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HERBAL MEDICINE KEY FEATURES AND CURRENT STATUS

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ABSTRACT
It is believed that medicinal plants have a vast array of bioactive compounds with a variety of therapeutic uses. Herbal medicines are not only more often utilized for basic medical requirements in developing nations, but they are also more culturally accepted, have fewer deleterious effects on the body, and are less likely to cause side effects. Thousands of years of traditional usage have provided essential insights that can guide the selection, preparation, and use of herbal formulations. In order to anticipate the future of herbal medicine and to establish the safety and efficacy of a therapeutical intervention, the same stringent procedure of scientific and clinical validation must be applied.

KEYWORDS: Herbal drug, Human health, Safety and efficacy.

INTRODUCTION

In the botanical literature, the term "herb" refers specifically to non-woody vascular plants that lack persistent woody stems, such as annual, biennial, and some perennial crops (including the majority of monocot species). But in the field of pharmacology, the phrase is used more broadly, encompassing all herbs, shrubs, and trees, much like a synonym for "plant".[1] Herbal medicines encompass a wider range of products, including herbal preparations, plants, plant parts, or combinations of plant origin as their primary ingredient, as well as herbal materials (leaves, flowers, fruits, seeds, stems, woods, barks, roots, rhizomes, or other plant parts and active ingredients).[2] Herbal remedies were employed in the healing rituals of indigenous civilizations, including Native American and African, and in the traditional medicinal systems developed by others, including Siddha, Ayurveda, Unani, and TCM.[3] However, once more reliable synthetic medications became widely accessible, the Western world saw a sharp decline in the therapeutic usage of herbs. 25% of medications prescribed globally are derived from plants. There are over 45,000 plant species in India, of which 15,000–20,000 have active ingredients with established therapeutic benefits. With regard to herbal medicine, India is ranked second in the world, and there is a great deal of potential for growth. The global pharmaceutical sector is once again interested in bio-prospecting as a result of customers' growing needs for herbal remedies in both developed and developing nations.[56] Many metabolites are those that plants produce and are directly involved in their own development, growth, and reproduction processes. However, secondary metabolites, or natural products, are produced from primary metabolites through a variety of enzymatic reactions and chemical transformations of molecules.[4] Secondary metabolites are categorized as (a) phenols, (b) terpenes, and (c) alkaloids based on their biosynthesis processes.[5&6]

Image 1.

Image2.

ADVANTAGES

a) Herbal medicine tend to be more effective for long standing health complaints that don't respond well to traditional medicine.
b) Herbs typically have fewer side effects, and may be safer to use over time. An example may be with herbs and alternative remedies are used to treat arthritis. Vioxx, a well known prescription drug uses to treat arthritis, was recalled due to increased risk of cardiovascular complications.
c) In addition, a growing body of scientific research source that herbal medicine can be highly effective for certain diseases and conditions. Moreover, as research in this area increases, the optimum doses for herbal medicine are known to ever greater accuracy.
d) Also, with increasing price of prescription medicine, herbal medicine is often cheaper than their conventional medicine counterparts.

CURRENT STATUS OF HERBAL MEDICINE

Herbal medicine is widely used worldwide and is not limited to underdeveloped nations; in France and Germany, 70% of doctors regularly prescribe herbal medicine.[7] Additionally, there is an exponential increase in the number of patients seeking treatment with herbal methods.[8] According to the figures that are currently accessible, the herbal medicine market in the European Union in 1991 was estimated to be worth $6 billion (it may currently be worth over $20 billion), with Germany accounting for $3 billion, France for $1.6 billion, and Italy for $0.6 billion.[9] Following a relaxation of regulations by the US Food and Drug Administration (FDA) regarding the selling of herbal supplements.[10] Herbal items are having a rise in the market.[11] A strange development has occurred in the field of herbal medicine in the past several decades. Rather of being eradicated by advances in pharmaceutical chemistry and medical research, it has returned.[12]

