



## Wound Healing: Concepts and Updates in Herbal Medicine

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### ABSTRACT

Wound is a common injury due to internal and or external factors, which are subsequently associated with many immunological events, including necrosis, inflammation, etc. Significant amounts of tissue damage and infection are two silent features of wound along with other co-morbidities. Wound healing is a complex process where immunohistochemistry, tissue regeneration, and remodeling are predominant events. Since early human life, there are many traditional procedures are in use to treat wounds of various kind. However, the modern medical practices are rapidly growing in wound healing, traditional herbal medicine and use of medicinal plant products are showing equal ability and drawing the attention of medical practitioners. Herbal/traditional medicine is one of the oldest procedures in countries like India and China. In recent days, it has become reliable option in developed nations such as USA, UK, and other European nations for treatment of many deadly diseases including cancer. India is one of the biggest biodiversity reservoirs in the world with vast range of plant species and high access to the ancient medical practices. According to the WHO data and available sources, there more than 80% world population depends on herbal medical products. This indicates that despite the lack of clinical and scientific evidences, the herbal or traditional market is growing at rapid pace. In this literature review, we presented the role of herbal medicine in wound healing, some of the common medicinal plants, the quality, safety, and efficacy concerns of herbal medical products.

**Keywords:** Plants, Medicinal, Developed countries, Wound healing, Phytotherapy, Medicine, Traditional

### INTRODUCTION

The human-plant relationship has been established in ancient civilizations and considerably one of the long-standing [1]. In the past medicinal preparations were mostly derived from plants, either in simple form from different plant parts or in complex form as crude extracts or mixtures. At present, a substantial number of drugs are derived from plants, which are highly effective for treating several life-threatening diseases [2]. Majority of the compounds isolated from plants are active ingredients or chemical compounds found particularly in that medicinal plant or a subsequent modification of it. Nearly 25% of the therapeutic drugs in developing countries are either plant based, or plant derivatives and their medicinal use is well known within the indigenous people of the rural areas in many countries [3,4]. Discoveries of the healing power of plants by our ancestors were a result of the many trail and errors, but the effectiveness of medicinal plant therapies based on the empirical findings of hundreds and thousands of years is remarkable, even after many erroneous attributions made of the therapeutic properties of plants [5].

Wound infection is one of the most common diseases in developing countries because of poor hygienic conditions [6]. Wounds are the physical injuries that result in an opening or breaking of the skin or break in the epithelial integrity of the skin and may be accompanied by disruption of the structure and function of underlying normal tissue which may result from a contusion, hematoma, laceration, or an abrasion [7,8]. Therefore, appropriate methods of healing are essential for restoration of skin and physiological conditions. Wound healing starts from the moment the injury cause and extend according to the rate at which the four stages completes: Hemostasis Phase, inflammatory phase, proliferate phase, and remodeling phase depending on the extent of damage and eventually determines the appearance and strength of the tissue healed [9]. Metabolic disturbances, disease conditions disrupt the regenerative

process, thus delaying the healing mechanism. Thereby, it imposes huge financial burden for both developing and undeveloped countries. This resulted in exploring alternative and cost-effective therapeutics based on traditional plant-based medicines [10].

A study conducted in Colombia reported that people from small isolated villages and native communities use folk medicine for the treatment of common infections [11,12]. These communities are familiar in diagnosing diseases, treating wounds, setting bones, and making herbal medicines. The patients of these communities have a reduced risk of getting infectious diseases from resistant organisms than people of urban areas treated with antibiotics and also have the possibility of getting nosocomial infections from hospitals. This is the reason traditional healers claim that herbal medicines are more effective than modern medicine [11,13].

