

“OPPORTUNITIES AND CHALLENGES IN RECENT TRENDS IN HERBAL MEDICINES”

Harsha V. Sonaye^{*1} Lalit G. Pund¹, Vikrant Chilate² and Dr. C.A. Doifode²

¹Assistant Professor, Taywade College of Pharmacy, Koradi, Nagpur.

²Principal, Taywade Institute of Diploma in Pharmacy, Koradi, Nagpur.

*Corresponding Author: Harsha V. Sonaye

Assistant Professor, Taywade College of Pharmacy, Koradi, Nagpur.

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ABSTRACT

Herbal medicines make up an important component of the trend toward alternative medicine. Herbal medicine is becoming ever more popular in today's world as people seek out natural remedies. Herbal medicines have been used since the dawn of civilization to maintain health and to treat various diseases. To compete with the growing pharmaceutical market, there is an urgency to utilize and scientifically validate more medicinally useful herbal products. With use of these advance techniques protection from toxicity, enhancement in stability, improved bioavailability of herbal formulations, protections from physical and chemical degradation can be achieved. These techniques provide improved patient compliance, sustained release and targeted action of plant actives and extracts. The present reviews gives information regarding various novel techniques used for improving safety and efficacy of phytomedicines, type of active ingredients, biological activity and application of novel formulation.

KEYWORDS: Phytomedicines, Novel drug delivery systems (NDDS), Phytosomes.

INTRODUCTION

Herbal drugs referred as plants materials or herbalism, involves the use of whole plants or parts of plants, to treat injuries or illnesses.^[1] Herbal drugs are use of therapeutic herbs to prevent and treat diseases and ailments or to support health and healing.^[2] These are drugs or preparations made from a plant or plants and used for any of such purposes. Herbal drugs are the oldest form of health care known to mankind.^[3] There are many herbal products offered that assert to treat the symptoms of a broad range of problems, from depression to cold and flu. World Health Organization^[4] (WHO) has distinct herbal drugs as complete, labelled medicinal products that have vigorous ingredients, aerial or secretive parts of the plant or other plant material or combinations. World Health Organization has set precise guidelines for the evaluation of the safety, efficacy, and quality of herbal medicines. WHO estimates that 80% of the world populations currently use herbal drugs for major healthcare. Exceptionally, in some countries herbal drugs may also enclose by tradition, natural organic or inorganic active constituents which are not of plant source. Herbal drug is a chief constituent in traditional medicine and a common constituent in ayurvedic, homeopathic, naturopathic and other medicine systems.^[5] Herbs are usually considered as safe since they belong to natural sources.^[6] The use of herbal drugs due to toxicity and side effects of allopathic medicines,

has led to rapid increase in the number of herbal drug manufacturers. For the past few decades, herbal drugs have been more and more consumed by the people with no prescription. Seeds, leaves, stems, bark, roots, flowers, and extracts of all of these have been used in herbal drugs over the millennia of their use. Herbal products have reached extensive adequacy as beneficial agents like antimicrobial, antidiabetic, antifertility, antiageing, antiarthritic, sedative, antidepressant, antianxiety, antispasmodic, analgesic, anti-inflammatory, anti-HIV, vasodilatory, hepatoprotective, treatment of cirrhosis, asthma, acne, impotence, menopause, migraine, gall stones, chronic fatigue, alzheimer's disease and memory enhancing activities.^[7] Herbal drugs have been recognized for approximately 4000 years. These drugs have survived real world testing and thousands of years of human testing. Some drugs have been discontinued due to their toxicity, while others have been modified or combined with additional herbs to counterbalance side effects.

