REVIEW ARTICLE

A review on the herbal plants and their novel drug delivery systems used in the treatment of cancer

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Abstract

Herbal medicines are now in great demand in the developing world for primary health care because they are inexpensive, better acceptability, better compatibility with the human body, and minimal side effects. Over the past several years, great advances have been made on development of novel drug delivery systems for plant actives and extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. Cancer is a major public health burden in both developed and developing countries. It is an abnormal growth of cells in body that can lead to death and globally, the numbers of cancer patients are increasing day by day. Herbal medicines have a key role in the prevention and treatment of cancer. With advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, various anticancer herbs have been identified, which execute their therapeutic effect by inhibiting cancer-activating enzymes and hormones, stimulating DNA repair mechanism, promoting production of protective enzymes, inducing antioxidant action and enhancing immunity of the body. More than 50% of modern drugs in clinical use are of natural products. In the present review, an attempt has been made to study the plants that have been used in the treatment of cancer.

Key words: Cancer, herbal medication, novel drug delivery system

INTRODUCTION

Natural products especially plants have been used for the treatment of various diseases for thousands of years. Alternative approach to drug discovery is through the medicinal plants. Most of the people have faith in traditional medicine, particularly plant drugs for their primary health. In India, 6000 plants are in use in traditional, folk, and herbal medicines. It is estimated that 70–95% of the population in developing countries uses traditional medicine. India has a very long, safe, and continuous usage of many herbal drugs in the official recognized alternate system of health.

Herbal therapy is an ancient science of Indian system of medicine. Today medicinal herbs are defined as plants that contain valuable substance with therapeutic or beneficial effect in healing and prevention of various ailments in man and animals. Traditional formulation contains plant material as its core ingredient[1] Herbs are derived products in different forms as extract, decoction, etc., and are used to aid the healing of wounds and various illness. The herbs act as tool to prevent from sickness as well as to maintain normal human health.

Herbal medicines are now in great demand in the developing world for primary healthcare not because they

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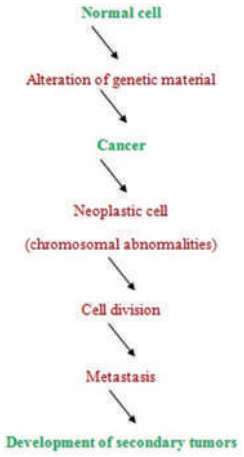
Received: 25-01-2023
Revised: 21-03-2023
Accepted: 31-03-2023

are inexpensive but also for better cultural acceptability, better compatibility with the human body, and minimal side effects. Most herbal products on the market today have not been subjected to drug approval process to demonstrate their safety and effectiveness. Thousand years of traditional use can provide us with valuable guidelines to the selection, preparation, and application of herbal formulation. To be accepted as viable alternative to modern medicine, the same vigorous method of scientific and clinical validation must be applied to prove the safety and effectiveness as a therapeutically effective product. In the present review, we attempted to describe the present scenario and project the future of herbal medicine.

Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The present review highlights the current status of the development of novel herbal formulations and summarizes their method of preparation, type of active ingredients, size, and entrapment efficiency, route of administration, biological activity, and applications of novel formulations.

Cancer is a major public health burden in both developed and developing countries. It is an abnormal growth of cells in body that can lead to death and globally, the numbers of cancer patients are increasing day by day. There are several medicines available in the market to treat the various types of cancer but no drug is found to be fully effective and safe. Herbal medicines have a key role in the prevention and treatment of cancer. With advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, various anticancer herbs has been identified, which execute their therapeutic effect by inhibiting cancer-activating enzymes and hormones, stimulating DNA repair mechanism, promoting production of protective enzymes, inducing antioxidant action, and enhancing immunity of the body. Plants have been used for treating diseases since time immemorial. More than 50% of modern drugs in clinical use are of natural products. In the present review, an attempt has been made to study the plants that have been used in the treatment of cancer.

SCHEME OF CANCER CAUSES[2]



CAUSES OF CANCER

Modern medicine attributes most cases of cancer to changes in DNA that reduce or eliminate the normal controls over cellular growth, maturation, and programmed cell death. These changes are more likely to occur in people with certain genetic backgrounds and in persons infected by chronic. The ultimate cause, regardless of genetic propensity or viruses that may influence the risk of the cancer, is often exposed to carcinogenic chemicals or to radiation coupled with a failure of the immune system to eliminate the cancer cells at an early stage in their multiplication. The immunological weakness might arise years after the exposure to chemicals or radiation. Other factors include tobacco smoking, alcohol consumption, excess use of caffeine and other drugs, sunshine, infections from such oncogenic virus, such as cervical papilloma viruses, adenoviruses Karposis sarcoma (HSV), or exposure to asbestos. However, a large population of people is often exposed to these agents. Consequently cancer cells continue to divide even in situations in which normal cells will usually wait for a special chemical transduction signal. The tumor cells would ignore such stop signals that are sent out by adjacent tissues. A cancer cell also has the character of immortality even *in vitro* whereas normal cells stop dividing after 50–70 generations and undergoes a programmed cell death (Apoptosis). Cancer cells continue to grow invading nearby tissues and metastasizing to distant parts of the body. Metastasis is the most lethal aspect of carcinogenesis.[3] The cancer risk becomes highly increased where workers are exposed to ionizing radiation, carcinomas chemicals, certain metals, and some other specific substances even exposed at low levels.

