QUALITY CONTROL PARAMETERS FOR STANDARDIZATION OF HERBAL DRUG

[1] Nikhil Kumar, [2] Shalini Vashisht, [3] Jyoti Gupta

1. Nikhil Kumar, Student of bachelors of Pharmacy, IEC School Of Pharmacy, IEC University (Baddi).

2. Shalini Vashisht, Assistant Professor, IEC School of pharmacy, IEC university, Baddi

3. Jyoti Gupta, Associate Professor, Head of Department, IEC School of Pharmacy, IEC University, Baddi

ABSTRACT

The increased usage of herbal goods has also lead to a variety of products abuses and adulterations, which have disappointed consumers and manufacturers and, in some cases, had disastrous results. Since the term "standardized" has no legal definition, the word's appearance on a product label is not a guarantee of a better level of product quality. Customers may become frustrated by inconsistent labeling of herbal goods and the fact that they are frequently left to determine what is safe and beneficial for them. The label must contain specific information, such as "the product has been made in accordance with Pharmacopoeia standards," a description of the active substances and their quantities, as well as dosage and frequency recommendations. Botanical materials are transformed into medications using herbal medicinal technology, where standardization and quality control with proper fusion of cutting-edge scientific methods and ancient wisdom are crucial. In light of the commercialization of formulations based on medicinal plants, the quality control criteria of diverse medicinal plants employed in indigenous systems of medicine are becoming increasingly important nowadays. This review aims to shed light on the methods used to standardize raw/finished compound medications up to this point, including macroscopic, microscopic, physical, chemical, and biological approaches. Herbal medication standardization entails verification of their identity, quality, and purity.

Keywords: DNA fingerprinting, Molecular markers, Chromatographic fingerprinting, Good agricultural practices (GAP), Fluorescence quenching, PCR-based markers.

1. INTRODUCTION

Herbal medicines can be made from herbs, herbal components, herbal preparations, or herbal finished goods. Several countries' traditional herbal remedies may include natural, organic, or inorganic active substances that are not derived from plants (e.g. animal and mineral materials). Herbs are unprocessed plant parts that may be whole, broken up, or ground up, such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes, or other plant parts. Together with herbs, herbal materials also include fresh juices, gums, fixed oils, essential oils, resins, and dry powders of various herbs. These materials may be prepared locally in some nations by different methods such steaming, roasting, or stir-frying them with honey, alcoholic beverages, or other ingredients. Herbal preparations, which can comprise comminuted or powdered herbal components as well as extracts, tinctures, and fatty oils of herbal materials, serve as the foundation for finished herbal medicines. They are created through various physical or biological processes, including as extraction, fractionation, purification, and concentration. Moreover, they consist of concoctions created by steeping or heating herbal components in alcoholic beverages, honey, or other substances. Herbal preparations created from one or more herbs make up finished herbal goods. The phrase "mixed herbal product" may also be used if more than one herb is utilised. Excipients may also be present in finished herbal products and herbal blends in addition to the active components. However, finish. However, finished goods or herbal mixtures that contain isolated ingredients from herbal materials or chemically defined active chemicals, such as synthetic compounds, are not regarded as being herbal. Herbal remedies are employed often in a variety of traditional medical procedures or treatments, including Chinese medicine, Ayurveda, Unani, Naturopathy, Osteopathy, and Homeopathy [1].

It has become crucial to establish dependable, precise, and sensitive quality control systems employing a combination of traditional and contemporary instrumental way of analysis in order to have a good coordination between the quality of raw materials, in process materials, and the final products. It is difficult to standardise

herbal medications since several factors can affect their bioefficacy and repeatable therapeutic impact. Care should be taken to ensure the quality of herbal products, starting with accurate plant identification, the season and location of harvest, the extraction and purification process, and rationalising the combination in the case of polyherbal medications [2].

