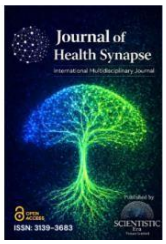
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Phytosome-Based Formulation for Enhanced Oral Bioavailability of a Polyphenolic Compound: A Review

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A B S T R A C T

Polyphenols are plant-derived bioactive molecules with antioxidant, anti-inflammatory, anticancer, hepatoprotective, cardioprotective and neuroprotective properties, yet their clinical use after oral administration is frequently limited by poor aqueous solubility, restricted intestinal permeability, gastrointestinal instability and extensive first-pass metabolism. Quercetin, a widely studied dietary flavonol, exemplifies this gap between pharmacological promise and oral bioavailability. Phytosome technology, in which a plant bioactive forms a molecular complex with a phospholipid (usually phosphatidylcholine) through hydrogen bonding and other non-covalent interactions, has emerged as a lipid-based strategy to address these limitations. This review summarises the biopharmaceutical background of polyphenols, the principles and proposed mechanisms of phytosome formation and absorption enhancement, candidate and excipient selection, preparation methods and critical process parameters, physicochemical and in-vitro characterisation, pharmacokinetic and safety assessment, scale-up, and regulatory and quality considerations. Emphasis is placed on quercetin phytosome, for which a randomised human crossover study reported substantially higher systemic exposure than unformulated quercetin, and on silybin and curcumin complexes as supporting examples. Eight tables and two figures consolidate the key concepts and the development workflow. The review also identifies current limitations, including small and manufacturer-associated clinical studies, limited long-term safety data and inconsistent characterisation, and outlines priorities for the development of effective phytosome-based oral formulations.

1. Introduction

Polyphenols are plant secondary metabolites defined by the presence of one or more aromatic rings carrying multiple hydroxyl groups. They are abundant in fruits, vegetables, cereals, tea, spices and medicinal plants, and several thousand distinct structures have been described [1–3]. Experimental and epidemiological studies have linked polyphenol-rich diets and isolated polyphenols with antioxidant, anti-inflammatory, antiviral, anticancer, hepatoprotective, lipid-lowering and neuroprotective effects, which are generally attributed to free-radical scavenging, modulation of inflammatory mediators and signalling pathways, and interaction with disease-related enzymes [3–5].

Translating this pharmacological promise into dependable oral products has proved difficult. Oral bioavailability, the fraction of an administered dose that reaches the systemic circulation in an unchanged or measurable active form, is governed by solubility, dissolution rate, membrane permeability, gastrointestinal stability, pre-systemic metabolism and the

activity of the gut microbiota [6–8]. For many polyphenols several of these barriers operate at once, so that plasma concentrations after a conventional oral dose are low, variable and often composed mainly of conjugated metabolites [4,7]. Poor aqueous solubility is a recurring theme: a large proportion of marketed drugs, and a still larger proportion of new chemical entities, are poorly soluble, and a wide range of enabling technologies has been developed in response [9,10].

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the most widely studied dietary flavonols. It occurs in onions, apples, berries, brassicas and many medicinal plants, mostly as glycosides [11], and it has antioxidant, anti-inflammatory, antimicrobial and cytoprotective activities [12–14]. Its therapeutic exploitation, however, is restricted by negligible aqueous solubility, a crystalline structure that dissolves slowly, and extensive intestinal and hepatic conjugation [15–17]. Because it combines clear pharmacological interest with well-documented biopharmaceutical limitations, quercetin is widely used as a model polyphenol for evaluating delivery technologies.

Many strategies have been explored to improve polyphenol delivery, including particle-size reduction and nanosuspensions [18–20], solid dispersions [21], self-nanoemulsifying systems [22], polymeric micelles, liposomes, cyclodextrin complexes and phospholipid complexes [23,24]. Among these, phytosome technology is notable because it relies on a molecular association between the bioactive and a phospholipid, usually phosphatidylcholine, rather than on physical entrapment [25–27]. A human crossover study of a quercetin phytosome reported markedly higher systemic exposure than unformulated quercetin [28], and similar principles have been applied to silybin, curcumin, green-tea catechins and grape-seed polyphenols [29,30].

This review examines phytosome technology as a platform for the oral delivery of poorly bioavailable polyphenols, using quercetin as the main example. It summarises the biopharmaceutical background, the proposed mechanisms of complex formation and absorption enhancement, the selection of excipients and preparation methods, physicochemical and in-vitro characterisation, pharmacokinetic and safety evaluation, scale-up and regulatory considerations, and the strength of the available clinical evidence. Current limitations and research priorities are discussed critically, because much of the published literature consists of small, short-term or manufacturer-supported studies.

2. Polyphenols and the Oral Bioavailability Barrier

2.1 Classification of polyphenolic compounds

Polyphenols are classified mainly by the number of phenolic rings and the structural elements that link them. Table 1 lists the principal classes with representative compounds and dietary sources. The classes differ widely in molecular size, polarity and ionisation, and these properties determine whether, and how, a given compound can be formulated as a phospholipid complex [1,3].

Table 1. Major classes of dietary polyphenols, representative compounds and typical biopharmaceutical challenges.

Class	Representative compounds	Typical sources	Main oral-delivery challenge
Flavonoids	Quercetin, kaempferol, rutin, catechin, epigallocatechin gallate	Onions, apples, berries, tea	Low solubility of aglycones; extensive conjugation; glycoside hydrolysis required
Phenolic acids	Gallic, caffeic, ferulic and chlorogenic acids	Coffee, cereals, fruits	Rapid metabolism; high polarity and limited passive permeability
Stilbenes	Resveratrol and related compounds	Grapes, berries	Poor solubility; rapid sulfation and glucuronidation
Lignans	Secoisolariciresinol, matairesinol	Flaxseed, whole grains	Dependence on gut-microbial conversion
Other polyphenols	Curcuminoids, ellagitannins and other tannins	Turmeric, pomegranate, nuts	Low solubility, chemical instability, high molecular weight (tannins)

2.2 Factors affecting oral bioavailability

Poor aqueous solubility and slow dissolution. Many polyphenolic aglycones are planar molecules with several hydrogen-bond donors and acceptors, which favour strong crystal-lattice interactions, high melting points and low dissolution rates. Solubility-limited absorption is the central concern of the Biopharmaceutics Classification System (BCS) [31], and several dietary polyphenols, including quercetin, curcumin and resveratrol, have been discussed as BCS class II or IV compounds depending on the permeability criteria applied [5].

Limited intestinal permeability. Passive transcellular permeability depends on molecular size, ionisation, hydrogen-bonding capacity and lipophilicity [32]. Highly hydroxylated

or glycosylated polyphenols may be too polar to cross the epithelium efficiently, whereas more lipophilic aglycones may be returned to the lumen by efflux transporters after entering the enterocyte [15].

Gastrointestinal instability. Changes in pH, dissolved oxygen, digestive enzymes and metal ions can cause oxidative degradation or structural modification of polyphenols before absorption. Compounds with catechol or pyrogallol moieties are particularly vulnerable [17].

First-pass metabolism. Absorbed polyphenols undergo glucuronidation, sulfation and O-methylation in enterocytes and hepatocytes, so that the circulating species are largely conjugates rather than the parent aglycone [15,16,33]. Because many biological activities are demonstrated in vitro with the aglycone, the pharmacological relevance of conjugates remains a matter of active investigation [8].

Gut-microbiota metabolism. Polyphenols that escape absorption reach the colon, where microbial enzymes hydrolyse glycosides and cleave the flavonoid skeleton into smaller phenolic acids that may be absorbed and may themselves be bioactive [34–36]. The composition of the microbiota differs between individuals, and this contributes to the large inter-subject variability in polyphenol pharmacokinetics [37].