TREATMENT OF CANCER

The causes for cancer are tobacco, viral infection, chemicals, radiation, environmental factors, and dietary factors. Surgery,

chemotherapy, and radiotherapy are the main conventional cancer treatment often supplemented by other complementary and alternative therapies in China. Plants have been used as an age old remedy of cancer history of use in the treatment of cancer. The anticancer activity of medicinal plants is due to the presence of antioxidants present in them. In fact, the medicinal plants are easily available, cheaper, and possess no toxicity as compared to the modern (allopathic) drugs. Oncogenes are regulators of cellular communication with the outside environment. They are derived through the mutation of proto-oncogenes. Mutated oncogenes are stimulated by exposure to chemical, environment, or viral carcinogens, which leads to cell changes and they produce proteins which are either wrongly expressed within their normal cell or expressed in inappropriate tissue which leads to cellular proliferation and there by result in cancer formation. Tumor suppressor genes are intended to keep oncogenes in check by halting uncontrolled cellular growth.

HERBALS USED IN THE TREATMENT OF CANCER

Discovery of plant-derived substances has evolved during the past 200 years due to the variety of experience and expertise needed to identify such compound. Herbal products such as plant extracts, dry powders and parts of plants, fungi, and algae have been used as complementary treatments along with the conventional drugs. A new trend that involved the isolation of plant active compounds begun during the early 19th century. This tendency led to the discovery of the analgesic (painkilling) drugs morphine and codeine from opium (*Papaver somniferum* L.); cocaine from *Erythroxylum coca*; the cardiac glycoside, digitoxin that was isolated from *Digitalis purpurea* and *Digitalis lanata* that has been used for cardiac conditions and as an anti-cancer drug, and quinine from *Cinchona calisaya* Wedd and *Cinchona succirubra* Pav ex Klotzsch that has antipyretic (fever reducing), antimalarial, analgesic, and anti-inflammatory properties. Some of these molecules are still in use which play a significant role in the development of therapeutics treatments. Plant extracts followed by biological screening assays are performed to identify the potential therapeutic activity followed by isolation of the active compound. Finally, molecular biology studies are required to reveal the mode of action and relevant molecular targets.

Interestingly, many isolated substances against cancer are connected with interactions between plants and microbes.[4] These microorganisms penetrate and reside within plants without injuring them or causing any disease. Such microbes serve as a barrier for colonization by pathogenic microorganisms and participate in plant growth and plant defense response by production of a large variety of secondary metabolites.

The ethno-medicinal plants were appraised all the way through systematic screening protocols and possess an imperative position in the drug invention and many innovative drugs have been justified with respect to effectiveness of their formulations in different cultures of traditional medicine system. Some herbal or traditional formulations from oriental medicines in some parts of India were found to be evidence for anti-cancer activities such as, antiproliferation, anti-angiogenesis, and apoptosis. The plants based medicines are stable which have unlimited capacity to produce active constituents that in turn attract researchers in the quest for innovative, novel and active chemotherapeutics. The long-lasting search for new-fangled anticancer lead molecules in plant medicines and traditional foods is a realistic and promising strategy for its prevention in the daily life.

Acronychia baueri: Utilizing a differential extraction technique for the examination of the bark of the Australian plant *A. baueri* Schott (*Bauerella australiana* Borzi), has resulted in the isolation of the triterpenelupeol and the alkaloids melicopine, acronycine, and normelicopidine. Acronycine has the broadest antitumor spectrum of any alkaloid isolated to date in the laboratories.

Garlic (*Allium sativum* L.) modern scientific research has revealed that the wide variety of dietary and medicinal functions of garlic can be attributed to the sulfur compounds present in or generated from garlic. Studies has demonstrated the chemo preventive activity of garlic using different garlic preparations including fresh garlic extract, aged garlic, garlic oil, and a number of organo sulfur compounds derived from garlic. The chemopreventive activity is due to the presence of organo sulfur compounds in garlic, which include its effect on drug metabolizing enzymes, antioxidant properties and tumor growth inhibition. Most of these studies were carried out in the animal models. The two major compounds in aged garlic, Sallylcysteine and S-allylmercapto-Lcysteine, have the highest radical scavenging activity. In addition, some organ sulfur compounds derived from garlic include Sallylcysteine have been found to retard the growth of chemically induced and transplantable tumors in several animal models. The consumption of garlic may provide some kind of protection from cancer development.

Artemisia capillaries are a major important food and medicinal resource found in Korea. The biological activities of *A. capillaries*, antioxidant, and anticancer activities were investigated from *in vitro* assays. These results suggest that the *A. capillaries* MeOH extracts have a potential alleviated oxidation process, cell motility activity, and tumor genesis.

Astragalus membranaceus, a commonly used Chinese medicinal plant, has been shown to be capable of restoring the impaired T cell functions in cancer patients. The *in vitro* and *in vivo* anti-tumor effects of *A. membranaceus* were investigated and the results showed that *A. membranaceus* could exhibit both *in vitro* and *in vivo* anti-tumor effects, which might be achieved through activating the anti-tumor immune mechanism of the host.

Green tea is an aqueous infusion of dried unfermented leaves of *Camellia sinensis* (Family *Theaceae*) from which numerous biological activities have been reported including antimutagenic, antibacterial, hypocholesterolemic, antioxidant, antitumor, and cancer preventive activities.

