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Application of Herbal extract and its medicinal value

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ABSTRACT

Herbal medicines have been broadly consumed since ancient times and the clinically proven by some researches regarding their advantageous have been realized by patients for their better therapeutic values with less toxic and adverse effects compared to contemporary or synthetic medicines. The active components inside the herbs are highly water soluble, but low absorption due to hardness to cross lipid membrane, huge molecular size, thus resulting into low bioavailability and efficacy. Phytotherapeutics need high scientific approach to deliver the active constituents in a sustained manner to achieve patients' compliance and cure diseases more safe and efficiently. Combining herbal medicine with nanotechnology is the best approach due to the nanostructuted system might be able to increase efficacy of plant extracts, reducing dose, toxicity, and side effects. Herbal drugs encapsulated with nanocarriers might be used at a sufficient concentration during the whole treatment process, and directing into the target site to give effective therapeutic effects. Thus, the aim of this study is to review nanocarriers used in herbal drugs delivery system.

Keywords: Herbs; therapeutics; medicinal values; Nanotechnology

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INTRODUCTION

The application of plants as herbal medicine has been used by various populations throughout human evolution, whereas people started to learn in selecting plants for food, to cure and prevent ailments and diseases. Allopathic medicines are currently used as replacement of traditional medicines, especially in Western developed countries. However, developing countries consume more in traditional medicines due to the increment price of synthetic medicines [1-6]. Quinine, digitalis, opium, and aspirin extracted from plants have long history to be used as herbal remedies, and have been developed by various pharmaceutical industries [7]. According to World Health Organization, about 80% of residents in Asian and African countries consume herbal medicine as their daily dietary supplements[8]. Unfortunately, the therapeutic use of natural resources which mainly consumed by whom cannot afford different treatment has greatly diminished due to the aspects of economic, political and social changes.

Several researches are struggling in developing innovative herbal based products with fewer side effects than existing products since medicinal plants chemical composition has become research focus among scientific communities. Plus, the uniqueness of plants' structure, biological and phytochemical properties, has impressed scientists [1]. Scientists from all places studied biological activity of herbal medicine which based on the different

application of different species and scientific use of medicinal plant. Besides, the research also concentrate on how far herbal medicine able to give benefits into pharmaceutical industries. In between 1981 to 2006, there are approximately 50% of drugs derived from natural plant are approved [9] .

Other than that, biological active inside each medicinal plants are established by phytochemical and phytopharmacological sciences where among the biological active constituents are consist of tannins, flavonoids, and terpenoids. These active constituents are highly water soluble, but low absorption due to hardness to cross lipid membrane, huge molecular size, thus resulting into low bioavailability and efficacy [1]. Therefore, vehicles are needed to be encapsulated with herbal drugs so as to improve drugs solubility, reducing degradation process, minimize toxicity, and level up drugs active absorption resulting into high bioavailability of herbal medicine.

Nanotechnology is a technology approached as herbal drugs delivery system which not only able to level up herbs' bioavailability and effectiveness, but also reintroduce other components that were discarded due to poor characteristics [1]. Plus, incorporation of herbs' drugs with nanoparticles possess to formulated in low drug dosage, low toxicity, and increase patience compliance [10,11].Polymeric nanoparticles, solid lipid nanoparticles (SLN), liposomes, liquid crystal system (LC), microemulsion, and nanoemulsion are the family of nanotechnological strategies, nanocarriers with extremely small size able to allow drugs easily targeted into cells and tissues so as to capable of circulating drugs in blood stream [1,12]. Besides, they also allow different characteristic substances to be mixed in one formulation, and even able to change substance's properties when react with biological environment. In addition, pharmacological activity, stability, sustained delivery, and protection of herbal drugs with physical and chemical degradation can be enhanced and improved by encapsulating herbal medicine with these nanocarries. Hence, nanocarrier integration in novel drug delivery system (NDDS) in herbal remedies is important and essential in order to cure efficiently, various ailments and diseases like cancer, diabetes, asthma, arthritis and others [12].

History of Applying Nanotechnology to Plant Extracts

Nanotechnology has been widely used in pharmaceutical industry. The used of nanotechnology application has been reported as success drug delivery system for various herbal drug or plant extract[13]. Drug delivery system like nanostructured materials can enhance the stability, absorption, and therapeutic concentration of the drug within the target tissue which is very effective to long-term release of the drug at the target site [14]. Therefore, the active compound in the plant extract can be transferred effectively to the target site and also increased the efficacy.