Infectious diseases are the world's leading cause of premature deaths, killing almost 50,000 people every day [14]. The major cause of morbidity and mortality in many developing countries is mainly due to diarrhea. Other bacterial etiologic agents such as pathogenic *Escherichia coli*, *Salmonella* spp., *Staphylococcus aureus* are also the reason for many common infections around the world. In recent reports, cases of drug resistance against human pathogenic bacteria are also reported from all around the world due to the excessive and extensive use of antibiotics [15-17]. In addition to the scenario, these antibiotics sometimes initiate certain adverse effects such as hypersensitivity, immunosuppression, and allergic reactions [18-20]. Therefore, treating infectious diseases in a clinical setting has become a global challenge [21]. This indicates the demand for developing alternative antimicrobial therapies and drugs for the treatment of infectious diseases. Among the well-known approaches, screening local medicinal plants for possible antimicrobial properties are a reliable option, as most of the plant materials remain an important recourse to combat serious diseases. According to World Health Organization (WHO), nearly 80% of the world's population depends on traditional medicine and therapies, which involves the use of active constituents from various plant extracts. Research on plants and identifying antimicrobial agents is an emerging field that integrates microbiology and Ethnobotany [22].

## LITERATURE REVIEW

### Commonly Used Medicinal Plants as Wound Healers

People from both developed and developing countries depend upon herbal therapeutics for primary healthcare. The use of traditional medicine is determined by various factors such as availability, affordability, and its firm embedment in the beliefs of people [23]. In this section, we present few plants that are widely available and have significant medicinal benefits including wound healing property.

#### *Aloe vera*

*Aloe vera*, commonly known as Kumari, used as an herbal medicine found in all over India. Morphologically *Aloe vera* has short stem with shallow root system and large fleshy leaves. It grows as wild plant in deserts of India [24,25].

There are more than 100 active components found in *Aloe vera*, possessing wound healing properties as well as astringent, hemostatic, antidiabetic, antiulcer, antiseptic, antibacterial, anti-inflammatory, antioxidant, anticancer, antidiarrheal [26]. According to a study by Saini, et al. [23], *Aloe vera* leaves pulp has comparatively better and faster wound healing capacity than Povidone Iodine ointment (5% w/w) on excision wound model [27].

It has also been reported that, *Aloe vera* not only speeds up healing but also protects affected surface from getting infected by microbes. *Aloe vera* is reported to enhance collagen turnover rate and enhance the level of lysyl oxidase which cross-links newly synthesized collagen [28]. *Aloe vera* also have ulcer healing property (when taken internally) and gives protection to skin [25].

*Aloe vera* gel if topically applied significantly increases wound contraction and wound closure. It has a significant influence on the level of collagen, which acts as the precursor protein for wound healing. Histological studies reported that *Aloe vera* gel accelerates epithelialization, neo-vascularization and increased wound contraction in the later stage of the wound healing process [29]. Its healing property is attributed to a compound called glucomannan, which consists of polysaccharides. This compound affects fibroblast growth factor and influences the activity and proliferation of these cells, thereby upregulates collagen production and secretion. The mucilage of *Aloe vera* also increases transversal connections among collagen bands without changing collagen structure, therefore accelerates wound improvement [30,31].

### Tulsi

*Ocimum sanctum* (Sanskrit: Tulasi; family: Labiaceae), is found entirely in subtropical and tropical parts of India. Different parts of the plant are traditionally used in Ayurveda and Siddha systems for the treatment of various ailments like infections, skin diseases, liver diseases and as an antidote for snake bite and scorpion sting [32,33]. *Ocimum sanctum* leaves consists of tannins like gallic acid, chlorogenic acid, etc. and contain alkaloids, glycosides, and saponins along with the volatile oil. The major active component of basil leave is urosolic acid. It consists of 70% eugenol, carvenol and eugenol-methyl-ether [34].

The free radical scavenging activity of *Ocimum sanctum* products is the major mechanism, by which it protects against cellular damage [35]. *Ocimum sanctum* plays a key role in wound healing process by actively involving at various levels of immune mechanisms, such as antibody production, release of hypersensitivity reaction mediators and response of tissues to these mediators in the target sites [36]. It has been reported that, *Ocimum sanctum* shows various activities such as gastroduodenal ulcer protection, antisecretory and gastric mucosal defense enhancement. The leaves of *Ocimum sanctum* contain volatile oil, which is composed of limonene, borneol, copaene, caryophyllene and elemol; phenolic compounds (rosmarinic acid, apigenin, cirsimaritin, isothymusin), flavonoids (orientin, vicenin) and aromatic compounds (methyl chavicol, methyl eugenol) [37,38] that are responsible for wound healing.