Camptothecin is an anticancer and antiviral alkaloid produced by the Chinese tree *Camptotheca acuminata* (*Nyssaceae*) and some other species belonging to the families *Apocynaceae*, *Olacaceae*, and *Rubiaceae*. Bark and seeds are currently used as sources for the drug.

Catharanthus roseus produces low levels of two dimeric terpenoid indole alkaloids, vinblastine, and vincristine, which are widely used in cancer chemotherapy. The dimerization reaction leading to *α*-3', 4'-anhydrovinblastine is a key regulatory step for the production of the anticancer alkaloids in planta has an potential application in the industrial production of two semisynthetic derivatives also used as anticancer drugs.

Inonotus obliquus: The Chaga mushroom (*I. obliquus*) has been used in folk medicine to treat cancers. The results suggest that *I. obliquus* and its compounds in these subfractions isolated from *I. obliquus* could be used as natural anticancer ingredients in the food and/or pharmaceutical industry.[5]

Curcuma zedoaria belonging to the family *Zingiberaceae* has been used in the traditional system of medicine in India and South-west Asia in treating many human ailments and is found to possess many biological activities like antitumor principles from the rhizomes of *C. zedoaria*. To determine its apoptosis inducing capacity in cancer cells, and to evaluate its tumor reducing properties on human and murine cancer cells, the cytotoxic effects was assessed in *in vivo* mice models. Isocurcumenol was found to inhibit the proliferation of cancer cells without inducing significant toxicity to the normal cells.[6]

Three constituents, β-sitosterol, laserine, and epilaserine, were isolated from the lipophilic fraction of *Daucus carota*. Among the three constituents epilaserine showed significantly inhibitory effect on leukemia cell, HL-60.19 Licochalcone (LA) is a novel estrogenic flavonoid isolated from PC-SPES composition herb licorice root (*Glycyrrhiza glabra*) which show significant antitumor activity in various malignant human cell lines.

Ethanolic extract of *Hydrastis canadensis* has been tested for its possible anti-cancer potentials against p-dimethylaminoazobenzene-induced hepatocarcinogenesis in mice. A critical analysis of results of this investigation shows anti-cancer potentials of the drug suitable for use as a supportive complementary medicine in liver cancer.[7]

The aqueous extract of *Larrea divaricata* has an antiproliferative activity on T lymphoma (BW 5147) cells in culture. Moreover, the extract has *in vivo* antitumor activity when it was administered to a pregnant rat which had a spontaneous mammary tumor. The aqueous extract of this plant has an *in vivo* antitumor activity with the intratumor route being most effective in induction of tumor regression.[8]

The cytotoxicity effect of tomato (*Lycopersicum esculentum*) leaves (methanol extract) on cancer cells to address potential therapeutic in MCF-7 breast cancer cell lines and its toxicity toward Vero cells was shown.

Ginseng (*Panax ginseng*), which is traditionally used in some parts of the world as a popular remedy for various diseases including cancer, was hypothesized that the ginsenoside Rp1, a component of ginseng reduces cancer cell proliferation through inhibition of the insulin-like growth factor 1 receptor (IGF-1R)/Akt pathway. It is suggested that Rp1 has potential as an anticancer drug and that IGF-1R is an important target for treatment and prevention of breast cancer.[9]

Roots of *Pfaffia paniculata* have been well documented for multifarious therapeutic values and have also been used for cancer therapy in folk medicine.

Three anthraquinones, Cdc25B phosphatase inhibitors, were isolated from the methanolic extract of the roots of *Polygonum multiflorum* Thunb. (*Polygonaceae*). Anthraquinones, physcion, emodin, and questin, inhibited the enzymatic activity of Cdc25B phosphatase with IC50 values of 62.5, 30, and 34 μg/mL^{-1}, respectively. Emodin and questin strongly inhibited the growth of human colon cancer cells.

Solanum nigrum L. (SNL) has been traditionally used as an herbal plant, whose fruit is believed to have anti-tumor properties. The DNA topoisomerase inhibitor β-lapachone is a quinone obtained from the bark of the lapacho tree (*Tabebuia avellanedae*) in South America has been reported to possess a wide range of pharmacological properties and is a promising cancer chemo preventive agent.

The synergistic effects of various components in *Scutellaria baicalensis* extract baicalin (80%), wogonoside (16%), baicalein (2%), wogonin (1%), and other compounds in trace amounts, inhibited cancer cell growth (*in vitro*), both in the extract and its pure compound-baicalein.

ADVANTAGES OF HERBAL DRUGS[10]

- Low risk of side effects
- More effectiveness
- Lower cost
- Widespread availability.

DISADVANTAGE OF CURRENT DRUG DELIVERY SYSTEM USED IN AYURVEDA[11]

- Bulk dosing
- Decrease bioavailability and decrease absorption
- Show poor effect or require high amount of dose to produce desire effect
- High amount of raw material require processing the medicine
- Loss "N" number of extinct or rare species
- No target specificity in formulation.