CURRENT STATUS OF HERBAL MEDICINE IN INDIA

Ayurveda, India's rich legacy of herbal therapy, is proof positive of this, having persisted for two millennia without any scientific foundation. Atharvaveda is where Ayurveda, which literally translates as "knowledge of life" (Ayur) originated. The two most well-known Ayurvedic treatises are Charak Samhita and Sushruta Samhita.[13] Charak, Sushruta and Vagbhata described 700 herbal drugs with their properties and clinical effects. Based on clinical effects 50 categories of drug have been described (such as appetizers, digestive stimulant, laxatives, anti-diarrhea, anti-hemorrhoid, anti-emetic, anti-pyretic, anti-inflammatory, anti-pruritic, anti-asthmatic, antiepileptic, anti-helminthes, haemoptietic, haemostatic, analgesics, sedative, promoter of life (Rasayna), promoter of strength, complexion, voice, semen and sperm, breast milk secretion, fracture and wound healing, destroyer of kidney stones etc).[14]

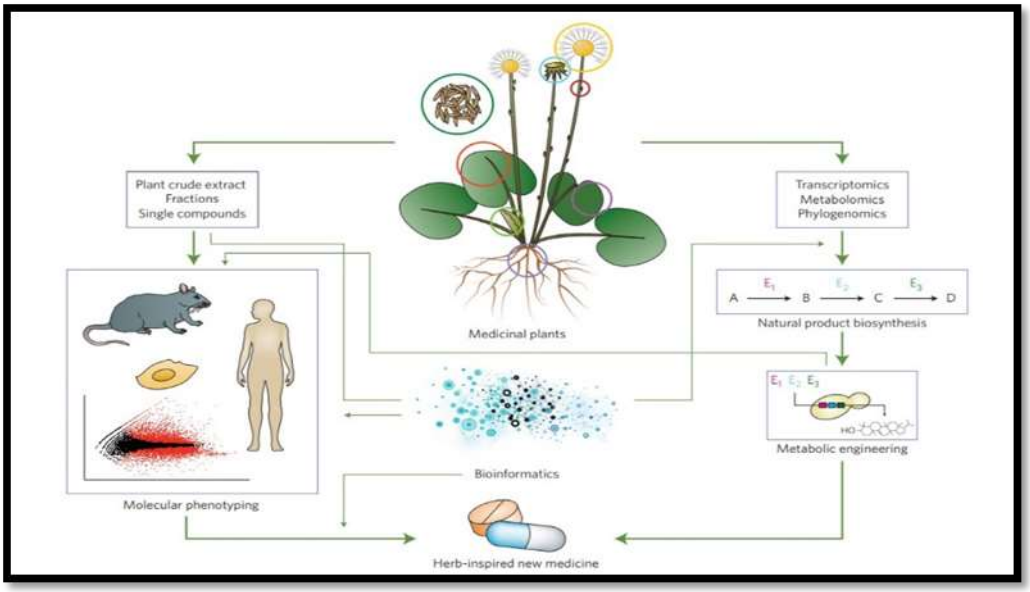

Figure 1: A new workflow for exploring and exploiting medicinal properties of plants in the post-omics era.

HERBAL MEDICINE IN TREATMENT OF CHRONIC DISEASE

Herbal medicines have been widely utilized as effective remedies for the prevention and treatment of multiple health conditions for centuries by almost every known culture. The first documented records of herbal medicine use date back 5,000 years in China.[15] Similarly, India's Ayurvedic medicine tradition is thought to be more than 5,000 years old and herbal medicines remain an essential component of its practice.[16]

1) It has been proposed that in certain regions of the world, plants may be the cause of chronic kidney disease (CKD). Many patients with chronic kidney disease (CKD) in the Indian subcontinent have a brief medical history, severe renal failure, minimal or absent oedema, mild hypertension, and small,

smooth kidneys at the time of presentation. In the majority of these cases, the underlying illness is still unknown.[17]

2) Strong cardioactive glycosides found in a variety of plants provide heart-beneficial inotropic effects. For many years, the medications digoxin (derived solely from Digitalis lanata) and digitoxin (derived from D purpurea, or foxglove) have been used to treat congestive heart failure. Due to their poor therapeutic index, cardiac glycoside dosages must be customized for individual patients. Digitoxin, digoxin, or digitalis powder in standardized powder form is the only way to regulate dosing. The total cardenolide output of 12 distinct strains of D lanata plants varied from 30 to nearly 1000 nmol/1 g when they were grown and analysed.[50] Heart glycosides are found in the venom glands of the cane toad, Bufo marinus, and are also utilized in the management of congestive heart failure.[51]

Image 3.

Image 4.

Table 1: Edible plants that have been associated with chronic kidney injury.