*Ocimum sanctum* products increase the level of TNF-alpha in the wound healing phase [39]. Phytochemical screening revealed that the presence of flavonoids in *Ocimum sanctum* helps in free radical scavenging, which helps to decrease oxidative stress, responsible for acute and chronic inflammatory conditions [40,41]. Since *Ocimum sanctum* grows ubiquitously or abundantly, it could be a cost effective therapeutic for wound management as a prohealer and abnormal healing controller [34].

### Eucalyptus

Eucalyptus is widely grown in Southern and some parts of Northern and Western India. It is a tall and evergreen tree, which grows well in deep, fertile, and well-drained rich soil having adequate moisture. It attains the height of more than 300 feet. Leaves of the tree on adolescent shoots are inverse, sessile, cordate-praise and secured with a somewhat blue white blossom [42]. The oil obtained from Eucalyptus globules by steam distillation of fresh leaves, is known as Dinkum Oil. It is used in skin care to treat wounds, herpes, burns, skin infections, blisters, cuts, and insect bites. Moreover, it boosts immune system and helps in the treatment of chicken pox, common cold, flu and measles. An oil extracted from Eucalyptus, is utilized against irritation, as an antiseptic and expectorant [25,43]. The extracts of *Eucalyptus citriodorais* are very effective for treating dermal wounds, both by topical and oral administration. These extracts accelerate wound healing in all the phases [44].

The mechanism of action of these concentrates was proposed by means of angiogenesis, collagen deposition, granulation tissue formation, epithelization, and wound contraction at the proliferative stage. These actions are attributed to the synergistic effects of the phytoconstituents like phenolic compounds, flavonoids, and tannins in the extract. These activities are attributed to the synergistic impacts of phytochemicals such as phenolic mixes, flavonoids, and tannins in the concentrates [44]. The antibacterial activity of Eucalyptus extracts is majorly due to their compounds such as 1,8-cineole, citronellal, citronellol, citronellyl acetate, p-cymene, eucamalol, limonene, linalool,  $\beta$ - pinene,  $\gamma$ -terpinene,  $\alpha$ - terpinol, alloocimene and aromadendrene [45,46]. In the international pharmacopeia, Eucalyptus species are represented as well-known medicinal plants because of their biological and pharmacological properties. Eucalyptus globulus (E. globulus) is the major furnisher of essential oils which are of great demand in the market [47], because of their applications in anesthetic, anodyne, antiseptic, astringent, deodorant, diaphoretic, disinfectant, etc. activities. It is also used as a remedy for arthritis, asthma, boils, bronchitis, burns, cancer, diabetes, diarrhea, diphtheria, dysentery, encephalitis, fever, flu, inflammation, laryngalgia, laryngitis, leprosy, malaria, sores, sore throat, spasms, trachalgia, worms and wounds [47-49].

### Neem (*Azadirachta indica*)

Neem is an evergreen tree with small green leaves, grows up to 100 feet tall. Neem tree is found throughout India and also known as Herbal Indian Doctor [42]. *Azadirachta indica* (AI) *A. Juss* (the neem tree), member of the Meliaceae family is a popular and common tree in India. The benefits of various parts of neem tree is mentioned in the earliest Sanskrit medical writings and therefore, since Vedic time, neem tree is closer to human culture and civilization

[50,51]. All parts of the neem tree have been used traditionally for the treatment of various infirmities such as bark as analgesic and cure for fever; twig for cough, asthma, piles, worms, urinary disorder, diabetes; leaf for leprosy, eye problem, intestinal worms, anorexia, skin ulcers, cancer; flower in elimination of intestinal worms, bile suppression, phlegm; fruit in piles, intestinal worms, urinary disorder, diabetes, wounds, eye problem, leprosy, seed in leprosy, intestinal worms, cancer; and oil for leprosy, intestinal worms, gum in scabies, wounds, ulcers, skin diseases, etc. [52]. Various phytochemical constituents such as alkaloids, triterpenoids, and their glycosides, limonoids, flavonoids, fatty acids and steroids from neem tree have proven to possess anti-inflammatory, anticarcinogenic, antiulcer, antioxidant, immunomodulatory, antifungal, antibacterial, antiviral, antimalarial, antimutagenic, and antihyperglycemic properties [53-57].

