*ejpmr, 2017,4(11), 223-232*

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# HERBAL MEDICINE BASED NOVEL DRUG DELIVERY SYSTEM USED FOR CANCER MANAGEMENT

**Sushil Kumar Sah*, B. Shrivastava, Rajesh Verma and Gaurav Gupta**

School of Pharmaceutical Sciences, Jaipur National University.

***Corresponding Author: Sushil Kumar Sah**

School of Pharmaceutical Sciences, Jaipur National University.

**Article Received on 22/08/2017** **Article Revised on 12/09/2017** **Article Accepted on 03/10/2017**

**ABSTRACT**

Herbal medicines, since ancient old age and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. It is considered as the world famous and useful The demand of herbal medicines increased in recent years because of their ability to treat different diseases with fewer side effects. The side effects of chemotherapy in cancer treatment are major concern and hence the need of the day is to find the effective treatment with fewer side effects. The novel herbal formulations like liposomes, phytosomes, ethosomes, microsphere, transferosomes, nanoparticles, and microemulsions has been reported using bioactive and plant extracts. The main reason behind development of alternative drug delivery is to increase efficiency and safety of drug delivery and provide more convenience to the patient. Herbal formulations may be more advantageous over conventional formulations by improving component solubility, enhancing bioavailability, reducing dose, achieving constant therapeutic dose over extended time, enhancing stability, protecting physical and chemical degradation. The use of herbal formulations for novel drug delivery systems is more beneficial and has more advantages compared to others.

**KEYWORDS:** Herbal; formulation; Cancer treatment.

## INTRODUCTION

Cancer is said to be one of the leading causes of death globally. Based on the available data, it is estimated that by year 2030 the annual death rate due to cancer would touch to 13.1 million people.[1] The current statistics project that 1 out of 8 dies with cancer and it is second main cause of death in US. The majority of deaths from cancer are found to be in middle and low income countries.[2] Cancer is caused when the cells multiply at a more rapid pace leading to formation of malignant tissues or tumours. Genes transmit the instructions for basic functions of cells Cancer is caused by damage of genes which control the growth and division of cells. Genes carry the instructions for basic functions of cells. Cancerous cell need blood supply for growth.[3] Cancer occurs at a molecular level with multiple subsets of genes undergoing genetic alteration resulting in either activation of oncogenes or inactivation of tumour suppressor genes. As a result, the malignant proliferation of cancer cells, tissue dysfunction and infiltration of organ would appear. Tumour is characterized with active angiogenesis and high vascular density which keep blood supply for their growth, but with defective vascular architecture. Combined with poor lmpathic drainage, they contribute to what is known as enhanced permeation and retention.[4]

The hallmarks of cancer comprise of six biological capabilities. They include sustaining proliferative signalling, angiogenesis, and evasion of growth suppressors, metastasis, resisting cell death, invasion and replicative immortality.[5] Cancer is still a field of bigger research with treatment limited to surgery, radio therapy and chemotherapy. There's been a lot of research for novel therapies as majority of the drugs not only kill the cancerous cells but also eliminate the healthy and normal cells.[6] The drawback of current chemotherapies is its inability to improve patient mortality and morbidity as they show severe adverse effect on normal tissues. As an alternative the targeted nanocarrier system can help in finding a solution to this problem. These nanoparticles can be designed to deliver drug to the targeted area solely to the tumour cells thereby avoiding side effects on over dosing the healthy and normal tissues. The nanocarrier can be structured and shaped according to the needs of the diseased tissues. Nanotherapeutics has many benefits which includes improving bioavailability and plasma solubility, decreases systemic toxicity, increase patient compliance and improve pharmacokinetics of biologics and small molecules that otherwise have short half-lives *in- vivo*.[7]

### Obstacles to cancer chemotherapy[5,8,9,10]

1. The conventional chemotherapeutic agents or anti-cancer drugs work by destroying the cells that are

rapidly dividing. Due to this reason chemotherapy also damages the normal and healthy cells which are rapidly dividing such as in the case of cells in bone marrow, macrophages, digestive tract and hair follicles.

2. Despite the advancement in therapeutic cocktails, the outcome of chemotherapy is not satisfactory. For example, the response rate of pancreatic cancer, esophageal cancer and ovarian cancer to chemotherapy are well below 20%.
3. The therapeutic agents have limitations like poor solubility, rapid deactivation, unfavourable pharmacokinetics, and limited bio distribution.
4. Cytotoxic agent soften bind with body tissues and serum protein in an unpredictable manner. Only a small fraction of the drugs reach the tumor site. This leads to reduce in the therapeutic efficacy and increase systemic drug toxicity. Ideally, cytotoxic drugs should only kill cancer cells, but in reality they are also toxic to non-cancerous cells, especially to rapidly dividing cells, ex. bone marrow cells and cells of the gastrointestinal tract.
5. The challenges that should be considered are bio-distribution (non-tumour selectivity), hypersensitivity, and acquisition of multi drug resistance (MDR). In general, drugs degrade to toxic moieties, resulting in nephrotoxicity and cardiotoxicity.
6. The most common side-effects as a result of chemotherapy are nausea, vomiting, fatigue, depression.
7. Other side effects of most chemotherapeutic agents include myelosuppression (decreased production of white blood cells causing immune suppression), mucositis (inflammation of the lining of the digestive tract), alopecia (hair loss), organ dysfunction, and even anemia or thrombocytopenia.
8. Patient compliance, genetic variation is also a major obstacle.

