



Novel Drug Delivery System for Herbal Formulations: Overview

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ABSTRACT

The different novel herbal formulations such as liposomes, phytosomes, pharmacosomes, nanoparticles, microspheres, transfersomes, ethosomes, transdermal drug delivery system (TDDS), and proniosomes has been reported using proactive and plant selections. The novel herbal formulations have advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, and low toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue distribution, sustained delivery, and protection from physical and chemical degradation. Phytosome is a patented technology developed and to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes. The herbal drugs can be used to enhance efficacy by incorporating them into modern dosage forms. This can be skilled by designing novel drug delivery systems for herbal ingredients. This review highlights the current condition of the development of novel herbal formulations and summarizes their type of active components, biological activity, and applications of novel formulations.

Keywords: Herbal formulations, novel drug delivery system, solubility, bioavailability.

INTRODUCTION

In the past few decades, considerable attention has been concentrated on the development of a novel drug delivery system (NDDS) for herbal drugs. Ayurveda is ancient science of Indian system of medicine. Traditional formulations contain plant material as its core ingredient. In Ayurveda Swarasa (Juice), Kalka (Paste), Kwath (Decoction), Sheeta kashyay, Phanta is considered as drug delivery devices. All of them had very low shelf life hence the introductions of rolled pills, e.g. Gutika, Vatika, Fermented syrups e.g. Asasva and Arishtas, Medicated oil e.g. Siddha tailas, Koopipakva rasayana comes in place. As it exhibits better preservation quality and enhance therapeutic effect. But all of them has their own restriction. Where all constituent may or may not be come in formulation as some of them is water soluble or lipid soluble in nature.¹

Herbal drug had many active constituents; as all of them provide pharmacological action and enhance the therapeutic value. Constituents like Alkaloids, Glycoside, Flavanoides, Tannins; Terpenoides when incorporate into novel techniques show enhance bio available activity and targeted action at low therapeutic dose. Traditional herbal formulations show efficacy but drug delivery device has lack of scientific justification, standardization, and identification of single chemical constituent in complex poly herbal formulation.

Disadvantage of current drug delivery system used in Ayurveda.²

- Bulk dosing
- Decrease bioavailability and decrease absorption

- Show poor effect or require high amount of dose to produce desire effect.
- High amount of raw material require processing the medicine.
- Loss 'N' number of extinct or rare species.
- Harmful effect on ecology which ultimately become cause of global warning.
- No target specificity in present formulation.

Advantage of novel drug delivery system.³

- Help to increase the efficacy and reduce the side effect of various herbal compounds.
- Quantity of component becomes less with improving quality of drug effect.
- Fewer raw material are required to achieve the desire effect and control drug delivery to provide exact specification regarding drug dose form.
- Ready to use devices are acceptable in today's fast life style where time is important.
- Carry maximum amount of drug to the site of action by passing all barriers. Such as acidic pH of stomach increase prolong circulation of drug into blood due to their small particle size.
- Reduce repeat dose administration. The main aim for adaptation of novel drug delivery devices in herbal formulations are to develop better system for proper drug delivery in terms of Target oriented.



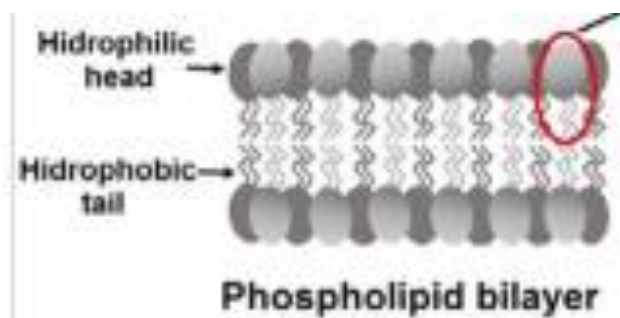
- Sustain and Controlled release of drug at the site which help to increase the efficacy and reduces side effects at the site of formulation.
- This administration not only reduces repeat administration but also helps to increase the therapeutic value by reducing toxicity and increase the bioavailability.

Types of Novel Herbal Drug Delivery Systems

In case of new herbal drug delivery system include different types such as liposomes, phytosomes, pharmacosomes, nanoparticles, microspheres, transfersomes, ethosomes, transdermal drug delivery system (TDDS), and proniosomes are discussed.

