Flavonosomes: A Systematic Review on Formulation Development, Analytical Characterization and Therapeutic Performance

Siddhesh Santosh Bandekar[1], Vrushali Vijay Patil[2], Raj Deelip Mayanna[3], Tanay Aniket Bhingurde[4], M. S. Palled Shailendra Sanjay Suryawanshi[5]

[1,2,3,4,5]*Department of Pharmaceutical Analysis, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India*

Abstract*— Flavonoids are natural polyphenolic compounds with diverse pharmacological properties, including antioxidant, anti-inflammatory, anticancer, cardioprotective, and antimicrobial effects. However, their therapeutic application is limited by poor aqueous solubility, low chemical stability, rapid metabolism, and minimal oral bioavailability. Flavonosomes, phospholipid-based vesicular systems, have emerged as a promising strategy to overcome these limitations. These complexes enhance flavonoid stability, improve membrane permeability, and provide controlled release, resulting in superior bioavailability and therapeutic performance compared to free flavonoids. This review consolidates current knowledge on the formulation development, pre-formulation considerations, analytical characterization, and evaluation parameters of flavonosomes, with particular emphasis on Indian research contributions. Preparation methods such as solvent evaporation, thin film hydration, anti-solvent precipitation, and supercritical fluid-assisted techniques are discussed, highlighting their influence on particle size, entrapment efficiency, and stability. Analytical tools, including spectroscopic, thermal, crystallographic, and chromatographic techniques, are employed to confirm flavonoid–phospholipid interactions and ensure quality control. Preclinical studies demonstrate that flavonosomes enhance in vitro and in vivo antioxidant, anti-inflammatory, anticancer, and antimicrobial activities, outperforming unformulated flavonoids. Despite their potential, challenges remain in reproducibility, scale-up, analytical standardization, stability, and the lack of clinical evidence. Future perspectives focus on targeted delivery, stimuli-responsive systems, green formulation strategies, and advanced chemometric analyses to facilitate clinical translation. Collectively, flavonosomes offer a versatile platform to optimize flavonoid delivery, bridging the gap between preclinical efficacy and therapeutic application.

***Index Terms*— Analytical Characterization, Bioavailability, Flavonoids, Flavonosomes, Drug Delivery.**

I. INTRODUCTION

Flavonoids are a large class of naturally occurring polyphenolic compounds widely distributed in fruits, vegetables, herbs, and medicinal plants. Chemically, they consist of a 15-carbon skeleton arranged as C6–C3–C6, comprising two aromatic rings (A and B) connected through a heterocyclic pyran ring (C) [1]. Flavonoids are generally subclassified into flavones, flavonols, flavanones, isoflavones, flavanols (catechins), anthocyanins, and chalcones, each differing in their degree of oxidation and substitution patterns on the ring structures, which influence their biological activities. These compounds exhibit diverse and potent therapeutic properties, including antioxidant, anti-inflammatory, anticancer, cardioprotective, neuroprotective, and antimicrobial effects. Preclinical studies demonstrate that flavonoids modulate multiple signalling pathways, such as kinases, receptor tyrosine kinases, and nuclear receptors, contributing to their broad pharmacological potential [2].

Indian research on flavonoids like quercetin and curcumin underscores these advantages, reporting significant antioxidant and anti-inflammatory bioactivities in experimental models [3]. Despite these benefits, the clinical application of flavonoids is severely constrained by poor water solubility, limited chemical stability, low intestinal permeability, rapid metabolism, and generally poor oral bioavailability [4–6]. Most flavonoids exhibit low solubility in

aqueous media and undergo extensive first-pass metabolism, leading to minimal systemic exposure after oral administration [4]. These pharmacokinetic limitations restrict the therapeutic levels achievable in target tissues, reducing the translational impact of flavonoid therapy [5,6]. To address these challenges, advanced drug delivery strategies have been explored. Among them, flavonosomes have emerged as a promising platform. Flavonosomes are phospholipid-based vesicular systems designed to encapsulate flavonoids and enhance their physicochemical properties, protecting them from premature degradation, improving membrane permeability, and increasing bioavailability. They can also provide controlled release and improved therapeutic performance compared to conventional formulations of free flavonoids [7,8].

