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A Review on Integration of nanotechnology in Herbal medicine

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Abstract:- From the ancient times animal kingdom remained dependent upon plant kingdom for it's abundant medicinal values. Herbal medicines gained popularity due to it is abundant sources as well as low cost which may solve the problems of unavailability. Different parts of plants contain different secondary metabolites which are the main components for the therapeutic effects of plants.The main disadvantage of herbal medicines was patient incompatibility.In some cases the solubility of active constituents of plants remains higher, however due to their high molecular weight they can't be absorbed in the lipid membrane of cells in sufficient quantity. Due to this, they show very limited bioavailability and rapid excretion. So to get the therapeutic benefits, it become essential to it's repeated administration with a large dose which deviates the patient compliance most times.One such use of nanotechnologyis to increase bioavailability and decrease toxicity. If it is possible to delivery herbal drugs in nanoscale, then improvements in solubility, bioavailability, pharmacological action and stability of novel herbal formulations are capable enhancing the distribution of macrophages in tissues as well as extended delivery, and prohibit the chemical and physical degradation.

"Novel Drug Delivery Systems" is a renowned technology was found to solve the noncompliance of herbal medicines. This technology is nothing but Nanotechnology.It studied that when herbal medicines and nanotechnology are fused, then the noncompliance of herbal medicine is successfully diminished.

Keywords: *Herbal drugs 1, bioavailability 2, nanotechnology 3, , nano-carriers 4, noncompliance 5.*

1. Introduction

Nanoparticles are biocompatible and biodegradable synthetic polymers with a very low range from one gauge to one hundred gauges. The basis of nanoparticles is lipids, polymers or nanoemulsions[1]. Natural and manufactured high molecular polymers that are biodegradable are the main carriers of nanoparticles. Poly-α-cyanoacrylate alkyl esters, polyvinyl alcohol, polylactic acid, polylactic-glycolic acid, and so on are typically included in the former. The latter are typically separated into two groups: polysaccharides (cellulose, starch and its derivatives, alginate, chitin and chitosan, etcetera) and proteins (albumin, gelatin, and vegetable protein). Nanotechnology is a rapidly growing science for the production and use of nanoparticles, which are measured in a pressure gauge. Stated differently, the art of systemically characterizing, modifying, and arranging matter is

known as nanotechnology, on a measurement scale, which has revolutionized the administration of herbal medicines and therapies[2].

Typical accessible structures are visible under an optical microscope and have a size in the order of submicrons, given the constraints of optical resolution. This scale is 1000 times larger than an atom, although it is approximately 1/1000th smaller than the structures that are visible to the unaided eye. Since a common structure size is in the gauge range, recent developments are in the size range below these sizes. We refer to these processes and procedures as nanotechnology[3].

Two requirements should preferably be met by the innovative carriers. First, over the course of therapy, it should administer the medication at a space according tothe desire of body. Secondly, incorporate the major ingredients intothe site of action.

Nowadays, there are many treatments that take a long time and are also very expensive. With the help of nanotechnology in the field of herbal medicines, faster and cheaper treatment methods can be developed[4]. Nanoparticle-sized drugs are capable to develop it's overall outer surface for faster dissolution within systemic circulation, decrease in toxicity without sacrificing the therapeutic benefit.The blood-brain barrier (BBB) may be crossed with the aid of nanoparticle's improved penetration and retention[5].Usually, herbal medicines work throughout the body before reaching the affected area. These herbal remedies with a nanotechnology base can be targeted to a specific area, increasing their effectiveness and decreasing the possibility of negative side effects. The two primary study areas where nanotechnology would be most helpful are targeted phytotherapy and techniques for early disease identification[6].

2. Nanotechnology-based systems in herbal medicine

It is a challenging undertaking to develop a drug delivery method that reduces the harmful side effects of a natural drug in vivo while enhancing its medicinal benefits. In herbal medicine, these demanding tasks can be mastered through the use of nanosystems.

Materials and devices in nanoscale are two basic types of nanotechnology have a significant impact on pharmaceutical nanotechnology and various other domains. Nanomaterials consist of materials collected from biological source and are widely utilised in the field of medicinal plants. Their surface can be modified with coatings that improve biocompatibility with living cells[7].

Materials that are nanocrystalline and nanostructured are two further categories for these. After being ground in specialized mills, the nanocrystals can be inhaled via the bronchial route or given intravenously as nanosuspensions.The surface area to volume ratio and bioavailability of almost insoluble herbal medications are enhanced by their tiny size. These consist of carbon nanotubes, fullerenes, dendrimers, and quantum dots[8].

Nanomaterials are frequently employed in the delivery of herbal medicine because they can improve the solubility of medications in herbal formulations and enable targeted or controlled delivery of drugs. They are utilized in the treatment of cancer, delivery of gene, inhalers for asthma, cutaneous and ocular drug delivery, oral and vaccine delivery systems, and hormone delivery.Biological assays of different kinds, microfluidics (control and artifices of micro or nanoliter fluids), nano and micro electromechanical systems (NEMS/MEMS), and microarrays are examples of nanodevices, which are nanoscale devices. Biosensors and detectors are very useful tools to detect various biohazard as well as disease causing microorganisms. Some intelligent devices include DNA, proteins, cells, and antibodies as instances[9].