Plant species	Common name	Toxic compound	Manifestation
Aristolochia spp.		Aristolochic acid	Chronic interstitial nephritis, renal tubular defects, urothelial malignancies
Larrea tridentata	Chapparal	Nordihydroguaiaretic acid	Renal cysts, renal cell carcinoma
Ephedra sinica	Ma-Huang, ephedra	Ephedrine	Nephrolithiasis, obstructive nephropathy
Pithecolobium lobatum, P. jiringa	Djengko	Djenkolic acid	Nephrolithiasis, obstructive nephropathy
Averrhoa carambola	Star fruit	Oxalic acid	Nephrolithiasis, obstructive nephropathy
Vaccinium macrocarpon	Cranberry	Oxalic acid	Nephrolithiasis, obstructive nephropathy
Glycyrrhiza glabra	Licorice	Glycyrrhizin	Hypokalaemic nephropathy
Salix daphnoides	Willow bark	Salicin	Renal papillary necrosis
Pausinystalia yohimbe	Yohimbe	Yohimbine	Lupus nephritis
Fucus vesiculosus	Bladder wrack	Heavy metals (contaminant)	Chronic interstitial nephritis
Rhizoma Rhei	Rhubarb	Anthraquinone	Chronic interstitial nephritis
Echinacea spp.	Coneflower	Arabinogalactan	Renal tubular acidosis

WHY PEOPLE USE HERBAL MEDICINE

An rising proportion of individuals who usually do not declare concurrent use to their providers are now using herbal medicines.[18] Patients use herbal remedies for a variety of reasons. A "sense of control, a mental comfort from taking action" is frequently mentioned, and this helps to explain why many patients who take herbs have chronic or incurable ailments like diabetes, cancer, arthritis, or AIDS. They frequently think that they have been let down by traditional treatment in such circumstances. When patients take home remedies for acute, sometimes self-limiting illnesses like a cold, sore throat, or bee sting, it's usually because access to expert care is too delayed, difficult to get, expensive, or time-consuming.[19] The Neanderthal era provides the earliest indications of human use of plants for medicinal purposes.[20] Other cultural elements, such as the environment and culture, or the "man earth relationship," promote the usage of botanicals in rural settings. There is a common belief that every place that is home to a certain disease would also herbal plants that can be utilized for its treatment.[19] To promote better unity among herbalists, the European Herbal Practitioner Association was established. It is an umbrella organization with approximately 1000 members. People believe that natural plant items are healthier than synthetic medications.[20] Furthermore, news of the negative effects of conventional drugs are discovered in the lay press far more frequently than reports of the negative effects of herbal remedies. This is partly because conventional drugs have procedures in place to track these effects, while it is more difficult to find this kind of information for self-treatment. Herbs are frequently written off as harmless placebos even by doctors.[21]

Table 2: Parts of Medicinal Plant Exported and imported From India.

Exporting Of Herbals		Importing Of Herbal	
Acoruscalamus	Rhizome	Aloe vera	Dried
Argemonemaxicana	Fruit	Adhatodavasica	Whole
Curcuma amada	Rhizome	Cinnamomuminers	Bark
Curcuma longa	Rhizome	Garciniaindica	Fruit
Curcuma	Wild	Juniperuscommunis	Fruit
Cassia lanceolata	Leaves	Ricinuscommunis	Seed
Glycyrrhizaglabra	Root	Rauvolfiaserpentina	Root
Withaniasomnifera	Vegetable	Ocimum sanctum	Leaf
Myricanagi	Leaf	Tylophorapupuria	Root
Zingiberofficinale	Rhizome	Vincarose	Leaf

CHALLENGES AND OPPORTUNITIES FOR TRADITIONAL HERBAL MEDICINE TODAY

Even though plant-based drug development programs have been successful over the last two to three decades, there are still significant obstacles facing these endeavors. To stay up with other drug discovery initiatives, scientists studying natural products and the pharmaceutical sector will need to consistently raise the caliber and number of molecules that make it into the drug development stage. It has been estimated that the drug discovery process takes an average of ten years and costs over eight hundred million dollars.[25] The variety of traditional herbal products varies. They provide several difficulties for the regulatory procedure, quality assurance, and qualification control. The majority of herbal products on the market today have not had their efficacy and safety verified by the drug approval procedure.[22] Some of them have dangerously high concentrations of lead, arsenic, mercury, corticosteroids, and toxic chemical compounds.[23] There have been reports of hepatic failure and even death after ingesting herbal medicine.[24] Only one out of every 5000 lead compounds are predicted to successfully complete clinical studies and receive approval for use. The initial phase in the drug discovery process is lead identification. It takes a lot of time to complete clinical trials, lead development (containing pharmacology, toxicology, pharmacokinetics, ADME, and drug delivery), and lead optimization (including medicinal and combinatorial chemistry).

