OPEN ACCESS
DOI: https://doi.org/10.52756/bhietm.2022.e01.008

Chapter- 8

Phytosomes: a cutting-edge technique for herbal drug delivery and its clinical applications

Sanjib Kumar Das, Rakesh Acharya and Koushik Sen*

Keywords: Phytoconstituents, Drug delivery, Phytochemicals, Phytosomes, Bioavailability.

Abstract:

In past few decades extensive research has been conducted worldwide to explore the therapeutic potential of various medicinal herbs and their active phytoconstituents. Although plant extracts or phytochemicals purified from plant parts, show robust pharmacological efficiency in vitro but poor bioavailability, low absorption rate and selectivity might limit the clinical application of these phytochemicals in the practical field. Different techniques have been employed to manufacture effective vehicle systems to overcome these obstacles. Among them, phytosome technology appears to be a promising one to enhance bioavailability and other impediments. Phytosomes are novel drug delivery techniques synthesized by conjugating phospholipids with water-soluble herbal compounds or bioactive phytochemicals. This novel approach ultimately improves the availability and absorption of these phytoconstituents and greatly enhances their clinical efficacy which can be employed in the treatment of several diseases. This chapter is designed to provide a piece of updated information on the structure, and characterization of phytosomes and its clinical application for the management of various ailments.

Introduction:

From ancient times, different parts of the plant and their active components have been utilized to treat different ailments. Modern drugs with several side effects are unable to cure all diseases. Natural products have been used to treat several diseases without any undesirable outcomes.

Sanjib Kumar Das
Department of Zoology, Jhargram Raj College, Jhargram, West Bengal, India
E-mail: sanjib.biology2012@gmail.com
Orcid iD: https://orcid.org/0000-0002-2436-0508
Rakesh Acharya
Department of Zoology, Jhargram Raj College, Jhargram, West Bengal, India
E-mail: rakeshjgm7@gmail.com
Dr. Koushik Sen*
Department of Zoology, Jhargram Raj College, Jhargram, West Bengal, India
E-mail: koushiksen1987@gmail.com
Orcid iD: https://orcid.org/0000-0002-6995-7682
***Corresponding Author**: koushiksen1987@gmail.com

© International Academic Publishing House, 2022
Bhanumati Sarkar (eds.), The Basic Handbook of Indian Ethnobotany and Traditional Medicine, Vol. 1
ISBN: 978-81-957954-1-3
Published online: 23rd August, 2022

However, due to poor bioavailability, less aqueous as well as lipid solubility, absorption rate, improper molecular size, destruction in the gut, highly distributed throughout the body, less plasma half-life, poor stability, the clinical application of numerous phytoconstituents is still questionable. To overcome all these obstacles several novel drug delivery systems have emerged to deliver phytochemicals. It includes novel herbal formulations like niosomes, transferosomes, liposome, ethosomes, proniosomes, and nano capsules. Amongst all these approaches, phytophospholipid complexes, popularly known as phytosomes, appeared to be a great technique for enhanced bioavailability (Anjana et al., 2017).

The term "Phyto" means plant, while "some" refers to cell-like. Phytosomes or Herbosomes are the cell-like vesicular drug delivery system; with enhanced absorption rate and improved bioavailability of drugs, phytosomes overcome the limitations of traditional drug delivery systems (Bhattacharya et al., 2009; Nagar et al., 2019). Phytosomes are complexes made up of bioactive plant extract or phytochemicals (like flavonoids, terpenoids and tannin, etc) surrounded and bounded by lipids. Phytosomes are developed via molecular association in which a hybrid bond formation occurs between plant extract or water-soluble phytoconstituents and phospholipids, producing a lipid-miscible molecular complex with reduced polarity having the capability to cross the plasma membrane. In a nutshell, phytosomes are active hydrophilic phytoconstituents covered by lipid-soluble phospholipid, having better drug encapsulation efficiency, enhanced bioavailability, absorption rate and high stability.

Phytosome Structure:

Phytosomes are formed by the interaction between active phytoconstituents and the polar head of phospholipids (Fig. 1.) (Khan et al., 2013). Interactions between phospholipids and bioactive phytoconstituents enable the phospholipid complexes to be an essential integrated part, involving the anchorage of phospholipid head groups but the long fatty acid chains do not take part in complex formation. The two long-moving fatty acid chains encapsulate the polar part of complexes to form a lipophilic outer layer. For the production of Phytosomes 2-3 moles or 1 mole of phospholipid such as phosphatidylcholine, phosphatidyl- ethanolamine or phosphatidyl-serine combined with 1 mole of bioactive component (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, ethyl acetate). The phyto-phospholipid complex formed agglomerates when diluted in water (Ghanbarzadeh et al., 2016).

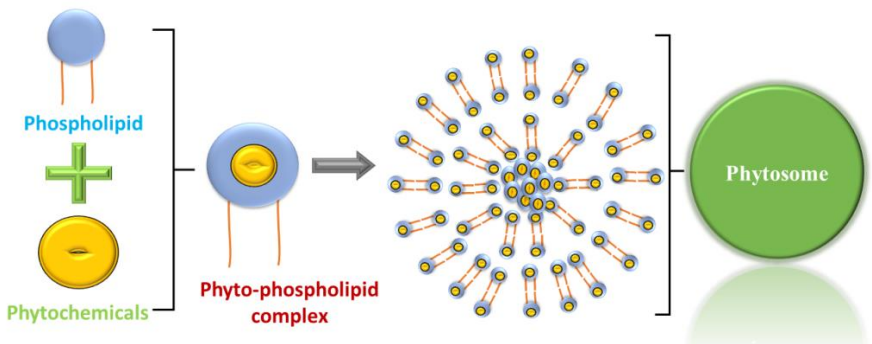

Figure 1. Diagram Representing Basic Principle of Phytosome Formulation

Phyto-active Components:

Phytochemicals or plant chemicals are a wide range of naturally occurring bioactive compounds of plant origin. Bioactive phytochemicals can interact with different types of components of living organisms, hence, exerting their beneficial effects. Alkaloids, phenolics, terpenoids, carbohydrates, lipids and other nitrogen-containing molecules are the key categories of phytochemicals. Among all these phytochemical compounds, molecules with an active hydrogen atom (-COOH, -NH, $-NH_2$, etc.), like polyphenols, has been selected as the suitable one to synthesize phytosome. A hydrogen bond can be formed between herbal derivatives and the hydrophilic parts of amphiphile molecules by an active hydrogen atom. Polyphenols are the most frequently found phytochemicals in plant-based foods. Many researchers reported that Polyphenols have potential health benefits in a variety of diseases, including inflammation, neurodegenerative disease, cancer, cardiovascular diseases, type 2 diabetes, and obesity (Kondratyuk et al., 2004; Tsao et al., 2010; Barani et al., 2021).

Phospholipids:

Phospholipids help in digestion and also have nutritional properties such as giving nutrition to brain cells, helping in liver cell regeneration and also can act as a carrier molecule for both polar and non-polar molecules (Singh et al., 2011). Different kinds of phospholipids obtained from various sources can be used such as soy lecithin, phosphatidylserine, and 1,2- distearoyl-Sn-glycero-3- phosphatidylcholine. Egg yolk and plant seeds are both rich sources of phospholipids and are classified depending on backbone *viz* sphingomyelins and glycerophospholipids. Amongst glycerophos-pholipids, phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS) and phosphatidylinositol (PI) are the key compounds (Li et al., 2015). PC, PS and PE are the main phospholipids used in phytosome synthesis. PC is frequently used for synthesizing phospholipid complexes. PC is an amphipathic molecule that enables its solubility in both water and lipid. Moreover, being an essential component of the plasma membrane, PC has strong biocompatibility and minimal toxicity (Suriyakala et al., 2014; Lu et al., 2019).

Solvents:

Researchers have produced phyto-phospholipid compounds using a range of solvents. Presently, protic solvents like ethanol and methanol were used to synthesize phyto-phospholipid complexes instead of aprotic solvents like methylene chloride, cyclic ethers, halogen derivatives, ethyl acetate, and hydrocarbons because of their higher success rates (Khan et al., 2013; Suryakala et al., 2014). Various solvents have been successfully investigated. Ethanol can be a beneficial and popular solvent that leaves minimum residue and cause minimum harm when the yield of phospholipid complexes is high enough (Lu et al., 2019). Many research studies have recently used the supercritical fluid (SCF) process to manipulate the size, shape, and morphology of the material of interest. Supercritical anti-solvent process (SAS), one of the SCF technologies,

becoming a promising technique for producing micronic and submicronic particles with controlled size and size distribution (Semalty et al., 2014).

Stoichiometric Ratio of Phospholipids and Active Phyto-Constituents:

Normally, phytosomes are developed by reacting phytoactive constituents with natural or synthetic phospholipids in the 0.5-2.0 molar ratio range. A stoichiometric ratio of 1:1, on the other hand, is thought to be the most efficient ratio for preparing phospholipid complexes, e.g., quercetin-phospholipid complexes have been produced through combining Lipoid S 100 and quercetin at a molar ratio of 1:1, curcumin phytosomal softgel and phytosomes have been developed by incorporating curcumin and SPC Lipoid® S 100 in molar ratio of 1:1. However, different stoichiometric ratios of phytoconstituents and phospholipids have also been used. Silymarin-phospholipid complexes have been synthesized with different stoichiometric ratios such as 1:5, 1:10 and 1:15 and the results indicate that phytosome complexes produced with a stoichiometric ratio of 1:5 showed the best physical properties and the highest loading capacity.

Properties of Phytosomes:

Chemical properties:

Phytosomes are made by reacting a stoichiometric amount of phospholipid with standardized plant extracts as the substrate. According to the spectroscopic data, the phospholipid substrate interaction is caused by the formation of a hydrogen bond between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate (Chauhan et al., 2009). The size of Phytosomes varies from 50 nm to a few hundred µm (Tripathy et al., 2013). Phytosome, after treating with water, changed their shape to a micellar-like structure and looks like liposomes when observed under photon correlation spectroscopy (PCS). The data gathered from H1 NMR and C13 NMR indicates, the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are wrapped around the active principle producing lipophilic envelope (Patel et al., 2013; Jain et al., 2005; Dayan et al., 2000). The complexes are usually soluble in aprotic solvents, less soluble in lipids and insoluble in water (Maffei et al., 1994)

Biological properties:

In comparison to traditional herbal extracts, phytosomes are more advanced herbal products that are better absorbed, utilized, and subsequently yield better results. The increased bioavailability of phytosomes over non-complexed botanical derivatives has been demonstrated by pharmacokinetics experiments or by pharmacodynamic tests in laboratory models and human subjects. (Franco and Bombardelli, 1998).

Preparation Method:

Several methods for preparing phytosomes have been proposed, including the rotary evaporator method, anti-solvent precipitation technique, freeze-drying co-solvency, and salting-out technique. The evaporator approach and solvent evaporation are popular and widely used

techniques for producing phyto-phospholipid complexes. Shan et al. (2012) applied the solvent evaporation method to synthesize oleanolic acid-phospholipid complexes whereas, berberine-phospholipid complexes (P-BER) prepared by rapid solvent evaporation method followed by a self-assembly procedure to develop more efficient berberine drug delivery system. In the solvent evaporation process, lipid components were combined with an organic solvent and then the solvent was pulled out by vacuum rotary evaporation (Yu et al., 2016). By using the solvent evaporation method, recently Telange et al. (2019) developed an apigenin-phospholipid phytosome to increase the bioavailability, solubility, and antioxidant activity of the compound in vivo. To increase the bioavailability of dihydromyricetin, which has the potential for antibacterial, antioxidant, hypoglycemic, anti-inflammatory, and hypolipidemic effects, Zhao et al. (2017) developed the dihydromyricetin-phospholipid complex via solvent evaporation approach. Singh et al. reported the synthesis of lawsone-loaded phytosome by using the anti-solvent precipitation method; during this process, lawsone and soy lecithin were refluxed with dichloromethane at a temperature not exceeding 60 °C and then, to get the precipitation, N-hexane was added and stored overnight in vacuum desiccators (Singh et al., 2015). Karole et al. (2019) employed an anti-solvent precipitation method to construct phytosomes utilizing *Bombax ceiba* extract. In addition to the above-mentioned methods, anhydrous co-solvent lyophilization is another method to produce phyto-phospholipid complexes. For example, Diosmin was first dissolved in DMSO, added to the SPC solution, and stirred for three hours for complex formation. Kaempferol-phospholipid complexes were also produced by using the lyophilization process (He et al., 2010; Al SJE et al., 2012; Freag et al., 2013; Telange et al., 2016). Li et al. devised supercritical anti-solvent precipitation to make puerarin phospholipid complexes, and they suggested that this method was better than other ones for making drug phospholipid complexes. The phyto-phospholipid complex was also developed by using the salting-out method and the film formation method (Lu et al.,2019).

Characterization of Phytosomes:

Solubility and partition coefficient:

Determining solubility in both water or natural solvents and the n-octanol/water partition coefficient (P) is critical to represent active constituents, active constituent phytophospholipid complexes and physical mixtures and generally, phyto-phospholipid complexes have higher lipophilicity and hydrophilicity than active constituents, and exhibit better lipophilicity (Pathan et al., 2011).

Surface Charge:

Zeta potential (total charge produced by medium) is defined as the electrical charge carried by the phytosomes in emulsions. Depending on the composition of phytosome, Zeta potential may be negative, positive, or neutral (Chibowski et al., 2016; Smith et al., 2017). The stability of phytosome in a medium is reflected by the value of Zeta potential. A stable phytosome emulsion represents a zeta potential greater than or less than 30 mV (Ojha, 2018). The electrostatic

characteristics of phytosomes can be measured using Doppler velocimetry, zeta sizer, fluorophores, high-performance capillary electrophoresis, and DLS instruments (Barani et al., 2021).

Surface Tension:

The surface tension of phyto-active constituents in aqueous solution can be measured utilizing ring method in a Du Nouy ring tensiometer (Pal et al., 2021).

Transition Temperature:

Differential scanning calorimetry (DSC) is frequently used to quantify the enthalpy and transition temperature of phospholipid complexes.

Drug content:

The volume of the drug can be measured through modified high performance liquid chromatographic method or any suitable spectroscopic technique.

Lamellarity and Stability:

The term "lamellarity" refers to the number of lipid bilayers in phytosomes. The most popular techniques for determining lamellarity include small-angle X-ray scattering, 31P nuclear magnetic resonance, and electron microscopy techniques. One of the most accurate and frequently used technique for figuring out lamellarity is 31P NMR. This method's drawback is that it is susceptible to experimental factors such as reagent concentration, vesicle type, and buffer concentration. Cryo-microscopy, freeze-fracture, and negative staining electron microscopy are further modern visualization techniques. Phytosomal stability is also an essential aspect in the development of an effective carrier. To investigate the phytochemical alterations of phytosomes during storage and general circulation, stability studies are carried out. By evaluating the mean vesicle size, zeta potential, size distribution, and trapping efficiency, stability can be assessed over several months. Rhamnolipids (RL) modified curcumin liposomes were evaluated for their thermal and photochemical stability, and the results revealed improved stability of the loaded liposomes under varying pH, ionic, and heat conditions (Gurunathan et al., 2018; Cheng et al., 2019)

Encapsulation Efficiency and Release Behaviour:

The amount of phytochemical that is encapsulated in the phytosomes is evaluated by encapsulation efficiency (EE percent). The Equation given below can be used to describe EE percent:

where EE% is for encapsulation efficiency, EP stands for encapsulated phytochemical, and IP stands for initial phytochemical content.

$$EE\% = \{(IP - EP) \div IP\} \times 100$$

The Encapsulation efficiency of phytoactive constituents in phospholipid complexes can be measured by utilizing ultracentrifugation method. The ultracentrifugation is conducted either at high rpm for shorter periods or low rpm for longer periods to find out % entrapment efficiency (Barani et al., 2021; Pal et al., 2021).

