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STANDERDISATION OF POLYHURBAL FORMULATION

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ABSTRACT

The herbal preparations standardization method is an important part to obtain the quality and efficacy of the product that considered as the rate-limiting step of the Ayurvedic formulations. Standardization is the need of the hour in Ayurvedic system of medicine. The traditional systems of medicine are really effective but the problem with them is they lack in quality assurance. This enables us to recognise the quality of the formulation. The Central Council of Research in Ayurveda and Siddha has prescribed the preliminary guidelines for testing the quality of these formulations. It is essential to derive a protocol or develop methods for evaluation of herbal formulation to maintain uniformity between batches during production. The present work aims to review to standardize a polyherbal formulations available in the market and prepared formulations.

Keywords: Ayurveda, WHO Guidelines, Standardization.

INTRODUCTION

Ayurveda is a centuries-old therapeutic system. This ancient Vedic wisdom, also known as Ayurvedic Medicine, is one of the oldest therapeutic sciences, and has been passed down through the generations. Ayurveda, or "Mother of All Healing," is an ancient Indian healing system that dates back thousands of years. [1] The Sanskrit terms ayur (life) and veda (science or knowledge) are combined to form Ayurveda, which means "the science of life," focused on bringing harmony and balance to all aspects of life, including mind, body, and spirit .[2]In order to assess the quality of medications based on the concentration of their active principle, standardization is a critical aspect in polyherbal formulation. Because the potential for diversity in different batches of medicine is significant, it is critical to establish a method of standardization for every plant medicine on the market .[3] The World Health Organization (WHO) recognizes the value of medicinal plants in public health in developing countries and has developed guidelines to assist member states in developing national policies on traditional medicine and researching their potential utility, including evaluation, safety, and efficacy.[4]Herbal medicines are made up of plants, herbs ingredients, herbal preparations, and herbal finished products. Herbal medications in some places may contain natural organic or inorganic active substances that aren't derived from plants, as a matter of tradition (e.g. animal and mineral materials). Herbs are plant parts that are whole, fragmented, or powdered, such as

leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes, or other plant components. Fresh juices, gums, fixed oils, essential oils, resins, and dry powders of herbs are examples of herbal materials in addition to herbs.[5]

In Ayurveda, Panchamahabhutas or the five elements: Vayu (air), Teja (fire), Aap (water), Prithvi (earth) and Akasha (aether) are believed to build up the living microcosm (human beings) and the macrocosm (external universe). When combined in pairs, the Panchamahabhutas form Tridosha or the three humors namely Vata (responsible for body movement), Pitta (responsible for bodily chemical reactions such as metabolism and temperature) and Kapha (responsible for growth, protection, lubrication and sustenance). All these present the constitution or Prakriti of an individual, which determines the physical as well as mental characteristic of human. The concept is that health is achieved when there is a balance between these three fundamental doshas, whereas imbalance causes diseases. Based on these Panchamahabhutas and Tridosha, the Prakriti of an individual is determined and a distinctive treatment plan can be prescribed according to their unique constitution.

The philosophy behind Ayurveda is preventing unnecessary suffering and living a long healthy life. Unlike the allopathic medicines which uses mainly synthetic chemicals designed for specific target receptors and primarily give symptomatic relief, Ayurveda involves the use of natural means such as diet, herbs, spices, minerals, exercise, meditation, yoga, mental hygiene, sounds, smells and mechano-procedures to eliminate the root cause of the disease by restoring balance, at the same time create a healthy life-style to prevent the reoccurrence of imbalance. Ayurveda is said to be holistic as it aims to integrate and balance body, mind and spirit to prevent illness and promote wellness, longevity, vitality and happiness.

