REVIEW ARTICLE

Herbal nanoparticles: A patent review

Namdeo R Jadhav, Trupti Powar, Santosh Shinde, Sameer Nadaf

Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India

Design and development of herbal nanoparticles has become a frontier research in the nanoformulation arena. To update researchers, an attempt has been made to review nanoformulation-based herbal patents. This article mainly covers herbal medicines are used for the treatment of cardiovascular diseases, Parkinsonism, pulmonary diseases, proliferative diseases, Alzheimer's disease, diabetes, cancer therapy, anti-osteoporosis, and the like. It has been revealed that nanoparticles of Curcumin have been widely designed to increase its bioavailability and for treatment of cancers like breast cancer, lung cancer, pancreatic cancer, and so on. The common nanoformulated herbal medicines are *Panax ginseng*, *Curcuma longa, Silybum marianum*, *Withania somnifera*, *Gymnema sylvestre*, *Salvia miltiorrhiza,* and the like, having a profound future potential.

Key words: *Alzheimer's disease, cardiovascular, nanoparticles, proliferative diseases, traditional herbal drugs*

INTRODUCTION

Nowadays phytotherapeutics are obtained in nanoparticle form for improvement of their pharmacokinetic and pharmacodynamic profile.[1] Nanoparticles (NPs) measure approximately 1 - 1000 nm in dimension and exhibit properties different from their macroscale counterparts.[2] The nanonization of phytoceuticals leads to a high surface area to volume ratio, enhancement in solubility and bioavailability, reticuloendothelial system (RES) uptake, an enhanced permeability and retention (EPR) effect, improvement in tissue distribution of macrophages, sustained release, enhanced physicochemical stability, and so on.[3] NPs contain the drug embedded in the matrix or absorbed onto the surface.[2] To reap the aforesaid benefits, novel carriers and methods to prepare herbal NPs have been investigated, numerous have been patented also. The present review is an attempt to focus on patents that have been filed on herbals in the form of nanoparticles and understand which are the prospective ones.[4]

Patents on herbal nanoparticles

Cancer cell targeting

Cancer is a term used to describe a broad group of diseases in which abnormal cells have undergone unregulated growth to form a mass of tissue (tumor) and are able to invade other tissues.[5] Cancer cells can spread to other parts of the body through the blood and lymphatic system.[6] There are different types of cancers, identified by the name of the organ in which they start. For example, the cancers that begin in the colon, liver, and breast are called colon, liver, and breast cancers, respectively.[7]

The development of all types of cancers starts in the cells. To maintain a healthy body, different cells grow and divide in a controlled manner to produce more cells. After the damaged cells undergo apoptosis (programmed cell death) they are replaced by new ones. However, sometimes this systematic process goes wrong. Mutation (changes in genetic material) affects normal cell growth and division. When this happens, instead of dying, new cells form, although the body does not need them. These extra cells may further form a mass of tissue called a tumor. Tumors can be benign or malignant.[8,9]

Benign tumors (non-cancerous)

A benign tumor is a mass of cells that lacks the ability to invade neighboring tissue or metastasize. The cells in benign tumors do not spread to other parts of the body.[10,11]

Malignant tumors (cancerous)

The cells in these tumors can invade nearby tissues and spread to other parts of the body.[10,11]

Address for correspondence:
Dr. Namdeo R Jadhav,
Department of Pharmaceutics,
Bharati Vidyapeeth College of Pharmacy,
Kolhapur - 416 013, Maharashtra, India.
E-mail: nrjadhav18@rediffmail.com

Access this article online	
Quick Response Code:	Website: www.asiapharmaceutics.info
	DOI: ***

Cancer is usually treated with chemotherapy, radiation therapy, and surgery. Different drugs directly acting on cells (cytotoxic drugs), antimetabolites, antibiotics, and the like, can be used to cure cancers. Radiation therapy involves the use of ionizing radiation in an attempt to either cure or improve the symptoms of cancer.[12-14]

KUO (2004, E. P. 2006, 2006) describes the process of preparing water-soluble extract from the plant's *solanum* genus consisting of 60 - 90% solamargine and solasonine. This extract is in nanoparticle size, less than 1 µm, which can be directly dissolved in water to produce a yellowish clear and transparent aqueous solution with a solubility range of 2 ~ 20 mg/ml or higher. The aforesaid extract is used as active agent in a pharmaceutical formulation, to treat or inhibit the growth of a tumor/cancer cells, particularly in the liver, lung, and breast cancer cells.[15-17]

Singh (2004), described the liposomal formulation of digitalis glycosides like oleandrin, digoxin, and digitoxin for the protein-stabilized nanoparticle (PSL) formulation, used for treating cell proliferation and reducing toxicity, the high drug to lipid ratio, and long circulating time in the blood stream, and also, it has the ability to deliver drugs to tumor sites. They also described a method for preparation of a variety of liposomal digitalis glycoside compositions used for treating cell proliferative diseases in humans and mammals. PSL are formed by the uniform coating of protein onto liposomes to overcome the problems of drugs like toxicity, low bioavailability, and low plasma distribution. This PSL nanoparticle formulation consists of a mixture of egg phosphatidylcholine (EPC), hydrogenated soya phosphatidylcholine (HSPC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylenositol (PI), monosialogangolioside, and spingomyelin (SPM), with digitalis glycoside. It is also used to treat cancer, acquired immunodeficiency syndrome (AIDS) and other diseases such as diabetes and cardiac disorders, in humans and mammals. This invention provides an effective method to reduce the growth of cancer or reduce the incidence of metastasis, inflammation, and arthritis in animals.[18]

Desai *et al.*, (2007, 2010, 2010) provided a method to treat proliferative diseases such as cancer by providing a combination therapy comprising of an effective amount of taxane in a nanoparticle form, with albumin as a carrier, as first therapy, and use of radiation, surgery, administration of chemotherapeutic agents or a combination as second therapy. They also described a method of administering an individual taxane in a nanoparticle form based on the metronomic dosing regimen, which includes, treatment of cancer by administering an effective amount of a nanoparticles consisting of taxane and carrier protein albumin, or an effective amount of chemotherapeutic agent, or administering an effective amount of nanoparticle consisting of paclitaxel and carrier protein albumin or administering nanoparticles and the chemotherapeutic agent simultaneously. A combination of paclitaxel and albumin nanoparticles called Abraxane were found to be effective for various cancers such as metastatic breast cancer, prostate cancer, malignant melanoma, carcinoma of the cervix, ovarian cancer, and so on.[19-21]

Gorur Amita *et al*., (2007) prepared agar bionanoparticles ranging from 50 nm - 80 nm. These bionanoparticles helped to prevent the calcium-induced clotting of human blood plasma and inhibited the growth of onion roots and human epidermoid carcinoma HEp2 cells.[22]

Sambandam *et al.,* (2007) described the preparation of oligosaccharide bionanoparticles from the Moringa oleifera Lam gum, with a particle size between 60 nm and 100 nm. They protected plasmid DNA and RNA from degradation, along with inhibition of the growth of onion roots and induced membrane blebbing (the cavity containing gas) leading to apoptosis and death of human epidermoid carcinoma HEp2 cells.[23]

Liang *et al.,* (2009) disclosed the making of nano-micellar vinca alkaloids (vincristine and vinblastine), which are a class of effective broad spectrum anti-tumor agents entrapped in polyethylene glycolylated phospholipids, for intravenous injection. The composition contains vinca alkaloid phosphatides derivatized with polyethylene glycol (PEG), with a pharmaceutical adjuvant. The PEG molecules provide a hydrophilic protective layer for the hydrophobic core of the encapsulated medicament. This hydrophilic protective layer gives protection for medicament against enzymes and other protein molecules in the blood and they are not recognized and phagocytozed by the reticuloendothelial system in the body, hence, their circulation time *in vivo* is prolonged. On account of its good stability, the nano-micellar preparation improves drug distribution in the tumor tissue, increases effectiveness, and decreases toxicity. It is an effective broad spectrum anti-tumor agent used in the clinical treatment of various cancers, such as, leukemia, lymphoma, breast cancer, lung cancer, liver cancer, and many other tumors.[24]

Zale *et al.,* (2010), proposed a formulation and use of anticancer polymeric nanoparticles of the vinca alkaloid (vincristine or vinorelbine) having a diameter of 70 - 140 nm. It has been also described as the method for making and using nanoparticles, which include the use of polylactic acid-polyethylene glycol copolymer or poly lactic-co-glycolic acid, polyethylene glycol copolymer, which helps therapeutic agents to be released at a controlled pace over a period of one day or more, when administered to patients. This particle immediately releases less than 7% of the therapeutic agent, when placed in phosphate buffer solution, at room temperature, and less than 10%, at 37°C. The patent has also included a method for treating prostate, breast, or non-small cell lung cancer, by administering an effective amount of the

composition containing the therapeutic nanoparticle to a patient.[25]

