INTRODUCTION

Natural products from plants empirically have been used as traditional medicines to treat and prevent diseases. Other than that, metabolite active compounds from plants have been studied that there is a lot of bioactivity and pharmacological properties. Besides curing and preventing the disease, plants can also be used as nutriceutical and cosmeceutical agents including skin whitening agent and skin antioxidant. Whitening agents are compounds that have activity to inhibit the action of tyrosinase enzyme, which plays an important role in the process of melanogenesis. However, antioxidants are the compounds that can neutralize the free radicals produced by various environmental insults such as cigarette smoke, air pollutants, and ultraviolet radiation, thereby preventing cellular damage.

Key words: Phytosome and cosmetic, skin antioxidant, skin whitening agent

Phytosome drug delivery system for natural cosmeceutical compounds: Whitening agent and skin antioxidant agent

Yasmiwar Susilawati, Anis Yohana Chaerunisa, Hesti Purwaningsih
Department of Biology Pharmacy and Pharmaceutical and Technology Pharmaceutics, Faculty of Pharmacy, Padjadjaran University, Sumedang, West Java, Indonesia

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Phytosome formulations have demonstrated their effectiveness in improving the physicochemical properties and effectiveness of active compounds in various applications, especially in the field of skin care. This review aims to summarize and discuss the phytosome formulations of potential active compounds as skin whitening agent and skin antioxidant, obtained from Scopus, PubMed, and Google Scholar databases. We assessed that the main purpose of these phytosome formulations was to improve penetration, stability, and solubility of the active compounds. These studies proved that phytosome formulations can improve the physicochemical characteristics and effectiveness of compounds. The phytosome drug delivery system becomes a promising modification technique for natural compounds due to the ability to improve the physicochemical properties and increase the effectiveness. Phytosome formulation could be the excellent approach for cosmeceutical product with good effectivity in the future.

Key words: Phytosome and cosmetic, skin antioxidant, skin whitening agent

Address for correspondence:
Dr. Yasmiwar Susilawati,
Department of Biology Pharmacy, Faculty of Pharmacy, Padjadjaran University, Sumedang, West Java, Indonesia.
E-mail: Yasmiwar.usie@gmail.com

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Natural products have been widely carried out and proven to have good effectiveness as a tyrosinase inhibitor and skin antioxidant. However, there are some limitations on their physicochemical properties such as the stability, solubility, and inadequate drug penetration, thus the desired therapeutic effect not to be achieved. Based on this consideration, researchers continue to develop techniques to improve the physicochemical properties.

Phytosome drug delivery system is a technique that utilizes a double-layer phospholipid membrane to form a vesicle system that is known to be able for binding with polar and nonpolar compounds; it also can reduce the surface tension between poorly soluble compound with the solvent, which can provide capability for increasing the solubility, permeability, and stability of the compounds.\[3\]

Based on the considerations, this is a review carried out toward the results of some researches related to the modification of potential compounds as tyrosinase enzyme inhibitors and skin antioxidant using the phytosome drug delivery system approach. The result of this paper is very important to learn and can be used as a main reference for further development to gain a cosmeceutical candidate that has better effectiveness and lower side effects.

**METHODOLOGY**

This review was based on the literature obtained from the Scopus, PubMed, and Google Scholar database using specific keywords of “phytosome,” “tyrosinase inhibitor,” and “skin antioxidant.” The journals obtained were excluded for the journal review categories, opinions, and unrelated topics. Journal publication years for main topics are limited to a range of years since 2010 to obtain a specific publication journal according to the inclusion and renewal criteria.

**NATURAL COMPOUNDS**

Natural products represent chemical entities with a wide variety of biological activities and pharmacological properties. They originate from fungal, bacterial, plant, and marine animal sources and plants. Plants contain secondary metabolites that have function as plant survival agent. Natural products from plants have been used and have excellent advantages in treating or preventing diseases. Other than that, nowadays, natural products have been used as an active agent for skin care on cosmeceutical and nutriceutical products.\[4\]