Table A.1: Herbal nanoparticle delivery systems

Formulations	Active ingrediants	Therapeutic effcts	Preparation procedures
Nanoparticles of *Ginkgo biloba*	Extract of *G. biloba*	Activate functions of Brain	Homogenization method with High pressure[10]
G. biloba	Flavonoids	Protect heart and can prevent	Phospholipids

phytosomes		oxidation	complexation[11]
Ginkgoselect phytosome	Flavonoids	Protect liver and can prevent oxidation[12]	Phospholipids complexation[13]
Curcumin liposome	Cucumin	Prevent cancer	Ethanol injection method[14]
Curcumin phytosomes	Cucuminoids	Prevent cancer, and can prevent oxidation	Curcumin– phospholipid complexation[15]
Solid-lipid nano particles of cucuminoids	Cucuminoids	Prevent cancer, and can prevent oxidation	Micro-emulsion technique[16]
Zedoary turmeric oil (ZTO) nanocapsule	ZTO	Protect liver, Prevent cancer, and can prevent bacterial growth	High pressure Homogenization method [17]
Microsphere of Zedoary oil	Zedoary oil	Protect liver	Quasi-emulsion solvent diffusion method[18]
Self-nanoemulsifying Zedoary essential oil	ZTO	Protect liver, Prevent cancer, and can prevent bacterial growth	Drawing ternary phase Diagram with droplet size 68.3± 1.6 nm[19]
Triptolide nanoparticle	Triptolid	Prevent inflammation	Emulsification-ultrasound
Micro- emulsion of Triptolide	Triptolide	Prevent inflammation	Homogenization method along with High pressure,with droplet size <100 nm
Micro- emulsion of Triptolide	Triptolide	Prevent inflammation	Homogenization method along with High pressure,with droplet size <100 nm[20]
Triptolide-loaded solid lipid nanoparticle	Triptolide	Prevent inflammation[21]	Emulsification-ultrasound[22]
Miltiorrhiza nanoparticles	miltiorrhiza	Prevent cancer	The method of evaporating solvents from an emulsion.
Nanoparticles Loaded with Taxel	Taxel	Prevent cancer	The method of evaporating solvents from an emulsion [23]
Nanoparticles of *Cuscuta chinensis*	Flavonoids and lignans	Protect liver and can prevent oxidation	Nanosuspension method[24]
Radix salvia	*R. salvia*	Protect heart	Spray-drying technique[25]
Naringenin (NAR) phytosomes	NAR	Prevent oxidation	NAR-phospholipid complex[26]

NAR loaded nanoparticles	NAR	Protect liver	Nanoprecipitation method[27]
Nano particles loaded With glycyrrhizic acid	Glycyrrhizic acid	Prevent inflammation and can decrease elevated blood pressure	Rotary-evaporated film ultrasonication method[28]
Nanoparticles loaded with Berberine	Berberine	Prevent cancer	Ionic gelation method[29]
Ammonium glycyrrhizinate ethosomes	Ammonium glycyrrhizinate	Prevent inflammation	Ethosome preparation with droplet size 350 nm to 100 nm[30]
Berberine nanoemulsion	Berberine	Prevent cancer	Drawing ternary phase diagram with droplet size 56.80 nm[31]
Silibini-loaded nanoparticles	Silibini	Protect liver	High pressure homogenization[32]
Silybin phytosome	Flavonoid	Protect liver and also prevent oxidation in liver and skin	Silybin- phospholipid complexation[33]
Silybin nanoemulsion	Silybin	Protect liver	Emulsification method with droplet size 21.20 nm[34]
Tetrandrine-loaded nanoparticles	Tetrandrine	Used to treat lung's disease	Self-emulsification and solvent evaporation[35]
Camptothecin (CPT) encapsulated nanoparticles	CPT	Prevent cancer[36]	Dialysis method[37]
Microspheres loaded with CPT	CPT	Prevent cancer	Oil-in-water evaporation method[38]
Artemisinin nanocapsules	Artemisinin	Prevent cancer	Self-assembly procedure[39]
Liposomal *Artemisia arborescens*	*A. arborescens* essential oil	Used to treat viral diseases	Film method and sonication[40]
Breviscapine-loaded nanoparticles	Breviscapine	Utilized for the treatment of cardiovascular and cerebrovascular disorders.	Technique involving spontaneous emulsification and solvent diffusion[41]
Quercetin-loaded nanoparticles	Quercetin	Prevent oxidation	Nanoprecipitation technique[42]
Quercetin liposomes	Quercetin	Prevent cancer and also can prevent oxidation	Reverse evaporation[43]
Quercetin phytosome	Quercetin	Prevent cancer and also can prevent oxidation	Quercetin– phospholipid complexation[44]

