Advances in Traditional Medicine (2024) 24:659–684
https://doi.org/10.1007/s13596-023-00712-3

REVIEW

Detailed review on phytosomal formulation attenuating new pharmacological therapies

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Received: 26 February 2023 / Accepted: 14 September 2023 / Published online: 6 October 2023

Abstract

Nowadays, numerous diseases are benefitted from phytosomal therapy. However, poor selectivity and bioavailability may be limiting factors of their therapeutic applicability. The distribution of hydrophobic phytochemicals has been proposed as a potential use for nanovesicles. Phytosomes are more stable, according to a recent assessment of the literature, since a chemical link is created between the phospholipid molecules and the phytoconstituent. Fewer phytoconstituents are needed, extending the action, and they are more bioavailable in their complex form. Due to the easy preparation of the bilayer vesicles and their adaptability, they have been widely used and approved by the scientific literature. In this review paper we describe the promising clinical and experimental findings of more than 100 phytosomal studies. The effects of phytosomes on the immunological, circulatory, gastrointestinal, genitourinary, respiratory, integumentary, central and peripheral nervous systems, and musculoskeletal systems have all been studied according to the research compiled. These results confirm the greater effectiveness of phytosomes, both in terms of biological activity or reduced dosage, highlighting curcumin and silymarin as the most formulated compounds. Using such formulations to increase the bioactivity of phytochemicals and their bioavailability generally has advantages, allowing for lower dosages or higher biological activity as compared to using unformulated compounds. The conclusion of this study encourages the researchers to transfer their findings from research laboratories to market, for a further development of these products. The potential role of phytophospholipid complexes has a promising future for pharmaceutical applications with the help of physicians and other researchers.

Keywords Phytosome · Phospholipid complex · Nanovesicles · Bowel cancer · Wound healing · Respiratory system diseases

Abbreviations

15-HETE	15-Hydroxyeicosatetraenoic acid
AKBA	Acetyl-11-keto-β-boswellic acid
AlCl3	Aluminum chloride
ALP	Alkaline phosphatase
ARG1	Arginase 1
BA	Boswellic acid
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BFGF	Basic fibroblast growth factor
BMI	Body mass index
BSE	Bovine spongiform encephalopathy
Caspase-3	Cysteine–aspartic acid protease
CAT	Chloramphenicol acetyl transferase
CCl4	Carbon tetrachloride
COX-2	Cyclooxygenase-2
CT26	Colon tumor 26 Cells
CYP	Cytochrome P450
DPPC	Dipalmitoylphosphatidylcholine
EGCG	Epigallocatechin gallate
GGTP	Gamma-glutamine transpeptidase
GOT	Glutamic oxalic transaminase
GPT	Growth promotion testing
GPx	Glutathione peroxidase 1
GR	Grain

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GSE	Grape seed extract
HCT116	Human colon cancer cell line
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HER2	Human epidermal growth factor receptor 2
HSP-47	Heat shock protein 47
HT29	Human colorectal adenocarcinoma cell line
IBS	Irritable bowel syndrome
ICAM-1	Intercellular adhesion molecule 1
ICOS	T cell co-stimulator
IGFBP-3	Insulin-like growth factor-binding protein 3
IGF-I	Insulin-like growth factor 1
IL-10	Interleukin 10
IL1RN	Interleukin-1 receptor antagonist protein
IL-2	Interleukin-2
IL-22	Interleukin-22
IL-6	Interleukin 6
KBA	11-Keto-β-boswellic acid
LC–MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MAO	Monoamine oxidase inhibitor
MDA	Mass drug administration
MHC	Major histocompatibility complex
MMP-3	Matrix metalloproteinase-3
MMP-9	Matrix metallopeptidase 9
mTOR	Mammalian target of rapamycin
NAD(P)H	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NDA	New drug application
NF-κB	Nuclear factor kappa B
NHDF	Normal human dermal fibroblasts
NLC	Nanostructured lipid carrier
NOR	Nucleolus organizer regions
Notch-1	Neurogenic locus notch homolog protein 1
Nrf2	Nuclear factor erythroid 2-related factor 2
NRS	Numerical rating scale
PC	Phosphatidylcholine
PPARs	Peroxisome proliferator-activated receptors
ppm	Parts-per-million
PSA	Prostate-specific antigen
RAW	Research and analysis wing
SOD	Superoxide dismutases
SPE	Solid-phase extraction
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TGF-β1	Transforming growth factor beta
TNF	Tumor necrosis factor
TRAMP	Transgenic adenocarcinoma of mouse prostate
UV–UV	Visible spectrophotometry
UVB	Ultraviolet B light/irradiation
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2

Introduction

Many studies discuss the bioavailability of phytosomes in relation to the formulated products. The phytosome absorbed to the active ingredient and distributed throughout the tissue (Negahdari et al. 2021). The components of the phytosome silymarin's capacity to defend embryonic rat brains under ethanol treatment and investigated a phytosome of curcumin's capacity to reduce an animal model of persistent glial activation in GFAPIL6 mice and the second study assessed the brain's anti-oxidant activity in rats following acute (14 days) and sub-acute (28 days) treatment (Ullah et al. 2020). In healthy participants suffering from mild to severe asthmatic and rhinitis the quercetin phytosomes were used in addition to conventional treatment (Saad 2015; Casula et al. 2021). The 11 people with diabetes-related macular edema improved optical coherence tomography measures of retinal thickness and visual acuity when given 500 mg twice daily tablet of the curcumin phytosme formulation (equivalent to 200 mg of curcuminoids) (Mazzolani et al. 2018).

Type 2 diabetes, obesity, and insulin resistance are just a few of the metabolic dysfunctions that make up the metabolic syndrome (Zimmet et al. 1999). During therapy of triglycerides, total cholesterol, and LDL or HDL cholesterol, hardly changed (Börgel et al. 2006). By the treatment's ability to induce a decrease in weight and enhance ratio reductions curcumin-based formulations may reduce levels of fat and BMI and help overweight people lose weight randomized, study to investigate the effectiveness of using grape seed phytosomes on the oxidation of (LDL) in heavy smokers (Moscarella et al. 1993).

Participants with borderline criteria who received the green tea catechins' phytosome composition had a better following a 24-week intervention research, blood lipid profile, blood pressure, and weight reduction (Stromsnes et al. 2021). Combination of the mixture with a reduced-calorie diet improved the loss of weight and decreased BMI (Sampson et al. 2021). Individuals treated with the formulation maintained their previously in hypertriglyceridemic rats, a phytosome formulation including silymarin increased the bioavailability of flavonolignans and reduced dyslipidemia (MacDonald et al. 2021). Male Wistar rats were given phytosomes with mulberry (Morus alba) and ginger (zingiber

officinale) extracts, which also made the alkaloid berberine 29 work better at lowering blood sugar (Kambale et al. 2022). Dementia in older people develops as a result of neurodegenerative brain malfunctions. After being administered of orally repeatedly for five days to rats (comparable to 134 mg/kg/diet of curcuminoids), it was shown that the phytochemical curcumin phytosome increased curcumin's capacity to be absorbed into the body's hippocampus and forward lobe studied the use of nanoparticle methods to enhance the delivery of drugs or other active substances that don't get to the brain well enough (Trushna et al. 2022).

History of phytosomes

Phytosomes, which are suitably named for their ability to transform water-soluble phytoconstituents into lipid-compatible molecular complexes (Bhattacharya et al. 2023) (Fig. 1). Soya phosphatidylcholine, are the lipid phase ingredients used to reduce phytoconstituents lipid-compatible (Dodle et al. 2023). It is readily absorbed when consumed orally, and the main membranes of cells are made up of molecules (Jafernik et al. 2023). Oil and water are miscible under Phosphatidylcholine (PC). A phytoconstituent molecule is often coupled with at least one PC molecule, according to a chemical study of phytosomes (Mahmoudabad et al. 2023) bioactive food that has been shown to be clinically effective for treating liver disease, such as alcohol-related liver steatosis and harm to the liver caused by drugs, and the intake of a phytosome preparation is enough to provide dependable clinical benefit, frequently resulting in significant PC intake (Ajoolabady et al. 2022). The phytosomes approach has been applied to a large number of well-known herbal extracts, including milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng, etc. (Kalita et al. 2013).

Specifications of phytosomes

The word "phytosome" refers to a mixture of a natural product and phospholipids from natural sources, such as soya phospholipids, which stand produced by the interaction between phospholipids and phytoconstituents in stoichiometric ratio with solvent (Gaikwad et al. 2021). According to spectroscopic data, the primary process of phospholipid-substrate interaction is caused by the creation of polarised hydrogen bond heads among the phospholipids (i.e., the groups' phosphate and ammonium), as well as the polar functions within the substrate (Banks et al. 1986).

1. Phytosomes may be able to accommodate the polar head of the phospholipids, which is the active ingredient, making it a permanent component inside the membrane as an example, suppose that the catechindistearoyl PC composite and phenolic hydroxyls from the flavone moiety phosphate, as well as the ion on the PC side, create H-bonds (Amit et al. 2013).
2. Phosphatidylcholine: analysis of nuclear magnetic resonance comparisons between complex and purely preliminary shows that the fatty chain's signals are mostly unaltered (Bosco et al. 2023). According to this evidence, the two lengthy aliphatic chains wrap around the active ingredient to create an envelope with catechin and phospholipid polar heads (Aranda et al. 2023).
3. Phytosomes are the more effective than traditional botanical herbal extracts because they are better absorbed and, reduce side effects (Bahloul et al. 2023). Pharmacoki-

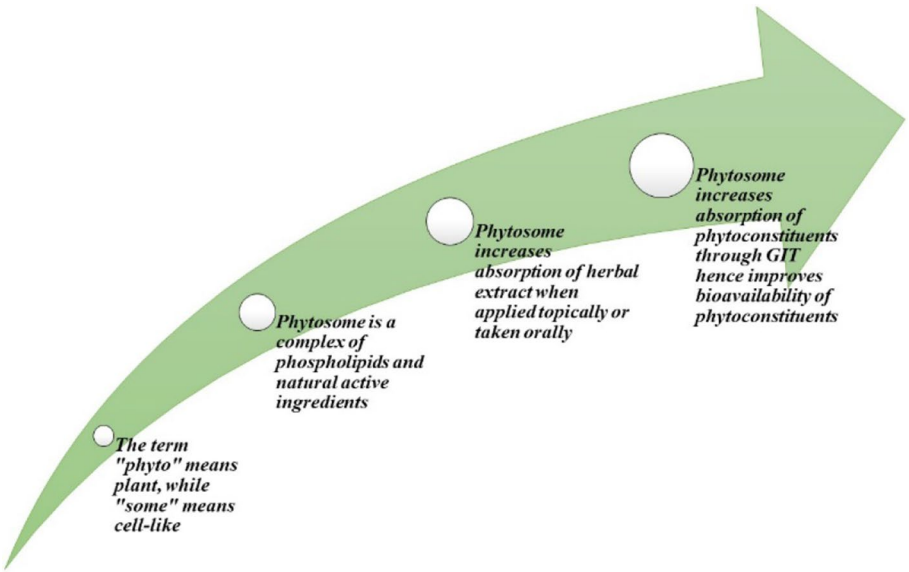

Fig. 1 A general overview of the phytosome

netic investigations or pharmacodynamic testing conducted on experimental animals or human volunteers that shown a greater bioavailability of the phytosome than the natural derivatives plant extract (Jain et al. 2010).
4. Phytosomes are made of the compounds that are lipophilic and have a fixed melting point they dissolve easily in non-polar solvents but not very well in lipids when they come in contact with water, they form structures that look like liposomes but are different in important ways (Göke et al. 2018).