Since the release rate achieved in vitro may serve as an indicator of the efficacy of the carrier in vivo, the drug release behaviour of vesicle carriers has been the focus of intensive investigation over the past few years. The most popular conventional methods for determining the release rate of active substances are sample and separate strategy, in situ process, continuous flow, membrane diffusion techniques (dialysis, micro-dialysis, fractional dialysis, and reverse dialysis), and membrane diffusion strategies (Barani et al., 2021).

Phytosomes & Disease Management:

Several research works have revealed the importance of phytosomes in disease control (Fig. 2) and management. Natural herbal extracts with potential therapeutic values are being retarded from its optimized clinical application due to poor gastrointestinal absorbance followed by low bioavailability. To overcome this problem scientists have been formulating different types of phytosomes encapsulated phyto-active components of plant extracts as one of the easiest ways of drug delivery system with increased structural stability and bioavailability with minimum/no side effects. Table.1 showing some popular phytosomes, their active components and the utilization of these drugs.

Phytosomes in Diabetes Management:

Allium cepa–phospholipid (ACP) complex has been prepared using one mole each of *Allium cepa* standard extract (ACE) and hydrogenated soya phosphatidylcholine (HSPC) in dichloromethane and tested for antidiabetic potentiality in streptozocin induced diabetic rats. Characterization of prepared phytosomes was done using DSC, SEM, and FT-IR studies. ACP showed high radical scavenging activity. ACE and ACP resulted in reduced hyperglycemia in two different treatment regimens (one dose one-day and multiple-dose fifteen-day) in diabetic studies. Also decreased STG, STC, VLDL-c, and LDL-c suggested low levels of lipolysis. Thus, ACP accelerated hypolipidemia, and showed antidiabetic activity along with antioxidation activity (Habbu et al., 2015). In another study, Yu et al. (2016) first developed the BER-SPC complex by mixing Berberine (an isoquinoline alkaloid with antidiabetic potentiality) and Soybean phosphatidylcholine (SPC) in a ratio of 1:5 using the rapid solvent evaporation method then BER-SPC complex was formulated into the P-BER by a self-assembly technique for preparing a better BER drug delivery system. 85% entrapment efficiency, nanoscale particle size, and negative surface charge highly suggested the stability of formulated phytosome. The oral bioavailability of the P-BER was found to increase 3-fold than normal orally administered BER. 9 weeks old, db/db mice were treated with BER (100 mg/kg, suspended in 0.5% CMC-Na) and P-BER (100 mg/kg) for 4 weeks respectively. End of the experiment, fasting glucose level showed a significant hypoglycemic effect, indicating glucose metabolism had been improved in

P-BER treated mice compared to only BER. Also found to decrease triglyceride (TG) levels in liver of db/db mice to near control value. Altogether suggesting anti-diabetic efficiency along with diabetogenic hyperlipidemia management. Improvement in the pharmacological activity of conventional herbal extracts, containing quercetin (a major flavonoid) from three fruit plants *Mamordica balsamina, Citrullus colocynthis,* and *Mamordica dioica* were loaded in phytosomes to formulate antidiabetic phytosomes, had been evaluated for enhanced efficacy. The particle size of vesicles ranged between 300-675 nm and entrapment efficiency was measured between 70% to 88%. Suggesting good stability of phytosomes with -22.7mV zeta potential. Phytosomes prepared with fruit plant extracts exhibited anti-diabetic activity at low doses equivalent to the conventional drug metformin (Rathee & Kamboj, 2018). Phytosomes loaded with *Casuarina equestifolia* extract have been successfully synthesized following the antisolvent precipitation method with average particle size, entrapment efficiency, and Span value of 295 ± 0.53nm, 82.43 ± 1.65% and 0.34 ± 0.14 respectively. 19.35mv zeta potential suggested the stability of the particle. While *in vitro* study depicted that the drug has been successfully released following Korsmeyer- Peppas kinetic model, *in vivo* experimental results suggested its antidiabetic efficacy compared to crude *Casuarina equestifolia* extract (Rani et al., 2019).

Table 1. Major Phytosome Formulations and Their therapeutic Applications:

Sl. No.	Common Name/ Trade Name	Composition	Disease Management	References
1.	18 ß-glycyrrhetinic acid Phytosome	18 ß-glycyrrhetinic acid from the rhizome of Licorice	Soothing, Anti-inflammatory activity	Bombardelli et al., 1989
2.	Berberine-phospholipid complex- based phytosomes	Berberine	Antidiabetic, anti hyperlipidemia	Yu et al., 2016
3.	Casperome® Phytosome	*Boswellia serrata* Roxb. ex Colebr. – Resin	Anti-inflammatory response, pain reliever, Joint health, promote tissue regeneration, anti-psoriasis and erythematous eczema	Riva et al., 2017; Togni et al., 2014
4.	Centevita®	Asiatic acid, madecassic acid from *Centella asiatica*	Anti-inflammatory, Cognitive improvement, skin disorders, antiulcer, wound healing, hair falling	Ju et al., 2018; Sbrini et al., 2020
5.	Crataegus Phytosome®		Antioxidant	Lu et al., 2019
6.	Cucurbita Phytosome/ Tocopherol, carotenoids Phytosome	*Cucurbita pepo*	Anti-inflammatory, Prostatic hyperplasia	Huang et al., 2020

7.	Curcumin Phytosome/ Meriva®	*Curcuma longa* L.- Rhizome	Antioxidant & anti-inflammatory, muscle injury recovery, pain reliever,	Zhang et al., 2013; Drobnic et al., 2014
8.	Escin β sitosterol Phytosome	Escin β-sitosterol of horse Chestnut fruit	Antihyperalgesic	Djekic et al., 2019
9.	Evodiamine phospholipids complex	Evodiamine	Anti-tumor	Liu et al., 2012
10.	Ginkgoselect® Phytosome	Flavonoids of *Ginkgo biloba*	Anti-aging & cognitive improvement	Naik et al., 2006
11.	Ginseng Phytosome	Ginsenosides of *Panax ginseng*	anti-inflammatory, antioxidant, and anticancer	Kiefer & Pantuso, 2003
12.	Ginseng Phytosome	*Panax ginseng*	Nutraceutical, immunomodulatory	Chen at al., 2011
13.	Greenselect®/ Green Tea Phytosome	*Camellia sinensis* (L.) O. Kuntze – Leaf	Bodyweight maintenance after intentional weight loss, Anti-obesity, Antioxidant activity, Anti-Cancer	Di Pierro et al., 2009; Gilardini et al., 2016
14	Gingerol	*Zingiber officinale*	Anti-bacterial, anti-inflammatory And antioxidant activity.	Singh et al., 2018
15.	Hawthorn Phytosome	Flavonoids of *Crataegus* species	Anti-hypertensive and Cardioprotective	Ja, 2011
16.	Leucoselect®/ Grape Seed Phytosome	*Vitis vinifera* L. – Seed	Cardiovascular protection and Anti-oxidant activities Effective against chronic allergic disorders	Nuttall et al., 1998; Magrone et al., 2014; Vigna et al., 2003
17.	Lymphaselect	*Melilotus officinalis*	Used for chronic venous insufficiency of the lower limbs	Albrigo et al., 2019
18.	Mirtoselect®/Anthocyanose Phytosome	*Vaccinium myrtillus*	Antioxidant, anti-inflammatory, diabetic retinopathy	Liu et al., 2013
19.	Naringenin Phytosome	*Citrus aurantium*	Suppress Oxidative stress, Prevent acute lung injury	Yu et al., 2020
20.	OleaselectTM Phytosome	Polyphenols of	Anti-inflammatory	Shivanand &

		Olea europaea	and Antihyperlipidemic	Kinjal, 2010
21.	Polinacea Phytosome	*Echinacea angustifolia* Root	Improve immune system, Counteract increased cortisol response	Sgorlon et al., 2012
22.	PolinaceaTM Phytosome	Echinacosides of *Echinacea angustifolia*	Immunomodulation and Nutraceuticals	Li et al., 2015
23.	Phytosome®	Proanthocyanidin A2 obtained from *Aeschylus hippocastanum*	vasokinetic activity, antiwrinkle, antioxidative, UV protection	Lu et al., 2019
24.	Quercefit™ Phytosome	Quercetin found mostly in citrus fruits, apples, onions, parsley, tea, grapes etc.	Antiasthma, Sports suppliment, suppress oxidative stress,	Cesarone et al., 2019
25.	Rhizoma paridis Phytosome	Rhizoma paridis from *Paris polyphylla*, steroidal saponins	Anticancer activity, immunity adjustment, antiviral and anti-inflammation	Liu et al., 2013
26.	Siliphos®	Silybin of *Silybum marianum*	Liver protection, antioxidant	Kidd & Head, 2005; Tedesco et al., 2003; Haddad et al., 2011
27.	Soyselect®/ Soybean extract Phytosome	*Glycine max* extract	Anti-obesity, Anti-angiogenic, anti-cancer, cardioprotective, and anti- hyperlipidemic	El-Menshawe et al., 2018
28.	Ubiqsome® Phytosome	CoQ10	Suppress oxidative stress in cardiac & skeletal muscle, Antiinflammation	Petrangolini et al., 2019
29.	Vazguard™ Phytosome	Citrus x bergamia Risso & Poit. - Fruit juice	Extremely effective in supporting healthy blood levels through the optimization of total cholesterol, c-LDL, c-HDL,	Riva et al., 2020

			triglycerides, and glucose levels	
30.	Vazguard™/Naringin Phytosome	*Bergamot extract*	Protection to cardiometabolic disorders, balance lipid profile & glucose level	Mollace et al., 2019
31.	Virtiva®/ Ginkgo biloba Phytosome	Ginkgo flavonglycosides like ginkgolides, bilobalide	UV protection, Improve cerebral insufficiency, vasokinetic activity, antiwrinkle, antioxidative,	Di Pierro et al., 2016; Lu et al., 2019
32.	Visnadex Phytosome	Visnadin from *Amni visnaga*	Microcirculation improvement	Alam et al., 2013
33.	Xanthones Phytosome	*Swertia alternifolia*	Suppress oxidative stress	Kalita et al., 2013

Phytosomes in Respiratory Disease Management:

The patients treated with *Boswellia serrata* phytosome as supplementation with the normal treatment (inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) required lower number of inhalations/days compared to other group of asthma patients that had not received supplementation (Ferrara et al., 2015). Gingerol, the antibacterial drug blended with soya lecithin to formulate phytosome (GP), was further loaded in chitosan (polysaccharide derived from chitin) solution to prepare phytosome complexed with chitosan (GLPC) and studied for its efficacy against respiratory infection. *In vitro* study results showed antioxidant activity, susceptible antibacterial activity and effective anti-inflammatory activity as well as *in vivo* results exhibited increased bioavailability, and sustained-release of gingerol as compared to GP in respiratory infection disease (Singh et al., 2018). A preliminary study by Cesarone et al. (2019) with patients (healthy but with mild-moderate asthmatic attacks and rhinitis) were given quercetin phytosome in addition to standard management (SM) for 30 days, showed better results compared to only SM treatment strategy in controlling, preventing and decreasing daily and night symptoms. Also found to reduce the use of inhalers, nasal drops, and rescue medications with improved rhinitis score. In a recent investigation Yu et al. (2020) prepared a unique naringenin (NG) loaded Dipalmitoylphosphatidylcholine (DPPC) phytosomes and evaluated its efficacy in rat with acute lung injury. Parameters of *in vitro* study showed superior drug delivery ability. *In vivo* data suggested inhibition of the phosphorylation of P38 in the MAPK pathway and suppression of oxidative stress following dry powder inhalation (NPDPIs).

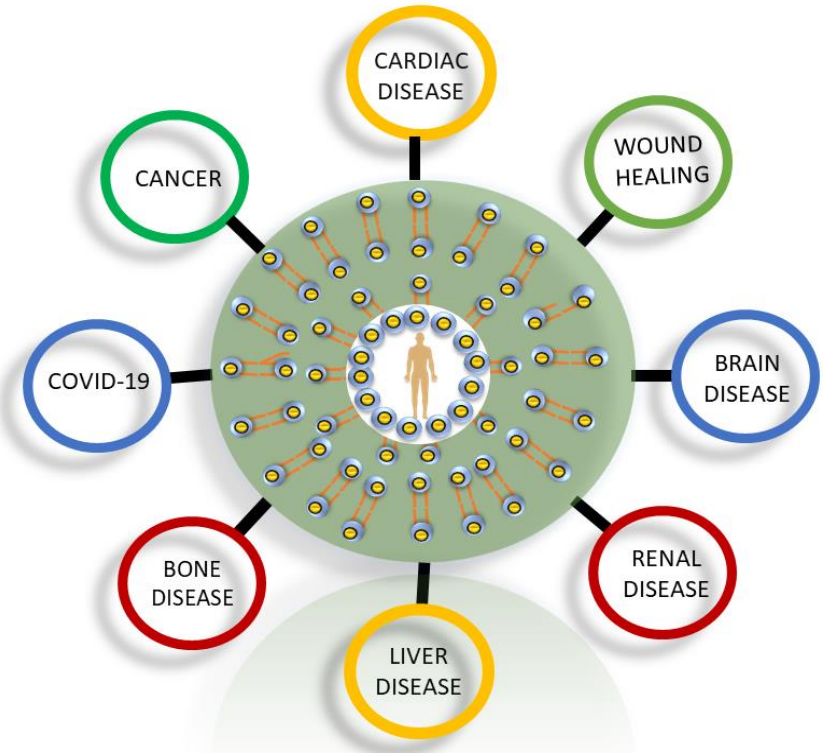

Figure 2. Human Diseases Controlled by Phytosome Based Therapeutic Approaches

Phytosomes in Wound Healing Management:

Sinigrin-phytosome complex was prepared to evaluate its cytotoxic as well as wound healing capability on Human immortalised keratinocyte (HaCaT) cells and A- 375 melanoma cells in *in vitro* experiment. DSC and FTIR analysis confirmed the successful formation of phytosome loaded with Sinigrin, characterized by an average particle size of 153 ± 39 nm and with 10.09 ± 0.98 mV zeta potentials. Topical application of formulated complex at a higher concentration of 0.14 mg/ml for 42 h resulted in cent percent wound cure compared to 71% achievement by Sinigrin alone, with minimum cytotoxicity for HaCat cells but higher cytotoxicity for A-375 cells. This study opens a new vista of therapeutic application of phytosomes in wound healing, even for cancerous wounds also (Mazumder et al., 2016). Phytosome filled with an aqueous extract of *Moringa oleifera* (MO) leaves (MOPCT) has been developed to verify the optimized bioavailability of topically applied MO across the wound. TEM study revealed multilamellar vesicular appearance (avg. size of 198 ± 21 nm) of phytosome with zeta potential of −28.3 ± 1.31 mV. The filtered MOPCT exhibited 82.8%, 52.2%, 15.6%, and 8.44% encapsulation efficiency for quercetin, kaempferol, chlorogenic acid, and rosmarinic acid respectively along with maximized migration (closing gaps) and proliferation rate in *in vitro* investigation with normal human dermal fibroblast NHDF cell compared to the controls. Non-cytotoxic effect at and below 1.5mg/ml concentration has been recorded, suggesting the functional wound-repairing potentiality of MO phytosomes (Lim et al., 2019).