**Herbal Formulation**

Herbal formulation is one of the major segments of traditional system of medicine; contribute immensely to the positive health of an individual.[11] By this formulation the drugs can be delivered with a safety, efficacy and acceptability among other factors and the formulation is usually known a dosage form or drug delivery system. Herbal drugs are becoming more popular in the modern world for their application to cure variety of disease with less toxic effect and therapeutic effect.[12] Herbal formulation should fulfil two prerequisites. Firstly should deliver the drug at a rate directed by the need of the body, over point of treatment. Secondly, it should channel the active entity of herbal drug at site of action.[13] For a long time herbal medicines are not considered to be developed as novel formulations owing to lack of scientific justification and processing difficulties. However, modern phytopharmaceutical research can solve the scientific needs of herbal medicines to be incorporated in novel drug delivery system.[14] The current review summarizes various herbal drug delivery for treatment of cancer and gaining more attention for improved therapeutic activity.

**Types of Herbal Formulation**

**1. Nanoparticles**

The word "Nano" is derived from Latin word, which means dwarf ($1nm=10^{-9}m$).[15] Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-100nm.[16] The drug in nanoparticles is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. The main motive behind designing a delivery system is to control the particle size, the 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.[17] Using nanoparticles, the drug is transported to a particular area in the patient's body, targeting the affected region resulting in visible activity at particular site and help in curing the particular diseases.[18] The modern phyto-pharmaceutical research can solve the scientific need of herbal medicine in developing novel drug delivery system, such as nanoparticles, micro-emulsion, matrix system, solid dispersion, liposomes and solid lipid nanoparticles.[19] The efficacy of many herbal drugs is often limited by their potential to reach the site of therapeutic action. Compared to micrometre size carrier, nano carrier provide more surface area and have potential to increase solubility, enhance bioavailability, improved controlled release and enhance precision targeting.[11] With advancement of technology, the greener and environmental friendly processes in chemistry and chemical technology are becoming popular. The techniques for obtaining nanoparticles using occurring reagent such as plant extracts, could be considered attractive for nanotechnology.[20] Nanopowders are agglomerates of ultrafine particles, nanoparticles, or nanoclusters. Nanometer-sized single crystals, or single-domain ultrafine particles, are often referred to as nanocrystals.[21] Nanoparticles mediated targeting plays significant role in inhibiting inflammation, angiogenesis and tumor progression.[22]

**Advantages of herbal nanoparticle delivery system[17,23,24,25]**

1. Nanoparticles are the choice of formulation, to promote the drugs through the biological barriers and increase the bioavailability of drugs.
2. Particles size and surface is easily manipulated for both active and passive targeting for parenterals.
3. Traditional medicines have advantage of low risk of side effects, widespread availability, low cost and efficacious for lifestyle diseases for prolonged period of time.
4. Controlled and sustained release of the drug during transportation and at site of localization, altering organ distribution of the drug.
5. Nanoparticle improves the absorbency of the herbal formulation and reduces the dose of formulation. Because of this, its solubility is increased and the

drug can reach the target site, as compared to other systems.
6. When drug is encapsulated within nanoparticles, it results in improvement of the solubility and pharmacokinetics of drugs.
7. Quantity of component becomes less with improving quality of dug effect.
8. Fewer raw materials are required to achieve the desired effect and control drug delivery to provide exact specification regarding dug dose form.
9. Carry maximum amount of drug to the site of action by passing all barriers. Such as the acidic PH of stomach increase prolong circulation of drug into blood due to small particles size.

**Methods of preparation of nanoparticles**

**The techniques commonly used for the formulation are**

**1. High-pressure homogenization method**

High pressure homogenization techniques basically used for the production of solid lipid nano dispersions. The dispersion quality often consists of the presence of micro particles. High-speed homogenization method is used to produce SLN by melt emulsification.[26] In this method, the lipid is passed with high pressure (100 to 2000 bars) through a very high shear stress, which results in disruption of particles down to the sub micrometer or nanometer range. It's much reliable and powerful technique for the large scale production of nanostructured lipid carriers, lipid drug conjugate, SLNs, and parenteral emulsions.[27]

**2. Salting out method**

Salting out method is based on the separation of a watermiscible solve from aqueous via a salting effect. The salting out procedure can be used for modification of the emulsification/solvent diffusion. Polymer and drug is firstly dissolved in a solvent such as acetone, which is then emulsified in to an aqueous gel containing the salting-out agent (electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose) and a colloidal stabilizer such as polyvinyl pyrolidone or hydroxyl ethyl cellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. The salting out agent plays an important role in the encapsulation efficacy of the drug. Both the solvent and the salting out agent are then eliminated by cross-flow filtration.[28]

**3. Cementation method**

Cementation method is widely used for purification and extraction. The cementaion method is the easiest, simplest and the most commonly used synthetic method for copper nanoparticles. The production of nanosized metal copper particles with good control of morphologies and sizes using chemical reduction of copper salts can be achieved by using this method.[29] The copper nanoparticles are prepared by cementation method which includes reduction of copper from a copper nitrate salt in presence of iron. The synthesized copper nanoparticles by cementation method are in the range particle size 90-150nm. About 90 ml of copper nitrate with the concentration of $10^{-3}$M is added to 1gm of iron plate having surface area of $1m^2$$Cu^2$ ions get reduced to elemental $Cu^0$ by $Fe^0$ resulting in formation of ferrous nitrate. The sample is continually ultrasonicated to prevent the formation of large size copper nanoparticles.[30]