Physico-chemical properties

By reacting the catechin and phospholipid polar heads with each other in the solvent, one can create this type of complex based on spectroscopic information, it has been demonstrated that the primary interaction between phospholipids and the substrate is caused by the creation of hydrogen bonds between the substrate's polar functions and the polar heads of phospholipids, which are the phosphate and ammonium groups (Bhattacharyya et al. 2013). The energetics of phytosomes include an ingredient that is fixed to the polar region head of phospholipids and transforms a structural component inside the membrane, in contrast to liposomes, where the current ingredient is suspended or dissolved in the internal part of the layered membrane (Chime et al. 2013). A respectable illustration of the catechindistearoyl phosphatidylcholine complex, where H-bonds are produced by the phosphate ion on the phosphatidylcholine moiety and the phenolic hydroxyl ends of the flavone moiety (Shakeri et al. 2016). When the complex's ^{1}H and ^{13}C NMR spectra are compared to the others, phosphatidylcholine can be inferred (Gandhi et al. 2012). Almost no change has been made to the signals of the fatty chain (Ong et al. 2010) (Kesharwani et al. 2022).

Biological properties

Phytosomes are more sophisticated herbal products than traditional herbal extracts since they are more readily absorbed and provide greater outcomes in pharmacokinetic investigations or pharmacodynamic trials in test subjects that included both humans and experimental (Mirzaei et al. 2017).

1. Phytosomes, when taken orally, improve the absorption of active substances as well as their systemic bioavailability (Saraf et al. 2010).
2. These herbal products are a step up from traditional herbal extracts, and they work better (Zhang et al. 2019).
3. The compared to traditional herbal medicines, phytosomes have improved pharmacokinetics (Mathur et al. 2016).

Mechanism of phytosome technology

There are two basic reasons for the reduced bioavailability and absorption of polyphenolic components (Cosme et al. 2020). The primary ingredients consist of a large number of ringed molecules that are not too small for diffusion to absorb (Bao et al. 2002). The second problem is that polyphenols' primary components, flavonoid molecules, are poorly soluble in lipids (Brglez Mojzer et al. 2016). The limitations listed above prevent their uptake across biological membranes in order to generate a phytosomal complex with a lipid coating over the contents, polyphenols must be complexed with phospholipids in a 1:1 or 1:2 ratio. By adding phospholipids to standardized plant extracts, phytosome technology increases the absorption and bioavailability of certain phytoconstituents (Ghanbarzadeh et al. 2016). The stoichiometric quantity of PC, a standardized extract, and a nonpolar solvent combined (Dundar et al. 2023). The term "phyto-lipid delivery system" also refers to phytosomes, which act as a link between traditional and cutting-edge delivery methods (El-Husseiny et al. 2022). In a phytophospholipid complex, the lipid-soluble part envelops the choline-bound material while the PC head binds to the phytoactive component (Pawar et al. 2015) (Fig. 2) (Semalty et al. 2012). Spectroscopic analysis revealed that molecules are chemically bound to the PC head (DeLong et al. 1999). The distribution of phytosomes to tissues has been shown to increase bioavailability and provide a higher therapeutic effect (Hüsch et al. 2013).

Advantages of phytosome

The following are some benefits of phytosomes: (Fig. 3).

1. They can be made bioavailable and have been used to provide flavonoids that protect the liver (Kidd et al. 2005).
2. The phytoconstituents provides synergistic effects and cost-effective (Raghavendra et al. 2013).
3. They may also be used to improve medication delivery through transdermal and dermal routes via the skin (Dhiman et al. 2011) (Roshini et al. 2022).
4. Because of the primary constituent's enhanced absorption, the dosage requirement is decreased (Du et al. 2005).
5. Low-risk outline: considering that the toxicological profiles of the phytosomal components are well-supported

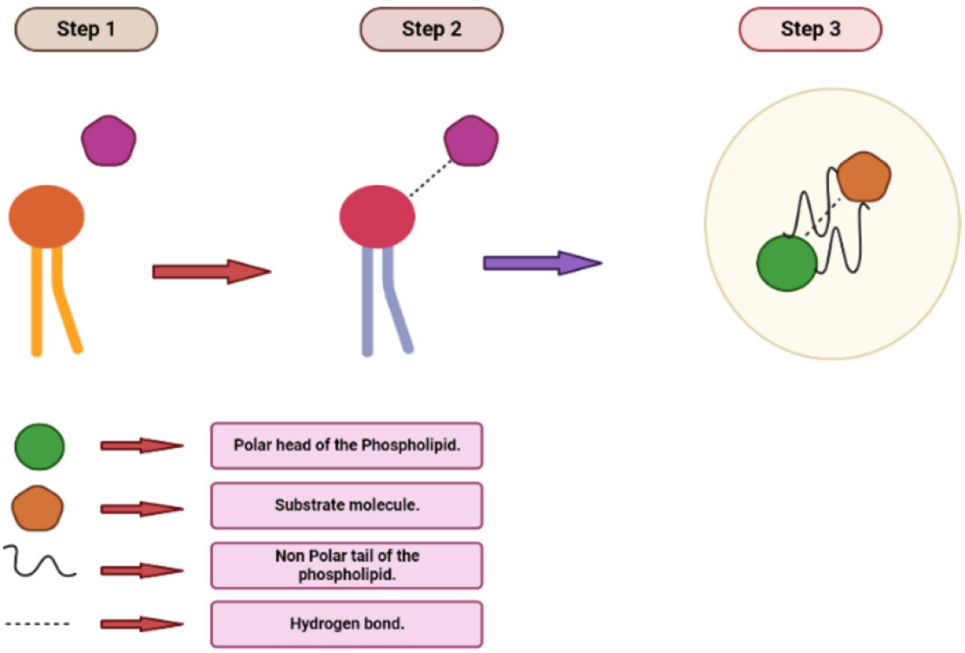

Fig. 2 Stages during phytosome synthesis (Prasad et al. 2016)

Fig. 3 Advantages of Phytosomes

by research published in academic journals, this method removes any danger associated with large-scale medication development using this method (Semalty et al. 2014).

Strength of phytosomes

1. Phytosomes are more stable because a chemical bond is

formed between the phytoconstituents and the phospholipid molecule because phytoconstituents are more bioavailable in their complex form, fewer phytoconstituents are required increasing the action's duration (Udapurkar et al. 2016).
2. Phospholipid-complexed, phytoconstituents are more stable in the stomach and less likely to be affected by bacteria in the gut (Ubong-Isaac et al. 2015).
3. Different absorption methods for lipid-insoluble polar phytochemical components exhibit improved absorption, they results in noticeably increased therapeutic benefits (Tang et al. 2023).
4. Phosphatidylcholine is used to make phytosomes it also acts as a carrier and has a number of medicinal properties when given with other substances, it makes them work better (Kumar et al. 2017) (Yu et al. 2016).

Liposomes and phytosomes differ from one another

In a specific ratio and under predetermined conditions, PC and a chemical that is liquid-soluble combine to form a liposome (Jain et al. 2017). Choline molecules present here to encircle the water-dissolved material; no chemical bonds are created (Fuhrhop et al. 2007). The PC molecule may be surrounded by hundreds or even thousands of other molecules (Bhattacharya 2009). In contrast, the plant and the phosphatidylcholine materials, in reality, create a 1:1 or 2:1 molecular complex during the herbosome process, depending on the substance(s) involved chemical bonding (hydrogen bonds) (Mukherjee et al. 2022). Because of this variation, phytosomes have substantially higher absorption than liposomes and exhibit greater bioavailability additionally, cosmetics and topical skin care items have shown phytosomes to be superior to liposomes (Alharbi et al. 2021). According to their structural differences, phytosomes and liposomes are not the same thing (Fig. 4) a liposome remains an aggregation of numerous molecules of phospholipids that may encapsulate additional phytoactive without being in direct contact with them, while several molecules make up a phytosome certain composed (Kumari et al. 2023). Because of this variation, phytosomes have substantially higher absorption than liposomes and exhibit greater bioavailability (Choubey 2011). Additionally, it has been discovered that phytosomes form topical and skin care treatments using liposomes (Tripathy et al. 2013). Popular liposomes, the water-soluble active ingredients are housed in the interior cavity with little to no contact between the hydrophilic ingredient as well as the lipid core around it (Gouin 2004). The lipophilic visitor's polar functions engage in interaction with the charged phosphate top of the phospholipids via hydrogen bonds and then polar interactions, starting a specific arrangement that can be demonstrated through spectroscopy phytosomes, on the other hand, their polyphenolic guest, which is typically poorly lipid- and water-soluble (Hashemzadeh et al. 2023). When applied topically to the skin, phytosome preparations promote the assimilation of energetic substances, and once taken orally, they increase systemic bioavailability a phytosome will become micellar in appearance in a water medium, generating a spherical assembly that is generally comparable to a liposome but with

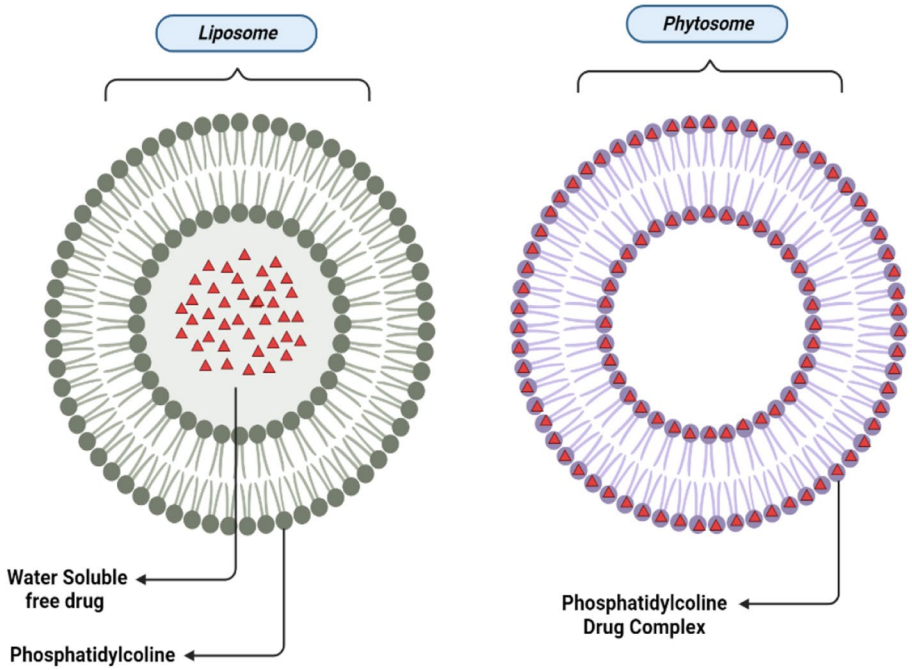

Fig. 4 Distinction between a phytosome and a liposome (Alharbi et al. 2021)

a distinct guest localization (Mishra et al. 2018). In Table 1, there is a comparison between phytosomes and liposomes (Awasth et al. 2011).