**Whitening agent cosmetics and melanin biosynthesis**

Whitening agent cosmetics generally consist of tyrosinase inhibitor compounds which can inhibit or interfere the tyrosinase activity, an enzyme that plays a crucial role in the process of melanogenesis.\[5\] A complicated process which represented by numerous chemical and enzymatic reactions. Tyrosinase enzyme plays a role in the process of a primary catalysis to convert tyrosine to L-3,4-dihydroxyphenylalanine (DOPA) and then oxidized to dopaquinone (DQ). Furthermore, cysteine will change DQ to be cysteinyl DOPA, and it will be oxidized and polymerized to be pheomelanin (reddish-yellow soluble melanin). If there are no thiol compounds (cysteine and glutathione or thioredoxin), DQ will immediately be converted to DOPAchrome which has a blackish brown color. DOPAchrome will spontaneously lose carboxylic acid and 5,6-dihydroxyindole (DHI) which is immediately oxidized and polymerized, to be blackish brown. DOPAchrome tautomerase (TYRP2/DCT) will convert DOPAchrome to DHI-2-carboxyl acid (DHICA). Then, tyrosinase and TYRP1 will be converted to be a melanin which has a light brown color. DHI and DHICA melanin have a blackish-brown color called eumelanin.\[5\] The biosynthesis reaction is shown in Figure 1.

**Skin antioxidant**

Antioxidants are the active substances that offer protection to cell membranes and prevent oxidative stress to the tissues of the body by neutralizing toxic oxygen molecules and free radicals. Collagen and elastin are what keep skin looking fresh and tight; as we get older, collagen and elastin slow in production, which leads to sagging and wrinkles. Antioxidants actively counter free radical attacks on the supple elasticity of the skin. Found naturally in the body and in plants, antioxidants can be ingested orally or applied topically. There are generally three categories of antioxidants: (1) antioxidant enzymes, (2) chain breaking antioxidants, and (3) preventive antioxidants.\[6\]

**PHYTOSOME DRUG DELIVERY SYSTEM**

Phytosome is a nanoparticle delivery system composed of monolayer or double-layer phospholipids which form vesicle and is used for the delivery of polar or nonpolar natural compounds. The phospholipid content in this system is able to mediate the increase in solubility by hydrogen-bonding
interaction between water molecules with phosphate groups in double-layer system of phytosome carrier and improve permeability of the active compounds by phospholipid deformation of cells membrane with phytosome carrier. Currently, the use of phytosome has been carried out for modification of natural ingredients compounds intended to improve its effectiveness.\textsuperscript{[7]}

Phytosome drug delivery system is shown in Figure 2.

