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HERBONANOCEUTICALS: A NEWER APPROACH FOR DELIVERING HERBAL DRUGS

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ABSTRACT: "Nanotechnology" is a science which deals with the particles less than the size of 100 nm. Materials at the atomic and molecular scales are engineered and manufactured by this technology. The use of nanotechnology for "phytotherapy" or treatment of various diseases by herbal medicines/drugs, including herbal drug delivery, where current and emerging nanotechnologies could enable entirely novel classes of therapeutics, has been reported. The researchers have succeeded in using nanotechnology to insert and simultaneously activate the genes delivered into plant cell walls. The nanomaterials can significantly enhance the pharmacokinetics and therapeutic index of plant origin drugs. Interestingly, pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs. Herbs and herbal derivatives are of great research interest owing to their wide applications in therapeutics. Several folk evidence has been recorded in the formulations of the ancient world's medicinal system, which have attracted researchers for their scientific validation. Various herbal compounds have been identified and showed their therapeutic efficiency against pathophysiological conditions. Employing these herbal compounds for synthesizing nanoparticles for biomedical applications has been ventured in recent times. This review tries to put forward the different metal nanoparticles formed from different herbal resources and their role in health and diseases. This review opens the door to a completely new dimension in medicinal plant research combining nanotechnology with herbs *i.e.*, Herbonanoceuticals.

INTRODUCTION: Herbal Medicines and natural products have been used to cure numerous diseases since ancient times. They are different from the most commonly used Allopathic system as the herbal remedies have thousands of constituents that all work simultaneously against the diseases [1].

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The common word used for therapy with phytoconstituents is known as Phytotherapeutics. Phytotherapeutics needs a scientific approach to deliver the various phytoconstituents in a sustained manner to improve patient compliance and avoid repeated administration. This can be successfully achieved by designing novel drug delivery systems for herbal constituents. These novel drug delivery systems offer various advantages like the reduction of the repeated administration to overcome non-compliance, but also an increase in the therapeutic value by reduction toxicity and improved bioavailability [2, 3].

The major problem faced with these herbal extracts is their bulk dosing and less absorption. But when these herbal extracts are incorporated into novel formulation systems, they overcome both the above problems of bulk dosing and less absorption.

Nanotechnology is an area of applied science and technology which works in developing devices and dosage forms in the range of 1 to 100 nm. When nanotechnology is applied for treatment, diagnosis, monitoring, and control of biological systems are now being referred to as Herbonanoceuticals. The nanocarriers which are used are made of safe materials, including synthetic biodegradable polymers, lipids, and polysaccharides.

Herbal medicines consist of a variety of active components. The pharmacological action of herbal medicines depends on the comprehensive performance of these active components, as all the constituents impart synergistic action and thus enhance the therapeutic value of the medicine. Each active constituent plays an important role, and these roles are all related to each other. However, the problem associated with most of the herbal origin drugs is their insoluble character, which leads to poor bioavailability and increased systemic clearance, so they require repeated administration or higher dose, which makes the drug a poor candidate to be used therapeutically. During the study of formulation development of these phyto-constituents, it was found that developing nano dosage forms like nanospheres, nanocapsules, liposomes, proliposomes, solid lipid nanoparticles and nanoemulsion, *etc*. offer large number of advantages for herbal drugs, namely improvement of solubility and bioavailability, safety, enhancement of pharmacological activity and stability, improving tissue macrophages distribution, sustained drug delivery, protection from physical and chemical degradation, etc. Therefore, the nano-sized drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Hence, integration of the nanocarriers as a NDDS in the traditional medicine system is essential to conflict with more chronic diseases like asthma, diabetes, cancer, and others.

Need for Nanotechnology for Herbal Drugs: As the various constituents of the herbal drugs reach the blood, they will be destroyed in the highly acidic pH of the stomach, and some of the constituents might be metabolized by the liver because of which the quantity of the herbal drugs reaching the blood may not be optimum. Therefore, if the drug does not reach the optimum amount to the target area at a "minimum effective level," then it will not show any therapeutic effect. Application of Nanotechnology with herbal medicines provides the drug in the optimum amount to the site of action, bypassing all the barriers like acidic pH of the stomach, liver metabolism and increase the prolonged circulation of the drug into the blood due to their nano size [1, 4].