Traditional way of medication depends on supply of active compound. Most of the active compounds are highly soluble in water but less absorbed during circulation. The therapeutic and phytochemical importance of herbal medicine has been built for the improvement of human health, but its application is restricted due to the low bioavailability. Many herbal products have low therapeutic action due to their solubility problems which results in low bioavailability despite their extraordinary potential. The nature of the molecule plays an essential role in enhancing the rate and extent of absorption of molecules when administered through any dosage form. In general, to overcome these limitations of absorption, novel herbal drug delivery system with better absorption profile was developed[12] and considerable attention has been focused on the development of NDDS for herbal drugs due to lack of scientific justification and processing difficulties, such as standardization, extraction, and identification of individual drug components in complex poly herbal systems**.** However, modern phytopharmaceutical research can solve the scientific needs such as determination of Pharmacokinetics, mechanism of action, site of action, and accurate dose required of herbal medicines to be incorporated in NDDS, such as nanoparticles, micro emulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles, and so on.[13] Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and to prevent side-effects and to increase drug bioavailability.

NDDS

The novel carriers should ideally fulfill two prerequisites. First, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Second, it should have the active entity of herbal drug to the site of action, whereas in the conventional dosage forms are unable to achieve these points. In phytoformulation, developing nanodosage forms have a number of advantages for herbal drugs, which enhances the solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation.

In novel drug delivery technology, the incorporation of the drug in carrier system is done to change the structure of the drug at molecular level and to achieve the distribution rate [Figure 1].The new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity,

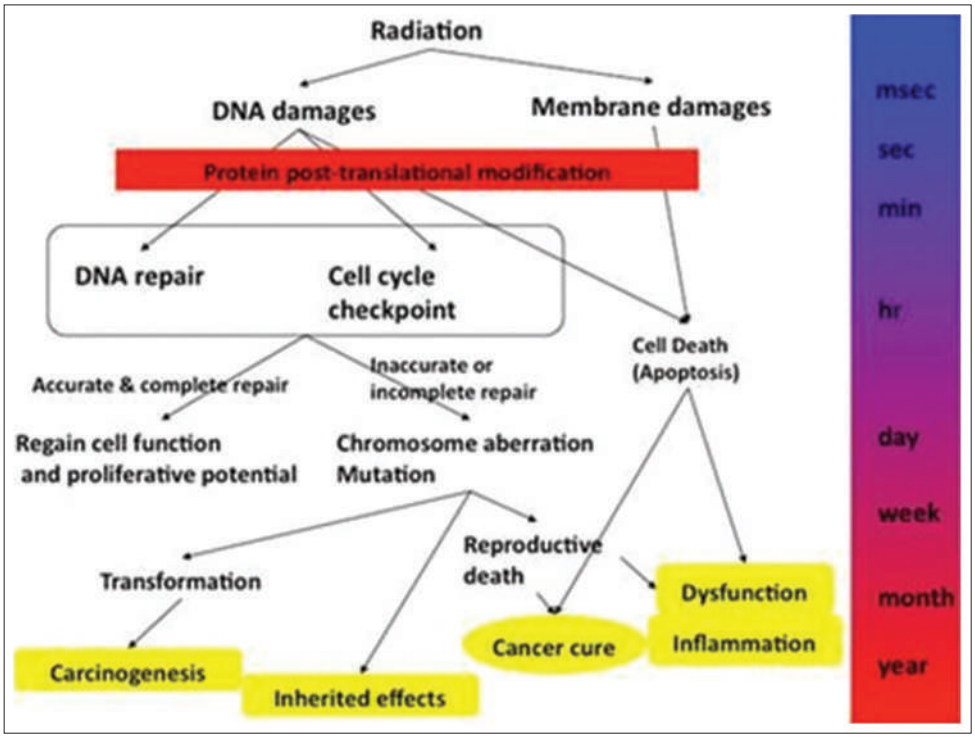


Figure 1: The mechanism on cancer therapy

biorecognition, and efficacy of drugs were generated. NDDS are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation as in Figure 2. NDDS is the booming technology in the field of medicine.

ADVANTAGE OF NDDS[14]

- Help to increase the efficacy and reduce the side effect of various herbal compounds
- Quantity of component becomes less with improving quality of drug effect
- Fewer raw materials are required to achieve the desire effect and control drug delivery to provide exact specification regarding drug dose form
- Ready to use devices are acceptable in today's fast life style where time is important
- Carry maximum amount of drug to the site of action by passing all barriers. Such as acidic pH of stomach increase prolong circulation of drug into blood due to their small particle size
- Reduce repeat dose administration
- The main aim for adaptation of novel drug delivery devices in herbal formulations are to develop better system for proper drug delivery in terms of target oriented
- Sustain and controlled release of drug at the site which help to increase the efficacy and reduces side effects at the site of formulation
- This administration not only reduces repeat administration but also helps to increase the therapeutic value by reducing toxicity and increase the bioavailability.

APPROACHES OF NANOTECHNOLOGY

Nano Carriers

Nano carriers entrapping herbal drug will carry optimum amount of drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism, and increase the prolonged circulation of the drug into the blood due to their small size. Nano carriers are currently used in drug delivery and their unique characteristics demonstrate potential use in chemotherapy. Nano carriers include polymer conjugates, polymeric nanoparticles, lipid-based carriers, dendrimers, carbon nanotubes, and gold nanoparticles. Lipid-based carriers include both liposomes and micelles.