Active compounds such as nimbidin, nimbin, and nimbidol present in neem, which have anti-inflammatory, antimicrobial activities help in accelerating the wound healing process. Neem also consists of a large amount of amino acids, vitamins and minerals that plays a major role in proliferation phase of wound healing process [55,58,59].

Neem alcoholic extract is used in the treatment of eczema, ringworm and scabies. Extracts neem leaves and oil from seeds have proven to show antimicrobial effect. This prevents secondary infections by microorganisms in any wound or lesion. According to clinical studies, neem inhibits inflammation as effectively as cortisone acetate, which further accelerates wound healing [60].

Neem (*A. indica*) oil is found to have significant effect in healing chronic wound and in the management of non-healing wounds, when applied topically. It helps in angiogenesis and increases DNA content. Neem and Haridra (*C. longa*) can be used in combination to treat diabetic chronic wounds in a more effective way, both have a great effect in leprotic, venous, and decubitus ulcers too [61].

### **Turmeric**

Turmeric is a spice that originates from the root of *Curcuma longa*. It is a member of the ginger family, Zingiberaceae. In Ayurveda, turmeric has been utilized for its therapeutic properties for various treatments and via various routes of administration such as topical, oral and by inhalation [62].

Turmeric (*C. longa*) used as herbal medicine for centuries in the treatment of various ailments. Curcumin (chemical compound of turmeric) has been reported of consisting significant wound healing properties along with anti-infective, anti-oxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic and anti-coagulant effects. It acts on different stages of wound healing process to fasten the process. Curcumin also has capacity to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction [63]. Curcumin accelerates the management of wound contraction by producing growth factors involved in the healing process [64].

*In vitro*, curcumin acts on wound healing in a dose dependent manner. It may be stimulatory at low doses and inhibitory at higher doses. It was reported that, curcumin facilitates fibrinolysis and cellular movement in wound healing by altering urokinase plasminogen activator expression [65].

The following properties of turmeric aids in wound healing:

- Antibiotic activity: It inhibits bacterial infection of wound by bacteria such as *E. coli*, *Staphylococcus* and *Bacillus*.
- Anti-inflammatory activity: It acts to relieve inflammation.
- Analgesic activity: Decreases pain.
- Helps in the synthesis of new skin cells and wound closure [66].

### **Bael (Stone apple)**

Bael (*Aegle marmelos*, family: Rutaceae) is a slender, aromatic, medium sized tree with 6.0-7.5 m height and 90-120 cm girth and found as a wild tree in the entire deciduous forests of India. The leaves of Bael are applied topically for wound healing [67].

The Indian subcontinental inhabitants have used *Aegle marmelos* for over 5000 years. It is an indigenous plant. In Ayurveda and in various folk medicines, its leaves, bark, roots, fruits, and seeds are extensively used to treat various

diseases. According to scientific reports, fruits of bael possesses wide range of therapeutic effects like free radical scavenging, antioxidant, inhibition of lipid peroxidation, antibacterial, antiviral, anti-diarrheal, gastroprotective, anti-ulcerative colitis, hepatoprotective, anti-diabetic, cardioprotective and radioprotective effects validating many of the ethnomedicinal uses [68,69]. Leaf extracts of *Aegle marmelos*, possesses good antioxidant power and it acts as an antigenotoxicant to heal wounds [70,71]. The active components of the root extract of *Aegle marmelos* accelerates wound healing and gives breaking strength to the healed wound [67]. Fruit pulp of *Aegle marmelos* shows wound healing effects as it increases collagen determinants and decreases inflammation [72].

### Comparison between Synthetic and Herbal Medicine

Traditional medicine (TRM) defined as the sum of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement, treatment of physical and mental illness [73]. According to WHO estimate in 1983, a majority of the population in developing countries depend on traditional and herbal medicines as their primary source of health care [74]. Over the past decade, there has been an increased global interest in traditional medical approaches and herbal medicinal products. Around the world, including 3rd world countries, where access to the modern medical technology is limited- the acceptance of traditional and herbal medicine is remarkable, alongside, large populations in developed nations also accepted herbal medicines and acupuncture [75].

