Review Article

DIFFERENT APPROACHES TO FORMULATION OF HERBAL EXTRACTS /PHYTOPHARMACEUTICALS /BIOACTIVE PHYTOCONSTITUENTS - A REVIEW

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ABSTRACT

The use of traditional medicines and phytopharmaceuticals for treating various ailments dates back several centuries. The aim of the present review is based on relevant data on the different approaches to formulation of various natural compounds from ethnomedicinal plants. Attempts are also being made to enumerate the possible leads from traditional medicinal system for the treatment of diseases. We tried to provide the readers with the array of processes, which can be further worked upon in clinical studies. Finally, this paper puts forth issues that need to be addressed by researchers in the future with respect to standardization of phytopharmaceuticals.

Keywords: Phytopharmaceuticals, bioactive, phytoconstituents, ethnomedicinal plants, phytosome, herbosome.

INTRODUCTION

Herbal medicine is a practice as old as mankind and during the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and to confirm the indications of traditional medicine. Interest in phytomedicine has exploded in the last few years and about 500 different plant species are used as key ingredients and many are still being collected from the wild[1]. The concept of complementary or alternative medicine is increasingly becoming more widely accepted and there is a corresponding rising interest in herbal remedies[2]. The whole leaf of *Aloe vera* (*A. barbadensis*) (Fam. Liliaceace) is known to aid cellular repair as well as digestion, assimilation of foods, vitamins, minerals and other vital nutrients to rejuvenate the skin[3]. The fresh gel, juice or formulated products have been used for medical and cosmetic purposes and to enhance general health[4]. Herbal medicine dates back thousands of years. It originated in India and China and it is still widely used in Asia[5]. Ethnopharmacologists, botanists, microbiologists and natural-products chemists are combing the earth for phytochemicals and which could be developed for treatment of infectious diseases. It is estimated that there are 250,000–500,000 species of plants on Earth. Recognition of their clinical, pharmaceutical and economic value is still growing, although this varies widely between countries. The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years [5]. Plants play a dominant role in the introduction of new therapeutic agents as they help to alleviate human ailments. The therapeutic potential including antioxidant, antimutagenic and anticarcinogenic properties of higher plants are due to the presence of secondary metabolites[6, 7]. The recent resurgence of interest in plant remedies has been spurred on by several factors: the effectiveness of plant medicines, the preference of consumers for natural therapies, a greater interest in alternative medicines and a commonly held erroneous belief that herbal products are superior to manufactured products, a dissatisfaction with the results from synthetic drugs and the belief that herbal medicines might be effective in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate, the high cost and side effects of most modern drugs, improvements in the quality, efficacy, and safety of herbal medicines with the development of science and technology, patients' belief that their physicians have not properly identified the problem; hence they feel that herbal remedies are another option, a movement towards self-medication[8-11]. Secondary metabolites are of prime importance for humankind as they prevent the onset of different degenerative diseases by scavenging free radicals and thus preventing chain-reactions mediated damage or binding with catalysts of the oxidative reactions, such as some metal ions[12-14]. Distilled essential oils have been employed as medicines since the invention of distillation in the eleventh century[15] when Avicenna isolated essential oils using steam distillation. Recently, the role of herbal drugs, herbal products and certain phytochemicals in the control of ageing has been shown[2, 16]. The leaves of *Aloe vera* (*A. barbadensis*) (Fam. Liliaceace) are the source of *aloe vera* Gel, *Emblica officinalis* Gaertn., commonly known as amla, is a rich dietary source of vitamin C, minerals and amino acids[17]. Saffron, the dried stigma of the plant *Crocus sativus* L, popularly used as a spice and food colorant, has been used in traditional medicine for the treatment of many diseases including tumors, *Peumus boldus* belonging to the family Monimiaceae (a tree whose leaves have been traditionally employed in folk medicine) is now widely recognized as an herbal remedy by a number of Pharmacopoeias[18].

In a recent study, it was found that the different extract/fractions of *Chukrasia tabularis* were helpful in minimizing the peroxyl radical mediated damage to the polyunsaturated fatty acids[19, 20]. Due to this property the plant may play a potential role in preventing food spoilage arising due to lipid peroxidation. Also the bark of the plant is rich in dyes, so it might be used as food additive.

Different approaches to drug discovery using higher plants can be distinguished: random selection followed by chemical screening; random selection followed by one or more biological assays; biological activity reports and ethnomedical use of plants[21]. The latter approach includes plants used in traditional medical systems; herbalism, folklore, and shamanism and the use of databases and objective are the isolation of new bioactive phytocompounds. When an active extract has been identified, the first task to be taken is the identification of the bioactive phytocompounds and this can mean either a full identification of a bioactive phytocompound after purification or partial identification to the level of a family of known compounds[22]. Quality control directly impacts the safety and efficacy of herbal medicinal products[23] as quality control for the efficacy and safety of herbal products is essential. A particular plant part will have many constituents and some of them may well be toxic. However, it may take more to cause toxicity, because herbs usually are not as potent as manufactured drugs, and compared with synthetic drugs the adverse effects of most herbal drugs are relatively infrequent[24,10,25]. In the early 1980s, however, there was a resurgence of interest in the use of natural substances generally known today as bioactive phytocompounds. Today, the use of medicinal plants and their bioactive phytocompounds and our scientific knowledge about them comprise the modern field of the phytosciences. It has long been known that garlic and onion have an anti-aggregation effect on platelets and several mechanisms appear to be associated with this process, such as modification of the platelet membrane properties, inhibition of calcium mobilization and inhibition steps of the arachidonic acid cascade in blood platelets[26, 27]. Administration of 800 mg of garlic powder to a human over a period of four weeks made spontaneous platelet aggregation disappear [28].

