IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# SAFETY EFFICACY OF HERBALISM: CURRENT REGULATION WITH WHO & ICH GUIDELINES, REGULATIONS OF ASU

**MANASI B. LOKARE*, ABHIJIT H. RAUT, VINOD V. CHADAR, MANISHA A. LAVATE**
**DEPARTMENT OF HERBAL DRUG TECHNOLOGY, SOJAR COLLEGE OF PHARMACY KHANDAVI, BARSHI 411038, MAHARASHTRA, INDIA.**

## ABSTARCT:-

To make sure the safety and effectiveness of herbal medicines used in national medicine in the region and elsewhere in the world, So provide research methods to assess the safety and efficacy of herbal medicines for members to develop their own methods for researching herbal medicine and also to facilitate the exchange of research and other information to maintain a large database of evidence on the uses of Herbalism. In India, more than 70% of the population uses herbal medicine for health. India has one of the wealthy botanical traditions in the world. About 25,000 potent herbal formulations are used in traditional medicine and are widely known in rural communities in India. This is more than 1.5 million practitioners of traditional medicine who use medicinal plants for prophylactic and therapeutic purposes. It is estimated that India has more than 7,800 pharmaceutical manufacturing companies consuming around 2,000 tonnes of medicinal herbs per year, and India's share in herbal exports is US$63 billion, accounting for only 0.2% of the global herbal market.

**KEY WORDS:** Safety, Efficacy, Herbal medicines, WHO & ICH Guidelines, Valerian Drug.

## INTRODUCTION:-

In general, herbs are plant with sweet or aromatic properties used to flavor and garnish foods, medicines or spices; Vegetables and other plant foods for macronutrients are not included. Herbs have many uses, including culinary, medicinal, and sometimes spiritual.(1) The general usage of the “plant” differs between food and plant; any part of plant including leaves, roots , flowers, seeds, rhizomes, bark (and cambium) , may be considered a plant in medicinal or spiritual use. (2)

Plants were used in prehistoric medicine. Evidence that the Sumerians used herb in medicines was written in cuneiform as early as 5000 BC.

In 162 AD, physician Gale introduced as herbal remedy containing up to 100 ingredients.

Some plants contain phytochemical that affect the body. There can be some side effects when taken in small amount meaning “spice” and some chemicals are toxic when taken in large amount. For example, some types of herbal extracts, such as extracts of Hypericum perforatum or kava (Piper methysticum), are used for therapeutic purposes of reduce depression and anxiety. (3)

## Safety and Efficacy: -

With respect to drugs, safety refers to the absence of harmful effects relative to the intended use, while efficacy refers to the ability to produce results from medicinal treatment. Safety and effectiveness depend on the drug's instructions; in principle, a product is not a medical device if it is "safe" but not effective, or if it is contrary to a medical purpose but is not safe to use. While these are seen as important characteristics of any drug, safety has historically been more important than effectiveness in drug administration. For example, in the United States, the Federal Food, Drug, and Cosmetic Act of 1938 required that the safety of new drugs be demonstrated through preliminary testing, but only 25 years later Kefauver-Harris expressed a similar need to demonstrate effective drug use revised in 1962 case. The origin of the well-known Latin phrase "primum non nocere" ("first, do no harm") expresses the idea that safety should be the first priority in medical care. (4, 34, 35)

## HERBALISM:-

Herbalism is the study of Pharmacogonsy and the use of medicinal plants. For most of human history, plants have been the basis of medicines, and these drugs are still widely used today. Medicinal plants include herbal plants and/or herbal preparations and /or finished plants suitable for patient consumption.

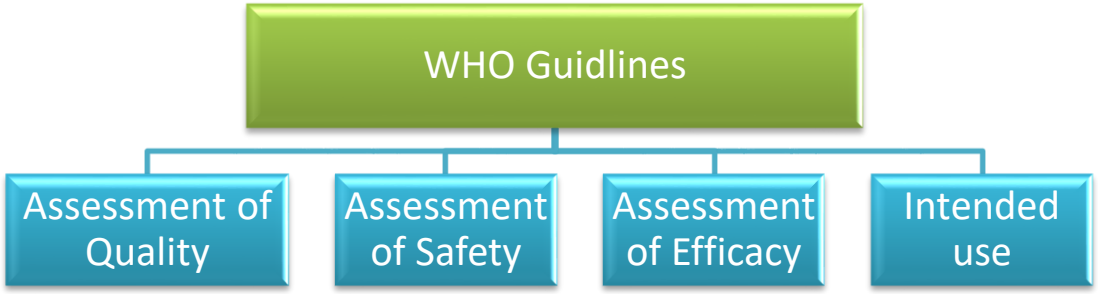
The world Health Organization (WHO) estimates that 80% of the populations in some Asian and African countries now use herbal medicines for some form of health care. Many of the drugs now available to physicians, including artemisinin, opium, aspirin, digitalis, and quinine have a history of herbal use. (5, 34)