Advantages of Herbal Drugs

- Low/Minimum cost
- potency and efficiency
- enhanced tolerance
- More protection
- fewer side-effects
- complete accessibility
- recyclable

Disadvantages of Herbal Drugs

- Not able to cure rapid sickness and accidents
- Risk with self-dosing
- Complexity in standardizations

Usage and Preparation of Herbal Drugs

The use of herbal drugs in the correct way provides effectual and safe treatment for many ailments. The efficiency of the herbal drugs is typically subjective to the patient.^[8] The strength of the herbal drugs varies based on the genetic distinction, growing conditions, timing and method of harvesting, revelation of the herbs to air, light and dampness, and type of conservation of the herbs. Some of the plants that make up herbal drugs are cultured and processed in the country and others are imported from around the world. Raw materials for herbal drugs may be derived from carefully cultivated plants or collected in the wild.^[9] Herbal drugs are accessible in several forms and often require preparation before their use. They can be normally purchased in mass form as dried plants, plant parts or insecurely packed for herbal teas and decoctions. Decoctions are made by boiling the herb in water, then straining out of the plant material. More intense forms of herbal drugs are available in the form of hydro alcoholic tinctures and fluid extracts. Methods of preparation may differ because of the nature of the plants active chemical constituents.^[10]

Analgesicactivity

The extracts of *Bougainvillea spectabilis*, *Chelidonium majus*, *Ficus glomerata*, *Dalbergia lanceolaria*, *Glauciumgrandiflorum*, *Glaucium paucilobum*, *Nepeta italic*, *Polyalthialongifolia*, *Sida acuta*, *Stylosanthes fruticosa*, *Toona ciliate*, *Zatariamultiflora*, *Zingiber zerumbet* are used as analgesic agents.

Anti-Inflammatoryactivity

The extracts of *Achillea millefolium*, *Artemisia vulgaris*, *Bauhinia tarapotensis*, *Curcuma longa*, *Forsythia suspense*, *Houttuynia cordata*, *Glycyrrhiza uralensis*, *Lonicera japonica*, *Rutagraveolens*, *Securidaca longipedunculata*, *Valeriana wallichii* have shown anti inflammatory activity.

Treatment of Diabetes Mellitus

From ancient period, peoples are using herbal plants as homeremedies for the treatment of diabetes.^[12] The various herbal plantswith antidiabetic activity are *Abroma augusta*, *Acacia melanoxyton*, *Acacia modesta*, *Acacia nilotica*, *Aconitum ferox*, *Adhatoda vasika*, *Adiantum capillus*, *Adiantum incisum*, *Agrimonia eupatoria*, *Alliumsativum*, *Aloe barbadensis*, *Althaea officinalis*, *Apiumgraveolens*, *Arctium lappa*, *Commiphora abyssinca*, *Embilicaofficinalis*, *Eucalyptus globules*, *Ginseng panax*, *Gymnema sylvestre*, *Inula helenium*, *Juniperus communis*, *Medicago sativa*, *Nigella sativa*, *Orthosiphon stamineus*, *Panax quinquefolius*, *Polygala senega*, *Plantago ovata*, *Punica granatum*, *Salvia officinalis*, *Scopariadulcis*, *Tanacetum vulgare*,

Taraxacum officinale, *Tecoma stans*, *Trifoliumalexandrinum*, *Trigonella foenum*, *Turnera diffusa*, *Urticadioica*, *Xanthium strumarium*, *Zea mays*, *Zingiber officinale*.^[11-14]

Treatment of Cancer

Medicinal plant products exhibiting anticancer activity continue to be the subject of extensive research aimed at the development of drugs for the treatment of different human tumors. The medicinal plants used for the treatment of skin cancer^[15] are, *Acalypha fruticosa*, *Alangium lamarki*, *Catharanthus roseus*, *Celastrus paniculatus*, *Embelia ribes*, *Ficus glomerata*, *Ficus racemosa*, *Nocimum basilicum*, *Plumbago zeylanica*, *Terminalia chebula*, *Tylophora indica*, *Wrightia tinctoria*. The extracts used for the treatment of breast cancer is *Buthus martensi*, *Colla cornu*, *Herba epimedii*, *Fructus lycii*, *Radix angelicae*, *Radix bupleuri*, *Rhizoma corydalis*, *Rhizoma curculiginis*, *Radix paeoniae*, *Radix glycyrrhizae*, *Scolopendra subspinipes*, *Squama manitis*, *Tuber curcumae*. The herbal medicines used for treatment of pancreatic cancer is *Emblica officinalis*, *Nigella sativa*, *Terminalia bellerica*.

