-1775 **(2011)**

14. Bhandari P. and Kamdod M., Emblica officinalis (Amla): A review of potential therapeutic applications, *Int J Green Pharm*., **6(4),** 257-269 **(2013)**

15. Brahmachari G:Neem - An omnipotent plant: A retrospection, *ChemBioChem*., **5(4),** 408-421 **(2004)**

16. Chalut D., Toxicological risks of herbal remedies, *Paediatr Child Heal*, **4(8),** 536-538 **(1999)**

17. Chander R., Rizvi F., Khanna A.K. and Pratap R., Cardioprotective activity of synthetic guggulsterone (E and Z-isomers) in isoproterenol induced myocardial ischemia in rats: A comparative study, *Indian J Clin Biochem*., **18(2),** 71-79 **(2003)**

18. Cheng K.K., Yeung C.F., Ho S.W., Chow S.F., Chow A.H.L. and Baum L., Highly Stabilized Curcumin Nanoparticles Tested in an In Vitro Blood–Brain Barrier Model and in Alzheimer's Disease Tg2576 Mice, *AAPS J*., **15(2),** 324-336 **(2013)**

19. Chithra P., Sajithlal G.B. and Chandrakasan G., Influence of Aloe vera on the glycosaminoglycans in the matrix of healing dermal wounds in rats, *J Ethnopharmacol.*, **59(3),** 179-186 **(1998)**

20. Commission Pharmacopoeia for Indian Medicine and Homoeopathy, The Pharmacopoeia of Ayurveda, 7th edition, http://ayush.gov.in/sites/default/files/Ayurvedic%20Pharmacopoeia%20of%20India%20part%201%20volume%20IX.pdf **(2016)**

21. Cooper H., Bhattacharya B., Verma V., McCulloch A.J., Smellie W.S.A. and Heald A.H., Liquorice and soy sauce, a life-saving concoction in a patient with Addison's disease, *Ann. Clin. Biochem*, **44**, 397–399 **(2007)**

22. Craker L.E., Medicinal and aromatic plants-future opportunities, Botanicals and Medicinals ASHS Press, Alexandria, VA, 248–257 **(2007)**

23. Da Costa C.L., Geraldo M.R.F., Arrotéia C.C. and Kemmelmeier C., In vitro activity of neem oil [Azadirachta indica A. Juss (Meliaceae)] on Aspergillus flavus growth, sporulation, viability of spores, morphology and Aflatoxins B1 and B2 production, *Adv Biosci Biotechnol*., **01(04),** 292-299 **(2010)**

24. Dargan Paul I. et al, Heavy Metal Poisoning from Ayurvedic Traditional Medicines: An Emerging Problem?, *International Journal of Environment and Health*, **2(3/4),** 463 **(2008)**

25. Dapper D.V., Achinike P.N. and Gwotmut M.D., The effects of Aloe vera [gel] on clotting time, prothrombin time and plasma fibrinogen concentration in albino Wistar rats, *Port Harcourt Med J*., **2(1),** 56-60 **(2011)**

26. Deo Y.K. and RKR C., Critical review on pharmacological properties of Brahmi, *Int J Ayurvedic Med*., **4(2),** 92-99 **(2013)**

27. Edeoga H.O., Okwu D.E. and Mbaebie B., Phytochemical Constituents of Some Nigerian Medicinalplants, *African J Biotechnol.*, **4(7),** 685-688 **(2005)**

28. Ekor M., The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety, *Front Neurol.*, **4**, 1-10 **(2014)**

29. Elliott Middleton, Effect of Plant Flavonoids on Immune, *Adv Exp Med Biol*, **439,** 175-182 **(1998)**

30. Ernst E., The efficacy of herbal medicine - An overview, *Fundam Clin Pharmacol*., **19(4),** 405-409 **(2005)**

31. Gaire B.P. and Subedi L., A review on the pharmacological and toxicological aspects of Datura stramonium L.J., *Chinese Integr. Med*, **1(1),** 73–79 **(2003)**