Liposome

Liposomes are spherical vesicles of a bilayer of phospholipids. These lipids are amphiphilic in nature because they have hydrophilic and hydrophobic part. Liposomes are useful in drug delivery system because they can encapsulate both hydrophilic and hydrophobic drugs. Liposomes have aqueous core which is enclosed by a bilayer of phospholipid. Liposomes provide controlled and prolonged release of the drug in the treatment of pain and liposomes are having increased therapeutic efficacy and increase the penetration of the drug through the skin. In the field of dentistry, liposomes are gaining popularity for anesthetics for increasing the bioavailability that will increase the pharmacological action and for decreasing the adverse effect and toxicity of the drug. Opioids show serious systemic side effects to decrease these side effects liposomes are alternative drug delivery system. Sometimes liposomes are also used for targeting the drug by using specific ligands which have good binding affinity towards the targeted site.⁴



Liposome-based drug delivery systems offer the potential to raise the therapeutic index of anticancer agents, by increasing the drug concentration in tumor cells or by lessening the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon or by utilizing targeting strategies. The primary advantages of using liposomes include (i) the high biocompatibility, (ii) the easiness of preparation, (iii) the chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds, and (iv) the simple modulation of their pharmacokinetic properties by varying the chemical composition of the player components. Few examples of

herbal formulations in liposomal drug delivery systems were given in Table 1.⁵

Table 1: Herbal formulations in liposomal drug delivery systems

Plants/constituents	Therapeutic category	Reference
Garlicin	Lungs	6
Wogonin	Anticancer	7
Curcumin	Anticancer	8
Paclitaxel Liposome	Anticancer	9
Usnic acid	Against Toxoplasma gondii pathogen, Antimycobacterial	10
Capsaicin	Analgesic	11
Ampelopsin	Anticancer	12

Nanoparticles

Nanoparticles are sub-nanosized colloidal structures composed of synthetic or natural polymers varying in size from 1-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles can be of nanospheres or nanocapsules. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.¹³

Herbal nanoparticles possesses many advantages^{14, 15, 16}

- Target the herbal medicine to individual organ which improves the selectivity, drug delivery, effectiveness and safety.
- To increase the herbal drug solubility.
- Nanoparticles can deliver high concentrations of drugs to disease sites because of their unique size and high loading capacities.
- Delivering the drug in small particle size enhances the entire surface area of the drugs therefore allocating quicker dissolution in the blood.
- Shows enhanced permeation and retention effect.
- Exhibits passive targeting to the disease site of action without the addition of any particular ligand moiety.

The examples of some herbal Nanoparticle drug delivery systems were given in Table 2.

Table 2: Herbal formulations in Nanoparticle drug delivery systems

Plants/ constituents	Therapeutic category	Reference
Triptolide nanoparticle	Hepatocellular carcinoma	17
Artemisinin nanocapsules	Anticancer	18
Taxel nanoparticle	Anticancer	19
Berberine nanoparticle	Anticancer	20
Curcuminoids solid lipid nanoparticle	Anticancer and Antioxidant	21
Naringenin nanoparticle	Hepatoprotective	22
Breviscapine nanoparticle	Cardiovascular and cerebrovascular	23
Glycyrrhizic acid nanoparticle	Anti-inflammatory, antihypertensive	24

Phytosomes

Phytosomes, also called phyto-phospholipid complexes, are the vesicular systems formed by the interaction between hydrophilic parts of phospholipids and the phyto-active components resulting in the formation of hydrogen bonds between them. The structural difference between liposomes and phytosomes is that liposomes have their active ingredient inside the hydrophilic cavity or within the layers of membranes while in phytosomes, those components are a part of the membrane itself.²⁵

Phytosomes have a higher capacity for nutraceutical compounds to be added to them, as they have a quite stable, chemically bound structure. Plant extracts can bind quite easily to phosphatidylcholines due to the presence of terpenoids and flavonoids.²⁶

The examples of some herbal Phytosomes drug delivery systems were given in Table 3.

