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Review

# Applications of novel drug delivery system for herbal formulations

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ABSTRACT

Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The present review highlights the current status of the development of novel herbal formulations and summarizes their method of preparation, type of active ingredients, size, entrapment efficiency, route of administration, biological activity and applications of novel formulations.



**Contents**



## 1. Introduction

In the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS) for herbal drugs. The novel carriers should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity of herbal drug to the site of action. Conventional dosage forms including prolonged-release dosage forms are unable to meet none of these. In phyto-formulation research, developing nano

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dosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion etc.) have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation etc. Thus the nano sized novel drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Liposomes, which are biodegradable and essentially non-toxic vehicles, can encapsulate both hydrophilic and hydrophobic materials [1]. Liposome based drug delivery systems offer the potential to enhance the therapeutic index of anti-cancer agents, either by increasing the drug concentration in tumor cells and/or by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and by utilizing targeting strategies [2]. The main 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 changing the chemical composition of the bilayer components [3]. Delivery of agents to the reticuloendothelial system (RES) is easily achieved, since most conventional liposomes are trapped by the RES [1]. The application of novel approaches can also improve the efficacy of herbal cosmetic formulations on the human body [4]. Similarly the other vesicular systems like nanoemulsion, ethosomes and transferosomes are highly useful assemblies and find various advantages in the delivery of herbal medicines; some of them are summarized in present article.

The phytosome process has also been applied to many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, milk thistle [5], green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosome is produced by binding individual components of herbal extracts to phosphatidyl choline, resulting in a dosage form that is better absorbed and thus, produces better results than the conventional herbal extracts [6]. The results indicate that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract [5]. Drugs can be embedded or dissolved in nanoparticles and can also be adsorbed or coupled on the surface [7]. Encapsulating drugs within NPs can improve the solubility and pharmacokinetics of drugs, and, in some cases, enable further clinical development of new chemical entities that have stalled because of poor pharmacokinetic properties [8]. The major carrier materials of nanoparticles are synthetic biodegradable high molecular polymer and natural polymer. The former usually includes poly-α-cyanoacrylate alkyl esters, polyvinyl alcohol, polylactic acid, and polylacticco-glycolic acid, etc. The latter is usually divided into two classes: proteins (albumin, gelatin and vegetable protein) and polysaccharides (cellulose, starch and its derivatives, alginate, chitin and chitosan, etc.) [9].

In this article, an attempt has been made to touch upon different aspects related to the development of novel herbal formulations, including method of preparation, type of active ingredient, entrapment efficiency, and applications etc.

## 2. Liposome

The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior. They can have one, several or multiple concentric membranes. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules [10]. Upon interaction with water, polar lipids self-assemble and form self-organized colloidal particles. Simple examples are detergents, components form micelles, while polar lipids with bulkier hydrophobic parts cannot associate into micelles with high curvature radii but form bilayers which can self-close into liposomes or lipid vesicles. A cross-section of a liposome (Fig. 1) depicts the hydrophilic heads of the amphiphile orienting towards the water compartment while the lipophilic tails orient away from the water towards the center of the vesicle, thus forming a bilayer. Consequently, water soluble compounds are entrapped in the water compartment and lipid soluble compounds aggregate in the lipid section. Uniquely, liposomes can encapsulate both hydrophilic and lipophilic materials. Liposomes usually formed from phospholipids, have been used to change the pharmacokinetics profile of, not only drugs, but herbs, vitamins and enzymes. A variety of herbal liposomal formulations has been studied which are summarized in Table 1. Because of their unique properties liposomes are able to enhance the performance of products by increasing ingredient solubility, improving ingredient bioavailability, enhanced intracellular uptake and altered pharmacokinetics and biodistribution [9] and in vitro and in vivo stability. Liposomes as a drug delivery system can improve the therapeutic activity and safety of drugs, mainly by delivering them to their site of action and by maintaining therapeutic drug levels for prolonged periods of time [11–13].

Milk thistle (*Silybum marianum*) is one of the few herbal drugs whose excellent pharmacological profile readily lends itself to proof of clinical efficacy [13]. Meanwhile, silymarin is poorly absorbed (20–50%) from the gastrointestinal tract [14] that causes the effects of silybin, one of the main active flavonoids commonly found in the dried fruits of silymarin, to be greater after parenteral than oral administration [15].

