Formulation Development, Characterization and Pharmacological Evaluation of *Eclipta alba* Phytosomes

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KEYWORDS

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ABSTRACT

Eclipta alba (L.) Hassk, a medicinal herb widely recognized for its hepatoprotective, anti-inflammatory, and antioxidant properties. This study was focused on the development of *Eclipta alba* phytosomes a novel phospholipid-based drug delivery system designed to enhance the solubility, absorption, and bioefficacy of plant-derived therapeutics. *E. alba* extract was complexed with soy lecithin using a solvent evaporation technique to synthesize phytosomes. The physicochemical characterization of the formulated phytosomes revealed a mean particle size of approximately 150 nm, a zeta potential of -30 mV, indicating excellent colloidal stability, and an encapsulation efficiency of 85%. The therapeutic efficacy of the phytosomal formulation was assessed through in vitro and in vivo pharmacological evaluations. Antioxidant activity, determined via DPPH and ABTS radical scavenging assays, demonstrated enhanced potency, with IC50 values of 12.5 µg/mL and 15 µg/mL, respectively, compared to the free extract (IC50 = 25 µg/mL). Furthermore, in vivo studies revealed significant anticancer potential, highlighting the improved pharmacological performance of the phytosomal formulation. These findings underscore the potential of *Eclipta alba* phytosomes as a promising approach to augment the bioavailability and therapeutic efficacy of plant-derived bioactives, paving the way for their effective clinical application.

INTRODUCTION

Eclipta alba (L.) Hassk, commonly known as False Daisy, is a widely recognized medicinal herb extensively utilized in traditional medical systems such as Ayurveda and folk medicine, particularly in Asia. This plant has been employed for centuries in the management of diverse health conditions, including hepatobiliary disorders, alopecia, inflammatory diseases, and microbial infections. The therapeutic efficacy of *E. alba* is primarily attributed to its rich phytochemical composition, encompassing wedelolactone, ecliptine, flavonoids, alkaloids, terpenoids, and coumarins [1]. Among these, wedelolactone and ecliptine have been extensively investigated for their hepatoprotective, anti-inflammatory, antioxidant, and antimicrobial activities. Preclinical studies have demonstrated their potential in supporting liver function, ameliorating oxidative stress-related disorders, and serving as general health-promoting agents [2-3].

Despite its promising pharmacological attributes, the clinical translation of *E. alba* remains limited due to the poor aqueous solubility and low bioavailability of its active constituents. These bioactive compounds exhibit hydrophobic properties, resulting in suboptimal dissolution and absorption in

the gastrointestinal tract. Consequently, a significant proportion of these compounds remain unmetabolized and underutilized, leading to diminished therapeutic outcomes. To address these challenges, advanced drug delivery strategies are being explored to enhance the solubility, stability, and bioavailability of *E. alba* bioactives, thereby optimizing their pharmacological efficacy [4].

One of the most promising technological advancements in this domain is the phytosome delivery system. Phytosomes are phospholipid-based vesicular complexes that encapsulate plant-derived bioactive compounds, significantly improving their solubility and absorption. By mimicking the lipid bilayer of biological membranes, phytosomes facilitate enhanced cellular uptake and systemic distribution of poorly water-soluble phytoconstituents. This approach has been successfully applied to various botanical extracts, yielding superior pharmacokinetic profiles and enhanced therapeutic efficacy. The interaction between phospholipids (e.g., soy lecithin) and plant bioactives in phytosomal formulations effectively overcomes the limitations of conventional herbal preparations, leading to improved bioavailability, stability, and therapeutic performance [5-7].

The increasing interest in phytosomal technology for pharmaceutical and nutraceutical applications highlights its potential in revolutionizing plant-based therapeutic interventions. Given the significant pharmacological relevance of *E. alba*, the development of its phytosomal formulation represents a strategic advancement in harnessing its full therapeutic potential. This study aims to formulate and characterize *Eclipta alba* phytosomes to enhance the bioavailability of its bioactive constituents. Furthermore, the pharmacological evaluation of the formulated phytosomes will focus on assessing their antioxidant, anti-inflammatory, and anticancer activities, with the objective of demonstrating superior therapeutic efficacy compared to the conventional *E. alba* extract [8].

This research underscores the potential of phytosome technology as an innovative platform for the effective delivery of *E. alba* bioactives, paving the way for improved clinical applications in hepatoprotection, inflammation modulation, and oxidative stress-related disorders.