2. NEED OF STANDARDIZATION

In the past, Rishis, Vaidyas, and Hakims treated patients on an individual basis and prepared medications based on their needs. The quality control issue has been taken into consideration in practically all traditional medical systems from its inspection of its Rishis, Vaidyas, and Hakims. In contrast to earlier times when traditional healers produced and evaluated the efficacy of herbal remedies, today's issues are economic ones related to industrial scale production, shelf life, and long-distance distribution. They have made the creation of contemporary, impartial standards for assessing the efficacy, quality, and safety of these medications necessary. Also, people are becoming aware of the strength and adverse effects.The researchers, the manufacturers, and the regulatory agencies must use exacting scientific methodologies to guarantee the quality and consistency of the traditional herbal products from lot to lot in order to win the public's trust and integrate them into the mainstream of the modern healthcare system [3]. The need for quality control and standardisation of herbal products is necessary because, at the time traditional medicines were created, technology and the idea of standardisation were quite different. Additionally, over the past 1,000 years, the dynamic process of evolution may have altered the identity of plant material, and due to commercialization, obtaining genuine raw materials has become difficult. It's also possible that the properties of botanicals have changed over time and as a result of environmental and temporal factors.

3. HERBAL DRUG STANDARDIZATION

In light of the commercialization of formulations based on medicinal plants, quality control standards of various medicinal plants used in indigenous systems of medicine are therefore becoming more important today than they were in the past when traditional doctors would dispense the medications themselves. A lot of adulteration or substitution occurs in the commercial markets as a result of the many geographic regions where these plants are grown, as well as the issue of diverse vernacular names these plants are recognised by. Hence, for efficient quality control, each factory needs to have replicable standards. Despite the fact that some of these plants are mentioned in different pharmacopoeias, their criteria, particularly in terms of chemical markers and TLC fingerprinting, have not been covered [6]. Having proper control over the quality of medicinal plants is a crucial component that can help ensure the consistent quality of herbal goods. The quality of herbal starting materials gathered from wild collections exhibits increasingly wide variations due to natural variety. As a result, recent years have seen a significant increase in the promotion of the cultivation of the most significant medicinal plants. It appears to be the only solution to satisfy the growing demand for herbal materials of consistent quality while taking into account managed environmental circumstances.

3.1. Standardization of herbal crude drugs process and procedure:

The standardization of natural drugs is a vast and complex topic. The WHO's recommendations can be summed up as follows: -

1. An allusion to the drug's name. Evaluation of plants using sensory characteristics, foreign organic matter, microscopic, histological, and histochemical analysis, among other methods.

2. Discusses the drug's physicochemical makeup. Physical and chemical identity, fingerprints left by the chromatography, ash and extractive values, moisture content, tests for volatile oils and alkaloids, quantitative estimation techniques, etc.

3. A mention of the biological activity profiles, bitterness values, hemolytic index, astringency, swelling factor, foaming index, etc.

4. Information on toxicity, including pesticide residues, heavy metals, total viable count of microorganisms.

5. Microbiological taint.

6. Radioactive taint.

Standardization and quality control of herbals, according to WHO [7-9], is the process involved in the physicochemical evaluation of crude drugs covering aspects, such as selection and handling of crude material,

assessment of finished product safety, efficacy, and stability, documentation of safety and risk based on experience, provision of product information to consumers, and product promotion.

The following quality indicators are typically given attention:

1. Macro and microscopic examination: To determine the proper variety and look for adulterants

2. Removal of foreign biological materials: is necessary in order to obtain the medicine in its purest form.

3. Ash values: such as total ash, sulphated ash, water soluble ash, and acid insoluble ash, are standards for determining the identity and purity of crude drugs.

4. Moisture content: By examining the moisture content, inaccuracies in estimating the real weight of medicinal material can be minimised. Reduced moisture signifies higher product stability against product degradation.

5. Extractive values: These are approximate weights of the chemical components of crude drugs that can be extracted under various solvent environments.

6. Crude fibre: This serve as a gauge of purity and aids in locating the woody material composition.

7 Qualitative Chemical Evaluation: It uses various analytical methods to find and isolate the active ingredients. Identification of the botanical material, extraction using the appropriate solvents, purification, and characterization of the pharmaceutically significant active ingredients are all steps in phytochemical screening approaches.