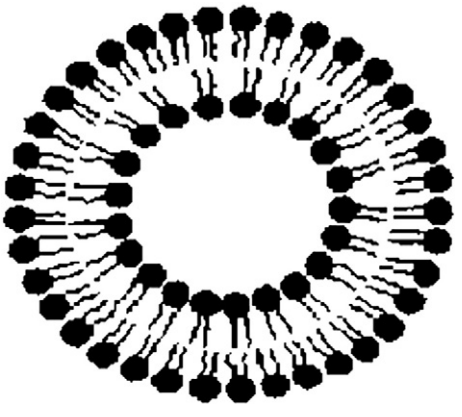

**Fig. 1.** Cross-section of a liposome [4].

**Table 1**
Liposomal herbal formulation.

| Formulations | Active ingredients | Applications of liposome formulations | Biological activity | Method of preparation | % Entrapment efficiency | Route of administration | Reference |
|---|---|---|---|---|---|---|---|
| Quercetin liposomes | Quercetin | Reduced dose, enhance penetration in blood brain barrier | Antioxidant Anticancer | Reverse evaporation technique | 60% | Intranasal | [18] |
| Liposomes encapsulated silymarin | Silymarin | Improve bioavailability | Hepatoprotective | Reverse evaporation technique | 69.22 ± 0.6% | Buccal | [16] |
| Liposoma artemisia arborescens | Artemisia arborescens essential oil | Targeting of essential oils to cells, enhance penetration into, cytoplasmatic barrier | Antiviral | Film method and sonication | 60–74% | In vitro | [19] |
| Ampelopsin liposome | Ampelopsin | Increase efficiency | Anticancer | Film-ultrasound method | 62.30% | In vitro | [20] |
| Paclitaxel liposome | Paclitaxel | High entrapment efficiency and PH sensitive | Anticancer | Thin film hydration method | 94% | In vitro | [21] |
| Curcumin liposome | Curcumin | Long-circulating with high entrapment efficiency | Anticancer | Ethanol injection method | 88.27 ± 2.16% | In vitro | [22] |
| Garlicin liposome | Garlicin | Increase efficiency | Lungs | Reverse-phase evaporation method | 90.77 % | – | [23] |
| Flavonoids liposomes | Quercetin and rutin | Binding of flavonoids with Hb is enhanced | Hemoglobin | Solvent evaporation | – | In vitro | [24] |
| Usnea acid liposome with β-CD | Usnea acid | Incrase solubility and localization with prolonged-release profile | Antimycobacterial | Hydration of a thin lipid film method with sonication | 99.5% | In vitro | [25] |
| Wogonin liposome | Wogonin | Sustained release effect | Anticancer | Film dispersion method | 81.20 ± 4.20% | In vivo | [26] |
| Colchicine Liposome | Colchicine | Enhance skin accumulation, prolong drug release and improve site specificity | Antigout | Rotary evaporation sonication method | 66.3 ± 2.2% | Topical | [27] |
| Catechins liposomes | Catechins | Increased permeation through skin | Antioxidant and chemopreventive | Rotary evaporation sonication method | 93.0 ± 0.1 | Transdermal | [28] |
| Breviscapine liposomes | Breviscapin | Sustained delivery of breviscapine | Cardiovascular diseases | Double emulsification process | 87.9 ± 3.1% | Intramuscular | [29] |

Incorporation of silymarin into liposomal dosage form administered buccaly can improve its bioavailability. In this connection to improve the bioavailability of silymarin through its incorporation in a stable liposomal buccal dosage form, using commercially available soybean lecithin. El-Samaligy et al. [16] prepared silymarin encapsulated hybrid liposomes which shows successful preparation with efficient encapsulation of silymarin. Mixing silymarin loaded hybrid liposomes with unloaded ones in a (1:1) proportion was useful in prevention of aggregates which threaten liposomal stability. M50 proved stability regarding encapsulation efficiency, turbidity measurement and particle size analysis after 3 months of storage at 4 °C or at ambient temperature. Refrigeration is recommended to achieve better stability. The introduced hybrid liposomal silymarin formula for buccal administration have the advantages of exerting a mucoadhesive effect [17] besides its deformability due to the presence of Tween 20 as edge activator allowing the medicated liposomes to squeeze through buccal mucosal cells. It was also shown to be safe upon contacting the rat buccal mucosa.

## 3. Nanoparticles

In recent year, the nanonization of herbal medicines has attracted much attention; [30] some of them are illustrated in Table 2. Nanoparticles and nanoemulsions (Fig. 2) are colloidal systems with particles varying in size from 10 nm to 1000 nm [31,32]. Nanoparticle systems with mean particle size well above the 100 nm standard have also been reported in literature, including nanonized curcuminoids [33], paclitaxel [34] and praziquantel [35] which have a mean particle size of 450, 147.7, and even higher than 200 nm, respectively. In addition, nanoparticles could also be defined as being submicronic (<1 lm) colloidal systems [36]. The nanospheres have a matrix type structure in which the active ingredient is dispersed throughout (the particles), whereas the nanocapsules have a polymeric membrane and an active ingredient core. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines compared with the respective crude drugs preparations [36].

## 4. Phytosome

Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological activities and health promoting benefits of numerous plant products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids, etc.)

**Table 2**
Nano structured herbal formulations.

| Formulations | Active ingredients | Applications of nanostructured formulations | Biological activity | Method of preparation | % Entrapment efficiency | Route of administration | Reference |
|---|---|---|---|---|---|---|---|
| Triptolide nanoparticle | Triptolide | Enhance the penetration of drugs through the stratum corneum by increased hydration | Anti-inflammatory | Emulsification-ultrasound | – | Topical (skin) | [30] |
| Nanoparticles of *Cuscuta chinensis* | Flavonoids and lignans | Improve water solubility, | Hepatoprotective and antioxidant effects | Nanosuspension method | 90% | Oral | [37] |
| Triptolide-loaded solid lipid nanoparticle | Triptolide | Decreasing the toxicity | Anti-inflammatory | Emulsification-ultrasound | – | Oral | [38] |
| Artemisinin nanocapsules | Artemisinin | Sustained drug release | Anticancer | Self-assembly procedure | 90–93% | In vitro | [39] |
| Radix salvia miltiorrhiza nanoparticles | R. salvia miltiorrhiza | Improve the bioavailability | Coronary heart diseases, angina pectoris and myocardial infarction | Spray-drying technique | Upto 96.68% | In vitro | [40] |
| Taxel-loaded nanoparticles | Taxel | Enhance the bioavailability and sustained drug release | Anticancer | Emulsion solvent evaporation method | 99.44% | – | [41] |
| Berberine-loaded nanoparticles | Berberine | Sustained drug release | Anticancer | Ionic gelation method | $65.40 \pm 0.70\%$ | In vitro | [42] |
| Silibini-loaded nanoparticles | Silibini | High entrapment efficiency and stability | Hepatoprotective | High pressure homogenization | 95.64% | – | [43] |
| Tetrandrine-loaded nanoparticles | Tetrandrine | Sustained drug release | Lung | Self-emulsification and solvent evaporating | 84% | In vitro | [44] |
| Glycyrrhizic acid-loaded nanoparticles | Glycyrrhizic acid | Improve the bioavailability | Anti-inflammatory, antihypertensive | Rotary-evaporated filmultrasonication method | 91.76% | – | [45] |
| Quercetin-loaded nanoparticles | Quercetin | Increase antioxidant activity and release of the drug 74 times higher | Antioxidant | Nanoprecipitation technique | over 99% | In vitro | [46] |
| Breviscapine-loaded nanoparticles | Breviscapine | Prolong the half-life and decrease RES uptake | Cardiovascular and cerebrovascular | Spontaneous emulsification solvent diffusion technique | 93.1% | Intra Venous | [47] |
| Zedoary turmeric oil nanocapsule | Zedoary turmeric oil | Increase the drug loading and stability of ZTO | Hepatoprotection Anticancer and anti-bacterial | High pressure Homogenization method | $1.62 \pm 0.15\%$ Loading Capacity | – | [48] |
| Naringenin-loaded nanoparticles | Naringenin | Improved the release of NAR and improved its solubility | Hepatoprotective | Nanoprecipitation method | – | Oral | [49] |
| Curcuminoids solid lipid nanoparticles | Curcuminoids | Prolonged-release of the curcuminoids | Anticancer and antioxidant | Micro-emulsion technique | 70% | In vitro | [50] |
| CPT-encapsulated nanoparticles | Camptothecin | Prolonged blood circulation and high accumulation in tumors | Anticancer | Dialysis method | >80% | In vitro | [51] |
| *Ginkgo biloba* nanoparticles | *Ginkgo biloba* extract | Improving the cerebral blood flow and metabolism | Brain function activation | High pressure homogenization method | – | Oral | [52] |