Treatment of Depression

Among the various treatment options, herbal treatment is preferable due to its nontoxic and inherent healing property. A number of nutritional and herbal supplements have shown promise as alternative treatments for depression.^[16] A large number of plants have potential functions to treat depression which are described as, *Bacopa monniera*, *Panax quinquefolius*, *Piper methysticum*, *Rhodiola rosea*, *Valeriana officinalis*. St. John's wort is today most widely known as an herbal treatment for depression. St. John's Wort is the plant species *Hypericum perforatum*.

Treatment of Psoriasis

Various natural proprietary formulas and preparations containing botanical agents have been used to provide symptomatic relief in psoriasis.^[17] The various herbal remedies for psoriasis are, turmeric, curcumin, shark cartilage extract, oregano oil, milk thistle. Various antimicrobial agents *Azadirachta indica*, *Calendula officinalis*, *Cassia tora*, *Wrightia tinctoria* have been used in the management of psoriasis.

Treatment of Dental Diseases

The plants having the dental care properties^[18] are *Acacia catechu*, *Acacia arabica*, *Althea officinalis*, *Anacyclus pyrethrum*, *Azadirachta indica*, *Barleria prionitis*, *Cinnamomum camphora*, *Cuminum cyminum*, *Eucalyptus globules*, *gardenia gummifera*, *Holarrhenia antidysenterica*, *Jasminum grandiflorum*, *Juglans regia*, *Mimusops elengi*, *Myrica sapida*, *Myroxylon balsamum*, *Ochrocarpus longifolius*, *Ocimum sanctum*, *Origanum vulgare*, *Piper longum*, *Piper nigrum*, *Pistacia lentiscus*, *Pterocarpus marsupium*, *Punica granatum*, *Salvadora persica*, *Salvia officinalis*, *Solanum xanthocarpum*, *Symplocos racemosa*, *Syzygium aromaticum*, *Thalictrum*

foliolosum, *Zanthoxylum alatum*. All these regimens plays a significant role in suppressing the dental problems.^[19]

Treatment of Vitiligo

Antivitaligo oil is a herbal remedy manufactured with potent herbs and is produced with traditional methods and is also a complete traditional herbal formulation. The plants which can be used in the treatment of vitiligo^[20] are *Acorus calamus*, *Adiantum capillus*, *Boswellia serrata*, *Cassia angustifolia*, *Cassia tora*, *Cinnamomum cassia*, *Fumaria officinalis*, *Glycyhizza glabra*, *Lavandulastoechas*, *Psoralea cordyfolia*, *Pterocarpus santalinus*, *Rosa damascene*, *Sphaetanthus indicus*, *Tephrosia purpuria*, *Vitis vinifera*, *Zingiber officinale*, *Zizyphus sativa*.

Treatment of Ageing

Cell membranes are especially vulnerable to the aggression of free radicals. When the nucleus is damaged, the cell loses its ability to replicate itself. The impaired cell replication results in the weakened immune system, skin ageing and many age related disorders.^[21] Various antioxidants deactivate the free radicals and prevent oxidation on a cellular level.^[22] The most effective antioxidants include pine bark extract, grape seed extract, and blue berries were effective against the aggression of free radicals. Some commonly used herbs as antiageing agents are *Allium sativum*, *Arnica montana*, *Cucumis sativum*, *Curcuma longa*, *Ficus bengalensis*, *Lycium barbarum*, *Ocimum sanctum*, *Panax ginseng*, *Prunus amygdalus*, *Santalum album*, *Rosa damascene*, *Withania somnifera*.

