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A Review on Phytosome Technology as a Novel Approach to Improve The Bioavailability of Nutraceuticals

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Abstract

The bioavailability and absorption of water soluble phytoconstituents is erratic due to poor solubility of these constituents in gastrointestinal tract. This can be overcome by a novel delivery system known as phytosome technology in which water soluble phytoconstituents are allowed to react with phospholipids. For better and improved bioavailability, natural phytoconstituents must have a good balance between hydrophilicity (helps in dissolution in gastro-intestinal fluids) and hydrophobicity (helps to cross lipid rich cell membranes). This is achieved through phytosome technology. Phospholipids have a dual solubility and acts as an emulsifier. Phytosome technology acts as a bridge between novel and conventional delivery systems. Many products are available in the market based on this phytosome technology which include popular herbal extracts such as Ginkgo biloba, Silybum marianum, grape seed, olive oil flavonoids etc.

Keywords*: Phytosome, liposome, phytoconstituent, bioavailability*

1. Introduction

Phytosomes are lipid compatible molecular complex and are little cell like structures which are composed of "phyto" which means plant and "some" meaning cell-like (Nilesh et al., 2010; Choubey and Ankur, 2011; Joseph et al., 2012). Phytosome is a patented process which was developed by a leading supplier of nutraceutical ingredients (Indena; Choubey and Ankur, 2011). The technology involves the incorporation of phospholipids into standardized extracts improving their absorption and bioavailability (Kidd and Head, 2005; Bombardelli et al., 1989). During phytosome process, a little cell like structure is produced as a result valuable

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components of any herbal extract are protected from destruction by digestive secretions and gut bacteria. Phytosomes show a transition from hydrophilic environment into the lipophilic environment of the enterocyte cell membrane followed by an entry into the cell finally reaching into blood (Yi., 2000). This increases the bioavailability of the nutraceutical components (Figure 1).

There are numerous plant products available in market and most of the biologically active constituents of these plant products are water soluble or polar molecules (Nilesh et al., 2010). Due to their multiple-ring large molecular size which cannot be absorbed by passive diffusion and poor lipid solubility and miscibility limiting their ability to cross the lipid-rich biological membranes, the bioavailability of water-soluble phytoconstituents (flavonoids, tannins, terpenoids etc.) is decreased (Manach et al., 2004; Choubey and Ankur, 2011; Swami et al., 2012).

In comparison to simple herbal extracts, phytosomes are more available and have an enhanced capacity to cross the lipid rich biomembranes finally reaching the blood (Ezio et al., 1989). Many plant drugs that are incorporated to phytosome process as herbal extracts including *Ginkgo biloba*, green tea, ginseng, milk thistle, hawthorn and grape seed.

Phytosome Technology

The water soluble constituents (flavonoids and terpenoid) of plant extracts have the affinity to bind directly with phosphatidylcholine (Choubey and Ankur, 2011; Bombardelli., 1991). A stiochiometric amount of phosphatidylcholine (phospholipid) is allowed to react with standard extract in a non-polar solvent (Bombardelli et al., 1994). Phosphatidylcholine being a bifunctional compound possessing a lipophilic phosphatidyl moiety and hydrophilic choline moiety helps in improvement of bioavailabiliity of water soluble phytoconstituents (like simple flavonoids). The hydrophilic moiety (choline group) binds with water soluble phytoconstituents and forms the body while as lipid soluble phosphatidyl moiety forms tail and envelops the choilne bound material. As a result, a lipid compatible molecular complex is formed called phytosome. The molecules are bound to polar choline moiety of phosphatidyl choline through chemical bonds which can be demonstrated by specific spectroscopic techniques (Bombardelli et al., 1991).

Method of Preparation

Phytosomes are obtained by reacting 2-3 moles or 1 mole of phospholipd such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of active phytoconstituents (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, ethy acetate). The complex is then

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isolated by evaporation of solvent under vacuum or precipitation with non solvent such as aliphatic hydrocarbons or by lyophilization (freeze-drying) or spray drying (Awasthi et al., 2011; Vitamedics, 2008). The most appropriate ratio of phospholipid to phytoconstituent is 1:1 (Phytosomes, 2010; Jose and Bombardelli, 1987). The organization of phytosome molecular complex in which a flavonoid molecule is enveloped by a phospholipid molecule is shown in Figure 2.