The latter strategy aims to isolate new bioactive plant products—that is, lead compounds with unique structures and action mechanisms—with a specific focus. A few classical examples have been supplied by this method; nonetheless, the most common issue here is insufficient availability. The availability issue can be solved via tissue-culture methods or semi-synthesis/synthesis (by genetically altering the biosynthetic pathway of the molecule of interest). The process of developing herbal drugs is linked to a number of issues. The most common forms of crude herbs and plants (different plant components and exudates) are tablets and capsules, with oral liquid formulations being used occasionally as well. These dose forms don't work because of issues with therapeutic efficacy, poor compliance, and absorption. The process of blending, compressing, and filling a tablet or capsule dosage form involves powdering raw herbs, and the size of the particles has an impact on these steps. Furthermore, the handling of huge bulk numbers, high moisture content, and intrinsic raw material (crude drug) nature make uniformity challenging to accomplish. Since crude extracts are hygroscopic, poorly soluble, and adhere to the skin, it is challenging to convert them into solid dosage forms. Faster and more effective techniques for plant collecting, bioassay screening, chemical isolation, and compound development must be used because drug discovery from plants has historically taken a long time.[26]

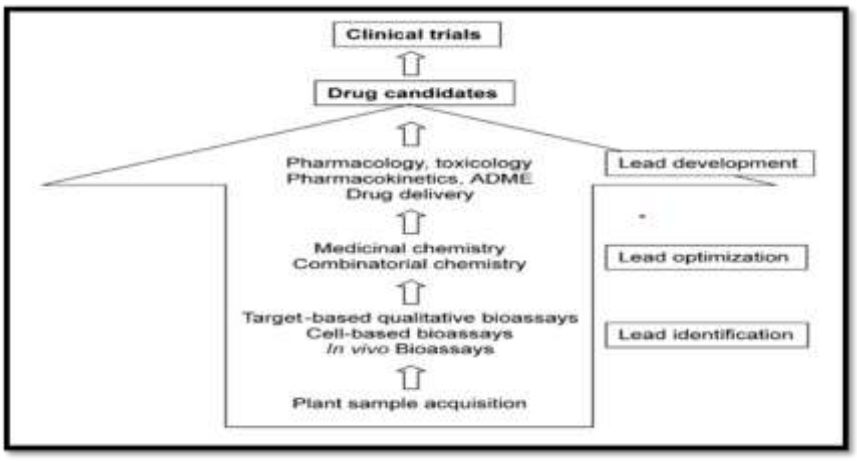

Figure 2: Drug discovery process from plants.

SAFETY AND EFFICACY OF HERBAL MEDICINE

Over the past 20 years, there has been a significant surge in the use of herbal treatments in the Western world.[27, 28] The promotion of health through the use of herbal treatments has been documented in a wide range of patient groups and the general public.[29, 30, 31, 32, 33] Part of the reason for the observed rise in the use of herbal therapies may be the desire for more "natural" options combined with the requirement to advise patients about all potential negative effects and precautions for conventional drugs. But unlike medicines, herbal cures are not subject to the same evaluation criteria, and the majority are not regulated but are instead marketed as dietary supplements. A bibliographic analysis of safety data forms the basis of the safety evaluation, and licenses are only granted for goods that are advertised as "traditional herbal medicinal products" in accordance with Directive 2004/24/EC.[34] The basis for evaluating efficacy has been conventional usage for a minimum of thirty years, which includes at least fifteen years in the European Union. The same rules that apply to medications also apply to quality documentation. Only 21 goods were licensed in the UK through this procedure as of October 2008.[35] Despite being used for thousands of years, CHM's effectiveness in many situations is still not supported by scientific evidence.[36] It is not adequate nor efficient to use the Western evaluation paradigm to examine the efficacy of CHM because the multi-component and multi-target mechanism of CHM differs intrinsically from the mono-substance and mono-target model of WM.[37] Two of the many obstacles still facing CHM are the difficulties of creating a research technique appropriate for studying the complicated nature of herbal formulations and getting to a point where CHM delivers products of guaranteed efficacy. One of the main issues regarding the efficiency of herbal remedies is the possibility of varying degrees of therapeutic effects resulting from the uneven quality of the material.[38]