The different approaches to formulation of novel drug delivery of bioactive phytoconstituents are explored in his review work

UNIT OPERATIONS/STAGES INVOLVED IN HERBAL FORMULATIONS

There are several methods or operation involved in obtaining the herbal extract/phytopharmaceuticals/ bioactive phytoconstituents and these depend to some extent on the particular part of the plant which is being used. The main objective of each process is to obtain the extract in a pure state and free from any contaminating materials which may affect the odor, the physicochemical or pharmacological properties of the final formulation.

Grinding

The selected plant material is dried and subjected to powdering with the help of a hammer mill or disc pulverizer which has built in sieves. This will help to disintegrate the organ, tissue and cell structure of the plant material so that the medicinal ingredients present therein are exposed to the solvents with which it is to be extracted.

Extraction

This involves the separation of medicinally active principles from the plant material with the help of a suitable solvent. It could be hot aqueous extraction (decoction), cold percolation or solvent extraction using soxhlet extractor.

Filtration

This technique entails the separation of the extract so obtained from the marc (exhausted plant material) by allowing it to trickle into a hold tank through the built-in false bottom of the extractor which is covered with a filter cloth.

Concentration

The liquid extract so obtained is fed into a wiped film evaporator and concentration is carried out under vacuum to get concentrated extract.

Spray drying

The concentrated extract is subjected to a spray drier with the help of a high pressure pump at a controlled feed rate to get dry powder.

Distillation

This process is used for the preparation of oils of geranium, neroli**,** lavender, chamomile, lemon grass, etc. It is one of the oldest methods used to obtain oil from plants. It is essentially a heat process, the heat being used to drive the oil from the plant tissue. The plant or part of a plant being used must be in such a condition that steam and water will readily penetrate it. Garlic oil extracted by distillation in boiling water consists of dimethylsulfides, diallylsulfides, methyl allyl sulfides, and others, which have all been shown to process biological properties such as antioxidant effects. However, it lacks bactericidal and antithrombotic activity. It is known that the processing of garlic and onion into extracts, essence and dehydrated foods leads to the formation of products with significantly different physicochemical and biological characteristics [29]. Essential oils as complex natural mixtures of volatile secondary metabolites can be isolated from plants by hydro or steam distillation (citrus peel oils).

Expression

This is use for example in citrus oils. Expression means that the oils are expressed or pressed out of the peel of the almost ripe fruit, usually by using powerful hydraulic presses enclosed in a hollow cylinder, the walls of which are perforated like a sieve to allow the juice and oils to

escape as the pressure is applied. The expressed liquid is of a milky appearance and is allowed to stand for several hours during which time the oil floats to the surface and can be separated and finally filtered. Essential oils which are complex natural mixtures of volatile secondary metabolites can also be isolated from plants by expression (citrus peel oils).

Extraction

This is the process of treating the flowers or plants with solvents selected to dissolve the essential part of the plant that contains the required active pharmaceutical ingredient (API). The choice of solvent and the process used has been determined by experience so as to give the best yield and the best quality of the active pharmaceutical ingredient. Some of the finest and most delicate natural fragrances are obtained by this method, as there is no possibility of the oil being affected by the action of heat or steam which can sometimes occur when a distillation process is used. Also this process is used for polymeric materials as increase in temperature due to heat application will affect the physicochemical properties of the polymeric material. According to Dibua and Nnamani [30], this method can be employed in extraction of tobacco leaves (*Nicotiana Spp*)**,** clove seeds (*S. aromaticum*) and bitter kola fruits (*C. cola*) by grinding them into powder using a local grinding machine and soaking 25 g each in 250 ml of n-hexane, hot water and ethanol.

Enfleurage

This is an extraction process. The process known as enfleurage is used for extraction of the oils of the jasmin and neroli flowers. Purified lard is used as the solvent and this is spread on to glass plates which are laid on wooden frames and covered with the flowers. Several frames are laid one above the other in tiers and left for a day or two, during which time the oil is absorbed on to the fat without application of heat. The withered flowers are then removed and replaced by fresh ones and the process is repeated until that fat has absorbed all the perfume present and has acquired the desired strength of odour.