### Table 1: Recent formulation of phytosome drug delivery system

| Active Pharmaceutical Ingredients | Carrier                  | Method                  | Objective study                                      | Reference |
|----------------------------------|--------------------------|-------------------------|------------------------------------------------------|-----------|
| Root extract of *clerodendron*   | Phosphatidyl choline     | Thin film hydration      | Anticancer                                           | [35]      |
| Extract of *terminalia*          | Hydrogenated Phosphatidylcholine Phospholipon 90H | Solvent evaporation and precipitation | Anti hyperlipidemic                                  | [36]      |
| Trigonellafoennum-graecum        | L-α-Phosphatidylcholine and cholesterol | Thin film hydration method | Rheumatiod arthritis                                 | [37]      |
| Tecomellaundulata                | Lecithin soya 30% and Cholestrol | Solvent evaporation     | Antitumors, and various diseases associated with liver, spleen and abdomen Hepatoprotective agent | [38]      |
| Gallic acid (GA, 3,4,5-trihydroxybenzoic acid) | Phospholipid complex | -                       | complementary intervention in asthmatic patients Anti tumor | [39]      |
| *Boswellia*                      | Phospholipid complex     | -                       | -                                                    | [40]      |
| Silinin and glycyrrhizic acid    | dipalmitoylphosphatidylcholine (DPPC), cholesterol (CHOL), and methoxy‑polyethylene glycol 2000 (PEG2000) ‑ derived distearoylphos- phatidylethanolamine (mPEG2000‑DSPE) | thin layer film hydration | -                                                    | [41]      |
| Green select                     | Phospholipid cimplex     | -                       | Borderline metabolic syndrome                         | [42]      |
| *Silymarin*                      | Soy Phosphatidylcholine/SPC | Solvent evaporation     | Hepatoprotective agent                                | [43]      |
| *Citrus colocolitis (L.)*, Momordica balsamina and Momordica dioica* | Phosphatidylcholine | Solvent evaporation | Antidiabetic                                           | [44]      |
| *Sinigrin*                       | phosphatidylcholine hydrogenated | Solvent evaporation- thin film hydration | Wound healing agent                                   | [45]      |
| *Mitomycin C-Soybean*           | Phosphatidylcholine      | Solvent evaporation     | Antiproliferative and anticancer agent                | [46]      |
| *Mitomycin C-Soybean*           | Phosphatidylcholine‑Folat | Solvent evaporation     | Folate targeted drug delivery                         | [47]      |
| *Silybin*                        | Soybean phospholipids    | high-pressure homogenization method | Hepatoprotective agent                                | [48]      |
| *Apigenin*                       | Phospholipon              | Solvent evaporation     | Antioxidant                                           | [49]      |
| *Sinigrin*                       | L-a-phosphatidylcholine hydrogenated (soya bean) | Thin film hydration | Wound healing agent                                   | [50]      |
| *Trichosanthescucumerina Linn and Abrusprecatorius* | Phosphatydilcholine | Solvent evaporation | Hair growth promoting agent                           | [51]      |
| *Boswellic acid*                 | Lecitin delivery form    | -                       | Anti-inflammatory                                      | [52]      |
| *Greenselect*                    | Phospholipid complex     | -                       | Weight maintenance                                     | [53]      |
| *Soybean, Glycine max (L.)* Merrill* | Phosphatidylcholine | solvent evaporation, cosolvency, and salting out | prevent or manage obesity                             | [17]      |
| *L-carnosine*                    | Phospholipid-Hyaluronic acid | Solvent evaporation     | Ocular delivery                                        | [54]      |
Phytosome formulation containing skin whitening agent which has regulated to inhibit tyrosinase enzyme had been conducted for various extracts or isolated compounds from several plants. Phytosome system was prepared by several methods including solvent evaporation, thin film hydration, solvent evaporation-lyophilization, and antisolvent precipitation method. Phosphatidylcholine becomes a primary carrier in the phytosome system which consists of double-layer phospholipid complex. The objective of the formulation of phytosome as a potential tyrosinase inhibitor compounds were to observe its potency in improving the solubility, the penetration, the bioavailability, and the effectiveness as an inhibitor.

**Cacao Husk phytosome**

*Cacao* fruit (*Theobroma cacao* L.) consists of polyphenol compounds which can act as tyrosinase enzyme inhibitors. In 2019, Priani *et al.* carried out a formulation of facial serum phytosome containing *Cacao* husk to increase the effectiveness of the tyrosinase inhibitor activity. The thin-layer hydration method was used in the production of phytosome. Here, the carrier that was used in improving the bioactive flavonoids of the phytosome was Phosphatidylcholine. The result was a phytosome with a particle size of 672nm with an entrapment efficiency value of 90.5%. Impressively, the *Cacao husk* phytosome has tyrosinase inhibitor activity of 199.98 ppm.[8]

**Moringa oleifera phytosome**

*Moringa* is a plant that is proven to have strong tyrosinase inhibitory activity. This plant contains a compound which is not only able to reduce a formation of melanin but also can interfere and inhibit the tyrosinase enzyme activity called flavonoids.[9] Phytosome formulation of *Moringa oleifera* had been conducted by Lim in 2019. This study has an objective study to maximize topical wound delivery of *M. oleifera*. The results shows that *M. oleifera* phytosome appeared as multilamellar vesicles with an average particle size of 198 ± 21 nm and zeta potential of −28.30 ± 1.31 mV. *M. oleifera* has encapsulation efficiency of 52.2%, 82.8%, 8.44%, and 15.6% for kaempferol, quercetin, rosmarinic acid, and chlorogenic acid, respectively. In addition, the filtered *M. oleifera* phytosome exhibited the highest normal human dermal fibroblast cell migration and proliferation rate compared to the control. In addition, based on toxicity study, a concentration *M. oleifera* below 1.5 mg/mL does not emerge cytotoxicity.[10]