**Fig. 2.** Cross-section of (a) nanoemulsion and (b) biopolymeric nanoparticle [4].

are poorly absorbed either due to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability [53]. It has often been observed that the isolation and purification of the constituents of an extract may lead to a partial or total loss of specific bio-activity for the purified constituent — the natural constituent synergy becomes lost. Very often the chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Extracts when taken orally some constituents may be destroyed in the gastric environment. As standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons. It has been observed that complexation with certain other clinically useful nutrients substantially improves the bioavailability of such extracts and their individual constituents. The nutrients so helpful for enhancing the absorption are the phospholipids. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes and so vastly improve their absorption and bioavailability [54] (Table 3). In liposomes no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water soluble compound. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance (s) complexed, involving chemical bonds (Fig. 3). Phospholipids are complex molecules that are used in all known life forms to make cell membranes. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. They are miscible both in water and in lipid environments, and are well absorbed orally. Phytosomes are more bioavailable as compared to conventional herbal extracts owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation.

**Table 3**
Phytosomal herbal formulations.

| Formulations | Active ingredients | Applications of phytosomal formulations | Biological activity | Method of preparation | Dose | Route of administration | Reference |
|---|---|---|---|---|---|---|---|
| *Ginkgo biloba* phytosomes | Flavonoids | Flavonoids of GBP stabilize the ROS | Cardio-protective, antioxidant activity | Phospholipids complexation | 100 mg and 200 mg/kg | Subcutaneous | [55] |
| Ginkgoselect phytosome | Flavonoids | Inhibits lipid peroxidation (LPO), stabilize the ROS | Hepatoprotective, antioxidant | Phospholipids complexation | 25 and 50 mg/kg | Oral | [56] |
| Silybin phytosome | Flavonoids | Absorption of silybin phytosome from silybin is approximately seven times greater | Hepatoprotective, antioxidant for liver and skin | Silybin-phospholipid complexation | 120 mg | Oral | [57] |
| Ginseng phytosome | Ginsenosides | Increase absorption | Nutraceutical, immunomodulator | Phospholipids complexation | 150 mg | Oral | [58] |
| Green tea phytosome | Epigallocatechin | Increase absorption | Nutraceutical, systemic antioxidant, anti-cancer | Phospholipids complexation | 50–100 mg | Oral | [58] |
| Grape seed phytosome | Procyanidins | The blood TRAP nTotal Radical-trapping Antioxidant Parameter) were significantly elevated over the control | Systemic antioxidant, cardio-protective | Phospholipids complexation | 50–100 mg | Oral | [58] |
| Hawthorn Phytosome | Flavonoids | Increase therapeutic efficacy and absorption | Cardio-protective and antihypertensive | Phospholipids Complexation | 100 mg | Oral | [58] |
| Quercetin phytosome | Quercetin | Exerted better therapeutic efficacy | Antioxidant, anticancer | Quercetin–phospholipid complexation | – | Oral | [59] |
| Curcumin phytosomes | Curcumin | Increase antioxidant activity and Increase bioavailability | Antioxidant, anticancer | Curcumin–phospholipid complexation | 360 mg/kg | Oral | [60],[49] |
| Naringenin phytosomes | Naringenin | Prolonged duration of action | Antioxidant activity | Naringenin–phospholipid complex | 100 mg/kg | Oral | [61] |

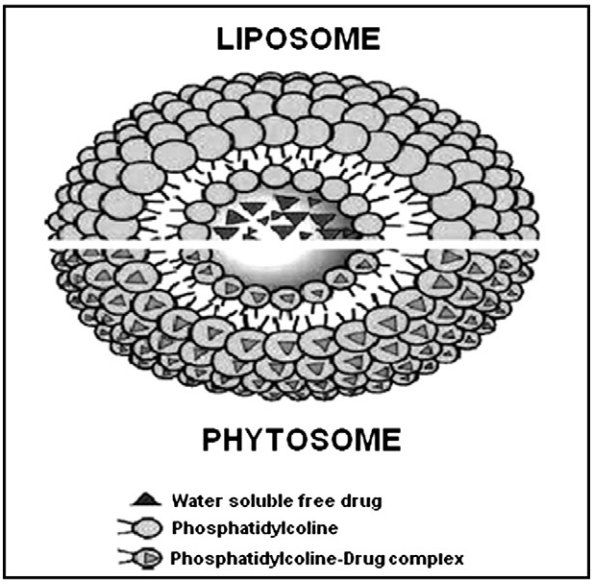


**Fig. 3.** Difference between liposome and phytosome [58].

Phytosome has been an emerging trend in delivery of herbal drugs and nutraceuticals.