Quercetin micro- emulsion	Quercetin	Prevent oxidation	High speed Homogenization with droplet size 10–100 nm[45]
Quercetin microspheres	Quercetin	Prevent cancer	Solvent evaporation[46]
Liposomes encapsulated silymarin	Silymarin	Protect liver	Reverse evaporation[47]
Paclitaxel liposome	Paclitaxel	Prevent cancer	Thin film hydration method[48]
Submicron emulsion of Docetaxel	Docetaxel	Prevent cancer	Homogenization method along with high pressure, with droplet size 166.00 nm[49]
Flavonoids liposomes	Quercetin and rutin	Used to treat Haemoglobin	Solvent evaporation[50]
Ampelopsin liposome	Ampelopsin	Prevent cancer	Film-ultrasound method[51]
Garlicin liposome	Garlicin	Used to treat lungs	Reverse-phase evaporation method[52]
Wogonin liposome	Wogonin	Prevent cancer	Film dispersion method[53]
Colchicine Liposome	Colchicine	Prevent Gout	Rotary evaporation sonication method
Colchicine transferosomes	Colchicine	Prevent Gout	Transferosome preparation[54]
Liposome of Usnea acid with β-CD	Usnea acid	Prevent the growth of microorganisms	Sonication-assisted hydration of a thin lipid film technique[55]
Catechins liposomes	Catechins	Prevent Gout	Rotary evaporation sonication method[56]
Breviscapine	Breviscapine	Used to treat cardiovascular diseases	Double emulsification process [57]
Ginseng phytosome	Ginsenosides	Used as Nutraceuticals and immunomodulating agents	Phospholipids complexation
Green tea phytosome	Epigallocatechin	Used as Nutraceuticals , systemic antioxidant and also used to prevent cancer	Phospholipids complexation
Grape seed phytosome	Procyanidins	Systemic antioxidant and also can protect heart	Phospholipids complexation[58]
Hawthorn Phytosome	Flavonoids	protect heart and used to decrease elevated blood pressure	Phospholipids Complexation[59]
Microsphere of *Cynara scolymus*	Extract of *C.scolymus*	Used as Nutritional supplement	Spray-drying technique[60]
Rutin–alginate–	Rutin	Employed for the management	Complex-coacervation

chitosan microcapsules		of cardiovascular and cerebrovascular disorders	method[61]
Capsaicin transferosomes	Capsaicin	Used as pain killer	Transferosome preparation with droplet size 150.6 nm[62]
Vincristine transferosomes	Vincristin	Prevent cancer	Transferosome preparation with droplet size 120 nm[63]
Matrine ethosome	Matrine	Prevent inflammation	ethosome preparation with droplet size 110±8 nm[64]

3.Types of nanosystems used in herbal medicine

3.1. Liposomes

The lipid vesicles known as liposomes, which were initially reported in 1976, were the first class of nano material utilised in the delivery of herbal drugs. Liposomes are hydrophilic and hydrophobic materials' carriers; they are biodegradable and basically non-toxic[65]. Liposomes are amorphous vesicles composed of cholesterol and amphiphilic phospholipids that form bilayers on their own to enclose an aqueous core[66]. For protection purposes from the water, present in the surroundings, the amphiphilic phospholipid molecules of liposomes, form a sealed bilayer sphere by shielding the hydrophobic groups. The hydrophilic head group of the molecule allows it to remain in contact with the aqueous phase because an aqueous solution with a hydrophobic exterior can be encapsulated by a liposome. Lipids are impermeable hydrophilic solutes. Liposomes can therefore carry hydrophilic molecules (found in the inner watery core) as well as hydrophobic molecules (found in the outer membrane)[67].

A portion of the solvent is encapsulated by the spherical liposomes, which allow the solvent to freely diffuse (float) into their core. One, several, or more concentric membranes may be present. Liposomes can be categorized into three types depending on the size and number of their bilayers: multilamellar vesicles, large unilamellar vesicles, and small unilamellar vesicles. This is where water and polar lipids combine to create self-organized colloidal particles. As a result, lipid-soluble substances gather within the lipid section and substances that dissolve in water become stuck in the water compartment. As for example in case of detergents, components create micelles. Here polar lipids with larger hydrophobic segments cannot form large radii of curvature micelles. Instead, they create bilayers lipid vesicles. In Fig. 1, transverse section of liposome revealed that the heads of the amphiphile,which are hydrophilic in nature, faced to the direction of aqueous phase. Again the tails which are lipophilic in nature, remains as a manner which directed to the vesicle's center, Liposomes are very efficient in case of proper delivery of herbal medicines by maintaining their bioavailability as well as safety profiles over prolonged durations. In many cases liposomes can improve the effectiveness of herbal medicines[68].

Fig.1: Cross section of liposome

In case of liposomes of anti cancer herbal drugs, it is possible to elevate the therapeutic index by amplifying concentration of drug into tumour cells along with rescue the disease free normal tissues from the major exposure of drugs.This can be achieved by taking advantages of some incidents like, elevation of permeability,elevation of sustainability and target specificity[69].