Maceration

Maceration is used to extract oils from acacia, rose, violet and neroli. The lard or else a mixture of lard and vegetable oil, is placed in enameled iron pots and heated to a temperature of about 40-5^{o}C. The flowers are either mixed loosely with warm fat or enclosed in linen bags and allowed to hang in the fat. The mix is stirred for one or two days. The flowers are then removed and fresh flowers added and the process is repeated until the fat/oil mixture is saturated. The essential oil is extracted from the fatty pomade by mixing and agitating gently with strong alcohol which dissolves the essential oils and separates them from the fat. The alcoholic oil solution is allowed to settle and the alcohol is removed by distilling at a low temperature.

Cold maceration with water

This method of preparation is certainly the easiest. The fresh or dried plant material is simply covered in cool water and soaked overnight. The herb is strained out and the liquid is taken. This is used for very tender plants and/or fresh plants or those with delicate chemicals that might be harmed by heating or which might be degraded in strong alcohol. This is also the easiest to adapt to western methods, since tablets or capsules can be used instead.

Maceration with non polar solvents

Maceration is used to extract oils from acacia, rose, violet and neroli. The lard or else a mixture of lard and vegetable oil is placed in enameled iron pots and heated to a temperature of about 40-50^{o}C**.** The flowers are either mixed loosely with warm fat or enclosed in linen bags and allowed to hang in the fat. The mix is stirred for one or two days. The flowers are then removed and fresh flowers added and the process is repeated until the fat/oil mixture is saturated. The essential oil is then extracted from the fatty pomade by mixing and agitating gently with strong alcohol which dissolves the essential oils and separates them from the fat. The alcoholic oil solution is allowed to settle. Finally, the alcohol is removed by distilling at a low temperature.

ORTHODOX FORMULATIONS AND METHODS OF DELIVERY OF HERBAL EXTRACTS

Infusions

Infusions are typically used for delicate herbs, leaves and fresh tender plants. Preparing an infusion is much like making a cup of tea. Water is brought just to a boil and then poured over an herb (or combination of herbs), covered and allowed to sit/steep for 10-15 minutes or so. It can be prepared in the drinking cup (by just pouring the heated water over the herb in the cup) or by dropping the herb into the pot which the water was heated in. Empty gauze tea-bags are even available at some herb stores which can be filled with herbs and then sealed with an iron. If an infusion is prepared in the heating pan/pot, it's best to use a ceramic pot with a lid (avoid metal pots). The ratio of herb to water can vary depending on the remedy, the plant, and whether cut herb or powdered herb is used. Standard dosages of infusions are generally one teacup (6-8 ounces), two to three times daily. The exceptions are the more aromatic plants with active essential oils. These are best prepared in single dosages (by the cupful) as needed and taken immediately (and while still hot/warm). According to [31] in preparation of *Ocimum gratissimum* infusion, fresh leaves of the plant are rinsed under running tap water. The leaves were placed in 100 ml of distilled water in a beaker placed in a boiling water bath, in order to ensure indirect heating of the plant materials.

Decoctions

Decoctions are usually the method of choice when working with tougher and more fibrous plants, barks and

roots (and which have water soluble chemicals)[32]. Instead of just steeping it in hot water, the plant material is boiled for a longer period of time to soften the harder woody material and release its active constituents. The amount of herbs needed is measured (usually a ratio of 1 teaspoon powdered herbs or 2 teaspoons of cut herbs to 8 ounces of water) into a ceramic pot with a snug fitting lid and the proper amount of cold water is added depending on how many cups of the decoction you wish to prepare and heated to boiling. If using cut herbs, strain the mixture through a tea strainer into a teacup. When straining, make sure to press on the cut herb pieces in the strainer to get as much liquid/decoction out of the herb pieces as possible. If using powdered herb, allow the powder to settle to the bottom of the pot and then pour off the decoction from the top into a teacup (any sediment missed will settle to the bottom of the teacup). Standard dosages for decoction are generally one-half to one cup, two or three times daily.

Strong Decoctions

Depending on the type of plant material used, strong decoctions are prepared in two general ways. The first involves boiling the mixture longer about 2 h or more which is indicated for working with larger woody pieces of bark to break it down. Alternatively, when smaller woody pieces are used yet a stronger remedy is wanted, the decoction is prepared as above (boiling 20 minutes), then it is allowed to sit/soak overnight before straining out the herb. When straining, again, make sure to press on the cut herb pieces in the strainer to get as much moisture/decoction out of the herb pieces [32]. This method can be applied for *Azadiractha Indica (*Neem*)* roots and stem for the treatment of malaria.

Tinctures

Tincture is an alcohol and water extract which is used when plants have active chemicals that are not very soluble in water, and/or when a larger quantity is prepared for convenience and wanted for longer term storage. Many properly prepared plant tinctures can last several years or more without losing potency. The percentage of alcohol usually helps determine its shelf-life: the more alcohol used, the longer the shelf life. Sometimes the percentage of alcohol and water is unique to the herbs that are used as some active ingredients are more soluble in alcohol and others more soluble in water. A "standard 4:1 tincture" usually means 1 part herb to 4 parts liquid (or 1 ounce herb to 4 ounces of liquid). When garlic is extracted with ethanol and water at room temperature, it yields the oxide of diallyl disulfide, allicin, which is the source of the garlic odor. Under the influence of allinase the precursor alliin decomposes to 2-propenesulfenic acid. Allicin possesses hypolipidemic, antimicrobial, and hypoglycemic activities[29] and heat-unstable allicin is considered to be a principal antibacterial constituent [33]. Thus it seems that garlic contains two types of antibacterial ingredients: the heat-labile allicin and heat-stable sulfur compounds [34], both of which work together against bacteria.