According to the World Health Organization (WHO) about 25 percent of the medicines used in the united State are derived from plants. In modern medicines at least 7,000 compunds are of plant origin of the 120 active compounds currently isolated from higher plants and widely used in modern medicines, 80% are well related. As we see among the traditional of the plants from which they are obtained with their daily medicinal uses. (6, 36)

## World Health Organization (WHO) Estimation of Herbal Drug:-

Plants grown in different area also differ in their chemical composition. The diversity in biological compound is seen not only in the species but also at the cultivar and breeder level. Many varieties with in the species will differ in histology and phytochemistry. These differences are found in many medicinal plants these changes may be related to climate altitude. Geographic or genetics the effectiveness of medicinal plants depends on the quality and quantity of
medicinal product it has been determined that the chemical composition of plant varies according to climate and seasons.
Their for the drug needs to be evaluated because

1. Biochemical variation in crude drug.
2. Deterioration due to transport and storage.
3. Change and adulteration control in crude drug due to neglect(7)




Medcinal plant studies should be carried out in a way to reveal similarities and differences between plants in terms of morphological, anatomical, microscopic, physiochemical and phytochemical properties.

Therefore, the evaluation of crude drugs is the accuracy and suitability of drugs (Verification) to obtain information about the quality, purity and adulteration of drugs. In other words, drug evaluation can be defined as the estimation of crude drug properties, morphological and microscopic analyses, various physical tests, behavioral biology, and drug analysis decision making.

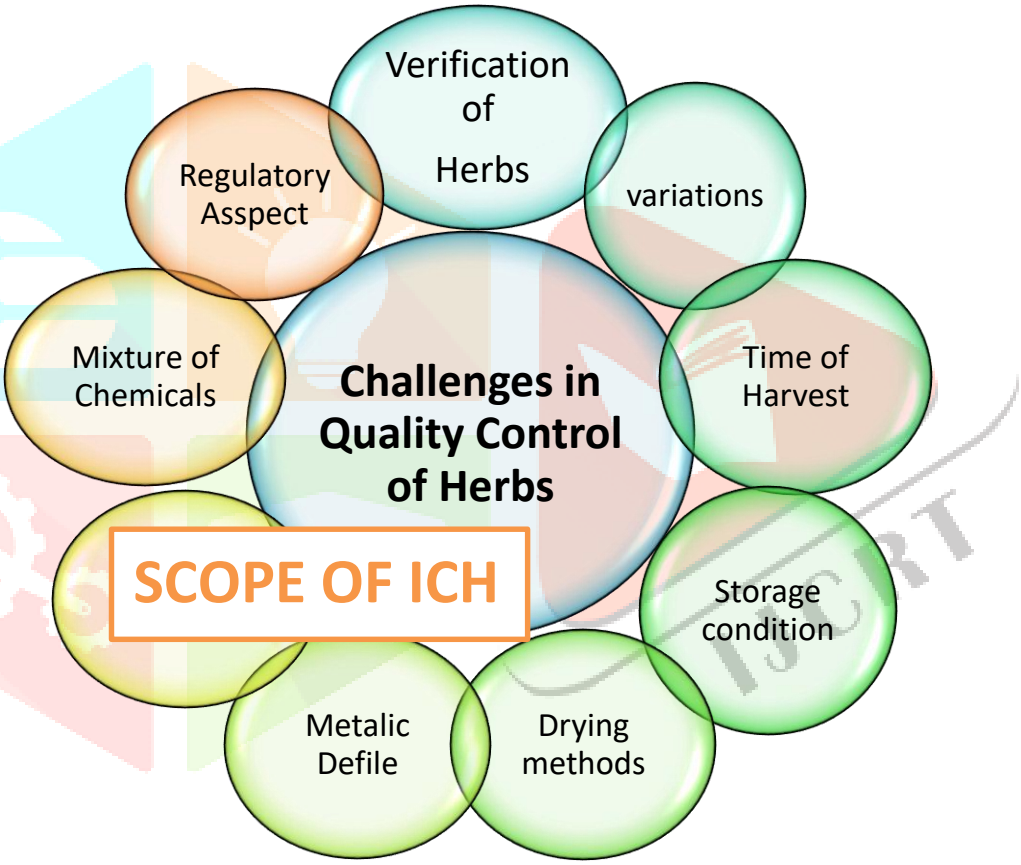
Law is designed to help countries that request develop appropriate laws and records. This process for evaluation of herbs is designed to facilitate the work of regulators, research organization and industry in the development, evaluation and registration of herbal medicine products. The assessment should reflect the scientific knowledge gathered in the field of herbal medicine and also form the basis for future classification of herbal medicine in different parts of the world. (8)

The World Health Organization (WHO) has finally stepped up and identified safe and effective herbs that can be used in national health care. (33) Earlier in 1978, the 31$^{st}$ World Health Assembly passed a resolution (WHA31.33) calling on the director-General to regularly prepare and update the classification of medicinal plants, including medicines. Later, the WHA40.33 resolution adopted in 1987 urged Member States to check the effectiveness of Phytotherapy using modern equipment and to use the WHA42 solution alongside the appropriate design and manufacturing quality.