Bioavailability of Phytosomes

It is evident from many research studies that phytosomes have an improved absorption and bioavailability when compared to the conventional means. Most of the research studies are focused on *Silybum marianum* (milk thistle), the fruit of which contains a water-soluble phytoconstituent (flavonoids) which is known to have a hepatoprotective effect. But these flavonoids are poorly absorbed. The chief and most potent constituent of milk thistle is Silybin. A brief summary of some of the research studies is given as:

- According to Crema et al., 1990, when single oral doses of Silybin directly bound to phosphatidylcholine (Silybin phytosome) are fed, its absorption was approximately seven times more than the absorption from regular milk thistle extract containing 70-80% silymarin content).
- A research study was conducted by (Yanyu et al., 2006) in which he prepared silymarin phytosome and has shown its pharmacokinetics in rats. The phytosome was administrated to rats orally. The results showed that the bioavailability and biological effects of Silybin was increased remarkably.
- Some of the studies have reported the better results produced by consuming ginkgo phytosome than the conventional gingko extract. A bioavailability study was conducted on healthy human volunteers in which it was found that the levels of flavonoids and terpenes (GBE constituents) peaked after 3 hours and persisted longer last for 5 hours.

  One study shows that some patients suffering from Reynaud's disease and intermittent circulation were fed with ginkgo phytosome which was shown to produce a 30-60% greater improvement compared to regular standardized GBE (*Ginkgo biloba* extract).

Advantages of phytosome technology

The phytosome technology has revolutionized the nutraceutical industry by serving the following benefits (Kidd & Head, 2005; Bombardelli et al. 1994; Bombardelli et al., 1991; Choubey and Ankur, 2011; Vyas and Khar, 2002;

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Sharma and Sikarwar, 2005; Joseph et al., 2012; Semalty et al., 2007; Naik and Panda, 2008):

- Phosphatidylcholine, one of the components of phytosome, has a dual function that it acts a carrier as well as has a health benefit such hepatoprotective effect.
- The composition of phytosome is safe and the components are approved for pharmaceutical use.
- The absorption and bioavailability of water soluble phytoconstituents is increased. This results in better therapeutic effects.
- Because the bioavailability of phytoconstituents is increased, therefore, the dosage required to produce desirable effect is reduced.
- The phytosomes have a better stability than liposomes. This is because the former consists of chemical bonds while as it is absent in the later.
- Phospholipids add to the nutritional value of the plant extract.
- High market demand for products.
- The process of manufacturing phytosomes is relatively simple.
- Phytosomes have the ability to permeate through skin with quite ease and thus enhances their effectiveness.
- The water soluble phytoconstituents are enveloped by phospholipid which prevents them from destruction by digestive enzymes and gut bacteria.
- It helps in proper drug delivery to targeted tissue.
- Phosphatidylcholine nourishes skin besides acting as a carrier because it is part of cell membrane.
- They can be used for systematic targeting as phytosomes are able to transit from hydrophilic environment into lipophilic environment of enterocyte cell and from there into cell.

Difference between phytosomes and liposomes

Applications of Phytosome Technology and commercially available products based on Phytosome Technology

Milk thistle (*Silybum marianum*). Much of the studies have been conducted on the application of phytosome technology to *Silybum marianum* (milk thistle) which contains flavonoids, a liver-protectant phytoconstituent. Milk thistle has shown positive effects in treating various kinds of diseases (hepatitis, cirrhosis, fatty infilteration of the liver, etc.) (Nilesh et al., 2010). *S. marianum* has a strong antioxidant activity which boosts the resistance of liver against toxic constituents (Valenzuela et al., 1989). The three flavonoids which are present in *S. marianum* include silybin,

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silydianin and silychristin with silybin predominating followed by silydianin and silychristin. Silybin is the most potent of the three and is actually a flavonolignan (Hikino et al., 1984). Silybin conserves glutathione in parenchymal cells (Valenzuela et al., 1989) and thus protects liver cells while as PC helps repair and replace cell membranes (Kidd, 1996). It is clear that silybin has a better hepatoprotective effect which is limited by its poor bioavailability which can be overcome by producing a Silybin phytosome (Nilesh Jain et al., 2010).

Green tea. Green tea is a strong antioxidant. According to a research from University of Kansas, the antioxidant potential of green tea is 100 times greater than vitamin C, 25 times greater than vitamin E and twice as strong as resveratol (CNN- American Chemical Society). A phytosome product with the commercial name GreenSelect® phytosome is available in the market. It contains a totally standardized poyphenolic fraction (containing not less than 66.5% and is mainly characterized by the presence of epigallocatechin and its derivatives. Francesco et al., (2009) conducted a research in which fifty subjects were fed with green tea extract plus hypocaloric diet while other fifty subjects were fed only with hypocaloric diet. After 90 days of treatment, a significant weight loss and decreased body mass index (BMI) was observed in the human subjects fed with both green tea extracts and hypocaloric diet than the human subjects fed with only hypocaloric diet. From the study, it was also observed that waistline in male subjects only (Nilesh et al., 2010).