32. George Watt, Commercial product of India, John Murrey, London, UK **(1908)**

33. Gianotti R.L., Bomblies A., Dafalla M., Issa-Arzika I., Duchemin J.B. and Eltahir E.A.B., Efficacy of local neem extracts for sustainable malaria vector control in an African village, *Malar J*., **7**, 1-11 **(2008)**

34. Giri R.P., Gangawane A.K., Giri S.G. and Spil M., Limited S. Regulations on herbal product used as medicine around the world : A Review, *Int Res J Eng Technol.*, **5(10),** 217-223 **(2018)**

35. Grover H., Deswal H., Singh Y. and Bhardwaj A., Therapeutic effects of amla in medicine and dentistry: A review, *J Oral Res Rev*., **7(2),** 65 **(2015)**

36. Gupta C.M.B., Bhalla T.N. and Gupta G.P., Anti-inflammatory activity of natural products (I) triterpenoids, *Eur J Pharmacol*., **6(1),** 67-70 **(1969)**

37. Gupta S.C., Prasad S., Sethumadhavan D.R., Nair M.S., Mo Y.Y. and Aggarwal B.B., Nimbolide, a limonoid triterpene, inhibits growth of human colorectal cancer xenografts by suppressing the proinflammatory microenvironment, *Clin. Cancer Res.*, **19**, 4465-4476 **(2013)**

38. Gupta U., Informed consent in clinical research: Revisiting few concepts and areas, *Perspect Clin Res*., **4(1),** 26 **(2013)**

39. H.H.S.F., Integration of herbal medicine into modern medical practices: Issues and prospects, *Integr Cancer Ther*., **1(3),** 287-293 **(2002)**

40. Halder N., Joshi S. and Gupta S.K., Lens aldose reductase inhibiting potential of some indigenous plants, *J Ethnopharmacol*., **86(1),** 113-116 **(2003)**

41. Hamman J.H., Composition and applications of Aloe vera leaf gel, *Molecules*, **13(8),** 1599-1616 **(2008)**

42. Heinrich M. and Teoh H.L., alanthamine from snowdrop - The development of a modern drug against Alzheimer's disease from local Caucasian knowledge, *J. Ethnopharmacol*, **92**, 147–162 **(2004)**

43. Jahan Rownak, Al-Nahain Abdullah, Majumder Snehali and Rahmatullah Mohammed, Ethnopharmacological Significance of Eclipta alba (L.) Hassk. (Asteraceae), *International Scholarly Research Notices*, **2014**, 1-23 **(2014)**

44. Jarial R. et al, Characterization of flavonoids from fern Cheilanthes tenuifolia and evaluation of antioxidant, antimicrobial and anticancer activities, *J King Saud Univ - Sci*., **30(4),** 425-432 **(2018)**

45. Jurenka J.S. and Ascp M.T., Curcuma Anti-inflammatory Properties, *Altern Med Rev*., **14(2),** 141-53 **(2009)**

46. Gurpret K. and Singh S.K., Review of Nanoemulsion Formulation and Characterization Techniques, *Indian J Pharm Sci.*, **80(5),** 1-25 **(2018)**

47. Kadajji V.G. and Betageri G.V., Water soluble polymers for pharmaceutical applications, *Polymers (Basel)*, **3(4),** 1972-2009 **(2011)**

48. Kalyan P., Kumar M.R., Kavitha K., Singh J. and Khan R., Pharmacological Actions of Ocimum sacntum - Review Article, *Int. J. Adv. Pharmacy, Biol. Chem.*, **1**, 406–14 **(2012)**

49. Ali Karimi, Majlesi and Rafieian-Kopaei Mahmoud, Herbal versus synthetic drugs; beliefs and facts, *Journal of Nephropharmacology*, **4(1),** 27–30 **(2015)**

50. Karolewicz B., A review of polymers as multifunctional excipients in drug dosage form technology, *Saudi Pharm J*., **24(5),** 525-536 **(2016)**

51. Karthikeyan K., Ravichandran P. and Govindasamy S., Chemopreventive effect of Ocimum sanctum on DMBA-induced hamster buccal pouch carcinogenesis, *Oral Oncol*., **35(1)**, 112-119 **(1999)**

52. Kesarwani K. and Gupta R., Bioavailability enhancers of herbal origin: An overview, *Asian Pac J Trop Biomed*., **3(4),** 253-266 **(2013)**