**4. Precipitation method**

Zinc oxide nanoparticles were synthesized by precipitation method using zinc nitrate and potassium hydroxide as precursor. In this aqueous sol (0.2M) of zinc nitrate and (0.4M) of potassium hydroxide (KOH) were prepared by deionised water. KOH sol was slowly added in to zinc nitrate solution at room temp under vigorous stirring which resulted in formation of suspension. The white product was centrifuged at 5000 rpm for 20min and washed with distilled water with absolute alcohol at last. The obtained product was calcined at $500^0$C in air atmosphere for 3 hours.[31]

**5. Nano precipitation method or solvent displacement method**

This method is based on interfacial deposition of a polymer after displacement of a semipolar solvent miscible with water from a lipophilic solution, thereby resulting in a decrease in the interfacial tension between the two phases, it increases the surface area with a subsequent formation of small droplets of organic solvent even without any mechanical stirring.[27]

**6. Fluid methods (SCF)**

This method can be used to prepare submicrometer sized and nanosized formulations. A supercritical fluid (SCFs) can either be a liquid or gas and used above its thermodynamic critical point of temperature and pressure. The most commonly used SCFs are carbon dioxide and water. This is an important technique for fabrication of inorganic and hybrid nanoparticles.[32]

**7. Solvent emulsification-diffusion method**

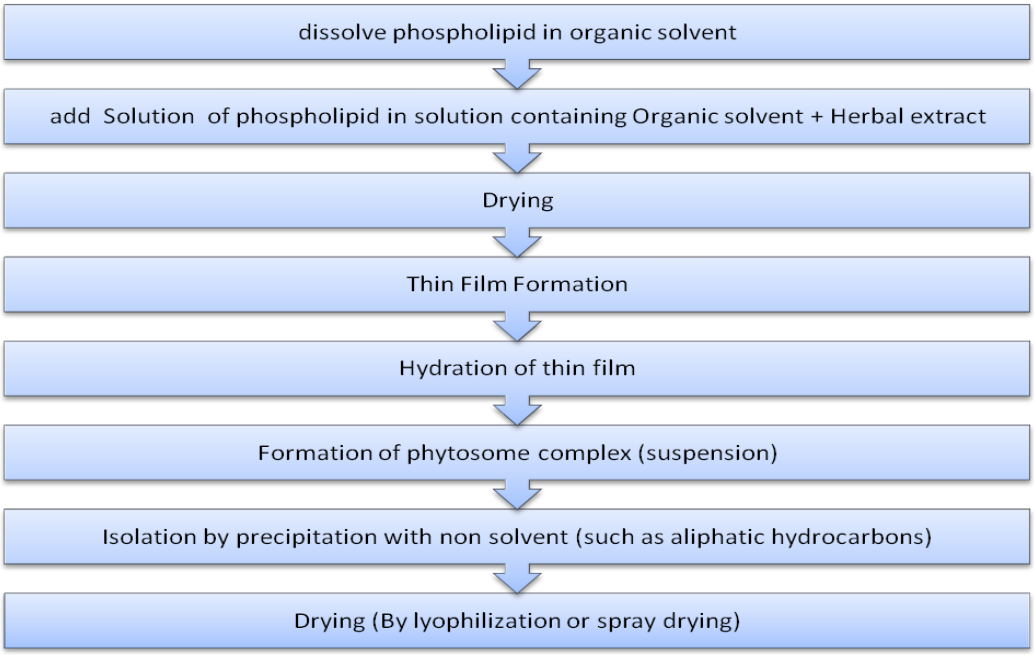
The method involves preparation of an o/w emulsion using oil phase containing polymer and oil in an organic solvent, which is emulsified with the aqueous phase, containing stabilizer, in high shear mixer, followed by addition of water to induce the diffusion of organic solvent, thus resulting in formation of nanoparticles.[18]

**Anticancer potential of herbal nanoparticles are presented in table 1**

**Table 1: Anticancer potential of herbal nanoparticles.**

| Name | Part | Metal | Activity. | References |
|---|---|---|---|---|
| Nigella sativa | Leaves | Silver | Anticancer | [33] |
| Triphala | Fruit | Copper | Anticancer | [34] |
| Panax ginseng | Leaves | Silver | Anticancer | [35] |
| Acalypha indica | Plant | Copper | Antimicrobial and anticancer | [36] |
| Abelmoschuses culentus | Pulp | _ | Anticancer | [37] |
| Bergenia cilita | Rhizomes | _ | Antimicrobial and anticancer | [38] |
| Clerodendrum phlomidis | Leaf | Silver | Anticancer | [39] |
| Melia dubia | Leaf | Silver | Anticancer | [40] |

1. It is able to permeate the hydrophilic botanical extract to be better absorbed in intestinal lumen.[23]
2. Improved absorption in GIT.[47]
3. Phytosome are widely used in cosmetics due to there more skin penetration and have the high lipid profile.[43]