There are some previous studies that used nanotechnology to optimize the properties of plant extracts. Chen *et al*. had been using solid lipid nanoparticles drug carrier for epidermal targeting of podophyllotoxin and the observed results had showed a good epidermal targeting effect. Solid lipid nanoparticles are a suitable carrier for topical delivery of podophyllotoxin[15]. Rajendran *et al.* used the methanol extract of *Ocimum sanctum* loaded nanoparticles on cotton fabrics to study about the antimicrobial activity and the results showed an excellent antimicrobial activity with good wash durability. The herbs encapsulated nanoparticle also can act as biocontrol agent against bacteria in fabrics [16]. Aimee *et al*. developed curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent. Nanoparticle encapsulation had overcome the curcumin's poor aqueous solubility and rapid degradation profile hinder usage by extended topical delivery of curcumin[17].

Therefore, the effectiveness of the medicinal plant is controlled by the active compound in the plant. The drug delivery system such as nanotechnology is needed to deliver the active constituent more effectively to the targeted area.

Recent Advances in Nano Carriers as Herbal Drugs Delivery

Polymeric Nanoparticles

Polymeric nanoparticle is one of nanotechnological processes, used to incorporate with herbal drugs have gained the focus of researches and developed various innovative delivery system [1]. Besides, these nanoparticles also broadly applied in nanoencapsulation of various types of bioactive molecules and synthetic drugs. Biodegradable polymeric nanoparticles are the most suitable polymer to be used in drug delivery system since they show promise in enhancing poor water soluble drugs' efficacy. Apart from this, these nanocarrier are nontoxic, noninflammatory, nonimmunogenic, and achieve high stability in blood [18]. Other than that, polymeric nanoparticles are colloidal system which acts as drugs' reservoir to control the drug release, so that drugs are able to be efficiently delivered into target and specific locations. They're able to increase the bioavailability of active constituents at low therapeutic dosage, and enhance absorption of active compounds. Furthermore, when drugs delivered to target site and loaded

by these nanoparticles, the drugs will able to stay longer and stable in blood circulation without any serious adverse effect since polymeric nanoparticles are non-toxic, nonimmunogenic, noninflammatory, inactivate neutrophils and avoiding reticuloendothelial system[1,18].

Nanocapsules (NCs) and nanospheres (NSs) are two different structures of polymeric nanoparticles while protecting the drugs. They also appear in different composition and structural organization. The core of the micelles in nanocapsules structure is oil-based core which surrounded with polymeric membrane. Active components may adsorb to the polymeric membrane or dissolved in oily core. Besides for nanospheres, they're made from polymeric structure, where active components are retained or adsorbed [15,16]. Numbers of herbal drugs are being encapsulated with polymeric nanoparticles whether to enhance their solubility or as alternative to replace synthetic chemotherapeutic agents. Some of chemotherapy drugs are low in bioavailability and efficacy which might due to significant difficulties such as incapability to deliver components into targeted sites, and needed to consumed with inappropriate doses. Presently, several natural antitumor therapeutics from plants extract have been formulated in polymeric nanoparticle formulations, and examined in preclinical and clinical studies. These nanocarriers able to solve problems in anticancer field by reducing toxicity, due to protective of active constituents from interaction with healthy cell [1, 19-21].

Application of polymeric nanoparticle in enhancing efficacy of herbal drugs as anticancer agent has been evaluated by several researches. Curcumin has been proved in potential to be functioned as antitumor agent, in several studies involving human tumor cells and animal models of carcinogenesis. In studies by Mukerjee's research team, Poly(lactic-co-glycolic acid) (PLGA) was used as carrier for curcumin by using solid/oil/water emulsion technique, and was examined to study the ability of curcumin's activity against prostate cancer. According to the results, the encapsulation efficiency of curcumin with PLGA nanosphere was found to be 90.88±0.14%, while the particle size average for the nanospheres was 45 nm. Various types of prostate cancer cells, LNCaP, PC3, and DU145, was used to evaluate the efficacy of curcumin-loaded PLGA nanospheres in arresting cell growth. The result from the MTT cell viability assay found IC50 of curcuminnanospheres reduced to 20 – 22.5µM, while the range of free curcumin was 32 - 34µM. Thus, it can be seen that the curcumin-PLGA nanosphere able to arrest cell growth by 35% reduction [22].