Strategies of Nanotechnology as Novel Drug Delivery System: Nano-sized delivery system of herbal medicine was selected because of the following reasons [5, 6, 7, 8].

- Because of their unique size and high loading capacities, Herbonanoceuticals appear to be able to deliver high concentrations of drugs to the site of action.
- Small particle size of the drug increases the entire surface area, thus faster dissolution of the drug in the blood.
- The concentration seems to remain at the sites for a longer period of time.
- They exhibit the EPR (enhanced permeation and retention) effect. Their small size offers enhanced permeation through the barriers and retention due to poor lymphatic drainage as in the case of tumors.
- They show passive targeting to the disease site of action without the addition of any particular ligand moiety.
- Decrease in the side effects.
- Decrease in the dose of the drug formulation.

Different Nanocarriers used for the Delivery of Herbal Bioactives (Table 1):

Anticancer: In recent years, significant attention has been received by advancements in the synthesis of metal nanoparticle using plant extracts and their anticancer activity. The phenolic compounds present in *Sasa borealis* showed anticancer activity

[9]. Patil *et al*., used this green approach for the synthesis of gold nanoparticles (AuNPs) using leaf extract of *Sasa borealis* [10]. In this study, AuNPs were of elemental compound was carried out using synthesized at 50 °C, and nanoparticle formation was observed after 20 min incubation. The confirmation of gold nanoparticles was confirmed by the UV–visible spectrum peak at 542 nm. The synthesized AuNPs were oval, spherical in shape and ranged in size around 10–30 nm observed using the transmission electron microscope. The detection Energy dispersive X-ray analysis. The X-ray diffraction pattern was applied to confirm the face centered cubic structure. Fourier transform infrared spectroscopy was used to determine the reduction of tetrachloroauric acid into AuNPs by the phytochemical compounds of *S. borealis* extract. The presence of biomolecules was studied by using GC–MS. The synthesized AuNPs were tested for toxic effect on HEK293 cells and anticancer activity on AGS cells by WST-1 assay. The condensation or fragmentation characteristics of apoptosis, were confirmed by 4,6-diamidino-2-pheynylindole dihydrochoride (DAPI) staining. The *S. borealis*-mediated AuNPs were found to have good anticancer activity agent and can be found beneficial in cancer therapeutics.

TABLE 1: NANOCARRIERS USED FOR DELIVERY OF BIOACTIVES

S. no.	Herbal Source	Type of nanocarriers	Pharmacological Use
1	Leaf Extract of *Sasa borealis*	Gold Nanoparticles	Anticancer[9]
2	Branch Extract of *Eurycoma longifolia*	Silver Nanoparticles	Anticancer[11]
3	Ethanolic extract of *Nilgirianthus ciliatus* Nees	Gelatin Nanoparticles	Antidiabetic[14]
4	Ethanlonic Extract of *Talinum portulacifolium*	Silver Nanoparticles	Antidiabetic[15]
5	Biocomponent from *Cassia auriculate*	Gold Nanoparticles	Antidiabetic[16]
6	Fruit extract of *Emblica officinalis*	Silver Nanoparticles	Hepatoprotective[17]
7	Aqueous extract of Fenugreek seeds	Gold Nanoparticles	Hepatoprotective[18]
8	Extract of *Euphrasia officinalis*	Gold Nanoparticles	Anti-inflammatory[19]
9	Aqueous extract of *Piper nigrum*	Silver Nanoparticles	Anti-inflammatory[20]
10	Extract of *Terminalia bellerica*	Silver Nanoparticles	Antibacterial[21]
11	Extract of *Salvia spinosa*	Silver Nanoparticles	Antibacterial[22]
12	Curcumin-Nisin	Polylactic acid nanoparticles	Cardioprotective[23]
14	Extract of *Salvia multiorrhiza*	Iron oxide Nanoparticles	Cardioprotective[24]
15	Bavachinin from *Psolarea coryfolia*	PLGA Nanoparticles	Anti-asthmatic[25]
16	Cardamom Extract	Gelatin Nanoparticles	Anti-epileptic[26]
17	Leaf extract of *Parthenium hysterophorus*	Zinc oxide Nanoparticles	Antifungal[28]