## 5. Emulsions

Emulsion refers to a non-homogeneous dispersion system that is composed of two kinds of liquids unable to dissolve each other, and one of which disperse in the other one in a form of droplets [62]. Generally, emulsion is composed of oil phase, water phase, surfactant and sub-surfactant. Its appearance is translucent to transparent liquid. Emulsion can be classified into ordinary emulsion (0.1–100 μm), micro-emulsion (10–100 nm), sub-micro-emulsion (100–600 nm), etc. (Table 4). Among them, the micro-emulsion is also called nanoemulsions, and the sub-micro-emulsion is also called lipid emulsion. As a drug delivery system, emulsion distributes in vivo in the targeted manner due to its affinity to the lymph. In addition, the drug can be 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 [63]. After the oily drugs or lipophilic drugs being made into O/W or O/W/O emulsion, the oil droplets are phagocytosised by the macrophage and get a high concentration in the liver, spleen, and kidney in which the amount of the dissolved drug is very large. While water soluble drug is produced into W/O or W/O/W emulsion, it can be easily concentrated in the lymphatic system by intramuscular or subcutaneous injection. The size of the emulsion particle has an impact on its target distribution.

Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs' stimulus to tissues. So far, some kinds of herbal drugs, such as camptothecin, Brucea javanica oil, coixenolide oil and zedoary oil have been made into emulsion. For example, Zhou et al. [64] studied the influence of the elemenum emulsion on the human lung adenocarcinoma cell line A549 and protein expression. Results showed that the elemenum emulsion has a significant inhibition on the growth and proliferation of the A549 in vitro and it showed a time and dose-dependent relationship. Elemenum emulsion is a type of new anti-cancer drug with great application prospects. Furthermore, it has no marrow inhibition and no harm to the heart and liver.

**Table 4**
Emulsion herbal formulations.

| Formulations | Active ingredients | Applications of emulsion formulations | Biological activity | Method of preparation | Droplet size | Drug loading | Route of administration | Reference |
|---|---|---|---|---|---|---|---|---|
| Self-nanoemulsifying Zedoary essential oil | Zedoary turmeric oil | Improved aqueous dispersibility, stability and oral bioavailability. | Hepatoprotection anticancer and anti-bacterial | Drawing ternary phase Diagram | 68.3± 1.6 nm | 30% | Oral | [65] |
| Triptolide micro-emulsion | Triptolide | Enhance the penetration of drugs through the stratum corneum by increased hydration | Anti-inflammatory | High pressure Homogenization method | <100 nm | – | Topical | [30] |
| Docetaxel submicron emulsion | Docetaxel | Improve residence time | Anticancer | High pressure Homogenization method | 166.00 nm | 90% | Intravenous | [66] |
| Berberine nanoemulsion | Berberine | Improve residence time and absorption | Anticancer | Drawing ternary phase diagram | 56.80 nm | 0.50% | Oral | [67] |
| Silybin nanoemulsion | Silybin | Sustained release formulation | Hepatoprotective | Emulsification method | 21.20 nm | – | Intramuscular | [68] |
| Quercetin micro-emulsion | Quercetin | Enhance penetration into stratum corneum and epidermis | Antioxidant | High speed Homogenization method | 10–100 nm | 0.3% solution | Topical | [69] |

**Table 5**
Other novel vesicular herbal formulations.

| Formulations | Active ingredients | Applications | Biological activity | Droplet size | Route of administration | Reference |
|---|---|---|---|---|---|---|
| Capsaicin transferosomes | Capsaicin | Increase skin penetration | Analgesic | 150.6 nm | Topical | [71] |
| Colchicine transferosomes | Colchicine | Increase skin penetration | Antigout | – | In vitro | [77],[79] |
| Vincristine transferosomes | Vincristine | Increase entrapment efficiency and skin permeation y | Anticancer | 120 nm | In vitro | [77] |
| Matrine ethosome | Matrine | Improve the percutaneous permeation | Anti-inflammatory | 110 ± 8 nm | Topical | [76] |
| Ammonium glycyrrhizinate ethosomes | Ammonium glycyrrhizinate | Increase of the in vitro percutaneous permeation | Anti-inflammatory | 350 nm to 100 nm | Topical | [78] |

## 6. Other novel vesicular herbal formulations

Transferosomes are applied in a non-occluded method to the skin, which permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. It can be applicable as drug carriers for a range of small molecules, peptides, proteins and herbal ingredients. Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting maintenance of skin [70] in this connection the transferosomes of Capsaicin has been prepared by Xiao-Ying et al. [71] which shows the better topical absorption in comparison to pure capsaicin. Ethosome, as a novel liposome, is especially suitable as a topical or transdermal administration carrier [72,73]. Ethosome has a high deformability and entrapment efficiency and can penetrate through the skin completely and improve drug delivery through the skin. Compared to other liposomes, the physical and chemical properties of ethosomes make the delivery of the drug through the stratum corneum into a deeper skin layer efficiently or even into the blood circulation [74]. This property is very important as the topical drug carrier and transdermal delivery system. Moreover, the ethosomes carrier also can provide an efficient intracellular delivery for both hydrophilic and lipophilic drugs [75], percutaneous absorption of matrine an anti-inflammatory herbal drug is increased; [76] it also permits the antibacterial peptide to penetrate into the fibrocyte easily [77]. The roles of these types of novel vasicular system over herbal drug delivery are summarized in (Table 5).