Honokiol (HK), a Chinese medicinal plants with potential to treat cancer and several activities like antirheumatic, anti-inflammatory, antioxidant, and anxiolytic have been incorporated with polymeric nanoparticles, monomethoxy poly(ethylene glycol)-poly(lactic acid) (MPEG-PLA) so as to improve hydrophobic characteristic of the herb. The formulation of HN-loaded- MPEG-PLA nanoparticles was conducted, by using solvent extract method to evaluate nanoparticles anticancer activity. Based on the result, free honokiol and honokiol-loaded-polymeric nanoparticles significantly decreased the cancer activity of A2780 cells (human ovary cancer cells) as the concentration of the herb was increase. Plus, cytotoxicity of HK loaded MPEG-PLA was comparable with free HK at IC50 was 8.45µg/mL. Thus, the result indicates that HK loaded with polymeric nanoparticles able to inhibit activity of cisplatin-sensitive (A2780s) human ovarian cancer cells [23].

Other than that, the studies of medicinal plant-loaded-polymeric nanoparticles not only limited for anticancer activity, but they also available to apply on the types of herbs with different activities. Quercetin is a natural flavonoid which can find in fruits, vegetables, and certain herbs like *GinkoBiloba*. This herb has pharmacological properties, such as anti-inflammatory, antiviral, antitumor, antioxidant, and hepatoprotective effects. Wu and his team made formulation of quercetin (QU) loaded with nanoparticles, poly vinyl alcohol (PVA) and Eudragit E (EE) named (QUEN), by using nanoprecipitation technique. Antioxidant activities assay results were shown QUEN found to be more effective than QU in analyses of di(phenyl)-(2,4,6-trinitrophenyl)iminoazanium (DPPH) scavenging, superoxide anion scavenging, anti-superoxide formation, and anti-lipid peroxidation activities [24].

Rajendran et al. evaluated antimicrobial of medicinal plant, Ocimum sanctum (OS) which extracted by petroleum ether, methanolic, and aqueous extraction. The minimum inhibitory concentration (MIC) against bacteria like *B.subtilis, E.coli, S.aureus, P.aeruginosa, and Penicillium*was determined by using agar diffusion and microdilution method. Methanolic extract found to be the best result of OS antimicrobial activity. Then, the OS extracted from methanolic extract was formulated with sodium alginate chitosan nanoparticles (OSN), through cation induced, controlled gelation method. The particles were deposited on cotton fabric, using pad dry cure method. Based on the result, OSN shown better and longer antimicrobial activity than the free OS, producingcotton fabrics with excellent

antimicrobial activity [25]. Table 1 below shows another herbs being encapsulated with various polymeric nanoparticles aimed to enhance herbs solubility, bioavailability, and efficacy.

Table 1 Polymeric Nanoparticles Herbal Formulation

Herbal Medicine	Pharmacological Activity	Polymer Nanoparticle Used	References
Camptothecin	Treatment of gastric rectum bladder, colon lung breast, and ovarian cancer	Hydrophobically modified glycol chitosan (HGC)	[26]
Harunganamadagascariensis Lam. Ex Poir	Antibacterial, antifungal, and antiviral	Poly(D,L-lactide-co-glycolide)	[27]
Catechins	Antiviral, antioxidative, anticarcinogenic, anti-inflammatory, antibacterial	Chitosan nanoparticles	[28]

Liposomes

Liposomes are one of nanocarrier family, functioned as drug delivery systems which have been developed since 40 years ago [11]. It contains composed of one or more phospholipids which are molecules with head and tail group. In aqueous medium, the lipids are separated whereas the hydrophilic drugs are encapsulated in aqueous compartment, while the membranes are incorporated with hydrophobic substances. Size, number of lamellae, and surface charge are three factors involve to characterize liposomes. As to surface charge, liposomes can be classifies into anionic, cationic, and neutral. Regarding to their size, and number of lamellae, they can be classified as oligo-, uni-, or multilamellar, and small, large or giant [1]. Liposomes in unilamellar pattern only contain of single bilayer and consist of various size ranges which are small unilamellar (25-100)nm, large unilamellar (100nm - 1µm), and giant unilamellar with diameters more than 1µm. Other than that, multilamellar liposomes contain several concentric lamellae which usually found in more concentrated system.