2.3 Quercetin as a model polyphenolic compound

Quercetin is the aglycone of numerous dietary glycosides. In foods such as onions it is present mainly as glucosides, which are hydrolysed by lactase-phlorizin hydrolase or cytosolic β-glucosidase before or during absorption [11,38]. In ileostomy volunteers, absorption of quercetin from onion glucosides was higher than from the pure aglycone [39], and pharmacokinetic comparisons of quercetin aglycone, rutin and other glycosides confirm that the sugar moiety strongly influences plasma profiles [40,41]. Plasma concentrations after ordinary dietary intake or conventional supplements are low, in the nanomolar range, and increase only gradually on repeated dosing [16,42].

The physicochemical profile summarised in Table 2 explains much of this behaviour. Quercetin satisfies the usual rule-of-five size and polarity criteria [32], so its limited absorption is more plausibly attributed to high crystal-lattice energy, slow dissolution and extensive conjugation than to molecular size. It dissolves in water only to the extent of a few micrograms per millilitre [43] and is considerably more soluble in ethanol, methanol and dimethyl sulfoxide [44]; its octanol–water partition coefficient is moderate (log P of about 1.8) [45].

Table 2. Physicochemical and biopharmaceutical characteristics of quercetin.

Parameter	Characteristics
Chemical name	3,3′,4′,5,7-Pentahydroxyflavone
Molecular formula / weight	$C_{15}H_{10}O_7$; 302.24 g/mol
Melting point	Approximately 316–317 °C (depends on material form and method)
Aqueous solubility	Very low (micrograms per millilitre range) [43]
Organic solvents	Soluble in ethanol, methanol and dimethyl sulfoxide [44]
Lipophilicity	Octanol–water log P approximately 1.8 [45]
Principal limitations	Slow dissolution, extensive Phase II metabolism, low and variable plasma levels [15,16]
Formulation approach discussed here	Complexation with phosphatidylcholine / lecithin

Quercetin therefore offers a stringent but informative test for phospholipid complexation: any improvement in dissolution, permeation or systemic exposure can be measured against a compound whose behaviour as the free aglycone is well documented. It also has a sizeable evidence base in inflammation, cardiovascular and metabolic disorders that gives practical motivation for improved formulations [46–48].

3. Phytosome Technology: Principles and Mechanisms

3.1 Concept and origin

The term phytosome describes a complex between a plant-derived bioactive compound and a phospholipid, most commonly phosphatidylcholine. The concept originated from work on phospholipid complexes of flavonoids and other plant constituents reported in the late 1980s and early 1990s [25,49], and "Phytosome" is now also a registered trademark of the company that pioneered it. In the literature the terms phytosome, phyto-phospholipid complex and phospholipid complex are often used interchangeably [23,27]. The typical stoichiometry of the complex is one or two moles of phospholipid per mole of phytoconstituent, although ratios up to 1:3 have been reported [23,26].

The defining feature is that the active compound interacts directly with the polar part of the phospholipid, whereas the fatty-acid chains remain free to orient away from it. A phytosome is therefore not a physical mixture, and it is not simply an herbal extract placed inside a liposome [26,50].

3.2 Mechanism of phytosome formation

Complexation is generally explained by hydrogen bonding

between phenolic hydroxyl groups of the polyphenol and the polar head of phosphatidylcholine, supported by hydrophobic and van der Waals interactions; spectroscopic studies on flavonoid–phosphatidylcholine systems have been interpreted as showing involvement mainly of the phosphate group, with the choline group less affected [23,26]. In quercetin, the five hydroxyl groups can act as hydrogen-bond donors towards the phosphate oxygen, as illustrated schematically in Figure 1A. The resulting complex has physicochemical characteristics that differ from those of the free compound, including altered crystallinity, an amorphous or partly amorphous solid state, and higher lipid compatibility [51,52].

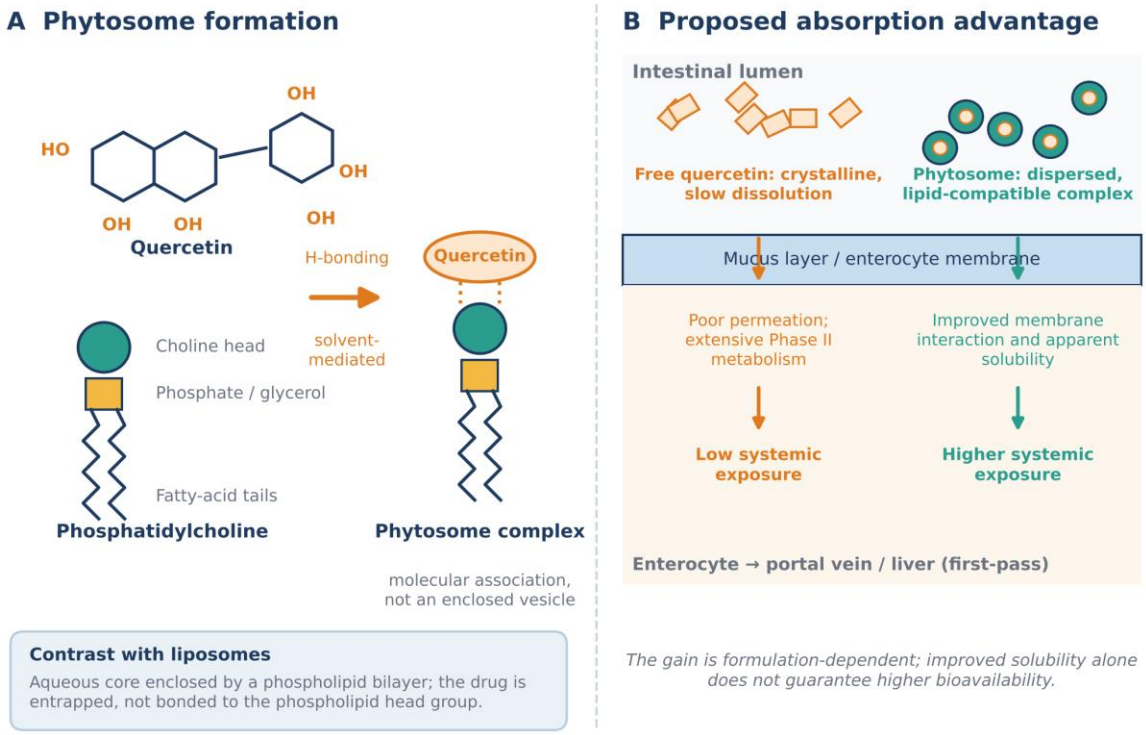


Figure 1. Schematic representation of phytosome formation and the proposed absorption advantage. (A) Hydroxyl groups of quercetin associate with the polar head of phosphatidylcholine through hydrogen bonding and other non-covalent forces during solvent-mediated complexation, whereas the fatty-acid tails remain free; this molecular association distinguishes the phytosome from a liposome, in which the drug is entrapped in a vesicle. (B) Proposed behaviour in the gastrointestinal tract: crystalline free quercetin dissolves slowly and is extensively conjugated, whereas the dispersed, lipid-compatible complex may interact better with the mucus layer and enterocyte membrane. The scheme is conceptual and is not drawn to scale.

3.3 Mechanisms of enhanced oral absorption

Several mechanisms have been proposed to explain how phospholipid complexation increases systemic exposure (Figure 1B):

- Molecular complexation changes the physicochemical environment of the polyphenol, reducing crystallinity and improving wettability and dispersion [23,51].
- Improved apparent solubility and dissolution rate raise the amount of dissolved compound available at the absorptive surface, particularly in lipid-containing intestinal fluids [28,53].
- The lipid-compatible nature of the complex may favour interaction with the mucus layer and the enterocyte membrane [26,27].
- Association with phospholipid may protect sensitive compounds from degradation in the intestinal lumen [23].
- Co-ingested lipids and phospholipids can promote solubilisation by bile salts and, for lipophilic compounds, lymphatic uptake, which may reduce hepatic first-pass loss [53,54].

These mechanisms remain largely inferential. Improved solubility does not automatically produce improved bioavailability: intestinal conjugation, efflux transporters, food effects and formulation-specific behaviour in the digestive milieu must also be considered [8,54]. Direct experimental evidence that intact phytosome complexes cross the intestinal barrier is limited, and in aqueous media the complex may partly dissociate or reorganise into vesicle- or micelle-like structures [23,50].