There are many evidenced showed that the popularity of Complementary and Alternative Medicine (CAM) has drawn significant attention. Eisenberg et al. conducted a survey in USA and showed that the use of CAM increased from 34% in 1990 to 42% of adults in 1997 [3]. Moreover, the survey showed that the American consumers spent \$27 billion on alternative treatments, and an estimated \$5.1 billion on herbal medicines in 1997; whereas, the estimated global market for herbal medicine was approximately \$20 billion [76-78].

In the recent past, there is an increased interest in multiple medical modalities and integrative methodologies, which open door for a new age 'integrative medicine'. Integrated medicine can be defined as practicing medicine in a way that selectively incorporates elements of CAM into comprehensive treatment plans alongside orthodox methods of diagnosis and treatment [79]. It can also mean the incorporation of TRM into the general health service systems, in which both orthodox and traditional systems of medical practices are recognized [80]. In developed countries such as the United States of America, integrative medicine is meant to be the former. The rational integration of herbal medicine into modern medical practices, including cancer therapy, should be accomplished on a scientific basis, taking into an account the interrelated issues of quality, safety, and efficacy.

### Quality

A current impediment to the integration of herbal medicines into modern medical practices is the quality of plant extracts, which can affect their efficacy and/or safety. . Nevertheless, the natural treatments are also associated with risk; hence, the research on herbal medicine should be intensified and reduce the chances of misleading the public beliefs [81,82]. Studies Herbal product quality ranges from very high to very low. Studies on the quality of St. John's wort (*Hypericum perforatum* L. Hypericaceae) products showed hypericin content ranging from 22% to 140% of label claim, when analyzed using an official spectrophotometric procedure, and from 47% to 165% employing an HPLC method [83,84]. Similarly, silymarin from milk thistle (*Silybum marianum* L. Gaertn Asteraceae) was detected at 58% to 116% of the label claim [85]. In addition, in herbal medical products, the chemical composition and pharmacological differences determine the quality of a product [81]. The quality variations in botanical products are due to a number of factors, ranging from intrinsic and extrinsic influences on regulatory practices. Intrinsic and extrinsic factors including species differences, organ specificity, diurnal and seasonal variation, environment, field collection and cultivation methods, contamination, substitution, adulteration, and processing and manufacturing practices greatly affect the quality [86,87]. Botanical product quality can also be influenced by regulatory status, which varies from country to country for instance, in the European community, herbal medicines are regulated as medicine and subject to mandated standards, whereas in the United States, very few botanical products are available as prescription or over the-counter (OTC) drugs. The majority of botanicals are marketed in the United States as dietary supplements under the provisions of the Dietary Supplement Health and Education Act (DSHEA) of 1994 [88,89].

### Safety

Safety is the primary challenge in clinical settings and drug administration and recommended therapeutic doses decrease the risk of adverse events. Plant products are hundreds in number; on one hand, most of them not in the purest form, on the other hand, few of them are toxic. Therefore, suggested doses and proper administration of all herbal medicine is undercover; furthermore, many plant products are associated with mild and infrequent gastrointestinal or dermatological reactions upon administration. It has been showed that the reported adverse events are significantly less in herbal products compared to synthetic drugs [90,91].

There are some medicinal plants that persistently evoke moderate to severe reactions and should not be employed in any medical therapy. Plants including species of *Senecio*, *Crotalaria*, and *Symphytum*, which contain pyrrolizidine alkaloids having an unsaturated 1,2-double bond in the pyrrolizidine ring, should be avoided due to the hepatotoxic effect of these compounds. On the other hand, Echinacea species that contain non-hepatotoxic saturated pyrrolizidine alkaloids are safe for consumption [92]. In addition to the toxic effects/interactions of intrinsic chemical constituents, adulteration of herbal medicine with synthetic drugs or contamination with heavy metals and microbes (see above) affect the safety of these products in therapy. Where safety information is lacking on any medicinal plants being contemplated for integrative medicine use, WHO has established guidelines for such studies.