Indian studies on flavonosome formulations co-loading flavonoids such as kaempferol and curcumin have reported improved stability and enhanced antioxidant activity, highlighting the potential of this approach in phytopharmaceutical delivery [7]. The rationale of this systematic review is to synthesize existing knowledge on the formulation development, analytical characterization, and therapeutic performance of flavonosomes, with a view toward understanding their design principles, evaluation strategies, and translational prospects in improving flavonoid delivery.

II. METHODOLOGY

A structured literature review was conducted to gather and analyze research on flavonosomes, focusing on formulation, characterization, evaluation, and therapeutic performance [24]. Databases including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched using keywords such as “flavonosomes,” “flavonoid phospholipid complex,” “phytosome,” “flavonoid delivery,” “formulation,” and “bioavailability” [25]. Both preclinical and clinical studies, review articles, and Indian research publications were considered. Inclusion criteria encompassed studies providing experimental, mechanistic, or translational insights into flavonosome preparation and evaluation, while non-scientific articles, duplicates, and studies lacking methodological clarity were excluded [26]. Data were extracted on formulation strategies, analytical techniques, evaluation parameters, and therapeutic outcomes. Study quality was assessed based on experimental design, reproducibility, and relevance [27]. This approach enabled a concise, evidence-based synthesis of flavonosomal research, highlighting advances, challenges, and future perspectives in flavonoid delivery.

III. CHEMISTRY OF FLAVONOIDS RELEVANT TO FLAVONOSOME DESIGN

Flavonoids have a C6–C3–C6 structure with multiple functional groups that influence their interaction with delivery systems such as phospholipid complexes [8, 9]. Hydroxylation and glycosylation significantly affect polarity, solubility, and hydrogen bonding capacities of flavonoids; glycosylated forms generally show increased hydrophilicity compared to aglycones [10]. Key physicochemical properties including pKa, log P, and aqueous solubility determine their membrane permeability and formulation behaviour, with many flavonoids exhibiting low intrinsic solubility and moderate lipophilicity, challenging conventional delivery [11]. In phospholipid complexes, hydrogen bonds and van der Waals interactions between flavonoid hydroxyl groups and phospholipid polar head groups drive stable assembly, enhancing solubility and bioavailability [12].

IV. PRE-FORMULATION CONSIDERATIONS IN FLAVONOSOMES

Pre-formulation studies are essential to understand how flavonoids behave before formulation into flavonosomes. One of the primary focuses is solubility and partition coefficient, as these parameters dictate how well a flavonoid can interact with phospholipids and ultimately be absorbed in vivo. Phospholipid complexation often enhances both aqueous and lipid solubility compared to the pure compound, improving dissolution and potentially bioavailability [13, 14]. Enhanced solubility and favourable partitioning into n-octanol typically indicate improved membrane permeability and better in vivo performance. Drug–excipient compatibility is another key aspect of preformulation. The interaction between the flavonoid and lipid excipients must be evaluated to ensure complex formation without degradation. Techniques like Fourier Transform Infrared Spectroscopy (FTIR)

and Differential Scanning Calorimetry (DSC) can reveal molecular interactions and confirm complexation with phospholipids, as well as detect any unwanted interactions. These analyses also provide insight into how stable the flavonoid–lipid combination remains under formulation conditions. The selection of phospholipids and solvents is driven by the solubility characteristics of both the flavonoid and the carriers. Phosphatidylcholine from soy or egg lecithin is commonly used due to its amphiphilic nature, facilitating strong hydrogen bonding and van der Waals interactions with flavonoids [15]. Solvent choice influences the efficiency of complex formation and residues, with solvents like ethanol, acetone, or tetrahydrofuran often preferred for efficient phospholipid dissolution and minimal toxicity. Finally, solid-state and thermal behavior of flavonoids and their complexes are evaluated to assess crystallinity and stability. Changes in melting point or disappearance of crystalline peaks in DSC and XRD analyses suggest successful complexation and potential improvement in solubility and stability [16].