3.4 Phytosomes compared with liposomes

Phytosomes and liposomes both contain phospholipids but differ in structure and formation (Table 3). In liposomes the drug is entrapped in the aqueous core or within the bilayer of a closed vesicle, whereas in a phytosome the active molecule is chemically associated with individual phospholipid molecules [50,55]. Consequently the characterisation priorities differ: vesicle size, lamellarity and encapsulation efficiency dominate liposome analysis, whereas evidence of molecular interaction and solid-state change dominates phytosome analysis [23,56].

Table 3. Comparison of phytosomes and liposomes.

Parameter	Phytosomes	Liposomes
Basic structure	Molecular phospholipid–phytoconstituent complex	Phospholipid bilayer vesicle
Drug association	Hydrogen bonding and other non-covalent interactions with the phospholipid	Entrapment in the aqueous core or bilayer
Drug location	Associated with the polar head of the phospholipid	Aqueous core or lipid bilayer
Main purpose	Improved delivery of plant-derived bioactives	Encapsulation of diverse hydrophilic and lipophilic agents
Key characterisation	FTIR, DSC, XRD, NMR (interaction and solid state)	Vesicle size, morphology, encapsulation efficiency
Typical physical form	Amorphous or partly amorphous solid complex	Dispersed spherical vesicles

The distinction matters in practice, because a product described as a phytosome should be supported by evidence of complexation rather than by the presence of phospholipid alone [23,26].

3.5 Phytosomes in the context of other enabling technologies

Phospholipid complexation is one of several routes to better quercetin exposure. Antisolvent precipitation and nanosuspension technology increase surface area and dissolution rate [18,19], self-nanoemulsifying systems solubilise the compound in lipid-based vehicles [22], and a food-grade micellar delivery system produced several-fold higher quercetin concentrations than the standard compound in a small human study [57]. In rats, a Ginkgo biloba extract phospholipid complex and a solid dispersion were both reported to improve the bioavailability of flavonol aglycones relative to the plain extract [58]. Direct head-to-head human comparisons between these technologies are scarce, so claims of superiority should be made cautiously, and the systematic review of human quercetin studies by Liu et al. highlights the diversity of study designs that complicates such comparisons [24].

4. Formulation Development for Phytosome-Based Delivery

Development of a phytosome formulation requires systematic selection of the active compound, phospholipid, solvent system and manufacturing conditions in order to obtain reproducible complex formation, suitable particle or powder characteristics, adequate dissolution and acceptable stability. The overall development pathway, from candidate selection to scale-up, is summarised in Figure 2, and the individual stages are discussed in the following sections.

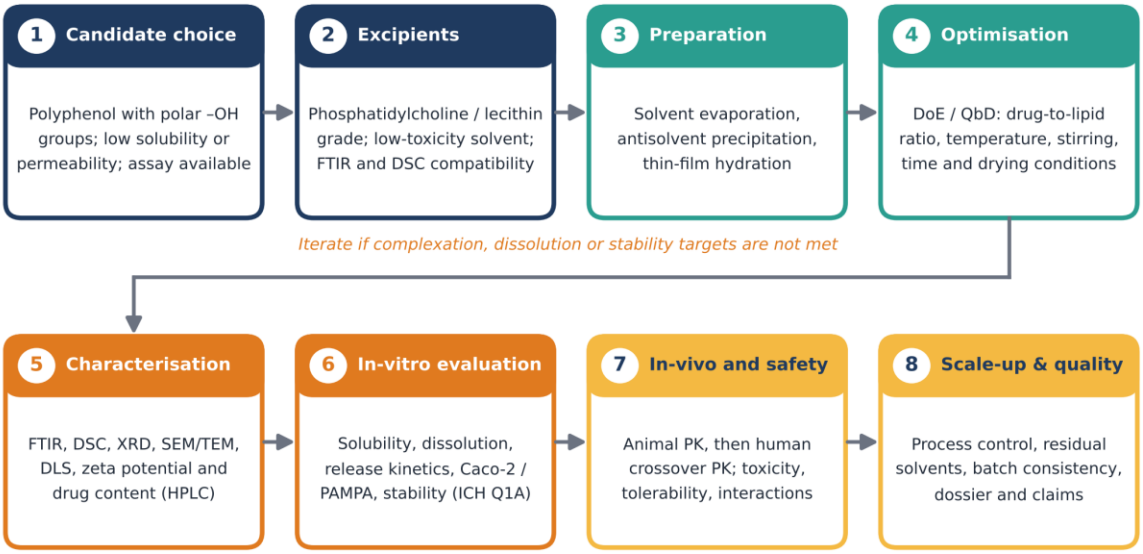


Figure 2. Stepwise workflow for the development and evaluation of a polyphenol phytosome.

Early stages (1–4) establish a robust, optimised complex; characterisation and in-vitro testing (5–6) confirm complex formation and performance and feed back into optimisation; in-vivo, safety, scale-up and quality considerations (7–8) determine translational feasibility. DoE, design of experiments; QbD, quality by design; PAMPA, parallel artificial membrane permeability assay; PK, pharmacokinetics.

4.1 Selection of the polyphenolic candidate

Candidate selection is based on pharmacological potential and a documented biopharmaceutical limitation that phospholipid complexation could plausibly address. Important criteria include molecular weight and structure, the number and position of hydroxyl groups, aqueous solubility and partition behaviour, chemical and thermal stability, susceptibility to gastrointestinal degradation, compatibility with phospholipids and the availability of validated analytical methods [23,52]. The compound must offer polar functional groups that can interact with the phospholipid head, so that preliminary compatibility studies are advisable before formulation work starts [26]. Phospholipid complexation has been applied not only to polyphenols but also to other poorly soluble molecules such as evodiamine and tamoxifen [59,60], indicating that the approach is not restricted to flavonoids.

4.2 Excipients and membrane compatibility

Phospholipids are the principal functional components of phytosomes. Phosphatidylcholine is widely used because of its amphiphilic nature and biocompatibility, and the grade selected (source, phosphatidylcholine content, degree of saturation, oxidative stability and pharmaceutical quality) influences complex formation and product stability [52,55]. Unsaturated phospholipids are prone to peroxidation, and hydrogenated grades are therefore sometimes preferred when oxidative stability is critical [55]. Table 4 lists the components commonly investigated in quercetin phytosome development.

Table 4. Components commonly investigated in quercetin phytosome formulations and their functions.

Component	Function	Remarks
Quercetin	Active polyphenol	Protect from light, oxygen and metal ions during processing
Phosphatidylcholine	Complex-forming phospholipid	Purity, source and oxidation state affect reproducibility
Soy or sunflower lecithin	Alternative phospholipid sources	Food-grade lecithin was used in the clinical quercetin phytosome [28]
Ethanol	Solvent for complex formation	Class 3 residual solvent [61]
Methanol / other organic solvents	Research solvents	Class 2 solvents need strict residual-solvent control and removal [61]
PVP	Binder or stabilising excipient	Use only where justified; may influence dissolution
Mannitol	Diluent and carrier	Supports flow and dispersion of dried complexes
Colloidal silica (Aerosil)	Flow and powder-handling aid	Improves flow of lipid-rich powders
Magnesium stearate	Lubricant for solid dosage forms	Level should be optimised to avoid retarding dissolution

Compatibility between the active compound and excipients should be assessed by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) and, where appropriate, by chromatographic analysis for degradation products [23].

4.3 Preparation methods

Phytosomes are prepared by bringing the polyphenol and phospholipid together in a medium in which both can interact, followed by removal or exclusion of the solvent. The conventional approach uses an organic solvent and mild heating (commonly 40–60 °C for one to three hours), after which the complex is isolated by solvent evaporation, precipitation with a non-solvent or other drying techniques [23,52]. Table 5 compares the principal methods.

Table 5. Principal methods for the preparation of phytosomes.