Decree No. 43/1989 requires members to control and care for medicinal plant and to establish and maintain appropriate standards. In 1991, the Director General of the World Health Organization emphasized the importance of medicinal plants for human and public health in the report he presented to the 44$^{th}$ World Health Assembly. He also said consumers and doctors in all countries should be given new evidence about the benefits and effectiveness of all herbs. Finally at the 50$^{th}$ International Conference Pharmaceutical Regulators (Paris, 1989), it was concluded the WHO should consider developing a standard. (9)


## ICH Guidelines:-

ICH:- The complete name of ICH is the International Conference on Harmonization of Technical Requirements of Registration of Pharmaceutical for Human Use.




## Objective:-

1. To eliminate unnecessary delay in the global development and availability of new medicines.
2. More economical use of human, animal, and material resources. (34)
3. To Maintain safeguards on Quality, Safety, Efficacy and regulatory obligations to protect public health.(10)

## Quality Guidelines:-

Harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk Management. (35)

## Quality:-

| | |
|---|---|
| Q1 | Stability testing of new drug products |
| Q2 | Definitions and terminology: analytical validation |
| Q3 | Impurities in new drug substances |
| Q4 | Pharmacopoeia |
| Q5 | Viral safety evaluation |
| Q6 | Specifications, test procedures and acceptance criteria for new drug substances |
| Q7 | GMP for active pharmaceutical ingredients |
| Q8 | Pharmaceutical development |
| Q9 | Quality risk management |
| Q10 | Pharmaceutical quality system |

## Safety ICH:-

Since the International Conference on Harmonization (ICH) on Regulatory Procedures for the Regulatory Procedures for Drugs for Human Use in 1990, the Six-Party Expert Working Group (EWG) has developed and updated several guidelines for safety assessment. ICH's six delegates represent regulators and pharmaceutical organizations from three regions of Europe, Japan and the United States, where most new drugs are being developed. The development of ICH guidelines is a step forward. In Step 1, the EWG produced the "Final Harmonized Draft". Step 2 requires that the draft be submitted to the Board for signature, which means acceptance of the consultation. (30)

The third step is the consultation and negotiation process with the governing bodies of our site, which usually takes 6 months or longer. As with Step 3, Step 2 guidelines will be posted for public comment. Step 4 creates an expert paper from the discussion and submits it to the Board. Step 4 takes place when the Board of Directors approves the implementation of management in our region, in the last step (step5). Guidelines are included in and apply to national or regional guidelines.

Experience over the past few decades, including the development of new drug designs, has prompted new ICH leaders to develop new guidelines and review some of the existing ones. The aim of this project is to advance the science and technology of the drug manufacturing process, ultimately reducing the use of animals while making the drug safe and effective. Key ideas from ICH (bold in Table 1) include the new ICH S9 guideline for the preclinical evaluation of antibiotics, the ICH S6 supplement on the safety assessment of biologics, the updated ICH M3. It refers to the epoch of clinical trials affecting different treatment levels and new guidelines (ICH S2) on genotoxicity testing that replace and integrate ICH S2A and S2B. In this article, we explain the rationale behind these ICH plans and some explanations for revisions and new guidelines. We also offer our comments and thoughts on the potential impact of these new guidelines on previous safety assessments. (11, 12)

**ICH Safety Guidelines and Their Current Status**

| Code | Title | Status |
|---|---|---|
| **S1A** | Need for Carcinogenicity studies of Pharmaceuticals | Step 5, 1995 |
| **S1A** | Testing for carcinogenicity of pharmaceutical | Step 5, 1997 |
| **S1C(R2)** | Dose selection for carcinogenicity studies of Pharmaceuticals | Step 5, 2008 |
| **S2(R1)** | Guidance on genotoxicity Testing and data interpretation for pharmaceuticals intended for human use | Step 3, 2008 |
| **S3B** | PK: guidelines for repeated dose issue distribution studies. | Step 5, 1994 |
| **S4** | Single Dose toxicity tests | Agreement , 1991 |
| **S4** | Duration of chronic toxicity testing in animals (rodent and nonrodent toxicity testing) | Step 5 , 1998 |
| **S5(R2)** | New title : Detection of toxicity to male fertility | Step 5 , 1995 |
| **S6** | Preclinical safety evaluation of biotechnology derived pharmaceuticals | Step 5, 1997 |
| **S6(R1)** | Addendum to ICH S6 : preclinical safety evaluation of biotechnology – derived pharmaceuticals | Step 3 , 2009 |
| **S7A** | Safety pharmacology studies for human pharmaceutical | Step 5 , 2000 |
| **S7B** | The preclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation ) by human pharmaceutical | Step 5, 2005 |
| **S8** | Immunotoxicity studies for human pharmaceuticals | Step 5 , 2005 |
| **S9** | Preclinical evaluation for anticancer pharmaceuticals | Step 5 , 2009 |
| **M3(R2)** | Guidance on preclinical safety studies for the conduct of human clinical trials and marketing and authorization for pharmaceuticals | Step 5 , 2009 |