NEED FOR NANO-SIZED DELIVERY SYSTEM FOR HERBAL REMEDIES

Nano-sized herbal delivery system was selected to overcome the drawbacks of the traditional herbal drug delivery systems because of the following reasons[15]

- Nanoparticle can be used to target the herbal medicine to individual organ which improves the selectivity, drug delivery, effectiveness, and safety and thereby reduces dose and increases patient compliance
- Nanoparticles can be utilized to increase the herbal drug solubility, localize the drug in a specific site, resulting in better efficacy[16]
- They deliver high concentrations of drugs to disease sites because of their unique size and high loading capacities

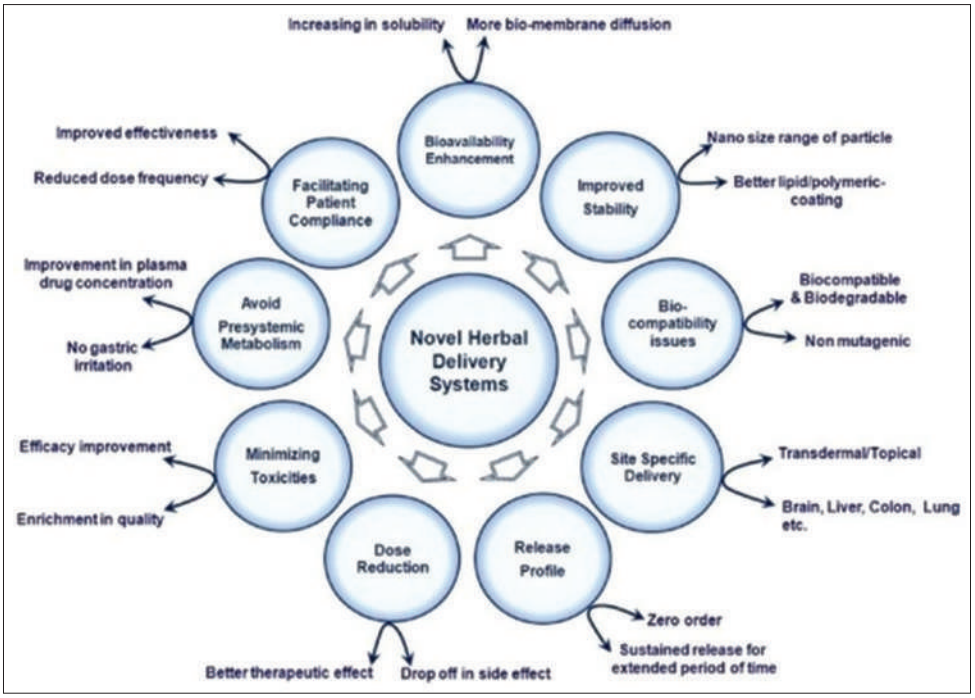


Figure 2: Salient features of novel drug delivery system

- Delivering the drug in small particle size enhances the entire surface area of the drugs therefore allocating quicker dissolution in the blood
- Decreases the side effects.

TYPES OF NOVEL HERBAL DRUG DELIVERY SYSTEMS

Various approaches in case of novel herbal drug delivery system include different types of formulations such as liposomes, phytosomes, niosomes, transferosomes, ethosomes, and dendrimers are discussed below.[17]

Phytosome

Phytosome is vesicular drug delivery system in which phytoconstituents of herb extract are surrounded and bound by lipid (one phytoconstituent molecule linked with at least one phospholipid molecule) Figure 3. Phytosome protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria and shows better absorption, better bioavailability, and improved pharmacological and pharmacokinetic parameters than conventional herbal extract.

Liposome

Liposomes are concentric bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are artificially prepared vesicles made of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes are micro particulate or colloidal carriers, usually 0.05–5.0 μm in diameter which form spontaneously when certain lipids are hydrated in aqueous media. Liposomes are composed of relatively biocompatible and biodegradable material, and they consist of an aqueous volume entrapped by one or more bilayer of natural and/or synthetic lipids. Drug with widely varying lipophilicity can be encapsulated in liposomes, either in the phospholipids bilayer, in the entrapped aqueous volume or at the bilayer interface[18] and the drug encapsulated in liposomes shown in Figure 4.

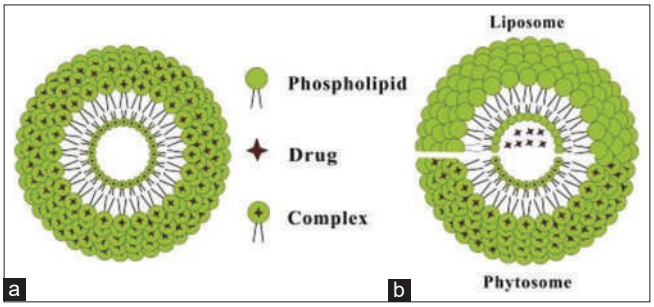


Figure 3: (a) Phytosome and (b) difference between liposomes and phytosomes

Liposome classification is based on structural features and based on method of liposome preparation.

Niosomes

Niosomes are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. Niosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility's. Niosomes have been evaluated in many pharmaceutical applications. In such therapeutic applications, important advantages of using Niosomes include their ability to reduce systemic toxicity by encapsulation of treatment agents and minimize clearance of such agents from the body by slow drug release[19] and the structure of Niosome shown in Figure 5.

Transfersome

A transfersomes carrier is an artificial vesicle which resembles the natural cell vesicle which is suitable for targeted and controlled drug delivery. Transfersomes is a highly adaptable and stress-responsive and complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. This enables the Transfer somes to cross various transport barriers efficiently, and act as a drug carrier for non-invasive targeted drug delivery and sustained release for therapeutic agents. Flexibility of Transfer somes membrane is achieved by mixing suitable surface-active components in the proper ratios Figure 6.