Poultices and Compresses

Poultices are prepared in various ways (from the jungle shaman chewing up fresh leaves or roots and spitting them out onto the skin, to mashing up fresh leaves or roots by hand or with a mortar and pestle). A light cotton bandage to bind the poultice to the area is generally used (or in the jungle, a nice large flexible leaf is commonly employed and tied with a bit of twine). Compresses are simply soaking a cloth in a prepared infusion, tincture or decoction and laying the cloth onto the affected part of the body/skin. More specific adaptations and directions where applicable are found in the main plant section under "Traditional Remedy" where it might say to apply an infusion or decoction topically [32].

Preparing plants in hot baths (in which the patient is soaked in it or bathed with it)

Quite a few popular remedies which have been used for thousands of years are prepared as vapor baths or medicinal plants are added to bath water and the patient is soaked in it. This method is not unlike some of the currently evolving dermal delivery systems for drug absorption being employed in conventional medicine. Since fresh plants are generally used for bathing remedies (chopped or crushed first before adding to the bath water), western adaptations are not always possible when only dried plant materials are available here [32].

Inhalation therapy

The use of therapeutic material whether powders, liquids, vapours or gases through the inspired air has revolutionised into a medical sub-speciality known as Inhalation therapy. Some medical centres adopted the term “Respiratory Therapy” which is a limited term for that specialisation that covers only the treatment of the respiratory troubles, ignoring the other body parts. Nowadays in nearly all medical specialities there is one procedure or more in which the medicaments are taken through inhalation by different means for many body ailments. Forms of Drug Inhalation**:** Smoke of burnt reeds, plants or minerals); powder for snuffing or insufflation; liquids inhaled by dropper, sprayer, atomizer or nebulizer; vapours inhaled by inhalers, aporizers or humidifier gases, therapeutic or anaesthetic exist [35-39].

Capsules

Powdered herbs are taken as capsule but can be sprinkled on food or taken with water. Externally they can be applied as dusting powder to the skin. In the preparation, pour the powder into a saucer and slide the capsule halves towards one another, scooping up the powder. When the halves of the capsule are full of powder, slide them together without spilling the powder and store in an air-tight, dark glass container in a cool place for up to 3-4 months. The preparations can be used for treatment

includes *Barosma betulina* for cystitis, *Allium sativum* for hypertension, *Zingiber officinale* for hyperacidity etc.

Medicated wines

Medicated wines are also called tonic wines. These are an agreeable way to take strengthening and tonic herbs to increase vitality and improve indigestion. Wine is less stimulating for the body than high proof spirit and can be used for sipping in small quantities. These wines can be used for digestive problems.

Syrups

These are preparations formulated by incorporation of sugar with infusions, decoctions, expressed juices, fermented liquors or simple water solutions. Honey and unrefined sugar are effective preservatives and can be combined with infusions or decoctions to make syrups and cordials. Syrups are made with equal proportions of a herbal infusion or decoction and honey or unrefined sugar. It may also be made with tinctures instead of infusions or decoctions. Examples of syrup which can be formulated include simple syrup, orange syrup, tolu syrup, raspberry syrup, wild cherry syrup etc

Tablets

These are the solid dosage forms of powdered herbs, herbal extracts or their constituents prepared by moulding or compression.

Ointments

These are a class of semi-solid dosage forms meant for external application to the skin or mucous membrane. Ointments perform emollient and protective action. An ointment can also be considered as a soothing, healing, slightly oily or fatty substance into which the essence of a healing plant has been dissolved; which can be accomplished by heating the fat or oil with the plant until it loses its normal colour and the oil or fat has absorbed the healing chemical principles. Ointment preparations can be used for sore legs, burns and scalds and for scabies.

Creams

Creams are viscous semi-solid ointment-like preparations which may be oil in water type (aqueous) creams or water in oil type (oily) creams.

Aromatherapy

Aromatherapy is a form of alternative medicine that uses volatile plant materials, known as essential oils and other aromatic compounds for the purpose of altering a person's mind, mood, cognitive function or health. Some essential oils such as tea tree[40] have demonstrated anti-microbial effects, but there is still a lack of clinical evidence demonstrating efficacy against bacterial, fungal or viral infections. Evidence for the efficacy of aromatherapy in treating medical conditions remains poor, with a particular lack of studies employing rigorous methodology[41], but some evidence exists that essential oils may have therapeutic potential[42]. Aromatherapy may have origins in antiquity with the use of infused aromatic oils, made by macerating dried plant material in fatty oil, heating and then filtering. Many such oils are described by Dioscorides, along with beliefs of the time regarding their healing properties, in his *De Materia Medica*, written in the first century[43] and essential oils, were used as antiseptics in the treatment of wounded soldiers during World War II[44]. The modes of application of aromatherapy include: aerial diffusion (for environmental fragrancing or aerial disinfection); direct inhalation (for respiratory disinfection, decongestion, expectoration as well as psychological effects); topical applications: for general massage, baths, compresses and therapeutic skin care. Other stated uses include pain and anxiety reduction, enhancement of energy and short-term memory, relaxation, hair loss prevention, and reduction of eczema-induced itching[45, 46]. Two basic mechanisms are offered to explain the purported effects. One is the influence of aroma on the brain especially the limbic system through the olfactory system and the other is the direct pharmacological effects of the essential oils [47].