HISTORY OF AYURVEDA

In terms of literature, the fourth Veda written during Indian Civilization, Atharva-veda serves as the earliest authentic text discussing on the nature of existence, health and disease, pathogenesis and principles of treatment. Here in Atharva-veda, the healing verses of Ayurveda can be primarily found, in which more than a hundred hymns were mentioned as the cures for diseases, including fever, leprosy, consumption, heart diseases, wounds, headaches, parasites, eye and ear diseases, poisoning, rheumatism and epilepsy. The uniqueness of this ancient medical system lies behind the vast variety of healing method used: Charms, plant and animal juices, natural forces (sun and water) as well as human contrivances. eight branches of treatment, Ashtanga was mentioned here as well: Kaya Chikitsa (Internal medicine), Shalya Tantra (Surgery), Shalakya Tantra (Ear, nose, throat and eye diseases), Kaumarbhritya (Pediatrics), Agada Tantra (Toxicology), Bhuta Vidya (Psychiatry), Rasayana (Rejuvenation therapy) and Vajeekarana (Aphrodisiac therapy). From the knowledge in Atharva-veda, early texts of Ayurveda such as Chakara Samhita and Sushruta Samhita were developed. Although the former focuses on the causes of diseases and the constitution of a person, the later emphasizes on Ayurvedic surgery and the details of its techniques.The history of Ayurveda can be traced back to the period between the pre-vedic periods (4000 B. C.-1500 B. C.). According to Ayurvedavatarana (the descent of Ayurveda), Lord Brahma, the Hindu God of Creation passed on his “knowledge of life” to Daksha Prajapati and Ashwins, subsequently to Indra. This knowledge is then transferred to different

rishis(sages), in which these disciples of Ayurveda wrote different treatises based on their interpretations. Here, both Bhardwaj and Dhanvantari received the knowledge from Indra. They later developed school of medicine and school of surgery respectively. In Chakara Samhita, it was stated that the Ayurvedic teaching is transferred by Indra to Bhardwaj, who in turn taught this to Atreya. The disciples of Atreya wrote their own samhitas, with Agnivesha Samhita being the one well-accepted. It is then revised, edited and supplemented by Chakara about 800 years later. On the other hand, Sushruta Samhita mentioned the transfer of knowledge from Indra to Dhanvantari, along with Bhardwaj. The disciples in this school such as Sushruta wrote Sushruta samhita, compiling Dhanvantari's teaching and his additional finding.

ADVANTEGES OF POLYHURBAL FORMULATION

• They have large amount of use.

• They have better patient tolerance as well as acceptance.

• The medicinal plants have renewable source of cheaper medicines.

• Improvements in the quality, efficacy and safety of herbal medicines with the development of science and technology .

. • Prolong and apparently uneventful use of herbal medicines may offer testimony of their safety and efficacy.

• They are cheap in cost.

• They are not harmful.

• They are more effective than any synthetic drug.

• Throughout the world herbal medicines have provided many of the most potent medicines to the vast arsenal of drugs available to modern medical science, both in crude form as well as a pure chemical upon which modern medicines are constructed. [6][7]

STANDERDISATION

In affluent countries, plant-derived goods have seen a surge in popularity in recent years. These products are growing in demand as medical, nutraceutical, and cosmetic products.[8] It has become critical to establish dependable, specific, and sensitive quality control procedures employing a combination of classical and modern instrumental methods of analysis in order to achieve good coordination between the quality of raw materials, in-process materials, and final products. Standardization is a crucial criterion for assuring herbal drug quality controls. The process of establishing a set of criteria or inherent features for herbal medicines is known as standardization. [9] The practice of prescribing a set of standards or inherent features, consistent parameters, definitive qualitative and quantitative values that convey an assurance of quality, efficacy, safety, and repeatability for herbal medicines is known as standardization. It is the procedure for creating and

approving technical standards. Experimentation and observations are used to develop specific criteria, which lead to the process of prescribing a set of qualities demonstrated by specific drugs. As a result, standardization is a tool used in the quality assurance process .[10] "Standardization refers to the body of knowledge and control required to produce material of adequate consistency," according to the American Herbal Product Association. This is accomplished by using quality assurance procedures in agricultural and manufacturing operations to reduce the inherent variation in natural product composition. [11]

The term "standardization" refers to the steps taken during the manufacturing process and quality control to ensure consistent quality. It also covers the complete field of study, from plant conception to therapeutic application. It also refers to adding excipients or mixing herbal medications or herbal drug preparations to get the herbal drug preparation to a specific content of a constituent or a respectively. [12] The phrase "evaluation" refers to the process of confirming a drug's identity, determining its quality and purity, and detecting its adulteration nature. [13]

NEED OF STANDERDISATION

The following is a summary of herbal product quality control and standardisation:

1. Technology and the concept of standardisation were very different when traditional medicines were created.

2. The identity of plant material may have altered over the last thousand years as a result of a dynamic process of evolution.