**Anticancer potential of herbal Phytosomes are presented in table 2**

**Table 2: Anticancer potential of herbal Phytosomes.**

| Sr.no | Phytosomes | Phytoconstituents | Activity | Reference |
|---|---|---|---|---|
| 1. | Quercetin | Quercetin | Antioxidant, Anticancer | [48] |
| 2. | Palmetto berries Phytosomes | Fatty acids, alcohols and sterols | Used for the treatment of Non-cancerous Prostate enlargement | [44] |
| 3 | Green tea. | Epigallocatechin 3-O gallate from Camellia sinensis | Anti-cancer, Antioxidant, nutraceutical | [47] |
| 4. | Curcumin | Curcumin | Antioxidant, Anticancer | [48] |
| 5 | Grape seed (Leucoselect) phytosome | Procyanidins from vitis vinifera | Antioxidant, Anticancer. | [45] |

### 3. Microspheres

Microspheres are spherical shaped particles. The size of microspheres ranges between 1-300 µm. Microspheres loaded with drugs are delivered to the target area by passive means (trapping by size) or active means (magnetic targeting).[84]

Each particle is matrix of the drug dispersed in the polymer and drug is released as a first order process. Firstly the outer dissolution media will diffuse the matrix make the entrapped drug to solubilize in it and then the drug is released from the system. In this mechanism the polymer showed surface erosion behavior and the release of drug occurs.[85]

A delivering drug through biodegradable microsphere has many advantages as compared to conventional delivery systems. Biodegradable polymer eliminates the

need of multiple dosing by offering a way to provide sustained release over a longer time.[86]

**Advantages**[87]

1. The therapeutic effect of the drug was increased by microspheres.
2. Microspheres reduce the dosing frequency and thereby improve the patient compliance.
3. Microspheres could be easily injected into the body due to the spherical shape and smaller size.
4. The incidence or intensity of adverse effects was reduced by microspheres and better drug utilization will improve the bioavailability.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

**Methods and techniques for preparation of microspheres**[88]

There are various methods and techniques using which microparticulate carriers for drug delivery Can be prepared

(1) Single emulsion technique:
(a) Thermal cross-linking.
(b) Chemical cross-linking agent.
(2) Double emulsion technique.
(3) Polymerization technique.
(a) Normal phase polymerization:
(4) Bulk.
i. Suspension.
ii. Emulsion.
(a) Interfacial polymerization.
(5) Spray-drying technique.
(6) Solvent evaporation.
(7) Wet inversion technique.
(8) Complex coacervation.
(9) Hot melt microencapsulation.
(10) Extrusion–spheronization.
(11) Quasi-emulsion solvent diff usion method

**1. Single emulsion technique**

In this method microparticulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique.The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g. oil. In the second step of preparation, cross-linking of dispersed globule is carried out. The cross linking is achieved by two methods i.e. either by heat or by means of chemical cross linking agents including glutaraldehyde, formaldehyde, diacid chloride etc.[89]

**2. Double emulsion technique**

In this method the formation of the multiple emulsion or double emulsion of type w/o/w take place. This is best suited to water soluble drugs, peptides, proteins and vaccines. This method can be used with both the natural as well as the synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenisation or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA).This results in formation of a double emulsion. Emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction process. The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. The emulsion is then added to large quantity of water into which organic phase diffuses out. The solid microspheres are subsequently obtained by filtration and washing with n-hexane, acetone or any organic solvent to remove traces of oil from the surface.[90]

**3. Polymerization Techniques**

The polymerization techniques of microspheres preparation are mainly classified as:
a. Normal polymerization b. Interfacial polymerization.

**a) Normal polymerization**

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization.[86]

**Suspension polymerization**

It is also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.[86]

**Emulsion polymerization**

It is differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles.[86]

**b) Interfacial polymerization:** Reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer.[86]

**4. Spray drying**

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenisation. This dispersion is then atomised in a stream of hot air. The atomisation leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of microspheres.[91]

**5. Solvent extraction**

Solvent extraction method is used for the preparation of the micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. The process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.[91]

**6. Complex Coacervation**

Principle of this method is under suitable conditions when solutions of two hydrophilic colloids were mixed, result into a separation of liquid precipitate. In this method the coating material phase, prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the temperature of the polymer solution; by changing the pH of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by inducing a polymer interaction. Generally coating is hardened by thermal cross linking or desolvation techniques, to form a self sustaining microsphere.[92]

**7. Quasi-emulsion solvent diffusion method**

This is a novel technique used for the preparation of the micro particulate system. In this method, an ethanol solution of drug and acrylic resin was poured into an aqueous medium with continuous stirring. The finely dispersed ethanolic droplet-like coacervates formed in the aqueous medium were solidified and transformed into microspheres during agitation.

The microspheres obtained have a sponge-like or matrix-like texture having a characteristic advantage compared with the conventional reservoir-type device drug, such as microcapsule.[93]

**8. Ionotropic Gelation**

This method was developed by Lim F and Moss RD14. Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.[92]

**Application of microspheres in pharmaceutical industry[94]**

1. For Taste and odor masking.
2. To delay the volatilization.
3. For Separation of incompatible substances.
4. For Improvement of flow properties of powders.
5. To Increase the stability of the drug against the external conditions.
6. For Safe handling of toxic substances.
7. To improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media.