V. FORMULATION DEVELOPMENT OF FLAVONOSOMES

Principles of Flavonosome Formation

Flavonosomes are lipid-based complexes in which flavonoid molecules become associated with phospholipid carriers through a combination of hydrophobic interactions and molecular entrapment within lipid bilayers or monolayers. The design principle aims to improve solubility, protect the bioactive compound from degradation, and enhance membrane permeability, ultimately leading to increased bioavailability. Successful formulation depends on choosing compatible flavonoids and phospholipids that can interact efficiently under controlled conditions [17].

Preparation Techniques

Several preparation methods are used to generate flavonosomes:

a) Solvent Evaporation: In this widely used method, the flavonoid and phospholipid are co-dissolved in organic solvents such as ethanol or dichloromethane. Upon evaporation of the solvent, a thin film forms on the flask surface. Hydration of this film under controlled stirring produces vesicular flavonosome structures. This approach was adapted for quercetin phospholipid complexes in an Indian study, demonstrating effective complex formation and enhanced physicochemical properties [17].

b) Anti-Solvent Precipitation: This method involves dissolving the components in a suitable solvent, followed by introduction into an anti-solvent in which the components have minimal solubility. Rapid precipitation results in nanoparticulate complexes with narrow size distributions. Although simple and rapid, it requires careful optimization of solvent selection.

c) Thin Film Hydration: A variation of solvent evaporation, the thin film hydration technique uses a rotary evaporator to produce a dry lipid film that is subsequently hydrated with aqueous media to produce vesicles. This method is common in lipid-based phytozoa preparations.

d) Supercritical Fluid-Assisted Methods: Utilizing supercritical CO_2 as an antisolvent or extraction medium can yield highly uniform particles with minimal solvent residues. Control of temperature and pressure allows fine tuning of particle characteristics. However, this technique demands specialized equipment and expertise, limiting its current widespread use [17, 18].

Process Parameters Influencing Formulation Quality and Role of Surfactants, Cholesterol, and Stabilizers

Critical process variables such as solvent choice, temperature, hydration time, and stirring speed affect particle size, entrapment efficiency, and stability. Organic solvent evaporation temperature must be optimized to prevent thermal degradation of both flavonoid and lipid components. Additives like surfactants and cholesterol are often incorporated to stabilize vesicles, prevent aggregation, and modulate membrane fluidity. Surfactants can reduce surface tension during hydration, while cholesterol can provide rigidity to the lipid architecture, improving in-vitro stability and controlling release.

VI. ANALYTICAL CHARACTERIZATION OF FLAVONOSOMES

Accurate characterization is essential to confirm the successful formation of flavonosomes and to understand their structural and functional attributes.

Multiple analytical tools are employed to evaluate chemical bonds, thermal behavior, particle properties, and quantitative composition (Table 1).

1. Spectroscopic Techniques

FTIR (Fourier Transform Infrared Spectroscopy) is widely used to detect changes in functional group vibrations that occur when a flavonoid interacts with phospholipids. Shifts in characteristic peaks, especially of –OH and C=O groups, indicate hydrogen bonding and complex formation between the flavonoid and lipid moiety, as demonstrated in diosmin phospholipid complexes prepared in India. NMR (Nuclear Magnetic Resonance) provides detailed insights into molecular interactions by revealing changes in chemical environments of specific protons or carbons after complexation. Although specific Indian flavonosome studies using NMR are limited, similar Phyto phospholipid complex research highlights its role in confirming structural association. UV–Visible Spectroscopy aids in quantifying flavonoid content and monitoring release patterns. It is often used alongside other techniques to validate flavonoid incorporation into flavonosomes [19, 20].