3. As a result of commercialization, finding genuine raw materials has become difficult.

4. Botanical properties may have changed through time and owing to environmental variables.[14]

The quality control of herbal crude drugs and formulations is critical in demonstrating their acceptability in today's medical system. With extremely well specified parameters of analysis, standardisation of synthetic pharmaceuticals is not an issue. It's not uncommon for a single mixture to have five or more different herbal constituents. In the lack of a reference standard for identification, batch to batch variance begins with the raw materials collection. The World Health Organization has stressed the importance of ensuring quality control of medicinal plant products through the use of contemporary technology and the application of appropriate criteria and guidelines. The value of standardised products and services cannot be overstated. Users evaluate user confidence builders as:

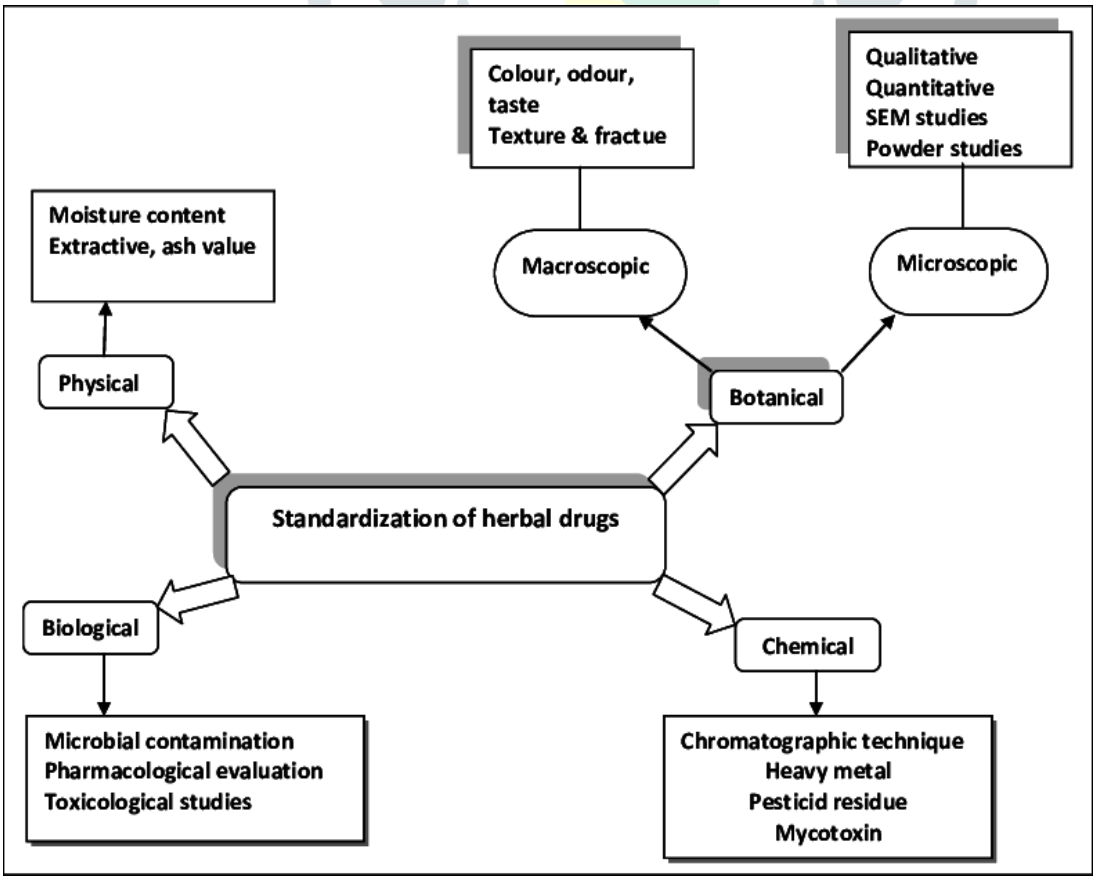
- Safe
- Healthy
- Secure
- high quality
- flexible.