(12, 30)

## Efficacy:-

According to an estimate from the World Health Organization, more than three-quarters of the population in developing countries use herbal remedies for primary health care. Herbs and their products have long-term health benefits and can be used to treat human diseases or conditions. In fact, herbal remedies often contain many ingredients that can form chemical compounds in the body. In practice, herbal medicines are often cheaper than buying expensive modern medicines to treat diseases. Many herbs have proven to be effective in the treatment of various ailments. (5, 12, 18,30)

Advances in biology and medicine have recently introduced new techniques to study the effects of herbs in a variety of human diseases and conditions. Therefore, understanding the mechanism of action of herbal medicines is crucial to understanding and improving treatment. (5, 34)

## Multidisciplinary Guidelines:-

It includes The ICH Medical Terminology (MedDRA) the Common technical Document (CTD) and the Development of electronic standards for the transfer of regulatory information (ESTRI)

| S. NO. | Guidelines |
|---|---|
| M1 | MedDRA Terminology |
| M2 | Electronic Standards for transfer of regulatory information |
| M3 | Non clinical safety studies |
| M4 | The common technical document |
| M5 | Elements and standards for drug dictionaries |
| M6 | Gene therapy |
| M7 | Genotoxic impurities |
| M8 | Electronic common technical document |

## Need of Regulations of Drugs:-

1. Develop and maintain standards for pharmaceutical production, distribution, sales, marketing and information.
2. Make sure people take good medicine.
3. Promote public protection against drugs/hazardous hazards.

Law also guarantees the quality and quality of traditional medicine: it will ensure the use of medicine, promote research, controls all cooperation in production. Setting penalties for workers and businesses, who sell and use drugs and abuse rules and regulations. (4, 15)

## Regulation of Ayurveda, Siddha, Unani (ASU):-

It is a requirement to formulate a standard pharmacopoeia for drugs under the medicines and cosmetic act as amended in 1964, which brought Ayurveda, Siddha, Unani medicines into sight. The Indian pharmacopoeia laboratory (PLIM) was established in 1970 as a first state to implement the law and its provisions and homoeopathic pharmacopoeia laboratory (HPL) was established in 1975 to facilitate drug development and testing in addition 13 more recognised laboratories have participated in the preparation of pharmcopoeial standards and monographs and established operating procedures (SOPs) for ASU drugs. The pharmacy division was created separately for the ASU system. This group sets standards for the quality, purity and potency of the drug and approves drug formularies. So far, 326 monographs on Ayurvedic medicines, 45 monographs on Unani medicines. More 98 monographs on Ayurvedic medicines are coming soon. The formularies of Ayurveda, siddha and unani have classic multi-component formulations of 636,248 and 745 respectively have been published top facilitate the creation and manufacturing processes of drug with ingredients.

Ayurveda, Siddha and Unani medicine are plant/herb-mineral preparations that are very different from the synthetic molecules of allopathic systems, which are mostly created under the control of laboratories. Much depends on the quality and availability of products from the facility. With this awareness, the National Board of Medicinal Plants (NMPB) was established in 2000 for the purpose of protection and growing quality herbal products in the region. In light of environmental pollution, NMPB is exploring how best to harvest and grow medicinal plants using good agricultural practices and harvesting practices to ensure good raw material supply for ASU medicine. Due to the consolidation and proliferation of our forest dwellers and smallholders, these practices need to be implemented in a way that does not affect their livelihoods. (21, 33)

Central Committee for Ayurveda and Siddha Studies (CCRAS), Pharmacopoeia Laboratories and Unani Medical Research Central Council Laboratories (CCRUM), Scientific and Industrial Research Council Laboratories (CSIR), and trade association Private sector and laboratories are working well. (29) It is important to emphasize that the quality control and formulation of herbal/herbal-mineral is multi-stage and constantly changing not only for ASU but also for other drugs. While there is a need to complete this work and simplify policy for ASU medicine worldwide, there will no longer be a need to seek the pharmaceutical industry of Ayurveda, Siddha and Unani. No control. It is important to remember that humans have relied on traditional medicine knowledge for thousands of years to survive.