Hesperetin. A novel hesperetin was developed by (Mukherjee et al., 2008) by combining and complexing hesperetin with hydrogenated phosphatidyl choline. Mukherjee et al. (2008) also studied its antioxidant activity and pharmacokinetic studies in CC14 intoxicated rats along. The results of the study showed the phytosome has shown high antioxidant activity. Pharmacokinetic studies have revealed the improved bioavailability of phytosomes than the parent molecule at the same dosage.

Quercetin. The commercially available quercetin phytosome is Meriva®(500mg) 60VC. The constituents present in Curcumin (curcumin, demethoxycurcumin, bisdemethoxycurcumin) are poorly absorbed when taken orally which could be overcome by phytosome technology. In Meriva®, each curcuminoid molecule is individually complexed with molecules of the vital cell membrane nutrient phosphatidylcholine (PC). This results in better and faster entry of curcumin molecules into the cells and improving beneficial effects such as: it protects against

Figure 1 Green Tea Extract

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premature molecular break down, promotes healthy functioning of joints and other organs.

Curcumins help in protecting cell membrane due to its high antioxidant activity. Curcumin helps to prevent the free radical damage on the cell membrane, DNA and genes (Soni and Kuttan, 1992). Membranes are prone to oxidative damage but curcumin acts as a guard to protect them from lipid peroxidation (Barry et al., 2009; Jurenka, 2009)

Ginkgo (*Ginkgo biloba*) phytosome. It contains 24% of ginkgoflavonoids from *Ginkgo biloba*. It protects brain and vascular linings and has an anti-skin ageing (Rajendra, 2011). According to some results, ginkgo phytosome produced better results as compared to conventional standardized *Ginkgo biloba* extract (GBE) containing 24% ginkgo flavones glycoside and 6% terpene lactones (Bhattacharya, 2009). A study was conducted on 15 healthy human volunteers in which the bioavailability of ginkgo phytosome has been compared with GBE. Volunteers were divided into two groups and were administered respectively with Ginkgoselct® and Ginkgoselect® phytosome. The subjects switched formulations after a week of wash out. Blood samples were taken from each human subject at 30, 60, 120, 180, 240, 300 and 400 minute after ingestion. Detection of terpenes lactones was performed by liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS). It was found from the results that Ginkgolides A, B and bilobalide were absorbed to a higher extent (about three times after administration of Ginkgoselect® phytosome as it can be seen in figure 5 (Source: (Phytosome- More bioavailable).

Olive (*Olea europaea)* oil. A commercially available phytosome- ***Oleaselect***™ PHYTOSOME is available in the market based on olive oil polyphenols (Pandey and Patel, 2010). It is a strong antioxidant, anti-inflammatory and anti-hyperlipidemic (Rajendra, 2011). It inhibits the oxidation of LDL cholesterol and is cardioprotective.

Bilberry. A commercially available phytosome based on bilberry is available in market with trade name - ***Mirtoselect*®** PHYTOSOME. It contains an extract of bilberry which is a source of anthocyanosides. These improve the permeability of blood vessels are strong antioxidants (Pandey and Patel, 2010).

Echinacea angustifolia*. *Polinacea™ is a preparation made from *Echinacea angustifolia* which contains echinacosides and a unique high-molecular polysaccharide. This helps in improving immune system.

Grape (*Vitis vinifera*). ***Leucoselect*®** PHYTOSOME is a phytosome preparation based on grape anthocyanidins. Grape seed phytosome is composed of polyphenols complexed with

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phospholipids. It has a strong antioxidant activity and is cardioprotective (Nilesh et al., 2010).

Melilotus officinalis. Lymphaselect™ PHYTOSOME includes a standardized extract from *Melilotus officinalis.* It is used to treat venous disorders.

Conclusion

There are many nutraceutical products available in markets which provide health benefits in addition to their basic nutrition-providing properties. Their poor bioavailability and absorption is limiting their use by consumers which could be overcome by phytosome technology. Phytosome preparation is done by non-conventional method. The absorption of phytosome in gastrointestinal tract is increased appreciably and thus its level in plasma is increased. This property is attributed to its dual solubility in lipophilic phase as well as aqueous phase. The nutraceutical products based on phytosome technology become present at the site of action of liver, kidney, brain, heart) at similar or less dose as compared to conventional plant extract.