**Camellia sinensis phytosome**

*Camellia sinensis* is a natural substance containing polyphenol including flavonols, flavonoids, catechins, glycosides, phenolic acids, and aglycones and has been proven to have effectiveness as enzyme tyrosinase inhibitors with *IC₅₀* values of 753.58.[11] Anwar and Farhana conducted a phytosome formulation and evaluation of *C. sinensis* using *Arabic maltodextrin–gum* as a carrier. The phytosome was made using thin-layer hydration method. It produced an average particle size of 42.58nm, entrapment efficiency of 50.61%, PDI of 0.276, and a zeta potential value of −48.2 mV. On the dissolution test results, this phytosome has a value of 85.21% within 4 h. In addition, the results of the stability study showed that the phytosome formula could improve the stability of the *C. sinensis* leaf extract.[12]

| Active pharmaceutical ingredients | Carrier | Method | Reference |
|----------------------------------|--------|--------|-----------|
| Cacao Husk                       | Phophatidylcholine | Thin layer | [8]       |
| *Moringa oleifera*              | Soybean-cholesterol | Thin film formation | [10]     |
| *Camellia sinensis*             | Arabic maltodextrin-gum | Thin layer hydration | [12]     |
| *Centella asiatica*             | Phosphatidylcholine | Solvent evaporation | [55]     |
| *Centella asiatica*®            | -      | -      | [56]       |
| *Vitis vinifera*                | Phosphatidylcholine | Thin layer hydration | [15]     |
| Mulberry extract                 | Phosphatidylcholine | Solvent evaporation-lyophilization | [57] | |
| Soybean                          | Phosphatidylcholine | solvent evaporation, cosolvency, and salting out | [17] |
| Catechin                         | Phospholipid | -      | [19]       |
| β-cytosterol                     | -      | -      | [21]       |
| Gingerol                         | Soya lecithin-chitosan | Anti-solvent precipitation | [23] |

**Figure 2:** Phytosome drug delivery system

Table 2: Phytosome formulation for potential tyrosinase inhibitor compounds
**Centella asiatica phytosome**

*Centella asiatica* (CA) is a plant that has been investigated to have activity as a tyrosinase enzyme inhibitor with an inhibition value of 31.25% at a concentration of 1.67 mg/mL. The potential of this compound as an inhibitor allows it to be used as an active skin whitening agent formulated into cosmetic dosage form.\(^{[13]}\) In 2018, Ho *et al.* carried out a CA formulation using phytosome delivery system. In 2018, Ho *et al.* carried out a formulation of CA by using phytosome delivery system with solvent evaporation method, and the primary carrier was phospholipids. Histological analysis results showed that CA inhibited hyperkeratosis and mast cells proliferated by CA phytosome were found at concentrations (5, 10, and 20 μL/ml) as indicated by the results of histological analysis caused by the phytosome, which inhibited the production of induction nitric oxide in lipopolysaccharide (1 μL/ml) RAW 264.7 macrophages. Infiltration of the inflammatory cells and a reduction in the production of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins also occurred in the concentration.

**Vitis vinifera phytosome**

*Vitis vinifera* is a plant that contains the major compound of flavonoids, gallic acid, chlorogenic acid, epicatechin, rutin, and resveratrol. The complement activity of its compounds was potential and effective as tyrosinase enzyme inhibitors with the IC\(_{50}\) values of 3.84 mg/mL.\(^{[14]}\) In 2018, Surini *et al.* performed a phytosome formulation containing *V. vinifera* extract. This formulation was made using the thin layer hydration method. A phytosome with an average particle size of 398.23 nm obtained as results, as well as a zeta potential value of ~25.2 mV, and absorption efficiency value of 75.01%. The utilization of phytosome drug delivery system in this formula was known to significantly increase penetration by 2.27 times as compared to extracts that are not formulated (27.25% and 11.97%). These results proved that the phytosome delivery system approach could be a perfect technique for increasing drug penetration through the skin.\(^{[13]}\)