## 7. Microspheres

Administration of medication via micro particulate systems is advantageous because microspheres can be ingested or injected and; they can be tailored for desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release [80]. So far, a series of plant active ingredients, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetine and *Cynara scolymus* extract has been made into microspheres (Table 6). In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer microspheres.

## 8. Proprietary novel drug delivery system of plant actives and extracts

Cosmetochem International AG is a Swiss-based company, specialized in the production of high quality, customized botanical extracts and actives, launch botanical, standardized, liposomal powders named Liposome Herbasec® [86] a novel range of standardized botanical extracts in a liposomal-based powder form. As the liposome carriers are very effective penetration enhancers which serve as carriers to the skin, increasing the bioavailability of the plant extracts. In present formulation the freeze-dried dispersion of Liposome Herbasec® is reformed when dispersed in water, re-encapsulating

**Table 6**
Microspheres encapsulated herbal formulations.

| Formulations | Active ingredients | Applications of formulations | Biological activity | Method of preparation | Size in μm | Route of administration | Reference |
|---|---|---|---|---|---|---|---|
| Rutin–alginate–chitosan microcapsules | Rutin | Targeting into cardiocascular and cerebrovascular region | Cardiovascular and Cerebrovascular diseases | Complex-coacervation method | 165.00–195.00 | In vitro | [81] |
| Zedoary oil microsphere | Zedoary oil | Sustained release and Higher bioavailability | Hepatoprotective | Quasi-emulsion–solvent diffusion method | 100–600 | Oral | [82] |
| CPT loaded microspheres | Camptothecin | Prolonged-release of camptothecin | Anticancer | Oil-in-water evaporation method | 10 | Intraperitoneally and intravenously | [83] |
| Quercetin microspheres | Quercetin | Significantly decreases the dose size | Anticancer | Solvent evaporation | 6 | In vitro | [84] |
| *Cynara scolymus* microspheres | *Cynara scolymus* extract | Controlled release of neutraceuticals | Nutritional supplement | Spray-drying technique | 6–7 | Oral | [85] |

**Table 7**
Marketed novel drug delivery formulations of plant active and extracts.

| SN | Brand name | Plant active/extracts | Type of NDDS | Company name | Reference |
|---|---|---|---|---|---|
| 1 | White tea liposome Herbasec® | *Camellia sinensis* extract | Liposome | Cosmetochem | [86] |
| 2 | Green tea liposome Herbasec® | *Camellia sinensis* Extract | Liposome | Cosmetochem | [86] |
| 3 | White hibiscus liposome Herbasec® | White hibiscus extract | Liposome | Cosmetochem | [86] |
| 4 | Aloe vera liposome Herbasec® | Aloe vera Extract | Liposome | Cosmetochem | [86] |
| 5 | Guarana liposome Herbasec® | Guarana extract | Liposome | Cosmetochem | [86] |
| 6 | 18ß-glycyrrhetinic acid Phytosome® | 18ß-glycyrrhetinic acid from licorice rhizome | Phytosome | Indena | [87] |
| 7 | Centella Phytosome® | Triterpenes from *Centella asiatica* leaf | Phytosome | Indena | [87] |
| 8 | Crataegus Phytosome® | Vitexin-2″-O-rhamnoside from Hawthorn flower | Phytosome | Indena | [87] |
| 9 | Escin ß-sitosterol Phytosome® | Escin ß-sitosterol from horse chestnut fruit | Phytosome | Indena | [87] |
| 10 | Ginkgoselect® Phytosome® | Ginkgoflavonglucosides, ginkgolides, bilobalide from *Ginkgo biloba* leaf | Phytosome | Indena | [87] |
| 11 | Ginselect® Phytosome® | Ginsenosides from *Panax ginseng* rhizome | Phytosome | Indena | [87] |
| 12 | *Ginkgo biloba* terpenes Phytosome® | Ginkgolides and bilobalide from *Ginkgo biloba* leaf | Phytosome | Indena | [87] |
| 13 | *Ginkgo biloba* dimeric flavonoids Phytosome® | Dimeric flavonoids from *Ginkgo biloba* leaf | Phytosome | Indena | [87] |
| 14 | Greenselect® Phytosome® | Polyphenols from green tea leaf | Phytosome | Indena | [87] |
| 15 | Leucoselect® Phytosome® | Polyphenols from grape seed | Phytosome | Indena | [87] |
| 16 | Meriva® | Curcuminoids from turmeric rhizome | Phytosome | Indena | [87] |
| 17 | $PA_2$ Phytosome® | Proanthocyanidin $A_2$ from horse chestnut bark | Phytosome | Indena | [87] |
| 18 | Sericoside Phytosome® | Sericoside from *Terminalia sericea* bark root | Phytosome | Indena | [87] |
| 19 | Siliphos® | Silybin from milk thistle seed | Phytosome | Indena | [87] |
| 20 | Silymarin Phytosome® | Silymarin from milk thistle seed | Phytosome | Indena | [87] |
| 21 | Virtiva® | Ginkgoflavonglucosides, ginkgolides, bilobalide from *Ginkgo biloba* leaf | Phytosome | Indena | [87] |
| 22 | Visnadex® | Visnadin from *Ammi visnaga* umbel | Phytosome | Indena | [87] |