Phytosomes' effects on the nervous system: evidence

Role of phytosomes in cognitive decline and neuronal injury

Upon delivery of a phytosome containing bogey, they discovered a higher concentration of the Boswellia serrata plant's boswellia acids (i.e., KBA, AKBA, and BA) (Iram et al. 2017). Also looked at a phytosome formulation including water extract from Annona muricata with the aim of increasing its cross-blood–brain barrier permeability and enhancing its antidepressant-like effect via blocking monoamine oxidase B it contains phytosomes (Domínguez et al. 2016). Demonstrated the optimum using an in-vitro transwell model of the BBB; the compound performs as a radical scavenger and an MAO inhibitor, serving as a suitable model to enhance the extract's antidepressive effects similar to (Tiwari et al. 2020). Looked into the phytosome silymarin's capacity to defend embryonic rat brains using ethanol treatment. Silymarin is a compound from flavonolignans derived from milk thistle, Gaertn's Silybum marianum. Gamma-Glutamyl Transpeptidase was one of the antioxidant enzymes with usually increased activity as a group that received the phytosomal preparation (Dixit et al. 2007) (Naik et al. 2007). Oral administration of 50 or 100 mg/kg decreased pentobarbitone-induced sleep, decreased the impact over time with chlorpromazine, and then increased involuntary movement in rodents (Kasture et al. 2000). Additionally, the preparation had antidepressant effects on scopolamine-induced amnesia, indicating an overall improvement in the behavioral assessments (Williams et al. 2012). In the additional research assessed after acute injury, the rat brain's antioxidant activity increased during subacute (28-day) therapy (Kopjar et al. 2018). It was discovered that phytosome-induced elevated activities were present in the investigated brain regions, which included the hippocampus, cerebral cortex, striatum, and cerebellum, and looked into whether a curcumin phytosome could lessen the chronic glial activation in GFAPIL6 mice, an animal model of the condition (Almajali et al. 2021). For four weeks, a given at three dosages (218, 438, and 874 ppm) reduced neuroinflammation and the percentage and cerebellum (48% and 26.2%, respectively) of activated microglia lately, administering adult male rats Centella asiatica phytosome for ten days at doses of 100 and 20 mg/kg (measured comparable to triterpenes) increased the prefrontal cortex was treated with BDNF, and the higher dose often corrected cognitive deficits (Mugabo et al. 2011) (Rapaport et al. 2013). Additionally, no negative effects were seen while the patient was receiving medication (Tschoner et al. 2007). A different study, showed that a phytosome including extracts from Centella asiatica as well as Curcuma longa, given to rats for ten days at doses of 50 or 250 mg/kg, impacted the production of localized proteins modifying the S6-mTOR-BDNF pathway (Sbrini et al. 2020). Our results provide evidence that this preparation was effective for participants with memory loss and cognitive dysfunction (Hampstead et al. 2017).

Involvement of phytosomes in neurodegenerative disorders

Dementia in older people develops as a result of neurodegenerative brain malfunction to enhance the delivery of drugs or active substances with low brain availability, (Agrawal et al. 2018). Stress from oxidation in PC12 cells (a neurological cell line) was reduced through a phytosomes-based therapy, and the result improved over that of Genestein in its raw form explored the brain transport of genistein, an isoflavone by trying several nanotechnological techniques after being administered orally repeatedly for five days to rats (134 mg/kg/die as comparable curcuminoids), it was shown that the phytochemical curcumin phytosome increased curcumin's ability to be absorbed into the body hippocampus and forward lobe (Jahangir et al. 2022). Curcumin showed up in the frontal lobe of the rat brain 30 min after treatment, peaked after one hour, then started to return to standard 3 h later, proving that the phytosome of curcumin enter the rat's mind (Merritt et al.

Table 1 Comparison between phytosomes and liposomes

S. No	Possessions	Phytosome	Liposome	References
1	Attachment	Associated with a select few molecules (mainly phospholipid and polyphenol extracts)	Even though there are many molecules, their connections are poor	(Ahmad et al. 2016)
2	Oral distribution	Preferred for oral delivery	Inadequate oral bioavailability	(Pajardi et al. 2014)
3	Phospholipid fraction	In order to prepare it, a 1:1 or 1:2 ratio is preferred	The ratio of lipids to the main active ingredients may be up to 10 times higher	(Vickers. 2017)

2022). The fact that curcumin has antioxidant and anti-inflammatory properties, the majority of which treat neurodegenerative diseases like Alzheimer's disease, future research on medication delivery strength benefit from this discovery (Marchetti et al. 2005).

Neurological ischemia: phytosomes

The same researcher examined the potential advantages of natural substances in two studies using the rat model of middle cerebral artery blockage a phospholipid molecule containing the flavonoid quercetin's glycoside rutin has been investigated for its bioavailability in a cerebral ischemia animal model rutin was administered at 100 mg/kg to Sprague–Dawley rats, and it was discovered using LC–MS/MS analysis that rutin entered the mental process of numbers between 20 and 50 mg/kg (Salehi et al. 2020). In a stroke-prone mammal, a rutin-loaded formulation greatly improves functional results rats received a phytosomal complex during the second trial comprising an alcohol-based extract of the roots one hour before ischemia and six hours after reperfusion, take ashwagandha (Withania somnifera) orally at a dose of 85 mg/kg after treatment, there was a substantial decline in the percentage of brain hemorrhage (82.7%) and better protection against complete neurological impairment indicators (Patel et al. 2018).

Phytosomes' impact on neuropathy

For a period of three months (n = 180), they examined the therapeutic efficacy of oral administration of the B group vitamins, 500 mg of the curcumin phytosome, and 300 mg of lipoic acid for a period three months (n = 180) in patients in need of surgery due to carpal tunnel syndrome intervention (Kattyar et al. 2022). The affected role who received supplements for a three-month period twice per surgical day and the post-operative day had fewer nights and were less likely to have issues at 40 days and have an optimistic Phalen's test three months later a comparable formulation based on piperine, either lipoic acid or the curcumin phytosome decreased pain (66%) in all combinations in neuropathic patients afterward 8 weeks (Phadke et al. 2015). While Lipoic acid by itself didn't provide quantitatively significant benefits, supplementation reduced the usage of conventional medication (i.e., dexibuprofen) by 40% (Himalian et al. 2022) (Fig. 5).

Role of phytosomes in headaches

In two investigations conducted by the same research team, fifty patients with migraine with aura examined to determine the effectiveness of vitamins B2 (8.7 mg), coenzyme

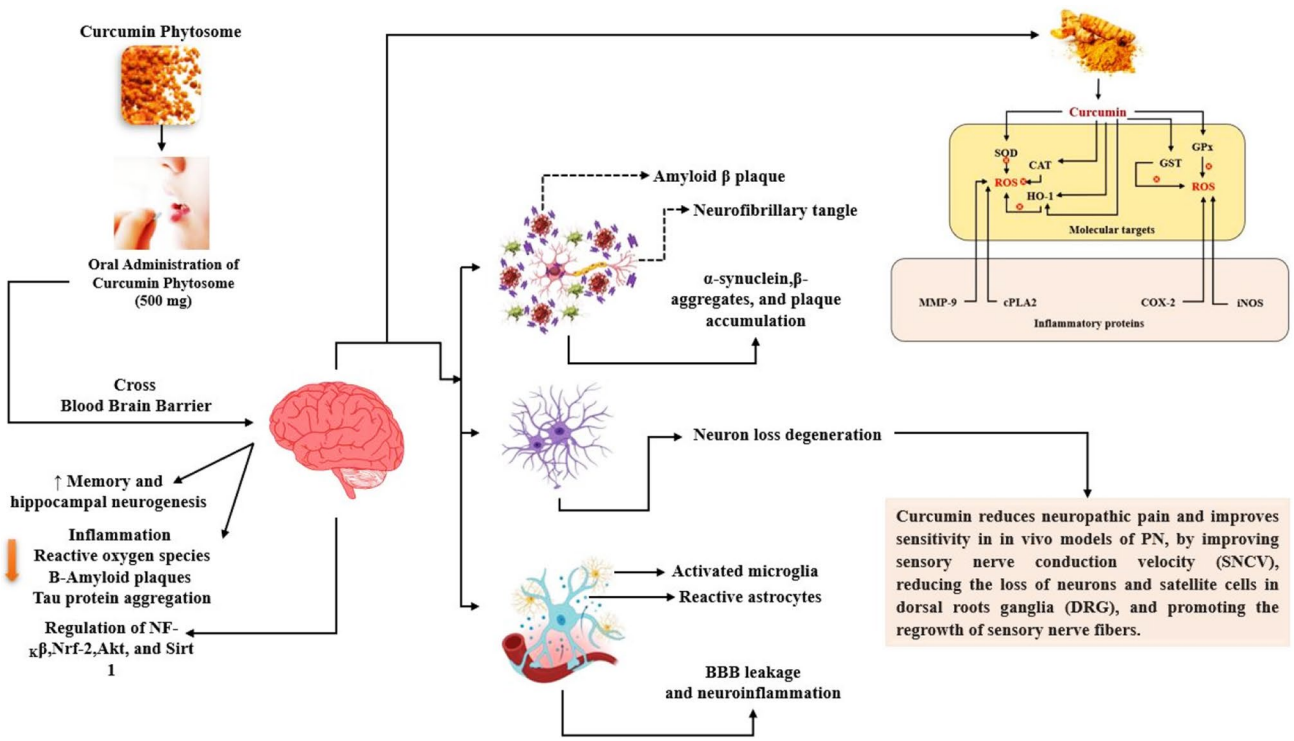

Fig. 5 Potential role of curcumin phytosomes in the treatment of neuropathy (Wolfrum et al. 2022)

Q10 (11 mg), and ginkgo biloba terpene phytosome (60 mg), given twice daily (D'Andrea et al. 2009). Within four months of therapy, positive results were already evident in the incidence and duration of migraine with aura (Allais et al. 2002). The most common ginkgolide, a prevalent terpene found in popular extracts from ginkgo biloba leaves, may be caused these results (Nakanishi et al. 2005). Ginkgolide B was discovered to control or lessen the central nervous system, which is crucial for the development of migraine an open study was conducted to determine the same formulation's effectiveness in treating the aura of severe migraine patients was instructed to take two capsules of Ginkgo biloba terpene phytosome orally during the early stages of the aura, with no restrictions on pain-relieving (Negro et al. 2018). The participants had a decline in neurological symptoms in almost 60% of cases, and in nearly 20% of cases, the pain phase was totally eliminated (Goffin et al. 2010). In a study on those who suffer from migraine without aura and transient tension headaches, researchers looked at the therapeutic benefits of a combination of L-tryptophan, magnesium, vitamins (riboflavin, niacin, and vitamin D), and phytosome-loaded extract of Boswellia serrata. The NRS scale for measuring pain, and painkiller use the reference substance was amitriptyline for patients who ingested the phytosome preparation, the scientists discovered an improvement in each of the results: improved agreement and the absence of adverse effects (Pratap et al. 2018).