8. Chromatographic analysis: Involve identifying raw drugs using their primary chemical components as markers.

9. Quantitative chemical analysis: To calculate the concentrations of the main ingredient classes.

10. Toxicological studies: These serve to identify pesticide residues, potentially hazardous substances, safety tests on animals like the LD50, and microbial assays to assess whether potentially harmful bacteria are present or absent.

The standardization of crude drug materials includes the following steps:

3.1.1. Authentication:

a) The collection stage.

b) Components of the gathered plant.

c) Geographic location.

d) Plant identification techniques such as phytomorphology, microscopy, and histological examination (characterstics of cell walls, cell contents, starch grains, calcium oxalate crystals, trichomes, fibers, vessels etc.) [6].

3.1.2. Histological parameter studies:

a) Leaf constants: Stomatal number, Stomatal index, Vein islet number, Palisade ratio, and Vein termination.

b) Trichomes

c) Stomata

d) Quantitative microscopy

e) Taxonomic identity

f) Foreign substance

g) Organoleptic assessment.

h) Extractive and Ash values.

i) Determining the moisture content.

j) Analysis using spectroscopy and chromatography.

k) Heavy metal analysis.

l) Pesticide remnants

m) Microbial contamination

n) Radioactive contamination and pesticide residue

3.1.3. Stability parameters:

The following are the physical, chemical, and microbiological stability characteristics for herbal formulations:

Physical characteristics include viscosity, moisture content, pH, disintegration time, friability, hardness, flowability, flocculation, sedimentation, settling rate, and ash values. Other characteristics include colour, odour, appearance, clarity, and viscosity.

Chemical parameters include assays, tests, and limit tests, among others. Herbals can be analysed chromatographically using a variety of methods, including fluorimetry, GC, UV, GC-MS, TLC, HPLC, and HPTLC.

Total viable content, total mould count, total enterobacterial count, and their totals are all examples of microbiological criteria. Limiters can be used as a quantitative or semiquantitative instrument to measure and manage a variety of impurities, such as chemicals employed during the abstraction of different herbs, contaminants originating directly from the manufacturing vessels and from the solvents, among others.

4. QUALITY CONTROL AND VALIDATION OF HERBAL DRUGS

The initial identification of herbs, the detection of foreign matter and adulterants, the identification of small fragments of crude or powdered herbs, and quality control of herbal drugs today all require microscopic evaluation. Traditionally, quality control of herbal drugs has been based on appearance. To confirm that the plant is of the desired species and that the proper section of the plant is being used, perform a preliminary visual inspection, which rarely requires anything more complicated than a simple magnifying lens. Other times, microscopic examination is required to identify the correct species and/or confirm the presence of the relevant component of the species. For example, in the case of flowers, pollen morphology may be used to determine the species, and the presence of specific microscopic features, like leaf stomata, may be used to determine the plant part used. Even though it might seem simple, this is crucial, particularly when several portions of the same plant are to be utilised for various treatments. Herbal medicines should only contain the specified plant portion and not additional parts of the same plant or other plants. They must be completely clear of all types of mould or insects, as well as visible contaminants such sand and stones, dangerous foreign objects, chemical residues, and excrement. Among the potential impurities of herbal medicines include animal materials like insects and "invisible" microbiological contaminants that might produce poisons [10–12].

Both wealthy and resource-poor nations share a common problem with fakers selling contaminated herbal medications, making the validity of herbal goods a significant public health concern. Despite the fact that the WHO and some other organizations have set forth standards in this area, there is no control by the government institutions. Whether or not the herbal products actually work to treat or lessen the severity of the ailment, if they are advertised as therapeutic agents, it is imperative to establish scientific validation and regular monitoring of the quality and efficacy by drug control administrators. It is conceivable that adding scientific validation would regulate the manufacturing of tainted or adulterated herbal items and finally guarantee their appropriate usage. Additionally, this can result in the business being regulated to allow only licensed medical professionals and healthcare professionals to write prescriptions for drugs. Standards for herbal medications are outlined in monographs found in several of the major pharmacopoeias. The main benefits of an official monograph that is included in a pharmacopoeia are the availability and definition of standards as well as the complete validation of the analytical techniques used. This is crucial because the validation procedure might be time-consuming. Depending on whether the analytical method utilized is qualitative or quantitative, validation investigations typically need to include research on specificity, linearity, accuracy, precision, range, detection, and quantitative limits [13].