the concentrated plant extract. Phospholipids used for the preparation of formulation are the safest, mildest substances which allow the penetration of the plant actives into the deeper layers of the epidermis and avoid the use of solvents. There are five extracts in the current Liposome Herbasec® range (Table 7) which are standardized for specific phytochemicals. White and green tea are standardized for caffeine and total polyphenols, white hibiscus for fruit acids, guarana for caffeine and aloe vera is aloin-free [86]. Liposome Herbasec® can be used in a wide range of personal care applications. Smilarly based on Phytosome® technology, a line of products has been developed and commercialized by Indena [87] (Table 7). The Phytosome® formulation increases the absorption of active ingredients when topically applied on the skin [88–97], and improves systemic bioavailability when administered orally [98–102]. A Phytosome® is generally more bioavailable than a simple herbal extract due to its enhanced capacity to cross the lipid-rich biomembranes and reach circulation [103–105]. To overcome the poor bioavailability of silybin, Indena has complexed it with soy phospholipids exploiting the Phytosome® technology. As demonstrated by comparative pharmacokinetic studies, Silipide® represents the most absorbable oral form of silybin known. The pharmacokinetics of Silipide® in healthy human subjects showed that complexation with phosphatidylcholine improved the oral bioavailability of silybin 4.6 fold compared with silymarin, presumably because of a facilitated passage across the gastrointestinal mucosa [97]. The good bioavailability of Siliphos® was confirmed in a human pharmacokinetic study in prostate cancer patients. The study employed high dosages, and was aimed at getting information on toxicity and phase II dosage of the product. Siliphos® at a daily oral dose of 13 g in 3 divided doses, was well tolerated in all patients, and this dosage was recommended for the phase II study [106].The results, including the optimal tolerability obtained in these "extreme" clinical situations, provide strong support for the use of Siliphos® also in less severe pathologies associated with liver damage. Ginkgoselect® Phytosome® was administered at a dosage of 360 mg/day (120 mg three times per day) to 22 subjects affected by the Raynaud's disease in a double-blind, placebo-controlled trial. Patients were required to record the frequency and duration of any vasospastic attack, also completing a scoring scale of the overall perception of the severity of the episodes. Patients were reviewed after two, four and ten weeks of treatment. This pilot study showed the efficacy of Ginkgoselect® Phytosome® in promoting a clear and highly statistically significant reduction in the frequency (56%) and severity of Raynaud's attacks per day [107]. Meriva® is a patented complex of curcumin, a dietary phenolic, with soy phosphatidylcholine [108]. A lot of work that has been published in the journal Cancer Chemotherapy and Pharmacology [109] demonstrated Meriva®'s superior bioavailability compared to a standardized curcumin extract in rats, while very promising initial preclinical results in terms of improved hydrolytical stability and human pharmacokinetics have been shown more recently[108]. Including the advantages of these above mentioned commercialized NDDS preparation of plant actives/extracts a variety of other preparations is also available (Table 7) which show the remarkable advantages over pure plant actives/extracts.

## 9. Conclusion

An extensive research is going on in the area of novel drug delivery and targeting for plant actives and extracts. However, research in this area is still at the exploratory stage. Many problems in the research, production and application

need to be solved. In addition, more attention should be paid to the research on the carrier materials in order to develop more suitable carriers which can reduce the toxicity of drugs, enhance their activity and improve the overall quality of the agents. Herbal drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytomolecules, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when administered through novel drug delivery system show much better absorption profile which enables them to cross the biological membrane, resulting enhanced bioavailability. Hence more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney, etc.) at similar or less dose as compared to the conventional plant extract or phytomolecule. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered using NDDS. Hence there is a great potential in the development of novel drug delivery systems for the plant actives and extracts.