2. Thermal and Crystallographic Analysis

Differential Scanning Calorimetry (DSC) examines thermal transitions of pure components versus complexes. A shift or disappearance of melting endotherms suggests interaction and reduced crystallinity, as observed in kaempferol-curcumin flavonosomes developed in India. X-Ray Diffraction (XRD) distinguishes crystalline from amorphous states; a loss of sharp peaks in flavonosomes compared to pure flavonoids indicates successful incorporation into the lipid matrix. Thermogravimetric Analysis (TGA) measures weight changes with temperature to assess thermal stability and decomposition patterns, useful for stability profiling of lipid-bound complexes [20].

3. Particle and Surface Characterization

Particle size, PDI, and zeta potential are determined using dynamic light scattering. Optimized flavonosomes typically exhibit nanometer-range sizes with low PDI, reflecting uniform distribution and good physical stability. Morphological analysis by SEM and TEM reveals surface shape and structure. Indian flavonosomes have shown mostly spherical and smooth surfaces, indicating consistent formulation quality.

4. Chromatographic and Hyphenated Techniques

HPLC and UHPLC are core tools for measuring flavonoid content, purity, and degradation products in flavonosome formulations. Indian analytical studies often develop and validate HPLC methods for flavonoid quantification as part of characterization workflows. LC–MS/MS allows precise marker quantification and structural confirmation of flavonoids within complex matrices, improving analytical reliability. Method validation is critical to ensure pharmaceutical quality and reproducibility of analytical results [21].

Table 1: Common Analytical Techniques Used for Flavonosomes

Technique	Application	Key Insights
FTIR	Detect functional group interactions, hydrogen bonding	Confirms flavonoid–phospholipid complex formation
NMR	Molecular interaction and structural confirmation	Reveals chemical environment changes of protons/carbons after complexation
UV–Visible	Flavonoid quantification and release monitoring	Monitors incorporation and sustained release patterns
DSC	Thermal transitions and crystallinity	Shifts/disappearance of melting endotherms indicate complex formation
XRD	Crystallographic analysis	Loss of sharp peaks indicates successful incorporation into lipid matrix
TGA (Thermogravimetric Analysis)	Thermal stability and decomposition	Assesses weight changes with temperature
HPLC / UHPLC	Quantification and purity analysis	Measures flavonoid content and degradation products
LC–MS/MS	Marker quantification and structural confirmation	Provides precise identification and accurate quantification of flavonoids

VII. EVALUATION PARAMETERS OF FLAVONOSOMES

After formulation, flavonosomes must be evaluated thoroughly to confirm their quality, performance, and potential for therapeutic use. Several key parameters are routinely assessed in this stage (Table 2) [22].

1. Entrapment Efficiency and Drug Loading

Entrapment efficiency (%EE) reflects how effectively the flavonoid molecules are incorporated into the flavonosome matrix. It is calculated by determining the amount of flavonoid that remains un-entrapped in the dispersion medium and subtracting that from the total amount used in formulation. In an Indian study on kaempferol and curcumin flavonosomes, %EE for the best formulation (F4) was found to be 94.12%, indicating a high level of incorporation into the lipid complex. Efficient drug loading is essential for maximizing dose delivery and for predictable release behavior.

2. In-Vitro Dissolution and Release Kinetics

In-vitro release profiles are studied to understand how flavonoids are released from flavonosomes over time. Dialysis methods combined with UV–visible spectrophotometry is commonly used in Indian research to monitor release over several hours. In the same kaempferol–curcumin flavonosome study, flavonoids exhibited a sustained release pattern, with near-complete release over 12 h, demonstrating controlled release behavior which may enhance bioavailability and reduce dosing frequency.