Treatment of Fertility

Plant products have attracted the attention of many scientists as a primary source of naturally occurring fertility regulating agents because of their little or no side effects.^[23] The plants that have been reported to have antifertility activity are *Amaranthus retroflexus*, *Artabotrys odoratissimus*, *Barberis vulgaris*, *Carica papaya*, *Dieffenbachia seguine*, *Evodia rutacapra*, *Fatsia horrid*, *Ferula assafoetida*, *Hibiscus rosasinensis*, *Lonicera ciliosa*, *Magnolia virginiana*, *Mardenia cundurango*, *Pisum sativum*, *Podophyllum peltatum*, *Punica granatum*, *Raphanus sativus*, *Rehmanniaglutinosa*, *Semecarpus anacardium*, *Sesbania sesban*, *Stemonajaponica*, *Thuja occidentalis*, *Taxus baccata*, *Verbena officinalis*.

Phytosomes

Phytosomes are lipid compatible molecular complex, which are composed of “phyto” which means plant and “some” meaning cell-like. Most of the bioactive constituents of phyto-medicines are water-soluble molecules such as phenolics, glycosides, and flavonoids. However, these are limited in their effectiveness because of poor absorption when taken orally or when applied topically as it cannot penetrate lipoidal membrane barrier.^[24] Phytosome is a patented technology developed

by a leading manufacturer of drugs and nutraceuticals, it incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes improving their absorption and bioavailability.^[25] The Phytosomes process produces a little cell to protect the valuable components of the herbal extracts from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the hydrophobic environment of the cell membrane and from there into the cell finally reaching the blood. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions.^[26]

Ethosomes

Transdermal administration of drugs is generally limited by the barrier function of the skin. Vesicular systems are one of the most controversial methods for transdermal delivery of active substances.^[27] Ethosomes are interesting and innovative vesicular systems that have appeared in the field of pharmaceutical technology and drug delivery in recent years. This carrier presents interesting features correlated with its ability to permeate intact through the human skin due to its high deformability. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes. Ethosomes entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic.^[28] Ethosomes are soft, malleable non-invasive vesicles for enhanced delivery of active agents. It is of great importance for the design of phytomedicine to be applied topically both for topical and systemic drug administration. The size range of ethosomes may vary from tens of nanometers (nm) to microns (μ).^[29] Ethosomes are lipid based elastic vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. High concentration of ethanol enhances the topical drug delivery and prolongs the physical stability of ethosomes with respect to liposomes.^[30]

Transfersomes

The term and concept of Transfersome were introduced in 1991 by Gregor Cevc. The name means “carrying body”, and is derived from the Latin word ‘transferre’, meaning ‘to carry across’, and the Greek word ‘soma’, for a ‘body’. A Transfersome carrier is an artificial vesicle which resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery.^[31] Transfersome is a highly adaptable and stress-responsive, complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimising. This enables the transfersome to cross various transport barriers

efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents.^[32] These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency.^[33] These vesicular transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. Flexibility of transfersome membrane is achieved by mixing suitable surface-active components in the proper ratios.^[34]

Herbal Transdermal Patches

Transdermal drug delivery systems are self-contained discrete dosage form topically administered in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects.^[35] It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches. Even herbal penetration enhancers like some terpenes are found to be potential enough to replace the conventionally available penetration enhancers like DMSO (Dimethyl Sulfoxide) which has several disadvantages.^[36] Herbal Transdermal patches are medicated adhesive pad designed to release active ingredients at a constant rate over a period of several hours or days after application to skin. Skin uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into blood stream.^[37] The first commercially available prescription patch was approved by the U.S. Food and Drug administration in December 1979, which administered scopolamine for motion sickness. The most common available transdermal drug delivery patches are the over-the-counter nicotine patches that help people quit smoking.^[38]