This indicates the need of well-versed validation methods in extraction, identification, and purification of plant products. In addition, well-controlled clinical cohorts are also necessary in finding the safety measures of herbal products with significant medicinal benefits.

### Efficacy

Efficacy can be defined in many ways based on procedures and methods employing in a healthcare need or treatment method and so on. However, it can be described as 'clinical effectiveness' in any medical practice. Efficacy refers the pharmacological effects and non-medical effects (drug and placebo/nocebo) of a bioactive compound. There is a criticism about herbal medicine is that there are not enough clinical data evidences available on herbal products. Moreover, lack of quality randomized trials and funding become the main problem in herbal medicine market. There were studied reported the efficacy of herbal products, for example in coherence review, plant extracts of *Harpagophytum procumbens* DC., *Salix alba* L. and *Capsicum frutescens* L., showed significant reduction in pain more than a placebo. Another coherence showed that *Hypericum perforatum* L. showed that it was equivalent in depression patients. Many studies reported that either plant part or entire plant juices can be used for treatment of common cold with no pharmacological effects. In a recent note, Medicines and Healthcare Products Regulatory Agency suggested that the use of herbal medicine is not recommended for children below 12 years of age as they are associated with risk of allergic reactions, but the estimated risk is significantly low [93-96].

Several factors are important in determining the outcome of any traditional treatment, both in experimental and clinical settings including forma mentis, beliefs, knowledge and practical abilities of the provider, as well as the positive or negative prejudices of the patient with respect to the provider of the therapy, cultural differences in the acceptability of the treatment and adherence to it, the patient-doctor encounter, and differences in access to other treatments [97]. It has been estimated that currently more than 1500 herbal products are available in the US market alone with little or no scientific documentation of either their safety or efficacy [98]. The most suitable method for a given herbal medicine should be used to assess its efficacy to validate its usefulness as an integrated therapeutic agent. In recent years, the effectiveness of a number of herbal medicines have been clinically validated, including garlic bulb [*Allium sativum* L. (Liliaceae)], andro-graphis [*Andrographis paniculata* (Burm. f) Nees (Acanthaceae)], senna leaf and fruit [*Cassia senna* L. (Fabaceae)], *Gotu kola* or Centellae herb [*Centella asiatica* (L.) Urban (Apiaceae)], black cohosh root [*Cimicifuga racemosa* (L.) Nutt. (Ranunculaceae)], turmeric or curcuma rhizome [*Curcuma longa* L. (Zingiberaceae)], Echinacea root (*Echinacea augusti-folia* and *E. pallida*), Echinacea herb (*E. pupurea*), ginkgo leaf (*Ginkgo biloba*), St. John's wort (*Hypericum perforatum*), ginseng root (*Panax ginseng*), kava kava [*Piper methysticum* Forst. (Piperaceae)], plantago seed and hustk (Plantago species), rauwolfia root (*Rauwolfia serpentine*), frangula bark (*Rhamnus frangula* L. (Rhamnaceae)), cascara (*Rhamnus purshiana* D.C.), rhubarb root (*Rheum officinale* Baill./*R. palmatum* L. (Polygonaceae)), saw palmetto (*Serenoa repens* Bartr. Small (Arecaceae)), milk thistle (*Silybum marianum*), valerian [*Valeriana officinalis* L. (Valerianaceae)], and ginger [*Zingiber officinale* Roscoe (Zingiberaceae)], among others [99]. All these herbal medicines although they have been evaluated in different