CHALLENGES/LIMITATIONS OF ORTHODOX FORMULATIONS AND DELIVERY

The integration of herbal medicine into modern medical practices, including treatments for infections and cancer, must take into account the interrelated issues of quality, safety, and efficacy[48]. Phytopharmaceuticals are always mixtures of many constituents and are therefore very variable and difficult to characterize. However, for many herbs the active constituents are not known and in such cases, products may be standardized on the content of certain marker compounds. However herbal medicines rarely meet this standard for several reasons, including the lack of scientific information about the acting pharmacological principles. The variability in the content and concentration of constituents of plant material, together with the range of extraction techniques and processing steps used by different manufacturers results in marked variability in content and quality of commercially available herbal products [49]. The use of chromatographic techniques and marker compounds to standardize herbal preparations promotes batch-to-batch consistency but does not ensure consistent pharmacological activity or stability. But standardization of correct dosage forms is not always easy, especially in polyherbal preparations or single plants that are not cultivated under controlled condition. And there is no guarantee that a product contains the amount of the compound stated on the label [50]. The lack of pharmacological and clinical data on the majority of herbal medicinal products is a major impediment to the integration of herbal medicines into conventional medical practice. For valid integration, pharmacological and especially clinical studies must be conducted on those plants lacking such data. Adverse events, including drug–herb interactions, must also be monitored to promote a

safe integration of efficacious herbal medicine into conventional medical practices**.**

NOVEL FORMULATIONS OF HERBAL EXTRACTS

Most of the herbal formulations have low bioavailability. The bioavailability can be improved with the use of different novel delivery systems like phytosomes, liposomes, marinosomes, niosomes and photosomes etc which can enhance the rate of release as well as the capacity to cross the lipid rich biomembranes[51, 52] and thereby addresses the limitations of a traditional drug delivery system.

Phytosome

Phytosome also called phytolipids delivery system[53] is a complex between polar polyphenolics and dietary phospholipids that shows definite physicochemical and spectroscopic features. Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than the conventional herbal extracts. Recent technology of drug delivery when applied to botanicals and phytoconstituents will open new avenues to explore maximum therapeutic potential of plant substances of polar nature[54]. Phytosomes are prepared by reacting from 3-2 moles but preferably with one mole of natural or synthetic phospholipids, with one mole of component like flavolignans, flavonoligans either alone or in the natural mixture in aprotic solvent such as-dioxane or acetone. Characterization of a solid phytosome complexation and molecular interactions between phytoconstituents and phosphatidylcholine in solution can be done[55]. Extract of *Serenoa repens* (CO2 extract) extract of *Viccinium myrtillus* (Fruit extract), extract of *Colues forskohlii*, Ximenoil and Ximenynic acid extracted from *Santalum album,* Esculoside, glycosidated coumarin obtained from *Aesculus hippocastanum*, Ruscogenins, group of saponins extracted from *Ruscus aculeatus* are highly worked upon for better bioavailability through the formation of phytosomes by patented process[56]. Phytosomes have the following advantages: are better bioavailable botanical extracts, dramatically enhance bioavailability due to their complex with phospholipids and delivers faster and improved absorption in intestinal tract, They enhance the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability with significantly better therapeutic benefit, Dose requirement can be minimized as the bioavailability is increased, Phosphatidylcholine used in preparation of phytosomes besides acting as a carrier also acts as a hepatoprotective substance showing the synergistic effect when hepatoprotective substances like flavanoids are employed to form complex, Phytosomes are widely used in cosmetics due to their more skin penetration and high lipid profile and Phytosomes show better stability profile owing to the chemical bonds formed between phosphatidylcholine molecule and phytoconstituents[57, 58]. The term "herbo" means plant, while "some" means cell-like and herbosomes is also often known as phytosomes[59].

Niosome

These are microscopic, lamellar structure of novel drug delivery system in which the medication is encapsulated in a vesicle. Niosome surfactants are biodegradable, biocompatible and non-immunogenic. Delivery by transdermal route, however appears to show that the more fluid membranes appear to be more efficient. Vesicle size has not been fully characterized from the biological point of view and studies designed to systematically define the size requirement for certain pharmacodynamic objectives are solely desired.

Liposomes

Liposomes are spherical, self closed vesicles of colloidal dimensions, in which phospholipid bilayer sequesters part of the solvent, in which they freely float, into their interior[60]. In the case of one bilayer encapsulating the aqueous core one speaks either of small or large unilamellar vesicles while in the case of many concentric bilayers one defines large multilamellar vesicles[61].