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## References

[1] Medina OP, Zhu Y, Kairemo K. Curr Pharm Des 2004;10:2981–9.
[2] Sharma G, Anabousi S, Ehrhardt C, Kumar MNVR. J Drug Target 2006;14:301–10.
[3] Terreno E, Castelli DD, Cabellab C, Dastru W, Saninoa A, Stancanellob J, et al. Chem Biodivers 2008;5:1901–2.
[4] Chanchal D, Swarnlata S. J Cosmet Dermatol 2008;7:89–95.
[5] Barzaghi N. Eur J Drug Metab Pharmacokinet 1990;15(4):333–8.
[6] www.doctormurray.com/articles/phytosomes html.
[7] Yuan DF, Yi YM. Her Med 2003;22:113–4.
[8] Alexis F, Basto P, Levy-Nissenbaum E, Radovic-Moreno AF, Zhang LF, Pridgen E, et al. Chem Med Chem 2008;3:1839–43.
[9] Xiao YL, Li B. Chine Trad Herb Drugs 2002;33:385–8.
[10] Lasic DD 'Liposomes: From Physics to Applications', Elsevier, Amsterdam/London, New York, Tokyo 1993.
[11] Abou El Wafa AA, Mursi NM, El-Shaboury KM. A pharmaceuticl study on certain ocular drug delivery systems. MS Thesis. Cairo Univercity, Cairo 2003.
[12] Barragan-Montero V, Winum J, Moles J, Juan E, Clavel C, Montero J. Eur J Med Chem 2005;40:1022–9.
[13] Weiss R, Fintelmann V. Herbal medicine. 2nd ed. Stuttgart, New York: Thieme; 2000.
[14] Blumenthal M, Goldberg A, Brinkmann J. Herbal medicine. Integrative Medicine Communications. Newton; 2000.
[15] Carini R, Comogoliom A, Albano A, Poli G. Biochem Pharmacol 1992;43:2111–5.
[16] El-Samaligy MS, Afifi NN, Mahmoud EA. Int J Pharm 2006;319:121–9.
[17] Takeuchi H, Matsui Y, Yamamoto H, Kawashima Y. 2003. J Control Release 2003;86:235–42.
[18] Aroonsri P, Jintanaporn W, Saengrawee S, Wathita P, Supaporn M. Nanomed Nanotechnol Biol Med 2008;4:70–8.
[19] Chiara S, Alessandro DL, Francesco L, Donatella V, Maria M, Giuseppe L, et al. Eur J Pharm Biopharm 2005;59:161–8.
[20] He ZF, Liu DY, Zeng S, Ye JT. J Chine Mat Med 2008;33:27–30.
[21] Rane S, Prabhakar B. Int J Pharm Technol Res 2009;1:914–7.
[22] Hong W, Chen DW, Zhao XL, Qiao MX, Hu HY. China J Chine Mat Med 2008;33:889–92.
[23] Sun P, Den SH, Yu WP. J Shand Univ TCM 2007;31:37–9.
[24] Juqun X, Rong G. Int J Biol Macromol 2007;40:305–11.
[25] Lira MCB, Ferraz MS, da Silva DGVC, Cortes ME, Teixeira KI, Caetano NP, Santos-Magalhães NS. J Incl Phenom Macrocycl Chem 2009;64: 215–24.
[26] Ke X, Xu Y, Yan F, Ping QN. J China Pharm Univ 2007;38:502–6.
[27] Godin B, Touitou E. J Control Release 2004;94(2–3):365–79.
[28] Fang J, Hwang T, Huang Fang C. Int J Pharm 2006;310(1–2):131–8.
[29] Zhong H, Deng Y, Wang X, Yang B. Int J Pharm 2005;301(1–2):15–24.
[30] Zhinan M, Huabing C, Ting W, Yajiang Y, Xiangliang Y. Eur J Pharm Biopharm 2003;56:189–96.
[31] Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. J Control Release 2006;113:189–207.
[32] Alle´mann E, Gurny R, Doelker E. Eur J Pharm Biopharm 1993;39: 173–91.
[33] Tiyaboonchai W, Tungpradit W, Plianbangchang P. Int J Pharm 2007;337:299–306.
[34] Arica YB, Benoit JP, Lamprecht A. Drug Dev Ind Pharm 2006;32: 1089–94.
[35] Mainardes RM, Evangelista RC. Int J Pharm 2005;290:137–44.
[36] Brigger I, Dubernet C, Couvreur P. Adv Drug Deliv Rev 2002;54: 631–51.
[37] Feng-Lin Y, Tzu-Hui W, Liang-Tzung L, Thau-Ming C, Chun-Ching L. Food Chem Toxicol 2008;46:1771–7.
[38] Zhinan M, Xiaokuan L, Qunrong W, Sheng H, Xiangliang Y. Pharmacol Res 2005;51:345–51.
[39] Youfang C, Xianfu L, Hyunjin P, Richard G. Nanomed Nanotechnol Biol Med 2009;5:316–22.
[40] Su YL, Fu ZY, Zhang JY, Wang WM, Wang H, Wang YC, et al. Powder Technol 2008;184:114–21.
[41] Fu RQ, He FC, Meng DS, Chen L. ACTA Academiae medicinae militaris tertiae, 28; 2006. p. 1573–4.
[42] Lin AH, Li HY, Liu YM, Qiu XH. China Pharm 2007;18:755–7.
[43] Li YC, Dong L, Jia K, Chang XM, Xue H. J Xi'an Jiaotong University (Med Sci) 2007;28:517–20.
[44] Xiaoyan A, Jun Y, Min W, Haiyue Z, Li C, Kangdec Y, et al. Int J Pharm 2008;350(1–2):257–64.
[45] Hou J, Zhou SW. ACTA Academiae medicinae militaris tertiae 2008;30: 1043–5.
[46] Tzu-Hui W, Feng-Lin Y, Liang-Tzung L, Tong-Rong T, Chun-Ching L, Thau-Ming C. Int J Pharm 2008;346(1–2):160–8.
[47] Liu M, Li H, Luo G, Liu Q, Wang Y. Arch Pharm Res 2008;31(4): 547–54.
[48] Lertsutthiwong P, Noomun K, Jongaroonngamsang N, Rojsitthisak P. Carbohydr Polym 2008;74:209–14.
[49] Feng-Lin Y, Tzu-Hui W, Liang-Tzung L, Thau-Ming C, Chun-Ching L. Pharm Res 2009;26(4):893–902.
[50] Mukerjee A, Vishwanatha JK. Anticancer Res 2009;29(10):3867–75.
[51] Min KH, Park K, Kim YS, Bae SM, Lee S, Jo HG, et al. J Control Release 2008;127:208–18.
[52] Shimada S. Composition comprising nanoparticle *Ginkgo biloba* extract with the effect of brain function activation IPC8 Class-AA61K914FI, USPC Class-424489; 2008.
[53] Manach C, Scalbert A, Morand C. Am J Clin Nutr 2004;79:727–47.
[54] Bombardelli E, Curri SB, Loggia DR, Del NP, Tubaro A, Gariboldi P. Fitoterapia 1989;60:1–9.
[55] Vandana SP, Suresh RN. Exp Toxicol Pathol 2008;60:397–404.
[56] Suresh RN, Vandana SP. Fitoterapia 2008;79:439–45.
[57] Yanyu X, Yunmei S, Zhipeng C, Quineng P. Int J Pharm 2006; 3; 307(1): 77–82.
[58] Bhattacharya S. Pharma Times 2009;41(3):9–12.
[59] Maiti K, Mukherjee K, Gantait A, Ahamed HN, Saha BP, Mukherjee PK. Iran J Pharmacol Ther 2005;4:84–90.
[60] Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Int J Pharm 2007;330(1–2):155–63.
[61] Maiti K, Mukherjee K, Gantait A, Bishnu PS, Mukherjee PK. J Pharm Pharmacol 2006;58:1227–33.
[62] Zhang Y. Chin Tradition Herbal Drugs 2006;37:641–7.
[63] Lu MF, Cheng YQ, Li LJ, Wu JJ. Mater Rev 2005;19:108–10.
[64] Zhou X, Li LY, Guo ZJ. Chin Clin Oncol 2004;9:229–34.
[65] Zhaoa Y, Wanga C, Albert HL, Chowb KR, Gongc T, Zhangc Z, et al. Int J Pharm 2010;383(1–2):170–7.
[66] Li L, Wang DK, Li LS, Jia J, Chang D, Ai L. J Shenyang Pharm Univ 2007;12:736–9.