Bioavailability and solubility of herbal drugs can be enhanced by incorporating with liposomes since these nanocarrier are biocompatible and biodegradable which suitable to be used as herbal drug delivery. Plus, they are also able to improve therapeutic efficacy, and sustained herbal drug release [29]. Applications of liposomes as herbal drug delivery have been widely cited by several literatures due to some advantageous of these nanoparticles. Silymarin, a herb extract from seeds of Silybummarianum (Compositae) has been encapsulated with liposomes for buccal administration. This is due to low oral bioavailability and poor absorption of this herb in gastrointestinal tract. Silymarin loaded with liposomes were prepared using reverse evaporation technique in the composed of lecithin (LC), cholesterol (Ch), sterylamine (AS), and Tween 20 (T20) with molar ratio of 9:1:1:0.5. The male albino rats received 0.25 mL of carbon tetrachloride in liquid paraffin, to induce liver damage. Serum glutamic oxaloacetate transaminase and serum glutamic pyruvate transaminase are the biochemical parameters for measurement of hepatoprotective degree of Silymarin. As the result, there was significant reduced in both transaminase level, which prove that hybridization of silymarin with liposomes able to cure liver damage in buccal administration [29].

A study from Sinico's research team investigated the efficacy of Artemisia arborescence L. essential oil loaded with liposomes in treating Herpes simplex virus, a common viral diseases which not being able to be treated by other synthetic drugs due to toxicity effect towards patients. The liposomes used from the experiment were positively charged multilamellar vesicles (MLVs) and small unilamelar liposomes (SUVs), prepared using sonication film method and obtained by soy phosphatidylcholine hydrogenated and non-hydrogenated processes. The research examined antiviral activity of free A. arborescence and liposomal of the herb against HSV-1 virus. Encapsulation efficiency of MLVs and SUVs with the essential oil was 60% and 74% respectively, showed good capabilities of the liposomes to entrap the herb's oil. Plus, within the incorporation of MLVs with the essential oil, there was significant increment in the level of antiviral activity of A. arborescence compared with the free oil [30]. Besides these two herbs experienced in encapsulating with liposomes, there are various types of other herbs being loaded with these nanoparticles. The herbs lists is shown in table 2 below:

Table 2. Liposomes Herbal Formulations

Herbal Medicine	Pharmacological Activity	Liposomes Used	References
Cratylliamollis	Antitumor activity	Soybean-phosphatidylcholine, cholesterol, and stearylamine	[31]
Quercetin	Anxiolytic and cognitive activity	Egg phosphatidylcholine and cholestrol	[32]
Erigeron breviscapus	Protecting brain damage	Multivesicular liposomes	[33]

Microemulsion

Hoar and Schulman, the guys who introduced microemulsion (MEs) term in 1943, claimed these nanocarriers as fluid system obtained by titration which contained composed of a simple emulsion with medium chain alcohol like hexanol or pentanol, initially appear as semi transparent, and titrated until clear. MEs considered as good alternative to enhance solubility of poorly water soluble for oral administration drug.

Microemulsions solution appear as transparent, which the oil phase dispersed in aqueous medium (oil/water emulsion) or water phase dispersed in oil medium (water/oil emulsion). Besides, surfactants with or without cosurfactants are compulsory to be considered since they're needed as emulsifier to stabilize dispersed phase of the solution [1]. These nanocarriers functioned to deliver herbal drugs into target site by solubilized the oil or aqueous phase with active components. The droplet sizes of these nanoparticles are in submicron range, and as a modern drug carrier, they are defined as single optically isotropic and thermodynamically stable. Besides improve solubility of poor water soluble drugs, microemulsions also capable to enhance drugs bioavailability, drugs protection against biological environment, ease of manufacturing, and longer shelf life [34].

Pharmaceutical researches have been evaluated the efficacy of microemulsions as nanocarrier for many types of plants extracted. A previous study about triplotide (TP), a purified compound from traditional Chinese herbal medicine has been encapsulated with microemulsions so as to enhance the herbs' anti-inflammatory activity and in vitro drugs permeation. The formulation was prepared from water (aqeous phase), isopropyl myristate TP (oil phase), Tween 80, and 1,2-propylene glycol as surfactant and co-surfactant respectively. In vitro drugs permeation result showed highest permeation profile for formulation contained 0.025% TP, 40% isopropyl myristate TP, and 50% Tween 80:1,2-propylene glycol (5:1v/v). Plus, encapsulation of triplotide with microemulsion also suppresses the carrageenan-induced rat paw edema and showed the highest anti-inflammatory effects [35].