Marinosome

These are liposomes made of a natural marine lipid extract, were envisaged for the prevention and treatment of skin diseases[62]. The natural lipid mixture was extracted from a marine organism and characterized in conditions that mimic that of topical application in terms of pH, temperature and calcium. Marinosomes are stable in storage conditions for up to 1 month. At low pH (pH 4) or in presence of high calcium concentrations (9 mM), complex structural rearrangements, such as aggregation and size reduction, occurred which were kinetically dependant.

Photosome

Photosome® is constituted of photolyases (a bacterial enzyme that can repair ultraviolet B (UVB)-induced cyclobutane pyrimidine dimers (CPD) in eukaryotic cells) included in liposomes[63]. Photolyases are specific enzymes that bind to the lesion and reverse the damage with the energy of light by photoreactivation. They are present from bacteria to multicellular eukaryotes, but they are missing in many species, including man[64] although recent studies have shown photorepair in humans[65]. Photolyases are monomeric flavoproteins of 50–60 kDa and contain two chromophores as cofactors. The catalytic cofactor is a flavin adenine dinucleotide (FAD) and the light-harvesting cofactor is either a folate or a deazaflavin. These photoreactivating enzymes repair directly and effectively CPD or 6-4 photoproducts by using the energy of near UV/visible light (300–500 nm). The enzymatic unit binds to the lesion in a light-independent process.

Advantages of novel formulations of herbal extracts

Herbal medicines have been widely used all over the world and have been recognized by physicians and

patients for better therapeutic value as they have fewer adverse effects as compared with modern medicines. Using scientific approach in novel drug delivery systems not only reduce the repeated administration o overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability.

FUTURE PROSPECTS OF NOVEL FORMULATIONS OF HERBAL EXTRACTS

Petiveria alliacea L. (tipi) roots has several medicinal uses in decoction or powder and the infusion of leaves is employed as antispasmodic, antirheumatic (topic use), anti-inflammatory [66], antinociceptive [67], hypoglycemiant and abortificient [68, 69], through any of the novel drug delivery formulations and has been standardized. As herbal novel drug delivery systems have a lot of potential, several researchers are working towards developing novel drug delivery systems like mouth wash dissolving tablets, sustained and extended release formulations, mucoadhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants etc of herbs; some at the laboratory stage and some have reached to the market [53]. Herbals should minimize side effects and provide safe, natural and cost effective alternatives to synthetic drugs and the detection and separation by High performance thin layer chromatography (HPTLC) confirmed the use of herbal drugs for the preparation of the polyhebral formulation possessing consistent active constituents [70].

EXPERT OPINION

The recommended approach for achieving more efficient treatments and synergistic effects of natural products should be to seek treatments using multiple products or products having multiple activities [71]. Most preparations are polyherbal in nature to take care of the multiple components of disease conditions [72].

CONCLUSION

The different approaches to formulation of bioactive constituents and the need to standardize the drug products were explored. Also to improve the bioavailability of the phytoconstituents, novel drug delivery technology should be introduced in the formulation of the products instead of the crude and conventional ways that have been in existence.