**Anticancer potential of herbal microspheres are presented in table 8**

**Table 8: Anticancer potential of herbal microspheres.[94]**

| Sr.no | Botanical name | Active ingredient | Biological activity. |
|---|---|---|---|
| 1. | Curcuma longa | Curcumin or diferuloylme thane (yellow phenol) | Antioxidant and Anticancer |
| 2. | Sophora japonica | Quercetin, flavones. | Antioxidant and anti-inflammatory and anti-cancer. |
| 3. | Camptotehc a acuminate | Camptothecin (CPT) is a cytotoxic quinoline alkaloid | Anticancer. |

**Some important patents of herbal formulations as anticancer agents are presented in Table-9.[95]**

| Patent no. publication date | Title | Description of Patent | Active ingredient | Action |
|---|---|---|---|---|
| US20100197584 08/05/2010 | Use of curcumin to block brain tumor formation in mice | The present invention provides compositions and methods of using curcumin or curcumin derivatives or analogs to activate the pro-apoptotic enzymes caspase-3/7 in cancer cells. | Curcumin and curcumin derivatives | Brain tumor prevent tumor formation, or tumor cell invasion or metastasis |
| US7709031 05/04/2010 | Angiogenic agents from plant extracts, gallic acid, and derivatives | An extract of Chinese blackberry (Rubus suavissimus) has been found to inhibit angiogenesis, and two active fractions isolated | Various derivatives of gallic acid | Various cancer Antiangiogenesis |
| US6664272 Dec 2003 | Curcumin analog with anti-tumor | Increased bioavailability | Demethoxycurcu min,Bisdemethox y-curcumin | Anti-tumor |

| | | | | |
|---|---|---|---|---|
| US6432454 08/13/2002 | Processes of making north american ginseng fractions, products containing them, and use as immunomodulators | The invention is directed to chemical processes of preparing fractions from North American ginseng (Panax quinquefolium) and pharmaceutical compositions containing these fractions. The products of the present invention may be used to stimulate the production of cytokines and/or antibodies, or as therapeutics targeted at conditions characterized Polysaccharide by low immunity, such as thcommoncold, influenza, chronic fatigue syndrome, AIDS and cancer | Polysaccharide | Anticancer |
| US5653981 08/05/1997 | Use of Nigella sativa to increase immune function | A pharmaceutical composition for treatment of cancer and other conditions and the prevention of side effects of anticancer chemotherapy and increasing the immune function contains an extract of the plant Nigella sativa | Plant seed extract of Nigella sativa Linn (N. sativa) | Prevention of side effects of anticancer Chemotherapy and increasing the immune function |
| EP185112 B1 15/5/2013 | Anticancer composition comprising liposomes containing phytosterols | Liposomsal composition in treatment of cancer | Phytosterol. | Liposomes membrane has strong ability to inhibit cancer metastasis. |

## CONCLUSION

Extensive research is going on herbal formulations 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. The herbal formulations were found effective, safe, convenient and economical. Many patents in herbal formulation were found beneficinal for human beings.

## REFERENCES


1. Alexandra RF, Pedro VB. Nanotechnology for Cancer Diagnostics and Therapy – An Update on Novel Molecular Players. Curr Canc Ther Rev, 2013; 9(3): 1-9.
2. Khazir J, Mir BA, Pilcher L, *et al*. Role of plants in anticancer drug discovery. Phytochem Lett, 2014; 7: 173–181.
3. Patil G, Patil SS, Sonawane S, *et al*. Comparative Study of Nanotechnology based Cancer Treatment: A Systematic Approach. Int J Sci Eng Res, 2014; 5(12): 1086-1092.
4. Anajwala CC, Jani GK, Swamy SMV. Current trends of nanotechnology for cancer therapy. Int J pharm sci nanotech, 2010; 3(3): 1043-1056.
5. Nazir S, Hussain T, Ayub A, *et al*. Nanomaterials in combating cancer: Therapeutic applications and developments. Nanomed: Nanotech Bio Med, 2014; 10: 19–34.
6. Jang SJ, Jang IJ, Tetty C, *et al*. In-vitro anticancer activity of green synthesized silver nanoparticles MCF-7 breast cancer cells. Mat Sci Engn, 2016; (C68): 430-435.
7. Kanapathipillai M, Brock A, Ingber DE. Nanoparticle targeting of anti-cancer drugs that alter intracellular signaling or influence the tumor microenvironment. Adv Drug Del, 2014; 79(80): 107–118.
8. Sutradha BK, Amin ML. Nanotechnology in Cancer Drug Delivery and Selective Targeting. Hindawi Publishing Corporation. ISRN Nanotechnology, 2014; 1-12 pages.
9. Wong HL, Bendayan R, Rauth AM, *et al*. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Adv Drug Del, 2007; 59: 491–504.
10. Krishnan SR and George SK. Nanotherapeutics in cancer prevention, diagnosis and treatment. Intech, 2014; 10: 235-253.
11. Mathur M, Vyas G. Role of nanoparticles for smart herbal drugs. Indian J nat prod resour, 2013; 4(4): 329-338.
12. Dhiman A, Nanda A, Ahmad A. Novel drug delivery system: the need of hour. Int conf environ chem bio, 2012; 49(34): 171-175.
13. Saraf AS. Application of novel drug delivery system for herbal Formulations. Fitoterapia, 2010; 81(7): 680-689.