Kurzrock *et al.,* (2011), disclosed the use of liposomal curcumin in the treatment/prevention of pancreatic cancer, melanoma, and breast cancer in human patients or other mammalians. It has been seen to suppress the growth of cancer in the laboratory and has prevented the appearance of cancer in animals, when used as a liposomal drug delivery, in the form of nanoparticles or nanocapsules, given parenterally. The patent has described a method to inhibit the growth of cancer, by exposing the cells *in-vitro* to the formulation of a liposomal drug delivery system containing encapsulated curcumin. The ratio of curcumin to the lipid combination (w/w) stated has been 1:75 to 1:10. It has been revealed that liposomal curcumin demonstrated a more significant effect on cancer than plain curcumin.[26]

Sanjeeb Kumar Sahoo, (2011), described a water-soluble, curcumin-loaded nanoparticle system for cancer therapy consisting of glyceryl monooleate (GMO), polyvinyl alcohol (PVA), and pluronic F-127, with a uniform particle size of less than 200 nm, having a high surface charge and high zeta potential, around - 32 mV, which enhances the solubility, stability, and bioavailability of the entrapped curcumin used for cancer therapy. The curcumin-loaded nanoparticle system is prepared by incorporating curcumin into a fluid phase of GMO, and then subjecting this mixture for emulsification with PVA and a pluronic F-127 solution. Next, the final emulsion is lyophilized with a freeze dryer, to produce lyophilized powder. It has been investigated that curcumin shows its anti-proliferative activity against cancer cell by inducing apoptosis.[27]

Ringas *et al.,* (2011) provided a method of treating pancreatic, colonic, breast, and lung cancer by administering phospho-valproic acid, phosphor-ibuprofen, phosphor-sulindac or their pharmaceutically acceptable salt, together with bioavailability enhancing agents like cimetidine and curcumin. The aforesaid bioavailability enhancer is in the form of a solid lipid nanoparticle, liposome or polymer molecule. This invention provides a method to treat cancer by periodical administration of phosphor-valproic acid or a pharmaceutically acceptable salt or combination with cimetidine/curcumin.[28]

Patel Ashok, (2012), provided nanoparticulate compositions of hydrophobic phenolic compounds like curcuminoids or isoflavones and polymethoxylated flavones in combination with hydrophobic polymers like zein, gliadin, hordein, secalin or a combination of these polymers. This composition has shown enhanced water dispersibility, stability against aggregation and sedimentation, and enhanced bioavailability. This is due to the nanonization of hydrophobic phenolic compounds and hydrophobic polymer-containing prolamins. These are used as antioxidant, anti-inflammatory and anticancer agents.[29]

Shen *et al.,* (2012), prepared a polyester unit containing curcumin and pyromellitic anhydride monomer residues, and a polyethylene glycol monomethyl ether side chain, bound to the polymer backbone. They also prepared another polyester and used this as an antitumor, antioxidant, anti-inflammatory, and antibacterial agent in the form of nanoparticles, colloidal particles, and vesicles. This patent also discloses the use of curcumin as a prodrug and prodrug carrier.[30]

Danek, (2013), described the use of a combination therapy for treating cancer by the administration of chemotherapeutic agents like vincristin, vinblastine, and the like, in an effective amount and cyanobacteria extract in the form of nanoparticles administered orally, intravenously, subcutaneously, via inhalation, or parenterally.[31]

Elinbond *et al.*, (2013), disclosed an invention containing a pharmaceutical composition that comprised a physiologically effective dose of triterpene glycoside or triterpenes like actein in a nanoparticle complex form, prepared by liposome-encapsulated or exosome-encapsulated compounds like black cohosh (rhizomes, fruits or other parts), edible plants, and so on, used to treat or prevent cancers or other inflammatory diseases, human immunodeficiency virus (HIV), lipid disorders, and osteoporosis.[32]

Einbond *et al.,* (2013), invented a pharmaceutical composition that contained a physiologically effective dose of nanoparticle triterpene glycoside or triterpene complex nanoparticles, which were liposome-encapsulated complex compounds or exosome-encapsulated compounds used to treat or prevent cancer and acted as chemopreventive or chemotherapy agents for breast cancer.[33]

Liu *et al.,* (2013), invented a herbal composition comprising of a therapeutically effective amount of *Scutellaria baicalensis, Glycyrrhiza uralensis, Ziziphus jujuba,* and *Paeonia lactiflora* with a chemotherapeutic compound used to treat cancer in mammals. It is useful to increase the therapeutic index of chemotherapeutic compounds, by administering the herbal composition PHY906 to mammals undergoing chemotherapy, in a nanoparticle formulation, by the oral or intravenous route, to improve the treatment of disease.[34]

Alzheimer's disease

Alzheimer's disease (AD) is characterized by cognitive impairment, progressive neurodegeneration, and formation of amyloid-β (Aβ)-containing plaques and neurofibrillary tangles, composed of hyperphosphorylated tau. The neurodegenerative process in AD is initially characterized by synaptic damage accompanied by neuronal loss.[35,36] AD is the most common cause of dementia.[37] Memory loss and behavioral changes are some symptoms of AD.[38]

Alzheimer's disease primarily affects the cholinergic neurons in the brain.[39] Hence, to augment brain acetylcholine (ACh),

acetylcholinesterase inhibitors (Tacrine, Rivastigmine, Galantamine, and Donepezil) and a glutamate receptor antagonist (Memantine) are generally preferred.[40,41]

Frautschy *et al.,* (2007, 2009), described solid lipid nanoparticles and the microemulsion of the curcuminoid, micellar form of curcumin and its derivatives. The carrier comprises of lipid micelles of phosphatidyl choline and microcapsulated oils. The antioxidant contains ascorbic acid and a glucuronidation inhibitor consisting of tetrahydrocurcumin, which is relatively stable in water at a physiological pH and helps to enhance absorption and the plasma level of curcumin for treating Alzheimer's disease and other age-related disorders. The present invention enhances the bioavailability of curcuminoid. The composition is suitable for administration to humans or mammals topically, enterally, parenterally or by some other mode of administration.[42,43]

Desai, (2010), has provided a curcumin cyclodextrin combination in the form of a microemulsion, solid lipid nanoparticles, solid powder, liquid, and a microencapsulated oil or gel, and this combination is used for the prevention and treatment of various diseases like Alzheimer's disease, asthma, rheumatoid arthritis, oncological diseases, and so on, because, curcumin has anti-inflammatory and anti-angiogenic properties. As curcumin is very poorly absorbed and has very low bioavailability, the patent has described a method to increase the delivery of curcumin by complexation with cyclodextrin, which has the capability to increase the bioavailability.[44]

DI Mauro, (2013), has disclosed methylated curcumin-methoxy stilbene hybrid molecules, particularly used in treating cancer. Curcumin does not penetrate easily through the human digestive tract and is subject to intestine-based metabolism and rejection and less than 1% of oral curcumin enters the plasma. The small amount of curcumin that enters the bloodstream is rapidly metabolized by the kidney and liver. Although curcumin is highly lipophilic (and easily crosses the blood-brain barrier), only very small amounts of orally administered curcumin are registered in the serum and in the brain tissue. It has been reported that high oral doses of curcumin cause problems such as rash and diarrhea, and headaches likely produced by metabolites of curcumin. They describe intranasal administration of a formulation comprising of an effective amount of curcumin to the olfactory mucosa across the cribriform plate and into the brain, to treat a neurodegenerative disease such as Alzheimer's disease.[45]

Mazed *et al.,* (2011), have disclosed a nutritional supplement, a synergistic liquid mixture used in the form of a food, drink, supplement, drug, cosmetics or a hygienic product, which is formulated and used to improve a person's well-being, lowering the risks of cardiovascular diseases and/or Alzheimer's disease, and/or lowering blood sugar and insulin resistance, using natural and synthetic ingredients, consisting of the aroma, color, flavor, flow (viscosity), taste, and uniformity, with ingredients like natural preservatives, sugar substitutes, nanodispersition, nanoemulsion, and nanoencapsulation of those ingredients, by using the apparatus for personalized nutrition by dilution with water or skimmed milk. This nutritional supplement consists of herbal components like *Azadirachta indica, Bacopa monnieri, Curcuma longa, Gymnema sylvestre, Panax ginseng, Panax quinquefolius, Paullinia cupana, Pfaffia paniculata, Phyllanthus emblica, Phyllanthus niruri, Pinus maritima, Polygonum cuspidatum, Scutellaria baicalensis, Silybum marianum, Syzygium cumini, Tinospora cordifolia, Trigonella foenum-graecum, Andrographis paniculata, Cinnamomum zeylanicum, Cnidium officinale, Coccinia indica, Crataegus oxyacantha, Juglans regia, Momordica charantia, Mucuna pruriens, Ocimum sanctum,* and *Withania somnifera,* with supplements like α-lipoic acid, astaxanthin, catechin, citicoline, coenzyme Q10, conjugated linolenic acid, glutathione, glycine, hesperidin, indole-3-carbinol, kaempferol, L-theanine, lycopene, myricetin, naringenin, pelargonidin, plant sterols encapsulated within an encapsulant-like chitosan, cyclodextrin, dendrimer, lecithin, liposomes and plant protein, an oxidant.[46]