5. RECENT APPROACHES IN HERBAL DRUG STANDARDIZATION

5.1. DNA fingerprinting:

In order to assure reproducible quality of herbal medicine, which adds to its safety and efficacy, proper identification and quality assurance of the beginning material are prerequisites that must be met [14–16].

5.2. Molecular markers:

In general, biochemical components such as primary and secondary metabolites, as well as other macromolecules like nucleic acids, are referred to as molecular markers. Secondary metabolites have been widely employed as markers in the standardisation and quality control of botanical medicines. Because each species' genetic makeup is distinct and unaffected by ageing, physiological conditions, or environmental influences, DNA markers are trusted for revealing polymorphisms [17]. Because DNA may be recovered from both fresh and dried [18] organic tissue of plant material, detection is not limited by the sample's physical shape.

DNA polymorphism is evaluated using several DNA-based molecular approaches [19]. These include procedures based on hybridization, polymerase chain reaction (PCR), and sequencing.

5.3. Hybridization-based methods:

Restrictions fragment length polymorphism (RFLP) [20] and variable number tandem repeats [21] are hybridization-based techniques. Labeled probes, such as cDNA clones, probes for microsatellite [22] and mini satellite [23] sequences, and random genomic clones are hybridised to filters containing restriction enzyme-digested DNA. By examining the presence or lack of bands after hybridization, polymorphisms are identified.

5.4. PCR-based markers:

PCR-based markers amplify specific DNA sequences or loci in vitro using the thermo stable DNA polymerase enzyme, arbitrary or specific oligonucleotide primers, and the target DNA sequences or loci. Random amplified Polymorphic DNA (RAPD), arbitrarily primed PCR (AP-PCR), and DNA amplification fingerprinting (DAF) are PCR-based methods that employ random primers. Amplified fragment length polymorphism, or AFLP, is a modern method that relies on PCR amplification to identify genomic restriction segments. After ligating adaptors to the ends of restriction fragments, amplification is carried out using primers that are homologous to the adaptors. AFLP can be applied with DNAs of any origin or complexity and has the ability to detect hundreds of distinct loci [30].

5.5. Chromatographic fingerprinting:

The identification and evaluation of the stability of the chemical ingredients seen by chromatography are often the main goals of the application of chromatographic fingerprinting for herbal medications. A herbal substance or extract can also be identified using chemical and chromatographic procedures. For identification tests, chromatographic methods such high performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography (GC), and capillary electrophoresis have been used. Examples of the use of "fingerprints"—marker chemicals and chromatographic profiles—to identify herbal remedies and gauge their efficacy and stability may be found in the literature [31].

5.6. Fluorescence quenching:

When a plant extract is spotted on a layer of fluorescent silica gel and exposed to UV radiation, it causes quenching and appears as a spot on a fluorescent backdrop, which is directly inversely proportional to the extract's concentration. The GF silica gel plate served as an adsorbent for dampening fluorescence. Hexane toluene, ether, ethyl acetate, butanol, methanol, and water were used as solvents [32].

5.7. Good manufacturing practices:

The following three qualities are desired for standardization and quality assurance purposes. three factors: authenticity, purity, and assay. As the name suggests, authenticity has to do with demonstrating that the information is accurate, that is, that it matches to the correct identity. The process of authentication involves a variety of factors, such as Genetic fingerprinting, microscopy, chemical analysis, and gross morphology. Purity refers to determining that the plant material is free of adulterants. Chemical and biological profiling, which may evaluate the effects of chemicals and define curative values, is a component of assay in standardization. This

metric could be used to evaluate safety for use. In biological tests, a pharmacological model is used to assess the drug activity. Chemo profiling is a flexible method that can be helpful in standardization. In essence, fingerprinting is chemo profiling, which entails creating a distinctive chemical pattern for plant material, including its cut, fraction, or extract [33].