Role of phytosomes in neurological cancer

Among the cancers of the central glioblastomas are the neurological system one of the most common in their new ways to treat the condition, they examined the capacity of intranasal administration (500 mg) of curcumin phytosome and found that equal amounts of curcuminoids (up to 96 mg) induce glioblastoma in the brain, which has remitted in the brains of mice with GL261 (glioblastoma cells) implants (Mukherjee et al. 2016). In 50% of animals with tumors, remission was shown; comparable results also obtained with intraperitoneal infusion in hypothesize that phytosomes containing curcumin may alter glioblastoma cell survival as well as cause microglia to repolarize to the tumor-crushing M1 state when the same research curcumin phytosomes affected macrophages and natural killer cells in mice implanted with GL261 (glioblastoma cells), they came up with findings that were comparable (Mukherjee et al. 2018). Additionally, the therapy caused the glioblastoma cells to exhibit suppressed activation of caspase 3 and inducible nitric oxide synthase, as well as STAT3 and ARG1 protein suppression and STAT1 protein increase by IL-10. The most common recurrence in a medulloblastoma animal model (D425MED) was a prevalent pediatric malignancy of the central nervous system; the same curcumin phytosome was examined (Lakshmanachetty et al. 2021). The findings show that the formulation, whether administered orally or intraperitoneally, has minor effects; however, the dosage utilized was not specified when radiotherapy causes cerebral edema in glioblastoma patients, investigated the effectiveness of a phytosome derived from a Boswellia extract 4500 mg of the drug formulation temozolomide administered to the patients (n = 20) for a maximum of 34 weeks (Sehm et al. 2016). In addition to evaluating steroid use, the illness stage was assessed at several points between 4 and 34 weeks after surgery. Significantly less cerebral edema was in two cases, which improved surgical resection that adding this type of phytosome to a patient's diet may have a positive impact on reducing the cerebral edema brought on by radio-chemotherapy additionally, the reducing brain edema, dexamethasone intake may be reduced, minimizing the side effects of steroids during conventional pharmaceutical treatment (Bertalanffy et al. 2002).

Phytosomes in the digestive system

Role of phytosome in gut microbiota

In recent research, the effects of lecithin-curcuminoid formulations and unformulated curcuminoids on human colonic metabolism examined (Fig. 6) an in vitro fermentation apparatus was used to expose both extracts to fecal fermentation, the curcuminoid measurement, assessment of possible curcuminoid degradation, and identification among the main metabolites popular in human fecal fermentation using mass spectrometry the results demonstrated that curcuminoid catabolites more often produced during the fermentation of curcuminoids made with lecithin than curcuminoids alone (Purpura et al. 2018).

Role of phytosomes in pancreatic cancer

The potential phase II investigation examine the interactions between gemcitabine and the curcumin phytosome researcher examined to if pancreatic cancer had progressed 44 individuals with either locally progressed or metastatic pancreatic cancer were evaluated recruited and were given every 28 days, on days 1, 8, and 15, a 100-min infusion of gemcitabine (10 mg/m^2/min) is administered (Hani et al. 2021). Along with 4 capsules each containing 500 mg of doxorubicin (2000 mg/diet) in trial, the response rate served as the main goal, while the quality of life, tolerability, overall survival, and progression-free survival served as secondary end points the findings imply that the use of curcumin phytosomes in combination with gemcitabine may be beneficial for the treatment of pancreatic cancer (El-Khoueiry et al. 2017).

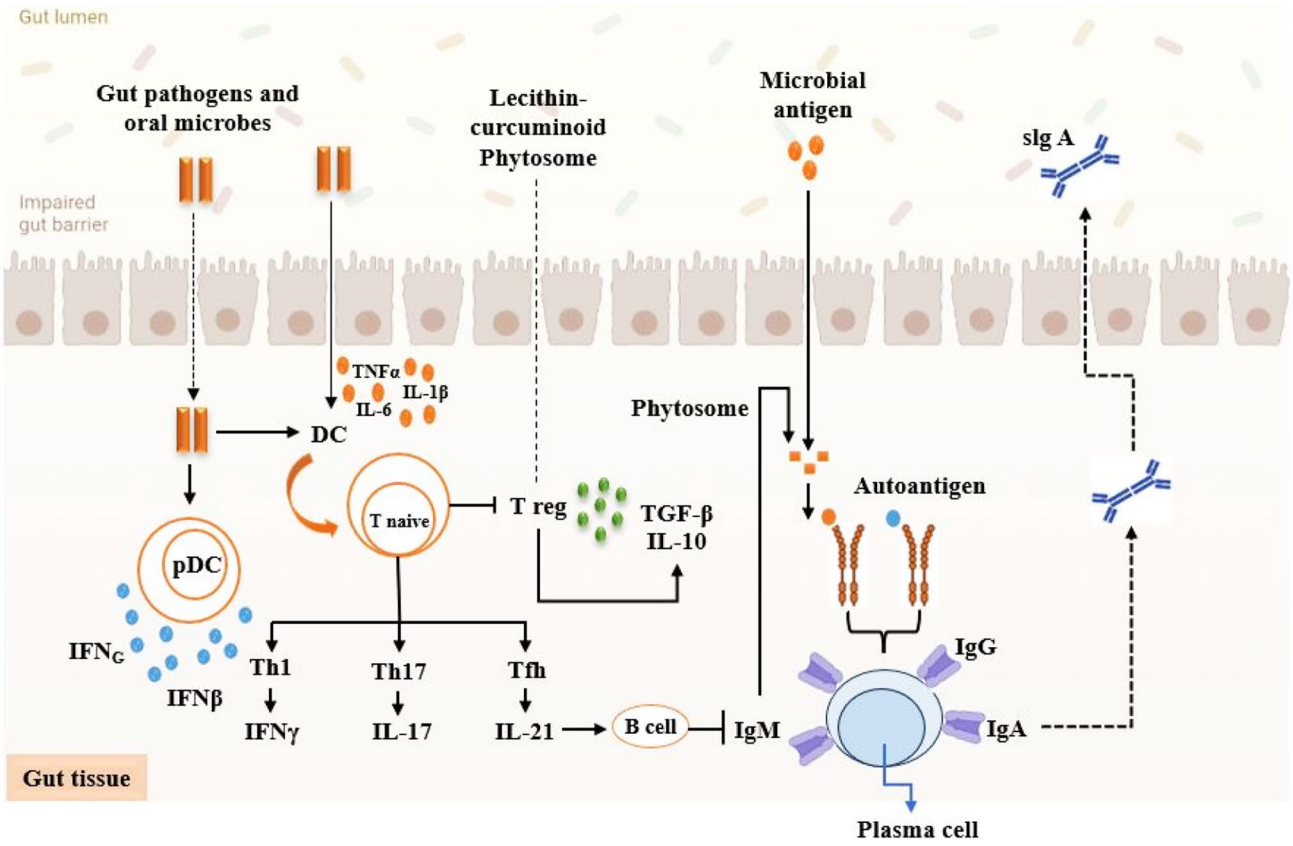

Fig. 6 Lecithin-curcumin phytosomes in colonic metabolism (Santhiravel et al. 2022)

Effects of phytosomes on bowel inflammation

A lecithin-based delivery method for delivering a standardized extract of Boswellia serrata was calculated in a registry study that is open-label and observational the 43 patients made a voluntary decision to either get one 250 mg tablet daily or receive no supplements at 4 weeks. The supplement group showed a reduction in symptoms such as generalized abdominal discomfort, bowel motions, cramps, watery stools, blood in stools, anemia, malaise, rectal involvement, and the number of white blood cells. There was also less need for further medications and medical tests (Yang et al. 2012) the effectiveness of irritable bowel syndrome: effectiveness and safety of phytosome Boswellia serrata extract assessed in two clinical investigations (IBS). In the first study, 71 well individuals in patients with idiopathy were divided into three groups, and given a 250 mg daily dose of phytosome tablet for four weeks, hydrochloride of papaverine, Atropa belladonna extract, and hyoscine butyl bromide all as required (Lange et al. 2001). In both groups, IBS symptoms improved, however, just in the phytosome ingestion assembly was there a significant drop in the requirement for therapeutic treatment and a decreased incidence of particularly stypsis. The second viewpoint was a controlled, randomized trial that assessed the phytosome's long-term effectiveness and safety for the treatment of moderate IBS symptoms in healthy people (Kumar et al. 2020). 71 participants were managed using the same techniques as in the last trial at the follow-up (6 months), the phytosome group had reduced mean scores for virtually all of the self-reported IBS indications and a considerably lower requirement for prescription drugs, advice, examinations, or admissions into the hospital compared to the groups receiving the usual therapy (Ali et al. 2014).

Phytosomes' efficiency in treating bowel cancer

In mice with no hair, silibinin, and silybin-phytosome were given orally to see if they could protect against the growth of human colorectal HT29 xenografts (Fig. 7) the silybin-phytosome dose is 100 mg/kg reduced tumor mass and volume with a level of effectiveness that was comparable to 200 mg/kg silibinin (El-Gazayerly et al. 2014) popular in-vitro experiments using cells resistant to oxaliplatin and in-vivo tests using mice developing colorectal tumors examined the effectiveness of a phytosome containing both oxaliplatin and curcumin. Oxaliplatin's in-vitro antiproliferative ability was enhanced by this combination in comparison

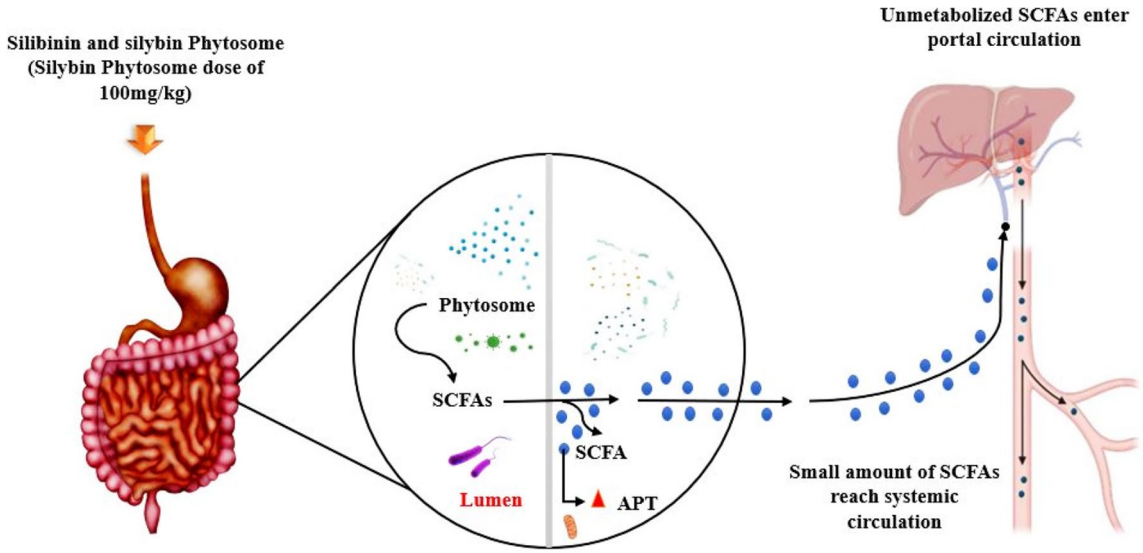

Fig. 7 Silibinin-Silybin phytosomes in the treatment of bowel cancer (Prokopidis et al. 2021)

to oxaliplatin by itself and a control. Additionally, in the HCT116 nude mice xenograft model, a beneficial impact was shown with a reduction in tumor and a reduction in volume in the drug-activity markers Notch-1 and Ki-67, together with a rise in Caspase-3. In a different investigation, the effectiveness of phytosomal curcumin or its combination with the antibiotic 5-fluorouracil (5-FU) was examined in-vivo before in-vitro intestine model tumors through colitis. Curcumin markedly increased the expression of E-cadherin among CT26 cells and reduced compartment proliferation in an amount-dependent manner (0–1000 g/mL). In mice, the tumor number and size were reduced when 25 mg/kg/day curcumin and 5-FU (35 mg/kg/week) were combined. In a colorectal cancer xenograft mouse model, a similar ratio was utilized together with 5-FU and phytosomal curcumin. The results of the research revealed a decrease in tumor development, an improvement in 5-FU's anticancer activity, and anti-angiogenic effects via regulation between VEGF and VEGFR2 (Vora et al. 2015).