The following key strategies have been adopted by the Central Government to ensure the safety and quality control of ASU medicines:

1. Good Manufacturing Practice (GMP) Act and 1945 Act for ASU medicines as per the Indian Pharmaceuticals and Cosmetics Schedule "T" of 23 June 2000, Requires a license to maintain compliance with product raw materials, manufacturing facilities, manufacturing processes, data storage, storage of raw materials and finished products, and quality control. Central Government and all State Legislatures received instruction from DDT, order of AYUSH Office. 13.10.2005 Ensuring strict inspection of ASU companies according to GMP, canceling the licenses of facilities that do not comply with GMP.
2. Provisions regarding the proper labeling, packaging and visibility of all ingredients and products in the formula on the label/container or container label were reiterated in an instruction issued by the AYUSH department in October 200510 strictly followed by the National Drug Controllers/License Authority.
3. To address domestic and foreign concerns about the presence of heavy metals in ASU medicines, ASU herbal medicine suppliers have been instructed to display the "heavy metal borderline" message on the volume of pure ASU herbs. Or the above Certificate or other approved laboratory and other shipping documentation issued by the appropriate local laboratory w.e.f. 1/1/2006. Heavy metal testing in ASU herbs, including home drug testing, will continue at the level of domestic sales of ASU herbs.
4. Vegetal Minerals/Vegetable Metals Bhasmas/Compounds Safety issues are also affected by Central Government. CSIR Laboratories in the Golden Triangle approved the project to run clinical and safety studies on eight of the most commonly used Rasaushadhis/Bhasmas: Kajjali, Rasmanikya, Nag Bhasma, Rasasindoor, Basantkusumkar Ras, Arogyavardhini Vati, Mahayograj Guggul and Mahalax Ras Project completed within 18 months.
5. ASU warns of the use of permitted drugs, antibiotics to extend the shelf life of drugs.
6. The regulation on ASU expiration dates was published in November 2005, and negotiations are ongoing to finalize these regulations.
7. Some guidelines have also been issued to state licensing authorities to limit the rapid development of ineligible ASU patent portfolios by proprietary methods. (22)

As noted above, the quality control and standardization issues of ASU drugs are complex and different from the control issues established by laboratory control of electronic products. This is a question facing traditional medicine regulators around the world. Research and strategies for the design and quality control of phyto/herbal minerals continue to be developed worldwide. Regulatory agencies have to keep up with developments in botany, phytochemistry and biochemistry.

In addition to public and private research facilities, ASU's pharmaceutical industry has been instrumental in developing industry standards and regulatory processes and standards. A number of private companies in India have contributed to the development of standards and monographs on herbal extracts. The Ministry of Health and Family Welfare, AYUSH, initiated a consultation process with Ayurveda, Siddha and Unani experts and Botany, Herbalists, chemistry, biochemistry experts and pharmaceutical industry representative at ASU to provide a centralized control in response. Expand scientific and technological fields.

Standard formulation and monograph collection of herbal plant extracts. The Ministry of Health and Family Welfare, AYUSH, initiated a consultation process with Ayurveda, Siddha and Unani experts and Botany, Herbalists, chemistry, biochemistry experts and pharmaceutical industry representative at ASU to provide a centralized control in response. Expand scientific and technological fields. Thanks to these measures, techniques such as chromatographic fingerprinting are used in the design and quality control of medicinal plants and plant-mineral formulations, and the use of medical devices and the linkage of marker had gained popularity in the ASU pharmaceutical industry. The AYUSH Department will soon develop more detailed information for the authorization of conventional and patented drugs and ASU members after consulting with all stakeholders to improve and strengthen ASU drugs licensing.

The AYUSH Department, after consultation with all stakeholders, will publish detailed guidelines on the licensing of classic and patented and proprietary ASU drugs under the product file system as soon as possible to further improve and strengthen the registration of ASU drugs. The Ministry reiterated that ASU's Pharmaceutical standards and Code of Conduct for quality control are in place and that regulatory processes are constantly evolving with science and technology outputs. However, the public should use ASU medications under medical supervision whenever possible and purchase them by Cash Bill after checking


The ingredients listed in the listing bar or on the box. In case of doubt, a qualified Ayurveda/Siddha/Unani practitioner should be consulted and any violation of the label should be reported to the district and state health authorities and office. (21, 23, 33)

## Safety and Efficacy of Herbal Drugs Valerian: An Overview

This article presents evidence for clinical efficacy and safety concerns (side effects and toxicity). The MEDLINE research focused on management and case studies on the search terms insomnia, hypnotics, valerian, kava, lavender, chamomile, hops, lemon balm, and passionflower from 1990 to March 2003.(28) Data on the safety and efficacy of herbal sedatives are from all clinical studies and abstracts**.** Background information regarding to herbal drugs used in insomnia was extracted from most current literature, including review articles and textbooks are as follow. (14, 18, 31)