Standardization provides major advantages to businesses, such as a stable platform for developing new technologies and the ability to share and improve existing processes. Standardization is also important. [15][16]

STANDERDISATION OF HURBAL / POLYHURBAL FORMULATION

In general, herbal formulation can be standardised by formulating the medicament with raw materials collected from various locations and comparing the chemical efficacy of different batches of formulation. The formulations with the highest clinical efficacy will be chosen. To choose the final finished product and validate the entire production process, all of the usual physical, chemical, and pharmacological criteria are tested for all batches [17]. As these are combinations of more than one herb to get the desired therapeutic effect, standardisation is a crucial feature for maintaining and analysing the quality and safety of the polyherbal formulation. Standardization reduces batch-to-batch variance and ensures the polyherbal compositions' safety, efficacy, quality, and acceptability.[18]

Good Manufacturing Practices (GMPs) are required for the standardisation of herbal formulations.[19] Furthermore, different factors such as pharmacodynamics, pharmacokinetics, dose, stability, self-life, toxicity evaluation, and chemical profiling of herbal formulations must be studied. Contaminations with heavy metals, as well as Good Agricultural Practices (GAP) in the standardisation of herbal drugs, are equally important.[20]



Standerdization of herbal drug

WHO GUIDELINES FOR QUALITY STANEDERDISED HURBAL FORMULATION

1) Controlling the quality of raw pharmaceuticals, plant preparations, and final goods.

2) Evaluation of stability and shelf life .

3) Safety evaluation and documentation based on experience or toxicological investigations.

4) Ethno-medical data and biological activity evaluations are used to assess efficacy.[21]

1) QUALITY CONTROL OF HURBAL DRUG

Quality control refers to the procedures used to ensure that a manufactured product's quality and validity are maintained. In general, quality control is based on three key pharmacopeial characteristics:

a. Identity or authenticity- it should have one herb

b. Purity - it should be free of all contaminants except the plant.

c. Assay or Content - the active ingredients must be contained within the prescribed limits.

Macro and microscopical exams can be used to determine identity. Additionally, identity tests, such as simple chemical tests, such as colour or precipitation, and chromatographic testing, are required. These chemical and chromatographic tests aid in batch to batch comparability, and the chromatogram can be utilised as a "fingerprint" for the herbal ingredient by displaying the profile of flavonoids, alkaloids, and terpenes. Criteria such as kind of preparation, sensory qualities, physical constants, and others are used to show identity and purity.[22][23]

To determine the consistent composition of herbal remedies, thin layer chromatography (TLC), high performance liquid chromatography (HPLC), high performance thin layer chromatography (HPTLC), and gas chromatography (GC) can be used. Different ideas such as "normalisation versus standardisation" must be utilised depending on whether the active principles of the preparation are known or unknown in order to develop suitable uniformity requirements. Because the active ingredients of most herbal medications are unknown, content or assay is the most challenging area of quality control to execute. Markers can be used on occasion. In all other circumstances, when no active ingredients or markers for the herbal drug can be identified, the percentage extractable materials with a solvent can be employed as an assay, which is a common strategy in pharmacopeia.[24][25] Steam distillation is a unique type of assay for determining essential oils. When active constituents (e.g. sennosides in senna) or markers (e.g. alkydamides in Echinacea) are identified, a wide range of modern chemical analytical methods can be used35, including ultraviolet/visible spectroscopy (UV/VIS), TLC, HPLC, HPTLC, GC, mass spectrometry, or a combination of GC and MS (GC/MS).[26]

2) STABILITY ASSESSMENT AND SHELF LIFE

Assesment of quality

All procedures should be carried out in accordance with good manufacturing practices.

Crude plant material

The botanical definition should include the genus, species, and authority, as well as a description, part of the plant, active and distinctive elements, and, if possible, content limitations. Impurities, foreign materials, and microbiological content should all be defined or limited. A certified botanist should authenticate voucher specimens for each lot of plant material treated, and they should be preserved for at least ten years. A lot number should be allocated to the product and displayed on the label.

Plant preparation

The manufacturing process should be thoroughly described. Other substances should be indicated in the production procedures if they are added throughout the manufacturing process to modify the plant preparation to a certain level of active or characteristic elements or for any other reason. An identification method and, if possible, an assay of the plant preparation should be included. If an active principle cannot be identified, a characteristic ingredient or mixture of chemicals should suffice to ensure that the product is of constant quality.

Finished product

The production process and formula, as well as the number of excipients used, should be detailed. To achieve consistent product quality, a finished product specification should be created. The final product must meet the general standards for certain dosage forms.

Stability

The product's physical and chemical stability in the container in which it will be marketed should be evaluated under specified storage conditions, and the shelf-life determined.