The source and quality of raw ingredients, ethical agricultural practices, and ethical manufacturing practices are only a few of the additional steps involved in the quality assurance and standardization of herbal medicines. The stability and excellent quality of herbal treatments must be guaranteed by these processes [34, 35]. The environmental variables that impact a plant's quality during growth can be controlled through accepted good agricultural practices (GAP).These consist of seed selection, the growth environment, fertilizer application, harvesting, drying, and storing. In actuality, GAP protocols are necessary for quality control.

Factors like the use of fresh plants, age and part of the plant collected, period, time, and method of collection, temperature of processing, exposure to light, availability of water, nutrients, drying, packing, transportation of raw material, and storage can all have a significant impact on the therapeutic value of herbal medicines. In addition to these requirements, the extraction procedure, microbial contamination, heavy metal contamination, and pesticide contamination are other factors that may affect the quality, safety, and efficacy of herbal medicines. Using plants that have been produced in controlled environments as opposed to those that have been collected from the wild can minimize the majority of these traits [36, 37]. Sometimes, during the long enzymatic processes from collection to marketing, the active components are eliminated, altering the composition. As a result, proper standardization and quality control should be applied to both the raw materials and the herbal products.

6. FUTURE PERSPECTIVES

Botanical materials are transformed into medications using herbal medicinal technology, where standardization and quality control with proper fusion of cutting-edge scientific methods and ancient wisdom are crucial. The conventional methods of standardizing herbal drugs use the botanical and organoleptic properties of crude drugs, as well as chemo profiling assisted characterization with spectroscopic techniques, to address quality-related issues. However, the modern methods of standardizing herbal drugs also include pharmacognostic, chemical, biological, biopharmaceutical, and molecular approaches. The standardization of natural drugs is a vast and complex topic. On the subject of herbal remedies and their connection to human physiology and brain function, there is a vast amount of information and many views that appear to be at odds with one another.

The standardization of herbal pharmaceuticals can now be accomplished using more modern and sophisticated techniques, such as fluorescence quenching, the combination of chromatographic and spectrophotometric methods, biological assays, the use of biomarkers in fingerprinting, etc. The standardization of herbal medications and the development of bioassay as a crucial approach for quality assurance and accurate product stability testing are all possible benefits [38]. India might become a significant nation and take the lead in producing standardized, therapeutically effective Ayurveda formulations. India must investigate the crucial herbs for medicine. Only if the herbal products are reviewed and studied utilizing advanced current standardized procedures, such as UV-visible, TLC, HPLC, HPTLC, GC-MS, and other methods can this be accomplished [39].

The diversity of species and ecological ethics should be taken into consideration while developing drugs from herbal medicine. To produce a medicine, it is ideal to first isolate and identify target chemicals from herbs or plants, then completely chemically synthesise the substance or compounds, as was done with aspirin [40].

7. CONCLUSION

Given the widespread acceptance of herbal products as treatments for a variety of disorders and mounting evidence of the risks associated with the indiscriminate use of some herbs, the necessity for standardization of herbals is now more important than ever. Monitoring the quality of the product from collection through processing to the finished packaged product is necessary to ensure the quality, safety, and efficacy of a herbal medication. It is advised that different government organizations accept the WHO recommendations and create monographs utilizing the numerous quality criteria mentioned above in order to take a more global approach to herbal quality. The regulatory framework will be strengthened, and quality breaches will be reduced. Herbal medications frequently have extensive human use prior to being evaluated in clinical trials, in contrast to conventional chemically defined drugs. It is crucial that the chemistry, production, and control of the product being used resemble those for the conventional formulation in order to make the most of this information's use in protocols to evaluate these products.

REFERENCES

1. General guidelines for methodologies on research and evaluation of traditional medicine. Geneva, World Health Organization, 2000 (WHO/EDM/ TRM/2000.1)

2. Patel PM, Patel NM, Goyal RK. The Indian Pharmacist, 2006; 5(45):26-30.

3. Wani MS. Pharma info, 2007; 5(6):1-6.

4. Patwardhan B. Indian Drugs, 2000; 37(5):2046- 2056.

5. Chaudhury RR. Herbal Medicine for Human Health, World Health Organization, New Delhi 1992: 51-57.

6. Indian Herbal Pharmacopoeia. Vol. I, A Joint Publication of RRL, Jammu Tawi and IDMA, Mumbai: 1998.

7. WHO. Quality Control Methods for Medicinal Plant Materials. World Health Organization, Geneva 1992.

8. WHO. Quality Assurance of Pharmaceuticals: A Compendum of Guidelines and Related Materials, Good Manufacturing Practices and Inspection. World Health Organization, Geneva 1996a.