Cosmetic nanoparticles

Gupta, (2004, 2004), invented controlled release or an ion pair nano-diffusion delivery system, with 1 - 70% zeolite for cosmetics and pharmaceuticals. This formulation or delivery system comprises of water and oil emulsion, suspension of nanoparticles or anhydrous compositions. Furthermore, the preparation is used for the treatment of skin aging, skin wrinkle reduction; skin exfoliating, UVA/UVB sunscreens, anti-wrinkle, skin whitening, acne treatment, rosaceous treatment, ultraviolet (UV) blocks, anesthetics, skin soothers, and te like.[47,48]

The details of the patent disclosure claiming plants and plant products have been given below.

- **To promote cellulite control, excess fat reduction or toning benefits:** The forskohlin extract, Hydroxycitric acid (*Garcinia cambogia*), Kola seed extract, caffeine, *Psyllium* husk, Phaseolamin, Theophylline, Theobromine, Roselle tea extract, *Tephrosia* extract, Laminaria extract, *Panax* genus plant extract, *Gymnema sylvestre* extract, Climbing ivy extract, Arnica extract, Rosemary extract, Marigold extract, Sage extract, Ginseng extract, St. Johns-wart extract, Ruscus extract, meadowsweet extract, and orthosiphon extract or in combinations
- **To promote collagen synthesis and impart elasticity to skin:** *Ascorbic acid, Glucosamine ascorbate, Arginine ascorbate, Lysine ascorbate, Chitosan ascorbate,* Vitamin E, Hesperedin, Diosmin, Mangiferin, Mangostin, Cyanidin, Astaxanthin, Lutein, Lycopene, Resveratrol, Tetrahydro curcumin, Rosmaric acid, Hypericin, Ellagic acid, Chlorogenic acid, Oleuropein, Andrographolide, *Potentilla* erecta extract, Grape seed extract, and Pycnogenol
- **Skin beneficial hydroxyl acid:** Citric acid, Malic acid, Ellagic acid, Rosmarinic acid, ascorbic acid, glycolic acid, and hyaluronic acid

- **Skin whitening agents:** Extract of Paper Mulberry, Mitracarpe, extract of Bearberry, extract of Yellow Dock, *Aspergillus orizae* extract, Licorice root extract, Rosmarinic acid, Green tea extract, extract of Yohimbe, *Ecklonia cava* extract, *Spondias mombin* extract, *Maprounea guianensis* extract, *Waltheria indica* extract, *Gouania blanchetiana* extract, *Cordia schomburgkii* extract, *Randia armata* extract, and *Hibiscus furcellatus*
- **Antioxidants:** Ascorbic acid, Vitamin E, Hesperedin, Diosmin, Mangiferin, Mangostin, Cyanidin, Astaxanthin, Lutein, Lycopene, Resveratrol, Tetrahydro curcumin, Rosmaric acid, Hypericin, Ellagic acid, Chlorogenic acid, Oleuropein, Andrographolide, *Potentilla* erecta extract, Grape seed extract, Pycnogenol, Green tea extract, White tea extract, and Black tea extract
- **Protection from ultraviolet A or B radiations:** Galanga extract (Kaempferia galanga), Lawsone, and Avobenzone
- **Blood microcirculation:** Horse Chestnut extract, Esculin, Escin, Yohimbine, Capsicum oleoresin, Capsaicin, Niacin, Niacin Esters, Ruscogenin, Diosgenin, *Emblica* extract, Asiaticoside, Boswellia extract, Grape seed extract, Ginger root, Piperine, Vitamin K, Melilot, Sericoside, *Ammi visnaga* extract, extract of Red Vine leaves
- **Antimicrobial:** Berberine
- **Vitamins:** Vitamin A, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Retinol, Retinoic acid, Tretinonin, Carotenes, Biotin, Folic acid
- **Hormone composition:** Progesterone
- **Skin protectant drugs:** Cocoa butter.

Nanbu, (2009), described the whitening cosmetic nanoparticle composition containing arbutin, a hydroquinone glucoside, having a melanin production inhibitory effect, which is incorporated into the whitening cosmetic products in a high concentration, to improve the whitening effect. Arbutin has low aqueous solubility, and hence, it is difficult to incorporate into a cosmetic product in a high concentration, thus production of emulsified nanoparticles has been carried out. This method includes incorporation of a specific amount of arbutin into lecithin, followed by a treatment to form nanoparticles, so that the emulsified nanoparticles will contain a bioactive substance such as a whitening material in each particle, which increases the concentration of arbutin in the cosmetic composition. α, β arbutin or a mixture of both can be used. The nanoparticles are prepared from the aqueous arbutin dispersion, and have a particle size of 10 - 150 nm. The said composition alleviates skin problems such as age spots, dullness, and pigmentation.[49]

Topical preparation

Wright, (1997), disclosed micellar nanoparticles (10 - 1000 nm in diameter) mostly less than 100 nm, prepared by hydrating a mixture of vegetable oils like almond oil, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, soybean oil, peanut oil, mineral oils, and so on, and a mixture of them with a stabilizer such as tween 60, tween 80, and nonylphenol polyethylene glycol ethers, and mixture of them, which is the lipophilic phase, and an alcohol-based initiator, hydrated with suitable aqueous solution. This is used for topical delivery by penetration due to their small size.[50]

Baktha *et al.,* (2003, 2004), proposed capsaicin, a pungent substance derived from the solanacae family, for topical treatment in nanoparticle, microemulsion or nanocapsule form to treat/modulate specific receptor activity *in vivo* or *in vitro* to treat chronic or acute pain, including neuropathic pain.[51,52]

Kanazawa, (2009), described a formulation, which includes a nanoparticle comprising of 0.1% to 100% w/w of a blood circulation promoter such as tocopherol-derivative, a nicotinic acid derivative (Niacin, vitamin B3), *Swertia japonica* extract (Makino), Sunflower, Tocopherols (vitamin-E), olive oil (Tocotrienols), palm oil, and a biodegradable polymer-like protein, such as, collagen, gelatin, albumin, casein, acid treated gelatin, ovalbumin, sodium casein, and so on. An α, β, γ, and κ casein, which is a milk-derived or bean-derived protein, is also used alone or in combination. The protein is then subjected to a cross-linking treatment after the formation of a nanoparticle by using transglutaminase obtained from guinea pig liver, goat, rabbit, or human liver, and treated with organic solvents like ethanol, acetone, and isopropanol. This composition can be used as a transdermal absorbable agent, topical therapeutic agent, oral therapeutic agent, intradermal parenteral injection, subcutaneous parenteral injection, cosmetic, functional food, supplement or a quasi-drug.[53]

Chaudhary *et al.*, (2011), described a novel herbal nano-emulsion containing lemon juice and er in 1:1 ratio or lemon alone as a pharmaceutically active aqueous layer/phase entrapped in essential oils like Tea tree oil (18 ± 5%), Rosemary oil (2 ± 5%), Tulsi oil (4 ± 5%), Lavender oil (5 ± 5%), and Mentha oil (7 ± 5%), used as an oil phase. The present nano-emulsion has been claimed for prophylactic and therapeutic topical treatment of acne and other skin disorders like eczema, psoriasis, aging, and scarring, with increased efficacy, improved percutaneous penetration, and excellent thermodynamic stability, with low skin irritation and long shelf life and reservoir effect, which promotes drug localization in the skin that enables controlled delivery of active or therapeutic agents.[54]

Leighlon *et al*., (2013), invented a method to treat a subject suffering from herpes simplex virus-induced inflammation by the topical application of a composition containing an effective amount of anti-histamine, with the base composition containing essential extracts of lemon balm (*Melissa officinalis*), calendula flowers (*Calendula officinalis*), green tea gunpowder (*Camellia seninsis*), and green rooibos (*Aspalatus linearis*) in the form of emulsion, nanoparticles, suspensions, patches, and the like.[55]