**Soybean phytosome**

Soybean is a plant that contains ortho-dihydroxy isoflavone derivative which is known as a potential inhibitor of the tyrosinase enzyme and plays a role in the melanin pigments formation. The content of compounds in soybean (7,8,40-trihydroxyisoflavone and 7,30,40-trihydroxyisoflavone) has potential as an inhibitor of the tyrosinase enzyme with the IC\(_{50}\) values of 11.21–5.23 μM and melanin formation with values of 12.23–7.83 μM.\(^{[14]}\) In 2018, El-Menshawe *et al.* conducted a soybean phytosome formulation resulting in phytosome with a particle size of 51.66–650.67 nm and a percentage value of 77.61%–9.78% released in a certain timescale. This study also succeeded in proving that the phytosome formulation was able to increase the effectiveness of soybean.\(^{[17]}\)

**Catechin phytosome**

The catechin group has been proved that can inhibit tyrosinase expression. Previous study has indicated that the catechin group could be the candidate as antimelanogenic agent and might be effective in curing hyperpigmentation disorders.\(^{[18]}\) Phytosome formulation of catechin had been conducted by Kazi *et al.* in 2016. G ultra-performance liquid chromatography (UPLC) analysis showed that 500 μg/ml epigallocatechin-3- gallate (EGCG) was present in green tea extract (GTE). The phytosome has a particle size of 130–270 nm with entrapment efficiencies value of 63%–86%, which was related to the particle size of the phytosomes. The study founded that catechin formulation in phytosome drug delivery system will have an excellent performance which can provide high soluble property and improve penetration, bioavailability, and effectiveness of the drug.\(^{[19]}\)

**β-sitosterol phytosome**

β-sitosterol is a compound known to have antioxidant activity and also acts as an enzyme inhibitor of tyrosinase which allows this compound to be used as an active ingredient in skin whitening.\(^{[20]}\) Phytosome formulation of this compound had been carried out in 2019 by Djekic *et al.*, aiming at increasing the effectiveness of β-sitosterol as an anti-hyperalgesic agent. From the results obtained that the phytosome system had a good physicochemical stability. The irritation test results showed that it was guaranteed safe for use on human skin. The results are impressive because it showed that the formula had a significantly effective activity as an anti-hyperalgesic compared to control.\(^{[21]}\)

**Gingerol phytosome**

Gingerol is an active compound contained in the ginger rhizome. In the concentration range of 25–100 μM, this compound is known to have an inhibitory activity of melanin synthesis through the activation of Akt/ PKB signaling pathway which is able to inhibit the melanogenesis process by decreasing the MITF and inhibit the enzyme tyrosinase activity.\(^{[22]}\) Singh in 2018 carried out a formulation of a gingerol compound for phytosome delivery system. The formulation was carried out using the antisolvent precipitation method and soya lecithin combined with chitosan as the carrier system. The results obtained a phytosome with an average particle size of 254–431 nm, zeta potential <−13 mV, and % release >80% at pH 7.4. In addition, the formulation of gingerol phytosome also significantly increased its bioavailability causing its effectiveness as an antioxidant, anti-inflammatory, and antibacterial activity also increased.\(^{[23]}\)

**Phytosome containing skin antioxidant agent**

Table 3 presents the phytosome formulation for antioxidant agent.

**Curcumin phytosome**

Curcumin is a polyphenol antioxidant compound derived
Table 3: Phytosome formulation for antioxidant agents

| Active pharmaceutical ingredients                  | Carrier             | Method                          | Reference |
|-----------------------------------------------------|---------------------|---------------------------------|-----------|
| Curcumin Meriva®                                    | Phosphatidyl choline| -                               | [58]      |
| Curcumin Meriva®                                    | Phosphatidyl choline| -                               | [24]      |
| Curcumin                                            | Soybean             | Solvent evaporation-ionic        | [25]      |
| Alpha-lipoic Acid, Curcumin Phytosome, and B-Group Vitamins | Phosphatidylycholine | -                               | [27]      |
| Curcumin-silybin-phytosome and α-R-Lipoic Acid      | Phosphatidylycholine| -                               | [28]      |
| Curcumin-silybin-phytosome and α-R-Lipoic Acid Mitigate | Phosphatidylycholine| -                               | [29]      |
| Curcumin                                            | Phosphatidylycholine| Solvent evaporation              | [26]      |
| Curcumin                                            | Phospholipid        | Solvent evaporation              | [30]      |
| Curcumin                                            | Phosphatidylycholine| Solvent evaporation              | [31]      |
| Quercetin                                           | Lecithin            | Solvent evaporation              | [34]      |
| Quercetin                                           | Phosphatidylycholine| Thin film hydration               | [32]      |
| Quercetin Phytosome®                                | Lecithin            | Solvent evaporation              | [33]      |
| Quercetin Phytosome®                                | Lecithin            | Solvent evaporation              | [59]      |