Effects of phytosomes on liver protection

They evaluated the effectiveness of silymarin-phytosome in preventing maternal ethanol consumption when pregnant in rats and its effectiveness was compared to that of subcutaneously administered phytosomes at dosages of 400–800 mg/kg. The activity of gamma-glutamine transpeptidase (GGTP), which was activated using ethanol in the tissue of the liver and brain of the fetuses, was inhibited by all dosages the greatest phytosome dosage that was orally provided seems to work best in lowering maternal brain, and fetal GGTP activity. The authors speculate that both direct suppression of GGTP without any protective function and the formulation of ethanol toxicity may have protective properties (Loeser et al. 2018) and CCl4-induced hepatotoxicity caused by carbon tetrachloride. Two dosages of the phytosome of ginkgo biloba, 25 mg/kg and 50 mg/kg intravenously, were given over the sequence of 10 days, with 200 mg/kg P.O and silymarin serving as the normative example alkaline phosphatase, glutamic-pyruvic transaminase, and glutamic-oxaloacetic transaminase (ALP) enzyme levels in serum were decreased by phytosome; GSH levels were discovered to be significantly higher, and levels of SOD, CAT, GPx, GR, albumin, and total proteins were all significantly elevated be close to regulating ranges. The impact of the greater dosage of phytosomes in Ginkgo biloba was equivalent to silymarin on some metrics. The same researcher looked into the hepatoprotective effects of phytosomes on rimpfacin-induced liver damage in rats in the study, Ginkgo biloba phytosomes were also given at 25 mg and 50 mg per kilogram dosages. In a dose-dependent way, the therapy raised the levels of total protein, albumin, SOD, GSH, GPx, GR, and CAT while also having effects on the liver that lowered the quantities of lipid peroxidation and serum marker enzymes (Sharma et al. 2016) with regard to those who have non-alcoholic fatty liver disease, the properties of silybin-coupled liver function are influenced by phosphatidylcholine and vitamin E and examined in Phase III, controlled, double-blind, randomized clinical study (NAFLD). A total of 180 NAFLD patients (36 through chronic HCV infection) were recruited, and 91 of them received oral active therapy for 12 months (94 mg of silybin, 194 mg of phosphatidylcholine, and 89.28 mg twice daily of vitamin E acetate at 50%), whereas the other 88 received a placebo. Improvements in transaminases, insulin resistance, and glutamyltransferase (GT) stages,

as well as numerous features in the histology of the liver, have been seen in popular individuals receiving dynamic therapy. The active therapy improved fibrogenesis markers in HCV-positive individuals. In a rat model of liver cirrhosis caused by thioacetamide, curcumin (400 mg/kg), R-lipoic acid (200 mg/kg), or silybin phytosome (400 mg/kg) all had different effects. Serum levels of GPT, GOT, LDH, and GT all considerably lowered by supplementation, with silybin phytosome being the sole exception. Additionally, the expression of the HSP-47 gene, collagen deposition, matrix metalloproteinase (MMP)-2 activity, and TGF-β1 level expression decreased. Furthermore, every supplement enhanced the state of oxidative stress by raising liver GSH and lowering MDA levels (Al-Kahtani et al. 2020) in a study, rats with CCl4-toxicated livers received 200 mg/kg/day of silybin equivalents along with milk thistle extracts and silymarin phytosomes over the course of 10 days. Silymarin phytosomes performed better than milk thistle extract in boosting SOD and lowering GPT levels (p 0.05). According to the study, other biochemical indicators did not differ significantly between the two treatments (Asghar et al. 2017). In rats given CCl4 treatment, when a substance is bioavailable, standard comparing soya phospholipids with pomegranate extract (30% w/w punicalagin-SPE) to those of SPE not yet developed Punicalagin levels in the blood were greater than SPE after the combination of soy phospholipids (500 mg/kg equivalent SPE) with pomegranate extract; C_{max} values were 192.5 ng/mL and 466.3 ng/mL, respectively according to pharmacokinetic investigations. Additionally, an antioxidant function was assessed at two levels (each 200 and 100 mg/kg). Pomegranate extract and soya phospholipids substantially maintained the levels of the CAT, SOD, and glutathione systems in the liver when compared to SPE (Teng et al. 2019) when mice were exposed to lipopolysaccharide, which causes systemic inflammation, phytosome derived from Boswellia serrata dramatically reduced the blood TNF and IL-6 levels, as well as other pro-inflammatory cytokines, and raised IL-10, a cytokine that reduces inflammation. Through a considerable reduction in lipid peroxides and a rise in GSH, total glutathione, and glutathione disulfide levels, the phytosome demonstrated its antioxidant abilities. Additionally, therapy was able to reinstate CYP transformation, which in turn restored the liver's potential for biotransformation. Comparisons were made between the hepatoprotective properties of a phytosome made from a mixture containing dry ethanolic extracts of the leaves and fruits of Piper longum and Abutilon indicum and those of LIV 52, an ayurvedic supplement, and dried ethanolic extracts of each plant remedy aimed at liver problems. Rats with liver damage brought on by CCl4 were given LIV 52 (1 mL/kg), extracts of ethanol, dry (100, 200, and 400 mg/kilogram), phytosome (100 mg/kg), and LIV 52 oral dosages of 100, 200, and 400 mg/kg. In a way comparable to LIV 52 and to a greater degree than dry ethanolic extracts, phytosomes decreased the liver injury indicators and bilirubin, GPT, GOT, and ALP in a rat model of aluminum chloride (AlCl3)-induced hepatotoxicity, the hepatoprotective effects of curcumin phytosomes were examined 21 days of treatment with 200 mg/kg/day of phytosome significantly normalized the liver markers raised through AlCl3 when compared to the untreated AlCl3 group (GOT, LDH, bilirubin, GPT, LDH, and ALP). Using a transgenic mouse model, the effect of curcumin phytosomes on chemoprevention was assessed and contrasted with unprepared curcumin applied to hepatocellular cancer associated with the hepatitis B virus. In comparison to unformulated curcumin, phytosomes were more effective in slowing the development of hepatocellular carcinoma, reducing the overall tumor volume, and inhibiting inflammation (Lazzeroni et al. 2017).

The effect of phytosomes on the genitourinary system

In this part, using biological processes that influence the genitourinary system, which includes a gland, and the breast connected in terms of the reproductive system, are discussed.

Phytosomes derived from plants: role of breast cancer

Prior to surgery, 12 early breast cancer patients were given a brand-name lecithin product that includes green tea catechins in a daily dosage of 300 mg (equivalent epigallocatechin-3-gallate, or EGCG, equivalent to 44.9 mg), concentrations of EGCG of a maximum of 8 ng/g were discovered in all the tumor tissues examined, demonstrating the potential of the active ingredients to penetrate the human breast tissue. For each patient, a strong negative connection between plasma levels of EGCG and the proliferation-related biomarker Ki-67 was found (Lazzeroni et al. 2016) that 12 women with breast cancer from a different group received 2.8 g of a silybin-phosphatidylcholine combination administered daily for 28 days to test its efficacy. Silybin concentrations in breast tumor tissues reached as high but no changes in popular Ki-67 and nitric oxide levels in the blood, also known as insulin-like growth factor I (IGF-I), were observed (Minaei et al. 2016) found that silybin-phosphatidylcholine treatments in-vitro produced a concentration and time-dependent decline in survival with regard to the human breast cancer cell line SKBR3, demonstrating better compared to pure silybin, there is a greater than 1.5-fold increase in membrane transmission and a greater than twofold increase in growth inhibition both silybin and silybin-phosphatidylcholine reduced the expression of HER2, although the complex was more

effective and required longer treatment periods (72 h). In pre-prepared research, the effects of luteolin-containing phytosomes breast cancer cells were assessed compared to the pure drug, phytosomes improved the effectiveness of doxorubicin in suppressing the proliferation of cancer cells. Additionally, associated phytosomes were more numerous and effective, unlike luteolin, in reducing an indication of the nuclear factor 2 linked to the erythroid 2 (Nrf2) gene, which lowers the protective agent defense of cancerous cells (Pang et al. 2019) in a similar vein, doxorubicin's effectiveness in inhibiting the growth of human breast cancer MCF-7 cells was enhanced by quercetin phytosomes. Despite the fact that Nrf2 gene expression was not significantly impacted, quercetin phytosomes reduced the expression of two Nrf2-activated genes more effectively than pure quercetin: multidrug resistance-associated protein 1 (43%), and NAD(P)H dehydrogenase (quinone) 1 (35%). A commercial phytosomal-curcumin treatment for MCF-7 cells brought about a dose-dependent suppression of proliferation and invasion this correlated with increased concentrations of E-cadherin and MMP-9 by favorably modulating total thiol content, SOD, catalase, MDA levels, and other parameters in breast cancer tissue, phytosomal-curcumin also improved the biological activity that fluorouracil has in preventing tumor growth in an implanted mouse model (female BALB/c). However, the phytosome alone, without the help of fluorouracil, only slightly decreased growth without modifying the other parameters (Hashemzehi et al. 2018) examined the metastatic breast in female BALB/c mice with phytosomal curcumin (4T1). For 14 days, mice were given 10 mg of phytosomal curcumin once every three days. At a dosage of 10 mg/mouse, the therapy considerably reduced the number of lung metastases while having very minimal effects on the underlying tumors. The absence of comparable information about pure curcumin the mice given phytosomes or cryoablation have a higher survival rate than animals treated just with cryoablation, using saline, or just phytosomal-curcumin (Wu et al. 2021) lastly, a similar research team did two experiments to compare the effects of folate-conjugated and PEGylated phytosome alterations on casein, such as phosphatidylcholine-encapsulated Monascus purpureus pigments and resveratrol found in casein micelles. In comparison, all kinds of phytosomes were added to the cotreatment of unbound resveratrol and Monascus yellow pigments caused more MCF-7 cell toxicity. Injections of pure substances, mixes, or phytosomes containing 5 mg/kg of resveratrol per day were given to tumor-bearing BALB/c mice over the course of 21 days. The proportion of hemolysis brought on by phytosomes was less than 5% at 250 g/mL. Regarding the administration of phytosomes and free resveratrol along with the Monascus yellow pigments, they were more effective in reducing tumor size. Treatments with phytosomes improved the reduction of CD1, NF-$_K$B, VEGF, and aromatase levels while boosting caspase-3 levels and necrosis (Paul et al. 2016).