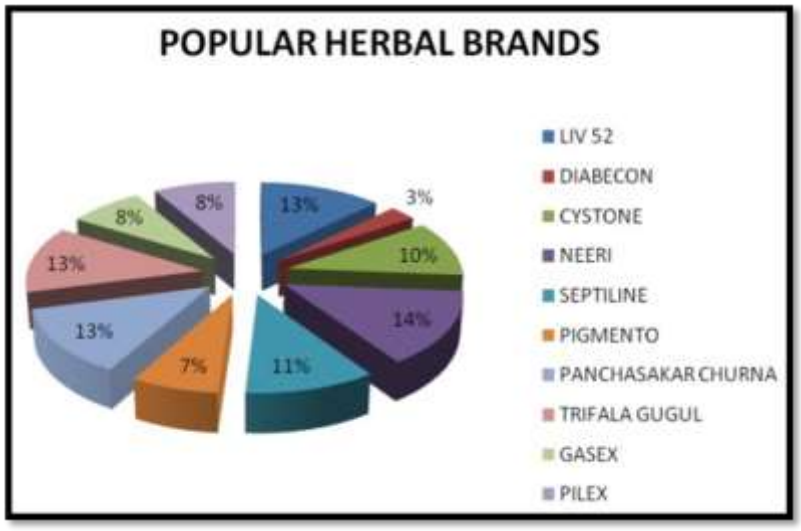

Figure 3: Popular herbal Brands for the treatment of chronic & acute disease.

BIOAVAILABILITY OF HERBAL MEDICINE

The herb's active ingredients' bioavailability is still another crucial factor. A chemical must enter the bloodstream from the GI tract in order to work systemically.[39] Although the insolubility of inorganic mercury has led to the assumption that it would not be significantly absorbed from the gastrointestinal tract, the toxic effects of this molecule are well identified.[40]

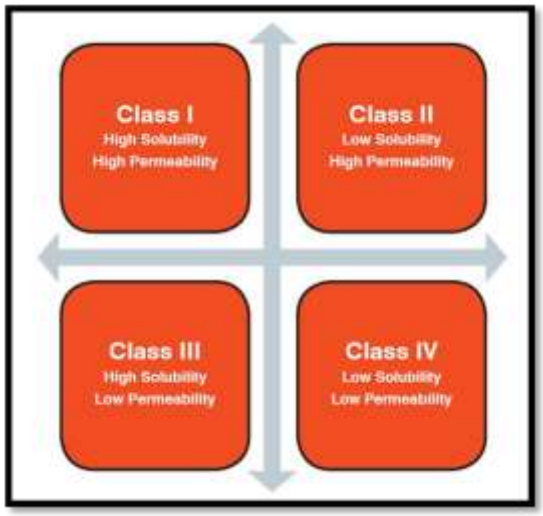

Figure 4: Biopharmaceutical Classification System (BCS).

A medication must be accessible as an aqueous solution at the site of absorption in order for it to be absorbed. This suggests that a drug's water solubility and dissolution rate are crucial characteristics that affect its oral bioavailability.[41] It is stated that approximately 70% of all new chemical entities (NCE) have low water solubility and fail to have commercial viability due to their restricted bioavailability.[42] Increasing the bioavailability of poorly water-soluble medication formulations is a major difficulty in this process. To enter the systemic circulation, the drug molecules must cross a biological membrane at the absorption site. As a result, a key element that influences the rate, degree, and bioavailability of medication absorption is the drug's gastrointestinal permeability.[43] The fact that solubility and permeability are used to build the Biopharmaceutic Classification Systems (BCS) demonstrates their significance in regulating bioavailability. When combined with data on dissolution rate, BCS, a scientific framework for analyzing medicinal substances based on their intestinal permeability and solubility, can be used to predict the absorption profile of drug products.[44, 45, 46]