Phytosomes in Cancer Management:

The efficacy of phytosome-formulated drugs has been enormously studied in various types of cancer therapy. Inhibition of cell proliferation, invasion, metastasis, cell cycle arrest and induction of apoptosis are some of the strategies employed by phytosomal formulation to control cancer.

Nervous System Cancer:

Intraperitoneal administration of Curcumin Phytosome (CCP), into the GL261-implanted glioblastoma (GBM) mice showed tumor regression and positive alterations in phenotype of the tumor-associated microglial cells (TAMs). Augmentation of the Arginase1^{low}, iNOS^{high} M1-type tumoricidal microglia and inhibition of the tumor-promoting Arginase1^{high} , iNOS^{low} M2-type TAM population have been observed. Findings indicate role of CCP in GBM killing and repolarization of TAMs towards the tumoricidal M1 state (Mukherjee et al., 2016). Conversely negligible effect of CCP against medulloblastoma (CNS cancer in children) in D425MED (animal model) has been reported (Wright et al., 2017). Immune-competent syngeneic C57BL6 mouse model along with the GL261-implanted glioblastoma (GBM) mice have been used to find out the effect of CCP on immune modulation. Suppression of tumor-promoting proteins in M2 type (STAT3, ARG1, and IL10), induction of anti-tumor proteins in M1 type (STAT1) and nitric oxide synthase in the TAM, caspase 3 activation, GBM stem cells elimination along with activated NK cells and M1 type macrophage were observed in GBM tumor following CCP treatment. Thus, indicating the role of CCP in GBM as well as GBM stem cell destruction (Mukherjee et al., 2018). A recent investigation by Di Pierro et al. (2019) showed treatment with *Boswellia serrata* extract phytosome can attenuate side effects of radio-chemotherapy. Radiotherapy-induced cerebral edema in 10% GBM patients treated with formulation were found to decreased. Suggesting less dexamethasone uptake by brain edema followed by low side effects of steroid treatment.

Oral Cancer:

Celastrol (CST), a promising herbal drug with anticancer potency suffers limitations due to limited aqueous solubility, and poor gastrointestinal absorption that resulted in its low oral bioavailability. CST-phospholipid complex (CST-PHY) nanocarrier has been prepared by solvent evaporation technique with a particle size of 178.4±7.07 nm and zeta potential of -38.7±3.61mV. In-vitro release investigation suggested increased CST-PHY release compared to free CST which confirmed enhanced solubility of CST- phytosomes. *In-vivo* pharmacokinetic study was carried out in adult healthy male rabbits and assessment indicated higher oral absorption of CST-PHY compared to CST alone. Increased oral bioavailability suggested its therapeutic application in oral cancer treatment (Freag et al., 2018).

Skin Cancer:

A nanostructured lipid carriers (NLC) prepared with silymarin (silymarin-NLC) showed increased permeation, better drug release and stability compared to phytosomes available in market. *In vitro* study with melanoma cell line (SK- MEL-2) revealed it's anticancer efficacy in dose-dependent manner and apoptotic induction ability (Singh et al., 2016). The formulation of stable and nearly monodisperse lipid nanoparticle carriers depends upon the surfactants used in the structural design. Two different types of lipids nanocarriers, viz. solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were prepared using 1,2-di(conjugated) linoleoyl-sn-glycero-3-phosphocholine ((CLA)PC) in relation to 1,2-distearoyl-sn-glycero-3-phosphocholine ((SA)PC) under high pressure homogenized condition and evaluated for the anticancer potentiality of both, in human cancer epidermoid carcinoma (A431) and malignant skin melanoma (MeWo) cell line. The higher efficiency of (CLA)PC phospholipid nanoparticles as effective drug delivery systems in the inhibition of cancer had been observed in both cell lines compared to nanosystems stabilized by (SA)PC. (CLA)PC phospholipid nanoparticles showed anticancer efficacy via increased necrosis, cell number reduction, and altered cellular morphology (Pucek et al., 2017).

Lung Cancer:

Mammary gland tumor cell line (ENU1564) inoculated into the mammary fat pad of athymic nude mice in a xenograft study, was treated orally with either curcumin or Curcumin formulated with phosphatidylcholine. Microscopic as well as histochemical results suggested the anticancer efficacy of fabricated phytosome over curcumin, along with reduced expression of MMP-9 hampered lung metastsis (Ibrahim et al., 2010). Diosgenin (3β- hydroxy-5-spirostene, Di), an herbal sterol was used to prepare phytosomes of different Di derivatives to evaluate its effect on human A549 and PC9 lung cancer cells. FZU-0021-194-P2 (P2), a derivative of DiP exhibited more cytotoxic and anti-proliferative effects compared to other DiPs after 72h of incubation. P2Ps were oval-shaped (53.6 ± 0.3 nm) with −4.0 ± 0.7 mV zeta potential. They were found to arrest the cell cycle at G0/G1 phase and induced apoptosis. The result suggested that P2P could be a potential anti-lung cancer formulation (Xu et al., 2019). A very recent study by Mao et al., 2021 showed, increased levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), omega-3 polyunsaturated fatty acids (n-3 PUFA) and unsaturated phosphatidylcholines (PC) after one month treatment with Grape seed procyanidin extract (GSE) complexed with soy phospholipids (leucoselect phytosome), could be correlated with anti-cancer properties. Again 3 months of treatment resulted in an increased serum level of prostaglandin (PG) E_3 (PGE_3) following a reduction in bronchial Ki-67 suggesting antineoplastic and anti-inflammatory responses. Further antiproliferation of human lung cancer cell lines A549 has been noticed.

Breast Cancer:

High expression of nuclear factor erythroid 2-related factor 2 (Nrf2) provide chemotherapeutic resistance to the cancer cell. *In vitro* investigation revealed co-treament of

phytosomes loaded with luteolin and doxorubicin facilitated highest cell mortality in MDA-MB 231 human cancer cells through inhibiting Nrf2 and its downstream gene expressions (Sabzichi et al., 2014). In another study Mahmoodi et al., 2015 showed superior inhibitory effect of Silybin-phosphatidylcholine on cellular growth and HER2 down regulation in human breast cancer SKBR3 cell line compared to silybin. Metastatic breast cancer (4T1) bearing mice when treated with cryoablation (killing of tumor cells by cryotechnology) combined with phytosomal curcumin resulted into delayed development of lung metastases and survival on the long-term compared to control or only phytosomal curcumin (Chandra et al., 2015). Breast cancer cells MCF-7 when treated with doxorubicin combined to nano-quercetin phytosome showed significant increase in apoptosis from 40.11 ± 7.72 to 58 ± 7.13 ($p < 0.05$). Also exhibited sharp decrease in the expression of downstream genes, NQO1 and MRP1(Minaei et al., 2016). Serial investigations by Lazzeroni et al. (2016), (2017) showed quasi success in phytosome mediated drug delivery in breast cancer therapy. Where in first investigation insignificant changes in plasma IGF-1 and nitric oxide or Ki-67 in breast tumor tissue was observed for orally taken Silybin-phosphatidylcholine (milk thistle extract), in second study administration of oral Greenselect Phytosome (GSP) (a caffeine-free green tea catechin extract formulated with lecithin) were found to increase the bioavailability of epigallocatechin-3-O-gallate in breast tumor tissue with significant changes of Ki-67, suggesting antiproliferative efficacy of GSP in breast cancer. Phytosomal curcumin alone was found to inhibit cell growth, reduce invasiveness and migration and induce necrosis and inflammation in MCF-7 cells. Application of curcumin and 5-FU together showed, decreased lipid peroxidation but the enhanced level of MDA/SOD. In thrombin-treated breast cancer cell, curcumin downregulates cyclin D1 expression through the activation of AMP-kinase (Hashemzehi et al., 2018). In two consecutive studies researchers have formulated multi reservoir phytosomal nanocarriers for delivering the antineoplastic cocktail drug. Incorporating both, Monascus yellow pigments - Monascin and ankaflavin (MYPs) and herbal drug, resveratrol (RSV) within the hydrophobic core of casein micelles CAS MCs were found to be very much effective in controlling tumor size through eliciting cytotoxic effect in MCF-7 cells. In another study, similar combinations were incorporated within the core of folate-conjugated casein micelles (FA-CAS MCs, F1) and PEGylated RSV-phospholipid complex bilayer enveloping casein-loaded micelles (PEGPC-CAS MCs) were also prepared for targeting breast cancer cells. Both coloaded MCs exhibited superior cytotoxicity to MCF-7 breast cancer cells than free drugs. *In vivo* antitumor efficacy study revealed PEGylated MCs, compared to folate-conjugated MCs showed better tumor regression ability. CUR/IR780@SMEDDS, a hybrid self-microemulsifying drug delivery system has been manufactured with NIR dye IR780 and curcumin phospholipid complex by Liu et al. (2019) for deciphering combinatorial (chemotherapeutic and phototherapeutic) effect on breast cancer. *In vitro* as well as *in vivo* studies revealed prominent photodynamic and photothermal potency of hybrid formulation with increased bioavailability of both IR 780 and curcumin, enhanced cytotoxicity along with inhibited invasion and migration of 4T1 breast cancer cells compared to simple suspensions made of curcumin and IR780.

Liver Cancer:

The efficacy of phytosomal curcumin on hepatocellular carcinoma (HCC) related to hepatitis B virus (HBV) infection has been investigated in a transgenic mouse model. Treatment resulted into improved liver histopathology, decreased lipid accumulation and infiltration of leukocyte, reduction in tumor volume and inhibition of HCC formation in transgenic mice. Also found to activate anti-inflammatory response (Tang et al., 2019).

Pancreatic Cancer:

Patients with advanced or metastatic pancreatic cancer given curcumin complexed with phytosome as a complementary drug along with gemcitabine, have shown improved safety and efficacy of gemcitabine. On analyzing data, the total disease control rate was found 61.3% (27.3% of response rate + 34% of cases with stable disease). The recorded value for free survival and overall survivals were 8.4 and 10.2 months respectively with significant tolerability. But non-significant changes had been observed in the quality of life of patients during the period of treatment (Solda et al., 2015; Solda et al., 2016; Pastorelli et al., 2018).

Bowel Cancer:

Nude mice implanted with human colorectal carcinoma (CRC) HT29 xenograft were tested with 200 mg/kg dose of silibinin or 100 and 200 mg/kg doses of silybin-phytosome (5 days per week) for 32 days to search for anticancer efficacy. The result suggested antiproliferative and proapoptotic activity (suppression of ERK1/2 and Akt pathway) and antiangiogenic effect (down-regulation of NOS, COX, HIF-1 alpha, and VEGF expression) of both silibilin and silybin-phytosome on CRC (Singh et al., 2008). Howells et al., 2011 checked the efficiency of oxaliplatin, oxaliplatin combined with curcumin phytosome and curcumin phytosome separately *in vitro* in Oxaliplatin-resistant HCT116 p53wt and p53(-/-) cell lines as well as *in vivo* in mice bearing colorectal tumor. Treatment with combination showed more antiproliferative activity *in vitro* compared to oxaliplatin treatment. *In vivo* experimental result showed the efficacy of treatment in the following order combination > Meriva > oxaliplatin > control. Phytosomal curcumin in combination with 5-Flurouracil (5-FU) when investigated in mouse model bearing colitis-associated colon cancer, showed decreased number as well as the size of tumors in both distal and middle parts of the colon and also, found to suppress colonic inflammation through modulating malondialdehyde (MDA), thiol level and catalase (CAT) (Marjaneh et al., 2018). Another study by the same group with a similar formulation showed antitumor activity along with oxidative stress induction and antiangiogenic effect via VEGF signaling pathway modulation (Moradi-Marjaneh et al., 2018).

Prostate Cancer:

Silybin-phytosome fed to 20-week-old TRAMP (palpable prostate cancer) mice for 11 weeks showed suppressed angiogenesis and epithelial-mesenchymal transition followed by inhibited tumor growth, progression, local invasion, and metastasis to distal parts of the body compared to

control (Singh et al., 2008). In a pilot study, patients with benign prostatic hyperplasia (BPH), were administered phytosomal curcumin in addition to the standard treatment (BSM). The result showed improved quality of life with a reduction of signs and symptoms of BPH evidenced by IPSS score, without creating any significant side effect compared to BSM alone (Ledda et al., 2012).

Endometrial Cancer:

Patients with endometrial carcinoma (EC) received 2 gm Curcumin Phytosome (CP) orally every day for 2 weeks showed decreased MHC expression levels on leukocytes, number of monocytes and ICOS expression on $CD8^+$ T cells but without any significant alterations in inflammatory biomarkers (Tuyaerts et al., 2019).

Overian Cancer:

Optimized phytosomal-Icariin (ICA) (a flavonol glycoside) formulation was found to induce cell cycle arrest at G2/M and pre-G1 stages in OVCAR-3 ovarian cancer cells. It also found to increase cytotoxicity along with apoptotic cell mortality and ROS generation (Alhakamy et al., 2020).

Phytosomes in Bowel Inflammation Management:

Symptoms of ulcerative colitis (UC) viz. intestinal pain, bowel movements and cramps, watery stools, blood in stools, anemia, malaise, rectal involvement, and white blood cells count were found to improve in UC patients following Lecithin-based delivery of *Boswellia serrata* extracts (BSE) (Pellegrini et al., 2016). In a similar experiment, abdominal pain, altered bowel movements, meteorism and cramps, the common symptoms of irritable bowel syndrome (IBS) have been found to improve without any side effects due to the administration of *Boswellia serrata* extract phytosome as a supplement with hyoscine butyl bromide, papaverine hydrochloride + *Atropa belladonna* extract (Belcaro et al., 2017). In another study with the same treatment regimen in healthy persons with mild IBS showed a lower mean score value for almost all the self-assessed IBS symptoms, compared to persons prescribed standard management. Altogether suggesting less need for medication or gastroenterologists' intervention (Rive et al., 2019).

Phytosomes in Integumentary Disease Management:

The effect of *Centella asiatica* phytosome (CA) has been examined through the application of CA dorsally to the skin of phthalic anhydride (PA) induced atopic dermatitis (AD) mouse model HR-1and RAW 264.7 murine macrophages. CA inhibited inflammatory cells infiltration, activity of NF-κB, release of TNF-α, IL-1β, IgE and expression of iNOS and COX-2 and also found to inhibit lipopolysaccharide-induced NO production as well as iNOS and COX-2 expression in murine macrophage (Ho et al., 2018).