Nanoparticles

Nanotechnology is science of matter and material that deal with the particle size in nanometers. The word "Nano" is derived from Latin word, which means dwarf (1nm=10⁻⁹m). Pharmaceutical nanotechnology embraces applications of Nano science to pharmacy as nanomaterial, and as devices like drug delivery, diagnostic, imaging and biosensor materials. Pharmaceutical nanotechnology has provided more fine-tuned diagnosis and focused treatment of disease at a molecular level. It helps in detecting the antigen associated with diseases such as cancer, diabetes mellitus, neuro-degenerative diseases as well as detecting the microorganisms and virus associated with infections. Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm.

The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.^[39] Nanoparticles offer some specific advantages such as they help to increase the stability of drugs/proteins and possess useful controlled release properties. It can be modified to achieve both active and passive targeting; drug loading is very high and can be administered by various routes such as parenteral, nasal, intra ocular and oral routes.^[40]

Nanoemulsions

Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. Nanoemulsion is a heterogeneous system and consist of two immiscible phase, one phase is oil phase other is aqueous phase, while the droplet is of submicron size range of 5-200nm.^[41] Nanoemulsions/Sub-micron emulsion (SMEs)/Miniemulsions/ Ultrafine emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. Nanoemulsion, which is categorized as multiphase colloidal dispersion, is generally characterized by its stability and clarity. Nanoemulsion is formed readily and sometimes spontaneously, generally without high energy input. In many cases a co-surfactant or co-solvent is used in addition to the surfactant, the oil phase and the water phase.^[42] Nanoemulsions are made from surfactants approved for human consumption and common food substances that are "Generally Recognized as Safe" (GRAS) by the FDA.^[43] There is an application of high shear generally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale.^[44] Since, the preparation of the first nanoemulsion in 1940s, it can be of three types such as oil-in-water (O/W), water in- oil (W/O), and bicontinuous. The transformation between these three types can be achieved by varying the components of the emulsions.^[45]

Microemulsion

The microemulsion concept was introduced in 1940 by Hoar and Schulman who generated a clear single-phase solution by titrating a formed milky emulsion with alcohol.^[46] In 1959, Schulman et al. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions".^[47] Microemulsions is homogeneous,

transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a co-surfactant and whose diameter is in the range of 10- 140 nm.^[48] They are promising delivery systems which allow sustained or controlled drug release for percutaneous, peroral, topical, transdermal, ocular and parenteral administration of medicaments. Enhanced absorption of drugs, modulation of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process.^[49] Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. Structurally, they are divided into oil-in-water (o/w), water in oil (w/o) and bicontinuous microemulsions. Recently, there has been a considerable interest for the microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilization capacity, long shelf life, ease of preparation and improvement of bioavailability. A microemulsion generally consists of four different components, a lipophilic phase, a hydrophilic phase, surfactant and co-surfactant.^[50]

CONCLUSION

Medicinal herbs as potential source of therapeutics aids has attained a significant role in health care system all over the world for human beings not only in the diseased condition but also as potential material for maintaining proper health. It is clear that the herbal industry can make great strides in the world. With the increased use of herbal products, the future worldwide labeling practice should adequately address quality aspects. Standardization of methods and quality control data on safety and efficacy are required for understanding of the use of herbal medicines. A major factor impeding the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants. Extensive research is going on for herbal drugs to incorporate them in novel drug delivery systems. Application of these novel techniques to natural medicines will led to enhanced bioavailability, reduced toxicity, sustained release action, protection from GI degradation which cannot be obtained through conventional drug delivery system due to large molecular size, poor solubility, degradation of herbal medicines in GI media. Constituents like flavonoids, tannins, terpenoids, when incorporated into novel techniques showed enhanced bioactivity and targeted action at low therapeutic dose. Hence incorporation of herbal drugs into novel delivery techniques is also adopted on the industrial scale.

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