REGULATION OF HERBAL MEDICINE

Herbal drug products constitute a major share of all the officially recognized systems of health in India viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. IMCC (Central Council of Indian Medicine) Act, Research Councils (ICMR and CSIR), Department of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy) & Drugs and Cosmetics Act 1940 (Amendment) regulates herbal medicines in India. Herbal remedies and medicinal plants to be incorporated in modern system (Allopathic) must follow Drug Controller General of India (DCGI's) regulations. As per Drugs and Cosmetics Act 1940 amended in 1964, "Ayurvedic, Siddha or Unani drug" includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani (Tibb) systems of medicine, specified in the First Schedule".[47] The first international recognition of the role of traditional medicine and use in primary health care was in The Declaration of Alma-Ata. It states, inter alia, that "…Primary health care relies, at local and referral levels, on health workers, including physicians, nurses, midwives, auxiliaries and community workers as applicable, as well as traditional practitioners as needed…".[48] Indian system of registration of herbal medicinal products has provision in each state via state drug licensing authority of Ayurvedic, Sidha and Unani drugs. Recent amendments in Drugs and Cosmetics (First Amendment) Rules 2008 has introduced Schedule TA for record of utilization of raw materials by Ayurvedic or Sidha or Unani licensed manufacturing units. Drugs and Cosmetics (Second Amendment) Rules 2008 permitted the use of excipients given in Indian Pharmacopoeia or Bureau of Indian Standards Act 1986 or Prevention of Food Adulteration Act 1954 and Food Products Order for use in Ayurvedic Sidha and Unani drugs. GCP guidelines published by ICMR also pertain to traditional drugs (Kumar NK, 2006). According to these guidelines traditional herbal medicines have been classified into three groups.[49]

1. Traditional Herbal drugs as per Classical text, regular use and prescribed pharmacopoeia – reverse pharmacology approach.
2. Traditional formulations for a new indication / new process / new combination/ new herbal or plant based NCE – acute, subacute and chronic toxicity data to be generated (Schedule Y of Drugs & Cosmetics Act, 1940).
3. Formulations – GMP compliant Standardisation.

QUALITY CONTROL OF HERBAL MEDICINE

Quality and stability of compound formulations have long been a neglected aspect in the trade of herbal medicine. Good manufacturing practices (GMP) need to be applied to the production of compound herbal drugs. Stability of drug substances and drug products is a critical feature in the process of drug development, based on which a shelf life for pharmaceutical products is established and storage conditions are recommended. Stability testing is done to explore how the quality of herbal products varies with time under the influence of environmental factors, and to establish a recommended storage condition and shelf life. Stability testing of herbal products is, however, a challenging task, because the entire herb or the herbal product is regarded as an active substance, irrespective of its constituents with defined therapeutic activity.[52] Product stability is affected by physical as well as chemical degradation of the product. Higher temperatures are known to have devastating effect on physical stability of preparations.[53] Several chemical reactions (mostly oxidation and hydrolysis) can cause degradation of drug substances and excipients. Exposure to high temperature, light, humidity, oxygen, and carbon dioxide may reduce drug stability. Other major factors affecting the drug stability include particle size (especially in emulsions and suspensions), pH, solvent system composition (percentage of free water and the overall polarity), compatibility of anions and cations, specific chemical additives and molecular binding, and diffusion of drugs and excipients. In addition to hydrolysis and oxidation, other reactions that destroy the therapeutic efficacy of drugs, include epimerization, decarboxylation, dehydration and photochemical decomposition.[54,55]

CONCLUSION

Herbal medicine is still the mainstay of about 75 - 80% of the world population, mainly in the developing countries, for primary health care. This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available. According to the World Health Organization (WHO), the use of herbal remedies throughout the world

exceeds that of the conventional drugs by two to three times. Though the efficacy of herbal requires development of quality consciousness in respect of the evaluation related evidences, supplying the demand for botanicals and herbals is a booming business. Undoubtedly the demand for plant derived products has increased worldwide. This means that scientists, doctors and pharmaceutical companies will be looking at country like India, for their requirements, as India have most number of medicinal plant species and is top exporters of medicinal plants. Classically trained physicians cannot ignore herbal medicines any more. They must realize that large number of patients are using herbal medicines. They must have adequate knowledge and should be more open to discuss with their patient regarding herbal medicine. Hence by keeping the facts in mind I have tried to highlight the key features and current status of herbal medicine so that researcher might get an idea to explore the search of new herbal based chemical entity, as the **"HERBAL MEDICINE ARE BOOMING"**.