53. Key Kim M., Ja Choi G. and Lee H.S., Fungicidal property of Curcuma longa L. rhizome-derived curcumin against phytopathogenic fungi in a geenhouse, *J Agric Food Chem*., **51(6),** 1578-1581 **(2003)**

54. Khan and Rauf, Medicinal Plants: Economic Perspective and Recent Developments, *World Applied Sciences Journal*, **31(11),** 1925-1929 **(2014)**

55. Khar A., Ali A.M., Pardhasaradhi B.V.V., Varalakshmi C., Anjum R. and Kumari A.L., Induction of stress response renders human tumor cell lines resistant to curcumin-mediated apoptosis : role of reactive oxygen intermediates, *Cell Stress Chaperones*, **6**, 368-376 **(2001)**

56. Kim H.S., Kacew S. and Lee B.M., In vitro chemopreventive effects of plant polysaccharides (Aloe barbadensis Miller, Lentinus edodes, Ganoderma lucidum and Coriolus versicolor), *Carcinogenesis*, **20(8),** 1637-1640 **(1999)**

57. Kim H.S. and Lee B.M., Inhibition of benzo[a]pyrene-DNA adduct formation by Aloe barbadensis Miller, *Carcinogenesis*, **18(4),** 771-776 **(1997)**

58. Kulkarni K.V. and Adavirao B.V., A review on : Indian traditional shrub Tulsi (ocimum sanctum): The unique medicinal plant, *Journal of Medicinal Plants Studies*, **6(2),** 106-1106 **(2018)**

59. Kumar G.H., Vidya Priyadarsini R., Vinothini G., Vidjaya Letchoumy P. and Nagini S., The neem limonoids azadirachtin and nimbolide inhibit cell proliferation and induce apoptosis in an animal model of oral oncogenesis, *Invest New Drugs*, **28(4),** 392-401 **(2010)**

60. Kumar Ravi and Singh Manish Pal, A brief lightening on medicinal activity and Pharmacological profile of plant Eclipta prostrata: A Review, *International Journal of ChemTech Research*, **12**, 131-140 **(2019)**

61. Kunle, Standardization of herbal medicines - A review, *Int J Biodivers Conserv*, **4(3),** 101-112 **(2012)**

62. Lawhavinit O.A., Kongkathip N. and Kongkathip B., Antimicrobial activity of curcuminoids from Curcuma Longa L. on pathogenic bacteria of shrimp and chicken, *Kasetsart J. Nat. Sci*., **44**, 364-371 **(2010)**

63. Lee J.Y., Pharmacodynamic and pharmacokinetic interactions between herbs andwestern drugs, *Orient Pharm Exp Med*., **8(3),** 207-214 **(2008)**

64. Lobay D., Rauwolfia in the Treatment of Hypertension, *Integr. Med*, **14**, 40-46 **(2015)**

65. Lorent J.H., Quetin-Leclercq J. and Mingeot-Leclercq M.P., The amphiphilic nature of saponins and their effects on artificial and biological membranes and potential consequences for red blood and cancer cells, *Org Biomol Chem*., **12(44),** 8803-8822 **(2014)**

66. Kashif M., Kim D. and Kim G., In vitro antiproliferative and apoptosis inducing effect of a methanolic extract of Azadirachta indica oil on selected cancerous and noncancerous cell lines, *Asian Pac. J. Trop. Med.*, **11**, 555 **(2018)**

67. Marketresearchfuture : Herbal Medicine Market Research Report - Forecast to 2023, 1-23 **(2018)**

68. Marques-marinho F.D. and Vianna-soares C.D., Cellulose and Its Derivatives Use in the Pharmaceutical Compounding Practice, 2014, Marques-marinho F.D. and Vianna-soares C.D., Cellulose and Its Derivatives Use in the Pharmaceutical Compounding Practice, eds., Theo Van De Ven and Louis Godbout, Cellulose - Medical, Pharmaceutical and Electronic Applications, 1st edition, Intech, London, 141-162 **(2014)**