Liposomes have several key benefits, such as their excellent biocompatibility, simple preparation, and chemical variations (allowing hydrophilic, amphiphilic, and lipophilic compounds to be loaded), and easy modulation of their pharmacokinetic properties through simple changes to the bilayer components' chemical composition.Since the reticuloendothelial system (RES) traps the majority of typical liposomes, delivering drugs to the RES is a simple process.

One herbal remedy whose superior pharmacological profile makes it simple to show the therapeutic effectiveness of milk thistle (*Silybum marianum*). Meanwhile, because of the actions of silybin, a significant active flavonoid frequently present in dried fruits containing silymarin. Silymarin shows low absorption rates (20–50%) in G.I.T. when administered parenterally as opposed to orally, there is a higher absorption[70]. But the stable liposome of silymarin as buccal dose form, produces high bioavailability. In this sense, soybean lecithin is the name under which it is sold commercially. Here during the formulation Tween 20 functions as edge activator, which gives it the property of mucoadhesive. So here the liposomes can’t travel from the buccal mucosal cells. It is advised to use refrigeration to improve stability[71].

A lot of research has been done on liposomes in relation to cancer treatment. Herbal drug delivery systems are known for their success because of their tiny size, low toxicity, regulated release time, ability to alter the pharmacokinetics and biological characteristics of medications, and ability to distribute medicinal herbs[72].

3.2. Ethosome

A unique liposome that can be applied topically or applied transdermally is called an ethosome. The encapsulation efficiency and deformability of entrapments allow them to fully enter into the skin to increase the transport through it[73].

Ethosomes are lipid vesicles that have a comparatively higher concentration of alcohol (ethanol or isopropyl alcohol) than water and phospholipids.Various medications have been claimed to be better delivered via the skin when encapsulated in ether. Additionally, penetration enhancers such propylene glycol have been added to the preparation of ethosomes, which have demonstrated increased penetration efficiency[74].

Age-activating substances, such as sodium cholate and ethanol, when present in the bilayers of lipid then significantly increase the entering of carrier by passing stratum corneum, facilitating the efficient herbal drug distribution (both local and systemic) of aquaphobic and water loving chemicals[75].

On the basis of physical characteristics and chemical nature, it is clear that ethosomes are very much efficient to deliver the herbal drugs into the deep layer of skin or into the blood vesselsby passing the layer of stratum corneum. As a transdermal delivery system and topical medication carrier, this feature is crucial. Moreover, the ethosomes carrier can effectively deliver hydrophilic and lipophilic medications inside cells.In the transdermal zone, ethosomes have shown to be effective transport routes. A variety of excipients, including phospholipids, polyglycol, alcohol, cholesterol, color, and carrier, are utilized in the ethosomal composition. Ethosoms have a higher rate of penetration through the skin than liposomes due to the collaborative impact of phospholipids and the elevated ethanolic concentration within ethosomes.

The ethosome of herbal medicine with properties that reduce inflammation called matrine is more readily absorbed via the skin, and this increases the antibacterial peptide's ability to enter fibrocytes.

3.3. Phytosome

Major therapeutically active phytoconstituents are composedof polar molecules. The molecule size of these types of phytoconstituents is so high. So they show poor absorption. Again due to large molecular size, also hampered their passive diffusion. Another drawback is their inability to crosslipid-rich biological layer due to poor lipid solubility of those phytoconstituents. As a result those phytoconstituents show poor bioavailability[76].

In many cases some constituentsof orally administered natural extracts, become destroyed in the presence of gastric juice. So their bioavailability as well as therapeutic utilities become decrease. Administration of those natural extracts combined with other phytoconstituents is a remedial method to increase their bioavailability as well as therapeutic activities[77].

Certain nutrients, such as phospholipids, are still very beneficial for improving absorption. Using patented technology, a top pharmaceutical and nutraceutical manufacturer created phytosomes, which are lipid-compatible molecular complexes that greatly increase phospholipid's absorption and bioavailability. In the formulation of phytosome,hydrophilic phytoconstituentsof standard plant extracts remains into the phospholipid barrier. A new development in the market for nutraceuticals and herbal remedies is phytosomes.The activity of phytochemical substances is enhanced by phytosomes. The phytosome mediated drug delivery facilitate to increases the solubility, permeability, and stability of compounds by diminishing the surface tension between a substance with low solubility and the solvent. It also forms a vesicle system which can bind with polar and non-polar compounds[78].

In case of phytosome there remains a molecular complex between phosphatidyl choline and plant constituents typically in a 1:1 or 2:1 ratio. That ratio depends on the nature of phytoconstituents used in that complex. Also some chemical bonds remain involve with that complex dosage form of phytosome.That type of complex formulation of phytosome enhance the absorption of therapeutically active phytoconstituents than traditional standard plant extract. So outcome is progressive drug delivery with phytosome.

Phospholipids are intricate molecules remain present in cell membranes of maximum living organisms[79]. Phospholipids act as naturally occurring digestion enhancer as well as carriers of both fat and water miscible foods. As a result, they are well absorbed when taken orally and miscible in both lipid and water media[80].