from the rhizome of Curcuma longa. Based on the results of several researches, curcumin has a lot of pharmacological activities such as cancer prevention, anti-inflammatory, antiviral, and antioxidant. Curcumin has also been shown to have benefits in the treatment of skin diseases, one of the derivatives of tetrahydrocurcumin that has been recommended in the use of cosmetics as a skin antioxidant. In recent year, curcumin phytosome (Meriva®) was studied its potential ameliorative on AlCl₃-induced hepatotoxicity. The result suggested that the curcumin phytosome has a good potential ameliorative activity on AlCl₃ hepatotoxicity.[24] Phytosome curcumin has a particle size around 23.21 ± 6.72 μm with the loading efficiency of 2.67 ± 0.23%,[25] 131.8 nm of particle size, Polydispersity Index (PDI) of 0.191, and zeta potential of -44.5 mV.[26] Phytosome formulation has successfully increased the performance of curcumin compound; curcumin phytosome could provide slower release profile and achieve a higher absorption level and longer half-life (3.16 h)[28] taking oral curcumin supplement twice a day before and after by a CTS patient scheduled for median nerve surgery was completely safe and effective[27] because it was not only increased the level of malondialdehyde and protein carbonyls and transformed the level of growth factor-b1, muscle actin smoothness and heat shock protein-47 gene expressions[29] but also decreased the glutathione, matrix metalloproteinase-2 activity, and collagen deposition. Besides, it induced the macrophage activation and nuclear factor kappa-B expression, significantly decreased the tumor necrosis factor-a and interleukin pancreatic cancers[30] and the enzyme level of antioxidant, and responses of the mice were increased.[31]

**Quercetin phytosome**

Flavonoid is a secondary metabolite that can be found in almost all plants. This compound acts as a survive agent and is known to have antioxidant, anticancer, anti-inflammatory, antiviral, and antiatherogenic activity. On its formulation, quercetin phytosomes have a particle size around 70 nm, zeta potential of (−44.6 mV), and high value of encapsulation efficiency of 98.4%,[32] which generally performed by thin film hydration method,[32] with the combination of phosphatidylycholine-cholesterol[32] or lecithin as a carrier. The same finding showed that the phytosome drug delivery system provided an excellent performance in increasing the quercetin performance; the erythema was significantly (P = 0.003) decreased, the effectiveness as a skin protector was increased; redness, itching, and inflammation were decreased, skin layers was improved; hydration was increased; was maintained,[34] and the solubility and absorption of the quercetin were also increased.[33]

**CONCLUSION**

Phytosome drug delivery systems have shown excellent results in improving bioactivity and pharmacological properties of natural product from plants including their capability as a brightening agent and antioxidant activity. Phytosome drug delivery system is able to improve solubility and penetration of active compounds through biological membranes allowing the maximum bioavailability. In addition, the capability to mediate controlled release systems, targeted delivery systems, and being able to increase the stability of active compounds make it as the first choice to increase the effectiveness and become promising technique for cosmeceutical product.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Zolghadri S, Bahrami A, Hassan Khan MT, Munoz-Munoz J, Garcia-Molina F, Garcia-Canovas F, et al. A comprehensive review on tyrosinase inhibitors. J Enzyme Inhib Med Chem. 2019;34:279-309.
39. Kuamway RS, Mruthunjaya K, Gupta MK. Hepatoprotective effect of Gallic acid and Gallic acid Phytosome against Carbon Tetrachloride induced damage in albino rats. Res J Pharm Technol. 2012;5:677-81.

40. Ferrara T, De Vincentiis G, Di Pierro F. Functional study on Boswellia phytosome as complementary intervention in asthmatic patients. Eur Rev Med Pharmacol Sci. 2015;19:3757-62.

41. Ochi MM, Amoabediny G, Rezayat SM, Akbarzadeh A, Ebrahimi B. In vitro co-delivery evaluation of novel pegylated nano-liposomal herbal drugs of silibinin and glycyrrhizic acid (nano-phytosome) to hepatocellular carcinoma cells. Cell J. 2016;18:135.