## VALERIAN

| | |
|---|---|
| **Drug Name** | Valerian |
| **Synonym** | Valerianae radix |
| **Biological Source** | Dried whole or fragmented underground part of *valeriana officinalis L.* Including the rhizomes surrounded by roots and stolons |
| **Family** | Valerianaceae |
| **Geographical Source** | Valerian is native to Europe and Asia and has neutralize in eastern North America |
| **Characteristics** | Rhizomes<br>• Obconic to ellipsoidal, branched or simple<br>• 2.5 to 7.5 cm long , 1 to 3 cm Diameter<br>• Yellowish brown to dark Brown in colour<br>• Numerous roots and root scars give a very rough surface |
| **Transverse section** | Bark thin, cortex broad, Wood forming a narrow circle around a large pith; light brown |
| **Taste & odour** | Drug has a campthoraceous, slightly bitter taste , disagreeable odour |

(32)

Valerian is a popular European herb that has been used since the 17th century for its soothing and calming properties. There are about 150 species in the genus valerian, but only valerian is the plant of choice. Valerian, previously listed in the USP, is native to Europe and Asia and is now grown in most temperate regions of the world. In many European countries, valerian still retains its legal pharmacopoeia and is a component of herbal preparations for sleep. Recent studies have aimed to establish the biochemical and pharmacological basis of the activity observed in many clinical and preclinical (in vivo and in vitro) studies. (14, 31)

## Cultivation, collection and preparation of valerian:

Valerian grows well in any soil, but prefers rich, moist, heavy loams.

↓

Farm manure should be applied to the soil first, then liquid fertilizer should be used from time to time after planting and watered more.

↓

For a good crop, the soil must be fertilized. Sorting requires a lot of attention.

↓

Can also be propagated by seed, sown on cold growth, can be opened in March or April.

↓

In the first two cases, May turned into permanent hotels. However, to ensure the best alkaloid content, it is best to replace and cultivate wild valerian

↓ .

Better rhizome should be obtained by cutting the flowering tops when they emerge.

↓

Many young plants do not flower the first year but are leafy and produce good rhizomes in the fall.

↓

In September or October cut off all the tops with a scythe and collect the rhizomes.

↓

Medicinal plants are usually whole or cut rhizomes, dark yellow-brown on the surface, about 1 inch long, 1/2 inch thick, 2 1/2 to 4 inches long and short, slender Side shoots (stolons) sometimes being prominent.

↓

Rootstocks, sometimes crowned with remnants of flower stalks and leaf scales, usually hard, horny inside, white or yellow, although older specimens may be hollow. (32)

## Pre-Clinical Study of Valerian:

In a study in rats, the mean dose of valerian extract was 3.3 g/kg intraperitoneally, while repeated administration of 300 and 600 mg/kg for 30 days did not cause changes in physical or body weight, hematological or blood chemistry. There are no reports of serious adverse events in humans at the dose considered normal in the literature (500 mg for 2 g in the morning), but clinical trials have reported some not goods. Safety 101 quantities up to 12 grams have been prepared.

European studies did not show adverse interactions with alcohol or other drugs, and morning sleepiness is less common. Valerian has been shown to prolong sleep in animals induced by thiopental and pentobarbital, so it may be necessary to avoid using this herb when using barbiturates. (31)

## Clinical Study of Valerian:

Clinical studies show valerian efficacy. In many human trials of valerian's sedative effect, most patients reported drowsiness. An earlier work by Vorbach et al. found 121 patients who were bedridden for at least 4 weeks. People who had depression or were currently using sleep aids were excluded. In a double-blind, randomized study, patients were given a placebo or 600 mg of valerian root ethanol extract daily for 4 weeks. Sleep quality was assessed with the Physician-Related Sleep Scale, the von Zerrsen Mood Scale, the Gortelmayer Sleep Questionnaire, and the Clinical Global Impressions Scale. There was no difference after 2 weeks, but after 4 weeks the valerian group differed from the placebo group on all scales, indicating a positive effect on sleep quality. (17,31)

## Uses:

1. Stress, anxiety, stress such as insomnia, neck pain, headache, muscle pain, irritability, stomachache, stomach pain, constipation and diarrhea.
2. The effects of valerian on the central nervous system are largely due to valerian trysters, their derivatives (baldrinals), valerenic acid, valerenal and valerianone and other important components of the essential oil.
3. Isovaleric Acid is the source of aromatic odor in plants.
4. Valerenic acid has an antispasmodic and muscle relaxant effect and prevents the breakdown of gamma-aminobutyric acid (GABA) in the central nervous system.
5. Lignan hydroxypinoresin also binds to benzodiazepine receptors in the amygdala and is thought to combine with bornyl acetate, pentenoic acid, and valerian triate in the general sedative effect of valerian.(14, 32)

## Side Effects:

1. Side effects may occur. While valerian is considered safe, side effects such as headaches, dizziness, stomach problems or insomnia may occur.
2. Valerian is probably not safe if you are pregnant or breastfeeding. And it has not been tested to determine if it is safe for children younger than 3 years old.
3. Do not take valerian if you have liver disease. And since valerian may make you drowsy, you should not drive or operate dangerous machinery after taking it.(19)

## Compliance with Ethical Standards:

Acknowledgements:

I'm very thank to Ms. Manisha A. Lavate mam Assistant Professor of Sojar College of Pharmacy, Khandvi Barshi for encouragement and providing the necessary facility for completion of this work.