REFERANCE

1. Iqbal, M. (2018). Botanical identity of traditional herbal drugs. Academic Staff College, JMI, New Delhi, India.
2. W.H.O. (2019). Global report on traditional and complementary medicine-2019. World Health Organization, Geneva.
3. Ampofo AJ, Andoh A, Tetteh W, Bello M. Microbiological Profile of Some Ghanaian Herbal Preparations-Safety Issues and Implications for the Health Professions, Open Journal of Medical Microbiology, 2012; 2: 121-130.
4. Thangavel, K.; Ebbie, M.G. and Ravichandran, P. (2014). Biotechnology and in vitro conservation of medicinal plants. Ann. Plant Sci, 3: 734-744.
5. Taiz, L. and Zeiger, E. (2010). Plant physiology, 3rd ed. (Chapter: Stress physiology). Sinauer Associates, Sunderland, MA.
6. Stavroula, M. and Rahul, J. (2016). Mediterranean climate affects the biosynthesis of secondary metabolites in common medicinal plants. Int. J. Bot, 6: 17-28.
7. Brevoort P, The booming US botanical market. A new overview. Herbal Gram, 1998; 44: 33-44. 38. Cragg G.
8. Cragg GM, Newmann DJ, Snader KM, Natural product in drug discovery and development. J Nat Prod, 1997; 60: 52-60.
9. Harvey AL, Medicines from nature: are natural product still relevant to drug discovery? Trends PharmacolSci, 1999; 20: 196-8.
10. Dwyer J and Rattray D, Anonymous. Plant, People and Medicine. In Magic and Medicine of Plant. Reader's Digest general book, 1993; 48-73.
11. Gottlieb S, US relaxes its guidelines on herbal supplements. BMJ, 2000; 320: 207.
12. Dwyer J and Rattray D (1993). Anonymous. Plant, People and Medicine. In Magic and Medicine of Plant. Reader's Digest general book, 48-73.
13. Pal SK, Complementary and alternative medicine: Anoverview. Curr Science, 2002; 82: 518-24.
14. Jain SK and DeFilipps RA, Medicinal plants of India. Reference Publication, Inc, 1991.
15. Garodia P, Ichikawa H, Malani N, Sethi G, Aggarwal BB, From ancient medicine to modern medicine: ayurvedic concepts of health and their role in inflammation and cancer. J SocIntegr Oncol, 2007; 5: 25-37.
16. Alschuler L, Benjamin SA, Duke JA, Herbal medicine -what works, what is safe. Patient Care, 1997; 31: 48-103.
17. Jha V. Current status of chronic kidney disease care in South-East Asia. Semin. Nephrol, 2009; 29: 487–96.
18. Mudur G. Mandatory rural practice proposed in India. BMJ, 1995; 311: 1186.
19. Miller LG, Herbal Medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med, 1998; 158: 2200–11.
20. Vickers A and Zollman C (1999). ABC of complementary medicine: herbal medicine. BMJ, 319: 1050 -3.
21. Miller LG, Herbal Medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med, 1998; 158: 2200–11.
22. Kew J, Morris C, Aihic A et al (1993). Arsenic and mercury intoxication due to Indian ethnic remedies. BMJ, 306: 506-7.
23. DeSmet PAGM (1997) Adverse effect of herbal remedies. Adverse Drug Reactions Bulletin, 183: 695-8.
24. Chattopadhyay MK (1996). Herbal medicines. Current Science, 71: 5.
25. Dickson, M. and Gagnon, J. P., Key factors in the rising cost of new drug discovery and development. Nature Rev. Drug Discov, 2004; 3: 417–429.
26. Koehn, F. E. and Carter, G. T., The evolving role of natural products in drug discovery. Nature Rev. Drug Discov, 2005; 4: 206–220.
27. Eisenberg, D.M., Davis, R.B., Ettner, S.L., et al., 1998. Trends in alternative medicine use in the United States, 1990–1997. Journal of the American Medical Association, 280: 1569–1575.
28. Barnes, P.M., Powell-Griner, E., McFann, K., Nahin, R.L., 2004. Complementary and alternative medicine use among adults: United States, 2002. Advance Data from Vital and Health Statistics, 343: 1–20.
29. Nordeng, H., Havnen, G.C., 2004. Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiology and Drug Safety, 13: 371–380.
30. Holden, W., Joseph, J., Williamson, L., 2005. Use of herbal remedies and potential drug interactions in rheumatology outpatients. Annals of the Rheumatic Diseases, 64: 790.