Table 3: Herbal formulations in Phytosomes drug delivery systems

Plants/ constituents	Therapeutic category	Reference
Ginkgo biloba	Cardioprotective, antioxidant activity	27
Ginsenosides	Nutraceutical, immunomodulator	28
curcumin-phospholipid complex	protect the liver, Anticancer, antioxidant	29
Quercetin	Antioxidant, anticancer	27, 30
Silybin	Hepatoprotective, antioxidant for liver and skin	30, 31

Emulsions

Emulsions are heterogeneous systems composed of at least two immiscible liquids, water and oil, one of which is usually uniformly dispersed as fine droplets throughout the other liquid phase by a mechanical agitation process. Emulsions are considered as a type of liquid-liquid colloid. The phase existing as small droplets is called the dispersed phase and the surrounding liquid is known as the continuous phase. Emulsions are commonly classified as oil-in-water (O/W) or water-in-oil (W/O) depending on whether the continuous phase is water or oil.³²

Emulsion can be split up into ordinary emulsion (0.1–100 μ m), microemulsion (10–100 NM), sub-micro-emulsion (100–600 NM), etc. Among them, the microemulsion is also called nanoemulsions, and the sub-micro-emulsion is also called lipid emulsion. As a drug delivery system, emulsion gets distributed in vivo in the targeted areas due to its affinity towards lymphatic fluids. In addition, the drug can be a sustained release in a long time because the drug is packaged in the inner phase and kept off direct touch with the body and tissue fluid. The size of the emulsion particle has an impact on its target distribution. Aside from its targeted sustained release, producing the herbal drug into emulsion will also beef up the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs' stimulus to the tissues. So far, some kinds of herbal drugs, such as camptothecin, *Brucea javanica* oil, coixenolide oil, and zedoary oil, have been made into emulsion.⁵

The examples of some herbal Emulsions drug delivery systems were given in Table 4.

Table 4: Herbal formulations in Emulsions drug delivery systems

Plants/ constituents	Therapeutic category	Reference
St John's wort extract, marigold extract, wheat germ oil, rose oil	anti-inflammatory, antimicrobial and wound healing properties	33
Docetaxel submicron Emulsion	Anticancer	34
Berberine nanoemulsion	Anticancer	35
Silybin nanoemulsion	Hepatoprotective	36
Quercetin	microemulsion Antioxidant	37

Pharmacosomes

Pharmacosome may be defined as a neutral molecule possessing both positive and negative charge, water-loving and fat-loving properties, and an optimum ratio of

polyphenol with phospholipids in a complex form. The drugs are present in a dispersion form in these lipoidal drug delivery system conjugated by electron pair sharings and electrostatic forces or by forming a hydrogen bond with lipids. Pharmacosome is derived from the word “Pharmakon” which means drug and “soma” meaning carrier. It means a vesicular system in which the drug is associated with the carrier. These lipid conjugated vesicles may exist as colloidal, nanometric size micelles, vesicles or may be in the form of hexagonal assembly enjoying a functional hydrogen atom banking upon the architecture of the complex. The drug molecule with a free carboxylic or functional hydrogen atom like amino, hydroxyl groups, is converted to an ester with the help of the hydroxyl moiety of the lipid, resulting in the formation of a prodrug. A spacer chain may or may not be used for this purpose. The prodrug possesses both hydrophilic and lipophilic properties. Despite these properties, prodrugs have the capability to reduce interfacial tension, increase the area of contact, and hence improve bioavailability. They aid the deportation through the cell membrane, cell wall, and tissues. If the concentration is increased beyond a level, it may exist in an intermediate state between liquid and crystal. On contact with water, these prodrugs assemble into a single or multiple layers resulting in the formation of pharmacosomes. This system is developed by keeping the surface properties as well as the bulk properties of the drug-lipid conjugate in consideration.³⁸

Microspheres

Microspheres are small, spherical particles usually made up of biodegradable and biocompatible polymers having the size ranging from 1 to 1000 µm and incorporating drugs and other bioactive within their core.

Table 5: Herbal formulations in Microspheres drug delivery systems

Plants/ constituents	Therapeutic category	Reference
Chitosan-based plumbagin microspheres	anti-tumor efficacy	40
Rutin-alginate-chitosan microcapsules	Cardiovascular and Cerebrovascular diseases	41
Zedoary oil microsphere	Hepatoprotective	42
Camptothecin loaded microspheres	Anticancer	43

They offer numerous advantages including masking and protecting the encapsulated drugs from the harsh environment of the gastrointestinal tract, sustained and controlled drug release, improved stability, and bioavailability, site-specific targeting of the active therapeutic moieties, etc. The drugs encapsulated within

the microspheres can be targeted either by their localization to specific sites of the body (for, e.g., in lungs), to a group of cells (for, e.g., in melanoma cells), or to an intracellular region.³⁹

The examples of some herbal Microspheres drug delivery systems were given in Table 5.