Phytosomes in Cardio Vascular Disease Management:

Serial investigations by Panda and Naik, 2008, 2009 revealed cardioprotective effect of *Ginkgo biloba* phytosomes (GBP) alone or in combination with *Ocimum sanctum* extract (Os) in subcutaneously administered isoproterenol (ISO)-induced myocardial necrosis in rat models. Histoarchitectural analysis of heart along with reduced marker enzymes in serum viz. AST, LDH, and CPK served as pieces of evidence that orally administered GBP (200mg/kg b w) alone or in combination i.e., GBP (100 mg/kg b w) with Os at two doses (50 and 75 mg/kg b w) have significantly reduced ISO (85 mg/kg b w)-induced cardiac necrosis in the rat. Antioxidant parameters (GSH, SOD, CAT, GPx, and GR) get augmented and malondialdehyde (MDA) levels decreased, suggesting inhibited lipid peroxidation. Though the combination of Os 75 mg/kg b wand GBP 100 mg/kg b w elicited greater protection compared to a combination of Os 50 mg/kg b w and GBP 100 mg/ kg b w but none of the combined treatments showed greater cardioprotection and antioxidation activity compared to the treatment with either GBP or Os singly. Cytokines/chemokines released by vein endothelial cells (VEC) of chronic venous disease (CVD) patient in response to an inflammatory reaction, has been investigated in presence of α-lipolic acid and GBP. GBP-mediated reduction in the basal PDGF release and the TNF-α-induced PDGF, RANTES, and CXCL10 release has suggested the anti-inflammatory activity of GBP. Though data established α-Lipoic acid had a greater anti-inflammatory activity compared to GBP. While GBP downregulates TNF-α-induced p38/MAPK and Akt activation, α-Lipoic acid significantly inhibited TNF-α-induced NF-κB activation and also diminished p38/MAPK activation (Tisato et al., 2013). The effectiveness of a commercially fabricated phytosome loaded with *Vitis vinifera* seed extract, *Melilotus officinalis* extract and 100mg bromelain was tested in 648 CVD patients from 54 Italian centers. Significant reduction in the malleolus circumference of the right and left limb including calf, knee, and metatarsal was observed in all groups either received monotherapy or combinational therapy with standard compression stockings (Albrigo et al., 2019).

Phytosomes in CNS-Related Disease Management:

Prevention of Neuronal Damage and Cognitive Improvement:

Protection of rat fetal brain from maternally ingested ethanol (EtOH) by administration of silymarin phytosome compound had been investigated by La Grange et al. (1999). The activity of the antioxidant enzyme, Gamma glutamyl transpeptidase (GGTP) was found to be higher in the phytosome-treated batch. Cognitive improvement in old aged people with memory loss has clearly shown the role of EGb 761 (*Ginkgo biloba* leaf extract) on hippocampal plasticity through its direct interaction with the glutamatergic system (Williams et al., 2004). Phytosome with *Ginkgo biloba* was found to decrease pentobarbitone-induced sleeping time, bring changes in general behavioral patterns, enhance spontaneous motility, and suppress chlorpromazine-induced blockade of conditioned and unconditioned responses in Wistar rats. Though phytosome failed to exhibit anticonvulsant activity but still showed moderate antiamnestic as well as antidepressant activity. The same authors, in other work, showed antioxidant activity of the same

formulated phytosome. Antioxidant enzymes get depleted in sodium nitrite-induced hypoxic conditions. In the brain tissue of treated rats, *Ginkgo biloba* phytosome was found to protect antioxidant enzymes against sodium nitrite (Naik et al., 2006a, 2006b). Husch et al. (2013) showed increased concentrations of KBA, AKBA, βBA in plasma as well as in Brain tissue following administration of BE (*Boswellia serrata* gum resin extract formulated with soy lecithin) in rodents compared to extract without phytosome. Mancini et al. (2018) searched for the efficacy of *Annona muricata* extract (antidepressant) loaded phytosome in amelioration of blood-brain barrier (BBB) permeability over the extract only. They found not only enhanced BBB permeability but also inhibited monoamine oxidase B (MAO-B) and scavenged H_2O_2. Thus, exhibited an enhanced antidepressant-like function of the extract. Chronic glial activation (increased number of activated microglia and astroglia) causes neuronal damage by secreting free radicals and cytotoxic cytokines. Soy-lecithin based phytosomal curcumin formulation has been tested for its ability to decrease glial activation in GFAPIL6 mice (mice with chronic glial activation). Reduction in the number of microglia in the Hippocampus and Cerebellum has been found following the treatment in GFAPIL6 mice brains. Also, the dose-dependent reduction in neuroinflammatory markers have suggested anti-inflammatory potentiality of phytosomal curcumin (Ullah et al., 2020). Brain-derived neurotrophic factor (Bdnf), a well-known neurotrophin of CNS play important role in brain development including neurite growth, survivability, and spine maturations mechanisms and maintenance. Cognitive performance increased in rats treated with phytosomes formulated with extracts of *Centella asiatica* paralleled with an increased level of Bdnf. In another study, phytosomes fabricated together with extracts of *Centella asiatica* and *Curcuma longa* was found to elicit Bdnf levels in the prefrontal cortex of adult rats. Increased Bdnf level upregulated expression of downstream genes and affected protein synthesis via mTOR-S6 pathway (Sbrini et al., 2020a, 2020b).

Neurodegenerative Diseases:

Formulated curcumin with phytosome showed increased bioavailability in the frontal lobe and hippocampus when given to adult male rat consecutively for 5 days compared to a single administration. Assessment of curcumin concentration in the brain, specifically in the frontal lobe revealed, the presence of 9 pg/mg after 30 mins, 20 pg/mg after 1 hr (highest) and 2 pg/mg after 3 hr (normalized) following administration (Dell'Agli et al., 2016). Formation and deposition of amyloid plaque in the intracellular and extracellular spaces of CNS is one of the main reasons for synaptic damage related to several neurodegenerative diseases. Curcumin (Cur) targeting amyloid protein has been found to rescue neuronal damage, restore normal cognitive and sensory-motor functions in different animal models with neurodegenerative diseases, suggesting its anti-amyloid, anti-inflammatory and neuroprotective activity (Maity & Dunbar, 2018). Application of GEN-TF2, a transfersome prepared by soybean phosphatidylcholine and isoflavone genistein showed decreased oxidative stress, and permeability efficiency with diminished apoptotic cell death in a neuronal cell line (PC12), suggesting a better drug delivery system compared to nonformatted genistin (Langasco et al., 2019). Improvisation of intranasal

drug delivery using nanotechnology (nanoparticles, liposomes, exosomes, phytosomes, nanoemulsion, nanosphere) facilitating permeability across BBB as well as increased bioavailability, for the better management of Alzheimer's disease (AD) had been successfully investigated (Bahadur et al., 2020).

Cerebral Ischemia, Neuropathy and Migraine:

Rutin–phospholipid complexes (Ru–PLC's) showed improved functional outcomes in middle cerebral artery occlusion MCAO (rats with experimental ischemic brain) stroke model,compared to treatment with effective rutin only (Ahmad et al., 2016a). In another study the phytosomal complex (NIMPLC) prepared by extract of Ashwagandha (*Withania somnifera*) roots NMITLI118RT + loaded in phytosome. NIMPLC showed better beneficial effects over NMITLI118RT + tested in 1 h pre and 6 h post treatment validated by reduction in MDA levels, increment in GSH levels, reduction in neurological deficit (ND) scores and reduction in infarct size (Ahmad et al., 2016b).

Patients (n=141) with neuropathic pain either with lumbar sciatica, lumbar disk herniation, and/or lumbar canal stenosis or carpal tunnel syndrome (CTS) were given dexibuprofen (400 mg twice/day) along with lipicur (lipoic acid + curcumin phytosome and piperine) showed > 66% have reduced neuropathic pain of both conditions, indicating safety and efficacy of complementary treatment (Di Pierro & Settembre, 2013). In another study, patients (n=180) with CTS, awaiting surgery of median nerve have given a combination of oral supplements prepared with curcumin phytosome (500 mg), α-lipoic acid (300 mg), and vitamins of the B group. Patients who have received supplementation before and after surgery twice a day for 3 months, have shown diminished nocturenal symtoms and decreased number of positive Phalen's test at 3 months post-surgery compared to other treatment groups that either received no treatment or received treatment prior to surgery only. Thus, combinatorial supplementation proved to be a safe and effective against CTS patients (Pajardi et al., 2014).

Fifty women with MA (migraine with aura) has been treated with a combination of *Ginkgo biloba* phytosome (Ginkgolide B the key component), vitamin B2 and coenzyme Q 10 (twice daily) to find out its efficacy. Observed result showed complete disappearance of MA in 11.1% of patients during T1 and in 42.2% of patients during T2. Both frequency and duration of MA also get reduced. In other experiment same formulation of *G. biloba* extract tested on 25 subjects with MA showed a similar trend of result (D'Andrea et al., 2009; Allais et al., 2013). Phytosome formulated with the *Boswellia serrata* extract, magnesium, L-tryptophan, and vitamins (riboflavin, niacin, vitamin D) administered in patients with transient tension migraine and migraine without aura showed improvement in the monthly attack number, pain modulation without any side effects (Balzano & Ciccone, 2018).

Phytosomes in Hepatic Disease Management:

Serial investigations by Naik & Panda, 2007, 2008 established hepatoprotective effects of *Ginkgo biloba* phytosome (GBP) against chemically induced liver toxicity. In the first study,

liver damage was induced in Wistar rats by administering carbon tetrachloride (CCl4) 1ml/kg daily for 7 days. GBP administered in two separate doses, 25 mg/kg and 50 mg/kg along with silymarin (200 mg/kg) as the standard reference drug. Treatment showed decreased lipid peroxidation, elevated level of SOD, CAT, GPx, GR, albumin, total proteins, but decreased levels of glutamic-pyruvic transaminase (GPT), alkaline phosphatase (ALP), glutamic oxaloacetic transaminase (GOT) but insignificant change in GSH level in serum. The second experiment was carried out in the same model but with rimpfacin-induced liver toxicity (500 mg/kg RMP administered daily for 30 days). Workers got similar results suggesting the hepatoprotective effect of GBP might be related to its antioxidant and free radical scavenging activity. Clinical trials of silybin phytosome complex in combination with Vitamin E for nonalcoholic fatty liver disease (NAFLD) patients showed improved hepatic histology with increased level of liver enzymes in plasma, and better insulin resistance with unchanged body weight.in body weight (Loguercio et al., 2012). Hepatoprotective efficacy of curcumin, silybin-phytosome and alpha-R-lipoic acid against thioacetamide induced liver cirrhosis in rat has been investigated. Result showed treatment reduced Glutathione (GSH) depletion, collagen deposition, matrix metalloproteinase-2 (MMP-2) activity, transforming growth factor-β1 (TGF-β1) level as well as α-smooth muscle actin (α-SMA) and heat shock protein-47 (HSP-47) gene expressions along with malondialdehyde (MDA) and protein carbonyls (Pr Co). Indicating antioxidant and antifibrotic potentials of supplements against chronic liver diseases (Ali et al., 2014). A comparative study has been made to understand superior hepatoprotective efficacy between silymarin phytosomes and milk thistle extract, administered in CCl4-induced hepatotoxicity in rats. Compared to milk thistle extract, Silymarin phytosome was found to increase SOD and decrease GPT levels (El-Gazayerly et al., 2014). Silymarin-phospholipid complex developed by solvent evaporation method using silymarin isolated from *Silybum marianum* and phospholipid showed improved bioavailability with stability and sufficient safety (Maryana et al., 2016). CCl4 induced liver damage in adult Charles foster rats was tested with a formulated phytosome prepared by extracts of *Abutilon indicum* leaves and *Piper longum* fruits in comparison to extracts from each plant separately with LIV 52 herbal medicine. Phytosomal formulation at a very low dose showed a greater hepatoprotective effect on liver toxicity CCl4 induced at a very low dose compared to a higher dose of the combined extract (Sharma & Sahu, 2016). Administration of phytosome curcumin formulation was found to be very much effective against paracetamol-induced liver injury. Efficacy was evidenced by decreased level of lipid peroxidation, the liver toxicity markers (ALT and AST) decreased, and enhanced antioxidant activities of superoxide dismutase, catalase, glutathione peroxidase enzymes in mice liver tissue receiving treatment (Tung et al., 2017). Hepatoprotection through increased anti-inflammatory cytokine (IL-10) and decreased pro-inflammatory cytokine (TNF-α and IL-6) levels following administration of *Boswellia serrata* extract phytosome in lipopolysaccharide- induced systemic inflammation in mice have been reported. Phytosomes also showed antioxidative efficacy (Loeser et al., 2018). Aluminum chloride ($AlCl_3$)-induced hepatotoxicity in rat characterized by increased concentrations of AST, ALT, ALP, LDH, total bilirubin, and LPO as well as decreased

albumin, GSH, SOD, and GPx levels found to be attenuated by administration of Curcumin phytosome (CP) (Al-Kahtani et al., 2020).

Phytosomes in Renal Disease Management:

Patients with temporary kidney dysfunction (TKD) were given either standard management (SM) or SM and Curcumin Phytosome together to find out the ameliorative effect. Significant improvements in macro and microalbuminuria in combination therapy were noticed compared to control along with controlled blood pressure, reduced oxidative stress and fatigue.

Phytosomes in Osteo-Muscular Disease Management:

Curcumin phytosomes were found to attenuate oxidative stress and inflammatory response related to muscle damage in eccentric continuous exercise-induced delayed onset muscle soreness (DOMS) induced, evidenced by reduced pain intensity and recovery of muscle (Drobnic et al., 2014). Same complex showed anti-inflammatory response in osteoarthritis (OA) patients with decreased joint pain and improvement in joint function suggesting its application in the prolonged treatment of OA (Belcaro et al., 2010). A comparative study between lecithin formulation of curcumin, acetaminophen and nimesulide showed curcumin formulation at higher dose (2 gm) exhibit almost equal analgesic activity as well as gastric tolerability of acetaminophen (1gm) but lower pain killing effect than nimesulide (1 gm). Though the gastric tolerability is better compared to nimesulide therapy (Di Pierro et al., 2013). In another study 4-month consecutive administration of phytosomal curcumin combined to glucosamine exhibited faster recovery in OA patients compared to other patients group given chondroitin sulfate combined with glucosamine group (Belcaro et al., 2014). Phytosomal curcumin along with standard management had been evaluated either or not in combination with other nutritional supplements in aged healthy persons (>65 years) with sarcopenia, showed ameliorated muscle mass and strength as well as physical performance compared to persons only receiving SM (Franceschi et al., 2016). Curcumine phytosome mediated pain reduction in radiculopathy patients affected with spine arthritis or discopathy has also been reported (Maida. G, 2016). Male rugby players (n=50) with osteo-muscular pain due to either physical overload, traumatic injuries, or acute episode of chronic pain, half were treated with conventional pain killer drugs and other half treated with curcumin based phytosome (Algocur®) for next 10 days. Phytosome complex exhibited more analgesic effect than the other with more tolerability with increased physical activities (Di Pierro et al., 2017). In a pilot study Riva et al. (2017) demonstrated significant increment of bone density of upper jaw, heal and small finger in tested persons with osteopenia, following curcumin supplement in addition to standard management (SM) compared to the group only receiving SM. Recently, Miserocchi et al. (2020) reported curcumin phytosomal complex in addition with chronic systemic immunosuppressive therapy improves mild chronic anterior chamber flare with good safety profile in children with juvenile idiopathic arthritis-associated uveitis.

lecithin-encapsulated *Boswellia serrata* extract (BSE) was investigated for its efficacy in relieving osteo-muscular pain in rugby players. Observed parameters showed reduced local pain on effort, joint effusion, structural damage (joint, tendons, muscles), pain-free walking, and intramuscular hematomas suggesting its potential therapeutic role (Franceschi et al., 2016). Treatment group with grade II ankle sprain induced by sports activities were divided into two groups and advised to follow either SM or SM with BSE (1 tab of 250mg/day) for 7 days. The group that recieved combined therapy showed much-reduced signs and symptoms of ankle sprains on 3rd and 7th day of evaluation without any side effects (Feragalli et al., 2017).