The function of phytosomes in prostate disorders

Three trials examined the impact of phytosomes containing silibinin in the treatment of prostate cancer. In the first in-vivo study experiment, male TRAMP rodents with visible prostate tumors were fed diets containing 0.5% or 1% phytosomes. The diet suppressed metastasis development by lowering VEGF, MMP-2, MMP-3, and bFGF (fibroblast growth factor), and after 11 weeks, it resulted in a dose-dependent reduction in the weight of the prostate and tumors (up to 60%). Silibinin increased E-cadherin levels while simultaneously lowering vimentin and snail-1 levels in tumors (El-Far et al. 2018) human impacts in two clinical investigations. Thirteen men with prostate cancer participated in the first pharmacokinetic Phase I research. Although the dosage of phytosome was raised from 2.5 g to 20 g orally daily, bilirubin levels in grade 2 persisted silibinin at 15 and 20 g was rapidly conjugated and discharged inside the urine, indicating a 1.79–4.99 h plasma half-life. None of the trial participants had a PSA drop of 50%, although some of them had long-term stable illnesses (El-Far et al. 2018a, 2018b) reported that in the second trial conducted by the same research team, six patients diagnosed with prostate cancer received 13 g of silibinin every day for 14 to 31 days with phytosome prior to radical prostatectomy. At the completion of the therapy, the plasma silibinin concentrations were rather low (1.2 M). Out of six individuals, only three had prostatic tissues with silibinin levels ranging from 14.9 to 496.6 pmol/g. There were not at all appreciable changes in IGF-I concentrations, IGFBP-3, or PSA (Singh et al. 2008) in the most recent study, individuals with benign prostatic hyperplasia were treated with the formation of curcumin phytosomes. In conjunction with the best standard of care, 33 participants (aged 55 to 65) received the phytosome in a pair of tablets at a daily dose of 2,500 mg, comparable to 200 mg of daily curcumin. Except for stream weakening, with curcumin, every symptom including frequency, intermittency, urgency, straining, and nocturia improved with treatment associated with usual care (Flaig et al. 2007).

Potential role of phytosomes in the female reproductive system

A scientific investigation examined the effects of curcumin phytosomes on six women suffering from endometrial cancer without concurrent oncological therapies, patients got the supplement for two weeks at a dosage of 2 g (4500 mg) daily. Supplementation reduced the amounts of CD8 + T cells

with the ICOS protein, the number of monocytes, and MHC expression on leukocytes. Inflammatory indicators such as the variety of many kinds of immune cells, T-cell activation, and the levels of the protein cyclooxygenase-2 did not exhibit any further substantial changes (COX-2) (Flaig et al. 2010) for a second experiment, 48 rats that needed ovariectomy were used to assess the effects of a phytosome with 10 or 50 mg/kg of quercetin for each OS. In comparison to the same free quercetin concentrations, phytosome therapy led to a discernible rise in blood levels of phosphorous that isn't organic, glutathione, and calcium. A phytosome considerably reduced blood levels of acid phosphatase, alkaline phosphatase, TNF, glucose, and MDA as compared to quercetin, and it also improved the lipid profile 131 the research also examined the effects of a phytosome that includes icariin on ovarian cancer OVCAR-3 cells. For example, cellular quantity in the G2 M-phase, cellular amount of caspase-3, and intracellular ROS increased after a phytosomes-based incubation (6.31 vs. 13.1 M). Plant phytosomes also displayed stronger cytotoxicity against cancerous ovarian cells than actual icariin (Tuyaerts et al. 2019).

Role of phytosomes in a dysfunctional urinary system

Two clinical studies assessed the impact of phytosomes on biological processes in the urinary system the antiadhesive characteristics of urine following cranberry extract phytosome ingestion, often known as comparable standardised extract ingestion, examined in the first study, which included 13 healthy participants. The adhesion of Candida albicans was significantly and similarly inhibited in the fractions that were recovered after 12 h of treatment with either the extract or phytosomal form, but the phytosome only contained 36 mg of proanthocyanidins per capsule of extract, compared to 12 mg in the phytosome, or 33% of the cranberry (Wang et al. 2020) in another trial, individuals with asymptomatic transient renal impairment examined to curcumin affected them for four weeks, patients took three curcumin phytosome capsules every day (300 mg of curcumin). When compared to those receiving normal care, the participants receiving curcumin phytosomes showed a considerably greater reduction in oxidative stress, microalbuminuria, and both. The curcumin phytosome dramatically decreased the number of fatigued patients, and it was well tolerated and well-complimented (Wang et al. 2021).

Function of phytosomes in immune system modulation

Several studies assessed how phytosomes affected variables related to immune function silymarin was loaded in to liposomes and phytosomes with lecithin: cholesterol ratio of 6:1 in the murine macrophage cell line RAW 264.7 and demonstrated superior inhibition in comparison to silymarin that has not been created a popular seven-day in-vivo experiment using 50 mg/kg Wistar rats protected against liver damage and similar inflammation brought on through paracetamol (Alhakamy et al. 2020) additional research examined the immune-suppressive properties of grape seed extract in its phytosomal form, which is notably high in epigallocatechin 3-O-gallate. Serum cytokine analysis revealed that giving older individuals 300 mg/day of grape seed phytosome for a month affected their immune response. The fact that the therapy specifically enhanced IL-2 and INF production suggests a potential Th1/Th2 role in rebalancing in elderly atopic patients before the improvement of the antiviral reaction (Baron et al. 2020).

Effects of phytosomes on the integumentary system

Preparations that are tested on the skin's surface are more varied and can be put into three main groups: those that cause skin inflammation, those that heal wounds, and those that treat skin cancer.

Potential role of phytosome's in skin inflammatory diaorders

Two scientific investigations demonstrated the uses of phytosomes on skin irritation a first-blind experiment examined the current effects of a phytosome containing quercetin and a 1% dexchlorpheniramine-containing formulation on various membrane injuries. Dexchlorpheniramine with 1% quercetin phospholipids at 1% substantially decreased histamine prick test (13.25% vs. 12.23%, respectively) and UV-induced erythema (10.05% vs. 14.05%, respectively), both of which showed significant differences. Only quercetin phytosome 1% significantly increased hydration when erythema was caused by glycolic acid (GA) or sodium lauryl sulfate (SLS), whereas both formulations decreased erythema (Ledda et al. 2018) conducted a Phase III randomized clinical trial with one dosage and a double-blind placebo study with 49 patients with persistent psoriasis received phytosome (2 g daily) or placebo orally for 12 weeks while receiving once-daily topically applied treatment for psoriasis plaques with methylprednisolone acetate 0.1% ointment. When comparing the impact on PASI of the curcumin phytosome to the placebo, while IL-17 serum levels were not significantly different, IL-22 serum levels were significantly higher in all groups less present (11.8 pg/mL) in the group treated with curcumin (Prasad et al. 2014) in a different study, mice treated with carrageenan the curcumin phytosomes' effects assessed

animals received 15 mg/kg oral doses of curcumin, indomethacin, or nano-phytosomes with curcumin for a week when it came to SOD, CAT, GPx, and GR, curcumin was not as antioxidant-rich as the nano-phytosome therapy (P 0.05) (Maramaldi et al. 2016). In three experiments, the impact of distinct phytosomes on the skin of Wistar rats brought on by carrageenan was examined at 4 h, the plant extract gel demonstrated a lower anti-inflammatory impact than the phytosome complex containing Lawsone (Lawsonia inermis L.; P 0.001) and Ibuprofen 5% gel contrasted with escin, and the antihyperalgesic effectiveness of thirty escin-sitosterol (ES) phytosome 10% hydrogels was dramatically enhanced (Antiga et al. 2015) in comparison to the groups receiving no medication (38.1%) and diclofenac sodium gel (23.2%), the edema was dramatically decreased by a resveratrol phospholipid complex administered topically in the form of patches to 6.1% after 24 h (P 0.05). Patches containing complex with resveratrol had no irritating effects on rabbits with albinism scored highly for skin rashes (erythema and edema) of less than 1 rats exposed to UVB radiation (0.115–0.23 J/cm2) received topically administered silymarin in a compound of carrier lipids with nanostructures after using NLC-Silymarin gel, UV-exposed animals' epidermal thickness, and wrinkle score were reduced (Baradaran et al. 2020).

Role of phytosomes in the healing of wounds

When treating persistent glucose ulcers in patients combining Ginkgo biloba, grape seed, and lipoic acid phytosomes with diabetic foot ulcers through cutting-edge drugs proved helpful (Fig. 8) (Djekic et al. 2019) in NHDF cells, phytosomes containing up to 3.0 mg/mL of aqueous leaf extract from Moringa oleifera have been demonstrated to be safe comparing the formulation at 1 mg/mL to the extract at the same concentration, the formulation had the fastest gap closing time (94.8% after 24 h). On the other hand, smaller dosages as well as greater concentrations (1.25 and 1.50 mg/mL) failed to produce results that were statistically significant. The effects of combining Calendula officinalis with gold nanoparticles (AuNP) in phytosomal systems were examined in a second in-vitro experiment using NHDF cells. With regards to calendula phytosomes and auNP-calendula phytosomes, respectively, the formulations decreased cell monolayer disruptions by 42.2% and 58.7% (p 0.01) up to 400 g/mL, the mixture exhibited no harmful effects 33 In

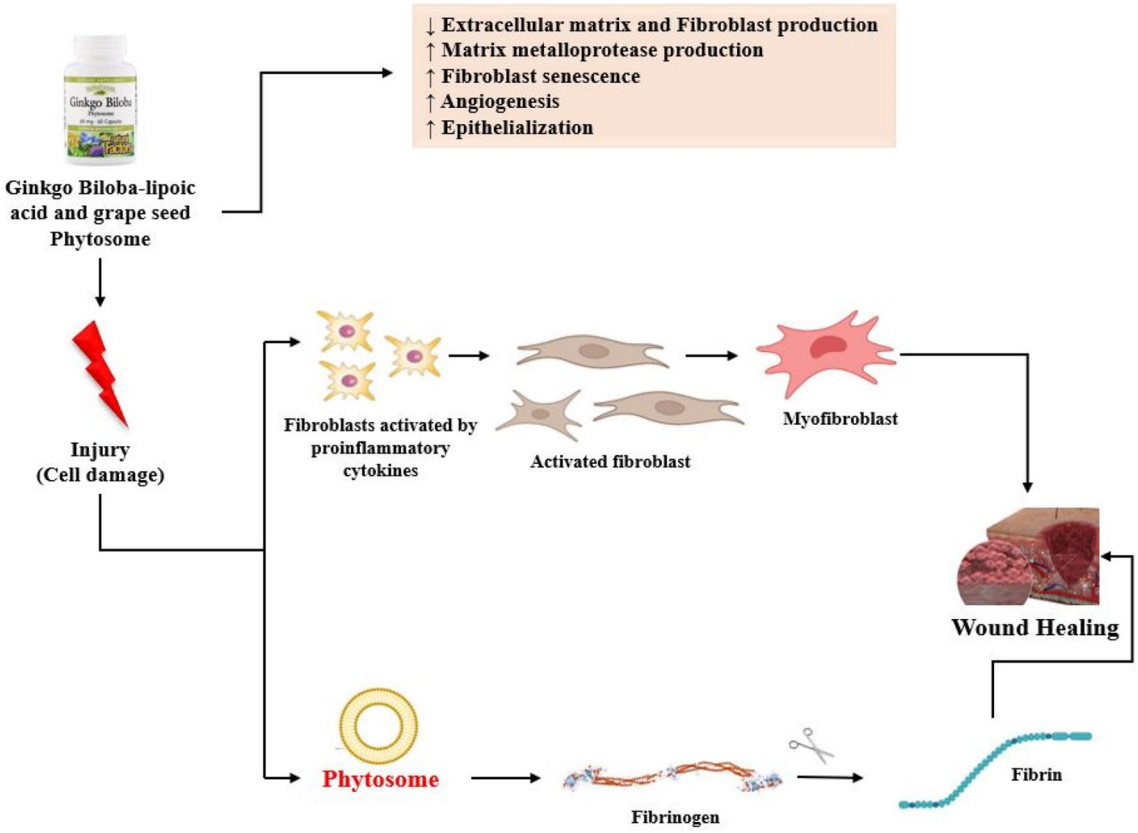

Fig. 8 Illustrates the function of a formulation that includes grape seed, lipoic acid, and ginkgo biloba phytosomes in the healing of wounds (Cunha et al. 2022)

HaCaT cells, a compound of sinigrin and phytosome had a favorable impact on the healing of wounds compared to sinigrin alone. In contrast to pure sinigrin, which only reached 71% of the lesion after 42 h and had little cytotoxicity against cells at 0.14 mg/mL, the phytosome totally healed the wound (Kalita et al. 2017).