3) SAFETY ASSESMENT

Herbal research must consequently prioritise assessing the safety of herbal products. There are several methods for assessing herbal medicine safety. The following factors may contribute to the harmful effects of herbal preparations: Plant components and compounds have inherent toxicity, as well as Contamination in the manufacturing process. To assess the toxicity of plant elements in herbal formulations, extensive phytochemical and pharmacological research is required. However, based on human experiences in many cultures, it is safe to believe that the usage of hazardous plant compounds has already been substantially reduced, and that current claims of toxicity may be attributable to misidentification and overdose of particular constituents.[27] Several investigations claim that many herbal items contain medications and heavy metals

that aren't mentioned.[28] Clinicians should not prescribe or advocate herbal therapies that have not been proven to be efficacious in a thorough study as if they were drugs.[29]

4) ASSESSMENT OF EFFICACY

Herbal medications are essentially different from standard pharmaceutical therapies, however there is currently no mechanism to assess their efficacy other than through current clinical trial procedures, in which efficacy is traditionally measured by clinical, laboratory, or diagnostic outcomes: Improved morbidity, reduced pain or suffering, enhanced appetite and weight gain, reduced blood pressure, reduced tumor size or extent, and improved quality of life are all examples of clinical outcomes. Laboratory/other diagnostic outcomes include changes in blood glucose, hemoglobin status, opacity as determined by radiographic or imaging modalities, and electrocardiogram (ECG) abnormalities.

Herbal medication standardizations and quality control entail a wide range of scientific research, including physical, chemical, and biological evaluations using a variety of analytical methods and techniques.

Physical evolution - Each volume includes botanical, macroscopic, and microscopic descriptions, as well as extensive illustrations and photographs that give visual documentation of precisely identified material. A microscopic examination ensures the material's authenticity and serves as an initial impurity screening test.

Chemical evolution - To determine the potency of vegetable material in terms of its active ingredients, a chemical analysis of the medication is performed. It includes chemical component screening, isolation, identification, and purification. It aids in the identification of the drug substance as well as the possibility of adulteration.

Biological evolution - Certain medications' pharmacological activity has been used to evaluate and standardise them. The strength of a drug or its preparation can be determined via assays on living animals and their intact or isolated organs.

Analytical method - It aids in determining the identification, quality, and relative potency of a substance. Sample preparation is the most critical step in developing analytical procedures for botanical and herbal medicines. To obtain a homogeneous sample and typically improve the kinetics of constituent extraction, the fundamental process involves procedures such as pre-washing, drying of plant materials or freezedrying, and grinding. Methods like as sonication, heating under reflux, Soxhlet extraction, and others are extensively used in pharmacopoeial monographs.[30][31] Newer sample preparation methods, such as microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), accelerated solvent extraction (ASE), or pressurised liquid extraction (PLE), have been introduced for the extraction of targeted constituents present in plant materials to reduce or eliminate the use of organic solvents and improve extraction processes.

Chromatography - It is critical to separate individual components from the herbal mixture in order to identify and assess their bioactivity. Chromatography is a sophisticated analytical technique that can separate and quantify a large number of chemicals from a complicated matrix. Paper chromatography (PC), thin-layer

chromatography (TLC), gas chromatography (GC), high-performance liquid chromatography (HPLC), and capillary electrophoresis are examples of these techniques (CE).

TLC is widely employed in the phytochemical evaluation of herbal medications because it allows for quick examination of herbal extracts with minimal sample preparation, as well as qualitative and semiquantitative information on the resolved chemicals. The chromatogram, retardation factor (Rf) values, the colour of the separated bands, their absorption spectra, and the max and shoulder inflection/s of all the resolved bands are among the data that may be recorded using a highperformance TLC (HPTLC) scanner in TLC fingerprinting. All of these, along with profiles on derivatization with various reagents, make up the TLC fingerprint profile of the compound. The chromatograms, retention times of specific peaks, and absorption spectra (recorded with a photodiode array detector) of different mobile phases are all recorded during HPLC fingerprinting. GLC is also used to create fingerprint profiles for volatile and fixed oils found in herbal drugs.[32][33] Low pressure HPLC (pressure less than 5 bar) and high pressure HPLC (pressure greater than 20 bar) are the two main forms of preparative HPLC.[34] HPTLC has been used to test numerous components in a multicomponent formulation at the same time.[35] It has been widely documented that by using a lesser amount of mobile phase than in HPLC, multiple samples can be processed simultaneously.[36] In several stages of drug development, LC-MS has become the method of choice.[37] C-MS was used to chemically standardise an aqueous extract of the herb mixture, yielding chemical components that served as reference markers.[38] The online LC-NMR technique provides for continuous registration of temporal changes as they occur in the chromatographic run, as well as automated data collecting and processing in LC-NMR, which increases detection speed and sensitivity.[39] Different types of fast scan mass spectrometers can be directly interfaced with GC equipment. Because of their sensitivity, stability, and efficiency, GC and GC-MS are widely used for the study of volatile components in herbal remedies. The hyphenation with MS, in particular, gives solid data for qualitative investigation of complicated elements.[40]