Transfersomes

Transfersomes word is derived from the latin word ‘transferee’ which means ‘to carry across’ and the greek word ‘soma’ which is used for a body. The basic structure of transfersomes is like classic liposomes, still it has some differences from liposomes by soft nature, ultra- deformable properties, and better adjustable nature of system membrane. An important property of transfersomes is its ability to bind with skin moisture and retain water. Transfersomes contains high amount of hydrophilic molecules to avoid dehydration.

The mechanism of transfersomes penetration can be explain in steps as initial interaction between hydrophilic lipid residue and proximal water, from there the polar lipid attracts water molecules, which leads induced hydration, the vesicle moves toward the site of more water concentration. A trans-epidermal osmotic gradient develops, leads to penetration of transfersomes across skin.⁴⁴

The examples of some herbal Transfersomes drug delivery systems were given in Table 6.

Table 6: Herbal formulations in Transfersomes drug delivery systems

Plants/ constituents	Therapeutic category	Reference
Capsaicin transfersomes	Analgesic	45
Colchicine transfersomes	Antigout	46, 47
Vincristine transfersomes	Anticancer	48

Proniosomes

Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant.

Plants/ constituents	Therapeutic category	Reference
<i>Withania somnifera</i> leaf extract proniosomal gel	Anti-inflammatory activity	50
Proniosomal gel of neem seed oil.	Anti microbial activity	51
Guggul lipid-loaded Proniosomal gel	Anti-inflammatory activity	52
Curcumin proniosomal gel.	Anti-inflammatory and anti-arthritis activity	53

They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes. Proniosomes are physically stable during storage and transport. Drug encapsulated in vesicular structure of proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity. Proniosomes can entrap both hydrophilic and lipophilic drugs.⁴⁹

Transdermal drug delivery system [TDDS]

TDDS is a drug delivery system in which a device usually known as patch is adhered on the skin surface to deliver the drug into the systemic circulation through the skin at predefined concentration for therapeutic effects, which avoids additional limitations due to other dosage forms. It offers constant permeation of drugs through the skin giving constant serum drug level, the goal of therapy. It can be used as an alternate to oral drug delivery system for those patients, who find difficulty in taking drugs through oral route.⁵⁴

Plants/constituents	Therapeutic category
Capsaicin ⁵⁵ , aconitine ⁵⁶ , turpentine ⁵⁷ , strychnine ⁵⁸ , triptolide (TPL) ⁵⁹ , sinomenine ⁶⁰ , colchicine ⁶¹ , curcumin ⁶² , berberine ⁶³ , lycopene ⁶⁴ , glycyrrhetic acid ⁶⁵ , catechin ⁶⁶ , geniposide ⁶⁷ , resveratrol ⁶⁸ , andrographolide ⁶⁹ , paeonol ⁷⁰ , mangiferin ⁷¹	Analgesic and anti-inflammation
Bufalin ⁷² , podophyllotoxin ⁷³ , paclitaxel ⁷⁴ , ligustilide ⁷⁵	Antitumor
harmaline ⁷⁶ , baicalin ⁷⁷ , hesperidin ⁷⁸	Psoriasis and Antifungal
Ferulic acid ⁷⁹ , cinnamic acid ⁸⁰ , usnic acid ⁸¹ , menthol ⁸² , pomegranate ⁸³	Reduce UVB damage, Repair DNA injury, Anti-oxidative activity and skin whitening

CONCLUSION

Herbal medications have been widely employed all over the globe since ancient times and have been acknowledged by doctors and patients for their better therapeutic value as they cause fewer adverse effects as compared with modern medications. The drugs of Ayurvedic origin can be utilized in a more upright course with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to render the components in a new way to increase patient compliance and avoid repeated administration. This can be accomplished by designing NDDS for herbal ingredients. NDDS not only reduce the repeated administration to overcome noncompliance, but

also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability and so on. Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach. The novel research can also aid in capturing as well as to remain in the market. But there are many challenges with herbal drugs which need to be overcome like difficulty of conducting clinical research in herbal drugs, development of simple bioassays for biological standardization, pharmacological and toxicological evaluation methods' development, investigation of their sites of absorption, toxic herbal drugs in use, discovering various animal models for toxicity and safety evaluation, legal and regulatory aspects of herbal drugs and so on.