14. Kharat A, Pawar P. Novel drug delivery system in herbals. Int J pharm Chem Bio sci, 2014; 4(4): 910-930.
15. Buzea C, Pacheco II, Robbie KK. Nanomaterials and Nanoparticles: Sources and Toxicity. Biointerphases, 2007; 2(4): 17-71.
16. Devi JS, Bhimba V, Ratman KA. Invitro anticancer activity of the silver nanoparticles synthesized using the extract of gelidiella sp. Int J Pharm Pharm Sci, 2012; 4(4): 710-715.
17. Yadav M, Bhatia VJ, Doshi G, *et al*. Novel Techniques in Herbal Drug Delivery Systems. Int J Pharm Sci Rev Res, 2014; 28(2): 83-89.
18. Mamillapalli V, Atmakuri AM, Khantamneni P. Nanoparticles of Herbal extract. Asian J Pharm, 2016; 10(2): 623-632.
19. Chakrobarty k, Shivakumar A, Ramachandran S. Nanotechnology in herbal medicine. Int J herb med, 2016; 4(3): 21-27.
20. Iravani, S. Green synthesis of metal nanoparticles using plant. Green chem, 2013; 13: 2638.
21. Abhilash M. Potential applications of Nanoparticles. Int J Pharm Bio Sci, 2010; 1(1): 1-12.
22. Jasmine MDC, Prabhu VV. polymeric nanoparticles- the new face in drug delivery cancer therapy. Malaya J Biosci, 2014; 1(1): 1-7.
23. Sharma M. Application of nanotechnology based dosage form for delivery of herbal drugs. Res Rev: J Pharm nanotechn, 2014; 2(1): 23-30.
24. Mohnaraj VJ, Chen Y. Nanoparticles – a review. Trop J Pharm res, 2016; 5(1): 561-573.
25. Atram S. Recent development of herbal formulation. A novel drug delivery system. Int Ayurveda Med J, 2014; 2 (6): 952-958.
26. Mukherji S, Ray S, Thakur RS. Solid nanoparticles: A modern formulation approach in drug delivery system. Indian J pharma sci, 2009; 71(4): 349-358.
27. Indalkar YR, Pimpodkar NV, Godase AS, *et al*. A Compressive Review on the Study of Nanotechnology for Herbal Drugs. Asian J Pharm Res, 2015; 5(4): 203-207.
28. kumar V, Sethi N, Banerji A. Method of preparatiom of polymeric nanoparticles. Int J rec adv pharm res, 2015; 5(3): 260-268.
29. Umer A, Naveed S, Ramza N. Selection of a suitable method for the synthesis of copper nanoparticles. World Sci Publish comp, 2012; 7(5): 12300051-12300055.
30. Sharma AK, Kumar A, Taneja A, *et al*. Synthesis and preliminary therapeutic evaluation of copper nanoparticles against diabetes mellitus and–induced micro-(renal) and macro-vasucular (vascular endothelial and cardiovascular) abnormalities in rats. RSC Adv, 2016; (6): 36870-3688.
31. Gorbani M, Nayak D, Pradhan S. Biologically synthsised zinc nanoparticles and there antipepltic property. Epidermoid, 2015; A431: 329-338.
32. Nagavarma BVN, Yadav HKS, VasudhaAA *et al*. Different techniques for preparation of polymeric nanoparticles-A review. Asian J pharm clin Res, 2012; 5(3): 16-23.
33. Amooaghaie R, Saeri MR, Aziz M. Synthesis, characterization and biocompatibility of silver nanoparticles synthesized from Nigella sativa leaf extract in comparision with chemical silver nanoparticles. Ecotoxic environ safety, 2016; 120: 400-408.
34. Shreedhara CS, Sowmya S, Sanghai DB, *et al*. Preparation and nanoformulation of Triphala extract and evaluation of it's *in-vitro* antioxidant and cytotoxic potential. Int J Pharmaceutical and Phytopharmacological research. In press.
35. Castro-Aceituno V, Ahn S, Simu SY, *et al*. Anticancer activity of silver nanoparticles From Panax ginseng fresh leaves in human cancer cells, 2016; 16(84): 158-165.
36. Sivaraj R, Rahman PK, Rajiv P, *et al*. Biosynthesis and charcterization of Acalypha indica mediated copper oxide nanopartices and evaluation of its antimicrobial and anticancer acitivity. spectrochim Acta A Mol Biomol Spectrosc, 2014; 129: 255-58.
37. Mollick MR, Rana D, Dash SK, *et al*. Studies on green synthesized silver nanoparticles using Abelmoschus esculentus.pulp extract having anticancer (in vitro) and antimicrobial applications. Arab J Chem, 2015; 4: 1-12.
38. Phull AR, Abbas O, Ali A, *et al*. Antioxidant, cytotoxic and antimicrobial activities of green synthsesized silver nanoparticles from crude extract of Bergina cilita. Fut J pharm sci, 2016; 10: 1-12.
39. Sriranjani R, Srinithya B, vellingiri V, *et al*. Silver nanoparticles synthsis using clerodendrum phlomidis leaf extract and preliminary investigation of its antioxidant and anticancer activities. J mol liq, 2016; 220: 926-930.
40. Kathiravan V, Ravi S, kumar AS. Synthesis of silver nanoparticles from Melia dubia leaf extract and their in vitro anticancer activity.spectrochim Acta A Mol spectrosc, 2014; 130: 116-21.
41. Jain N, Gupta BP, Thakur N, et al. Phytosome: A Novel Drug Delivery System for Herbal Medicine. Int J Pharm Sci Drug Res, 2010; 2(4): 224-228.
42. Sravanthi M, Krishna SJ. Phytosomes: A novel drug delivery for herbal extract. Int J pharm sci res, 2013; 4(3): 949-959.
43. Awasthi R, Kulkarni GT, Pawar V. Phytosomes: An approach to increase the bioavailability of plant extract. Int J Pharm Sci, 2011; 3(2): 1-3.
44. Gandhi A, Dutta A, Pal A, et al. Recent Trends of Phytosomes for Delivering Herbal Extract with Improved Bioavailability. J Pharm Phyt, 2012; 1(4): 6.
45. Pawar HA, Bhangale BD. Phytosome as a Novel Biomedicine: A Microencapsulated Drug Delivery System .Vol Bioanal Biomed, 2015; 7(1): 6-12.
46. Amin T, Bhat SV. A Review on Phytosome Technology as a Novel Approach to Improve The Bioavailability of Nutraceuticals. Int J Adv Res & Tech, 2012; 1(3): 1-15.