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Table 1: Table showing difference between phytosome and liposome

Property	***Phytosome***	***Liposome***	***Source***
Bonding	It is a unit of few molecules bonded together	It is an aggregate of many phospholipid molecules that encloses other phytoactive molecules without specifically bonding to them.	(Pandey and Patel, 2010)
Bioavailability and Absorption	It has much better bioavailability and absorption	Its bioavailability and absorption is lesser than phytosome.	(Prashant et al., 2009)
Arrangement of molecules	In phytosome, phospholipid (phosphatidylcholine) and an individual phytoconstituent are present in 1:1 or 2:1 ratio depending on the substance.	In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.	(Sharma and Roy, 2010)

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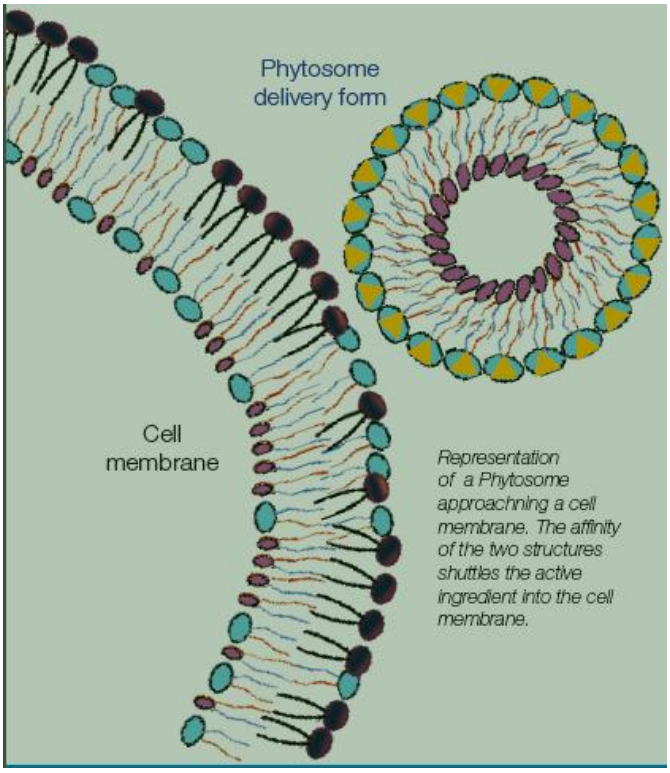

Figure 1 Representation of a phytosome approaching a cell membrane

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Figure 2 Organization of the phytosome

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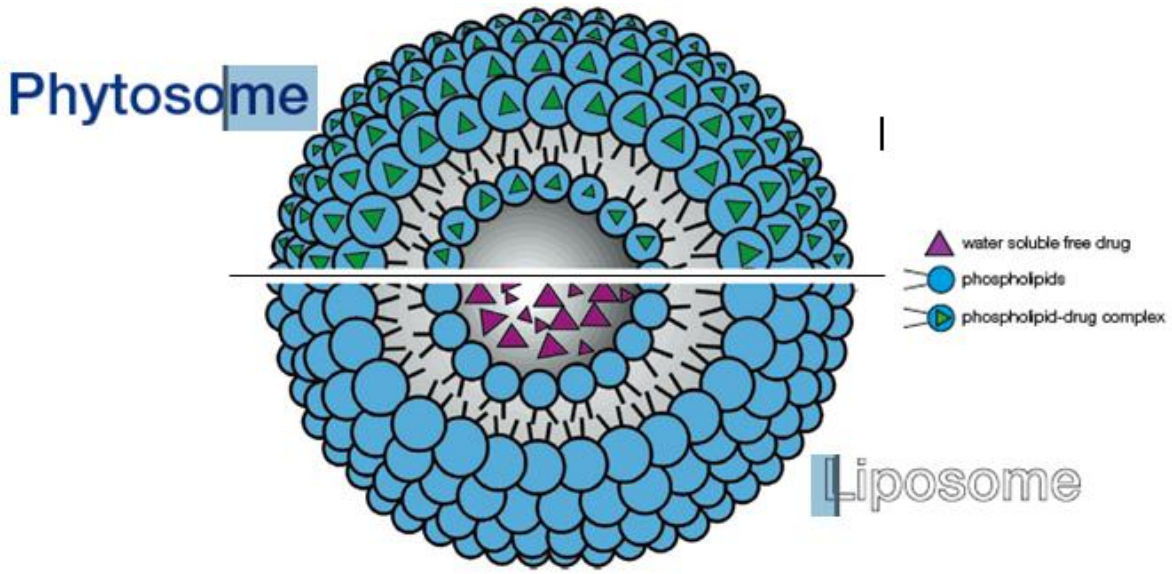

Figure 3 Diagram representing the difference between liposomes and phytosomes

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Figure 3 Green Tea Extract

