Review Article

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

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Abstract

Plants have been used as traditional medicine since ancient times for treating the diseases, metabolite active compounds from plants have excellent bioactivity, and pharmacological properties from plants are used as skin whitening agent and antioxidant in multiple mechanisms of action. However, these compounds have physicochemical limitations in terms of its poor solubility and penetration into the cells membrane. Phytosome drug delivery system can be the primary choice to improve the physicochemical properties, which allows increasing the effectiveness. This review aimed to summarize and discuss the phytosome formulations of potential active compounds as skin whitening agent and skin antioxidant, which 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

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.[1] 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.[2]

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Natural product has 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 also 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

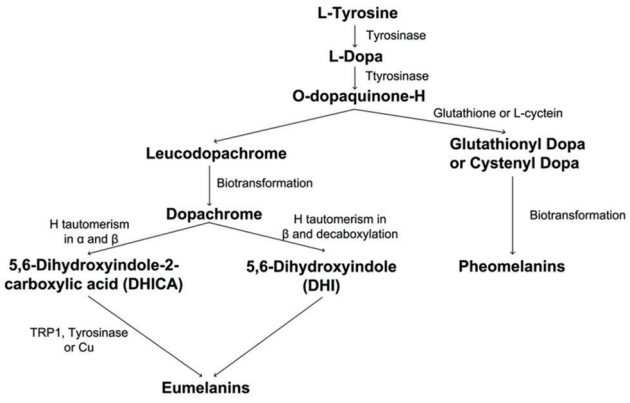

Figure 1: Melanin biosynthesis

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.[7] Phytosome drug delivery system is shown in Figure 2.

Recent formulation of phytosome drug delivery system

Table 1 provides recent formulation of phytosome drug delivery system.

Phytosome drug delivery system for tyrosinase inhibitor as a skin whitening agent

Table 2 presents the phytosome formulation for potential tyrosinase inhibitor compounds.

Table 1: Recent formulation of phytosome drug delivery system

Active Parmaceutical 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]
Trigonellafoenum-graecum	L-α-Phosphatidylcholine and colestrol	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	[38]
Gallic acid (GA, 3,4,5-trihydroxybenzoic acid)	Phospholipid complex	-	Hepatoprotectiv agent	[39]
Boswellia	Phospholipid complex	-	complementary intervention in asthmatic patients	[40]
Silinin and glycyrhizic acid	dipalmitoylphosphatidylcholine (DPPC), cholesterol (CHOL), and methoxy-polyethylene glycol 2000 (PEG2000) - derived distearoylphos-phatidylethanolamine (mPEG2000-DSPE)	thin layer film hydration	Anti tumor	[41]
Green select	Phospholipid cimplex	-	Borderline metabolic syndrome	[42]
Silymarin	Soy Phosphatidylcholine/SPC	Solvent evaporation	Hepatoprotective agent	[43]
Citrullus colocynthis (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	Phospolipon	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	Lechitin delivery form	-	Anti-inflammatory	[52]
Greenselect	Phospholipid complex	-	Weight maintenance	[53]
Soybean, *Glycine max (L.)* Merrill	Phosphatydilcholine	solvent evaporation, cosolvency, and salting out	prevent or manage obesity	[17]
L-carnosine	Phospholipid-Hyaluronic acid	Solvent evaporation	Ocular delivery	[54]

Table 2: Phytosome formulation for potential tyrosinase inhibitor compounds

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

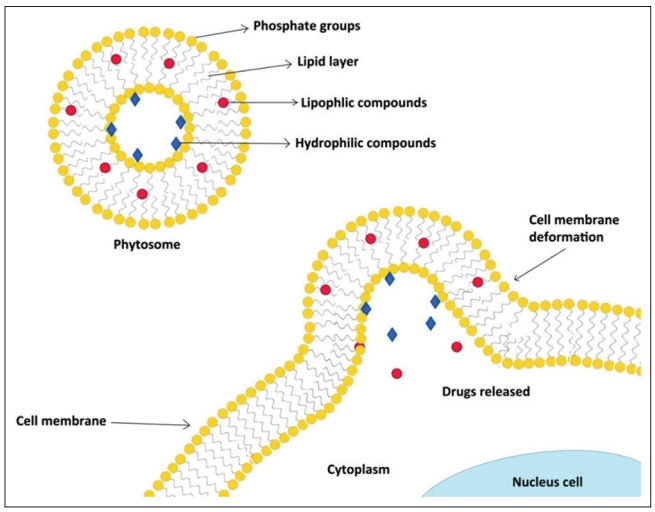

Figure 2: Phytosome drug delivery system

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 polyphenyl including flavonols, flavonoids, catechins, glycosides, phenolic acids, and aglycones and has been proven to have effectiveness as enzyme tyrosinase inhibitors with IC_{50} 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]

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 absorbtion 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.[15]

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.[16] 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 antihyperalgesic 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 antihyperalgesic 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	Refference
Curcumin Meriva®	Phosphatydil choline	-	[58]
Curcumin Meriva®	Phosphatydil choline	-	[24]
Curcumin	Soybean Phopholipid-Chitosan	Solvent evaporation-ionic gelation method	[25]
Aplha-lipoic Acid, Curcumin Phytosome, and B-Group Vitamins	Phosphatidylcholine	-	[27]
Curcumin, silybin-phytosome and α-R-Lipoic Acid	Phosphatidylcholine	-	[28]
Curcumin, silybin phytosome and α-R-Lipoic Acid Mitigate	Phosphatidylcholine	-	[29]
Curcumin	Phosphatidylcoline	Solvent evaporation	[26]
Curcumin	Phospholipid	Solvent evaporation	[30]
Curcumin	Phosphatidylcholine	Solvent evaporation	[31]
Quercetin	Lecithin	Solvent evaporation	[34]
Quercetin	Phosphatidylcoline	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 $AlCl_3$-induced hepatotoxicity. The result suggested that the curcumin phytosome has a good potential ameliorative activity on $AlCl_3$ 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);[25] 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[28] 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 cancer;[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 phosphatidylcholine-cholesterol[32] or lecithin as a carrier.[33] 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.

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