Because phytosomes can easily penetrate through lipid rich biological membrane and enter into the blood stream, they are more accessible than traditional herbal extracts. There are different herbal phytosomes, such as phytosome version of green tea, quercetin, curcumin, *G. biloba*, grape seed, hawthorn, milk thistle, ginseng etcetera [81].These plant extract's flavonoid and terpenoid constituents make them very suitable for direct binding to phosphatidylcholine.

3.4. Polymeric nanoparticles

Polymeric nanoparticles means in colloid the size range of particles from 10 nm to 1000 nm are known as nanoparticles and the colloid is considered as nanoemulsions. Here the nanoparticles with mean particle size significantly larger than the 100 nm are considerable. Another way to describe the polymeric nanoparticles are nanoparticles within submicronic colloidal systems. In case of herbal polymeric nanoparticles the therapeutically active plant extract remains distributed allover the particles of the nanosphere's matrix-like structure. So the active ingredient is contained within the nanocapsule's polymeric membrane[82].

The polymeric nanoparticles are an efficient herbal drug administration systems of herbal medicines because of their passive tumor targeting characteristics, resulting in increased therapeutic activity and decreased undesired effects of plant derived cancer healing medicines. Furthermore, the ability of nanoparticles to selectively gather in and around tumor masses offers a platform for enhanced tumor identification and establishes the groundwork for the creation of multifunctional nanoparticle systems for cancer treatment[83].

Polymeric nanoparticles are includes nanospheres and nanocapsules. They are colloidal solid matter with a size of the order of 10 to 500 nm. These nanoparticles ensure this because of their innate qualities, which include

biodegradability, non-toxicity, immunogenicity, and biocompatibility, they represent an alternative to the nanosystems[84].

Polymers are suitable for the preparation of nanoparticles include polyalkylcyanocrystalates, polymythylidenemalnolate, polyesters etcetra. Examples polylactic acid, polyandcaprolactone and their copolymers. Lipids, metal oxides and silica can also be used. A variety of plant nanoparticle formulations are available, such as nanoparticles loaded with quercetin, nanoparticles loaded with berberine, nanoparticles loaded with glycyrrhizic acid, curcuminoids with solid lipids, and so on.

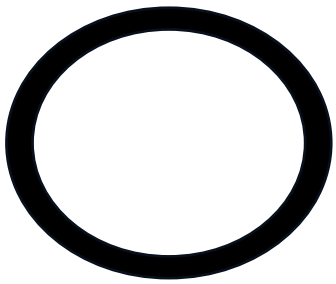

Fig.2: Cross section of Bio-polymeric nanoparticle

3.5. Nanoemulsions

An emulsion is a heterogeneous mixture composed of two different liquids, one of which disperses as droplets into the other and the other of which is utilised to disperse another as continuous phase. It has a transparent to translucent liquid appearance. In case of classification of emulsions there are sub-micro-emulsions (100–600 nm), micro-emulsions (10–100 nm), and general emulsions (0.1–100μm).The lipid emulsion is another name of sub-micro-emulsion, and the micro-emulsion is also known as a nanoemulsion.Because of its affinity for the lymph, after administration of herbal extract through nano emulsion, the *in-vivo* drug distribution is occurs in a focoused way. Furthermore, in case of nanoemulsion the therapeutically active ingredient remains in the interior segment.This criteria of that formulation provide two major advantages like there is no chance of direct contact between the therapeutically active ingredient and the body as well as tissue fluid andanother advantage is prolonged sustained release of the therapeutically active ingredient. Again macrophages affect the oil globules by the technique phagocytosis from the formulation of O/W or O/W/O emulsion with lipid loving like oily therapeutically active herbal extracts. So elevated concentrations of the herbal extracts able to reach in the kidney, spleen, and liver, where a substantial portion dissolves. Again in case of hydrophilic herbal extracts formulated as W/O or W/O/W emulsion, when administered as intramuscular or subcutaneous injection can be efficiently concentrated in the lymphatic system. The target distribution of the emulsion particle is affected by it's size[85].

When some hydrolysable herbal extracts like camptothecin, *Brucea javanica* oil, coixenolide oil, zedoary oil etcetera are formulated as sustained release nanoemulsion then there are some advantages as following:

- Increase the stability of formulation
- Enhance the penetration power of the formulation through the topical route
- Decrease the stimulant effect of medication on tissues

Some herbal nanoemulsions areuseful for protein expression and human lung adeno-carcinoma cell line. According to the in vitro findings of those cases the nanoemulsions can significantly inhibits the growth and proliferation and this effect is dose and time dependent. One class of novel anti-cancer medication with

promising application potential is elemenum emulsion. Moreover, it does not cause harm to the liver or heart, nor does it inhibit the marrow[86].

Fig.3: Cross section of Nano emulsion

3.6. Transferosome

Transferosomes are mainly topical formulation with skin hydration property. So this formulation is capable to penetrate into the lipid lamellar regions of the stratum corneum as carrier of various necessary nutrients for localized skin maintenance. Transferosomes are helpful to carry therapeutically active constituents of herbal extracts including proteins, peptides, small moleculesand other constituents.The transferosomes of Capsaicin shows advance rate of absorption through the skin than pure capsaicin[87].