REFERENCES

1. Atram Seema, Recent Development of Herbal Formulation- A Novel Drug Delivery System, International Ayurvedic Medical Journal; November- December – 2014;2(6):25-31.
2. Kumar K, Rai AK, Miraculous therapeutic effect of herbal drug using novel drug delivering system, International Research journal of Pharmacy, 2012;3(2):27-30.
3. Kharat A, et al, Novel Drug Delivery System in herbal's, Intl. J. of pharmaceutical and biological science, 2014;4(4): 910-930.
4. Rahul Shukla et. al. Theory and Applications of Nonparenteral Nanomedicines CHAPTER 15, Nanomedicine in pain management, Elsevier Inc., 2021;15:355-381.
5. Manoj Kumar Sarangi et. al. Novel herbal drug delivery system: An overview. Arch Med Health Sci 2018;6:171-9.
6. Sun P, Den SH, Yu WP. Evaluation of garlicin liposomes. J Shan Univ TCM 2007;31:37-9.
7. Tian J, Wang L, Wang L, Ke X. A wogonin-loaded glycyrrhetic acid-modified liposome for hepatic targeting with anti-tumor effects. Drug Deliv. 2014 Nov;21(7):553-9.
8. Hong W, et. al. Preparation and study in vitro of long-circulating nanoliposomes of curcumin. Zhongguo Zhong Yao Za Zhi 2008;33:889-92.
9. Yang T, Cui FD, Choi MK, Lin H, Chung SJ, Shim CK, Kim DD. Liposome formulation of paclitaxel with enhanced solubility and stability. Drug Deliv. 2007 Jul;14(5):301-8.
10. Si K, Wei L, Yu X, Wu F, Li X, Li C, Cheng Y. Effects of (+)-usnic acid and (+)-usnic acid-liposome on Toxoplasma gondii. Exp Parasitol. 2016 Jul;166:68-74.
11. Manoel Jacobsen Teixeira et. al., Liposomal topical capsaicin in post-herpetic neuralgia: a safety pilot study, Arq Neuropsiquiatr 2015;73(3):237-240.
12. He ZF, Liu DY, Zeng S, Ye JT. [Study on preparation of ampelopsin liposomes]. Zhongguo Zhong Yao Za Zhi. 2008 Jan;33(1):27-30. Chinese. PMID: 18338614.
13. Arulanandraj N, Dhivya S, Gopal V; A review on Herbal Nanoparticles; PharmaTutor; 2018; 6(5):32-37.
14. Ansari SH, Farrha I, Sameem M: Influence of nanotechnology on herbal drugs: A Review. Journal of advanced pharmaceutical technology and research 2012; 3(3): 142.
15. Chidambaram M, Manavalan R, Kathiresan K: Nanotherapeutics to overcome conventional cancer chemotherapy limitations. Journal of pharmacy and pharmaceutical sciences 2012; 14: 67–77.
16. Sharma M: Applications of Nanotechnology Based Dosage Forms for Delivery of Herbal Drugs. Research and Reviews: Journal of pharmaceuticals and nanotechnology 2014; 2(1):52-59.