Eurychoma longifolia a well-known medicinal plant in South–East Asian countries, was found to have anti-tumor activity [11]. Prasad *et al*., synthesized silver nanoparticles (AgNPs) by adding 1 mM Silver nitrate solution to different concentrations (1%, 2.5%, 5%) of branch extracts of *Eurycoma longifolia.* AgNPs were characterized using techniques such as ultraviolet-visible spectrophotometry, X-ray diffractometry, Fourier transform infrared–attenuated total reflection spectroscopy (FTIR–ATR), scanning electron microscopy [12]. X-Ray Diffraction analysis was utilized to reveal the face center cubic structure of AgNPs. FTIR–ATR showed that primary and secondary amide groups in combination with the protein molecules present in the branch extract, were responsible for the reduction and stabilization of AgNPs. Antioxidant, antimicrobial, and anticancer activities of AgNPs were investigated. AgNPs showed significant anticancer activity against human glioma cells (DBTRG and U87) and human breast adenocarcinoma cells (MCF-and MDA-MB-231) with IC_{50} values of 33, 42, 60, and 38 µg/ml.

Liposomes are widely used as nano-carriers with great significance for various herbal drugs. Artemisinin, which is used as an effective anticancer drug, was found to have some side effects. In order to reduce these side effects, liposomes can be employed. Pegylated nano-liposomal artemisinin was prepared by combining particular proportions of phosphatidylcholine, polyethylene glycol 2000 and artemisinin [13]. The mean diameter of nano liposomes was found to be 455 nm. The Pegylated nanoliposomes were characterized for encapsulation efficiency and drug release. The encapsulation efficiency and drug release from pegylated nanoliposomes for pegylated nanoliposomal artemisinin were found to

be respectively 91.62 ± 3.5 and 5.17%. The results also show that IC_{50} of the produced formulation is less than that of the standard drug. This study affirms that the amount of artemisinin cytotoxicity compared to the standard drug is increased by pegylated nanoliposomal formulation.

Diabetes: *Nilgirianthus ciliatus* Nees is known to treat numerous physiological disorders in the traditional Indian system of medicine. As per previous investigations, it was found that various bioactive compounds have been isolated from this plant for the treatment of various physiological disorders. But these compounds were found to be unstable in the gastrointestinal tract due to the high pH and harsh conditions that make the bioactive compounds ineffective. Therefore, to improve the pharmacokinetic and pharmacodynamic properties of various drugs, nanoparticles were developed by various techniques. Ethanolic extract of *Nilgirianthus ciliates* was used to prepare a nano-particles using the solvent evaporation technique using gelatin as carriers, and its antidiabetic effects were evaluated in L6 myoblasts and 3T3L1 adipocytes [14]. The mean particle size of plant extract loaded gelatin nanoparticles was found to be approximately 110 nm. The nanoparticles were spherical in shape when observed using transmission electron microscope. The ethanolic extract of *Nilgirianthus ciliatus* was encapsulated in biodegradable gelatin with 80% efficiency in this nano-sized formulation. The toxicity study of nanoformulation was performed using MTT assay. The nanoencapsulation formulation does not produce any toxicity upto 1000 µg/ml concen-trations. The nanoformulation of *Nilgirianthus ciliatus* prepared was also evaluated for its antidiabetic activity by glucose uptake assay in L6 cells and anti-adipogenic assay in 3T3L1 preadipocytes. The plant extracts loaded nanoparticles showed a significant antidiabetic effect in both assays in a dose-dependent manner when compared to the ethanolic extract. Therefore nanoencapsulated *Nilgirianthus ciliatus* could be treated as a potential antidiabetic drug.