42. Gianni B, Andrea L, Shu H, Maria RC, Beatrice F. Greenselect Phytosome for Borderline Metabolic Syndrome. Evidence-Based Complement Altern Med. 2013;1-7.

43. Maryana W, Rahma A, Mudhakir D, Rachmawati H. Phytosome containing silymarin for oral administration: Formulation and physical evaluation. In: Journal of Biomimetics, Biomaterials and Biomedical Engineering. Trans Tech Publ; 2015. p. 54-65.

44. Rathee S, Kamboj A. Optimization and development of antidiabetic phytosomes by the Box–Behnken design. J Liposome Res. 2018;28:161-72.

45. Mazumder A, Dwivedi A, Fox LT, Brümmer A, Du Preez JL, Gerber M, et al. In vitro skin permeation of sinigrin from its phytosome complex. J Pharm Pharmacol. 2016;68:1577-83.

46. Hou Z, Li Y, Huang Y, Zhou C, Lin J, Wang Y, et al. Phytosomes loaded with mitomycin C–soybean phosphatidylcholine complex developed for drug delivery. Mol Pharm. 2013;10:90-101.

47. Li Y, Wu H, Jia M, Cui F, Lin J, Yang X, et al. Therapeutic effect of folate-targeted and PEGylated phytosomes loaded with a mitomycin C–soybean phosphatidylcholine complex. Mol Pharm. 2014;11:3017-26.

48. Chi C, Zhang C, Liu Y, Nie H, Zhou J, Ding Y. Phytosome-nanosuspensions for silybin-phospholipid complex with increased bioavailability and hepatoprotection efficacy. Eur J Pharm Sci. 2020;144:105212.

49. Telange DR, Patil AT, Pathe AM, Fegade H, Anand S, Dave VS. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. Eur J Pharm Sci. 2017;108:36-49.

50. Mazumder A, Dwivedi A, Du Preez JL, Du Plessis J. In vitro wound healing and cytotoxic effects of sinigrin–phytosome complex. Int J Pharm. 2016;498:283-93.

51. Sandhya S, Chandra SJ, Vinod KR, Rao KN V, Banji D. Preclinical studies of a novel polyherbal phyto–complex hair growth promoting cream. Asian Pac J Trop Biomed. 2012;2:S296-304.

52. Häsch J, Bohnet J, Fricker G, Skarke C, Artaria C, Appendino G, et al. Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome®) of Boswellia extract. Fitoterapia. 2013;84:89-98.

53. Gilardini L, Pasqualinotto L, Di Pierro F, Rioso P, Invitti C. Effects of Greenselect Phytosome® on weight maintenance after weight loss in obese women: a randomized placebo-controlled study. BMC Complement Altern Med. 2016;16(1):233.

54. Abdelkader H, Longman MR, Alany RG, Pierscience B. Phytosome-hyaluronic acid systems for ocular delivery of L-carnosine. Int J Nanomedicine. 2016;11:2815.

55. Ju PH, Jun JS, Ki KC, Jin HT. Anti-inflammatory effect of Centella asiatica phytosome in a mouse model of phthalic anhydride-induced atopic dermatitis. Phytomedicine Int J Phyther Phytopharm. 2018;43:110-9.

56. Sbrini G, Brivio P, Fumagalli M, Giavarini F, Caruso D, Racagni G, et al. Centella asiatica L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex. Nutrients. 2020;12:355.

57. Palachai N, Wattanathorn J, Muchimapura S, Thukham-mee W. Antimetabolic Syndrome Effect of Phytosome Containing the Combined Extracts of Mulberry and Ginger in an Animal Model of Metabolic Syndrome. Oxid Med Cell Longev. 2019;2019.

58. Maida, Giuseppe. Clinical usefulness of oral supplementation with curcumin phytosome in patients with radiculopathy due to spondyloarthritis or discopathy. Minerva Ortopedica e Traumatologica, 2016;67.2:75-8.

59. Riva A, Vitale JA, Belcaro G, Hu S, Feragalli B, Vinciguerra G, et al. Quercetin phytosome® in triathlon athletes: a pilot registry study. Minerva Med. 2018;109:285-9.