17. Zhang YQ, Shen Y, Liao MM, Mao X, Mi GJ, You C, Guo QY, Li WJ, Wang XY, Lin N, Webster TJ. Galactosylated chitosan triptolide nanoparticles for overcoming hepatocellular carcinoma: Enhanced therapeutic efficacy, low toxicity, and validated network regulatory mechanisms. *Nanomedicine*. 2019 Jan;15(1):86-97.
18. Youfang C, et.al. Study of artemisinin nanocapsules as anticancer drug delivery systems, *Nanomed Nanotechnol Biol Med* 2009;5:316-22.
19. Fu RQ, He FC, Meng DS, Chen L. Taxol PLA nanoparticles. *ACTA Acad Med Mil Tertiae* 2006;28:1573-4.
20. Lin AH, Li HY, Liu YM, Qiu XH. Characterisation of berberine nanoparticles. *Chin Pharm* 2007;18:755-7.
21. Mukerjee A, Vishwanatha JK. Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy. *Anticancer Res* 2009;29:3867-75.
22. Liu M, Li H, Luo G, Liu Q, Wang Y. Pharmacokinetics and biodistribution of surface modification polymeric nanoparticles. *Arch Pharm Res* 2008;31:547-54.
23. Feng LY, Tzu HW, Liang TL, Thau MC, Chun CL. Preparation and characterization of *Cuscuta chinensis* nanoparticles. *Pharm Res* 2009;26:893-902.
24. Hou J, Zhou SW. Formulation and preparation of glycyrrhizic acid solid lipid nanoparticles. *ACTA Acad Med Mil Tertiae* 2008; 30:1043-5.
25. Monjurul Hoque et. al. , 3.34 - Lipid Nanostructures in Food Applications, *Innovative Food Processing Technologies, A Comprehensive Review* 2021;18:565-579.
26. Ali Asghar et. al., Chapter 10 - Nutraceutical Formulation Strategies to Enhance the Bioavailability and Efficiency: An Overview, *Role of Materials Science in Food Bioengineering, Handbook of Food Bioengineering*, 2018;11:329-352.
27. Semalty A, Semalty M, Rawat MS. The phyto-phospholipid complexes- phytosomes: A potential therapeutic approach for herbal hepatoprotective drug delivery. *Pcog Rev* 2007;1:369-74.
28. Vandana SP, Suresh RN. Cardioprotective activity of Ginkgo biloba phytosomes in isoproterenol-induced myocardial necrosis in rats: A biochemical and histoarchitectural evaluation. *Exp Toxicol Pathol* 2008;60: 397-404.
29. Maiti et al.. Curcumin-phospholipid complex: Preparation, therapeutic evaluation and pharmacokinetic study in rats. *Int J Pharm*. 2007 Feb 7;330(1-2):155-63.
30. therapeutic benefit of quercetin-phospholipid complex in carbon tetrachloride-induced acute liver injury in rats: A comparative study. *J Pharm Pharmacol* 2006;58:1227-33.
31. Yanyu X, Yunmei S, Zhipeng C, Qineng P. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. *Int J Pharm* 2006;307:77-82.
32. Guang Wei Lu et.al., CHAPTER 3 - Emulsions and Microemulsions for Topical and Transdermal Drug Delivery, In *Personal Care & Cosmetic Technology, Handbook of Non-Invasive Drug Delivery Systems*, William Andrew Publishing, 2010;4:59-94.
33. Tuncay Tanrıverdi S, et. al., Preparation and characterization of herbal emulsion formulations. *Marmara Pharm J* 2017; 21(4):756-761.
34. Li L, Wang DK, Li LS, Jia J, Chang D, Ai L. Preparation of docetaxel submicron emulsion formation for intravenous administration. *J Shenyang Pharm Univ* 2007;12:736-9.35.
36. Sun HW, Ouyang WQ. Preparation, quality and safety evaluation of berberine nano emulsion for oral application. *J Shangh Jiaotong Univ (Agric Sci)* 2007;1:60-5.
37. Song YM, Ping QN, Wu ZH. Preparation of silybin nano emulsion and its pharmacokinetics in rabbits. *J Chin Pharm Univ* 2005;5:427-31.
38. Archana Pandita et. al., "Pharmacosomes: An Emerging Novel Vesicular Drug Delivery System for Poorly Soluble Synthetic and Herbal Drugs", *International Scholarly Research Notices*, 2013; Article ID 348186, 1- 10.