3. Stability Studies (Physical, Chemical, and Accelerated)

Stability testing is conducted under standard and accelerated conditions to ensure that flavonosomes maintain their size, structure, and payload over time. After three months under accelerated ICH conditions, the optimized flavonosome formulation showed minimal changes in particle size, suggesting good physical stability. Stability studies also monitor changes in drug content and visual appearance to detect any chemical degradation or phase separation.

4. In-Vitro Permeation and Absorption Models

Although direct flavonosome permeation studies are limited in Indian literature, ex-vivo intestinal models are often used for related phytosome systems to evaluate how lipid complexation enhances intestinal uptake compared with crude extracts. Enhanced permeation across lipid barriers correlates with improved in-vivo absorption and bioavailability predictions.

VIII. THERAPEUTIC PERFORMANCE OF FLAVONOSOMES

1. Enhancement of Bioavailability and Pharmacokinetics

One of the main goals in developing flavonosomes is to improve the bioavailability and pharmacokinetic profile of poorly absorbed flavonoid compounds. Indian researchers have demonstrated that complexation of flavonoids with phospholipids significantly enhances absorption into systemic circulation compared with the free compouns. This enhancement is primarily due to the amphiphilic nature of the phospholipid complex, which facilitates better integration into biological membranes and protection from early metabolic degradation [23].

2. In-Vitro Bioactivity Studies

Flavonosomes exhibit potent biological activities in vitro that often surpass their unformulated counterparts. Formulated flavonosomes show stronger free radical scavenging effects than free flavonoids, suggesting enhanced therapeutic potential. In studies where flavonoids were complexed into phytosome-like structures, antioxidant activity was significantly improved, likely due to improved interaction with assay substrates and sustained release over time. Enhanced anti-inflammatory effects have also been observed, as flavonosomes can maintain higher intracellular concentrations of bioactive flavonoids, supporting stronger inhibition of inflammatory pathways compared to free forms. This property has been documented in formulations showing better inhibition of radical-induced inflammation relative to non-formulated flavonoids [23].

3. In-Vivo Pharmacological Evaluations

Animal studies on flavonoid phospholipid complexes have demonstrated improved therapeutic outcomes compared with free flavonoids. In liver injury models, formulations of curcumin and naringenin enhanced antioxidant enzyme levels and reduced markers of

tissue damage more effectively than the native compounds, evidencing better in-vivo performance [23].

Table 2: Parameters in Flavonosome Formulation and Evaluation

Parameter	Description	Impact on Formulation / Performance
Solubility & Partition Coefficient	Determines flavonoid compatibility with lipids	Enhances dissolution, absorption, and bioavailability
Drug–Excipient Compatibility	Interaction between flavonoid and phospholipids	Ensures stable complex formation, avoids degradation
Phospholipid & Solvent Selection	Choice of lipid and solvent system	Affects entrapment efficiency, particle size, and stability
Particle Size & PDI	Nanometer range size and distribution	Influences cellular uptake, stability, and release kinetics
Zeta Potential	Surface charge of vesicles	Determines colloidal stability and aggregation tendency
Entrapment Efficiency	Amount of flavonoid incorporated into vesicles	Reflects delivery potential and dose predictability
In Vitro Release & Kinetics	Flavonoid release over time	Sustained release enhances bioavailability
Stability Studies	Physical, chemical, and accelerated conditions	Determines shelf-life and formulation robustness
Therapeutic Performance	Antioxidant, anti-inflammatory, anticancer, antimicrobial	Confirms efficacy compared to free flavonoids

IX. CHALLENGES, LIMITATIONS, AND RESEARCH GAPS

Despite the promise of flavonosomes in improving flavonoid delivery, several key challenges and limitations must be acknowledged to guide future research and eventual clinical translation.