69. McCalla G., Parshad O., Brown P. and Gardner M., Beta Cell Regenerating Potential of Azadirachta indica (Neem) Extract in Diabetic Rats, *West Indian Med J.*, **1**, 876 **(2015)**

70. Moga M.A., Bălan A., Anastasiu C.V., Dimienescu O.G., Neculoiu C.D. and Gavriș C., An overview on the anticancer activity of azadirachta indica (Neem) in gynecological cancers, *Int. J. Mol. Sci*., **19**, 1-26 **(2018)**

71. Mohamed M., El A., Ashour A.S., Sadek A. and Melad G., A review on saponins from medicinal plants : chemistry , isolation , and determination, *J Nanomedicine Res*., **8(1),** 6-12 **(2019)**

72. Moongkarndi P., Kosem N., Luanratana O., Jongsomboonkusol S. and Pongpan N., Antiproliferative activity of Thai medicinal plant extracts on human breast adenocarcinoma cell line, *Fitoterapia*, **75**, 375–377 **(2004)**

73. Musmade P. et al, Informed consent: Issues and challenges, *J Adv Pharm Technol Res.*, **4(3),** 134 **(2013)**

74. N.D. of Health, National policy on traditional medicine and regulation of herbal medicines Report of a WHO global survey World Health Organization, World Health ORganization, 1-156 **(2005)**

75. N.F. and Nayeem N., Toxic Effects as a Result of Herbal Medicine Intake, Toxicol.-New Asp. to This Sci. Conundrum, 1st eds., Intechopen, London, 193-207 **(2016)**

76. Nandkarni D.K. and Dr. K.M. Nadkarni's, Indian materia medica, with Ayurvedic, Unani-Tibbi, Siddha, Allopathic, Homeopathic, Naturopathic, *Indian Materia Medica*, **1954**, 1-2 **(1982)**

77. Nardini C., The ethics of clinical trials Introduction: research and experimentation on human subjects, *E Cancer Medical Science*, **8(387),** 1-9 **(2014)**

78. Nejatzadeh-Barandozi F., Antibacterial activities and antioxidant capacity of Aloe vera, *Org Med Chem Lett.*, **3(1)**, 5 **(2013)**

79. Ngoci S.N., Matasyoh J.C., Mwaniki C.G. and Mwendia C.M., Antibacterial activity of methanol root extract of Indigofera lupatana Baker F, *East J Med.*, **17(1),** 11-16 **(2012)**

80. Nguyen L.T. et al, Quercetin induces apoptosis and cell cycle arrest in triple-negative breast cancer cells through modulation of Foxo3a activity, *Korean J Physiol Pharmacol.*, **21(2),** 205-213 **(2017)**

81. Ni Y., Turner D., Yates K.M. and Tizard I., Isolation and characterization of structural components of Aloe vera L. leaf pulp, *Int Immunopharmacol.*, **4(14),** 1745-1755 **(2004)**

82. Njerua S.N., Matasyoh J., Mwaniki C.G., Mwendia C.M. and Kobia G.K., A Review of som e Phytochemicals commonly found in Medicinal Plants, *Int J Med Plants Cit*., **105**, 135-140 **(2013)**

83. Obiageri:Pharmacokinetics and Drug Interactions of Herbal Medicines: A Missing Critical Step in the Phytomedicine/Drug Development Process, eds., Ayman Noreddin, Readings Adv. Pharmacokinet. - Theory, Methods Appl, 1st edition, Intechopen, London, 127-156 **(2012)**

84. Oboh H.A. and Omofoma C.O., The effects of heat treated Lima beans (Phaseolus lunatus) on plasma lipids in hypercholesterolemic rats, *Pakistan J Nutr*., **7(5),** 636-639 **(2008)**

85. Padma T., Ayurveda, *Nature*, **436(July),** 2005-2005 **(2005)**

86. Pandey S.K. and A.K., Chemistry and Biological Activities of Flavonoids: An Overview, *Sci J.*, **2013**, 1-20 **(2013)**

87. Parasuraman S., Thing G.S. and Dhanaraj S.A., Polyherbal formulation : Concept of ayurveda, *Pharmacogn Rev*, **8**, 73-80 **(2014)**