In a recent study treatment with phytosome fabricated with *Zingiber officinale* and *Acmella oleracea* extracts ameliorated pain intensity, knee function, quality of life, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in 50 patients with moderate knee osteoarthritis (OA) (Rondanelli et al., 2020).

Phytosome in COVID-19 Management:

In the recent past SARS-CoV-2 the causative agent of COVID-19 pandemic was the major threat to human civilization. Serial investigations by Di Pierro et al. (2021a, 2021b, 2021c) had reported that quercetin can inhibit the 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and spike (S) protein of SARS-CoV-2. In their first study, they treated 152 COVID-19 patients with early symptoms, with 1000mg Quercetin Phytosome® (QP) for 30 days. Observation suggested, a reduction in the number of deaths, ICU admission, duration of hospitalization, as well as severity in patients. In another investigation, supplementation of QP in addition to standard of care (SC), negative RT-PCR results suggested early recovery in patients (within 7 -14 days) along with decreased symptomatic severity compared to patients receiving only SC. Long COVID syndrome resulted in cognitive dysfunction and fatigue collectively known as Brain fog. Mitigation of such symptomatic conditions by using phytosomal formulation of luteolin has been documented by Theoharides et al. (2021). In a pilot study, Rondanelli et al. (2022) have proven that by receiving Quercetin phytosomes at a dose of 250mg twice/day for 3 months, prevented healthcare workers from symptomatic covid-19.

Conclusion

Phyto-phospholipid complexation strategy might increase the in vivo bioavailability of phytoactive components. Although the polyphenolic compounds found in plants, such as flavonoids, etc., have a high degree of therapeutic potential, their utility in the treatment and management of various illnesses like rheumatism, cancer, diabetes, and liver disease has remained unsolved as they cannot invade the lipid barrier. This issue has been successfully addressed by the encapsulation of plant-active ingredients with dietary phospholipids, which has allowed the production of herbal active pharmaceuticals with a high degree of lipid penetrability, persistent therapeutic action, and a slower elimination rate. Phytosomal technology has made a significant amount of phytoactive medication available at the site of action. The development of innovative drug delivery strategies creates a promising future for plant actives and extracts for

their use as a successful medication. The phytosome technology connects cutting-edge medication delivery techniques with the traditional distribution method of phytoconstituents. In short, phytosomes are a blessing for naturally occurring herbal extracts that are not properly absorbed.

Conflict of Interest:

None

References:

Ahmad, H., Arya, A., Agrawal, S., Mall, P., Samuel, S. S., Sharma, K., ... & Dwivedi, A. K. (2016a). Rutin phospholipid complexes confer neuro-protection in ischemic-stroke rats. *RSC advances*, *6*(99), 96445-96454. https://doi.org/10.1039/C6RA17874J

Ahmad, H., Arya, A., Agrawal, S., Samuel, S. S., Singh, S. K., Valicherla, G. R., Sangwan, N., Mitra, K., Gayen, J. R., Paliwal, S., Shukla, R., & Dwivedi, A. K. (2016b). Phospholipid complexation of NMITLI118RT+: way to a prudent therapeutic approach for beneficial outcomes in ischemic stroke in rats. *Drug delivery*, *23*(9), 3606–3618. https://doi.org/10.1080/10717544.2016.1212950

Alam, M. A., Al-Jenoobi, F. I., & Al-Mohizea, A. M. (2013). Commercially bioavailable proprietary technologies and their marketed products. *Drug discovery today*, *18*(19-20), 936–949. https://doi.org/10.1016/j.drudis.2013.05.007

Albrigo, R., Andreoni, C., Anello, G., Barboni, M. G., Barzaghi, E., Bianchi, D., ... & Giacomelli, L. (2019). Nédemax® mese (Leucoselect®, Lymphaselect®, bromelain) in the treatment of chronic venous disease: a multicenter, observational study. *Acta Phlebol*, *20*(1), 8-14. https://doi.org/10.23736/S1593-232X.19.00437-5

Albrigo, R., Andreoni, C., Anello, G., Barboni, M. G., Barzaghi, E., Bianchi, D., ... & Giacomelli, L. (2019). Nédemax® mese (Leucoselect®, Lymphaselect®, bromelain) in the treatment of chronic venous disease: a multicenter, observational study. *Acta Phlebol*, *20*(1), 8-14.

Alhakamy, N. A., A Fahmy, U., Badr-Eldin, S. M., Ahmed, O., Asfour, H. Z., Aldawsari, H. M., Algandaby, M. M., Eid, B. G., Abdel-Naim, A. B., Awan, Z. A., K Alruwaili, N., & Mohamed, A. I. (2020). Optimized Icariin Phytosomes Exhibit Enhanced Cytotoxicity and Apoptosis-Inducing Activities in Ovarian Cancer Cells. *Pharmaceutics*, *12*(4), 346. https://doi.org/10.3390/pharmaceutics12040346

Ali, S. O., Darwish, H. A. E. M., & Ismail, N. A. E. F. (2014). Modulatory effects of curcumin, silybin-phytosome and alpha-R-lipoic acid against thioacetamide-induced liver cirrhosis in rats. *Chemico-Biological Interactions*, *216*, 26-33. https://doi.org/10.1016/j.cbi.2014.03.009

Al-Kahtani, M., Abdel-Daim, M. M., Sayed, A. A., El-Kott, A., & Morsy, K. (2020). Curcumin phytosome modulates aluminum-induced hepatotoxicity via regulation of antioxidant, Bcl-2, and caspase-3 in rats. *Environmental science and pollution research international*, *27*(17), 21977–21985. https://doi.org/10.1007/s11356-020-08636-0

Allais, G., D'Andrea, G., Maggio, M., & Benedetto, C. (2013). The efficacy of ginkgolide B in the acute treatment of migraine aura: an open preliminary trial. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *34 Suppl 1*, S161–S163. https://doi.org/10.1007/s10072-013-1413-x

Amit, P. Y. S. T., Tanwar, Y. S., Rakesh, S., & Poojan, P. (2013). Phytosome: Phytolipid drug delivery system for improving bioavailability of herbal drug. *J Pharm Sci Biosci Res*, 3(2), 51-57. http://jpsbr.com/index_htm_files/2_JPSBR13RV0203.pdf

Anjana, R., Kumar, S., Sharma, H., & Khar, R. (2017). Phytosome drug delivery of natural products: A promising technique for enhancing bioavailability. *International Journal of Drug Delivery Technology*, 7(03), 157-165. https://doi.org/10.25258/ijddt.v7i03.9559

Bahadur, S., Sachan, N., Harwansh, R. K., & Deshmukh, R. (2020). Nanoparticlized System: Promising Approach for the Management of Alzheimer's Disease through Intranasal Delivery. *Current pharmaceutical design*, *26*(12), 1331–1344. https://doi.org/10.2174/1381612826666200311131658

Balzano, L., & Ciccone, B. (2018, September). Preliminary efficacy study in prophylaxes of episodic tension cephala and hemicrania without aura using a combination of magnesium, L-triptofano, Boswellia serrata Casperome (r), niacina, riboflavina and vitamin d compared with amitriptiline. In *JOURNAL OF HEADACHE AND PAIN* (Vol. 19). CAMPUS, 4 CRINAN ST, LONDON, N1 9XW, ENGLAND: SPRINGEROPEN.

Barani, M., Sangiovanni, E., Angarano, M., Rajizadeh, M. A., Mehrabani, M., Piazza, S., ... & Nematollahi, M. H. (2021). Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. International Journal of Nanomedicine, 16, 6983. https://doi.org/10.2147/IJN.S318416

Belcaro, G., Cesarone, M. R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M. G., Togni, S., & Appendino, G. (2010). Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Alternative medicine review : a journal of clinical therapeutic*, *15*(4), 337–344.

Belcaro, G., Dugall, M., Luzzi, R., Ledda, A., Pellegrini, L., Cesarone, M. R., Hosoi, M., & Errichi, M. (2014). Meriva®+Glucosamine versus Condroitin+Glucosamine in patients with knee osteoarthritis: an observational study. *European review for medical and pharmacological sciences*, *18*(24), 3959–3963. http://www.europeanreview.org/wp/wp-content/uploads/3959-3963.pdf

Belcaro, G., Gizzi, G., Pellegrini, L., Corsi, M., Dugall, M., Cacchio, M., Feragalli, B., Togni, S., Riva, A., Eggenhoffner, R., & Giacomelli, L. (2017). Supplementation with a lecithin-based delivery form of Boswellia serrata extract (Casperome®) controls symptoms of mild irritable bowel syndrome. *European review for medical and pharmacological sciences*, *21*(9), 2249–2254.

Bhattacharya, S. (2009). Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals. International Journal of Health Research, 2(3), 225-232. https://doi.org/10.4314/ijhr.v2i3.47905

Bombardelli, E., Curri, S. B., Della Loggia, R., Del Negro, P., Gariboldi, P., & Tubaro, A. (1989). Anti-inflammatory activity of 18-ß-glycyrrhetinic acid in phytosome form 29-37.

Carini, M., Aldini, G., Bombardelli, E., Morazzoni, P., & Morelli, R. (1994). Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittel-Forschung, 44(5), 592-601.

Cesarone, M. R., Belcaro, G., Hu, S., Dugall, M., Hosoi, M., Ledda, A., Feragalli, B., Maione, C., & Cotellese, R. (2019). Supplementary prevention and management of asthma with quercetin phytosome: a pilot registry. *Minerva medica*, *110*(6), 524–529. https://doi.org/10.23736/S0026-4806.19.06319-5

Cesarone, M. R., Belcaro, G., Hu, S., Dugall, M., Hosoi, M., Ledda, A., Feragalli, B., Maione, C., & Cotellese, R. (2019). Supplementary prevention and management of asthma with quercetin phytosome: a pilot registry. *Minerva medica*, *110*(6), 524–529. https://doi.org/10.23736/S0026-4806.19.06319-5

Chandra, D., Jahangir, A., Cornelis, F., Rombauts, K., Meheus, L., Jorcyk, C. L., & Gravekamp, C. (2015). Cryoablation and Meriva have strong therapeutic effect on triple-negative breast cancer. *Oncoimmunology*, *5*(1), e1049802. https://doi.org/10.1080/2162402X.2015.1049802

Chen X-M, Wu XK, Kong DG, Chen S. Preparation and preliminary study of quality evaluation of ginsenosides phospholipid compound. *Qilu Pharma Spain*. 2011;9:102–114.

Cheng, C., Wu, Z., McClements, D. J., Zou, L., Peng, S., Zhou, W., & Liu, W. (2019). Improvement on stability, loading capacity and sustained release of rhamnolipids modified curcumin liposomes. Colloids and surfaces B: biointerfaces, 183, 110460. https://doi.org/10.1016/j.colsurfb.2019.110460

Cheng, C., Wu, Z., McClements, D. J., Zou, L., Peng, S., Zhou, W., & Liu, W. (2019). Improvement on stability, loading capacity and sustained release of rhamnolipids modified curcumin liposomes. Colloids and surfaces. B, Biointerfaces, 183, 110460. https://doi.org/10.1016/j.colsurfb.2019.110460

Chibowski, E., & Szcześ, A. (2016). Zeta potential and surface charge of DPPC and DOPC liposomes in the presence of PLC enzyme. Adsorption, 22(4), 755-765. https://doi.org/10.1007/s10450-016-9767-z

D'Andrea, G., Bussone, G., Allais, G., Aguggia, M., D'Onofrio, F., Maggio, M., Moschiano, F., Saracco, M. G., Terzi, M. G., Petretta, V., & Benedetto, C. (2009). Efficacy of Ginkgolide B in the prophylaxis of migraine with aura. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *30 Suppl 1*, S121–S124. https://doi.org/10.1007/s10072-009-0074-2

Dayan, N., & Touitou, E. (2000). Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. Biomaterials, 21(18), 1879-1885.

Dell'Agli, M., Sangiovanni, E., Risè, P., Rossetti, A. C., Morazzoni, P., Riva, A., ... & Molteni, R. (2016). Bioavailability of curcumin in the rat frontal lobe and hippocampus after repeated administration of MERIVA®. *Planta Medica*, *82*(S 01), P895.

Di Pierro, F., & Settembre, R. (2013). Safety and efficacy of an add-on therapy with curcumin phytosome and piperine and/or lipoic acid in subjects with a diagnosis of peripheral neuropathy treated with dexibuprofen. *Journal of pain research*, *6*, 497–503. https://doi.org/10.2147/JPR.S48432

Di Pierro, F., Derosa, G., Maffioli, P., Bertuccioli, A., Togni, S., Riva, A., Allegrini, P., Khan, A., Khan, S., Khan, B. A., Altaf, N., Zahid, M., Ujjan, I. D., Nigar, R., Khushk, M. I., Phulpoto, M., Lail, A., Devrajani, B. R., & Ahmed, S. (2021b). Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study. *International journal of general medicine*, *14*, 2359–2366. https://doi.org/10.2147/IJGM.S318720

Di Pierro, F., Iqtadar, S., Khan, A., Ullah Mumtaz, S., Masud Chaudhry, M., Bertuccioli, A., Derosa, G., Maffioli, P., Togni, S., Riva, A., Allegrini, P., & Khan, S. (2021c). Potential Clinical Benefits of Quercetin in the Early Stage of COVID-19: Results of a Second, Pilot, Randomized, Controlled and Open-Label Clinical Trial. *International journal of general medicine*, *14*, 2807–2816. https://doi.org/10.2147/IJGM.S318949

DI Pierro, F., Khan, A., Bertuccioli, A., Maffioli, P., Derosa, G., Khan, S., Khan, B. A., Nigar, R., Ujjan, I., & Devrajani, B. R. (2021a). Quercetin Phytosome® as a potential candidate for managing COVID-19. *Minerva gastroenterology*, *67*(2), 190–195. https://doi.org/10.23736/S2724-5985.20.02771-3

Di Pierro, F., Menghi, A. B., Barreca, A., Lucarelli, M., & Calandrelli, A. (2009). Greenselect Phytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. *Alternative medicine review: a journal of clinical therapeutic*, *14*(2), 154–160.