Osteoporosis

Osteoporosis is an age-related progressive bone disease that is characterized by a decrease in bone mass and density

causing them to become weak and fragile, which can lead to an increased risk of fracture.[56] These fractures usually occur in the spine, wrist, and hips but can affect other bones such as the arm or pelvis.[57] To reduce the risk of fracture supplements of vitamin D and K are found to be beneficial in post-menopausal women.[58,59] Bisphosphonates, Raloxifene, Denosumab, and Teriparatide (a recombinant parathyroid hormone) have been shown to be effective in the treatment of women with postmenopausal osteoporosis.[60]

Maurya *et al.*, (2007), has invented a formulation with the *Butea monosperma* extract, which is used to treat or prevent bone disorders like osteoporosis. The inventor has prepared its nano formulation and used it to treat osteoporosis. The present formulation is availed as a microemulsion, nanoparticle, nanoemulsion, and a micro particle with a dose of 0.1 - 5000 mg weekly or bi-weekly or daily.[61]

Mousa *et al.,* (2011), proposed a composition and methods to prepare nanoformulations of active ingredients like *Lepidium sativum* or other Lepidium extracts, calcium, vitamin D, and antioxidants like flavonoids and/or isoflavones, lycopene, green tea extract, pomegranate extract, and a combination that is used for treatment of osteoporosis in animals. The active ingredient is encapsulated within the nanoparticles selected from a group of chitosan nanoparticles, poly (lactic-co-glycolic acid) (PLGA) nanoparticles, chitosan cross-linked to fatty/bile acids, alginate-chitosan nanoparticles, polyvinylpyrrolidone (PVP) hydrogel nanoparticles, and so on. The present composition is meant for oral, topical, injectable, via toothpaste, and in combination, in cases of osteoporosis and bone fracture in animals.[62]

Hair care formulation

Kim, (2010), invented nanoparticles, which, when applied to the scalp, get deeply infiltrated into the dermis, thus promoting blood circulation and provide nutrition to the hair in case of alopecia. The inventor described this herbal nanoparticle composition, which is used for preventing hair loss and promoting hair growth, with no harmful side effects. This nanoparticle composition stimulates and activates hair follicles, to promote the metabolism of hair with antioxidant activity on the scalp, thus inhibiting depilation and aiding hair growth. It contains lecithin-capsule nanoparticles prepared from an admixture of herbal extracts like the *Salvia miltiorrhiza* extract, Safflower extract, *Zanthoxylum piperitum* extract, *Torilis japonica* fruit extract, *Cnidium officinale makino* extract, Green tea leaf extract, Pomegranate extract, Pine tree leaf extract, Red ginseng extract, Ginseng extract, Angelicae extract, 9% vitamin mixture of nicotinamide and tocopherol acetate, and distilled water.[30]

Canham *et al.*, (2011), disclosed mesoporous microparticulate materials (silicon) loaded with active ingredients like Aloe vera, Asian ginseng, Capsicum species, Cascara sagrada, Garlic, Ginger, and so on. Encapsulation of a mesoporous microparticulate material is done by sealing the openings of the pores, which are then coated with a capping layer called 'beads', with a thickness of 0.1-50 µm, and are used for cosmetic preparation to treat or prevent acne, oily skins, wrinkles, psoriasis on the body, and/or face. The hair care composition is used for treating and/or cleaning the hair and scalp of humans or animals. The oral hygiene composition is used for treatment and prevention of gingivitis and plaque.[63]

Parkinson's disease

Parkinson's disease (PD) is a progressive degenerative disorder of the central nervous system, characterized by rigidity, tremor, and hypokinesia. PD results primarily from the death of the dopaminergic neurons in the substantia nigra, a region of the midbrain.[64,65]

As PD is associated with dopamine deficiency, drugs affecting the brain dopaminergic system like Levodopa (Dopamine precursor), Carbidopa and Benserazide (decarboxylase inhibitors) have been shown to be beneficial.[66]

Nelson, (2002, 2009), described a composition to increase cellular respiration of melanized catecholamine neurons and invented a method to alleviate or stop the appearance and progress of Parkinsonism disease symptoms. The composition contains (-) chloroquine, which is adsorbed on suitable carriers like nanoparticles to cross the blood-brain barrier.[67,68]

Hyperlipidemia

Hyperlipidemia is characterized by abnormally elevated levels of any or all lipids and/or lipoproteins in the blood.[69]

Aburdeinch *et al*., (2005, 2008), disclosed a method to lower blood cholesterol in non-diabetic patients by 30%. The method includes oral administration of fenugreek seed extract to the patient, in nanoparticle, microparticle, pill, capsule, granule or liposome form, for 30 consecutive days. The fenugreek seed extract composition to be formulated in NPs is prepared by grinding approximately one-third cup of dry fenugreek seeds to a powder. Next, the powder is combined with 15 cups of water and the mixture is boiled for 10 minutes. Then, the mixture is cooled to room temperature to obtain a cooled extract. The extract is strained and refrigerated prior to oral administration.[70,71]

Gokaraju *et al*., (2010), disclosed a herbal formulation used to inhibit, ameliorate or prevent adipogenesis mediated diseases like obesity, lipid storage disease, and hyperlipidemia. The composition contains extracts of *Piper betle* in 1 to 99% by weight, with one or more extracts of *Dolichos biflorus, Commiphora mukul, Boerhaavia diffusa, Tribulus terrestris,* and *Zingiber officinale*. These are formulated as nanoparticles having controlled release due to the polymer-based coatings. These compositions have

been formulated in the form of nutritional bars, creams, jams, gels, chocolate bars, and beverages selected from the group, comprised of a milk-containing beverage, lactic acid bacteria-containing beverage, coffee, tea, drops, candies, chewing gums, chocolates, gummy candies, yoghurt, ice cream, puddings, soft adzuki-bean jellies, jellies, and cookies.[72]

Medasani, (2011), described NPs containing terpenes, fatty acids, other lipophilic constituents, and aglycons of glycosides extracted from the roots and rhizomes of a mixture of *Picrorhiza kurroa Royle, picrorhiza* scrophulariiflora *panel,* and *neopicrorhiza scrophulariiflora* of a family of Scrophulariaceae. This formulation is claimed effective against both DNA and RNA, viruses, fungal, bacterial, parasitic, and protozoal infections and diseases, and is used as a hepatoprotective, antihyperlipidemic, antidiabetic, and kidney-protective agent, administered through intravenous, intramuscular, subcutaneous, oral, peritoneal, rectal, dermal, sublingual, vaginal, nasal, transdermal or other routes. He also described the process of the solid-liquid extraction of plants, wherein the extract is in the form of nanogels, nanoparticles or processed to constitute a vaccine or an adjuvant. The extraction process involves absorbent gel extraction, reverse-phase extraction, liquefied gas (like C02) extraction, membrane filtration, liquid-liquid extraction, liquid-solid extraction, solvent extraction, enzymatic process, resin extractions or others.[73]

Medasani *et al.,* (2012), disclosed an antiviral composition consisting of terpenes and fatty acids found in *Picrorhiza kurroa Royle* extract of the Scrophulariaceae family. It also consists of lipophilic constituents and aglycons of the glycosides. The composition is formed by the extraction of the roots and rhizomes of mixtures of *Picrorhiza scrophulariiflora, Pennell Picrorhiza kurroa Royle,* and *Neopicrorhiza scrophulariiflora*. The composition is effective against both DNA and RNA viruses and against fungal, bacterial, parasitic, and protozoal infections and diseases, and is also used as an antihyperlipidemic, antidiabetic, hepatoprotective, and kidney-protective agent. The formulation is available in the form of softgels, capsules, nanogels, NPs, parenteral, powders, syrups, drinks, tablets, caplets, transdermal patches or absorbent gels, and is administered by one of the known routes such as oral, intramuscular, subcutaneous, peritoneal, rectal, nasal, intravenous, transdermal, dermal, sublingual, vaginal, and so on.[74]

Clark *et al.,* (2011), provided a method of treating patients with ischemic tissue damage by administering a curcuminoid or pharmaceutically active salt, metabolite in the form of liposome, nanoparticle, microparticle or block copolymer micelle, intravenously. They discovered that when curcumin is administered intravenously in low doses, it causes vasodilation and helps to treat burn injuries. Thus, administration of curcuminoid should be done in a manner where it maintains the circulating level of the curcuminoid in a nanomolar or picomolar concentration.[75]