Diabetes mellitus is a complex metabolic disease characterized by severe hyperglycemia and huge metabolic disturbances. In this present study, Bindu *et al.,* loaded ethanolic extract of *Talinum portulacifolium* (Forssk.) (EETP) into suitable lipids to prepare solid lipid nanoparticles using ultrasonication homogenization method [15]. The nanoparticles were prepared to improve the solubility and in turn the bioavailability of extract. In this study both extract and solid lipid nano-particles of Talinum were used to study anti diabetic activity in streptozotocin and high-fat diet-induced diabetic rats. The parameters evaluated were Blood glucose level, serum insulin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), lipid peroxidase, catalase, glutathione. These parameters were evaluated both in normal and diabetic rats. The results showed that solid lipid nanoparticles of Talinum treatment reduced all the elevated parameters tested in the rats at doses of 250 mg/kg. The histopathological studies of the pancreas of these animals showed comparable regeneration on treatment with solid lipid nanoparticles of Talinum. Glibenclamide was used as a standard drug at a dose of 0.5mg/kg.

In another study, Venkatachalam *et al.,* formulated gold nanoparticles synthesized using propanoic acid 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl) (PAT) [16]. This PAT is an active biocomponent which was isolated from *Cassia auriculate*. The functionalization of these gold nanoparticles was studied in detail. Stable gold nanoparticles were formed when PAT reacted with aqueous Tetrachloroauric acid. The Formation of gold nanoparticles was confirmed by applying various techniques like UV-vis spectroscopy, XRD, GC-MS, FTIR, TEM, and SEM with EDAX. Gold nanoparticles formed were mostly monodisperse, spherical in shape, and ranged in size 12-41 nm. The male albino rats were induced with diabetes using alloxan (150 mg/kg body weight). These Gold nanoparticles were administered at different doses 0.25, 0.5, 0.75, and 1.0mg/kg bodyweight for 28 days. It was found that plasma glucose level, cholesterol, and triglyceride were significantly ($p<0.001$) reduced in experimental animals treated with gold nanoparticles at a dosage of 0.5mg/kg body weight and plasma insulin increased significantly. The newly fashioned green gold nanoparticles showed remarkable protein tyrosine phosphatase 1B inhibitory activity.

Hepatoprotective: A study was conducted by Bhuvaneswari *et al*., to check out the hepato-

protective and antioxidant properties of aqueous fruit extract of *Embilica officinalis* and silver nanoparticles synthesized using *Embilica officinalis* fruit extract in wistar male albino rats [17]. The study was conducted by dividing the rats into eight groups with six animals in each group. Group I control rats were given normal feed. The hepatotoxic agent CCl_4 was administered to group II rats at a dose of 2 ml/kg/day. Group III was given aqueous fruit extract of *Embilica officinalis* in a dose of 300mg/kg body weight. Group IV was treated with aqueous fruit extract of *Embilica officinalis* (300 mg/kg) and CCl_4 (2 ml/kg/day). Group V rats received Silver nanoparticles of *Emblica officinalis* and CCl_4 (2 ml/kg/day). Group VI was treated with Silymarin (100 mg/kg). Group VII was treated with Silymarin (100 mg/kg) along with CCl_4 (2ml/kg/day). Group VIII rats received Silymarin, silver nanoparticles and CCl_4 (2 ml/kg/day). The consiquestial elevated enzymatic levels of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Lactate dehydrogenase (LDH), and Bilirubin by CCl_4 were revived toward normal when treated with aqueous fruit extract of *Embilica officinalis*. The total protein level was also found to achieve normal values. Assilymarin has significant hepatoprotective action so it was used as standard reference against the CCl_4 induced hepatotoxicity in rats. The *Embilica officinalis* and Silymarin silver nanoparticles also restored the level of the enzyme to a normal level significantly. The biochemical observation and histopathological examination proved that they have the antioxidant and hepatoprotective activity. After this study, it can be concluded that the fruit extract of *Embilica officinalis*, Silymarin, and its silver nanoparticles are rich antioxidants and has hepatoprotective activity.