Di Pierro, F., Rapacioli, G., Di Maio, E. A., Appendino, G., Franceschi, F., & Togni, S. (2013). Comparative evaluation of the pain-relieving properties of a lecithinized formulation of curcumin (Meriva(®)), nimesulide, and acetaminophen. *Journal of pain research*, *6*, 201–205. https://doi.org/10.2147/JPR.S42184

Di Pierro, F., Simonetti, G., Petruzzi, A., Bertuccioli, A., Botta, L., Bruzzone, M. G., Cuccarini, V., Fariselli, L., & Lamperti, E. (2019). A novel lecithin-based delivery form of Boswellic acids as complementary treatment of radiochemotherapy-induced cerebral edema in patients with glioblastoma multiforme: a longitudinal pilot experience. *Journal of neurosurgical sciences*, *63*(3), 286–291. https://doi.org/10.23736/S0390-5616.19.04662-9

Di Pierro, F., Togni, S., Franceschi, F., Eghenhofner, R., & Giacomelli, L. (2016). Effects of standardized Ginkgo biloba extract complexed with phosphatidylserine (Virtiva®) on physiological response to prolonged, intense physical activity. *Minerva Ortop Traumatol*, *67*(3), 119-123.

Di Pierro, F., Zacconi, P., Bertuccioli, A., Togni, S., Eggenhoffner, R., Giacomelli, L., & Scaltrini, S. (2017). A naturally-inspired, curcumin-based lecithin formulation (Meriva® formulated as the finished product Algocur®) alleviates the osteo-muscular pain conditions in rugby players. *European review for medical and pharmacological sciences*, *21*(21), 4935–4940. PMID: 29164565

Djekic, L., Čalija, B., Micov, A., Tomić, M., & Stepanović-Petrović, R. (2019). Topical hydrogels with escin β-sitosterol phytosome and escin: Formulation development and in vivo assessment of antihyperalgesic activity. *Drug development research*, *80*(7), 921–932. https://doi.org/10.1002/ddr.21572

Drobnic, F., Riera, J., Appendino, G., Togni, S., Franceschi, F., Valle, X., Pons, A., & Tur, J. (2014). Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): a randomised, placebo-controlled trial. *Journal of the International Society of Sports Nutrition*, *11*, 31. https://doi.org/10.1186/1550-2783-11-31

Drobnic, F., Riera, J., Appendino, G., Togni, S., Franceschi, F., Valle, X., Pons, A., & Tur, J. (2014). Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): a randomised, placebo-controlled trial. *Journal of the International Society of Sports Nutrition*, *11*, 31. https://doi.org/10.1186/1550-2783-11-31

El-Far, S. W., Helmy, M. W., Khattab, S. N., Bekhit, A. A., Hussein, A. A., & Elzoghby, A. O. (2018a). Phytosomal bilayer-enveloped casein micelles for codelivery of monascus yellow pigments and resveratrol to breast cancer. *Nanomedicine (London, England)*, *13*(5), 481–499. https://doi.org/10.2217/nnm-2017-0301

El-Far, S. W., Helmy, M. W., Khattab, S. N., Bekhit, A. A., Hussein, A. A., & Elzoghby, A. O. (2018b). Folate conjugated vs PEGylated phytosomal casein nanocarriers for codelivery of fungal- and herbal-derived anticancer drugs. *Nanomedicine (London, England)*, *13*(12), 1463–1480. https://doi.org/10.2217/nnm-2018-0006

El-Gazayerly, O. N., Makhlouf, A. I., Soelm, A. M., & Mohmoud, M. A. (2014). Antioxidant and hepatoprotective effects of silymarin phytosomes compared to milk thistle extract in CCl4 induced hepatotoxicity in rats. *Journal of microencapsulation*, *31*(1), 23–30. https://doi.org/10.3109/02652048.2013.805836

El-Menshawe, S. F., Ali, A. A., Rabeh, M. A., & Khalil, N. M. (2018). Nanosized soy phytosome-based thermogel as topical anti-obesity formulation: an approach for acceptable level of evidence of an effective novel herbal weight loss product. *International journal of nanomedicine*, *13*, 307–318. https://doi.org/10.2147/IJN.S153429

Feragalli, B., Ippolito, E., Dugall, M., Cacchio, M., Belcaro, G., Cesarone, M. R., Abdel-Tawab, M., Riva, A., Togni, S., Eggenhoffner, R., & Giacomelli, L. (2017). Effectiveness of a novel boswellic acids delivery form (Casperome®) in the management of grade II ankle sprains due to sport trauma - a registry study. *European review for medical and pharmacological sciences*, *21*(20), 4726–4732. PMID: 29131239

Ferrara, T., De Vincentiis, G., & Di Pierro, F. (2015). Functional study on Boswellia phytosome as complementary intervention in asthmatic patients. *European review for medical and pharmacological sciences*, *19*(19), 3757–3762. PMID: 26502867

Franceschi, F., Feregalli, B., Togni, S., Cornelli, U., Giacomelli, L., Eggenhoffner, R., & Belcaro, G. (2016). A novel phospholipid delivery system of curcumin (Meriva®) preserves muscular mass in healthy aging subjects. *European review for medical and pharmacological sciences*, *20*(4), 762–766. PMID: 26957282

Franceschi, F., Togni, S., Belcaro, G., Dugall, M., Luzzi, R., Ledda, A., Pellegrini, L., Eggenhoffner, R., & Giacomelli, L. (2016). A novel lecithin-based delivery form of Boswellic acids (Casperome®) for the management of osteo-muscular pain: a registry study in young rugby players. *European review for medical and pharmacological sciences*, *20*(19), 4156–4161. PMID: 27775780

Franco, P. G., & Bombardelli, E. (1998). Complex compounds of bioflavonoids with phospholipids, their preparation and uses and pharmaceutical and cosmetic compositions containing them. US Patent No-EPO, 275005.

Freag, M. S., Elnaggar, Y. S., & Abdallah, O. Y. (2013). Lyophilized phytosomal nanocarriers as platforms for enhanced diosmin delivery: optimization and ex vivo permeation. International journal of nanomedicine, 8, 2385. https://doi.org/10.2147%2FIJN.S45231

Freag, M. S., Saleh, W. M., & Abdallah, O. Y. (2018). Self-assembled phospholipid-based phytosomal nanocarriers as promising platforms for improving oral bioavailability of the anticancer celastrol. *International journal of pharmaceutics*, *535*(1-2), 18-26. https://doi.org/10.1016/j.ijpharm.2017.10.053

Ghanbarzadeh, B., Babazadeh, A., & Hamishehkar, H. (2016). Nano-phytosome as a potential food-grade delivery system. Food bioscience, 15, 126-135. https://doi.org/10.1016/j.fbio.2016.07.006

Gilardini, L., Pasqualinotto, L., Di Pierro, F., Risso, P., & Invitti, C. (2016). Effects of Greenselect Phytosome® on weight maintenance after weight loss in obese women: a randomized placebo-controlled study. *BMC complementary and alternative medicine*, *16*, 233. https://doi.org/10.1186/s12906-016-1214-x

Gurunathan, S., Kang, M. H., Qasim, M., & Kim, J. H. (2018). Nanoparticle-mediated combination therapy: Two-in-one approach for cancer. International journal of molecular sciences, 19(10), 3264. https://doi.org/10.3390/ijms19103264

Habbu, P., Madagundi, S., Shastry, R., Vanakudri, R., & Kulkarni, V. (2015). Preparation and evaluation of antidiabetic activity of allium cepa-phospholipid complex (phytosome) in streptozotocin induced diabetic rats. *RGUHS J Pharm Sci*, *5*(4), 132-141.

Haddad, Y., Vallerand, D., Brault, A., & Haddad, P. S. (2011). Antioxidant and hepatoprotective effects of silibinin in a rat model of nonalcoholic steatohepatitis. *Evidence-based complementary and alternative medicine : eCAM*, *2011*, nep164. https://doi.org/10.1093/ecam/nep164

Hashemzehi, M., Behnam-Rassouli, R., Hassanian, S. M., Moradi-Binabaj, M., Moradi-Marjaneh, R., Rahmani, F., Fiuji, H., Jamili, M., Mirahmadi, M., Boromand, N., Piran, M., Jafari, M., Sahebkar, A., Avan, A., & Khazaei, M. (2018). Phytosomal-curcumin antagonizes cell growth and migration, induced by thrombin through AMP-Kinase in breast cancer. *Journal of cellular biochemistry*, *119*(7), 5996–6007. https://doi.org/10.1002/jcb.26796

He, N., Zhang, L., Zhu, F., Rui, K., Yuan, M. Q., & Qin, H. (2010). Formulation of self-nanoemulsifying drug delivery systems for insulin-soybean lecithin complex. West China J Pharm Sci, 25(4), 396-399.

Ho, P. J., Sung, J. J., Cheon, K. K., & Tae, H. J. (2018). Anti-inflammatory effect of Centella asiatica phytosome in a mouse model of phthalic anhydride-induced atopic dermatitis. *Phytomedicine*, *43*, 110-119. https://doi.org/10.1016/j.phymed.2018.04.013

Howells, L. M., Sale, S., Sriramareddy, S. N., Irving, G. R., Jones, D. J., Ottley, C. J., Pearson, D. G., Mann, C. D., Manson, M. M., Berry, D. P., Gescher, A., Steward, W. P., & Brown, K. (2011). Curcumin ameliorates oxaliplatin-induced chemoresistance in HCT116 colorectal cancer cells in vitro and in vivo. *International journal of cancer*, *129*(2), 476–486. https://doi.org/10.1002/ijc.25670

Huang, Z., Brennan, C. S., Zhao, H., Liu, J., Guan, W., Mohan, M. S., Stipkovits, L., Zheng, H., & Kulasiri, D. (2020). Fabrication and assessment of milk phospholipid-complexed antioxidant phytosomes with vitamin C and E: A comparison with liposomes. *Food chemistry*, *324*, 126837. https://doi.org/10.1016/j.foodchem.2020.126837

Hüsch, J., Bohnet, J., Fricker, G., Skarke, C., Artaria, C., Appendino, G., Schubert-Zsilavecz, M., & Abdel-Tawab, M. (2013). Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome(®)) of Boswellia extract. *Fitoterapia*, *84*, 89–98. https://doi.org/10.1016/j.fitote.2012.10.002

Ibrahim, A., El-Meligy, A., Fetaih, H., Dessouki, A., Stoica, G., & Barhoumi, R. (2010). Effect of curcumin and Meriva on the lung metastasis of murine mammary gland adenocarcinoma. *In vivo (Athens, Greece)*, *24*(4), 401–408. https://iv.iiarjournals.org/content/invivo/24/4/401.full.pdf

JA, S. S. (2011). Phytosome: an emerging trend in herbal drug treatment. *Journal of Medical Genetics and Genomics*, *3*(6), 109-114.

Jain, N. K., & Jain, N. K. (2005). Liposomes as drug carriers, controlled and novel drug delivery. CBS publisher, 308, 321-326. ISBN: 978-953-51-1628-8

Jain, S., Dhanotiya, C., & Malviya, N. (2012). Physicochemical characterization and determination of free radical scavenging activity of rutin-phospholipid complex. International Journal of Pharmaceutical Sciences and Research, 3(3), 909. https://doi.org/10.3390/molecules14093486

Kalita, B., Das, M. K., & Sharma, A. K. (2013). Novel phytosome formulations in making herbal extracts more effective. *J Pharm Technol*, *6*(11), 1295-1301.

Karole, S., & Gupta, G. K. G. S. (2019). Preparation and evaluation of phytosomes containing ethanolic extract of leaves of Bombax ceiba for hepatoprotective activity. Evaluation, 6(2), 1-5. https://www.thepharmajournal.com/archives/2019/vol8issue2/PartA/8-1-61-396.pdf

Khan, J., Alexander, A., Saraf, S., & Saraf, S. (2013). Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. Journal of controlled release, 168(1), 50-60. https://doi.org/10.1016/j.jconrel.2013.02.025

Khan, J., Alexander, A., Saraf, S., & Saraf, S. (2013). Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. Journal of controlled release, 168(1), 50-60. https://doi.org/10.1016/j.jconrel.2013.02.025

Kidd, P., & Head, K. (2005). A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylcholine complex (Siliphos). *Alternative medicine review : a journal of clinical therapeutic*, *10*(3), 193–203.

Kiefer, D., & Pantuso, T. (2003). Panax ginseng. *American family physician*, *68*(8), 1539–1542.

Kondratyuk, T. P., & Pezzuto, J. M. (2004). Natural product polyphenols of relevance to human health. Pharmaceutical biology, 42(sup1), 46-63.

La Grange, L., Wang, M., Watkins, R., Ortiz, D., Sanchez, M. E., Konst, J., Lee, C., & Reyes, E. (1999). Protective effects of the flavonoid mixture, silymarin, on fetal rat brain and liver. *Journal of ethnopharmacology*, *65*(1), 53–61. https://doi.org/10.1016/s0378-8741(98)00144-5

Langasco, R., Fancello, S., Rassu, G., Cossu, M., Cavalli, R., Galleri, G., Giunchedi, P., Migheli, R., & Gavini, E. (2019). Increasing protective activity of genistein by loading into transfersomes: A new potential adjuvant in the oxidative stress-related neurodegenerative diseases?. *Phytomedicine : international journal of phytotherapy and phytopharmacology*, *52*, 23–31. https://doi.org/10.1016/j.phymed.2018.09.207

Lazzeroni, M., Guerrieri-Gonzaga, A., Gandini, S., Johansson, H., Serrano, D., Cazzaniga, M., Aristarco, V., Puccio, A., Mora, S., Caldarella, P., Pagani, G., Pruneri, G., Riva, A., Petrangolini, G., Morazzoni, P., DeCensi, A., & Bonanni, B. (2016). A Presurgical Study of Oral Silybin-Phosphatidylcholine in Patients with Early Breast Cancer. *Cancer prevention research (Philadelphia, Pa.)*, *9*(1), 89–95. https://doi.org/10.1158/1940-6207.CAPR-15-0123

Ledda, A., Belcaro, G., Dugall, M., Luzzi, R., Scoccianti, M., Togni, S., Appendino, G., & Ciammaichella, G. (2012). Meriva®, a lecithinized curcumin delivery system, in the control of benign prostatic hyperplasia: a pilot, product evaluation registry study. *Panminerva medica*, *54*(1 Suppl 4), 17–22. PMID: 23241931

Ledda, A., Belcaro, G., Feragalli, B., Hosoi, M., Cacchio, M., Luzzi, R., ... & Cotellese, R. (2018). Temporary kidney dysfunction: supplementation with Meriva® in initial, transient kidney micro-macro albuminuria. Panminerva Medica, 61(4), 444-448. https://doi.org/10.23736/S0031-0808.18.03575-9

Li, F., Yang, X., Yang, Y., Li, P., Yang, Z., & Zhang, C. (2015). Phospholipid complex as an approach for bioavailability enhancement of echinacoside. *Drug development and industrial pharmacy*, *41*(11), 1777–1784. https://doi.org/10.3109/03639045.2015.1004183

Li, J., Wang, X., Zhang, T., Wang, C., Huang, Z., Luo, X., & Deng, Y. (2015). A review on phospholipids and their main applications in drug delivery systems. Asian journal of pharmaceutical sciences, 10(2), 81-98. https://doi.org/10.1016/j.ajps.2014.09.004

Lim, A. W., Ng, P. Y., Chieng, N., & Ng, S. F. (2019). Moringa oleifera leaf extract–loaded phytophospholipid complex for potential application as wound dressing. *Journal of Drug Delivery Science and Technology*, *54*, 101329. https://doi.org/10.1016/j.jddst.2019.101329

Liu, S. (2012). Preparation, characterization and in vitro anti-tumor activities of evodiamine phospholipids complex. *Chinese Pharmaceutical Journal,* 517-523.