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REFERENCES

1. Mendelsohn R, Balick MJ. The value of undiscovered pharmaceuticals in tropical forests. Econ. Bot. 49:1995; 223-228.
2. Mishra AK, Mishra A, Chattopadhyay P. Herbal Cosmeceuticals for Photoprotection from Ultraviolet B Radiation: A Review. Tropical Journal of Pharmaceutical Research. 10(3):2011; 351-360.
3. Ramachandra CT, Ramachandra P. Processing of Aloe Vera Leaf Gel: A Review. Amer. J. Agri. Biol. Sci. 3(2):2008; 502-510.
4. Chithra P, Sajithlal GB, Gowri F. Influence of Aloe vera on collagen characteristics in healing dermal wounds in rats. Molecular and Cellular Biochemistry, 181:1998; 71–76.
5. Ghosh VK, Nagore DH, Kadbhane KP, Patil MJ. Different approaches of alternative medicines in acne vulgaris treatment. A Review. Orient Pharm Exp Med. 11:2011; 1–9.
6. Ko TF, Weng YB, Lin SB, Chiou RYY. Antimutagenicity of Superficial CO2 Extracts of *Terminalia catappa* Leaves and Cytotoxocity of the Extracts to Human Hepatoma Cells. J. Agric. Food Chem. 51:2003; 3564-7.
7. Schwab CE, Huber WW, Parzefall W, Hietsch G, Kassie F, Hermann RS, Knasmuller S. Search for compounds that inhibit the genotoxic and carcinogenic effects of heterocyclic aromatic amines. Crit. Rev. Toxicol. 30:2000; 1-69.
8. WHO. WHO Monographs on Selected Medicinal Plants, Vol. 2, World Health Organization, Geneva, 2002.
9. WHO. WHO Global Atlas of Traditional, Complementary and Alternative Medicine. 2 vol. set. Vol. 1 contains text and Vol. 2, maps. World Health Organization, Geneva, 2005.
10. Calixto JB. Braz. J. Med. Biol. Res. 33: 2000; 179.
11. Kong JM., Goh NK, Chia LS, Chia TF. Acta Pharm. Sinic. 24:2003; 7.
12. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers, L, Whelton PK. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am. J. Clin. Nutr. 76:2002; 93-99.
13. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. Nutr. Cancer. 18:1992; 1-29.
14. Slemmer JE, Shaka JJ, Sweeney MI, Weber JT. Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging. Curr. Med. Chem. 15: 2008; 404-414.
15. Forbes RJ. A short history of the art of distillation. Leiden: E.J. Brill. 1970. OCLC 2559231.
16. Kapoor VK, Dureja J, Chadha R. Herbals in the control of ageing. Drug Discov. Today., 14(19-20):2009; 992-998
17. Barthakur NN, Arnold NP. Chemical analysis of the emblic (*Phyllanthus emblica* L.) and its potential as a food source. Scientia Horticulturae. 47(1):1991; 99-105.
18. Peter OB, Catalina CP, Hernan S. Boldine and its antioxidant or health promoting properties. Chemico-Biological Interactions, 159:2006; 1–17.
19. Kaur R, Thind TS, Singh B, Arora S. Inhibition of lipid peroxidation by extracts/subfractions of Chickrassy (Chukrassia tabularis A. Juss.). Naturwissenschaften. 196:2009; 129-133.
20. Rajbir Kaur and Saroj Arora.Chemical constituents and biological activities of Chukrasia tabularis A. Juss - A review. Journal of Medicinal Plants Research. 3(4):2009; 196-216.
21. Eloff JN. J. Ethnopharmacol. 60:1998; 1–8.
22. Miles DH, Nguyen CL, Miles, DH. Curr. Med. Chem. 5:1998; 421–440.
23. Bannerman R, Burton J, Chen WC. eds. Traditional Medicine and Health Care Coverage. World Health Organization, Geneva, 1983.
24. Bisset NG. (ed.). Herbal Drugs and Phytopharmaceuticals. CRC Press, Boca Raton, FL, 1994.
25. Pal SK, Shukla Y. Asian J. Cancer Prev. 4:2003; 281.
26. Ariga T, Oshiba S, Tamada T. Lancet . 2:1981; 150–154.
27. Apitz-Castro R, Cabrera S, Cruz MR, Ledezma E, Jain MK. Thromb. Res. 42:1986; 303–311.
28. Nakamura YK, Matsuo T, Shimoi K, Nakamura Y, Tomita I. Biosci. Biotechnol. Biochem. 60:1996; 1439–1443.
29. Mazza G (ed.). Functional Foods. Technomic Publishing, Lancaster, PA, 1998.