Method	Principle	Advantages	Limitations
Solvent evaporation	Polyphenol and phospholipid dissolved, refluxed or stirred, solvent removed under reduced pressure	Simple, widely used, good control of stoichiometry [52]	Residual solvent; thermal exposure; batch process
Antisolvent precipitation	Complex formed in solution, then precipitated by adding a non-solvent	Mild temperatures; easy separation [23]	Solvent / antisolvent consumption; possible loss of unreacted material
Thin-film hydration	Solvent evaporated to a film, then hydrated in aqueous medium	Gives dispersed systems directly [27]	May form vesicles rather than discrete complexes; stability issues
Mechanical and advanced processing	Homogenisation, ultrasonication, spray drying, supercritical fluid techniques	Particle-size control; scalability [27]	Equipment cost; heat or shear may degrade sensitive compounds

In the solvent-evaporation procedure the polyphenol and phosphatidylcholine are weighed accurately, dissolved in a suitable solvent or solvent mixture, and stirred at a controlled temperature for sufficient time to allow complexation. The solvent is then removed under reduced pressure in a rotary evaporator, and the resulting complex is dried and stored in an airtight, light-protective container. In antisolvent precipitation a non-solvent is added under controlled stirring to precipitate the complex, which is separated, washed if required and dried. In thin-film hydration the solvent is evaporated to leave a film that is subsequently hydrated, a route that may yield dispersed phospholipid-complex systems depending on composition and processing [27]. High-pressure homogenisation, ultrasonication and similar techniques may be added to control

dispersion and particle size, as appropriate to the final dosage form and the stability of the active compound.

4.4 Critical process parameters and optimisation

Variables that influence complex formation and product quality include the drug-to-phospholipid ratio, the type and purity of phospholipid, solvent composition and volume, reaction temperature, stirring speed, complexation time, solvent-evaporation rate, drying temperature and duration, hydration conditions and any particle-size reduction step [23,52]. These interacting factors are best studied by design of experiments (DoE), such as factorial designs or response-surface methodology [62]. Within a quality-by-design framework, critical quality attributes (for example complexation efficiency, drug content, dissolution and stability) are linked to critical process parameters, and a design space is defined [63,64].

4.5 Physicochemical characterisation

The characterisation strategy should demonstrate that a molecular complex, and not merely a physical mixture, has been formed, and should describe the physical state and quality of the product. Table 6 summarises the principal techniques.

Table 6. Techniques for the physicochemical characterisation of phytosomes and the information they provide.

Technique	Information obtained	Typical indication of complexation
FTIR	Interactions between functional groups	Shifts, broadening or attenuation of O–H and P=O bands compared with the physical mixture [23,51]
DSC	Thermal behaviour and crystallinity	Loss or shift of the polyphenol melting endotherm [51]
XRD	Crystalline or amorphous state	Reduced or absent characteristic diffraction peaks [51]
SEM / TEM	Surface morphology and structure	Change from crystalline particles to amorphous or aggregated structures
Dynamic light scattering	Hydrodynamic size and polydispersity index (PDI)	Narrow, reproducible distribution after dispersion; PDI ≤ 0.3 is often regarded as acceptable for lipid carriers [65]
Zeta potential	Surface charge and electrostatic stability	Interpret with the formulation composition and any steric stabiliser [66]
HPLC	Drug content and entrapment / complexation efficiency	Validated, stability-indicating assay [67]
Solubility and dissolution	Apparent solubility and dissolution rate	Superior to free drug and to the physical mixture [23,28]

Particle size and PDI are determined by dynamic light scattering after dispersion; they describe the hydrodynamic diameter and size distribution of the dispersed system [65]. Zeta potential indicates electrostatic stability but cannot be interpreted in isolation, particularly when steric stabilisers are present [66]. Drug content and complexation efficiency should be measured by a validated analytical method, preferably HPLC. Entrapment efficiency is commonly calculated as:

$$EE\ (\%) = [(Total\ drug - Free\ drug) / Total\ drug] \times 100$$

For a molecular complex the separation procedure used to determine free drug must be validated, because it has to discriminate truly uncomplexed drug from complex-associated drug [23]. FTIR is used to explore interactions between polyphenol and phospholipid, and changes in characteristic bands should be interpreted together with other techniques rather than as proof of complexation by themselves. DSC reveals changes in melting behaviour, and the disappearance or shift of the original endotherm may indicate reduced crystallinity or molecular interaction, while XRD gives complementary evidence of decreased crystallinity [51]. SEM and TEM provide information on surface morphology and shape. Finally, solubility and dissolution of the phytosome should be compared with those of the unformulated compound and of a physical mixture of the two components, so that any improvement can be attributed to genuine complexation rather than to simple excipient addition [28].

5. In Vitro Evaluation

In-vitro studies assess formulation performance before animal or human pharmacokinetic work and help to select candidates and optimise processing [23].

5.1 Stability studies

Stability studies establish the physical, chemical and

performance characteristics of the formulation during storage under long-term and accelerated conditions appropriate to the intended market, in line with ICH Q1A(R2) [68]. Parameters to monitor include appearance and colour, drug content, degradation products, particle size and PDI where relevant, zeta potential, redispersibility, dissolution behaviour, moisture content, phospholipid oxidation and, where applicable, microbiological quality. Particular attention should be paid to the oxidative degradation of quercetin and of unsaturated phospholipids; protection from light and moisture and selection of suitable packaging are essential [17,55].

5.2 Permeation and transport studies

Permeation studies investigate the transport of polyphenols across biological membranes. The Caco-2 monolayer is the most widely used in-vitro model of intestinal epithelial permeability and correlates with human absorption for many drugs [69,70]. The apparent permeability coefficient is calculated as:

$$P_{app} = (dQ/dt) / (A \times C_0)$$

where dQ/dt is the rate of appearance of compound in the receiver compartment, A is the membrane surface area and C_0 is the initial donor concentration. Efflux ratios may be derived from bidirectional experiments. The parallel artificial membrane permeability assay (PAMPA) provides a cell-free estimate of passive transcellular permeability [71], and ex-vivo studies with excised intestinal tissue can supply complementary information. Comparisons should include free quercetin, a physical mixture and the optimised phytosome. It should be remembered that standard Caco-2 monolayers lack a physiological mucus layer and do not reproduce lipid digestion, so their ability to predict the in-vivo performance of lipid-based complexes is limited [53,70].

5.3 In-vitro drug release

Release studies describe the dissolution of quercetin from the phytosome under conditions chosen to match the final dosage form. The procedure should specify the medium (including simulated fasted and fed intestinal fluids where relevant), maintain the temperature at 37 ± 0.5 °C, control agitation, collect samples at predetermined times with replacement of the withdrawn volume, and quantify quercetin by a validated HPLC or suitable analytical method [28,72]. Release profiles should be compared with those of unformulated quercetin and the physical mixture, using model-independent comparisons such as the similarity factor where applicable [72].

5.4 Release kinetics

Release data can be fitted to mathematical models to explore the release mechanism: zero-order (constant release), first-order (release proportional to remaining drug), Higuchi (diffusion from a matrix) [73] and Korsmeyer–Peppas (empirical power law) [74]. In the Korsmeyer–Peppas model, the release exponent n is interpreted according to the geometry of the dosage form, for example about 0.43 for Fickian diffusion from spheres and about 0.5 for thin films, and the model should be applied only to the initial part of the release curve [72,74]. Fitting can be carried out using dedicated software [75], and the best-fitting model should be selected using appropriate statistical criteria rather than the correlation coefficient alone. Because a phytosome powder typically dissolves or disperses instead of releasing drug from an inert matrix, mechanistic interpretations should be made with caution.

6. In Vivo Pharmacokinetics and Bioavailability

Pharmacokinetic evaluation shows whether improvements seen in vitro translate into higher systemic exposure. The optimised phytosome should be compared with an equivalent dose of the unformulated polyphenol, usually a standard commercial grade of the aglycone [16].