Liu, Y., Huang, P., Hou, X., Yan, F., Jiang, Z., Shi, J., ... & Feng, N. (2019). Hybrid curcumin–phospholipid complex-near-infrared dye oral drug delivery system to inhibit lung metastasis of breast cancer. *International Journal of Nanomedicine*, *14*, 3311. https://doi.org/10.2147/ijn.s200847

Liu, Z., Wang, J., Gao, W., Man, S., Guo, H., Zhang, J., & Liu, C. (2013). Formulation and in vitro absorption analysis of Rhizoma paridis steroidal saponins. *International journal of pharmaceutics*, *441*(1-2), 680–686. https://doi.org/10.1016/j.ijpharm.2012.10.028

Loeser, K., Seemann, S., König, S., Lenhardt, I., Abdel-Tawab, M., Koeberle, A., Werz, O., & Lupp, A. (2018). Protective Effect of Casperome®, an Orally Bioavailable Frankincense Extract, on Lipopolysaccharide- Induced Systemic Inflammation in Mice. *Frontiers in pharmacology*, *9*, 387. https://doi.org/10.3389/fphar.2018.00387

Loguercio, C., Andreone, P., Brisc, C., Brisc, M. C., Bugianesi, E., Chiaramonte, M., Cursaro, C., Danila, M., de Sio, I., Floreani, A., Freni, M. A., Grieco, A., Groppo, M., Lazzari, R., Lobello, S., Lorefice, E., Margotti, M., Miele, L., Milani, S., Okolicsanyi, L., … Federico, A. (2012). Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *Free radical biology & medicine*, *52*(9), 1658–1665. https://doi.org/10.1016/j.freeradbiomed.2012.02.008

Lu, M., Qiu, Q., Luo, X., Liu, X., Sun, J., Wang, C., Lin, X., Deng, Y., & Song, Y. (2019). Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian journal of pharmaceutical sciences*, *14*(3), 265–274. https://doi.org/10.1016/j.ajps.2018.05.011

Magrone, T., Pugliese, V., Fontana, S., & Jirillo, E. (2014). Human use of Leucoselect® Phytosome® with special reference to inflammatory-allergic pathologies in frail elderly patients. *Current pharmaceutical design*, *20*(6), 1011–1019. https://doi.org/10.2174/13816128200614022014441 1

Mahmoodi, N., Motamed, N., Paylakhi, S. H., & O Mahmoodi, N. (2015). Comparing the Effect of Silybin and Silybin Advanced™ on Viability and HER2 Expression on the Human Breast Cancer SKBR3 Cell Line by no Serum Starvation. *Iranian journal of pharmaceutical research: IJPR*, *14*(2), 521–530. https://pubmed.ncbi.nlm.nih.gov/25901160

Maida, G. (2016). Clinical usefulness of oral supplementation with curcumin phytosome in patients with radiculopathy due to spondyloarthritis or discopathy. *Minerva Ortop Traumatol*, *67*(2), 75-78.

Maiti, P., & Dunbar, G. L. (2018). Use of Curcumin, a Natural Polyphenol for Targeting Molecular Pathways in Treating Age-Related Neurodegenerative Diseases. *International journal of molecular sciences*, *19*(6), 1637. https://doi.org/10.3390/ijms19061637

Mancini, S., Nardo, L., Gregori, M., Ribeiro, I., Mantegazza, F., Delerue-Matos, C., Masserini, M., & Grosso, C. (2018). Functionalized liposomes and phytosomes loading Annona muricata L. aqueous extract: Potential nanoshuttles for brain-delivery of phenolic compounds. *Phytomedicine: international journal of phytotherapy and phytopharmacology*, *42*, 233–244. https://doi.org/10.1016/j.phymed.2018.03.053

Mao, J. T., Xue, B., Fan, S., Neis, P., Qualls, C., Massie, L., & Fiehn, O. (2021). Leucoselect Phytosome Modulates Serum Eicosapentaenoic Acid, Docosahexaenoic Acid, and Prostaglandin E3 in a Phase I Lung Cancer Chemoprevention Study. *Cancer prevention research (Philadelphia, Pa.)*, *14*(6), 619–626. https://doi.org/10.1158/1940-6207.CAPR-20-0585

Marjaneh, R. M., Rahmani, F., Hassanian, S. M., Rezaei, N., Hashemzehi, M., Bahrami, A., Ariakia, F., Fiuji, H., Sahebkar, A., Avan, A., & Khazaei, M. (2018). Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. *Journal of cellular physiology*, *233*(10), 6785–6798. https://doi.org/10.1002/jcp.26538

Maryana, W., Rachmawati, H., & Mudhakir, D. (2016). Formation of phytosome containing silymarin using thin layer-hydration technique aimed for oral delivery. *Materials today: proceedings*, *3*(3), 855-866. https://doi.org/10.1016/j.matpr.2016.02.019

Mazumder, A., Dwivedi, A., Du Preez, J. L., & Du Plessis, J. (2016). In vitro wound healing and cytotoxic effects of sinigrin–phytosome complex. *International journal of pharmaceutics*, *498*(1-2), 283-293. https://doi.org/10.1016/j.ijpharm.2015.12.027

Minaei, A., Sabzichi, M., Ramezani, F., Hamishehkar, H., & Samadi, N. (2016). Co-delivery with nano-quercetin enhances doxorubicin-mediated cytotoxicity against MCF-7 cells. *Molecular biology reports*, *43*(2), 99–105. https://doi.org/10.1007/s11033-016-3942-x

Miserocchi, E., Giuffrè, C., Cicinelli, M. V., Marchese, A., Gattinara, M., Modorati, G., & Bandello, F. (2020). Oral phospholipidic curcumin in juvenile idiopathic arthritis-associated uveitis. *European journal of ophthalmology*, *30*(6), 1390–1396. https://doi.org/10.1177/1120672119892804

Mollace, V., Scicchitano, M., Paone, S., Casale, F., Calandruccio, C., Gliozzi, M., Musolino, V., Carresi, C., Maiuolo, J., Nucera, S., Riva, A., Allegrini, P., Ronchi, M., Petrangolini, G., & Bombardelli, E. (2019). Hypoglycemic and Hypolipemic Effects of a New Lecithin Formulation of Bergamot Polyphenolic Fraction: A Double Blind, Randomized, Placebo-Controlled Study. *Endocrine, metabolic & immune disorders drug targets*, *19*(2), 136–143. https://doi.org/10.2174/1871530319666181203151513

Moradi-Marjaneh, R., Hassanian, S. M., Rahmani, F., Aghaee-Bakhtiari, S. H., Avan, A., & Khazaei, M. (2018). Phytosomal Curcumin Elicits Anti-tumor Properties Through Suppression of Angiogenesis, Cell Proliferation and Induction of Oxidative Stress in Colorectal Cancer. *Current pharmaceutical design*, *24*(39), 4626–4638. https://doi.org/10.2174/1381612825666190110145151

Mukherjee, S., Baidoo, J., Fried, A., Atwi, D., Dolai, S., Boockvar, J., Symons, M., Ruggieri, R., Raja, K., & Banerjee, P. (2016). Curcumin changes the polarity of tumor-associated microglia and eliminates glioblastoma. *International journal of cancer*, *139*(12), 2838–2849. https://doi.org/10.1002/ijc.30398

Mukherjee, S., Fried, A., Hussaini, R., White, R., Baidoo, J., Yalamanchi, S., & Banerjee, P. (2018). Phytosomal curcumin causes natural killer cell-dependent repolarization of glioblastoma (GBM) tumor-associated microglia/macrophages and elimination of GBM

and GBM stem cells. *Journal of experimental & clinical cancer research : CR*, *37*(1), 168. https://doi.org/10.1186/s13046-018-0792-5

Nagar, G. (2019). Phytosomes: a novel drug delivery for herbal extracts. Int J Pharm Sci Res, 949-59. http://dx.doi.org/10.13040/IJPSR.0975-8232.4(3).949-59

Naik, S. R., & Panda, V. S. (2007). Antioxidant and hepatoprotective effects of Ginkgo biloba phytosomes in carbon tetrachloride-induced liver injury in rodents. *Liver international : official journal of the International Association for the Study of the Liver*, *27*(3), 393–399. https://doi.org/10.1111/j.1478-3231.2007.01463.x

Naik, S. R., & Panda, V. S. (2008). Hepatoprotective effect of Ginkgoselect Phytosome in rifampicin induced liver injury in rats: evidence of antioxidant activity. *Fitoterapia*, *79*(6), 439–445. https://doi.org/10.1016/j.fitote.2008.02.013

Naik, S. R., Pilgaonkar, V. W., & Panda, V. S. (2006). Evaluation of antioxidant activity of Ginkgo biloba phytosomes in rat brain. *Phytotherapy research : PTR*, *20*(11), 1013–1016. https://doi.org/10.1002/ptr.1976

Naik, S. R., Pilgaonkar, V. W., & Panda, V. S. (2006a). Neuropharmacological evaluation of Ginkgo biloba phytosomes in rodents. *Phytotherapy research : PTR*, *20*(10), 901–905. https://doi.org/10.1002/ptr.1973

Naik, S. R., Pilgaonkar, V. W., & Panda, V. S. (2006b). Evaluation of antioxidant activity of Ginkgo biloba phytosomes in rat brain. *Phytotherapy research : PTR*, *20*(11), 1013–1016. https://doi.org/10.1002/ptr.1976

Nuttall, S. L., Kendall, M. J., Bombardelli, E., & Morazzoni, P. (1998). An evaluation of the antioxidant activity of a standardized grape seed extract, Leucoselect®. Journal of clinical pharmacy and therapeutics, 23(5), 385-389.https://doi.org/10.1046/j.1365-2710.1998.00180.x

Ojha, S. (2018). In vitro and In vivo neuroprotective study of solid lipid nanoparticles loaded with dimethyl fumarate. Asian Journal of Pharmaceutics (AJP), 12(01). https://doi.org/10.22377/ajp.v12i01.2044

Pajardi, G., Bortot, P., Ponti, V., & Novelli, C. (2014). Clinical usefulness of oral supplementation with alpha-lipoic Acid, curcumin phytosome, and B-group vitamins in patients with carpal tunnel syndrome undergoing surgical treatment. *Evidence-based complementary and alternative medicine: eCAM*, *2014*, 891310. https://doi.org/10.1155/2014/891310

Panda, V. S., & N, S. R. (2009). Evaluation of cardioprotective activity of Ginkgo biloba and Ocimum sanctum in rodents. *Alternative medicine review: a journal of clinical therapeutic*, *14*(2), 161–171. https://altmedrev.com/wp-content/uploads/2019/02/v14-2-161.pdf

Panda, V. S., & Naik, S. R. (2008). Cardioprotective activity of Ginkgo biloba Phytosomes in isoproterenol-induced myocardial necrosis in rats: a biochemical and histoarchitectural evaluation. *Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie*, *60*(4-5), 397–404. https://doi.org/10.1016/j.etp.2008.03.010

Pastorelli, D., Fabricio, A. S., Giovanis, P., D'Ippolito, S., Fiduccia, P., Soldà, C., ... & Ursini, F. (2018). Phytosome complex of curcumin as complementary therapy of advanced pancreatic cancer improves safety and efficacy of gemcitabine: Results of a prospective

phase II trial. *Pharmacological research*, *132*, 72-79. https://doi.org/10.1016/j.phrs.2018.03.013

Patel, J., Patel, R., Khambholja, K., & Patel, N. (2009). An overview of phytosomes as an advanced herbal drug delivery system. Asian J Pharm Sci, 4(6), 363-371. 10.19080/CTBEB.2017.03.555621

Pathan, R. A., & Bhandari, U. (2011). Preparation & characterization of embelin–phospholipid complex as effective drug delivery tool. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 69(1), 139-147. https://doi.org/10.1007/s10847-010-9824-2

Pellegrini, L., Milano, E., Franceschi, F., Belcaro, G., Gizzi, G., Feragalli, B., Dugall, M., Luzzi, R., Togni, S., Eggenhoffner, R., & Giacomelli, L. (2016). Managing ulcerative colitis in remission phase: usefulness of Casperome®, an innovative lecithin-based delivery system of Boswellia serrata extract. *European review for medical and pharmacological sciences*, *20*(12), 2695–2700. PMID: 27383325

Petrangolini, G., Ronchi, M., Frattini, E., De Combarieu, E., Allegrini, P., & Riva, A. (2019). A New Food-grade Coenzyme Q10 Formulation Improves Bioavailability: Single and Repeated Pharmacokinetic Studies in Healthy Volunteers. *Current drug delivery*, *16*(8), 759–767. https://doi.org/10.2174/1567201816666190902123147

Pucek, A., Niezgoda, N., Kulbacka, J., Wawrzeńczyk, C., & Wilk, K. A. (2017). Phosphatidylcholine with conjugated linoleic acid in fabrication of novel lipid nanocarriers. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *532*, 377-388. https://doi.org/10.1016/j.colsurfa.2017.04.061

Rani, A., Kumar, S., & Khar, R. K. (2019). Casuarina equisetifolia extract loaded phytosomes: Optimization, characterization and in vivo evaluation of antidiabetic and antihyperlipidemic activities in Wistar rats. *Drug Delivery Letters*, *9*(2), 116-133. http://dx.doi.org/10.2174/2210303109666190118162157

Rathee, S., & Kamboj, A. (2018). Optimization and development of antidiabetic phytosomes by the Box–Behnken design. *Journal of liposome research*, *28*(2), 161-172. https://doi.org/10.1080/08982104.2017.1311913

Riva, A., Allegrini, P., Franceschi, F., Togni, S., Giacomelli, L., & Eggenhoffner, R. (2017). A novel boswellic acids delivery form (Casperome®) in the management of musculoskeletal disorders: a review. *European review for medical and pharmacological sciences*, *21*(22), 5258–5263. https://doi.org/10.26355/eurrev_201711_13849

Riva, A., Giacomelli, L., Togni, S., Franceschi, F., Eggenhoffner, R., Zuccarini, M. C., & Belcaro, G. (2019). Oral administration of a lecithin-based delivery form of boswellic acids (Casperome®) for the prevention of symptoms of irritable bowel syndrome: a randomized clinical study. *Minerva gastroenterologica e dietologica*, *65*(1), 30–35. https://doi.org/10.23736/S1121-421X.18.02530-8

Riva, A., Longo, V., Berlanda, D., Allegrini, P., Masetti, G., Botti, S., & Petrangolini, G. (2020). Healthy Protection of Bergamot is linked to the Modulation of Microbiota. *J Appl Microb Res.* 2020;3(2):45-51.