Solubility, bioavilability, and stability enhancement

Chaniyilparampu *et al.,* (2010, 2012) prepared an ophthalmic and nasal formulation of curcuminoid and its metabolites. The nasal nanoemulsified formulation is used in animals or humans in an ocular or nasal diseased condition. They prepared nanoemulsified curcumin with pharmaceutically acceptable surfactants, namely, polysorbate 80 and 20, poloxamers, octoxynol, and the like, which were effective in increasing the bioavailability of the active compound, curcumin. These were used to treat several allergic and inflammatory diseases in humans and animals in the form of nasal sprays and ophthalmic gels or aqueous ophthalmic eye drops. The diseases to be treated or prevented were several inflammatory diseases of eye and nose, like allergic conjunctivitis or allergic rhinitis characterized by itching, redness, and edema of the eye, due to histamine release.[76,77]

Khar *et al.*, (2011), described a method to enhance the bioavailability of curcumin by preparing their nanoparticles with sizes from 50 nm to 284 nm by using chitosan, which binds curcumin and enhances its bioavailability 10-fold. The present patent has disclosed a method of coating the chitosan nanoparticles by curcumin, which includes dissolving the curcumin in alcohol, and spraying this solution stored at 25 - 40°C, under high pressure and nitrogen atmosphere, into an aqueous solution with a low percentage of organic acid, which is stirred continuously at room temperature.[78]

Nair *et al.,* (2011), proposed a process for the nanoemulsification of curcumin with pharmaceutically acceptable nonionic surfactants like polysorbate 80, polysorbate 20, poloxamers, octoxynol, and a non-ionic co-solvent like PEG 400 and PEG 6000. The process employs sonar energy, which enhances the aqueous solubility of the curcumin, because it is a highly lipophilic compound. The main objective of the present study was to enhance the aqueous solubility of curcumin.[79]

Xu *et al.,* (2011), disclosed a silymarin nanoparticle formulation, which is highly efficient and long-acting, thus, given only once in three days. The bioavailability of silymarin is low due to its poor water solubility; hence, this invention focuses on increasing its oral bioavailability. Silymarin is useful for liver protection, blood lipid reduction, prevention of diabetes, and protection of myocardial and anti-platelet aggregation. The present formulation is in the form of loaded nanoparticles, which enable silymarin to function for a long time, continuously, in slow release mode, with a triple release mechanism comprising of a quick release of solid dispersion, regular release of a hydrophilic gel matrix, and a long-acting slow release of the ordered mesoporous material. It is prepared by combining the techniques of solid dispersion, ordered mesoporous nanoparticle, and hydrophilic gel matrix, and it is then converted into granules.

The drug loading rate of a silymarin loaded silica nanoparticle is 51.95 to 52.87%. This nanoparticle technique enhances the speed and extent of physical absorption of silymarin. Using those slow-release granules, the silymarin formulation can be prepared in the form of a tablet or capsule, which enhances the bioavailability of silymarin.[80]

Jacob, (2012), disclosed a composition in the form of nanoparticles or encapsulated in liposomes, to enhance the bioavailability of curcumin, which consists of the curcumin plant extract, vanilla, and ginger, which are rich in gingerol and vanillin, or capsaicin can also be used in this composition along with ginger and vanilla.[81]

Payne *et al.,* (2013), described a method that consists of curcumin dissolved in an aqueous solution like water, alcohol and the like, at an enhanced concentration, which increases the stability by reducing the precipitation and degradation of the solution. This composition, that is, the curcumin nanoparticles are used for an antioxidant, anti-inflammatory, antiviral, antibacterial and antifungal effect.[82]

Tengler *et al.,* (2013), described a composition and methods to control the release of active agents in a shelf-stable liquid formulation containing a herbal extract like oregano leaf extract, prepared by blending one or more controlled-release microbeads or nanoparticles containing one or more active agents, which are used to prepare a dense thixotropic solution, with a density of one or more microbeads, thixotropic agent, water or a preservative. These are used to reduce bubble formation, and then the nanoparticles are mixed with that thixotropic solution in a mixer without scraping paddles.[83]

Wertz *et al.,* (2008), described a nanoparticulate composition containing a poorly soluble active agent from a group consisting of a drug, vitamin, herb, cosmetic agent, hair cosmetic agent, hair dye, and lysozyme as a surface stabilizer. In this they have claimed a bioadhesive nanoparticulate composition containing a lysozyme, having an average particle size of less than about 200 nm.[84]

Hu *et al.,* (2011), have proposed that nanoparticles of curcumin can be produced with a high repetition rate ultrafast pulsed laser ablation in liquids, which is a highly efficient method and has higher production rates, producing an organic nanoparticle colloidal suspension with particles of 100 nm, stable at 25°C for at least one week in the absence of any stabilizing agents. Through proper control of laser parameters like pulse repetition rate, pulse duration, pulse energy, and movement of the laser beam over stable nanoparticles, a colloidal suspension can be produced.[85]

Mirkin *et al.,* (2011, 2012), described delivery of an oligonucleotide along with other compounds like papain, bromelain, salmon oil, digoxin, balsam peru, and so on, modified nanoparticles, and therapeutic agents like chemotherapeutics, present in a ratio of 1:2, which allow sufficient transport of the therapeutic agent molecule into the cell. These therapeutic agents are both hydrophobic and hydrophilic in nature, having low molecular weight. The present invention describes the direct attachment of a therapeutic agent and oligonucleotide independently to nanoparticles, covalently or non-covalently, or the attachment of a therapeutic agent to an oligonucleotide that is attached to nanoparticles. The therapeutic agent is covalently or non-covalently attached to an oligonucleotide that is attached to nanoparticles.[86,87]

Lillard *et al.,* (2007), invented novel milled nanoparticles for delivery of active agents consisting of biologically active agents like *Curcuma longa, Melia azadirachta, Terminalia arjuna, Zingiber officinale, Capsicum annum,* and *Withania somnifera,* and biopolymers, such as, alginate, cellulose, and/or starch, and a coating consisting of polymer or ligand, produced by using milling and coating. The aforesaid nanoparticles have been claimed to protect, control, and target release.[88]

Inflammatory diseases

Plas *et al.,* (2013), invented a composition containing isolated ido-BR1 a cosmetic, nutraceutical, herbal medicine or pharmaceutical composition in the form of nanoparticles, microemulsion, and emulsion droplets, used in therapy or prophylaxis for the treatment of inflammatory diseases, to reduce inflammation. He also described methods to monitor the quality of the cucurbitaceae extract along with the process of producing the extract. The cucumber is a fruit of the species *cucumis sativus,* which is ground or squashed to obtain the extract.[89]

Ross (2013), invented a device to deliver the rheumatoid arthritis drug, which is herbal-based, like boswellic acid (extract of *Boswellia serrata)* and curcumin (curcuminoids from *curcuma longa)* and the like, across a dermal barrier, in the form of microneedles, to penetrate the stratum corneum. It also includes a structure fabricated on the surface of the microneedles to form nanotopography. Generally a random or non-random pattern of structures is fabricated like a complex pattern, which includes structures of different sizes and shapes. It may also include a nanosized structure or nanoparticle structure on the surface of the needles.[90]

Lung targeting

Banerjee *et al.,* (2012), invented a nanoparticulate protein-free surfactant formulation of eugenol, comprising of dipalmitoyl phosphatidylcholine and albumin. The particle size, 150 - 300 nm, was obtained by preparing dipalmitoyl phosphatidylcholine solution in an organic solvent and drying it to form a thin film under vacuum in a rotary vacuum evaporator at 40°C. Then 0.9% normal saline containing 2 mmol of calcium chloride at a pH 7.4 was added, and the film was hydrated for a period of one hour at 45°C, with gentle shaking. Next eugenol was added in

a ratio of 3:5 of dipalmitoylphosphatidylcholine, to the preformed nanovesicles, after hydration, to form eugenol surface-adsorbed nanovesicles and networked tubes. This composition formed non-lamellar phases in the presence of albumin and acids, which adsorbed to the air-liquid interface, in the presence of albumin, in the form of nanovesicles and networked tubes, 100 - 250 nm in size. The composition could be delivered along with dexamethasone, gentamycin or salbutamol to treat acid lung injury (ALI), Adult Respiratory Distress Syndrome (ARDS), Neonatal Respiratory Distress Syndrome (NRDS), and the Meconium Aspiration Syndrome (MCS).[91]

Chen (2006), has invented a method of nanoparticle production under cryogenic conditions, having a temperature less than or equal to -40, -80, -120, -160°C. He has also described a method to prepare larger particles with a size more than 100 µm, for herbs, calcium oxalate, calcium sulfate, silicon dioxide, cellulose, insulin, taxine, and so on. The nanosized particles of some herbs/drugs can be inhaled directly into the lung and then onward into the blood.[92]