39. Hemant R. B., Chapter 13 - Phytoconstituent plumbagin: Chemical, biotechnological and pharmaceutical aspects, *Studies in Natural Products Chemistry*, Elsevier, 2019;63:415-460.
40. Sunil Kumar Mandala Rayabandla et. al. Preparation, in vitro characterization, pharmacokinetic, and pharmacodynamic evaluation of chitosan-based plumbagin microspheres in mice bearing B16F1 melanoma, *Drug Delivery*, 2010; 17(3): 103–113.
41. Xiao L, Zhang YH, Xu JC, Jin XH. Preparation of floating rutin-alginate-chitosan microcapsule. *Chin Trad Herb Drugs* 2008;2:209-12.
42. You J, Cui FD, Han X, Wang YS, Yang L, Yu YW, et al. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. *Colloids Surf B Biointerfaces* 2006;48:35-41.
43. Machida Y, Onishi H, Kurita A, Hata H, Morikawa A, Machida Y, et al. Pharmacokinetics of prolonged-release CPT-11-loaded microspheres in rats. *J Control Release* 2000;66:159-75.
44. Chauhan P. et. al. Herbal novel drug delivery systems and transfersomes , *Journal of Drug Delivery and Therapeutics*. 2018; 8(3):162 – 168.
45. Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Preparation and in vitro and in vivo evaluations of topically applied capsaicin transfersomes. *Zhongguo Zhong Yao Za Zhi* 2006;31:981-4.
46. Zheng Y, Hou SX, Chen T, Lu Y. Preparation and characterization of transfersomes of three drugs in vitro. *Zhongguo Zhong Yao Za Zhi* 2006;31:728-31.
47. Singh HP, Utreja P, Tiwary AK, Jain S. Elastic liposomal formulation for sustained delivery of colchicine: In vitro characterization and in vivo evaluation of anti-gout activity. *AAPS J* 2009;11:54-64.
48. Lu Y, Hou SX, Zhang LK, Li Y, He JY, Guo DD. [Transdermal and lymph targeting transfersomes of vincristine]. *Yao Xue Xue Bao*. 2007 Oct;42(10):1097-101. Chinese. PMID: 18229621.
49. akshmi Radhika K et.al., Proniosomal Gel A Novel Approach For Drug Delivery: A Review, *Indo American Journal of Pharmaceutical Research*.2017;7(03):18-25.
50. Joon M, Garg M. Formulation and evaluation of *Withania somnifera* leaf extract loaded transdermal gel for anti inflammatory activity. *Journal of Medical Sciences*. 2013; 13(8): 814-8.
51. Chandel A, Saroha K, Nanda S. Preparation and evaluation of Proniosomal gel of neem seed oil. *International Journal of Pharmaceutical sciences and Nanotechnology*. 2012; 5(3):40-46.
52. Goyal C, Ahuja M, Sharma SK. Preparation and evaluation of anti-inflammatory activity of gugul lipid loaded proniosomal gel. *Acta Poloniae Pharmaceutica-Drug Research*. 2011; 68(1): 147-50.
53. Kumar K, Rai AK. Development and valuation of proniosome encapsulated curcumin for transdermal administration. *Tropical Journal of Pharmaceutical Research* December. 2011; 10(6): 697-703.
54. Chetan Ghulaxe et. al. A review on transdermal drug delivery system, *The Pharma Innovation Journal* 2015; 4(1): 37-43.
55. Kim, C.-S.; Kawada, T.; Kim, B.-S.; Han, I.-S.; Choe, S.-Y.; Kurata, T.; Yu, R. Capsaicin exhibits anti-inflammatory property by inhibiting IκB-α degradation in LPS-stimulated peritoneal macrophages. *Cell. Signal*. 2003;15:299–306.
56. Chan, T.; Tomlinson, B.; Tse, L.; Chan, J.; Chan,W.; Critchley, J. Aconitine poisoning due to Chinese herbal medicines: A review. *Vet. Hum. Toxicol*. 1994;36:452–455.
57. Gülçin,İ.; Büyükkokuroğlu,M.E.; Oktay,M.; Küfrevioğlu,Ö.İ. Antioxidant and analgesic activities of turpentine of *Pinus nigra* Arn. subsp. *pallsiana* (Lamb.) Holmboe. *J. Ethnopharmacol*. 2003;86:51–58.