47. Dhandapani NV, Sumanraj KS, Sai Charitha CH, *et al*. Phytosomes- A Review. Int J Pharma Sci, 2014; 4(4): 622-625.
48. Prasad SB, Bhatia S, Singh S. Phytosomes: phytoconstituent based lipid derived drugs delivery system. J chem. Pharm Res, 2016; 8(5): 664-670.
49. Walve JR, Bakliwal SR, Rane BR, *et al*. Transferosomes: A Surrogated carrier transdermal drug delivery. Int J applied biology pharm technology, 2011; 2(1): 204-211.
50. Kumar R, Singh M, Bala R, *et al*. Transferosomes: A Surrogated carrier transdermal drug delivery. Int res J pharm, 2012; 3: 20-24.
51. Sudheer P, Kar k, Saha C. Microemulsion–a Versatile Dimension of Novel Drug Delivery System. RGUHS J Pharm Sci, 2015; 5(10): 21-30.
52. Lawrence MJ, Rees G D. Microemulsion-based media as novel drug delivery systems. Adv Drug Delivery Reviews, 2000; 45: 89–121.
53. Saini JK, Nautiyal U, Kumar, *et al*. Microemulsions: A potential novel drug delivery system. Int J Pharm Med Res, 2014; 2(1): 15-20.
54. Muzaffar F, Singh UK, Chuhan L. review on microemulsion as futuristic drud delivery. Int J Pharmacy Pharm Sci, 2013; 5(3): 39-53.
55. Singh Pk, Iqubal Mk, Shukla Vk, *et al*. Microemulsion: current trends in novel drug delivery system.J pharm chem Bio sci, 2014; 1(1): 39-51.
56. Bhattacharya R, Mukhopadhyay S, Kothiyal P. Review on microemulsion- As a potential novel drug delivery system. World J Pharmacy Pharm Sci, 2016; 5(6): 700-729.
57. Dhakar RC, Maurya SD, Sagar BPS, *et al*. Microspheres: A Pharmaceutical Review. Der Pharmacia Letter, 2010; 2(5): 102-116.
58. Dhanapal R. A review –microemulsion. Asian J Pharm, 2011; 2(1): 23-29.
59. Karima N, Ghanbarzadeh B, Hamishehkar H, *et al*. phytosome and liposomes: The beneficial encapsulation system in drug delivery and food applications. Appl food Biotech, 2015; 2(3): 17-27.
60. Bhokare SG, Dongaonkar CC, Lahane SV, *et al*. Herbal novel drug delivery- A review. World J Pharma Pharm Sci, 2016; 5(8): 593-611.
61. Popovska O, Simonovska J, Kavrakovski Z, *et al*. An Overview: Methods for Preparation and Characterization of Liposomes as Drug Delivery Systems. Int J Pharm Phytopharmacol Res, 2013; 3(3): 182-189.
62. Chaturvedi M, Kumar M, Sinha A, *et al*. Recent development in novel drug delivery systems of herbal drugs. Int J green pharmacy, 2011; 10: 87-94.
63. Marripati S, Umasankar K, Reddy PJ. A review on liposomes. Int J Res Pharm Nano Sci, 2014; 3(3): 159-169.
64. Kalepu S, Kumar SKT, Betha S, *et al*. Liposomal drug delivery system - A Comprehensive Review. Int J Drug Dev Res, 2013; 5(4): 62-75.
65. Pratyusha K, Muthukumaran M, Krishnamoorthy B. liposomes as Targeted drug delivery system present and future prospective: a review. J drug Del Ther, 2013; 3(4): 195-201.
66. Buboltz JT, Feigenson GW. A novel strategy for the preparation of liposomes: rapid solvent exchange. Biochim Bio phys Acta, 1999; 1417(2): 232-45.
67. Sharma P, Verma S, Misri P. Global Need for Novel Herbal Drug Formulations. Int J Phcog Phytochem Res, 2016; 8(9): 1535-1544.
68. Akabarzadeh A, Sadabady RR, Davaran S, *et al*. liposome: classification, preparation, and application. Nanoscale Res lett, 2013; 8: 102.
69. Rathore GS, Tanwar YS, Sharma A. Fluconazole Loaded Ethosomes Gel and Liposomes Gel: An Updated Review for the Treatment of Deep Fungal Skin Infection. The Pharm Chem J, 2015; 2(1): 41-50.
70. Shelke S, Shahi S, Kale S, *et al*. Ethosomes: A Novel Deformable Carrier. World J Pharm Sci, 2015; 3(9): 1830-1839.
71. Chandel A, Patil V, Goyal R, *et al*. Ethosomes: A Novel Approach towards Transdermal Drug Delivery. Int J pharm chem Sci, 2012; 1(2): 563-569.
72. Nirwan LS. Therapeutic potential of novel drug carrier ehosomes: An overview. Int J Chem Phram Sci, 2013; 1(6): 427-432.
73. Parashar T, Soniya, Sachan R, *et al*. Ethosomes: A recent vesicles of transdermal drug delivery system. Int J Res Dev Pharm life Sci, 2013; 2(2); 285-292.
74. Prajapati ST, Patel CG, Patel CN. Transfersomes: A Vesicular Carrier System for Transdermal Drug Delivery. Asian J Biochem Pharm Res, 2011; 1(2): 507-524.
75. Grace FX, Raj RS, Reshma I, *et al*. Herbal Ethosomes - A Novel Approach in Herbal Drug Technology. American J Ethnomed, 2014; 1(4): 226-230.
76. Sachan R, Parashar T, Soniya, *et al*. Drug carrier transferosomes: A novel tool for transdermal drug delivery system. Int J Res Dev Pharm Life Sci, 2013; 2(2): 309-316.
77. Venkatesh N, Kalyani K, Tulasi K, *et al*. Transferosomes: A novel technique for transdermal drug delivery. Int J Res Pharm Nano Sci, 2014; 3(4): 266–276.
78. Sharma S, Nautiyal U. Transferosomes: novel approach for transdermal delivery. Euro J Pharm Med Res, 2015; 2(3): 218-233.
79. Gavali SM, Pacharane SS, Jadhav KR, *et al*. Clinical transferosmes technique for transdermal drug delivery. Int J Res pharm chem, 2011; 1(3): 735-740.
80. Yadav M, Bhatia VJ, Doshi G, *et al*. Novel Techniques in Herbal Drug Delivery Systems. Int J Pharm Sci Rev Res, 2014; 28(2): 83-89.
81. Shaji J, Lal M. Preparation, optimization and evaluation of transferosomal formulation for