Dendrimers

Dendrimers are spheroid or globular nanostructures of polymeric materials. They are highly branched, monodisperse nanoparticles bind the drug at the surface or entrap within their inner cores. There is a unique property of branching around the inner space that has huge effect on physical and chemical properties. Preparations of these particles are either by divergent or convergent methods. The performance and individual properties of dendrimers can be at variance deeply from their linear complements. Due to very low polydispersity of dendrimers, they contribute to their efficacy as drug delivery strategy.[20] Structure of the dendrimers is shown in Figure 7.

There are broadly two mechanisms for drug delivery.

- First, is by *in vivo* degradation of drug dendrimer conjugate (covalent bonding of drug to dendrimer), which depends on presence of suitable enzymes or an environment capable of degrading bonds
- The second one is by releasing the drug due to changes in physical environment such as pH, temperature. This

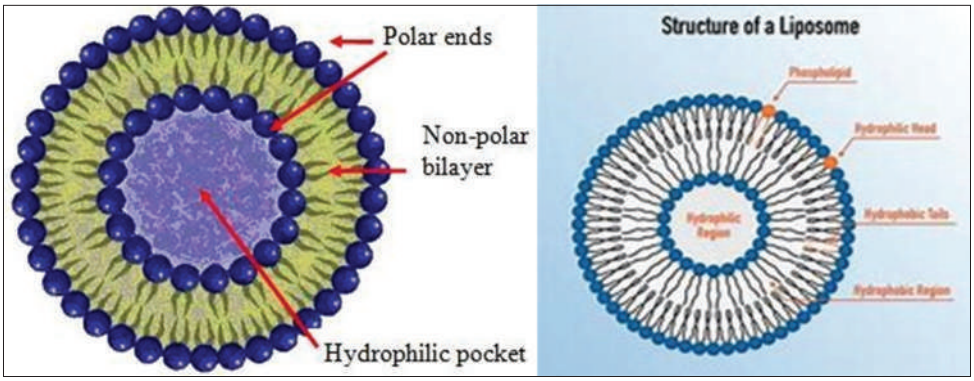


Figure 4: Drug encapsulation in liposomes

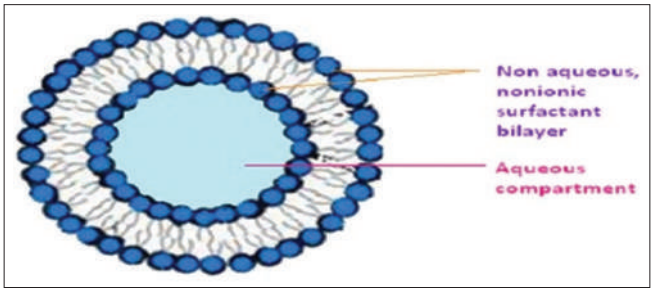


Figure 5: Structure of niosome

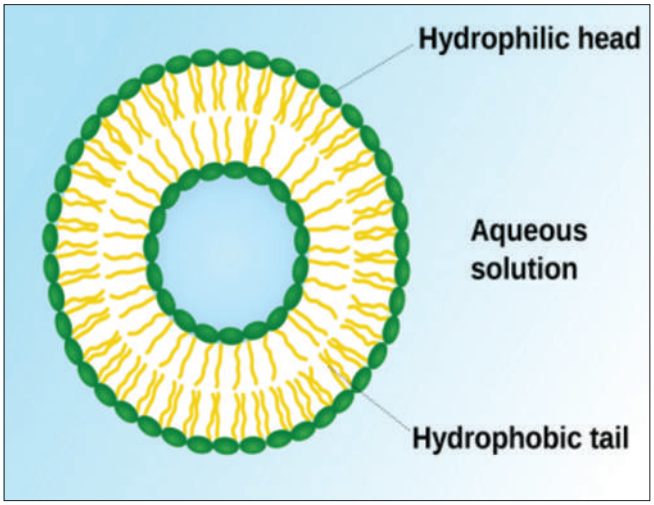


Figure 6: Undeform able vesicle transferosome

approach is independent of the external factors and takes place in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor)

- There are two types of delivery; one is to a specific type of cell and other as a controlled release from a depot (which may be present in circulation or imbedded in some suitable tissue).

Ethosomes

Ethosomes are the slight modification of well-established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration of water. Ethosomes are soft vesicles made of phospholipids components,[21] ethanol (in higher quantity) and water. Themicron size range of ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux as shown in Figure 8.[22]

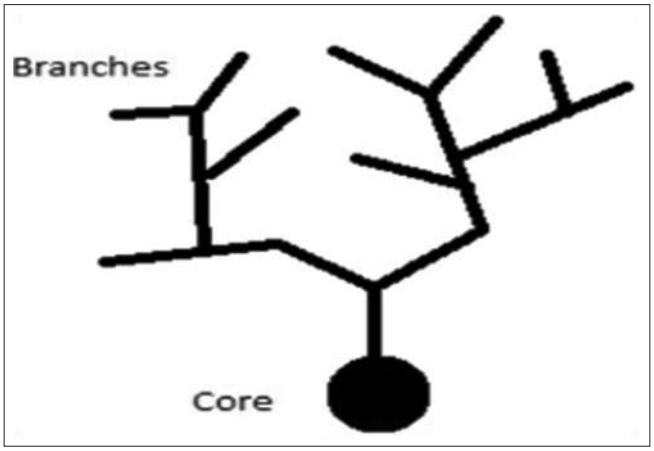


Figure 7: Structure of a dendrimer

Solid-lipid Nanoparticle

Solid-lipid nanoparticles are sub-micron colloidal system and its size ranges from 50 to 100 nm. It is prepared by dispersing the physiological solid lipids particles in nanometer range in water or in an aqueous surfactant solution Figure 9. These are monolayer phospholipid carrier system having a solid hydrophobic core, that is, they have a tendency to carry lipophilic or hydrophilic drugs. SLNPs are biocompatible, non-toxic, biodegradable, etc. SLNPs have long-term stability and better control over the release kinetics of encapsulated compound.[23]