1. Reproducibility and Scalability Issues

Reproducibility of flavonosome manufacturing is a major concern. Laboratory-scale methods like solvent evaporation or thin film hydration can yield batch-to-batch variability in particle size, entrapment efficiency, and release profiles. Indian research on flavonosomes, such as the kaempferol–curcumin system, highlighted challenges in achieving uniform particle sizes across batches, which directly affects therapeutic performance [30]. Additionally, the lack of standardized protocols makes direct comparison between studies difficult, reducing confidence in reproducibility and slowing progress toward commercialization.

2. Lack of Clinical Data

One of the most pressing gaps in flavonosome research is the absence of robust clinical evidence demonstrating safety and efficacy in humans. While preclinical models and in-vitro studies suggest enhanced bioavailability and activity, very few flavonoid-based lipid carriers have advanced to clinical trials, and none specifically focus on flavonosomes [13]. The limited clinical research on flavonoid delivery systems reflects broader trends in natural product therapeutics: low systemic exposure, wide variability in individual responses, and limited standardized dosing regimens in trials [1].

3. Analytical Standardization Constraints

Analytical characterization of flavonosomes is complicated by the complex nature of the lipid–flavonoid matrix. Methods such as particle sizing, spectroscopic analysis, and chromatographic quantification often vary between laboratories, leading to inconsistent reporting of key quality attributes like drug loading, stability, and release kinetics. For example, different HPLC conditions for flavonoid quantification can yield inconsistent results, making cross-study comparisons difficult. Furthermore, lack of universally accepted reference standards and validated analytical procedures hampers regulatory acceptance and quality control, echoing observations in phytopharmaceutical quality research [7].

4. Stability and Storage Concerns

Flavonosomes, while designed to enhance flavonoid stability, are themselves susceptible to physical and chemical degradation. Exposure to heat, light, oxygen, and moisture can degrade both the phospholipid carriers and the flavonoid payload, leading to reduced efficacy over time. Indian phytosome studies have documented changes in particle size and entrapment efficiency under accelerated stability conditions, underscoring the need for careful optimization of formulation and packaging [34].

X. FUTURE PERSPECTIVES

While challenges remain, several emerging directions and technologies offer promising pathways for advancing flavonosomes toward practical therapeutic applications. Emerging analytical technologies such as hyphenated techniques, high-resolution NMR, and chemometric modelling promise deeper insights into flavonosome structure, composition, and performance. These tools can help delineate the relationship between formulation variables and therapeutic outcomes, enabling predictive optimization. Targeted delivery holds significant promise for enhancing therapeutic specificity and minimizing systemic side effects. Incorporation of targeting ligands or stimuli-responsive moieties that release payloads in response to pH, temperature, or enzymes could increase accumulation at disease sites. While such strategies have been more widely studied in liposomal systems [21], their adaptation to flavonosomal platforms could dramatically enhance efficacy in cancer, inflammation, or infection models. For flavonosomes to move into clinical practice, comprehensive translational strategies are required. This includes robust preclinical toxicology studies, standardized pharmacokinetic profiling, and carefully designed human trials to assess safety and efficacy. Collaboration with regulatory bodies will be critical to define acceptable quality criteria, dosing guidelines, and risk–benefit assessments. Market experiences with related lipid carriers such as liposomes suggest that clinical translation is achievable, but requires systematic optimization and validation [8].

XI. CONCLUSION

Flavonosomes represent a significant advancement in the delivery of flavonoid bioactives, addressing major limitations of conventional formulations such as poor solubility, low bioavailability, and rapid metabolic degradation. By leveraging phospholipid-based complexes, these vesicular systems enhance flavonoid stability, facilitate membrane permeation, and provide sustained release, thereby improving therapeutic efficacy. Indian research highlights their potential in antioxidant, anti-inflammatory, anticancer, and antimicrobial applications, demonstrating superior performance compared to free flavonoids. Despite these advantages, challenges remain, including reproducibility, scalability, analytical standardization, stability, and the lack of robust clinical evidence. Addressing these limitations will require optimized formulation strategies, standardized evaluation protocols, and comprehensive preclinical and clinical studies. Emerging approaches such as targeted delivery, stimuli-responsive systems, green formulation techniques, and advanced analytical tools offer promising directions for future research. Overall, flavonosomes hold considerable potential to transform flavonoid-based therapies, bridging the gap between preclinical promise and clinical application. Strategic efforts in formulation design, characterization, and translational evaluation can enable their progression toward safe, effective, and commercially viable therapeutic platforms, maximizing the pharmacological benefits of flavonoids.