3.7. Microsphere

Microspheres are a type of advance formulationwhich has several success in the field of medication administration because

- This formulation is very much suitable for inject or swallow
- Formulation with expected release rate of medication is possible
- Easy to formulate as the release of medication is occurs into specific site and depending upon the situation in specific organ also[88].

Several plant's active ingredients are used to formulate as microspheres; like quercetine, rutin, camptothecin, zedoary oil, tetrandrine, and *Cynara scolymus* extract. In current era magnetic and immune microspheres become more demanding where the polymeric microspheres have a coating of antibody and antigen to provide the immune competence.

4. Applications of nano formulations of herbal medicines

Recently, new technologies for herbal drug transportation protocols have been established. Microencapsulation of plant extracts in nanoparticles is a successful strategy to prevent food or medicine ingredients from deteriorating, loss of volatile compounds or incomplete reactions. Small doses of herbal medicines can show more solubility along with better absorptionwhen it is administered in the form of nanoparticles. For example from Brassicaceae family sinigrin which is a glucosinolate in the form of phytosome provide better bioavailability as well as solubility. In addition, the sinigrin phytosome enhance its healing activity. Dihydroquercetin, or taxifolin, is another example of a bioactive flavonoid with antioxidant qualities[89].

Glycyrrhizic acid-loaded nanoparticles with 91.76 % entrapment efficiency improve the bioavailability.Again during topical administration into skin.Triptolide nanoparticles increase hydration, which improves entry of drugs through the skin. Oral administration of nanoparticles like *C. chinensis* with 90% entrapment efficiency enhance the water solubility.*G.biloba* enhances cerebral metabolism and blood flow. NAR-loaded nanoparticles improved the solubility as well as release of NAR and Triptolide-loaded solid lipid nanoparticle decreasing it's toxicity[90].

Again *in-vitro* administration of nanoparticles like Artemisinin nanocapsules with 90–93% entrapment efficiency,Tetrandrine loaded nanoparticles with 84% entrapment efficiency[91]and Berberine loaded nanoparticles with 65.40 ± 0.70% entrapment efficiency are employed for sustained release[92], Radix salvia

upto 96.68% entrapment efficiency is employed to improve it's bioavailability [93] , Quercetin loaded nanoparticles over 99% entrapment efficiency is employed to increase the antioxidant activity and here release of drug is 74 times higher[94],Curcuminoids solid lipid nanoparticles with 70% entrapment efficiency is employed to Prolonged-release of the curcuminoids[95], and CPT-encapsulated nanoparticles over 80% entrapment efficiency is employed to extended blood flow and significant tumor accumulation[96].

A powerful natural anti-cancer agent, Taxol is an natural alkaloid obtained from *Taxus brevifolia* stem bark whose local name is Pacific yew tree which is very poisonous in nature. Taxel-loaded nanoparticles with 99.44% entrapment efficiency increase the medication's sustained release and bioavailability[97]. Because of the modified pharmacokinetic profile of the paclitaxel-albumin nanoparticle formulation, it is more soluble and has improved tissue distribution[98]. Paclitaxel liposome is pH sensitive and shows higher entrapment efficiency that is 94% when administered *in-vitro*[99].

Taxifolin can improve immune function and reduce the formation of cancer cells in the human body. Nevertheless, the clinical application of taxifolins is restricted due to their water-loving nature along with higher molecular dimensions. However, the lipid loving nature of the active constituents enhanced when ethyl acetate fraction of taxifolin, which was extracted from *Cedrus deodara* stem bark, was formulated as phytosome. This improved the active compound's absorption and increased its capacity to cross biological membranes [100].

Compared to ethyl acetate, phytosomes exhibited higher antioxidant activity and a lower IC50 value, at that concentration wherea chemical loses half of it's maximum inhibition power.The conclusion that the dilution of the phytosome demonstrated specific antitumor action in comparison to the ethyl acetate fraction was influenced by the outcomes of the TB test and the MTT test using the MCF7 cell line [101].

Silybin is another polyphenol that protects the liver against damage free radicals, prevents the formation of cancer, and mitigates ongoing inflammatory processes. Nevertheless, there is minimal gastrointestinal absorption and poor water solubility of this silybin. When silybin was loaded into phytosome nanosuspensions, the liver protective characteristics of silybin was enhanced[102]. Again absorption of silybin phytosome is approximately sevenfold greater than absorption of silybin obtained from milk thistle extract. Nanoparticles loaded with Silibini having high capacity of entrapment that is 95.64% with high stability[103].Again Liposomes encapsulated silymarin having 69.22 ± 0.6% entrapment efficiency and itshows higher bioavailability during it's buccal administration [104].