88. Paswan S.K., The Indian Magical Herb ' Sanjeevni ' (Selaginella bryopteris L .) - A Promising Anti-inflammatory Phytomedicine for the Treatment of Patients with Inflammatory Skin Diseases, *J Pharmacopuncture*, **20**, 93–99 **(2017)**

89. Pathan H. and Williams J., Basic opioid pharmacology: an update, *Brazilian Journal of Pain*, **6**, 11-6 **(2012)**

90. Patra J.K. et al, Nano based drug delivery systems: Recent developments and future prospects, *J Nanobiotechnology*, **16(1),** 1-33 **(2018)**

91. Petrovska B., Historical review of medicinal plants usage, *Pharmacognosy Reviews*, **6(11),** 1-5 **(2012)**

92. Purnima M.B. and Kothiyal P., A review article on phytochemistry and pharmacological profiles of Nardostachys jatamansi DC-medicinal herb, *J. Pharmacogn. Phytochem*, **3**, 102–106 **(2014)**

93. Purohit A. and Dixit V.P., Hypoglycemic Effect of Neem Bark and Flower on streptozotocin-induced diabetes in mice, *Anc Sci Life*, **1**, 28-30 **(1991)**

94. Raj A.J. et al, Indigenous uses of ethnomedicinal plants among forest-dependent communities of Northern Bengal, India, *J Ethnobiology Ethnomedicine*, **14**, 8 **(2018)**

95. Rasheed A., Roja C., Reddy G.A.K. and Reddy B.S., Formulation, standardization and pharmacological evaluation of a poly herbal traditional remedy -Ashwagandharishtam, *Orient Pharm Exp Med.*, **12(1),** 51-58 **(2012)**

96. Ravishankar and Shukla, Indian systems of medicine: Review, *African Journal of Traditional, Complementary and Alternate Medicine*, **4(3),** 19-33 **(2007)**

97. Rezazadeh F., Moshaverinia M., Motamedifar M. and Alyaseri M., Assessment of Anti HSV-1 Activity of Aloe Vera Gel Extract: an In Vitro Study, *J Dent*, **17(1),** 49-54 **(2016)**

98. Think Change India, India is world's second largest exporter of herbal medicines after China, https://yourstory.com/2018/01/india-second-exporter-herbal-med, 1-2, **(2018)**

99. Roy A., A Review on the Alkaloids an Important Therapeutic Compound from Plants, *Int. J. Plant Biotechnol*, **3**, 1-9 **(2017)**

100. Sahoo N. and Manchikanti P., Herbal Drug Regulation and Commercialization: An Indian Industry Perspective, *J Altern Complement Med.*, **19(12),** 957-963 **(2013)**

101. Sahu R., Medicinal properties of nardostachys jatamansi (A Review), *Orient. J. Chem*, **32**, 859-866 **(2016)**

102. Santra S., Naik M.R., Behera R., Agrawal D., Kumar S. and Patnaik S., Antipyretic effect of Azadirachta indica leaf extract (Neem Leaf Extract) on albino rats, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **6(4),** 1159-1164 **(2015)**

103. Sarup P., Bala S. and Kamboj S., Pharmacology and Phytochemistry of Oleo-Gum Resin of Commiphora wightii (Guggulu), *Scientifica (Cairo)*, **2015**, 1-14 **(2015)**

104. Sharma N.K., Singh P.K., Pramanik V., Maji B. and Mishra V.K., Traditional ethnomedicinal knowledge of Indian tribes, *Curr Sci*., **110(4),** 486-487 **(2016)**

105. Singh N., Bhalla M., De Jager P. and Gilca M., An overview on Ashwagandha: A Rasayana (Rejuvenator) of Ayurveda, *African J Tradit Complement Altern Med*., **8(Suppl.),** 208-213 **(2011)**

106. Singh R.K., Rai D., Yadav D., Bhargava A., Balzarini J. and De Clercq E., Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid, *Eur J Med Chem.*, **45(3),** 1078-1086 **(2010)**

107. Singh S. and Majumdar D.K., Evaluation of antiinflammatory activity of fatty acids of Ocimum sanctum fixed oil, *Indian J Exp Biol.*, **35(4),** 380-383 **(1997)**