The majority of these technologies allow for the measurement of chemical components in plant material or herbal products. The use of mass spectrometry is possible due to the availability of high-speed processors and appropriate software (MS). This method not only allows for the detection of component peaks in a mixture separated by chromatography, but also allows for its molecular characterization when used in conjunction with UV (using a photodiode array detector), multistage MS, and nuclear magnetic resonance spectrometry (LC–UV–MS–NMR).[41][42]

NMR metabonomics has lately been acknowledged as a very powerful method for classifying samples according to their overall chemical composition when combined with chemometrics, particularly principal component analysis (PCA) and simulated independent modelling of class analogies (SIMCA) algorithms. High-field NMR has a resolution that is orders of magnitude higher than existing fingerprinting technologies like traditional NMR spectrometry or HPLC. This is a way of fingerprinting the whole chemical composition of materials that is nonreductive.[43]-[46]

One of the factors mentioned in pharmacopoeias is the presence of hazardous metals. Atomic absorption spectrometry is the most common method for detecting and quantifying components in most tests (AAS).

Inductively coupled plasma–optical emission spectrometry (ICP–OES) is one of several instruments that have been created based on the same idea. Inductively coupled plasma–mass spectrometry (ICP–MS) has been used to detect and quantify substances using mass spectrometry.[47]

DNA FINGERPRINTING TECHNIQUE

DNA analysis has been shown to be a significant tool in the standardization of herbal drugs. This technique can be used to distinguish genuine medicine from substituted or counterfeit drug that is phytochemically indistinguishable. According to reports, the DNA fingerprint genome remains constant regardless of the plant part employed, however phytochemical content varies depending on the plant part, physiology, and environment.[48] Because most plants, even those belonging to the same genus and species, can display significant diversity between strains, genotypic characterization of plant species and strains is helpful.

The availability of intact genomic DNA from plant samples after they have been treated is another reason for employing DNA fingerprinting on commercial herbal medications. Even in processed samples, adulterants can be identified, allowing the medicine to be authenticated.[49]

DNA markers are useful for identifying cells, individuals, or species because they may be utilised to replace faulty proteins with normal, working proteins. Furthermore, these markers aid in the treatment of a variety of ailments and aid in the differentiation of genuine herb from contaminated medicine. ISSR markers have been used to distinguish Cannabis sativa and Arabidopsis thaliana L. Heyne from their contaminated counterparts.

ROLE OF GENERIC MARKER IN STANDERDISATION OF POLYHURBAL FORMULATION

A short DNA sequence, such as one surrounding a single base-pair alteration (single nucleotide polymorphism SNP), a lengthy one, such as minisatellites, can be used as a genetic marker. RFLP (Restriction fragment length polymorphism), AFLP (or Amplified fragment length polymorphism), RAPD (Random amplification of polymorphic DNA), VNTR (Variable number tandem repeat), Micro satellite polymorphism- SNP (Single nucleotide polymorphism), STR (Short tandem repeat), SFP (Short tandem repeat) are some of the most commonly used genetic markers (Single feature polymorphism).[51][52] They can be classified further. Differentiating distinct accessions of neem gathered from different geographical regions has proven to be effective using RAPD-based molecular markers. Crop fingerprinting is used extensively on rice wheat, chickpea, pigeon pea, pearl millet, and other crops.[53]

SCAR, AP–PCR, RAPD, and RFLP have all been used to successfully distinguish these plants and detect substitution by closely related species. P. quinquefolium (American ginseng) is a common alternative for P. ginseng [54]. Piper longum micropropogated plants have been selected for conservation using RAPD markers in the past.[55][56]

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