Ghosh *et al.,* synthesized Gold nanoparticle using fenugreek seed aqueous extract and established their hepatoprotective activity in animal model [18]. For this, they used 4 swiss albino male mice and grouped them into five groups. Group1- Sham Control, Group 2- CCl_4 treated (1.5 ml/kg), Group 3- Standard Drug (Silymarin) treated (100 mg/kg/ p.o.), Group 4- Fenugreek treated (100 mg/kg/p.o.), Group 5- FG-GNP treated (0.5 mg/kg/p.o.). Various biochemical parameters (AST, ALT, γGT, ACP, ALP, total bilirubin), proinflammatory parameters (IL 1β, IL 17, TNF α), anti-inflammatory parameters (IL 10, Cathepsin K), antioxidant parameters (GSH, SOD, Catalase) and prooxidant parameter (LPO) were assayed. Histological studies of liver tissue were also done. The liver slice model was used to determine AST and ALT release from liver tissue. Statistical analysis was done by one-way ANOVA, values expressed as mean ± SE, PFG. The study concluded that fenugreek gold nanoparticles exerted their hepatoprotective effects in Swiss albino male mice by acting as an anti-inflammatory agent, and its antioxidant action also helped to reduce the pathogenesis of chemical/drug-induced hepatotoxicity.

Anti-inflammatory: Gold nanoparticles (AuNPs) have been potentially used in the treatment and diagnosis process due to their attributes like biocompatibility and high efficiency of drug delivery. In a study, Liu *et al.,* utilized an extract of *Euphrasia officinalis*, traditional folk medicine, and synthesized gold nanoparticles (EO-AuNPs) [19]. They also investigated their anti-inflammatory effects on lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages.

The AuNPs were synthesized from an ethanol extract of leaves of *E. officinalis*. These AuNPs were characterized using several analytical techniques. The anti-inflammatory activities of EO-AuNPs were detected by a model of LPS-induced upregulation of inflammatory mediators and cytokines, including nitric oxide (NO), inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 in RAW 264.7 cells. Western Blot method was used to investigate the activation of nuclear factor (NF)-κB and Janus kinase/signal transducer and activators of transcription (JAK/STAT) signaling pathways.

The AuNPs by *E. officinalis* were successfully synthesized. The obvious uptake of EO-AuNPs and internalization into intracellular membrane-bound compartments, resembling endosomes and lysosomes by RAW 264.7 cells was shown by transmission electron microscopy images. Cell viability assays exhibit that EO-AuNPs exhibited little cytotoxicity in RAW 264.7 cells at 100 μg/mL concentration after 24 h. EO-AuNPs were found to suppress the LPS-induced release of NO, TNF-α,

IL-1β, and IL-6 as well as the expression of the iNOS gene and protein in RAW 264.7 cells. It was also found that the study demonstrated that pretreatment with EO-AuNPs also reduced the phosphorylation and degradation of inhibitor kappa B-alpha and inhibited the nuclear translocation of NF-κB p65. In addition, EO-AuNPs suppressed LPS-stimulated inflammation by blocking the activation of JAK/STAT pathway. The synthesized EO-AuNPs showed anti-inflammatory activity in LPS-induced RAW 264.7 cells, suggesting they may be potential candidates for treating inflammatory-mediated diseases.

The synthesis of silver nanoparticles assisted with phytochemicals is an eco-friendly and cost-effective method for the development of silver nanoparticles with additional properties provided by the capping phytochemicals. Silver nanoparticles were synthesized using the aqueous extract of the unripe fruits of Piper nigrum and their *in-vitro* anti-inflammatory activity were evaluated [20]. The synthesized silver nanoparticles were characterized using various techniques like UV-Spectroscopic analysis, Scanning Electron Microscopy (SEM), Fourier Transform Infra-Red Spectroscopy (FTIR) analysis, Atomic Absorption Spectroscopy (AAS) and High-Performance Thin Layer Chromatography (HPTLC). The *Piper nigrum* extract contains alkaloids and proteins which act as both reducing and capping agents. The silver nanoparticles synthesized were found to be spherical and cuboidal with a size range of 40-100 nm. It was found by HPTLC studies that 856 ng of piperine capped 1 mg of silver nanoparticles.