Ampelopsin, one of the ordinary flavonoid, reported to give various pharmacological activities like antioxidation, anti-inflammatory, relieving cough, antimicrobial activity, antihypertension activity and hepatoprotective effect [36]. Poor water solubility characteristic of this drug possess several researches to formulate ampelopsinmicroemulsions in order to study the formulation's efficacy towards enhancement of ampelopsin in orally drug administration. The formulation named Capmul MCM-based ME contained Cremophor EL and Transcutol as surfactant and co-surfactant respectively. The formulations was optimized based on the results of their transparency, viscosity, and etc. Optimized formulation was contain ampelopsin, Capmul MCM (5.5%), Transcutol P (8.5%), Cremophor EL (25%), and distilled water resulted the highest in vitro drug release, which proved the potential use of microemulsion as ampelopsinnanocarrier in enhancing bioavailability and solubility of the herb. Numbers of other plants are being encapsulated with microemulsions and the lists of the herbs are as listed in table 3 below:

Microemulsions Herbal Formulations

Herbal Medicine	Pharmacological Activity	Microemulsion Components Used	References
Curcumin	Antitumor, antioxidant activity.	Phospholipids-based microemulsions	[37]

Solid Lipid Nanoparticles

Solid lipid nanoparticles are ranged in size between 50 – 1000 nm which made from lipids and remain as solid state in a room and body temperature. These nanocarriers are colloidal carrier, as the alternative for emulsion, liposomes, and polymeric nanoparticles in drug delivery system. They are new invention of lipid emulsion where the liquid lipid (oil) has been replaced by solid lipid. These nanoparticles may use in pharmaceutical industries for several administration like parenteral, oral, and percutaneous due to their small range and biocompatibility. Besides, solid lipid nanoparticles also offer the other advantageous such as large surface area, and high drug loading which able to improve the efficacy of pharmaceuticals, neutraceuticals and other components [38].

A research about encapsulation of Quercetin (QU) with lipid carriers has been conducted by Li research team. Quercetin is a natural flavonoid with poorly soluble characteristic was being incorporated with SLNs using emulsification-solidification method at low temperature. The SLNs used were glycerylmonostearate and soy lecithin and at the result of in vitro analysis, quercetin-loaded solid lipid nanoparticles exhibited controlled release. Elsewhere in the in vivo experiment, QU-SLN bioavailability resulted to be more than five times greater and enhanced absorption in intestine compared to free quercetin[39].

Other than that, oral bioavailability of curcumin is being enhanced by incorporating it into SLNs composed of soy lecithin. Microemulsification was applied in order to prepare this nanocerrier formulation. The study was evaluated the encapsulation stability of curcumin-loaded SLNs, and in vitro drug release analysis. The result showed only 9% incorporation efficiency of SLNs loaded curcumin decreased after being stored in $5^0C\pm3^0C$ for 12 month, indicating the formulation was stable. Besides, the formulation also indicates to be exhibited prolonged drug release in vitro.
Elsewhere, triplotide (TP) was encapsulated with SLNs which consist of tristearingluyceride and stearic acid, aimed to improve TP solubility and increase the rate of TP absorption into skin. Studies have shown that triplotide extracted from vine are effective in curing certain diseases, including inflammatory diseases like rheumathoid arthritis. The result shown that anti-inflammatory activity of TP was increased after being incorporated with SLNs due to the easiness of TP to be penetrated onto skin [35]. Other than that, another plants extracted formulated with solid lipid nanoparticles are listed as table 4 below:

Table 4 Solid Lipid Nanoparticles Herbal Formulations

Herbal Medicine	Pharmacological Activity	SLNs Used	References
Camptothecin	Treatment of gastric rectum bladder, colon lung breast, and ovarian cancer	CetylPalmitate	[40]
Podophyllotoxin	Antivirus for warts treatment through topical application, and antivirus actyivity	Soy Lecithin	[41]

FUTURE PROSPECTIVE AN CONCLUSION

Nanocarriers drug delivery system for herbal medicines are proved to have potential in enhancing biological activity and overcome problems associated with plants medicine. However, toxicity effects may happen to consumer due to the small size of the nanomaterials could be interacts with other materials which could lead to toxicity. A better delivery system is needed to deliver the drugs properly to the target sites in the whole body at correct dosage which will not same technique with existing treatment (improve a bit with the system). Patients will fully satisfy if they consume medicines without any side effects like toxicity and hypersensitive reactions.

Thus, the application of nanocarrier in herbal remedies may give bright future of nanotechnology involved in the treatment of more chronic diseases and wellness benefits. The nanocarriers application is not limited for diseases treatment, but they're also relevance to be used in food technology since various study have been proved the efficacy of nanocarrier in holding some constituents used in food like curcumin against cytotoxic effect.

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