[67] Sun HW, Ouyang WQ. J Shanghai Jiaotong Univ (Agric Sci) 2007;1:60–5.
[68] Song YM, Ping QN, Wu ZH. J China Pharm Univ 2005;5:427–31.
[69] Fabiana TMCV, Thaí s RMS, Jose ODC, Nilce OW, Dimitrius LP, Mamie MI, et al. Eur J Pharm Biopharm 2008;69:948–57.
[70] Benson HA. Expert Opin Drug Deliv 2006;6:727–37.
[71] Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Zhongguo Zhong Yao Za Zhi 2006;31(12):981–4.
[72] Jain S, Tiwary AK, Sapra B. AAPS PharmSciTech 2007;8:E111.
[73] Fang YP, Tsai YH, Wu PC. Int J Pharm 2008;356(1–2):144–52.
[74] Dayan N, Touitou E. Biomaterials 2000;21:1879–85.
[75] Touitou E, Godin B, Dayan N. Biomaterials 2001;22:3053–9.
[76] Zhaowu Z, Xiaoli W, Yangdel Z, Nianfeng L. J Liposome Res 2009;19(2):155–62.
[77] Zheng Y, Hou SX, Chen T, Lu Y. China J Chin Mater Med 2006;31(9):728–31.
[78] Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M. J Control Release 2005;106:99–110.
[79] Singh HP, Utreja P, Tiwary AK, Jain S. AAPS J 2009;2:54–64.
[80] Sanli O, Karaca I, Isiklan N. J Appl Polym Sci 2009;111:2731–40.
[81] Xiao L, Zhang YH, Xu JC, Jin XH. Chine Trad Herb Drugs 2008;2:209–12.
[82] You J, Cui F, Han X, Wang Y, Yang L, Yu Y, et al. Colloids Surf B 2006;48(1):35–41.
[83] Machida Y, Onishi H, Kurita A, Hata H, Morikawa A, Machida Y. J Control Release 2000;66(2–3):159–75.
[84] Chao P, Deshmukh M, Kutscher HL, Gao D, Rajan SS, Hu P, et al. Anticancer Drugs 2010;21(1):65–76.
[85] Gavini E, Alamanni MC, Cossu M, Giunchedi P. J Microencapsul 2005;22(5):487–99.
[86] http://www.cosmetochem.com.
[87] http://www.phytosomes.info/public/bioavailability.asp.
[88] Bombardelli E, Curri SB, Gariboldi PG. Fitoterapia 1989;60:55–70.
[89] Bombardelli E. Boll Chim Farma 1991;130:431–8.
[90] Bombardelli E (Indena S.P.A.). Pharmaceutical and cosmetic compositions containing complexes of flavanolignans with phospholipids. Patent EP0300282B1, 1992.
[91] Bombardelli E, Patri G, Pozzi R (Indena S.p.A.). Complexes of saponins and their aglycons with phospholipids and pharmaceutical and cosmetic compositions containing them Patent US5166139, 1992.
[92] Bombardelli E, Patri G (Indena S.p.A.). Complex compounds of bioflavonoids with phospholipids, their preparation and use, and pharmaceutical and cosmetic compositions containing them Patent EP0275005B1, 1993.
[93] Bombardelli E, Patri G, Pozzi R (Indena S.p.A.). Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them Patent EP0283713B1, 1993.
[94] Bombardelli E, Sabadie M (Indena S.p.A.–Sanofi S.A.). Phospholipidic complexes of Vitis vinifera extracts, process for their preparation and pharmaceutical and cosmetic compositions containing them Patent EP0300282B1, 1993.
[95] Di Pierro F (Indena S.p.A.). Pharmaceutical and cosmetic compositions against skin aging Patent EP0283713B1, 1993.
[96] Bombardelli E, Cristoni A, Morazzoni P. Fitoterapia 1994;65:387–401.
[97] Bombardelli E, Patri G, Pozzi R. (Indena S.p.A.). Complexes of neolignan derivatives with phospholipids the use thereof and pharmaceutical and cosmetic formulations containing them Patent EP0464297B1, 1995.
[98] Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E. Eur J Drug Metab Pharmacokinet 1990;15:333–8.
[99] Morazzoni P, Magistretti MJ, Giachetti C, Zanolo G. Eur J Drug Metab Pharmacokinet 1992;17:39–44.
[100] Morazzoni P, Montalbetti A, Malandrino S, Pifferi G. Eur J Drug Metab Pharmacokinet 1993;18:289–97.
[101] Maiti K, Mukherjee K, Gantait A, Ahamed HN, Saha BP, Mukherjee PK. Iran J Pharmacol Ther 2005;4:84–90.
[102] Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Cancer Chemother Pharmacol 2007;60:171–7.
[103] Mauri PL, Simonetti P, Gardana C, Minoggio M, Morazzoni P, Bombardelli E. Rapid Commun Mass Spectrom 2001;15:929–34.
[104] Kidd PM, Head K. Altern Med Rev 2005;10:193–203.
[105] Rossi R, Basilico F, Rossoni G, Riva A, Morazzoni P, Mauri PL. J Pharm Biomed Anal 2009;50:224–7.
[106] Flaig TW, Gustafson DL, Su L, Zirrolli JA, Crighton F, Harrison GS. Invest New Drugs 2007;25:139–46.
[107] Muir AH, Robb R, McLaren M, Daly F, Belch J. Vasc Med 2002;7:265–7.
[108] Kidd PM. Alt Med Rev 2009;14:226–46.
[109] Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Cancer Chemother Pharmacol 2007;60(2):171–7.