enhanced transdermal delivery of a COX-2 inhibitor. Int J pharm sci, 2013; 6(1): 467-477.
82. Kaur N. Transdermal drug delivery through carriers: Transfersomes. Pharmatutor, 2014; 2(12): 77-85.
83. Abirami A, Halith SM, Pillai Kk, *et al*. Herbal nanoparticles for anticancer potential-A review. World J pharm Phamaceutical sci, 2014; 3(8): 2123-2132.
84. Beyatricks J, Kumar Sk, Suchitra D, *et al*. Recent microsphere formulation and its application in herbal drugs- A review. Int J Pharm Development & Technology, 2014; 4(1): 58-62.
85. Kaur D, Saini S, Singh G, *et al*. Biodegradable Microsphere: A Review. Int Res J Pharm, 2012; 3(12): 15-20.
86. Kataria S, Middha A, Sandhu P, *et al*. Microsphere: A review. Int J res pharm chem, 2011; 1(4): 1184-1198.
87. Garg A, Upadhyay P. Mucoadhesive Microspheres: A Short Review. Asian J Phrm Clinc Res, 2012; 5(3): 24-27.
88. Tadwee IAK, Shahi S, Thube M, *et al*. Review on Microspheres. Int J Pharm Res Allied Sci, 2011; 1(1): 24-33.
89. Gupta S, Parvez N, Bhandari A, *et al*. Microspheres based on herbal actives: the less-explored ways of disease treatment Somya. Egyt Pharm J, 2015; 14: 148–157.
90. Ramteke KH, Jadhav VB, Dhole SN. Microspheres: as carrieres used for novel drug delivery system. IQSR J Pharm, 2012; 2(4): 44-48.
91. Mohan M, Hazari S, Rao UM, *et al*. A brief review on mucoadhesive microsphere. Int J Res Rev Pharm Appl sci, 2014; 4(1): 975-986.
92. Rathore A, Yadav G, Nayak G, *et al*. K. A review on microspheres as drug delivery carriers for management of diabetes mellitus B. Int J Pharm Life Sci, 2012; 3(10): 2064-2070.
93. Patel NR, Patel DA, Bharadia PD, *et al*. Microsphere as a novel drug delivery. Int J Pharm Life Sci, 2011: 2(8): 992-997.
94. Mathur M. Approaches for improving the pharmacological and pharmacokinetic properties of herbal drugs. Int Res J Pharm App Sci, 2013; 3(4): 40-50.
95. Feng Y, Wang N, Zhu M, *et al*. Recent progress on anticancer candidates in patents of herbal medicinal product. Recent patents on food, nutrition and agriculture, 2011; 3: 30-48.