Phytosomes' potential for treating skin cancer, according to the research

The likelihood that phytosomes might be useful in preventing skin cancer and at a time only two studies examined the aforementioned sinigrin-phytosome complex was shown in the first investigation to be cytotoxic to A-375 melanoma cells. Almost 74% of the cell viability was decreased by the complex at 0.14 mg/mL, compared to more than 46% for free sinigrin, whereas non-tumour HaCaT cells showed only very little toxicity. The second investigation focused on silymarin in vitro action on nanostructured lipid carriers the comparing silymarin-NLC to an unidentified commercial phytosome formulation, silymarin-NLC demonstrated a greater suppression of cell viability (IC50: 21 g/mL) in the melanoma cell line from humans (SK-MEL-2) (Singh et al. 2016).

Impact of phytosomes on the musculoskeletal system

The majority of non-steroidal pain reliever medicines are used in the pharmacological treatment of musculoskeletal dysfunctions. However, these medications often have a number of negative effects. In 16 investigations, turmeric (Curcuma longa) extracts or curcumin were mentioned in 62.5% and Indian frankincense (Boswellia serrata) extracts in 31.2% of the studies on natural product-loaded phytosomes for the therapy of musculoskeletal problems. The management of patients with osteopenia was the subject of one research pilot and the curcumin-based supplement, curcumin phytosome, was administered for 24 weeks to individuals. The bone mass of the rats was measured at 4, 12, and 24 weeks in contrast to the control group, which received 1000 mg of curcumin phytosomes each day, there were widespread improvements in the group's bone density after receiving treatment (Lim et al. 2019) similar formulation, evaluated both at once, whether before or not paired through other dietary vitamins and physical activity, revealed good outcomes in senior adults (> 65 years) who were characterized by a lack of strength, helping towards improving fitness and physical ability (Giuliana et al. 2013) used rugby players with various bone and muscle discomfort issues brought on by physical overuse or traumatic injuries in clinical trials to determine the effectiveness of curcumin phytosomes (1 g for 5 and 10 days, every 12 h).

The groups of 25 people who used curcumin phytosome and received traditional analgesics (n = 25) were contrasted at various times, and the pain and latest function were assessed. Patients with various chronic inflammatory disorders were shown to benefit from the painkiller effects of the turmeric phytosome (2 g, equivalent to 400 mg of curcumin) showed that administering curcumin in the phytosomal form thay reduced delayed-onset muscular pain (1 g twice every day for four days). These results indicate that phytosomes containing turmeric may be a beneficial treatment for discomfort and musculoskeletal problems during strenuous physical exercise.

Additional fascinating human studies have looked at the advantages of the aforementioned (1 g/diet) phytosome administered for 8 months alone before the (0.5 g/diet) curcumin phytosome combined for four months along with glucosamine (0.5 g/diet) (Tabrizi et al. 2019) in osteoarthritis patients with discopathy or spondyloarthritis-related radiculopathy demonstrated a decrease in pain score after receiving a 100-day curcumin phytosome regimen (two 50-day cycles) on doses of 500 mg with 300 mg for the first 30 days or 1000 mg daily of used lipoic acid for the last 30 days of every cycle. In addition to the standard pharmacological regimen of immunosuppressive medications, the effectiveness of a curcumin-phosphatidylcholine combination in treating juvenile idiopathic arthritis-related uveitis in children was evaluated. The treatment relieved a moderate flare-up of the chronic anterior chamber and decreased the process of inflammation when combined with curcumin phytosome the curcumin-loaded phytosome has been shown to reduce COX-2 levels and have anti-inflammatory benefits in mares and foals with chronic osteoarthritis or osteochondrosis, TNF, IL-1, despite the fact that the impact was only statistically significant for the final two measures, interleukin 1 receptor antagonist (IL1RN) the effect of (Miserocchi et al. 2020) dietary supplements, nutrition, and allergies the EFSA panel (NDA) has developed the advantages of curcumin and the functionality of linkages.

The panel came to the conclusion that there was insufficient evidence to support a link between curcumin therapy and the ability to sustain joint function. Boswellia phytosome, a different formulation with phytosomes made from individual BSE or extracts of the Boswellia serrata plant, was also clinically tested to relieve the osteo-muscular discomfort that rugby players have. A group combined the regular treatment with the dietary supplement (500 mg of BSE daily), while the control group simply underwent conventional therapy. A single dose of 500 mg daily phytosome of Boswellia was given as a supplement (2 tablets, each containing 250 mg), which was followed by a 23-day dose of 250 mg daily (1 tablet).

In addition to the standard form of treatment, supplementation seems to be a successful treatment for inflammation

and pain control, according to results from both the VAS Pain (visual analog scale for pain) and a decrease in inflammation-related biomarkers. With healthy volunteers, boswellia phytosome (250 mg/die) reduced sprained ankles of modest severity (grade II) brought on by sports injuries; the criteria were assessed 3 and 7 days after therapy. Recently, an evaluation of the effectiveness of Boswellia phytosomes in the treatment of musculoskeletal problems was published 24 osteoarthritis patients were examined for 4 weeks with a different formulation with phytosomes, including 100 mg of Commiphora wightii resin, 200 mg of Boswellia, and 100 mg of Curcuma longa rhizome valerian from officinalis (25 mg). The primary results remained the ability to function and the management of symptoms the formulation had show positive outcomes in the treatment of osteoarthritis.

The effectiveness of the phytosome (350 mg) containing extracts from 7.5 mg of Acmella oleracea and 37.5 mg of Zingiber officinale against pain and inflammation in people with intermediate osteoarthritis was recently investigation was 30 days long. The drug's good modifications to inflammatory biomarkers and consequences on physical activity were accompanied by not all negative side effects (Farinacci et al. 2009) improved osteoblast adiposity and mineralization have been investigated in relation to non-loaded liposomes. The effects on osteoblast differentiation and inflammatory conditions were evaluated after cholesterol and its derivatives, glycerol-phosphoethanolamine, and PC were used to make liposomal formulations. According to the research, neutral lipids promoted increased osteoblast mineralization and reduced adiposity more than cationic lipids phosphatidylcholine suppressed COX-2 and MMP-3 expression genes in 7F2 mouse bone-forming cells, which suggests that this lipid is especially important for making phytosomes to treat the symptoms of bone disorders (EFSA et al. 2017).

The function of phytosomes in diseases of the respiratory system

Asthma and bronchitis: potential role of phytosomes

A pilot study examined the benefits of quercetin phytosomes in healthy populations in addition to participants with moderate-to-severe asthma and rhinitis in conjunction with SM or just this, subjects took one or two QFit tablets each day (control group) in comparison to the control group, quercetin phytosome + SM showed better outcomes after 30 days by avoiding and minimizing day time and night time symptoms, maintaining a greater highest rate of expiration, reducing its variability, and having a favorable protection profile. The treatment, which combines beta-agonists and corticosteroids as conventional treatment aimed at individuals with moderate or very bad ongoing asthma, was given to 32 asthmatic volunteers who were recruited in a multicenter research study. In contrast to those who simply got conventional medication, fewer inhalations were necessary for the phytosome group minimal to severe adverse consequences, such as sleeplessness and nausea, were reported with phytosome therapy, which was well received to increase naringenin's pulmonary bioavailability and naringenin was successfully administered using a significant lipid in lung surfactant called dipalmitoylphosphatidylcholine (DPPC). Rats with acute lung damage were used to study the naringenin-loaded DPPC phytosomes for dry powder inhalation (NPDPIs 10 mg/rat, including around 3 mg naringenin): pharmacodynamics and to investigate the necessary action mechanisms direct administration of these phytosomes into the lungs of rats showed protection against lung damage according to the research, NPDPIs decreased fluid exudation, which decreased pulmonary edema, and greatly reduced the production of cytokines such as COX-2 and ICAM-1. Furthermore, the administration of NPDPIs enhanced the ability of DPPC and naringenin to decrease rat oxidative stress by upregulating SOD movement (Belcaro et al. 2018) to treat respiratory conditions, a gingerol phytosome complexed with chitosan is used has been studied in-vitro and in-vivo by in-vitro testing revealed both the phytosome's prolonged release of gingerol and its anti-inflammatory and antioxidant properties. Antibacterial activity against the bacterial species that cause respiratory infections was concentration-dependent. In an in-vivo pharmacokinetic analysis, the complex of phytosomes demonstrated an essential extended-release profile, which helped improve gingerol oral absorption. The pharmacodynamic parameters against respiratory infection-causing bacteria simultaneously in gram-positive and gram-negative bacteria indicated significant anti-inflammatory action and effective, sustained antibacterial activity (Rondanelli et al. 2020).

Role of phytosomes in lung cancer

An ENU1564 mammary gland tumor cell line was grown in the mammary fat of athymic nude mice administered curcumin compounded with phosphatidylcholine for evaluation as an anticancer agent (Fig. 9) although the tumor volume was unaffected by either chemical, the curcumin phytosome dramatically reduced the lung metastases and produced a protein called MMP-9 linked to tumor invasion and development, including breast cancer (Chang et al. 2018) assessed the biological effects of giving grape seed phytosomes orally to volunteers taking part in a lung cancer chemoprevention experiment in premalignant and malignant cells of the human lung, the phytosome's influence on the 15-HETE eicosanoid pathways and prostacyclin was identified. These