The anti -inflammatory activity of the synthesized silver nanoparticles was evaluated using *in-vitro* assays for Tumour Necrosis Factor α (TNFα), Interleukins-1β and 6 (IL-1β and IL-6). The synthesized silver nanoparticles were also compared with the commercial silver nanoparticles, synthesized by standard chemical methods in these assays. It was found that the synthesized silver nanoparticles showed greater inhibition of all three cytokines at concentrations ranging from 10-20 µg/ml. So, it can be concluded that the synthesised silver nanoparticles showed an enhanced anti-inflammatory activity due to the synergistic effect of alkaloids of Piper nigrum extract and the silver ions.

Antibacterial: In another investigation, Alagan *et al.,* used the herbal extract of *Terminalia bellerica* (*T. bellerica*) [21]. This extract has both the properties of an efficient reducing as well as capping agent for successful synthesis of herbal silver nanoparticles (AgNPs) at room temperature. The high resonance Transmission electron microscopy results of AgNPs concluded that, the nanoparticles were found to be spherical in shape with an average diameter of ~30 ± 6 nm. XRD shows that, AgNPs showed the face centered cubic (FCC) structure. A nanosenser probe was utilized by AgNPs for the detection of mercury ions (Hg^{2+}). A color change from brownish yellow to colorless was observed on exposure to Hg^{2+} due to the redox reaction of mercury and silver. A lower limit of detection of 0.3 ± 0.005 µM was shown by the sensor probe. The selectivity of the sensor towards other environmentally heavy metal ions has also been evaluated, and found that this sensor is highly selective to Hg^{2+}. AgNPs loaded polyvinylalcohol (PVA) films and nanofibers were prepared by solvent casting and electrospinning methods, respectively. These AgNPs loaded PVA films and nanofibers were evaluated for anti-bacterial studies against *E. coli* and *B. subtilis*. The results indicate that the green synthesized AgNPs possess high anti microbial activity towards *E. coli*. These AgNPs based functional materials were found to have great potential for application in sensors, anti-microbial coatings, wound dressing, and smart textiles.

Researchers use a newly emerging field bio-nanotechnology technique tofabricate nanoparticles and nanomaterials. This technique is very eco-friendly and cost-effective. The present study conducted by Saba *et al*., demonstrates the use of plant extract of *Salvia spinosa* grown under *in-vitro* condition for the biosynthesis of silver nanoparticles (Ag NPs) for the first time [22]. The confirmation of the formation of AgNPs was confirmed by the surface plasmon resonance at 450 nm confirm. Moreover, Field Emission Scanning Electron Microscope (FESEM) images showed that nanoparticles had a spherical shape. The crystalline nature of the particles was confirmed by XRD analysis. FTIR analysis was to identify possible biomolecules responsible in the bioreduction of silver ions. The bactericidal activity of biosynthesized Ag NPs against Gram-positive and Gram-negative bacteria was verified by Anti-

microbial assay. The results showed that it is possible to synthesize nanoparticles with desired properties by growing the plants under controlled conditions.

Cardioprotective: Myocardial infarction (MI) is the most prevalent cause of cardiovascular death. Dietary supplements may be possible ways of preventing MI. Nabofa *et al.,* formulated curcumin and nisin based poly-lactic acid nanoparticle (CurNisNp) and determined their cardio-protective effect of on isoproterenol (ISO) induced MI in guinea pigs [23]. Animals were divided into five groups A to E, with five animals in each group. These groups were pretreated for 7 days. Normal saline was given to groups A and B animals at a dose of 0.5 ml/kg, group C metoprolol (2 mg/kg), groups D and E CurNisNp 10 and 21 mg/kg, respectively ($n = 5$). On the 7^{th} day in MI was induced groups B-E animals. On the 9^{th} day electrocardiogram (ECG) was recorded, blood samples and tissue biopsies were also collected for analyses. CurNisNp were also evaluated for toxicity studies. Atrial fibrillation was caused due to MI induction, which was prevented by pretreatment of metoprolol or CurNisNp. The increased expressions of cardiac troponin I, which was found to be associated with MI and kidney injury molecule-1 (KIM-1) which were significantly reduced in guinea pig's pretreated with metoprolol or CurNisNp ($P < 0.05$). The LC_{50} of CurNisNp was found to be 3258.2 µg/mL. This study demonstrated that the formulated curcumin is based nanoparticle showed a significant level of cardio-protection in the guinea pig and is also considered nontoxic.