During *in-vitro* administration of liposomal formations like liposomal *Aarborescens* with 69.22 ± 0.6% entrapment efficiency enhance the penetration intocytoplasmatic barrier [105], Ampelopsin liposome with 62.30% entrapment efficiency shows higher efficacy [106],Usnea acid liposome withβ-CD having 99.5% entrapment efficiency provide higher solubility and localization as well as prolonged- release profile [107],Wogonin liposome with 81.20 ± 4.20% entrapment efficiency produce sustained release effect[108],Garlicin liposome with 90.77% entrapment efficiency shows higher efficacy [109] and last but not least is Curcumin liposomes have a long half-life and a high entrapment effectiveness that is 88.27 ± 2.16% [110].

Topical administration of Colchicine Liposome with 66.3 ± 2.2% entrapment capacity can increase skin accumulation, extend the duration of medication release, and enhance site specificity[111]. Again transdermal administration of Catechins Liposome with 93.0 ± 0.1 % entrapment efficiency enhanced penetration through skin[112]. Intramuscular Breviscapine liposomes with 87.9 ± 3.1% entrapment efficiency employed as sustained drug delivery [113].

A hydrophobic flavonoid compound with good hepatoprotective and antioxidant qualities is called apigenin. Apigenin's low oral bioavailability, quick metabolism, and poor aqueous solubility, however, restrict its clinical applicability [114].The water solubility as well as releaseof apigenin phytosome (APLC) is always greater. Also the bioavailability and antioxidant properties of APLC also increased[115].

Oral administration of Quercetin is poor but in the phytosome delivery system, this problem is reduced and the absorption and activity of quercetin is increased. As a phytoestrogen, quercetin stimulate estrogen receptors and is therefore used in hormone replacement therapy[116].Quercetin-phytosome treatment showed increased serum inorganic calcium, phosphorus and glutathione levels and improved lipid profile. Additionally, Qurcetin Phytosome has been found to reduce the levels of alkaline phosphatase, acid phosphatase, malondialdehyde, tumor necrosis factor alpha, and serum glucose in the blood [177] Compared to free quercetin, the quercetin phytosome at a dosage of 50 mg/kg produced superior outcomes. This results from the quercetin phytosome's improved absorption. The findings demonstrated that loading quercetin into the phytosome delivery system enhanced its antioxidant, anti-inflammatory, lipid-lowering, and other properties [118]. Again Quercetin liposomes having 60% entrapment efficiency and in reduced dose, it shows higher penetration in blood brain barrier during it's intranasal administration.

By *in-vitro* administration of flavonoids liposomes including quercetin and rutin enhanced the flavonoids and haemoglobin binding. This kind of phenomenon increases it's bioavailability[119].

To address the issue of respiratory infections, the gingerol preparation was placed into a phytosome and combined with chitosan. *Zingiber officinalis* is the source of gingerol, a polyphenol with a diverse array of biological effects. However, the profiles of these gingerols' water solubility and bioavailability are low. Inhibiting both gram-positive and gram-negative organisms, the gingerol phytosome complexed with chitosan (GPLC) exhibited a stronger inhibitory effect compared to the gingerol phytosome alone (GP)[120].

The aqueous extract of *Moringa oleifera* (MO) have medicinal properties because it contains quercetin, gallic acid, kaempferol, chlorogenic acid, and vicenin-2. But this aqueous MO extract is unable to cross biological membranes where lipid content is high by inhibiting local uptake because of it's highermolecular dimensions and high solubility in aqueous phase.However, the migration and proliferation rates of normal human dermal fibroblast(NHDF) cells showed higher with MOPCT, a phytosome delivery system without any cytotoxicity[121].

A phytosome delivery system (LCP) employs the methanol extract of *Lantana camara* leaves, and the antibacterial and antifungal activity that results is monitored. The findings demonstrated that LCP increased the inhibition zone diameter (IZD) against *C. albicans, L. ivanovii,* and *E. Coli*[122].

Murraya koenigii exhibits many biological activities, but absorption across biomembranes is low, so bioavailability also very low. Factorial design phytosomes have been used to conquer the constraints of *Murraya koenigii*. By modifying the characteristics of release, the phytosome delivery system not only improves absorption but also has the ability to release phytochemicals continuously[123].

G.biloba extract (GbE) has multiple therapeutic effects including free radical scavenger, auto-oxidation, antitumor and central nervous system protection. However, when administered orally, the limited bioavailability (10%) and short half-life (2.1 h) of GbE led to bioavailability issues[124]. Drug diffusion across biological membranes is generally increased by the utilization of niosomes, which can inhibit the modification of the pharmaceutically active constituents in presence of any enzymes, and also enhance it's bioavailability[125]. Subcutaneous administration of *G.biloba* phytosomes with 100 mg and 200 mg/ kg used to stabilize the ROS[126].

Again oral administration of Ginkgoselect phytosome with 25 and 50 mg/ kg reduces the rate of lipid peroxidation (LPO) and stabilizes ROS[127],Silybin phytosome with 120 mg shows seven times greater absorption[128],Ginseng phytosome 150 mg and Green tea phytosome 50– 100 mg also show greater absorption, Grape seed phytosome 50– 100 mg shows the significantly elevated antioxidant parameter of blood trap & total Radical-trapping over the control, Hawthorn Phytosome 100 mg increase therapeutic efficacy and absorption[129],Quercetin phytosome shows better therapeutic efficacy[130],Curcumin phytosomes 360 mg/ kg increase antioxidant activity[131] and bioavailability and NAR phytosomes 100 mg/ kg shows prolonged duration of action [132].