Nutraceuticals

Priem *et al*., (2010, WO 2010), invented a pharmaceutical nanoparticle formulation consisting of nutraceuticals or pharmaceuticals like curcumin, quercetin, resveratrol, genistein, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, 6-gingerol, ellagic acid, ursolic acid, silibinin, anethol, catechins, eugenol, indole-3-carbinol, limonene, beta carotene, dietary fibers, and emulsifiers, with size of less than 100 nm, and used it to treat or prevent inflammation and inflammation-related syndromes or disorders. To improve the bioavailability of curcumin, adjuvants like piperine were used, which interfered with glucuronidation in order to increase their water solubility and excretion. Co-supplementation with 20 mg of piperine might increase the plasma concentration of curcumin.[93,94]

Karnik *et al.,* (2010), described the microfluidic synthesis of organic nanoparticles by nanoprecipitation, using controlled mixing of the polymeric solution in water by using a microfluidic device along with therapeutic agents (nutraceutical agent) like vitamins (A, B, C, D, E, and K), plant or animal extracts, fruit and vegetable extracts, aloe vera, guggul, and green tea extract. They claimed a microfluidic system consisting of two channels that came together into a mixing apparatus. It had two steps - first, flowing of the polymeric solution through a central channel containing a polymer and a solvent. Second, flowing of the non-solvent through the outer channel. This finally consisted of mixing the polymer solution with the non-solvent in a mixing apparatus. The present invention provided the large-scale combinatorial screening of particle production conditions, which consisted of serial and parallel combinatorial syntheses.[95]

Oral care agent

Spengler *et al.,* (2006), have disclosed a method and composition of solid nanoparticle dispersion to enhance delivery of herbal oral care actives with high loading capacity that included a wide range of oral care agent-carriers and emulsifiers like dry mouth alleviating agents (citrus flavor extract and oil, cinnamon flavor extract and oil), pain relievers, expectorants, antioxidants, vitamins like tocopherol that have the desired effect in the oral cavity, dry mouth alleviating properties, and oral care (gingivitis, dry mouth, dental carries) properties.[96]

Matuschek *et al.,* (2010), described a method for taste modulation by using water dispersible carotenoid nanoparticles as taste modulators. In the present invention, carotenoids are present in the form of solubilized mixed micelles used particularly to reduce the bitter taste.[97]

Porter *et al.*, (2013), revealed oral care oils like rosemary extract, thymol, menthol, eucalyptol and so on, along with antimicrobial agents like herbal extracts with orally acceptable vehicles, metal oxide particles in the form of powders or nanoparticle solutions or suspension of nanoparticles with amino acids, which are capable of chelating metal oxides. This is used as dentifrice composition with a particle size of 5 microns or less.[98] Total numbers of patents filed per year is shown in Figure 1.

Summary of patents

- Curcumin - Nanoparticles[26-29,39,42-45,47,48,75-79,81,82,85,90,93,94]
- Carotenoids - Nanoparticles[97]
- Silymarin - Nanoparticles[80]
- Vinca alkaloids - Nanoparticles[24,25]
- *Panax ginseng* - Liquid mixture[46,68]
- *Salvia miltiorrhiza* extract - Nanoparticles[27,46]
- *Gymnema sylvestre extract* - Nanoemulsion[46-48]
- *Withania somnifera* - Liquid mixture[46,88]
- *Silybum marianum* - Tablets or capsules[46]
- *Curcuma longa* - Nanoparticles[42,46,81]
- *Andrographis paniculata, Azadirachta indica, Bacopa monnieri, Cinnamomum*
- *Zeylanicum, Cnidium officinale, Coccinia indica, Crataegus oxyacantha*
- *Curcuma longa, Gymnema sylvestre, Juglans regia, Momordica charantia*
- *Mucuna pruriens, Ocimum sanctum, Panax ginseng, Panax quinquefolium, Paullinia cupana, Pfaffia paniculata, Phyllanthus emblic, Phyllanthus niruri, Pinus*
- *Maritima, Polygonum cuspidatum, Scutellaria baicalensis, Silybum marianum*
- *Syzygium cumini, Tinospora cordifolia, Trigonella foenum-graecum* and *Withania somnifera* - Nanoemulsion, nanoencapsulation, nanodispersion or synergistic liquid mixture[43]
- Lemon juice, *Lepidium sativum* - Nanoemulsion[54]
- Safflower extract, Zanthoxylum piperitum extract, Torilis

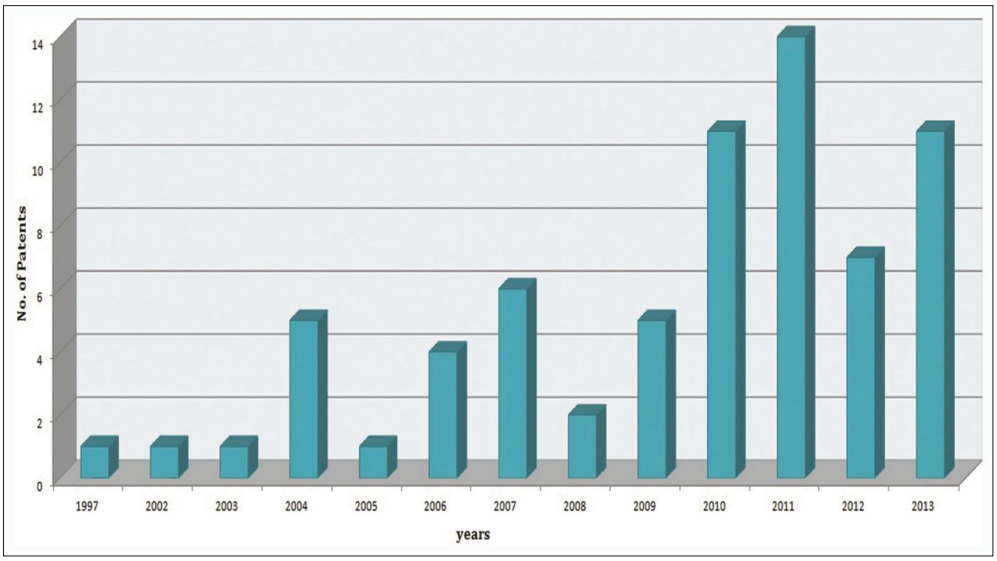

Figure 1: Graph showing total number of patents filed year-wise

japonica fruit extact, Green tea leaf extract, Pomegranate extract, Pine tree leaf extract, Red ginseng extract, Ginseng extract, Angelicae extract, Salvia miltiorrhiza extract, Safflower extract, *Zanthoxylum piperitum* extract, Torilis japonica fruit extact, *Cnidium officinalis makino* extract, Green tea leaf extract, Pomegranate extract, Pine tree leaf extract, Red ginseng extract, Ginseng extract, Angelicae extract, *Truigonella foenum graecum* (Fenugreek) - Nanoparticles, Nanoparticles mixture, Nanosuspensions, nano emulsions[30]

- *Lepidium sativum*, Green tea extract, Pomegranate extract - Nanoformulation[54]
- Arbutin - Emulsified nanoparticle[49]
- Aloe vera, guggul, green tea - Organic nanoparticles[95]
- Capsicum species, Cascara sagrada - Mesospore microparticulate[47,48,63,88]
- Citrus and cinnamon - Solid nanoparticle dispersion[96]
- Vitamin, herb - Bioadhesive nanoparticulate[84]
- Herbs - Nanoparticles[92]
- *Swertia japonica* - Nanoparticles[53]
- Almond oil, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, soybean oil, peanut oil etc. - Micellar nanoparticles[50]
- *Moringa oleifera* - Bionanoparticles[23]
- Agar - Bio nanoparticles[22]
- Solanum - Nanoparticles[15-17]
- Eugenol - Nanoparticles[91]
- *Piper betle, Dolichos biflorus, Commiphora mukul, Boerhaavia diffusa, Tribulus terrestris and Zingiber officinale* - Nanoparticles[72]
- *Picrorhiza kurroa Royle, Picrorhiza scrophulariiflora Pennell and Neopicrorhiza scrophulariiflora* - Nanogel, nanoparticle[73]
- Capsaicin - Nanoparticle, nanocapsules[93,94]
- Butea isoflavones - Nanoparticle, nanoemulsion[61]
- Chloroquine - Nanoparticles[67]
- Fenugreek extract - Nanoparticle[27,53]
- *Picrorhiza kurroa Royle* - Nanoparticles[74]
- *Picrorhiza kurroa Royle, Picrorhiza scrophulariiflora, Pennell Picrorhiza kurroa Royle, and Neopicrorhiza scrophulariiflora*- Nanoparticles[74]
- Triterpene Glycoside - Nanoparticles[32,33]
- *Melissa officinalis, Calendula officinalis, Camellia seninsis, Aspalatus linearis* - Nanoparticles[55]
- Oregano leaf extract - Nanoparticles[83]
- *Scutellaria baicalensis, Glycyrrhiza uralensis, Ziziphus jujuba,* and *Paeonia lactiflora* - Nanoparticles[34]
- Black cohosh - Nanoparticle[32]
- *Cucumis sativus* - Nanoparticle.[89]

CONCLUSION

In the last decade, a gradual increase in patents filed on herbal nanoformulations has been noted. The reason mainly lies in addressing the solubility and bioavailability problems of phytoceuticals. Curcumin, the multifunctional phytoceutical, has especially been patented maximally, and is used in the treatment of tumors and cancers. The review has also demonstrated that herbals have been formulated in the nanoparticle form to increase not only the solubility and bioavailability of poorly soluble herbals, but to improve tissue distribution, to achieve sustained delivery, to protect from physicochemical degradation, and so on. In the year 2011, maximum patents have been filed and an increase can be foreseen from 2013 onwards, post nanotechnology regulation enforcement.