EVALUATION OF VALIDATED HERBAL MEDICINE FORMULATION

The standardization of crude drug materials is done by authentication, stage of collection, parts of the plant

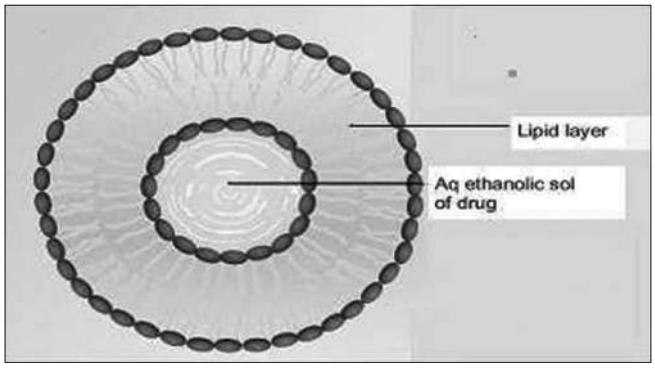


Figure 8: Structure of ethosomes

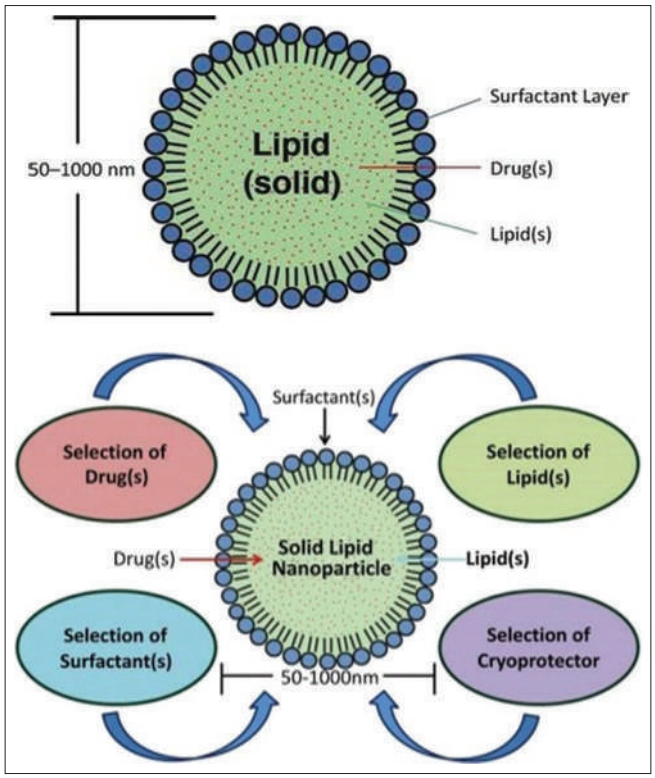


Figure 9: Structure of solid lipid nanoparticle

collected, identity like phytomorphology, microscopical, and histological analysis (characteristic of cell walls, cell contents, starch grains, calcium oxalate crystals, trichomes, fibers, vessels, etc.), and Leaf constant: palisade ratio, vein islet number, vein termination, stomatal number, and stomatal index. Other histological test is trichomes, stomata, quantitative microscopy, taxonomical identity, foreign matter, organoleptic evaluation, ash values and extractive values, moisture content determination, chromatographic and spectroscopic evaluation, heavy metal determination, pesticide residue, microbial contamination, and radioactive contamination.

The herbal formulation in general can be standardized schematically as to formulate the medicament using raw material collected from different localities and a comparative chemical efficacy of different batches of formulation are to be observed. The preparations with better clinical efficacy are to be selected. All the routine physical, chemical, and pharmacological parameters are checked for all the batches to select the final finished product and to validate the whole manufacturing process.

The stability parameters for the herbal formulations which include physical, chemical, and microbiological parameters are as follow:

Physical parameters include color, odor, appearance, clarity, viscosity, moisture content, pH, disintegration time, friability, hardness, flow ability, flocculation, sedimentation, settling rate, and ash values.

Chemical parameters include limit tests, chemical tests, and chemical assays. Chromatographic analysis of herbals can be done using thin layer chromatography (TLC), HPLC, high performance thin layer chromatography (HPTLC), gas liquid chromatography (GC), UV, gas chromatography (GC-MS), and fluorimetry.