6.1 Experimental design

Oral absorption may first be examined in an appropriate animal model and then, where scientifically and ethically justified, in human volunteers. Design considerations include dose equivalence, route, fasting or fed state, blood sampling times that adequately capture both the absorption phase and the elimination phase, washout between periods in crossover designs, validated bioanalytical methods, and ethical approval and animal-welfare compliance [16,28]. Because quercetin is extensively conjugated, plasma samples are often treated with β-glucuronidase and sulfatase before analysis to report total quercetin, and the analytical approach must be stated explicitly because it influences the apparent Cmax and AUC [33,41].

6.2 Pharmacokinetic parameters

The parameters normally derived are listed in Table 7.

Table 7. Pharmacokinetic parameters commonly evaluated in bioavailability studies of phytosomes.

Parameter	Significance
C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach maximum concentration
AUC	Total systemic exposure over a defined period
$t_{1/2}$	Elimination half-life
MRT	Mean residence time
Relative bioavailability	Exposure from the test formulation relative to a reference formulation

Relative bioavailability is calculated as:

$$F_{rel}\,(\%) = (AUC_{test} / AUC_{reference}) \times (Dose_{reference} / Dose_{test}) \times 100$$

The calculation requires comparable analytes, the same pharmacokinetic endpoint and the same validated analytical method for both formulations. Because quercetin shows marked inter-individual variability [41,42], crossover designs with adequate numbers of subjects are preferable to parallel-group studies.

6.3 Human pharmacokinetic evidence for quercetin phytosome

The principal human evidence is the randomised, single-dose, crossover study of Riva et al., which compared a food-grade lecithin-based quercetin phytosome with unformulated quercetin in 12 healthy volunteers under fasting conditions [28]. Participants received unformulated quercetin at 500 mg and the phytosome at two dose levels (250 mg and 500 mg of the phytosome product, which contains roughly 40% quercetin), and the phytosome was prepared with food-grade sunflower lecithin. The investigators also reported higher solubility of the phytosome in simulated gastrointestinal media than unformulated quercetin and than a physical mixture of identical composition. Plasma quercetin concentrations and systemic exposure were substantially higher after phytosome administration. At the 500 mg dose, the mean maximum plasma concentration was approximately 223 ng/mL for the phytosome compared with approximately 10.9 ng/mL for unformulated quercetin, and the AUC was approximately 18 times higher [28].

These findings provide human evidence that phospholipid complexation can markedly raise quercetin absorption. Their interpretation requires care, however. The study was small, evaluated single-dose administration in healthy adults, and was conducted by investigators associated with the manufacturer of the formulation [28]. The magnitude of the increase is also unusually large when compared with several other quercetin formulations [57], which makes independent replication desirable. Larger independent studies, including repeated dosing and patient populations, are needed to establish long-term clinical efficacy and safety [24].

7. Safety, Tolerability and Toxicological Considerations

Safety evaluation is an essential part of phytosome development. Although phosphatidylcholine is widely used in pharmaceutical and nutritional products, and quercetin itself has been reviewed as having a favourable safety profile at customary supplement doses [76,77], the safety of the complete formulation, at the higher systemic exposure it produces, must be established. Increased bioavailability also means that exposure to the parent compound and its metabolites may exceed that of the conventional product at the same nominal dose. The following assessments should be considered.

- **Acute toxicity:** single- or limited-dose studies give preliminary information on adverse effects.
- **Repeated-dose toxicity:** prolonged exposure studies, including haematological, biochemical and histopathological end points.
- **Gastrointestinal tolerability:** assessment of irritation, changes in digestive function and other local effects.
- **Excipient safety:** purity, source, residual solvents, oxidation products and pharmaceutical quality of the phospholipid and other excipients [61].
- **Interactions:** polyphenols may interact with drug-metabolising enzymes and transporters and with co-administered medicines, and such interactions should be considered during clinical development [16,77].

The available human quercetin phytosome study reported no notable adverse effects in its small group of healthy volunteers [28]. This observation should not be interpreted as proof of long-term safety in all patient populations.

8. Scale-Up and Manufacturing Considerations

Moving from laboratory preparation to industrial manufacture is a major challenge. Small batches may show successful complex formation, but the same physicochemical characteristics must be preserved at scale. Important considerations include consistent quality and phosphatidylcholine content of raw materials, accurate control of the drug-to-phospholipid ratio, uniform mixing and complexation, control of temperature and solvent evaporation, efficient solvent recovery, reproducible drying and moisture control, control of particle size and distribution, prevention of oxidation, batch-to-batch consistency and suitable packaging

[27,52].

Industrial processes may use rotary evaporation, vacuum drying, spray drying or other drying technologies, depending on the product. Quality-by-design principles and process analytical technology can help identify and control critical process parameters, and quality risk management according to ICH Q9 supports decisions on control strategy [63,64,78]. Environmental and safety aspects of solvent use also favour processes based on ethanol or other low-toxicity solvents wherever the chemistry allows [61].

9. Regulatory and Quality Considerations

Regulatory development requires comprehensive documentation of the active compound, phospholipid source, excipients, manufacturing process, analytical methods and final product quality. The quality assessment should cover identification and assay of the active polyphenol, phospholipid identity and composition, drug content and content uniformity, residual solvents, related substances and degradation products, particle size and PDI where relevant, dissolution and release characteristics, microbiological quality, and stability with packaging compatibility [64,67].

For botanical materials the identity, source, chemical composition and batch-to-batch consistency of the plant material are especially important. ICH Q1A(R2) provides a framework for stability testing [68], ICH Q3C governs residual solvents [61], and ICH Q2(R1) addresses validation of analytical procedures [67]. For products developed as botanical drugs, the US FDA botanical drug development guidance gives recommendations on raw-material control, chemical characterisation, manufacturing consistency and clinical development [79]. The regulatory classification of a phytosome product depends on composition, intended use, claims and jurisdiction; it should not be assumed that a product qualifies as an approved drug or as a dietary supplement simply because it contains natural ingredients.

10. Case Studies and Comparative Analysis

Several polyphenols and other natural products have been investigated as phospholipid complexes. Table 8 summarises representative examples, the formulation limitation addressed and the nature of the evidence.

10.1 Quercetin phytosome

Quercetin phytosome is the best-documented example of phospholipid complexation for a polyphenol in humans. A quercetin–phospholipid complex was characterised as an amorphous solid by spectroscopic and thermal methods [51], and a quercetin–phospholipid complex improved hepatoprotective activity in a rat model of liver injury compared with free quercetin [80]. The food-grade lecithin phytosome developed by Riva et al. showed higher solubility and approximately 18-fold higher AUC than unformulated quercetin when the 500 mg doses of the two products were compared [28]. Laboratory-scale reports describe the preparation and characterisation of quercetin phytosomes by solvent-based methods [81].

10.2 Silybin phospholipid complex

Silybin, the main constituent of silymarin, has poor water solubility and limited oral absorption. The silybin–phosphatidylcholine complex is an established example of phytosome technology: in healthy volunteers it produced higher plasma silybin levels than conventional silymarin preparations [82], and a silybin–phospholipid complex improved oral bioavailability in rats [83].

10.3 Curcumin phytosome

Curcumin is poorly soluble and extensively metabolised, which has encouraged work on phospholipid-based formulations. A curcumin–phospholipid complex was prepared and evaluated in rats [84], and curcumin formulated with phosphatidylcholine showed greater systemic availability than unformulated curcumin in a rodent study [85]. In healthy volunteers, a lecithin formulation of a standardised curcuminoid mixture produced markedly higher absorption of total curcuminoids than the unformulated mixture [32], and extended administration of a curcumin–phosphatidylcholine complex was investigated in osteoarthritis patients. Reviews of phytosomal curcumin nevertheless caution that formulation-specific pharmacokinetic evidence should be kept separate from evidence for other curcumin delivery systems [30].

10.4 Other polyphenols and comparative summary

Phytosome-type complexes of green-tea catechins and grape-seed polyphenols have also been reviewed [29], and a rutin phytosome has been reported by the authors' group [85]. Table 8 compares these examples.

Table 8. Representative phospholipid-complex studies of polyphenols and the main formulation objective.