31. Carpenter, C.L., Ganz, P.A., Bernstein, L., 2008. Complementary and alternative therapies among very long-term breast cancer survivors. Breast Cancer Research and Treatment, 116: 387–396.
32. Hess, S., De Geest, S., Halter, K., Dickenmann, M., Denhaerynck, K., 2008. Prevalence and correlates of selected alternative and complementary medicine in adult renal transplant patients. Clinical Transplantation, 23: 56–62.
33. Zhang, A.L., Story, D.F., Lin, V., Vitetta, L., Xue, C.C., 2008. A population survey on the use of common medicinal herbs in Australia. Pharmacoepidemiology and Drug Safety, 17: 1006–1013.
34. European Parliament, 2004. Directive 2004/24/EC of the European Parliament and of the Council, 31 March 2004.
35. Medicines and Healthcare Products Regulatory Agency, 2008.
36. Pal, S.K.; Shukla, Y. Herbal medicine: Current status and the future. Asian Pac. J. Cancer Prev, 2003; 4: 281–288.
37. Leung, A.Y. Traditional toxicity documentation of Chinese Materia Medica—An overview. Toxicol. Pathol, 2006; 34: 319–326.
38. Kam, A.; Li, K.M.; Razmovski-Naumovski, V.; Nammi, S.; Chan, K.; Li, G.Q. Variability of the Polyphenolic Content and Antioxidant Capacity of Methanolic Extracts of Pomegranate Peel. Nat. Prod. Commun, 2013; 8: 707–710.
39. Tyler VE (1999). Phytomedicine: Back to the Future. J Nat Prod, 62: 1589–1592.
40. Yeoh TS, Lee AS, Lee HS (1986). Absorption of mercuric sulphide following oral administration in mice. Toxicology, 41: 107- 11.
41. Kumar S, Dilbaghi N, Rani R, Bhanjana G, Umar A. Novel approaches for enhancement of drug bioavailability. Rev Adv Sci Eng, 2013; 2: 1–22.
42. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm, 2011; 420: 1- 10.
43. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and Bioavailability. Asian J Pharm Sci, 2014; 9: 304–16.
44. Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with chitosan-DNA nanoparticles generate immunologic protection in a marine model of peanut allergy. Nature Med, 1999; 5: 387-91.
45. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, et al. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. Pharm. Res, 2002; 19: 921-5.
46. Wagh MP, Patel JS. Biopharmaceutical classification system: Scientific basis for biowaiver extensions. Int J Pharm Pharma Sci, 2010; 2: 12-19.
47. Drugs and cosmetics (first and second amendment) rules 2008. Ministry of Health and Family Welfare, Govt. of India.
48. World Health Organization. The Declaration of Alma-Ata, 1978.
49. ICMR, Ethical guidelines for biomedical research on human participants. DirectorGeneral, Indian Council of Medical Research, New Delhi, 2006.
50. Stuhlemmer UKreis WEisenbeiss MReinhard E Cardiac glycosides in partly submerged shoots of *Digitalis lanata*. *Planta Med*, 1993; 59: 539- 545.
51. Radford DJGillies ADHinds JADuffy P Naturally occurring cardiac glycosides. *Med J Aust*, 1986; 144: 540- 544.
52. Noor-ul-Basar, S.; Rani, M. and Zaman, R. (2013). A review on stability studies of unani formulations. J. Pharm. Sci. Innov, 2: 1-8.
53. Pandey, A.; Rath, B. and Dwivedi, A.K. (2011). Pharmaceutical pre-formulation studies with special emphasis on excipients compatibility. Int. J. Pharm. Technol, 3: 1029-1048.
54. Walter, L. (1994). The pharmaceutical codex-principles and practice of pharmaceutics, twelfth ed. The Pharmaceutical Press, UK, 277-288.
55. USP-N.F. (2018). The United States pharmacopeia 41 + National formulary 36. 1st Vol. US Pharmacopeial Convention Inc., Rockville, MD (US).
56. Dagmar, L., 2006. International Trade in Medicinal and Aromatic Plants, Actors, Volumes and Commodities, Plants. In: Medicinal and Aromatic Plants, Bogers, R.J., L.E. Craker and D. Lange (Eds.). Springer, USA., 155.