Disclosure of conflict of interest

No-conflict of interest

## Reference:

1. Rehman SU, Choe K, Yoo HH. Review on a Traditional Herbal Medicine, Eurycoma longifolia Jack (Tongkat Ali): Its Traditional Uses, Chemistry, Evidence-Based Pharmacology and Toxicology. Molecules. 2016 Mar 10; 21(3):331. doi: 10.3390/molecules21030331. PMID: 26978330; PMCID: PMC6274257.
2. Zunic L, Skrbo A, Dobraca A. Historical Contribution of Pharmaceutics to Botany and Pharmacognosy Development. Mater Sociomed. 2017 Dec;29(4):291-300. doi: 10.5455/msm.2017.29.291-300. PMID: 29285002; PMCID: PMC5723202.
3. Falzon CC, Balabanova A. Phytotherapy: An Introduction to Herbal Medicine. Prim Care. 2017 Jun;44(2):217-227. doi: 10.1016/j.pop.2017.02.001. PMID: 28501226.
4. European legislation on herbal medicines : a look into the future Author – G. Calapai , Drug Saf; 31 (2008) Page No. 428-431
5. Drug And FDA Safety Efficacy And the Public Trust Author- Mikkael A. Sekeres First Edition 2022 Chapter NO. 29
6. Textbook of Herbal Drug Technology Author – Swati N. Deshmukh & Sandip G. Laware First Edition. 2022 Page no. 1-2
7. Herbal medicines : old and new concept, thruths and misunderstandings Rev. Bras. Farmacogn., 23 (2013) Page No. 379-385
8. Akerele o 1993 summery of WHO Guidelines for assessment of herbal medicines.
9. Textbook Of Herbal Drug Technology Author – Varsha Tiwari Second Edition 2021 Page No. – 9.5-9.11
10. Quality Control Methods For medicinal Plant materials WHO Geneva, 1996
11. ICH Guidelines. Available At : http://www.ich.org.
12. J.B. Calixto : Efficacy , Safety, Quality control, marketing and regulatory guidelines for herbal Medicines : Brazilian Journal of Medical and Biological Research (2000) 33:179-189