Iron Oxide Nanoparticles (IONPs), including Fe_2O_3 and Fe_3O_4 NPs, have been extensively used as medical diagnostic agents, drug carriers, hyper-thermia for cancer treatment, separation tools, and cancer diagnoses and therapies. IONPs are generally considered as inert materials. These NPs can also be provided with biological properties; therefore, they are often bound to certain biologically active molecules such as antibodies, drugs, and DNAs to create nano-composites. In some studies, it has been recently reported that Fe_3O_4 NPs showed a peroxidase-like activity in a catalytic activity depending upon sizes in a range from 30 to 300 nm. After that, a dual enzyme (peroxidase and catalase-like) activities of IONPs *in-vitro* were also reported, and the relative potency of Fe_3O_4 NPs is higher than that of Fe_2O_3 NPs. However, it is unclear whether IONPs themselves can actually be used as a drug to treat diseases. Xiong *et al.,* 2, 3-dimercaptosuccinic acid-modified Fe_2O_3 NPs (Fe_2O_3@DMSA NPs) in a range of small sizes exhibit a cardioprotective activity *in-vitro* and *in-vivo*. They also compared the activity with those of Verapamil (calcium channel blockers) and *Salvia miltiorrhiza* extract (antioxidant), that have been extensively used as cardioprotective drugs in the treatment of angina pectoris, coronary artery heart disease, and so on24. The study suggests that these NPs have a clinically potential to treat cardiovascular diseases.

Anti-asthmatic: T helper type 2 (Th2) cytokines, such as interleukin (IL)-4, IL-5, and IL-13, are the chief therapeutic targets in the development of anti-asthmatic drugs. It is found recently that bavachinin, a very small molecule present in *Psoralea corylifolia*, has very efficient therapeutic function in asthma treatment in a murine model via the selective inhibition of Th2 cytokine production. However, its clinical potential of bavachinin is limited because of its extremely low water solubility, which is less than 30 ng/ml. Therefore, a nanoparticle delivery system was fabricated for the oral administration of bavachinin to treat asthma, with the aim of solving problems of its administration [25]. Wang *et al.,* prepared bavachinin-loaded PEG_{5000}-PLGA Nanoparticles using an emulsion-solvent evaporation technique, and also characterized their physical properties. These Nanoparticles exhibited strong enrichment capability towards inflamed lung tissues. These Nanoparticles showed very good anti-asthma therapeutic effects in the murine asthma model when administered orally. It was demonstrated by histological analysis of lung sections, enzyme-linked immunosorbent assay (ELISA) analysis of Th2 cytokine expressions, and fluorescence-activated cell sorting (FACS) analysis of Th1/Th2 cell differentiation. These nanoparticlescan be potentially used for the oral delivery of bavachinin to treat asthma and also for oral delivery of other drugs that have limited pharmacokinetic efficacy.