REFERENCES

1. Nanoscience and Nanotechnologies: Opportunities and uncertainties. Royal Society and Royal Academy of Engineering. The Royal Society. Great-Britain: Latimer Trend Ltd, Plymouth, UK 2004. p. 116.
2. Rajendran R, Radhai R, Maithili N, Balakumar C. Production of herbal-based nanoparticles for medical textiles. Int J Nanosci 2011;10:209-12.

3. Goyal A, Kumar S, Nagpal M, Singh I, Arora S. Potential of novel drug delivery systems for herbal drugs. Ind J Pharm Educ Res 2011;45:225-35.
4. Ansari SH, Islam F. Sameem M. Influence of nanotechnology on herbal drugs: A Review. J Adv Pharm Technol Res 2012;3:142-6.
5. How many different types of cancer are there? Cancer Research UK: CancerHelp UK. Retrieved 11 May 2012. Available from: http://www.cancerresearchuk.org.
6. Cancer Glossary. American Cancer Society. Retrieved September 11, 2013. Available from: http://cancer.org.com.
7. What is cancer? National Cancer Institute. Retrieved September 11, 2013. Available from: http://www.cancer.gov.
8. Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med 2002;53: 615-27
9. Liu X, Kim CN, Yang J, Jemmerson R, Wang X. Induction of apoptotic program in cell-free extracts: Requirement for dATP and Cytochrome. Cell 1996;86:147-57.
10. Wilson KA, Waugh A, Chambers G, Grant A, Ross J. Ross and Wilson Anatomy and Physiology in Health and Illness. 2nd ed. Edinburgh: Churchill Livingstone; 2006. p. 53-4.
11. Silverstein A, Silverstein VB, Nunn LS. Cancer. Twenty-First Century Books. Brookfield, Conn: Minneapolis, Minn. 2006. p. 11-2.
12. Sioka C, Kyritsis AP. Chemotherapy, hormonal therapy, and immunotherapy for recurrent meningiomas. J Neurooncol 2009;92:1-6.
13. Cassileth BR, Deng G. Complementary and alternative therapies for cancer. Oncologist 2004;9:80-9.
14. Tripathi KD. Essentials of Medical Pharmacology. 6th ed. Delhi: Jaypee Brothers: Medical Publishers (P) Ltd; 2008. p. 819-34.
15. Kou WK, Kaohsiung KW. Water Soluble Extract from Plant of Solanum Genus and the Preparation Process Thereof, and Pharmaceutical Composition Containing the Water Soluble Extract. US Patent 20040247715 A1, 9 December 2004.
16. Kou WK, Kaohsiung KW. Water Soluble Extract from Plant of Solanum Genus and the Preparation Process Thereof, and Pharmaceutical Composition Containing the Water Soluble Extract. EP Patent 1508334 B1, 23 February 2006.
17. Kou WK, Kaohsiung KW. Water Soluble Extract from Plant of Solanum Genus and the Preparation Process Thereof, and Pharmaceutical Composition Containing the Water Soluble Extract. US Patent 007078063 B2, 18 July 2006.
18. Singh CU. Novel Formulation of Digitalis Glycosides for Treating Cell-Proliferative and Other Diseases. US Patent 20040082521 A1, 29 April 2004.
19. Desai NP, Soon-Shiong P, De TK. Combinations and modes of administration of therapeutic agents and combination therapy. US Patent 20070166388 A1, 19 July 2007.
20. Desai NP, Soon-Shiong P, De TK. Methods and compositions for treating proliferative diseases. US Patent 007780984 B2, 24 August 2010.
21. Desai NP, Soon-Shiong P. Nanoparticles of paclitaxel and albumin in combination with bevacizumab against cancer. US Patent 20100112077 A1, 6 May 2010.
22. Gorur A, Shanmugasundaram S, Shanmugasundaram S. Preparation of agar bionanoparticles. IP Patent 376MAS200 3A, 6 January 2007.
23. Shanmugasundaram S, Krupakar P, Shanmugasundaram S. Preparation of oligosaccharide bionanoparticles from moringa oleifera lam. IP Patent 375MAS2003 A, 6 August 2007.
24. Liang W, Lou M, Si W. Nano anticancer micelles of vinca alkaloids entrapped in polyethylene glycolated phospolipids. US Patent 20090053293 A1, 26 February 2009.
25. Zale SE, Troiana G, Ali MM, Hrkach J, Wright J. Therapeutic polymeric nanopartcles comprising vinca alkaloids and methods of making and using them. US Patent 20100104655 A1, 29 April 2010.
26. Kurzrock R, Li L, Mehata K, Aggarawal BB. Liposomal curcumin for treatment of cancer. US Patent 007968115 B2, 28 June 2011.
27. Sahoo SK, Mohanty C. Novel water soluble curcumin loaded nanoparticulate system for cancer therapy. WO Patent 2011101859 A1, 25 August 2011.
28. Rigas B, Mackenzie G, Yu S, Huang L, Zhu R, Nie T. Combination treatments and formulations for cancer. WO Patent 2011130486 A2, 20 October 2011.
29. Patel AR, Tiwari JK, Velikov KP. Particles comprising hydrophobic polymer and hydrophobic phenolic compound. WO Patent 2012000757 A1, 5 January 2012.
30. Kim JH. Nanoparticle Composition for prevention of hair loss and promotion of hair growth. US Patent 20100104646 A1, 29 April 2010.
31. Danek. Combination anti-cancer therapy. WIPO Patent WO/2013/066864 10 May 2013.
32. Linda E, Stepehn R. Growth inhibitory effects of nanoparticles containing triterpene glycosides or triterpenes. US Patent 20130177627 7 July 2013.
33. Einbond L, Redenti S. Growth inhibitoyr effects of nanoparticles containing triterpene glycosides or triterpenes. US Patent 2013/0177657 A1, 11 July 2013.
34. Liu S, Zaoli J, Cheng Y. Herbal composition phy906 and its use in chemotherapy. US Patent 20130101688, 25 April 2013.
35. Crews L, Masliah E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. Hum Mol Genet 2010;19:R12-20.
36. Pleckaityte M. Alzheimer's disease: A molecular mechanism, new hypotheses, and therapeutic strategies. Medicina (Kaunas) 2010;46:70-6.
37. Ashford JW. APOE genotype effects on Alzheimer's disease onset and epidemiology. J Mol Neurosci 2004;23:157-65.
38. Katzman R. Alzheimer's disease. N Engl J Med 1986;314:964-73.
39. Geula C, Mesulam MM. Cholinesterases and the pathology of Alzheimer disease. Alzheimer Dis Assoc Disord 1995;9 Suppl 2:23-8.
40. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: Memantine and beyond. Nat Rev Drug Discov 2006;5:160-70.
41. Stahl SM. The new cholinesterase inhibitors for Alzheimer's disease, part 2: Illustrating their mechanisms of action. J Clin Psychiatry 2000;61:813-4.
42. Chole GM, Frautschy SA. Bioavailable curcuminoids formulations for treating Alzheimer's disease and other age-related disorders. WO Patent 2007103435 A2, September 13 2007.
43. Frautschy SA, Cole GM. Bioavailable curcuminoids formulations for treating Alzheimer's disease and other age-related disorders. US Patent 20090324703 A1, 31 Dec 2009.
44. Desai K. Curcumin cyclodextrin combination for preventing or treating various diseases. US Patent 20100179103 A1, 15 July 2010.
45. DiMauro TM. Methylated curcumin-resveratrol hybrid molecules for treating cancer. US Patent 008350093 B2, 8 January 2013.
46. Mazed MA, Mazed S. Nutritional supplement for the prevention of cardiovascular disease, Alzheimer's disease, diabetis, and regulation and reduction of blood sugar and insulin resistance. US Patent 008017147 B2, 13 September 2011.
47. Gupta SK. Controlled-release nano-diffusion delivery systems for cosmetic and pharmaceutical compositions. US patents 20040208902 A1, 21 October 2004.
48. Gupta SK. Ion-pair delivery system for cosmetic and pharmaceutical compositions. US Patents 20040228884 A1, 18 November 2004.
49. Nanbu T. Whitening cosmetic composition containing arbutin nanoparticles. US Patent 20090069253 A1, 12 March 2009.
50. Wright DC. Micellar nanoparticles. US Patent 005629021 A, 13 May 1997.
51. Bakthavatchalam R, Blum CA, Brielmann H, Caldwell TM, Lombaert SD. Substituted quinazolin-4-ylamine analogues as modulators of capsaicin. WO Patent 2003062209 A2, 31 July 2003.
52. Bakthavatchatam R, Blum CA, Brielmann HL, Caldwell TM, De LS, Hodgetts KJ, *et al*. 2-Substituted quinazolin-4-ylamine analogues as capsaicin receptor modulators. WO Patent 2004055003, 7 January 2004.
53. Kanazawa K. Water-dispersible nanoparticle which contains blood circulation promoter. US Patent 20090104291 A1, 23 April 2009.
54. Chaudhary M, Naithani V. Topical herbal formulation for treatment of acne and skin disorder. US Patent 20110262499 A1, 27 October 2011.
55. Leighton HJ, Frangakis GJ. Methods and compositions for treating inflammation of skin. US Patent 20130059019 7 March 2013.