13. Tao Wang, David Jacobson-Kram, Anne M. Pilaro, Daniel Lapadula, Abigail Jacobs, Paul Brown, John Lipscomb, William David McGuinn, ICH Guidelines: Inception, Revision, and Implications for Drug Development, Toxicological Sciences, Volume 118, Issue 2, December 2010, Pages 356–367, https://doi.org/10.1093/toxsci/kfq286
14. Leach MJ, Page AT. Herbal medicine for insomnia: A systematic review and meta-analysis. Sleep Med Rev. 2015 Dec;24:1-12. doi: 10.1016/j.smrv.2014.12.003. Epub 2014 Dec 17. PMID: 25644982.
15. Zhang J, Hu K, Di L, Wang P, Liu Z, Zhang J, Yue P, Song W, Zhang J, Chen T, Wang Z, Zhang Y, Wang X, Zhan C, Cheng YC, Li X, Li Q, Fan JY, Shen Y, Han JY, Qiao H. Traditional herbal medicine and nanomedicine: Converging disciplines to improve therapeutic efficacy and human health. Adv Drug Deliv Rev. 2021 Nov;178:113964. doi: 10.1016/j.addr.2021.113964. Epub 2021 Sep 6. PMID: 34499982.
16. Tomassoni AJ, Simone K. Herbal medicines for children: an illusion of safety? Curr Opin Pediatr. 2001 Apr;13(2):162-9. doi: 10.1097/00008480-200104000-00014. PMID: 11317060
17. Park JH, Lee MJ, Song MY, Bose S, Shin BC, Kim HJ. Efficacy and safety of mixed oriental herbal medicines for treating human obesity: a systematic review of randomized clinical trials. J Med Food. 2012 Jul;15(7):589-97. doi: 10.1089/jmf.2011.1982. Epub 2012 May 21. PMID: 22612295.
18. Zamawe C, King C, Jennings HM, Mandiwa C, Fottrell E. Effectiveness and safety of herbal medicines for induction of labour: a systematic review and meta-analysis. BMJ Open. 2018 Oct 17;8(10):e022499. doi: 10.1136/bmjopen-2018-022499. PMID: 30337313; PMCID: PMC6196873.
19. Boniel T, Dannon P. [The safety of herbal medicines in the psychiatric practice]. Harefuah. 2001 Aug;140(8):780-3, 805. Hebrew. PMID: 11547487.
20. Boullata JI, Nace AM. Safety issues with herbal medicine. Pharmacotherapy. 2000 Mar;20(3):257-69. doi: 10.1592/phco.20.4.257.34886. PMID: 10730682.
21. Lopus M. Nano-ayurvedic medicine and its potential in cancer treatment. J Integr Med. 2023 Mar;21(2):117-119. doi: 10.1016/j.joim.2022.12.001. Epub 2022 Dec 24. PMID: 36610811.
22. Sathasivampillai SV, Rajamanoharan PRS, Munday M, Heinrich M. Plants used to treat diabetes in Sri Lankan Siddha Medicine - An ethnopharmacological review of historical and modern sources. J Ethnopharmacol. 2017 Feb 23;198:531-599. doi: 10.1016/j.jep.2016.07.053. Epub 2016 Jul 19. PMID: 27448453.
23. Yasmeen A, Sofi G, Khan K. Aamar-e-Advia (shelf-lives) of drugs in Unani system of medicine: A conceptual review. J Integr Med. 2020 Mar;18(2):114-124. doi: 10.1016/j.joim.2020.01.003. Epub 2020 Jan 13. PMID: 31983657.
24. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO expert committee on specifications for pharmaceutical preparations. Fortieth report. World Health Organ Tech Rep Ser. 2006;937:1-461, back cover. PMID: 16836287.
25. Maithani M, Raturi R, Gupta V, Bansal P. Assessment of compliance level of ICH guidelines for organic volatile impurities in common ayurvedic hepatic formulations. J Complement Integr Med. 2019 Mar 13;16(3):/j/jcim.2019.16.issue-3/jcim-2018-0159/jcim-2018-0159.xml. doi: 10.1515/jcim-2018-0159. PMID: 30870142.
26. Wang X, Chen Y, Yao L, Zhou Q, Wu Q, Estill J, Wang Q, Yang K, Norris SL. Reporting of declarations and conflicts of interest in WHO guidelines can be further improved. J Clin Epidemiol. 2018 Jun;98:1-8. doi: 10.1016/j.jclinepi.2017.12.021. Epub 2017 Dec 30. PMID: 29292204.
27. Zhao J, Song C, Li D, Yang X, Yu L, Wang K, Wu J, Wang X, Li D, Zhang B, Li B, Guo J, Feng W, Fu F, Gu X, Qian J, Li J, Yuan X, Liu Q, Chen J, Wang X, Liu Y, Wei D, Wang L, Shang L, Yang F, Jiang W; GATE-ICH Study Group. Efficacy and safety of glibenclamide therapy after intracerebral haemorrhage (GATE-ICH): A multicentre, prospective, randomised, controlled, open-label, blinded-endpoint,

phase 2 clinical trial. EClinicalMedicine. 2022 Sep 23;53:101666. doi: 10.1016/j.eclinm.2022.101666. PMID: 36177443; PMCID: PMC9513728.

28. Block KI, Gyllenhaal C, Mead MN. Safety and efficacy of herbal sedatives in cancer care. Integr Cancer Ther. 2004 Jun;3(2):128-48. doi: 10.1177/1534735404265003. PMID: 15165499.
29. Mukherjee PK, Nema NK, Venkatesh P, Debnath PK. Changing scenario for promotion and development of Ayurveda--way forward. J Ethnopharmacol. 2012 Sep 28;143(2):424-34. doi: 10.1016/j.jep.2012.07.036. Epub 2012 Aug 2. PMID: 22885133.
30. Reference book of Natural Bio-active Compounds" Springer Science and Business Media LLC, 2019
31. Reference book of S. Frantz, C. Johnson. "Role of Study Director and Study Monitor in Drug Development Safety Studies" Elsevier BV, 2017.
32. Reference book of Evidence Based Validation of Traditional Medicines" Springer Science and Business Media LLC, 2021
33. Reference book of "The Textbook of Pharmaceutical Medicine" Wiley, 2009
34. Reference book of Davyson de L. Moreira, Sabrina Schaaf Teixeira, Maria Helena D. Monteiro, Ana Cecilia A.X. De-Oliveira et al. "Traditional use and safety of herbal medicines1" Revista Brasileira de Farmacognosia, 2014
35. Reference book of Puneet Sharma, Srinivas Ganta, Sanjay Garg. "Scale-Up and Postapproval Changes (SUPAC) Regulations" Wiley, 2010
36. Bashar Saad, Omar Said. "Greco-Arab andIslamic Herbal Medicine" Wiley, 2011