108. Singh S., Taneja M. and Majumdar D.K., Biological activities of ocimum sanctum L. fixed oil-an overview, *Indian J Exp Biol*., **45(5),** 403-412 **(2007)**

109. Srinivasan K., Black pepper and its pungent principle-piperine: A review of diverse physiological effects, *Crit. Rev. Food Sci. Nutr,* **47**, 735–748 **(2007)**

110. Suanarunsawat T., Boonnak T., Ayutthaya W.D.N. and Thirawarapan S., Anti-hyperlipidemic and cardioprotective effects of ocimum sanctum l. fixed oil in rats fed a high fat diet, *J Basic Clin Physiol Pharmacol*., **21(4),** 387-400 **(2010)**

111. The Economic Times, Indian Ayurvedic Industry to Grow to $ 4.4 Billion by the End of This Year Fortis Calls off Process, https://economictimes.indiatimes.com/industry/healthcare/biotech /healthcare/indian-ayurvedic-industry-to-grow-to-4-4-billion-by-the-end-of-thisyear/articleshow/66694089.cms? from=mdr, 1-2 **(2019)**

112. Thornburg et al, NCI Program for Natural Product Discovery: A Publicly-Accessible Library of Natural Product Fractions for High-Throughput Screening, *ACS Chem. Biol.*, **13,** 2484–2497 **(2018)**

113. Tuncay Tanriverdi S. and Algin Yapar E., Preparation and characterization of herbal emulsion formulations, *Marmara Pharm J.*, **21(4),** 756-761 **(2017)**

114. Uma Devi P., Radioprotective, anticarcinogenic and antioxidant properties of the Indian Holy Basil, Ocimum sanctum (Tulasi), *Indian J Exp Biol.*, **39(3),** 185-190 **(2001)**

115. Upadhyay S.N., Dhawan S., Garg S. and Talwar G.P., Immunomodulatory effects of neem (Azadirachta indica) oil, *International Journal of Immunopharmacology*, **14(7),** 1187-1193 **(1992)**

116. Urizar N.L. and Moore D.D., GUGULIPID : A Natural Cholesterol-Lowering Agent, *Annu Rev Nutr*., **23(1),** 303-313 **(2003)**

117. Verma S. and Singh S.P., Current and future status of herbal medicines, *Vet. World,* **1(11),** 347–350 **(2008)**

118. Vfizquez B., Antiinflammatory activity of extracts from Aloe Vera gel, *J Ethnopharmacol*, **55**, 69-75 **(1996)**

119. Vijayananthan A. and Nawawi O., The importance of Good Clinical Practice guidelines and its role in clinical trials, *Biomed Imaging Interv J.*, **4(1),** 1-4 **(2008)**

120. Vimala G. and Gricilda Shoba F., A Review on Antiulcer Activity of Few Indian Medicinal Plants, *Int J Microbiol*., **2014**, 1-14 **(2014)**

121. Waheed A., Barker J., Barton S.J., Owen C.P., Ahmed S. and Carew M.A., A novel steroidal saponin glycoside from Fagonia indica induces cell-selective apoptosis or necrosis in cancer cells, *Eur J Pharm Sci*., **47(2),** 464-473 **(2012)**

122. Wang Chong-Zhi, Tyler Calway and Chun-Su Yuan, Herbal Medicines as Adjuvants for Cancer Therapeutics, *The American Journal of Chinese Medicine*, **40(04),** 657-69 **(2012)**

123. World Health Organization:Programme on Traditional Medicine, General guidelines for methodologies on research and evaluation of traditional medicine, World Health Organization, https://apps.who.int/iris/handle/10665/66783WHO **(2000)**

124. World Health Organization:WHO guidelines on good herbal processing practices (GHPP) for herbal medicines, https://www.who.int/medicines/areas/quality_safety/quality_assurance/V-2ndGlobalReview-RevisedDraft-WHO-GHPP-March2017.pdf, 1-60 **(1999)**

125. Yadav N., Yadav R. and Goyal, Chemistry of Terpenoids, *Int. J. Pharm. Sci. Rev. Res*., **27**, 272–278 **(2014)**.

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