9. WHO. Guidelines for the Assessment of Herbal Medicines. WHO Technical Report Series, World Health Organization, Geneva. 863 1996b.

10. EMEA. Points to Consider on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin. EMEA/HMPWP/31/99 Review. European Agency for the Evaluation of Medicinal Products (EMEA), London 2002.

11. WHO Guidelines on Good Agricultural and Collection Practices (GACP). World Health Organization, Geneva 2003. 12. WHO. Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants. World Health Organization, Geneva 2004.

13. Solecki RS. Science, 1975; 190:880.

14. Joshi K, Chavan P, Warude D, Patwardhan B. Current Science, 2004; 87(2):159-165.

15. Straus SE. N. Engl. J. Med., 2002; 7:1997-1998.

16. De Smet PAGM. N. Engl. J. Med., 2002; 347:2046- 2056.

17. Chan K. Chemosphere, 2003; 52:1361-1371.

18. Warude D, Chavan P, Kalpana J, Patwardhan B. Plant Mol. Biol. Rep., 2000; 21:1.

19. Joshi SP, Ranjekar PK, Gupta VS. Curr. Sci., 1999; 77:230-240.

20. Botstein B, White RL, Skolnick M, Davis RW. Am. J. Hum. Genet., 1980; 32:314-331.

21. Nakamura Y, Julier C, Wolff R, Holm TO, Connell P, Lepert M, White R. Nucleic Acids Res., 1987; 15: 2537-2547.

22. Litt M, Luty JA. Am. J. Hum. Genet., 1989; 44:397- 401.

23. Jeffrey AJ, Wilson V, Thein SL. Nature, 1985; 314:67-73.

24. Willams JGK, Kubelik AR, Livak KL. Nucleic Acids Res., 1990; 18 6531-6535.

25. Welsh J, Mcclelland M. Nucleic Acids Res. 1990; 18: 7213-7218.

26. Welsh J, McClelland M. Nucleic Acids Res., 1991; 19:861-866.

27. Caetano-Anolles G, Bassam BJ, Gresshof PM. Biotechnology, 1991; 9:553-557.

28. Caetano-Anolles G, Bassam BJ. Appl. Biochem. Biotechnol., 1993; 42:189-200.

29. Zabeau M. European Patent Application, Publication No. 0534858A1.1993.

30. Kumar LS. Biotechnol. Adv., 1999; 17:143-182.

31. Lazarowych NJ, Pekos P. Drug Information Journal, 1998; 32:497-512.

32. Gokhale, SB, Surana SJ. Planta indica, 2006; 2(3): 47.

33. Bhutani KK. The Eastern Pharmacist, 2000; 2:21-26.

34. Blumenthal M, Brusse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS. The Complete German Commission E Monographs. Therapeutic Guide to Herbal Medicines. The American Botanical Council, Austin, TX. 1998.

35. Roberts JE, Tyler VE. Tyler's Herbs of Choice. The Therapeutic Use of Phytomedicinals. The Haworth Press, New York 1997.

36. Eskinazi D, Blumenthal M, Farnsworth N, Riggins CW. Botanical Medicine: Efficacy, Quality, Assurance, and Regulation. Mary Ann Liebert, New York 1999.

37. Bauer R. Drug Inform. J., 1998; 32:101-110.

38. Bhutani KK. Indian Journal of Natural Products, 2003; 19(1):3-8.

39. Shrikumar, S., Maheshwari, U., Sughanti, A., Ravi, TK. WHO guidelines for herbal drug standardization, 2006.

40. Mahdi JG, Mahdi AJ, Mahdi AJ, Bowen ID. Cell Proliferation, 2006; 39:147-155.