Riva, A., Togni, S., Giacomelli, L., Franceschi, F., Eggenhoffner, R., Feragalli, B., Belcaro, G., Cacchio, M., Shu, H., & Dugall, M. (2017). Effects of a curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 24-week supplement study. *European review for medical and pharmacological sciences*, *21*(7), 1684–1689.

Rondanelli, M., Perna, S., Gasparri, C., Petrangolini, G., Allegrini, P., Cavioni, A., Faliva, M. A., Mansueto, F., Patelli, Z., Peroni, G., Tartara, A., & Riva, A. (2022). Promising Effects of 3-Month Period of Quercetin Phytosome® Supplementation in the Prevention of Symptomatic COVID-19 Disease in Healthcare Workers: A Pilot Study. *Life (Basel, Switzerland)*, *12*(1), 66. https://doi.org/10.3390/life12010066

Rondanelli, M., Riva, A., Allegrini, P., Faliva, M. A., Naso, M., Peroni, G., Nichetti, M., Gasparri, C., Spadaccini, D., Iannello, G., Infantino, V., Fazia, T., Bernardinelli, L., & Perna, S. (2020). The Use of a New Food-Grade Lecithin Formulation of Highly Standardized Ginger (*Zingiber officinale*) and *Acmella oleracea* Extracts for the Treatment of Pain and Inflammation in a Group of Subjects with Moderate Knee Osteoarthritis. *Journal of pain research*, *13*, 761–770. https://doi.org/10.2147/JPR.S214488

Sabzichi, M., Hamishehkar, H., Ramezani, F., Sharifi, S., Tabasinezhad, M., Pirouzpanah, M., Ghanbari, P., & Samadi, N. (2014). Luteolin-loaded phytosomes sensitize human breast carcinoma MDA-MB 231 cells to doxorubicin by suppressing Nrf2 mediated signalling. *Asian Pacific journal of cancer prevention: APJCP*, *15*(13), 5311–5316. https://doi.org/10.7314/apjcp.2014.15.13.5311

Sbrini, G., Brivio, P., Fumagalli, M., Giavarini, F., Caruso, D., Racagni, G., Dell'Agli, M., Sangiovanni, E., & Calabrese, F. (2020a). *Centella asiatica* L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex. *Nutrients*, *12*(2), 355. https://doi.org/10.3390/nu12020355

Sbrini, G., Brivio, P., Fumagalli, M., Giavarini, F., Caruso, D., Racagni, G., Dell'Agli, M., Sangiovanni, E., & Calabrese, F. (2020). *Centella asiatica* L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex. *Nutrients*, *12*(2), 355. https://doi.org/10.3390/nu12020355

Sbrini, G., Brivio, P., Sangiovanni, E., Fumagalli, M., Racagni, G., Dell'Agli, M., & Calabrese, F. (2020b). Chronic Treatment with a Phytosomal Preparation Containing *Centella asiatica* L. and *Curcuma longa* L. Affects Local Protein Synthesis by Modulating the BDNF-mTOR-S6 Pathway. *Biomedicines*, *8*(12), 544. https://doi.org/10.3390/biomedicines8120544

Semalty, A. (2014). Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: a critical and meta-analysis. Expert opinion on drug delivery, 11(8), 1255-1272. https://doi.org/10.1517/17425247.2014.916271

Sgorlon, S., Colitti, M., Asquini, E., Ferrarini, A., Pallavicini, A., & Stefanon, B. (2012). Administration of botanicals with the diet regulates gene expression in peripheral blood cells of Sarda sheep during ACTH challenge. *Domestic animal endocrinology*, *43*(3), 213–226. https://doi.org/10.1016/j.domaniend.2012.03.001

Sharma, S., & Sahu, A. N. (2016). Development, Characterization, and Evaluation of Hepatoprotective Effect of Abutilon indicum and Piper longum Phytosomes. *Pharmacognosy research*, *8*(1), 29–36. https://doi.org/10.4103/0974-8490.171102

Shivanand, P., & Kinjal, P. (2010). Phytosomes: technical revolution in phytomedicine. *International Journal of PharmTech Research*, *2*(1), 627-631.

Singh, A., Saharan, V. A., Singh, M., & Bhandari, A. (2011). Phytosome: drug delivery system for polyphenolic phytoconstituents. Iranian Journal of Pharmaceutical Sciences, 7(4), 209-219.

Singh, P., Singh, M., Kanoujia, J., Arya, M., Saraf, S. K., & Saraf, S. A. (2016). Process optimization and photostability of silymarin nanostructured lipid carriers: effect on UV-irradiated rat skin and SK-MEL 2 cell line. *Drug delivery and translational research*, *6*(5), 597–609. https://doi.org/10.1007/s13346-016-0317-8

Singh, R. P., & Narke, R. (2015). Preparation and evaluation of phytosome of lawsone. International Journal of Pharmaceutical Sciences and Research (IJPSR), 6(12), 5217-5226.

Singh, R. P., Gangadharappa, H. V., & Mruthunjaya, K. (2018). Phytosome complexed with chitosan for gingerol delivery in the treatment of respiratory infection: In vitro and in vivo evaluation. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, *122*, 214–229. https://doi.org/10.1016/j.ejps.2018.06.028

Singh, R. P., Gangadharappa, H. V., & Mruthunjaya, K. (2018). Phytosome complexed with chitosan for gingerol delivery in the treatment of respiratory infection: In vitro and in vivo evaluation. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, *122*, 214–229. https://doi.org/10.1016/j.ejps.2018.06.028

Singh, R. P., Gu, M., & Agarwal, R. (2008). Silibinin inhibits colorectal cancer growth by inhibiting tumor cell proliferation and angiogenesis. *Cancer research*, *68*(6), 2043–2050. https://doi.org/10.1158/0008-5472.CAN-07-6247

Singh, R. P., Raina, K., Sharma, G., & Agarwal, R. (2008). Silibinin inhibits established prostate tumor growth, progression, invasion, and metastasis and suppresses tumor angiogenesis and epithelial-mesenchymal transition in transgenic adenocarcinoma of the mouse prostate model mice. *Clinical cancer research: an official journal of the American Association for Cancer Research*, *14*(23), 7773–7780. https://doi.org/10.1158/1078-0432.CCR-08-1309

Smith, M. C., Crist, R. M., Clogston, J. D., & McNeil, S. E. (2017). Zeta potential: a case study of cationic, anionic, and neutral liposomes. Analytical and bioanalytical chemistry, 409(24), 5779-5787. https://doi.org/10.1007/s00216-017-0527-z

Solda, C., Bardini, R., Sperti, C., Da Dalt, G., Gion, M., Fiduccia, P., ... & Pastorelli, D. (2015). Phase II study of Gemcitabine and Curcumin (Meriva®) as first line treatment for locally advanced or metastatic pancreatic cancer: preliminary results. *Annals of Oncology*, *26*, vi102. https://doi.org/10.1093/annonc/mdv344.41

Solda, C., Sperti, C., Romeo, B., Da Dalt, G., Gion, M., Ursini, F., ... & Pastorelli, D. (2016). Use of Meriva as complementary therapy of locally advanced or metastatic pancreatic cancer (PC) with gemcitabine (GEM). *J Clin Oncol*. 2016;34(15_suppl): e15696–e15696. doi:10.1200/JCO.2016.34.15_suppl.e15696204

Suriyakala, P. C., Babu, N. S., Rajan, D. S., & Prabakaran, L. (2014). Phospholipids as versatile polymer in drug delivery systems. Int J Pharm Pharm Sci, 6(1), 8-11. https://innovareacademics.in/journal/ijpps/Vol6Issue1/7714.pdf

Tedesco, D., Tameni, M., Steidler, S., Galletti, S., & Di Pierro, F. (2003). Effect of silymarin and its phospholipid complex against AFM1 excretion in an organic dairy herd. *Milchwissenschaft*, *58*(7-8), 416-419.

Telange, D. R., Patil, A. T., Pethe, A. M., Fegade, H., Anand, S., & Dave, V. S. (2017). Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for

improved solubility, in vivo bioavailability, and antioxidant potential. European Journal of Pharmaceutical Sciences, 108, 36-49. https://doi.org/10.1016/j.ejps.2016.12.009

Telange, D. R., Patil, A. T., Pethe, A. M., Tatode, A. A., Anand, S., & Dave, V. S. (2016). Kaempferol-phospholipid complex: formulation, and evaluation of improved solubility, in vivo bioavailability, and antioxidant potential of kaempferol. Journal of excipients and food chemicals, 7(4), 1174.

Teng, C. F., Yu, C. H., Chang, H. Y., Hsieh, W. C., Wu, T. H., Lin, J. H., Wu, H. C., Jeng, L. B., & Su, I. J. (2019). Chemopreventive Effect of Phytosomal Curcumin on Hepatitis B Virus-Related Hepatocellular Carcinoma in A Transgenic Mouse Model. *Scientific reports*, *9*(1), 10338. https://doi.org/10.1038/s41598-019-46891-5

Theoharides, T. C., Cholevas, C., Polyzoidis, K., & Politis, A. (2021). Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. *BioFactors (Oxford, England)*, *47*(2), 232–241. https://doi.org/10.1002/biof.1726

Tisato, V., Zauli, G., Rimondi, E., Gianesini, S., Brunelli, L., Menegatti, E., Zamboni, P., & Secchiero, P. (2013). Inhibitory effect of natural anti-inflammatory compounds on cytokines released by chronic venous disease patient-derived endothelial cells. *Mediators of inflammation*, *2013*, 423407. https://doi.org/10.1155/2013/423407

Togni, S., Maramaldi, G., Di Pierro, F., & Biondi, M. (2014). A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. *Clinical, cosmetic and investigational dermatology*, *7*, 321–327. https://doi.org/10.2147/CCID.S69240

Tripathy, S., Patel, D. K., Barob, L., & Naira, S. K. (2013). A review on phytosomes, their characterization, advancement & potential for transdermal application. Journal of Drug Delivery and Therapeutics, 3(3), 147-152. https://doi.org/10.22270/jddt.v3i3.508

Tsao, R. (2010). Chemistry and biochemistry of dietary polyphenols. Nutrients, 2(12), 1231-1246. https://doi.org/10.3390/nu2121231

Tung, B. T., Hai, N. T., & Son, P. K. (2017). Hepatoprotective effect of Phytosome Curcumin against paracetamol-induced liver toxicity in mice. *Brazilian Journal of Pharmaceutical Sciences*, *53*. https://doi.org/10.1590/s2175-97902017000116136

Tuyaerts, S., Rombauts, K., Everaert, T., Van Nuffel, A., & Amant, F. (2019). A Phase 2 Study to Assess the Immunomodulatory Capacity of a Lecithin-based Delivery System of Curcumin in Endometrial Cancer. *Frontiers in nutrition*, *5*, 138. https://doi.org/10.3389/fnut.2018.00138

Ullah, F., Liang, H., Niedermayer, G., Münch, G., & Gyengesi, E. (2020). Evaluation of Phytosomal Curcumin as an Anti-inflammatory Agent for Chronic Glial Activation in the GFAP-IL6 Mouse Model. *Frontiers in neuroscience*, *14*, 170. https://doi.org/10.3389/fnins.2020.00170

Vigna, G. B., Costantini, F., Aldini, G., Carini, M., Catapano, A., Schena, F., Tangerini, A., Zanca, R., Bombardelli, E., Morazzoni, P., Mezzetti, A., Fellin, R., & Maffei Facino, R. (2003). Effect of a standardized grape seed extract on low-density lipoprotein susceptibility to oxidation in heavy smokers. *Metabolism: clinical and experimental*, *52*(10), 1250–1257. https://doi.org/10.1016/s0026-0495(03)00192-6

Williams, B., Watanabe, C. M., Schultz, P. G., Rimbach, G., & Krucker, T. (2004). Age-related effects of Ginkgo biloba extract on synaptic plasticity and excitability. *Neurobiology of aging*, *25*(7), 955–962. https://doi.org/10.1016/j.neurobiolaging.2003.10.008

Wright, A., Benjamin, S., & Ruggieri, R. (2017, June). Meriva and a novel chemically-modified curcumin for the treatment of medulloblastoma. In *4th Biennial Conference on Pediatric Neuro-Oncology Basic and Translational Research*. https://doi.org/10.1093%2Fneuonc%2Fnox083.186

Xu, L., Xu, D., Li, Z., Gao, Y., & Chen, H. (2019). Synthesis and potent cytotoxic activity of a novel diosgenin derivative and its phytosomes against lung cancer cells. *Beilstein journal of nanotechnology*, *10*(1), 1933-1942. https://doi.org/10.3762/bjnano.10.189

Yu, F., Li, Y., Chen, Q., He, Y., Wang, H., Yang, L., Guo, S., Meng, Z., Cui, J., Xue, M., & Chen, X. D. (2016). Monodisperse microparticles loaded with the self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V*, *103*, 136–148. https://doi.org/10.1016/j.ejpb.2016.03.019

Yu, F., Li, Y., Chen, Q., He, Y., Wang, H., Yang, L., Guo, S., Meng, Z., Cui, J., Xue, M., & Chen, X. D. (2016). Monodisperse microparticles loaded with the self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V*, *103*, 136–148. https://doi.org/10.1016/j.ejpb.2016.03.019

Yu, Z., Liu, X., Chen, H., & Zhu, L. (2020). Naringenin-Loaded Dipalmitoylphosphatidylcholine Phytosome Dry Powders for Inhaled Treatment of Acute Lung Injury. *Journal of aerosol medicine and pulmonary drug delivery*, *33*(4), 194–204. https://doi.org/10.1089/jamp.2019.1569

Yu, Z., Liu, X., Chen, H., & Zhu, L. (2020). Naringenin-Loaded Dipalmitoylphosphatidylcholine Phytosome Dry Powders for Inhaled Treatment of Acute Lung Injury. *Journal of aerosol medicine and pulmonary drug delivery*, *33*(4), 194–204. https://doi.org/10.1089/jamp.2019.1569

Zhang, D. W., Fu, M., Gao, S. H., & Liu, J. L. (2013). Curcumin and diabetes: a systematic review. *Evidence-based complementary and alternative medicine : eCAM*, *2013*, 636053. https://doi.org/10.1155/2013/636053

Zhao, X., Shi, C., Zhou, X., Lin, T., Gong, Y., Yin, M., ... & Fang, J. (2019). Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. European Journal of Pharmaceutical Sciences, 138, 104994. https://doi.org/10.1016/j.ejps.2019.104994

HOW TO CITE

Sanjib Kumar Das, Rakesh Acharya and Koushik Sen (2022). Phytosomes: a cutting-edge technique for herbal drug delivery and its clinical applications. © International Academic Publishing House (IAPH), B. Sarkar (eds.), *The Basic Handbook of Indian Ethnobotany and Traditional Medicine*,Vol. 1, pp. 96-133. ISBN: 978-81-957954-1-3. DOI: https://doi.org/10.52756/bhietm.2022.e01.008