56. Kim DH, Vaccaro AR. Osteoporotic compression fractures of the spine; current options and considerations for treatment. Spine J 2006;6:479-87.
57. Alldredge BK, Kimble K, Anne M, Young, L Y., Kradjan WA, Guglielmo BJ. Applied therapeutics: The clinical use of drugs. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins. 2009. pp. 101-3.
58. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2005;20:CD000227.
59. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: Systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:1256-61.
60. Body JJ. How to manage postmenopausal osteoporosis? Acta clin Belg 2011;66:443-7.
61. Maurya R, Singh G, Murthy PS, Mehrotra S, Singh D, Bhargava B, *et al*. Pharmaceutical composition containing butea isoflavones for the prevention/treatment of bone disorders and a process for the preparation thereof. WO Patent 2007099432, 7 September 2007.
62. Mousa SA, Qari MH, Ardawi MS. Composition and methods of natural products in nanoformulations for the prevention and treatment of osteoporosis. US Patent 20110104283 A1, 5 May 2011.
63. Canham L, Shabir QU, Loni A. Porous materials. US Patent 20110236493 A1, 29 September 2011.
64. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-76.
65. Dauer W, Przedborski S. Parkinson's disease: Mechanisms and models. Neuron 2003;39:889-909.
66. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Impulse control disorders in Parkinson's disease: Definition, epidemiology, risk factors, neurobiology and management. Parkinsonism Relat Disord 2009;15Suppl 4:S111-5.
67. Jodi N. Chloroquine derivatives for the treatment of parkinson's disease. US Patent 6417177 B1, 9 July 2002.
68. Jodi N. Compositions and methods for the treatment of parkinson's disease. EP Patent 1261340 B1, 13 May 2009.
69. Nobuhiro Y. Molecular mechanism of hyperlipidemia and future aspects on the therapy. Nihon Rinsho 2001;59:170-4.
70. Aburdeineh SG, Aburdeineh HG. Methods of lowering blood cholesterol via oral fenugreek seed extract compositions. US Patent 20050153001 A1, 14 July 2005.
71. Aburdeineh SG, Aburdeineh HG. Methods of lowering blood cholesterol via oral fenugreek seed extract compositions. US patent 20080299235, 4 December 2008.
72. Gokharaju GR, Gokharaju RR, Golakoti T, Sengupta K, Bhupathiraju K, Krishna V, *et al*. Anti-adipogenic compositions containing Piper betle and Dolichos biflorus. US 20100203117 A1, 12 August 2010.
73. Medasani M, Divi SB. Picrorhiza Kurroa extract for prevention, elimination and treatment of rna viruses and infection or diseases caused by the same in humans, animals and in biotech industry. WO Patent 2011027364 A2, 10 March 2011.
74. Medasani M, Divi SB. Picrorhiza Kurroa extract for prevention, elimination and treatment of rna viruses and infection diseases. US Patent 20120148569 A1, 14 June 2012.
75. Clark RA, Singer A, McMohan MF. Treatment of ischemic tissue. WO Patent 2011047309 A2, 21 April 2011.
76. Nair AK, Parthasarathy K, Gokaraju GR, Bhuphatiraju K, Somushekara N, Nanappan R, *et al*. Curcumoids and its metabolites for the application in allergic ocular/nasal conditions. US Patent 2012/0010297 A1, 12 January 2012.
77. Nair AK, Parthasarathy K, Gokaraju GR, Bhuphatiraju K, Somushekara N, Nanappan R, *et al*. Curcumoids and its metabolites for the application in allergic ocular/nasal conditions. WO Patent 2010/109482 A2, 30 September 2010.
78. Kar SK, Akhtar F, Ray G, Pandey AK. Curcumin nanoparticles and methods of producing the same. US Patent 20110190399 A1, 4 August 2011.
79. Nair AK, Chaniyilparampu RN, Bhupathiraju K, Gokaraju RR, Gokaraju GR, Golakoti T. Process for nanoemulsification of curcumin and derivatives of curcumin. US Patent 20110229532 A1, 22 September 2011.
80. Xu X, Yu J, Tong S, Zhu Y, Cao X. Formulation of silymarin with high efficacy and prolonged action and the preparation method thereof. US Patent 20110201680 A1, 18 August 2011.
81. Jacob CV. Synergistic composition for enhancing bioavaliability of curcumin. US Patent 20120058208 A1, 8 March 2012.
82. Payne AJ, Kurien BT, Scofield RH. Solubilization of curcuminoid compounds and products thereof. WO Patent 2013078477 A2, 30 May 2013.
83. Tengler M, Taskey P, Lockhart D, McMahen R. Composition and methods of making sustained release liquid formulations. US Patent 20130084340, 4 April 2013.
84. Wertz CF, Ryde NP. Nanoparticulate compositions having lysozyme as a surface stabilizer. US Patent 007459283 B2, 2 December 2008.
85. Hu Z, Che Y. Production of organic compound nanoparticles with high repetition rate ultrafast pulsed laser ablation in liquid. US Patent 20110196044 A1, 11 August 2011.
86. Mirkin CA, Giljohann DA, Daniel WL. Delivery of therapeutic agents using oligonucleotide-modified nanoparticles as carriers. WO Patent 2011028850 A1, 10 March 2011.
87. Mirkin CA, Giljohann DA, Daniel WL. Delivery of therapeutic agents using oligonucleotide-modified nanoparticles as carriers. US Patent 20120283316 A1, 8 November 2012.
88. Lillard JW, Singh R, Singh S. Novel nanoparticles for delivery of active agents. US Patent 20070224280 A1, 27 September 2007.
89. Gogerddan P, Ceredigion A. Anti-inflammatory compounds. WIPO Patent WO2013054070 18 April 2013.
90. Ross RF. Device for delivery of rheumatoid arthritis medication. US Patent 2013144257 A1, 6 June 2013.
91. Banerjee R, Kaviratna A. Protein free surfactant composition for pulmonary diseases and a process for preparing the same. WO Patent 2012077127 A1, 14 June 2012.
92. Chen TD. Nano-particle production. US Patent 20060008498 A1, 12 January 2006.
93. Priem F, Jacquemond-Collet I. Pharmaceutical composition presenting anti-inflammatory and anti-histaminic properties. EP Patent 2229940 A1, 22 September 2010.
94. Priem F, Jacquemond-Collet I. Pharmaceutical composition presenting anti-inflammatory and anti-histaminic properties. WO Patent 2010106191 A1, 23 September 2010.
95. Karnik R, Gu FX, Cannizzaro C, Khademhosseini A, Langer RS, Farokhzad OC. Microfludic synthesis of organic nonoparticles. US patent 20100022680 A1, 28 January 2010.
96. Spengler EG, Dahms GH. Composition and method employing membrane structured solid nanoparticles for enhanced delivery of oral care actives. US Patent 20060024248 A1, 2 February 2006.
97. Matuschek M, Ernst A, Köpsel C, Jager MB, Kleber A, Krohn M, *et al*. Use of water-dispersible carotenoid nanoparticles as taste modulators, taste modulators containing water-dispersible carotenoid nanoparticles, and method for test modulation.US Patent 20100028444 A1, 4 February 2010.
98. Porter V, Morgan A, Prencipe M. Oral care composition. US Patent 20130017240, 17 January 2013.

How to cite this article: ???

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