Compound	Main formulation limitation	Phytosome / complex objective	Representative evidence
Quercetin	Poor solubility; extensive conjugation	Improve dissolution and oral exposure	Human crossover PK (n = 12) [28]; amorphous complex [51]
Silybin	Poor water solubility	Improve intestinal absorption	Human PK [82]; rat PK [83]
Curcumin	Low solubility; rapid metabolism	Improve dispersion and systemic exposure	Rat PK [84,85]; human PK; clinical use
Green-tea catechins	Chemical instability; metabolism	Improve protection and delivery	Reviewed [29]
Grape-seed polyphenols	Complex composition; variable absorption	Improve consistency and delivery	Reviewed [29]
Rutin	Poor solubility; low permeability of the glycoside	Improve dissolution and delivery	Formulation and evaluation report

The evidence suggests that phospholipid complexation can benefit several polyphenols, but the extent of improvement depends on the chemical characteristics of the active compound, the phospholipid, the preparation method and the study design. Cross-compound generalisation is therefore not justified without compound-specific pharmacokinetic data [23,27].

11. Challenges and Future Perspectives

Phytosome technology offers considerable opportunities for improved oral formulations of natural bioactives, but several scientific and technological challenges remain.

Formulation optimisation. Future studies should investigate systematically how phospholipid composition, drug-to-phospholipid ratio, solvent system and manufacturing conditions influence complex formation, and should report these variables in sufficient detail to allow replication [52,62].

Advanced analytical characterisation. Nuclear magnetic resonance spectroscopy, XRD, DSC, FTIR and HPLC can give more detailed information on molecular interactions and stability. Many published reports rely on a limited set of techniques and lack a physical-mixture control, which weakens the claim that a true complex has been formed [23,26].

Improved manufacturing technologies. Continuous manufacturing, advanced solvent-recovery systems and process analytical technology could improve reproducibility and scalability [63,64].

Combination phytosomes. Incorporating several compatible polyphenols into phospholipid systems may allow combination formulations, but compatibility, dose standardisation and interaction studies are required [29,30].

Personalised delivery. Differences in gastrointestinal physiology and gut microbiota between individuals may influence phytosome absorption and metabolite profiles, and could be explored in future clinical studies [34,36].

Clinical validation. Although promising preclinical and preliminary human findings are available, randomised, controlled and adequately powered clinical studies are needed to establish the clinical benefits of phytosome formulations. Research priorities include long-term safety, dose optimisation, food effects, pharmacokinetic variability and comparative effectiveness against other enabling technologies [8,24,28]. The antioxidant rationale for polyphenol therapy should also be examined critically, because plasma levels of the parent compounds are only one of several determinants of efficacy [8].

12. Conclusion

Phytosome technology is a promising phospholipid-based approach to the oral delivery of polyphenols that suffer from poor aqueous solubility and limited bioavailability. Molecular complexation between polyphenol and phospholipid alters the physicochemical properties of the active compound, improves apparent solubility and may enhance its interaction with biological membranes. Quercetin is a suitable model compound, and the available human pharmacokinetic evidence shows that a quercetin phytosome can produce substantially higher systemic exposure than the unformulated compound, although this evidence comes from a small, single-dose, manufacturer-associated study. Silybin and curcumin provide further support for the applicability of phospholipid complexation.

Successful development nevertheless requires systematic optimisation, detailed physicochemical characterisation with appropriate physical-mixture controls, validated in-vitro and in-vivo evaluation, stability testing and robust quality control. Independent clinical trials and industrial-scale investigations are needed to define the long-term therapeutic value of phytosome-based systems and to translate the pharmacological

potential of natural polyphenols into effective and reproducible oral products.

References

1. Williamson G. Bioavailability of food polyphenols: current state of knowledge. Annu Rev Food Sci Technol. 2025;16(1):315-332. doi:10.1146/annurev-food-060721-023817.
2. D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C, Masella R. Polyphenols, dietary sources and bioavailability. Ann Ist Super Sanita. 2007;43(4):348-361.
3. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. 2005;81(1 Suppl):230S-242S. doi:10.1093/ajcn/81.1.230S.
4. Liu L, Barber E, Kellow NJ, Williamson G. Improving quercetin bioavailability: a systematic review and meta-analysis of human intervention studies. Food Chem. 2025;477:143630. doi:10.1016/j.foodchem.2025.143630.
5. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved oral absorption of quercetin from Quercetin Phytosome®, a new delivery system based on food grade lecithin. Eur J Drug Metab Pharmacokinet. 2019;44(2):169-177. doi:10.1007/s13318-018-0517-3.
6. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev. 2009;14(3):226-246.
7. Semalty A, Semalty M, Rawat MSM, Franceschi F. Supramolecular phospholipids-polyphenolics interactions: the PHYTOSOME strategy to improve the bioavailability of phytochemicals. Fitoterapia. 2010;81(5):306-314.
8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Q1A(R2): stability testing of new drug substances and products. Geneva: ICH; 2003.
9. US Food and Drug Administration. Botanical drug development: guidance for industry. Silver Spring (MD): FDA; 2016.
10. Pande SD, Dhawale SC. Preparation and characterization of quercetin phytosome. Int J Drug Deliv Technol. 2025;15(3):941-946. doi:10.25258/ijddt.15.3.5.
11. An Overview on Dietary Polyphenols and Their Biopharmaceutical Classification System (BCS). 2021. PMID:34073709.
12. The human microbial metabolism of quercetin in different formulations: an in vitro evaluation. 2020. PMCID.
13. Chhajed M, Rathore AS, Chhajed AJ, Lodha RJ, Yadav J, Sinha P, Bukkawar A, Patil P, Wathore S, Dubey I. Impact of National Education Policy 2020 on Internationalization of Pharmacy Education in India: Progress, Opportunities and Challenges.
14. Yadav J, Gupta D, Chhajed M, Rathore AS. Artificial Intelligence-Driven Design and Optimization of Micro needle-Based Drug Delivery System: A Review. International Journal of Advanced Research in Science, Communication and Technology. 2025 Oct;5(1):920-
15. Chhajed M, Rathore AS, Dulkar D, Sharma G. Autonomus Incident Remediation: A Closed Analytical Methods Validation in Pharmaceutical Analysis From Assumption to Realistic Optimization : A Review. International Journal of Advanced Research in Science, Communication and Technology. 2025 June; 5(8):737
16. Chhajed M, Chhajed AJ, Lodha RJ, Rathore AS, Bukkawar A, Mandloi M. Chronobiology and its Relevance to Drug Administration : Advancing Chronotherapeutic for Precision Medicine. International Journal of Advanced Research in Science, Communication and Technology. 2025 Dec;5(1):850
17. Chhajed M, Chhajed AJ, Rathore AS, Dwivedi SK, Verma Swapnil. Phytochemical Investigation and Pharmacological Evaluation for Antimicrobial, Anthelmintic and Antioxidant Activity of Solanum xanthocarpum Sehrad & Wendl. International Journal of Advanced Research in Science, Communication and Technology. 2026 Jan;6(4):767
18. Chhajed M, Rathore AS, Chouhan S, Mandloi M, Waghela R. Potential Herbal Drugs for the Treatment of Epileptic Seizures:A Review. International Journal of Advanced Research in Science, Communication and Technology. 2025 March;5(8):620
19. Dulakar D, Sinha P, Yadav J, Ahirwar S, Rathore AS, Chhajed M. Phytochemical Study of Murraya Koenigii:A Review. International Journal of Advanced Research in Science, Communication and Technology. 2026 Feb;6(3):758
20. Rathore AS, Chhajed M, Rathore M, Yadav J, Patidar M, Jain A. Antioxidants in Indian Culture: A Comprehensive Study. International Journal of Advanced Research in Science, Communication and Technology. 2025 May;5(10):543
21. Chhajed M, Rathore AS, Jain A, Tanwar A, Patidar M. Formulation and Evaluation of Nanosuspension for Solubility and Dissolution Enhancement of Poorly Water soluble drugs. International Journal of Advanced Research in Science, Communication and Technology. 2025 July;5(1):794
22. Rathore AS, Chhajed M, Sinha P, Tanwar A, Awasthy A, Patidar Rajnandni. Anti- Aging: the way You Manage The Age. International Journal of Advanced Research in