58. Saraswati, S.; Agarwal, S. Strychnine inhibits inflammatory angiogenesis in mice via down regulation of VEGF, TNF- α and TGF- β . *Microvasc. Res.* 2013;87:7–13.
59. Matta, R.; Wang, X.; Ge, H.; Ray, W.; Nelin, L.D.; Liu, Y. Triptolide induces anti-inflammatory cellular responses. *Am. J. Transl. Res.* 2009;1:267–71.
60. Wang, W.; Wang, P. Selective inhibitory effect of sinomenine on activity of cyclooxygenase 2. *J. Guangzhou Univ. Tradit. Chin. Med.* 2002;19:46–47.
61. Deftereos, S.; Giannopoulos, G.; Panagopoulou, V.; Bouras, G.; Raisakis, K.; Kossyvakis, C.; Karageorgiou, S.; Papadimitriou, C.; Vastaki, M.; Kaoukis, A. Anti-inflammatory treatment with colchicine in stable chronic heart failure: A prospective, randomized study. *JACC Heart Fail.* 2014;2:131–137.
62. Kunnumakara, A.B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N.K.; Prasad, S.; Aggarwal, B.B. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. *Br. J. Pharmacol.* 2017;174:1325–1348.
63. Kuo, C.-L.; Chi, C.-W.; Liu, T.-Y. The anti-inflammatory potential of berberine in vitro and in vivo. *Cancer Lett.* 2004;203:127–137.
64. Yaping, Z.; Wenli, Y.; Weile, H.; Ying, Y. Anti-inflammatory and anticoagulant activities of lycopene in mice. *Nutr. Res.* 2003;23:1591–1595.
65. Finney, R.; Somers, G. The anti-inflammatory activity of glycyrrhetic acid and derivatives. *J. Pharm. Pharmacol.* 1958;10:613–620.
66. El-Aziz, A.T.A.; Mohamed, R.H.; Pasha, H.F.; Abdel-Aziz, H.R. Catechin protects against oxidative stress and inflammatory-mediated cardiotoxicity in adriamycin-treated rats. *Clin. Exp. Med.* 2012;12:233–240.
67. Song, X.; Zhang, W.; Wang, T.; Jiang, H.; Zhang, Z.; Fu, Y.; Yang, Z.; Cao, Y.; Zhang, N. Geniposide plays an anti-inflammatory role via regulating TLR4 and downstream signaling pathways in lipopolysaccharide-induced mastitis in mice. *Inflammation* 2014;37:1588–1598.
68. Das, S.; Das, D.K. Anti-inflammatory responses of resveratrol. *Inflamm. Allergy-Drug Targets* 2007;6:168–173.
69. Abu-Ghefreh, A.A.A.; Canatan, H.; Ezeamuzie, C.I. In vitro and in vivo anti-inflammatory effects of andrographolide. *Int. Immunopharmacol.* 2009;9:313–318.
70. Chou, T.C. Anti-inflammatory and analgesic effects of paeonol in carrageenan-evoked thermal hyperalgesia. *Br. J. Pharmacol.* 2003;139:1146–1152.
71. Márquez, L.; García-Bueno, B.; Madrigal, J.L.; Leza, J.C. Mangiferin decreases inflammation and oxidative damage in rat brain after stress. *Eur. J. Nutr.* 2012;51:729–739.
72. Yin, P.-H.; Liu, X.; Qiu, Y.-Y.; Cai, J.-F.; Qin, J.-M.; Zhu, H.-R.; Li, Q. Anti-tumor activity and apoptosis-regulation mechanisms of bufalin in various cancers: New hope for cancer patients. *Asian Pac. J. Cancer Prev.* 2012;13:5339–5343.
73. Gordaliza, M.; Castro, M.D.; del Corral, J.M.; Feliciano, A.S. Antitumor properties of podophyllotoxin and related compounds. *Curr. Pharm. Des.* 2000;6:1811–1839.
74. Milross, G.C.; Mason, K.A.; Hunter, N.R.; Chung, W.-K.; Peters, L.J.; Milas, L. Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. *JNCI J. Natl. Cancer Inst.* 1996;88:1308–1314.
75. Long, R.; Yang, F.; Du, J.-R.; Qian, Z.-m.; Wang, C.-Y.; Chen, C. Effects of ligustilide on tumor growth and immune function in institute of cancer research mice. *Trop. J. Pharm. Res.* 2012;11:421–428.
76. Zaidi, M. Antifungal activity of harmaline, HgCl₂ and their complex. *Phys. Chem.* 2007;16:11–14.
77. Wang, T.; Shi, G.; Shao, J.; Wu, D.; Yan, Y.; Zhang, M.; Cui, Y.; Wang, C. In vitro antifungal activity of baicalin against *Candida albicans* biofilms via apoptotic induction. *Microb. Pathog.* 2015;87:21–29.
78. Salas, P.M.; Céliz, G.; Geronazzo, H.; Daz, M.; Resnik, S.L. Antifungal activity of natural and enzymatically modified flavonoids isolated from citrus species. *Food Chem.* 2011;124:1411–1415.
79. Srinivasan, M.; Sudheer, A.R.; Menon, V.P. Ferulic acid: Therapeutic potential through its antioxidant property. *J. Clin. Biochem. Nutr.* 2007;40:92–100.
80. Sova, M. Antioxidant and antimicrobial activities of cinnamic acid derivatives. *Mini Rev. Med. Chem.* 2012;12: 749–767.
81. Kohlhardt-Floehr, C.; Boehm, F.; Troppens, S.; Lademann, J.; Truscott, T.G. Prooxidant and antioxidant behaviour of usnic acid from lichens under UVB-light irradiation—Studies on human cells. *J. Photochem. Photobiol. B Biol.* 2010;101:97–102.
82. Rozza, L.A.; de Faria, F.M.; Brito, A.R.S.; Pellizzon, C.H. The gastroprotective effect of menthol: Involvement of anti-apoptotic, antioxidant and anti-inflammatory activities. *PLoS ONE* 2014, 9, e86686.
83. Afaq, F.; Zaid, M.A.; Khan, N.; Dreher, M.; Mukhtar, H. Protective effect of pomegranate-derived products on UVB-mediated damage in human reconstituted skin. *Exp. Dermatol.* 2009;18:553–561.

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