30. Dibua EU, Nnamani PO. Antimicrobial properties of clove, tobacco and bitter on tooth decay. Asian Pacific Journal of Tropical Medicine. 4(10):2011; 412-420.
31. Okore VC, Asogwa CI and Nnamani PO. Evaluation of anti-diarrhoeal action of a hot-water infusion of Ocimum gratissimum, Linn. Bio-research. 7(1):2009; 422-425.
32. Leslie Taylor. The healing power of rainforest herbs (Square One Publishers, Inc.) 2004.
33. Block E. Sci. Am. *252*:1985; 114–119.
34. Steiner M, Khan AH, Holbert, D, Lin, RI-S. Am. J. Clin. Nutri. 64:1996; 866–870.
35. Collier's Encyclopedia "Tobacco" William Halsey and Louis Shores, Inc, U.S.A., Vol. 22, 1966.
36. Abdol Hafize. "Medical Pharmacologies Series" The Scientific Book Centre, Cairo, First edition, 1980.
37. A Osol. "Remington's Pharmaceutics Sciences" 16th edition, 1980.
38. St. Clair Thomson. "Diseases of the Nose and Throat". Cassell and Company LTD, 6th edition, London, 1955.
39. Wollman H., Smith T. "The Therapeutic Gases". In: The Pharmacological Basis of Therapeutics by Gilman, Goodman, 6th edition, Macmillan Publishing Company, New York, 1980.
40. Carson CF, Hammer KA, Riley TV. "Melaleuca alternifolia (Tea Tree) Oil: a Review of Antimicrobial and Other Medicinal Properties". Clinical Microbiology Reviews. 19(1): Jan. 2006; 50–62.
41. Van der Watt G, Janca A. "Aromatherapy in nursing and mental health care". Contemporary Nurse. August 30(1):2008; 69–75.
42. Edris AE. "Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: A review". Phytotherapy Research. 21(4): April 2007; 308–23.
43. Gunther RT(ed.). The Greek Herbal of Dioscorides (translated by John Goodyer in 1655). New York: Hafner Publishing.1959. OCLC 3570794.
44. Valnet J, Tisserand R. The practice of aromatherapy: A classic compendium of plant medicines & their healing properties. Rochester, VT: Healing Arts Press.1990.
45. Jennifer A. Kingston. "Nostrums: Aromatherapy Rarely Stands Up to Testing". The New York Times (Style). 28 July 2010. Retrieved 29 December 2010.
46. Eric Nagourney. "Skin Deep: In Competition for your Nose". The New York Times (Health). 11 March 2008. Retrieved 29 December 2010.
47. Prabuseenivasan S, Jayakumar M, Ignacimuthu S. "In vitro antibacterial activity of some plant essential oils". *BMC* Complementary and Alternative Medicine. 6: 2006; 39.
48. Schwartsmann G, Ratain MJ, Cragg GM, Wong JE, Saijo N, Parkinson DR, Fujiwara Y, Pazdur R, Newman DJ, Dagher R, DiLeone LJ. Clin. Oncol. *20* (Suppl. 18): 2002; 47S–59S.
49. Schulz V, Hansel R, Tyler VE. Rational Phytotherapy. A Physicians Guide to Herbal Medicine, 4th edn. Springer, Berlin, 2000.
50. Goldman P. Ann. Intern. Med. 135:2001; 594–600
51. Manach C, Scalbert A, Morand C: Polyphenols: food sources and bioavailability. Am. J. Clin. Nutr. 79:2004; 727-47.
52. Uchegbu IF, Vyas SP: Non ionic surfactant based vesicles (Niosomes) in drug delivery. International Journal of Pharmaceutics. 172:1998; 33–70.
53. Nimisha J, Devi V.K, Valli K.S. Importance of novel drug delivery systems in herbal medicines. Pharmacognosy Review. 4(7):2010; 27-31.
54. NS Acharya, GV Parihar, SR Acharya. Phytosomes: novel approach for delivering herbal extract with improved bioavailability.Pharma science monitor An Int. J. of Pharm. Scs 2(1):2011; 144-160.
55. Ricotti M. unpublished results, 2004.
56. Phytosomes: A technical revolution in phytomedicine: Available at:
57. http://www.indena.com Accessed- Feb. 22, 2012.
58. Bombardelli E, Mustich G. Bilobalide phospholipid comlex, their uses and formulation containing them.1991. U.S. Patent No.EPO-275005.
59. Kidd P, Head K: A review of the bioavailability and clinical efficacy of milk thistle Phytosome: a silybinphosphatidylcholine complex. Altern. Med. Rev. 10(3):2005; 193-203.
60. Kumar Vishal Saurabh, Asha Kesari. Herbosome a Novel carrier for herbal drug delivery. International Journal of Current Pharmaceutical Research. 3(3):2011; 36-41.
61. Bangham, A.D. and R.W. Horne. Negative staining of phospholipids and their structured modofication by surface active agents as observed in the electron microscope, J. Mol. Biol. 8:1964;660–8.
62. Papahadjopoulos, D. (ed.). Liposomes and their use in biology and medicine, Ann. NY Acad.Sci. 308: 1978; 1–412.
63. Moussaoui N, Cansell M, Denizot A. Marinosomes®, marine lipid-based liposomes: physical characterization and potential application in cosmetics. Int J of Pharmaceutics. 242:2002; 361–5.
64. Laetitia Decome' Michel De Méo, Anne Geffard, Olivier Doucet, Gérard Duménil, Alain Botta. Evaluation of photolyase (Photosome®) repair activity in human keratinocytes after a single dose of ultraviolet B irradiation using the comet assay. Journal of Photochemistry and Photobiology B: Biology. 79(2): 2005; 101–8.
65. Y.F. Li, S.-T. Kim, A. Sancar. Evidence for lack of DNA photoreactivating enzyme in humans. Proc. Natl. Acad. Sci. 90:1993; 4389–4393
66. B.M. Sutherland, H. Hacham, P. Bennett, J.C. Sutherland, M. Moran, R.W. Gange. Repair of cyclobutyl pyrimidine dimers in human skin: variability among normal humans in nucleotide excision and in photorepair. Photodermatol. Photoimmunol. Photomed. 18:2002; 109–116.
67. Morales C, Gómez-Serranillos MP, Iglesias I, Villar AM, Càceres A. LI Fàrmaco. 56:2001; 523-526.
68. Distasi LC, Costa M, Medacolli L, Kirizana M, Gómes C, Trolin G. J. Ethnopharmacol. 56:1988; 205-211.
69. De Lima TC, Morato GS, Takahashi RN. Mem. Inst. O. Cruz. 86:1991; 153-158.
70. De Sousa JR, Demuner AJ, Pedersoli JL, Afonso AMM. Ciencia e Cultura. 39:1987; 646-648.
71. O.S. Nimmi, Philmena G. Phytochemical investigation and physicochemical analysis of Polyherbal formulation for antiobesity. Journal of Pharmacy Research. 5(3):2012; 1528-1536
72. Siddiqui, Hakim MA, Format for the pharmacopoeial analytical standards of compound formulation, workshop on standardization of Unani drugs, (appendix) New Delhi: Central Council for Research in Unani Medicine (CCRUM); 1995. Jan 24-25.
73. Mradu Gupta, B.P.Shaw,A. Mukherjee, A new glycosidic flavonoid from Jwarhar mahakashay (antipyretic) Ayurvedic preparation, International Journal of Ayurveda Research. 1(2):2010; 112-121.

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