XII. ABBRIVIATIONS

FTIR: Fourier Transform Infrared Spectroscopy; NMR: Nuclear Magnetic Resonance; UV–Vis: Ultraviolet–Visible Spectroscopy; DSC: Differential Scanning Calorimetry; XRD: X-Ray Diffraction; TGA: Thermogravimetric Analysis; HPLC: High-Performance Liquid Chromatography; UHPLC: Ultra-High-Performance Liquid Chromatography; LC–MS/MS: Liquid Chromatography–Tandem Mass Spectrometry; PDI: Polydispersity Index; %EE: Percent Entrapment Efficiency; QbD: Quality by Design; ICH: International Council for Harmonisation; CO_2: Carbon Dioxide.

Conflicts of Interest: The authors declare no conflicts of interest, financial or otherwise.

Funding: Nil
Ethics Approval and Consent to Participate: Not applicable.
Consent for Publication: Not applicable.

ACKNOWLEDGEMENTS

The authors express heartfelt gratitude towards the Principal Dr. Sunil S. Jalalpure, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, for providing constant guidance and support.

REFERENCES

[1] M. D. Dere and A. A. Khan, "Potentials of encapsulated flavonoids in biologics: A review," American Journal of Biomedical and Life Sciences, vol. 8, no. 4, pp. 97–113, 2020.

[2] K. Thombre et al., "The natural flavone quercetin: An extensive analysis of its pharmacological mechanisms and medicinal prospects," Indian Journal of Pharmacy and Pharmacology, vol. 11, no. 4, pp. 185–194, 2024.

[3] P. Kumar, P. Kumar, and N. P. Jain, "Preparation, characterization and evaluation of antioxidant flavonosomes," Journal of Drug Delivery and Therapeutics, vol. 14, no. 6, pp. 114–120, 2024.

[4] M. Ferreira, D. Costa, and Â. Sousa, "Flavonoids-based delivery systems towards cancer therapies," Bioengineering (Basel), vol. 9, no. 5, p. 197, 2022.

[5] R. Costa, S. A. Costa Lima, P. Gameiro, and S. Reis, "On the development of a cutaneous flavonoid delivery system: Advances and limitations," Antioxidants (Basel), vol. 10, no. 9, p. 1376, Aug. 2021.

[6] D. J. Kanojiya et al., "Flavonoids: A class of polyphenols with diverse anti-inflammatory activities and mechanisms," Pharmacognosy Research, vol. 17, no. 3, pp. 755–768, 2025.

[7] V. Dhakad, U. S. Narwaria, and S. Jain, "Formulation and evaluation of flavoursome encapsulated with sesamol and curcumin," Journal of Neonatal Surgery, vol. 14, Suppl., p. 6611, 2025.

[8] R. Tiwari, M. S. Bhadouria, and A. K. Kondalkar, "Development and characterization of flavonosome formulation loaded with hesperidine and berberine," National Journal of Pharmaceutical Sciences, vol. 5, no. 2, pp. 55–60, 2025.

[9] "Flavonoid," [Online]. Available: https://en.wikipedia.org/wiki/Flavonoid. Accessed: Mar. 31, 2026.

[10] M. Sharafan et al., "Impact of structural modifications on flavonoid hydrophilicity and bioavailability," Applied Sciences, vol. 13, no. 15, p. 7101, 2023.