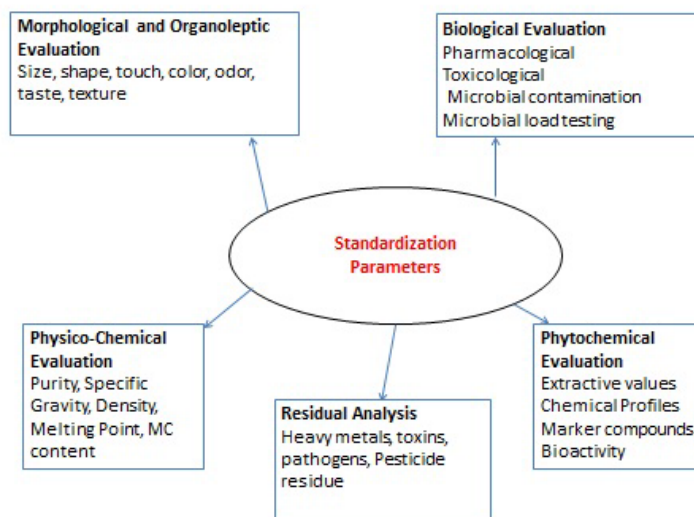
clinical trials, additional well-controlled and appropriate randomized clinical trials are still needed in order to prove their efficacy [91].

**DISCUSSION**

**Need of Standardization**

The plant extracts are providing extensive opportunities in treatment of many chronic diseases as drug leads and ingredients. Due to the unmatched availability and chemical diversity, there is great demand for plant extracts, pure forms and derivatives as medicinal products. An interesting fact is that the plant environment and genetic factors highly affect the plant biochemical composition, hence; it is necessary to standardize herbal medicinal products. Moreover, standardization protocols guarantee the quality, safety, and efficacy of the content of one or more active constituents and marker compounds. It is important to produce genetically uniform plant generations by using monocultures from the source plant; in addition, assure the biochemical consistency and optimize safety and efficacy profiles of the plant products. Another important factor affects the safety and efficacy of pant products is production at commercial scale and manufacturing protocols. Therefore, adherence to good agricultural and collection practices, good plant authentication and identification practices, good laboratory practices and good manufacturing practices are critical during analysis and manufacturing. After manufacturing, establishment of harmonized multilaboratory-validated analytical methods and vendor audits in supply chains are also equally important in post marketing (phase IV) clinical validation of the herbal medical products [100-102].

The standardization refers to prescribing a set of standards include genetic characters, constant parameters, definitive qualitative and quantitative values that determine the reproducibility, safety and efficacy of herbal medicine. The methods of standardization should include all basic aspects include botanical parameters (Identification of plants, parts of plants, phytochemical evaluation), physical parameters (ash values, extraction values, fluorescence analysis), chemical parameters (qualitative and quantitative parameters and analytical validations) and biological parameters (pharmacological, toxicological, presence of xenobiotics, microbial loading tests, contamination) in order to maintain compound consistency and quality. In herbal medical usage, pharmacopeia standards are also important that include analytical, physical and structural standards for the herbal drugs. The schematic presentation of parameters of herbal medical products is presented in Figure 1 [103,104]. However, the herbal medicine industry is one of the rapidly growing alternative medical approaches, the lack of good agricultural and collection practices and lack of transparency in raw material supply chains remain as major challenges in standardization of herbal medical products.



**Figure 1 Standardization parameters of herbal medicine**

**CONCLUSION AND FUTURE PROSPECTIVES**

The herbal/traditional medical sector is limited due to the lack of clinical evidences; however, it is not a considerable problem in current alternative and complementary medicinal era. The use of herbal products as therapeutic drugs, nutraceuticals and treatment options for many years and generations without significant side effects are influencing

researchers around the world. Moreover, being in natural forms, these herbal medicinal products are safer than synthetic drugs. In the context of understanding molecular mechanisms, it is very difficult to study pharmacokinetics and pharmacodynamics due to the availability of the multiple constituents, complexity, and their broad-spectrum bioactivity. The complexity, availability in purest forms, species differences, and genetic compositions of the plant constituents reduce the chances of standardization of procedures, quality, safety, and efficacy measures. More or less, combination of 'omics' studies with bioinformatics and other analytical techniques may provide tools for analyzing these compounds at biomolecular level, their mechanism of action and metabolic changes in biological systems. In addition, these analytical techniques may be useful in establishing the standardized chemical, pharmacological, and toxicological protocols. Within next few years, it is likely to increase the evidence-based practice in herbal medicine and establish a holistic approach for both community pharmacists and consumers with well-designed prescription protocols alongside overall pharmacovigilance of these products.

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