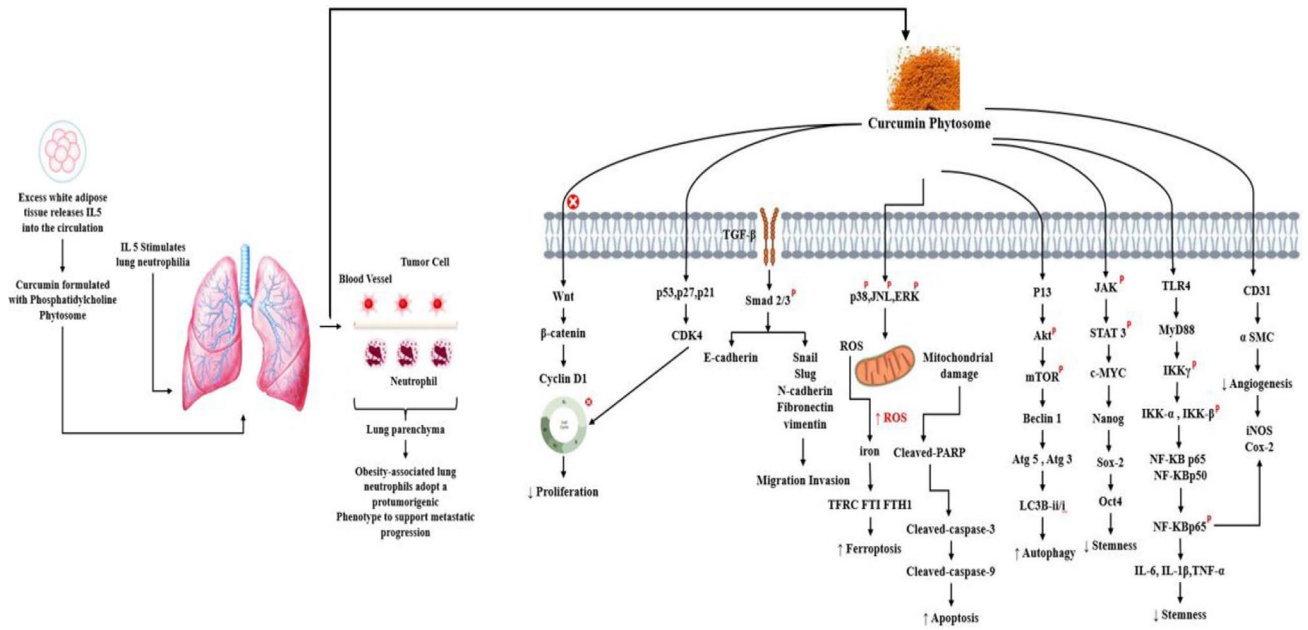

Fig. 9 Role of Curcumin phytosomes in the management of lung cancer (Sorbo et al. 2022)

research results encourage the usage of phytosome groups as a lung cancer chemopreventive and anti-neoplastic drug (Cesarone et al. 2019) in different research, athymic nude mice were given oral doses of grape seed phytosomes. The group received daily doses of 200, 300, and 400 mg, including GSE 56, 84, and 112 daily mg/kg, respectively, that reduced the expression of the MiR-19a/b, miR-17-92, and oncomiR cluster host genes (MIR17HG). Cells with lung cancer exhibit in-vitro grape seed phytosome activity that was popular, and a similar investigation related to this (Yu et al. 2020) found that grape seed phytosomes were tolerated at maximal dosage. Upon completion of therapy, bronchial biopsies showed a considerable reduction in Ki-67 labeling directory (55%), a significant decrease in miR-19a, miR-19b, and miR-106b levels, and significantly downregulated bronchial histopathology grade expression levels in serum (Singh et al. 2018).

Effectiveness of phytosomes in metabolic syndrome

Multiple metabolic dysfunctions examples including type 2 diabetes, insulin resistance, and obesity are present in the metabolic syndrome (MS), and the pathological state is also defined by persistent, low-grade inflammation (Galet et al. 2014) conducted randomized, crossover research with double-blinding to investigate the effectiveness of grape seed phytosomes and the effects of excessive smoking on low-density lipoprotein (LDL) oxidation. Two capsules twice daily, every one of which contained 75 mg of a grape procyanidin extract or the same quantity of lactose used as a placebo, given to the participants for the duration of the study, which lasted four weeks (phytosome) during therapy, subjects' levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol hardly changed. Because the reactive amount of thiobarbituric acid compounds (TBARS) was reduced, this formulation is especially intriguing in disorders characterized by oxidative stress according to 11 people who have macular degeneration, improvements were seen in the optical coherence tomography retinal thickness and visual acuity in diabetic edema when given tablets containing a phytosomal preparation of turmeric (500 mg twice daily, equivalent to a daily intake of 200 mg curcuminoids). After three months of treatment, 84% of patients displayed an increase in visual activity, 16% exhibited stability, and none of the patients displayed a decrease additionally, 92% of the eyes in the open-label research demonstrated a decrease in macular edema and 8% stability, with no instances of increasing pathological severity (Mao et al. 2019) reported that microangiopathy and retinopathy in diabetic individuals received the same curcumin formulation for 4 weeks along with traditional treatment.

Generally speaking, patients displayed their microangiopathy at the conclusion of the course of therapy. Indicators of improved microcirculation included an improvement in the veno-arteriolar reaction and a decrease in peripheral edema. The Steigerwalt and Snellen's scales, which measure changes in visual acuity and retinal edema, respectively,

indicated improvement. In a different trial, 44 individuals given either phosphatidylserine (400 mg/diet) or a product having a curcumin basis (complexed with 20% sunflower phospholipid, 800 mg/die of curcumin, and 8 mg/die of piperine) for 30 days of therapy. As shown by the treatment's ability to induce weight loss and enhance percentage reductions curcumin-based formulas may reduce levels of fat and BMI to help overweight people lose weight. The same formulation, which is phytosomal curcumin 800 mg and contains curcumin 200 mg, PC 480 mg, phosphatidylserine 120 mg, and piperine 8 mg, was recently tested on 80 overweight individuals with fasting plasma glucose levels. Fasting plasma insulin levels and waist circumference significantly improved in the curcumin group. Several studies looked at how flavonoid-containing phytosomes affected MS parameters.

Participants with borderline MS criteria After a 24-week intervention trial, those who got the phytosome formulation of green tea catechins showed improved blood lipid profiles, blood pressure, and weight reduction (Diamond et al. 2007) found that in a different trial, obese females were given 150 mg of green tea phytosome and 15 mg of piperine daily for three months to prevent weight gain following weight loss. The study's findings showed that individuals treated with the formulation maintained their previously attained body weight decrease better than those receiving a placebo (Vigna et al. 2003) these most recent findings support earlier findings, according to which the formulation dramatically decreased BMI and boosted weight loss when paired with a low-calorie diet (Cicero et al. 2020) pure flavonoids like quercetin or chrysin have been used in formulations to explore several MS-related characteristics. In particular, ovariectomized rats given quercetin-loaded phytosomes orally for 4 weeks at 50 and 10 mg/kg dosages with anti-inflammatory agents and reduced mediators like TNF, and treatment is reduced. Improvements were made to the lipid profile, MDA, and glucose levels. Although these experiments have not yet been replicated in people, a different investigation found no significant medication interactions between combinations of phytosomes filled with quercetin and diabetes medications like metformin. Furthermore, the formulation of quercetin phytosome outperformed flavonoids not yet synthesized in terms of oral absorption and solubility in healthy individuals. Chrysin, a dihydroxy flavonoid, has been researched both unformulated and complexly in a variety of formulations, including phytosomes. In C_2C_{12} cells, complexing phospholipid-containing chrysin was found to increase solubility and then encourage glucose absorption is facilitated by the nanoformulation CSP-1:3, which is a chrysin-loaded phytosome produced with soya phosphatidylcholine at a mole fraction of 1:3. It activates the genes for GLUT4 glucose transporter type 4 and peroxisome proliferator-activated receptor (PPAR) (Kriplani et al. 2021). The same research showed that the preparation of phytosomes might have a significant impact on their bioavailability and, therefore, their biological activity in a silymarin-containing phytosome formulation increased the availability of flavonolignans in the body, reducing dyslipidemia linked to MS in hypertriglyceridemic rats.

In contrast to raising HDL cholesterol levels, silymarin phytosome at 1% reduced total cholesterol and plasma triglycerides after 4 weeks of therapy. The same group showed that due to its ability to raise HDL and then lower the pure amounts of glucose and insulin, the chemical silybin seems to serve as the main factor causing the benefits a phytosome containing a standardized fragment of bergamot (Citrus x bergamia), which is high in naringin, was tested on sixty people with hyperlipidemia and type 2 diabetes in a randomized, double-blind, placebo-controlled study in conjunction with a rise in HDL cholesterol, the reported a substantial drop in fasting triglycerides, LDL cholesterol, and plasma glucose. In comparison to the similar unformulated bergamot extract, phytosome was to have better absorption of the alkaloid berberine's improvement of the hypoglycemic impact, as well as a phytosome containing Citrullus colocynthis, Citrullus balsam, and Momordica dioica, are examples of other research utilizing plant extracts or phytosomes containing phytochemicals (Belcaro et al. 2013) additionally, a phytosome containing ginger (zingiber officinale) and mulberry (Morus alba) extracts has shown anti-inflammatory properties in adipose tissue. when given orally to male Wistar rats for 21 days (50–100–200 mg/kg). The mixture was also able to reduce HDAC3 and oxidative stress mediators while increasing PPARs in adipose tissue phytosomes shown to have anti-obesity action in popular albino rats, but only minor benefits were seen in their lipid profile there also non-loaded phytosomal preparations investigated, at their positive implications for reducing obesity. Table 2 Shows a summary of the plant extracts and dosage ranges utilized for clinical research for changing medical conditions (Gilardini et al. 2016).

Conclusion

The combination that phytochemicals and phospholipids create in phytosomes enhances the absorption and bioavailability of bioactive compounds. The most popular nanocarriers for phytochemicals are phytosome, ethosomes, liposomes, transfersomes, and niosomes. A brief summary of the biological functions of phytosomes for commercial as well as non-commercial things are provided in this review according to the research compiled, using such formulations to increase the bioactivity of phytochemicals and their bioavailability generally has advantages, allowing for lower dosages or higher biological activity as compared to using

Table 2 Phytosomes in clinical trials for various pathological conditions

Herbal species	Quantity (mg/Day)	Application	References
Boswellia Serrata	200–4500 250–500 250–500 500	Central and peripheral nervous system Gastrointestinal system Musculoskeletal system Respiratory system	(Riva et al. 2018)
Camellia sinensis	150–300 300	Genitourinary system Metabolic syndrome	(Riva et al. 2019)
Citrus × bergamia	500–1000	Metabolic condition	(Kim et al. 2019)
Curcuma longa	2000 900–2000 2000 500–2000 800–1000 800–1000	Gastrointestinal system Genitourinary system Integumentary system Musculoskeletal system Metabolic syndrome Central and peripheral nervous system	(Poruba et al. 2015)
Ginkgo biloba	360 120	Cardiovascular system Nervous system, both central and peripheral	(Mollace et al. 2019)
Silybum marianum	2500–20000 188 2800	Genitourinary system Hepatoprotective effects Genitourinary system	(Rathee et al. 2018); (Palachai et al. 2019)
Vaccinium macrocarpon	24	Genitourinary system	(Palachai et al. 2019)
Vitis vinifera	300–1200 150 300	Respiratory system Immune system Metabolic syndrome	(Giori et al. 2020)

unformulated compounds silybum marianum and Curcuma longa both contain the most scientific data that supports their health benefits. The only exception is the use of silibinin to treat prostate cancer, which had only moderate success. The data for these formulations is generally favorable, although clinical investigations are still inadequate to make judgments about the biological activity of specific preparations studies on the bioavailability of bergamot (292) and quercetin (288) are two exceptions. Clinical research on standardised products with greater effectiveness relative to unformulated components or extracts will be essential in the future to promote these technologies.

Acknowledgements The study was supported by Pranveer Singh Institute of Technology, Kanpur.

Data availability Not applicable.

Declarations

Conflict of interest Jyotsana Dwivedi has no conflict of interest. Pranjal Sachan has no conflict of interest. Pranay Wal has no conflict of interest. Sumeet Dwivedi has no conflict of interest. Mukesh Chandra Sharma has no conflict of interest. Surada Prakash Rao has no conflict of interest.

Ethical statement This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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