Antiepileptic: Glioblastoma is the most common and aggressive type of brain tumor. The Blood-

Brain Barrier presents physical and biological limitations for the diffusion of drugs to reach target tissues. Nejat *et al.*, prepared and characterized cardamom extract loaded gelatin nanoparticles (CE-loaded GNPs) as a potent delivery system for the treatment of glioblastoma. Polymeric nanoparticles, like gelatin, are suitable vehicles for drug delivery into the central nervous system (CNS). They are able to cross the BBB. CE-loaded GNPs were prepared by a two-step desolvation method. Seizures are detrimental secondary effects of brain tumors [26]. Therefore, cardamom extract was used because it is a herbal anticancer and antiepileptic drug without any side effects, as compared to synthetic drugs for loading in gelatin nanoparticles. For comparison of size, both gelatin Type A and Type B nanoparticles were used. Encapsulation efficiency, mean particle size, zeta potential, and *in-vitro* release profile were performed, and particle size analysis, dynamic light scattering (DLS), UV–Vis spectrophotometry, differential scanning calorimetry (DSC), X-Ray diffraction (XRD), scanning electron microscopy (SEM) and field emission scanning electron microscopy (FE-SEM) were utilized to evaluate structural and physicochemical properties of the samples.

CE-loaded GNPs were obtained with diameters of 40–200 nm, zeta potential of − 40.1 mV and entrapment efficiency (EE) of 70%. The ratio of extract to polymer, 1:20, was found to be more suitable in obtaining smaller nanoparticles without any precipitate or aggregation. Cytotoxic effects of CE and CE-loaded GNPs on human glio-blastoma cancer U87MG cells were also studied.

Antiepileptic drugs used these days are synthetic molecules, which have numerous associated side effects, and 30% of the patient remains with the seizure in this therapy. Several natural plant products, such as quinone derivatives that are considered safe and have effective anticonvulsant activity, are available. Embelin, a benzoquonone derivative, has been reported for its anticonvulsant activity Embelin shows its anticonvulsant effect by decreasing dopaminergic level and increasing GABAnergic transmission. Sharma et al. enquired about the potential use of embelin-loaded nano lipid carriers for brain targeting [27]. The average particle size and polydispersity index (PDI) of optimized formulation (F19) were found to be 152 ± 19.7 nm and 0.143 ± 0.023, respectively. Nanolipid carrier (NLC) also significantly reduced levels of pentylenetetrazole (PTZ)-induced biochemical parameters in comparison to plain embelin that, on the other hand, results in an increase in the level of malondialdehyde (MDA), nitrite, and reduction in the level of glutathione. From the above study, it can be concluded that embelin-NLCs developed as a beneficial carrier to achieve sustained release and brain targeting through the nasal route.

Antifungal: Rajiv *et al.*, synthesized zinc oxide nanoparticles from *Parthenium hysterophorus* L. by an inexpensive, eco-friendly, and simple method [28]. Different concentrations of 50% and 25% parthenium leaf extracts were used to prepare zinc oxide nanoparticles. The nanoparticles were found to be highly stable, spherical, and hexagonal in shape. These concentrations of the leaf extract acted as both reducing and capping agents for the conversion of nanoparticles.

Various techniques like UV-Vis absorption spectroscopy, X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) analysis with energy dispersive X-ray analysis (EDX) confirmed the formation of nano-particles. SEM, TEM, and EDX analysis showed that spherical and hexagonal zinc oxide nano-particle sizes were 27±5 nm and 84±2 nm, respectively and also confirmed their chemical composition.

These zinc oxide nanoparticles of different sizes exhibited the size-dependent antifungal activity against plant fungal pathogens. Zinc oxide nanoparticles in a concentration of 25 µg/ml and size of 27±5 nm showed the highest zone of inhibition against *Aspergillus flavus* and *Aspergillus niger*. Parthenium mediated zinc oxide was found to be environment friendly and proved to be good antifungal agents.

CONCLUSION: This exhaustive study shows that nanotechnology, when applied on phytochemicals to evolve phytopharmaceuticals, can be employed for effective management and treatment of a variety of diseases. Diseases like mental disorders,

epilepsy, cancer, hepatotoxicity, inflammation, asthma, diabetes, heart diseases, microbial and fungal infections *etc*. can be successfully and efficiently treated using nano phytopharmaceuticals with reduced toxicities, enhanced tissue penetration ability and increased safety and patient compliance. These nano phytopharmaceuticals needed to be explored a lot in other rare and drug-resistant pathological conditions.

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