Science, Communication and Technology. 2025 Jan;5(2):807
23. Chhajed M, Rathore AS, Patil S, Patel AL, Kushwah N. Formulation and Evaluation of Rutin Phytosomes. International Journal of Advanced Research in Science, Communication and Technology. 2026 March;6(1):761
24. Rathore AS, Panwar AS. Formulation Optimization and Biological Evalution of Spinach based Glutathione Mouth Dissolving Granules for Anti Aging Potential. Journal of Health Synape. 2026 Oct;1(4):33- 48
25. Panwar AS, Rathore AS, Kaithwar K, Dhokpande A. Nanoengineered Drug Delivery Systems to Overcome Multidrug Resistance in Cancer. Journal of Health Synape. 2026 June;1(2):65-74
26. Rathore AS, Panwar AS, Dongre N. International Journal of Taxicological and Pharmacological Research. 2021 April;11(2):37-45
27. Gandhi MY, Prasad SB, Kumar V, Soni H, Rawat H, Mishra SK, et al. Quantification of phytochemicals and metal ions as well as the determination of volatile compounds, antioxidant, antimicrobial and antacid activities of the *Mimosa pudica* L. leaf: Exploration of neglected and under-utilized part. Chem Biodivers. 2023;20(10):e202301049.
28. Shamim, Ali S, Ali T, Sharma H, Kishor BN, Jha SK. Recent advances in monodisperse gold nanoparticle delivery, synthesis, and emerging applications in cancer therapy. Plasmonics. 2025;20(9):7121–41.
29. Jha SK, Singh N, Shanker OR, Antil I, Baghel JS, Huddar V, et al. A review on integrative approaches in oncology: Bridging Ayurvedic medicine and modern cancer therapeutics. Front Nat Prod. 2025;4:1635197.
30. Sharma S, Kumar C, Kushwaha H, Jha SK, Chawla S, Sharma A, et al. Advancing anticancer drug development: Overcoming challenges and exploring new therapeutic strategies. Ayush J Integr Oncol. 2025;2(1):8–27.
31. Gandhi Y, Kumar V, Singh G, Prasad SB, Mishra SK, Soni H, et al. Chemoprofiling and medicinal potential of underutilized leaves of *Cyperus scariosus*. Sci Rep. 2024;14(1):7263.
32. Singh A, Jha SK, Dwivedi PC, Srivastava U, Pal A. Revolutionizing healthcare: Integrating electronics, AI, traditional, and conventional methods. World J Adv Res Rev. 2024;23:2426–34.
33. Jha SK, Islam M, Kumar R, Rana L, Saifi MA, Ali S, et al. Evaluation of *Vernonia amygdalina* Del. containing phytoconstituents as potential inhibitors of monkeypox virus using molecular docking analysis. World J Adv Res Rev. 2023;17(1):1112–22.
34. Jha SK, Mishra AK, Kumar V, Dane G, Kumari S, Charde V, et al. Ecological and behavioral impacts of COVID-19 on human existence and potential preventive measures through traditional and alternative medicine: A narrative review. Pharmacol Res Nat Prod. 2024;3:100042.
35. Sonawane SM, Lohiya GV, Rao AK, Beniwal M, Chavan SU, Aparadh VM, et al. Conjunctivitis in unusual populations: A review of rare cases and challenges in diagnosis and management. World J Adv Res Rev. 2023;19(3):1326–36.
36. Khan R, Maheshwari D, Chauhan S, Lohiya GV, Kumar C, Antil I, et al. Exploring the potential therapeutic value of *Solanum lycopersicum* L. phytoconstituents for Parkinson's disease through molecular docking analysis. World J Adv Res Rev. 2023;20:488–501.
37. Sonkar V, Jha SK, Tiwari S, Akarsh A, Priya S, Sharan P, et al. Characterization and explanation of the soil fertility state of Sakaldiha block in the Chandauli District of Uttar Pradesh's industrial area. World J Adv Res Rev. 2023;18:63–72.
38. Singh NK, Sengar AS, Jha SK. A review of Ayurvedic measures for preventing COVID-19 and promoting health during pregnancy. J Indian Syst Med. 2024;12(2):61–5.
39. Trivedi LM, Saxena S, Sharma S, Beniwal M, Jha SK, Rao AK, et al. Characterization, profiling, and molecular docking analysis of phytochemicals derived from *Daucus carota* for evaluating their potential role in cardiovascular disease assessment. World J Adv Res Rev. 2023;20:159–75.
40. Mehta V, Zargar AA, Attri P, Jha SK. Bagging the role of herbal drugs in the management of cervical cancer. Ayush J Integr Oncol. 2025;2(1):35–43.
41. Chauhan S, Jha SK, Tamta A, Sharma V, Kumar C, Lohiya G, et al. Descriptive analytical study based on profiling, morphological, pomological and pharmacological traits to identify the genotypes of the promising mango *Mangifera indica* L. World J Adv Res Rev. 2023;19:1544–53.
42. Tamta, Arnima, and Sudhanshu Kumar Jha. "Screening of Germplasms and Population Dynamics of Major Insect Pests of Spring Green Gram Vigna radiata (Linn.)." PhD diss., Doctoral Dissertation, Doctoral Dissertation, GB Pant University of Agriculture and Technology, Pantnagar-263145 (Uttarakhand).
43. Kumar R, Verma H, Ali M, Midha T, Kumar D, Jha SK. Review of mitigating cancer risk through Ayurvedic practices: A holistic approach to combating sedentarism. Ayush J Integr Oncol. 2025;2(2):86–90.
44. Patel S, Singh S, Gupta AK, Dalimbe AY, Muthoju SM, Pawar AR, et al. Ayurveda and common Indian spices: A natural alternative for cancer therapy. Ayush J Integr Oncol. 2025;2(2):91–102.