In the field of nanoemulsion also there have a broad range of efficacy enhancement instances of herbal formulations. Oral administration of 68.3± 1.6nm droplet with 30% drug loaded Self-nanoemulsifying Zedoary essential oil improve the oral bioavailability, stability, and aqueous dispersibility [133] and 56.80 nm droplet with 0.50% drug loaded nanoemulsion of Berberine enhance the duration of stay and absorption [134].

Again topical administration of <100 nm droplet of Triptolide microemulsion increase the drug penetration through enhanced hydration, via the stratum corneum [135] and 10–100 nm droplet with 0.3% drug loaded Quercetin micro-emulsion improves epidermis and stratum corneum penetration[136].

The residence time can be extended by intravenous administration of 166.00 nm droplet with 90% drug loaded docetaxel submicron emulsion[137] and 21.20 nm droplet of Silybinnanoemulsion is a sustained release formulation in intramuscular administration[138].

Some other novel formulations like topical administration of 150.6 nm droplet of Capsaicin transferosomes increase skin penetration[139],110±8 nm droplet of Matrine ethosome enhances the penetration through the skin [140] and 350 nm to 100 nm droplet of in vitro ethosomes containing ammonium glycyrrhizinate, enhance percutaneous penetration [141].

Again *in-vitro* administration of 120 nm droplet of Vincristine transferosomes enhance skin penetration and entrapment effectiveness [142] and also Colchicine transferosomes increase skin penetration [143].

In the spectrum of microspheres encapsulated herbal formulations *in-vitro* administration of 165.00– 195.00 µm microcapsules composed of rutin, alginate, and chitosan, are target specific and involving the cardiovascular and cerebrovascular region [144] and 6 µm Quercetin microspheres are efficient to significant decrease of dose size [145].

Oral administration of 100–600µm Zedoary oil microsphere provide longer-lasting and more bioavailability [146] where at the same route 6–7 µm *Cynara scolymus* microspheres provide Controlled release of neutraceuticals [147].

Again *in-vitro* administration of 6µm Quercetin microspheres can significantly reduces the size of dose [148] where intra-peritoneal and intravenous administration of 10µm CPT loaded microspheres provides Extended-release of camptothecin [149].

4.1. Polymeric Nanoparticle

For increasing the activity of phytochemicals, polymeric nanoparticles have shown much higher efficacy. Pepper's primary bioactive component is piperine, an alkaloid compound. The effects of piperine include anti-inflammatory, antibacterial, antifungal, antitumor, antiasthmatic, antipyretic, analgesic, and antioxidant properties. Nevertheless, piperine has drawbacks such as systemic excretion, quick metabolism, and poor water solubility. Here piperine is encapsulated within sustained-release polymer nanocapsules to overcome these drawbacks[150].

Jatropha pelargoniifolia (JP) is a traditional herbal plant with medicinal properties with broad therapeutic effects and rich in phenols and flavonoids. Unfortunately, JP cannot be given with it's traditional formulation because here it's stability, solubility and bioavailability is very less and also here it Shows sensitivity with the pH of stomach acid. But JP-loaded chitosan nanoparticles (JP-CSNP) showed higher antioxidant, anticancer, and antimicrobial activity[151].

The mixed micellar(MM) nanoformulation delivery system like ethanolic extract of *Argyreia pierreana*(APEECE) and *Matelea denticulate*(MDECE) has antidiabetic and antihyperlipidemic activity. Micellar encapsulation possesses are beneficial for enhancing water solubility, stability, pharmacokinetic properties, and also prolongation of the circulation time of the drug. Curcumin is also a traditional crude drug with high biological activity [152]. However, Curcumin's low solubility in water, instability, and decreased

bioavailability are its drawbacks [153]. PLGA (CNP) nanoparticles mixed with chitosan/PEG and loaded with curcumin are the ideal delivery system to achieve potent cytotoxicity, enhanced anti-migratory and anti-invasive characteristics, and caused pancreatic cancer metastases to undergo apoptosis[154]. ZTO nanocapsule shows 1.62 ± 0.15% entrapment efficiency where improve the drug loading capability and stability.

5. Discussion

Nanotechnology is a reliable and secure medication delivery system. Nanotechnology based delivery system is one of the best system for herbal medicine. Nanotechnology holds great potential and innovative technology to enhancephyto-therapeutic efficiency of herbal medicine. Due to this in the recent era there was a priority to incorporate nanotechnology into herbal formulations to develop a safe and efficient drug delivery system. Phytosome, Solid lipid nanoparticles and nanostructured lipid carriers, polymeric nano particle, nano emulsions etcetra are some popular types of nanotechnology to use successfully and abundantly in herbal formulations.So in the field of herbal medicine, incorporation of nano technology can overcome each and every difficulties related to herbal drug administration as well as treatment and also increase the potency and therapeutic activity of herbal formulations.

6. References

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