Microbiological parameters include total viable content, total mold count, total enterobacterial, and their count. Limiters can be utilized as a quantitative or semi quantitative tool to ascertain and control the amount of impurities like the reagents used during abstraction of various herbs, impurities coming directly from the manufacturing vessels and from the solvents.[24]

Morphological or Organoleptic Evaluation

It includes the evaluation of herbal drugs by size, shape color, odor, taste, and particular characteristics such as touch and texture. This is a technique of qualitative evaluation related to the study of morphological and sensory report of whole drugs, for example, Fractured surfaces in cascara, cinchona, and quillia bark and quassia wood are essential characteristics. Umbelliferous fruits have aromatic odor and liquorice have sweet taste are the example of this type of evaluation. Shape of drug may be conical (aconite), subcylindrical (*podophyllum*), cylindrical (sarsapilla), fusiform (jalap). Size represents thickness, length, breadth, and diameter. Color represents external color which various from white to brownish black are essential diagnostic features. Taste is a specific type of sensation felt by epithelial layer of tongue. Taste may be sweetish (saccharic), sour (acidic), salt like (saline), and bitter or tasteless.[25,26]

Macroscopic and Microscopic Examination

Medicinal plant materials are categorized according to sensory, macroscopic, and microscopic characteristics. An examination to determine these characteristics is the first step towards establishing the identity and the degree of purity of such materials and should be carried out before any further tests are

Figure 10: Flow chart on standardization and evaluation of herbal drug

undertaken. Visual inspection provides the simplest and quickest means to establish identity, purity, and, possibly, quality. However, judgment must be exercised when considering odor and taste, due to variability in assessment from person to person or by the same person at different times.[33]

Macroscopic identity of medicinal plant materials is based on shape, size, color, surface characteristics, texture, fracture characteristics, and appearance of the cut surface. However, since these characteristics are judged subjectively and substitutes or adulterants may closely resemble the genuine material. It is often necessary to substantiate the findings by microscopy and/or physicochemical analysis.

Microscopic inspection of medicinal plant materials is indispensable for the identification of broken or powdered materials; the specimen may have to be treated with chemical reagents. Any additional useful information for preparation or analysis should also be included in the test procedures for individual plant materials, for example, the determination of vein islets[27] and the palisade ratio. It involves the detailed assessment of the herbal drugs and it is used to recognize the organized drugs on the basis of their known histological characters. It is regularly used for qualitative analysis of organized crude drugs in total and powder form with the help of microscope [Figure 10].

Physical Evaluation

Each monograph contains detailed botanical, macroscopic and microscopic descriptions with detailed illustrations and photographic images which provide visual documentation of accurately identified material. A microscopic analysis assures the identity of the material and as an initial screening test for impurities.

- Determination of ash
- Determination of extractable matter
- Determination of foreign matter.[28]

Chemical Evaluation

The most of drug contains definite chemical constituents to which their pharmacological and Biological activity is depended. Qualitative chemical test used to identify drug quality and purity. The identification, isolation, and purification of active chemical constituents depend on the chemical methods of evaluation. Preliminary phytochemical investigation is also a part of chemical evaluation. Some of the qualitative chemical test for chemical evaluation crude drug is saponification value and acid value.

Chromatographic fingerprinting and market compound analysis

TLC, HPTLC, HPLC, Liquid Chromatography, Mass Spectroscopy, Liquid Chromatography-Nuclear Magnetic Resonance, GC-MS, GC-FID, and Supercritical Fluid Chromatography.

DNA fingerprinting

Genetic Marker and Radioactive Contamination

Biological Evaluation

Determination of Bitterness Value, Determination of Hemolytic Activity, Determination of Swelling Index, Determination of Foaming Index, Determination of Pesticide Residues, Determination of Arsenic and Heavy Metals, Stability Testing of Herbal Products, Analytical Methods for Herbal Products, Shelf-Life, Challenges in Stability testing of Herbal Medicinal Product, Mechanisms Involved in Change Product, Predictable Changes in Herbal Medicinal Product, Hydrolysis, Oxidation, Racemization, Geometric Isomerization, Polymerization, Temperature, Moisture, and Light.

EVALUATION OF ANTICANCER ACTIVITY

The evaluation of anticancer activity was performed by phytochemical analysis, ABTS radical scavenging activity, TLC, Cell Lines and Cell Culture Preparation, Anti-proliferative activity, MTT bioassay, Trypan Blue Assay, and Hoechst Stain Assay methods.

CONCLUSION

Medicinal plants have contributed a rich health to human beings. Herbal medicines have been widely used all over the globe since ancient times and it has been believed by large population for its better therapeutic value as they have fewer adverse effects when compared with allopathic medicines. The assurance of the safety and efficacy of the herbal drug requires monitoring of the quality of the product from collection through processing to the finished packaged product. Medicinal plants maintain the health and vitality of individual and also cure various diseases including cancer without causing toxicity. Natural products discovered from medicinal plants have played an important role in treatment of cancer. Plant extracts and their bioactive compounds present in them are responsible for anticancer activity. Nowadays, people are opting for herbal medicines for their better therapeutic values and lesser adverse effects. The area in development of novel drug delivery and targeting system for herbal drugs is going on at a great extent. NDDS not only provides a safe and effective delivery, enabling people to regain faith over herbal drug delivery systems but also increases the market for herbal drugs. Several NDDS can be used for enhancing the efficacy of drugs as compared to modern medicine. Collaboration of modern technology with herbal drugs will led to enhanced bioavailability and improved solubility, reduced toxicity, controlled release delivery, and effectiveness with dose reduction. However, research is still at the exploring stage that NDDS will provide a great platform for chemist to conquer various challenges coupled with herbal formulations therapy to humans.

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Source of Support: Nil. **Conflicts of Interest:** None declared.