45. Jha KT. Stereoisomerism in chemistry and drug development: Optical, geometrical, and conformational isomers. 2025.
46. Jha SK, Gupta A, Huddar VG. Botanical breakthroughs: The growing impact of plant-derived compounds in cancer treatment. Ayush J Integr Oncol. 2025;2(2):62–7.
47. Sharma A, Jha SK, Huddar VG. Integrative role of Ayurvedic phytochemicals in cancer treatment: Targeting signaling pathways, boosting chemosensitivity, and utilizing traditional therapeutics. Ayush J Integr Oncol. 2025;2(2):77–85.
48. Jha SK, Charde V, Kumar V, Narasimhaji CV. Vitiligo treatment with natural bioactive: A narrative review. Nat Prod J. 2026;16(3):e22103155337960.
49. Zargar AA, Mehta V, Gupta R, Bhandari K, Sharma MC, Balaji P, et al. Incretin hormones: Mechanisms, therapeutic implications, and future directions in glucose regulation and diabetes management. Curr Proteom. 2025;22:100014.
50. Doshi R, Lohiya G. Synthesis, in-silico design and spectral characterization, elucidation of *Cannabis sativa* L. (Cannabaceae) containing phytoconstituents demonstrating novel therapeutic efficacy against epilepsy.
51. Shrivastav S, Tyagi R, Singh M, Jha S. The effectiveness of curcumin on dysmenorrhea. Int J Med Sci Pharma Res. 2022;8(4):8–12.
52. Sharma S, Yadav C, Chawla S, Jha SK. Beyond chemotherapy: Exploring the potential of phytomedicine in oncology. Ayush J Integr Oncol. 2025;2(3):133–45.
53. Badal R, Ranjan S, Jha SK, Kumar L, Patel AK, Yadav P, et al. GC-MS/MS and HR-LCMS-QTOF analysis of various extracts of Saraswata Ghrita: A comprehensive dataset on phytochemical compounds. Data Brief. 2025;61:111675.
54. Ahlawat A, Chauhan S, Antil I, Jha SK, Huddar VG. Examining the impact of the microbiome on cancer immunotherapy outcomes: A review. Ayush J Integr Oncol. 2025;2(3):118–24.
55. Gupta AJ, Huddar VG, Jha SK, Soni U. Traditional wisdom in modern oncology: Ayurvedic pain relief and supportive care. Ayush J Integr Oncol. 2025;2(3):178–87.
56. Sandrepogu J, Khandelwal P, Tiwari SK, Jha SK, Chauhan S, Sharma H, et al. A holistic paradigm for cancer care: Merging Ayurveda with contemporary oncology. Ayush J Integr Oncol. 2025;2(4):254–61.
57. Antil I, Bangarwa S, Jha SK, Gupta AJ, Soni U, Huddar VG, et al. Exploring the chemopreventive and anticancer effects of green tea. Ayush J Integr Oncol. 2025;2(3):158–68.
58. Attri P, Zargar AA, Mehta V, Mushtaq SU, Jha SK, Soni U. Genetic basis of cancer: Harnessing natural remedies for therapeutic potential. Ayush J Integr Oncol. 2025;2(3):188–94.
59. Chauhan S, Jha SK, Huddar VG, Ahlawat A, Sharma S, Tripathi A, et al. Targeting cancer at the molecular level: A biochemical and medicinal chemistry approach. Ayush J Integr Oncol. 2025;2(3):169–77.
60. Pandey JK, Verma SK, Kumar J, Perwej Y, Jha SK, Panchal BY, et al. Transformative role of advanced neural computation in clinical image diagnostics: A review of key concepts and applications. Semin Ultrasound CT MR. 2026;47(5):374–90.
61. Sharma H, Mahto RR, Jha SK, Chauhan S, Khandelwal P, Tiwari SK. Rasayana-based adjuvant strategies in cancer care: An Ayurvedic-oncologic perspective. Iran J Blood Cancer. 2025;17(4):35–68.
62. Raj H, Sharma S, Tripathi A, Huddar VG, Jha SK. Herbal medicine in cancer therapy: A comprehensive review of phytoconstituents, mechanisms, and clinical applications. Ayush J Integr Oncol. 2025;2(3):146–57.
63. Shamim PT, Khatri N, Yadav AK, Mishra B, Khan MR, Behera SK, et al. Role of human chorionic gonadotropin in frozen-thawed embryo transfer cycles for secretory transformation: A narrative review. Eur Chem Bull. 2023;12(8):5477–93.
64. Mandal P, Kumar J, Bora D, Hashmi SA, Tiwari M, Gupta R, et al. Literature review on forensic implications of illicit drug metabolism: A medicinal chemistry perspective. J Forensic Leg Med. 2026;103158.
65. Kumar C, Chauhan P, Chauhan S, Jha SK, Lohiya G. Phyto-pharmacognostic experimental study of *Epimedium sagittatum* and *Gloriosa superba* L. for the treatment of hypogonadism. Int J Innov Sci Res Technol. 2023;8(6):254–60.
66. Raj H, Jha SK, Negi M, Khandelwal P, Chauhan S, Sharma H, et al. Integrative oncology: A comprehensive comparative analysis of herbal and allopathic medicine in cancer treatment. Curr Pharm Res. 2025;1:427–35.
67. Dhiman S, Thakur N, Dwivedi PC, Pande P, Jha SK, Lohiya GV. Phytochemicals: Investigating bioactive compounds for antifungal uses and quality issues in functional foods and therapeutics. 2024:258–68.
68. Singh V, Mandal P, Kaur N, Bora D, Gupta R, Kumar A, et al. Synthesis, characterization, and binding interactions of rhodanine-3-acetic acid-based compound for latent fingerprint development. J Forensic Sci. 2026;71(1):584–92.
69. Jha SK, Chaturvedi SK, Singh SK, Chauhan S, Chauhan P, Singh H, et al. Synthesis and in-silico design of a novel silver metal ciprofloxacin compound. World J Adv Res Rev. 2023;18(1):885–92.
70. Mahto RR, Bansal KS, Soni H, Tiwari SK, Sandrepogu J, Bhatted SK. Efficacy of Vidangadi Loha and Phalatrikadi

Ghana Vati with and without the prior administration of Virechana Karma in Madhumeha (obese diabetic): A randomized controlled trial. Int J Drug Deliv Technol. 2026;16(41s):1275–81.

71. Shivani, Thakur N, Lohiya GV, Gupta R, Dhiman S, Bharadwaj S, et al. Natural origins, bioavailability and therapeutic potential of astaxanthin: A systematic review across diverse health applications. 2024:5929–39.
72. Tamta A, Jha SK. Implications of green technology for climate change mitigation minimizing waste and pollution. TIDEE. 2023;22(4):476.
73. Kaur AK, Venkatasubramanian H, Sarma S, Gupta R, Singh RG, Chaudhary B, et al. Targeting cancer pathways with phytochemicals: Molecular mechanisms and clinical potential. Curr Proteom. 2026;23(6):100182.
74. Patel S, Paliwal A, Jha SK, Singh R, Mishra AK. Environmental neurotoxicants as accelerators of brain ageing: Exposomic mechanisms linking pollution to amyloidogenesis and Alzheimer's disease. Int J Environ Health Res. 2026:1–21.
75. Dhiman S, Thakur N, Jha SK, Karkare P, Bora D, Sahu RK, et al. Pyrazole derivatives: A comprehensive review of synthesis, antimicrobial activity, structure-activity relationships, and therapeutic potential. Curr Proteom. 2026;23(5):100154.
76. Mundada AB, Mundada PA, Kathirvel S, Kumar PR, Krishnamoorthy P, Ezzaoui N, et al. Ion channels as emerging drug targets: Pharmacological insights and therapeutic advances. Curr Proteom. 2026;23(4):100141.
77. Midha T, Kumar D, Kumar A, Jha SK. Rasayana therapy in Ayurveda: A promising approach for cancer support and immunomodulation. [Publication details required].
78. Garg N, Sharma R, Bhojani MK, Rai S, More AB, Jha SK. Bridging traditional wisdom and modern science: An integrative approach to breast cancer care. Ayush J Integr Oncol. 2026;3(2):81–9.
79. Jha SK, Negi M, Singh K, Shukla D, Sharma H, Khandelwal P, et al. Harmonizing traditional Ayurvedic knowledge with modern science: A comprehensive review. Curr Pharm Res. 2026:393–410.
80. Antil I, Jha SK, Negi M, Sharma H, Tiwari SK. Baicalein from *Scutellaria baicalensis* as natural therapeutic agent for glioblastoma. Curr Pharm Res. 2025;1:411–26.
81. Mahto RR, Sharma H, Bhatted SK, Jha SK, Tiwari SK, Chauhan S, et al. Diabetes and erectile dysfunction: Exploring the Ayurvedic understanding of Madhumehaj Klaibya. Curr Pharm Res. 2026:446–57.
82. Gangurde RB, Goel P. Approach towards type 2 diabetes mellitus-induced erectile dysfunction (DMED): A case study.
83. Baghel JS, Maheshwari RK. Novel application of mixed solvency concept in the development of fast dissolving solid dispersion of poorly water-soluble drug, torsemide and its evaluations. World J Pharm Res. 2020;9(1):1820-1839. doi:10.20959/wjpr20201-16587.
84. Maheshwari RK, Jain S, Padria A, Mulani P, Baghel JS, Maheshwari N. Eco-friendly extraction using solids: a novel application of mixed solvency concept. J Drug Deliv Ther. 2019;9(2):244-249. doi:10.22270/jddt.v9i2.2409.
85. Kushwah P, Jain G, Patidar A, Baghel JS, Agarwal A. From ancient remedies to modern marvels: unveiling the medicinal secrets of Nyctanthes arbor-tristis and Piper betle Linn. leaves - a comprehensive review. Int J Pharm Sci Med. 2023;8(12):11-24. doi:10.47760/ijpsm.2023.v08i12.002.