[11] M. Berga et al., "Flavonoids in the spotlight: Bridging the gap between physicochemical properties and formulation strategies," Pharmaceuticals (Basel), vol. 16, no. 10, p. 1407, 2023.

[12] H. Hashemzadeh et al., "The combination of polyphenols and phospholipids as an efficient platform for delivery of natural products," Scientific Reports, vol. 13, p. 2501, 2023, doi: 10.1038/s41598-023-29237.

[13] S. D. Pande and S. C. Dhawale, "Preparation and characterization of quercetin phytosome," International Journal of Drug Delivery Technology, vol. 15, no. 3, 2025.

[14] M. Peanparkdee and R. Yooying, "Enhancement of solubility, thermal stability and bio accessibility of vitexin using phosphatidylcholine-based phytosome," NFS Journal, vol. 31, pp. 28–38, 2023.

[15] J. Fan et al., "Application of Soluplus to improve the flowability and dissolution of baicalein phospholipid complex," Molecules, vol. 22, no. 5, p. 776, 2017.

[16] B. Kalita and B. N. Patwary, "Formulation and in vitro evaluation of hesperidin-phospholipid complex and its antioxidant potential," Current Drug Therapy, vol. 15, no. 1, pp. 28–36, 2020.

[17] M. S. Chavan et al., "Supercritical fluid drying in nanoparticle production and drug delivery," Asian Journal of Pharmaceutical Research and Health Care, vol. 17, no. 2, pp. 101–108, 2025.

[18] T. Amin and S. V. Bhat, "A review on phytosome technology as a novel approach to improve the bioavailability of nutraceuticals,"

International Journal of Advanced Research in Technology, vol. 1, no. 3, pp. 1–5, 2012.

[19] P. P. Udapurkar, O. G. Bhusnure, and S. R. Kamble, “Diosmin phytotomies: Development, optimization and physicochemical characterization,” Indian Journal of Pharmaceutical Education and Research, 2025.

[20] Semalty, M. Semalty, M. S. Rawat, D. Singh, and G. P. Joshi, “Phyto-phospholipid complex of catechin in value added herbal drug delivery,” Journal of Inclusion Phenomena and Macrocyclic Chemistry, vol. 73, no. 1, pp. 377–386, 2012.

[21] R. Sindhumol et al., “Enhanced pharmacokinetic profile and antioxidant activity of flavonoid phospholipid complexes compared to free flavonoids,” International Journal of Pharmacy and Pharmaceutical Sciences, vol. 2, no. 4, pp. 10–14, 2025.

[22] R. Costa, H. Oliveira, T. Silva, et al., “On the development of a cutaneous flavonoid delivery system: Advances and limitations,” Antioxidants (Basel), vol. 10, no. 9, p. 1376, 2021.

[23] S. Ranjbar et al., “Lipid-based delivery systems for flavonoids and flavonolignans: Liposomes, nanoemulsions, and solid lipid nanoparticles,” Pharmaceutics, vol. 15, no. 7, p. 1944, 2023.

[24] U. Harahap et al., “Current insights and future perspectives of flavonoids: A promising antihypertensive approach,” Phytotherapy Research, vol. 38, no. 6, pp. 3146–3168, 2024.

[25] S. Kumar et al., “Regulatory considerations of herbal bioactive-based formulations,” in Herbal Bioactive-Based Drug Delivery Systems. Academic Press, 2022, pp. 419–436.

[26] K. Chettupalli et al., “Polyherbal formulations and phytosome-based delivery in diabetic wound healing: An integrative review,” Journal of Biomaterials Science, Polymer Edition, vol. 36, pp. 1–28, 2025.

[27] Y. F. Zverev and A. Y. Rykunova, “Modern nanocarriers as a factor in increasing the bioavailability and pharmacological activity of flavonoids,” Applied Biochemistry and Microbiology, vol. 58, no. 9, pp. 1002–1020, 2022.