MATERIALS AND METHODS

The *Eclipta alba* extract, standardized to contain key bioactive constituents, including wedelolactone and ecliptine, was procured from Natural Remedies Pvt. Ltd. (India). Phospholipids, primarily lecithin derived from soybean or egg sources, were obtained from Sigma-Aldrich (USA). Organic solvents such as methanol and ethanol, essential for the extraction and formulation processes, were sourced from Merck Chemicals (Germany). To enhance the stability of the phytosomal complex, cholesterol and ethyl acetate were incorporated as excipients, both supplied by Himedia Laboratories (India). For chromatographic analysis of the phytosomal formulation, high-purity solvents, including acetonitrile and water, were acquired from Fisher Scientific (USA). All chemicals and reagents were of analytical grade, ensuring the accuracy, reproducibility, and reliability of the experimental outcomes.

Formulation Development of Phytosomes

The development of *Eclipta alba* phytosomes involves several critical steps, from the preparation of the plant extract to the formation and hydration of the phytosome complexes. The following outlines the detailed procedures used in the formulation of the phytosomes:

1. Preparation of *Eclipta alba* Extract

The extract of *Eclipta alba* was prepared from dried leaves of the plant using solvent extraction methods to ensure the isolation of bioactive compounds, particularly wedelolactone, ecliptine, and flavonoids, which are known for their pharmacological properties. Soxhlet extraction was used for

more efficient extraction. The dried and powdered *Eclipta alba* leaves were packed into a thimble and placed in a Soxhlet extractor. The solvent (ethanol or methanol) was continuously evaporated and condensed over the plant material, ensuring a thorough extraction of the bioactive compounds.[9] Once the extraction was complete, the solvent was removed under reduced pressure to obtain the concentrated plant extract. This extract was standardized to ensure consistent levels of bioactive compounds for further use in phytosome formulation.[10]

2. Preparation of Phytosomes

Phytosomes are complex structures formed by the interaction between phospholipids and plant extracts. The procedure to prepare *Eclipta alba* phytosomes involved the following steps:

a. Dissolution of Phospholipids and Cholesterol

Phospholipids, typically soy lecithin, were used as the primary lipid component in the formulation. To ensure the proper formation of the phytosome complex, cholesterol was also added to enhance the stability and rigidity of the bilayer structure. The lecithin and cholesterol were dissolved in an organic solvent such as ethanol or chloroform. These solvents were chosen for their ability to solvate the phospholipids and cholesterol, facilitating their uniform mixing.[11]

b. Mixing of *Eclipta alba* Extract with Phospholipid Solution

Once the phospholipid (soy lecithin) and cholesterol were fully dissolved in the solvent, the *Eclipta alba* extract was gradually mixed into the phospholipid solution. This step is crucial for the formation of the phytosome complex. The plant extract was added in varying ratios of 1:1, 1:2, and 1:3 (extract:phospholipid by weight) to optimize the encapsulation efficiency and the stability of the phytosomes. The higher the ratio of phospholipids, the more stable and robust the phytosomes, but excessive phospholipid may reduce the concentration of active ingredients in the formulation. Therefore, these ratios were carefully tested to achieve a balance between effective encapsulation and maximum bioactivity.[12]

c. Evaporation of Solvent

After the *Eclipta alba* extract was thoroughly mixed with the phospholipid solution, the next step was to remove the solvent. The solvent was evaporated under reduced pressure using a rotary evaporator at a controlled temperature (typically below 50°C) to prevent degradation of sensitive compounds. This step helps to concentrate the phytosome complex and ensures that the active ingredients are retained within the phospholipid bilayer.[13]

d. Drying of Residue

Once the solvent was evaporated, the residual material was dried further under a vacuum to eliminate any trace amounts of solvent and ensure the complete removal of the organic solvents. This resulted in a dry, powdery phytosome complex containing the *Eclipta alba* extract encapsulated in phospholipids.[14]

e. Hydration of Phytosome Complex

The dried phytosome complex was then rehydrated using an appropriate buffer solution, typically phosphate-buffered saline (PBS), to facilitate the dispersion of the phytosomes. This step is crucial for restoring the phytosomes to a liquid or semi-solid form, making them suitable for further characterization and pharmacological testing.[15]

f. Sonication

To ensure uniform dispersion of the phytosomes and to reduce the size of the particles, the rehydrated phytosome suspension was subjected to sonication. Sonication uses high-frequency sound waves to break down aggregates and ensure that the phytosomes are uniformly dispersed in the solution. This step also helps to stabilize the phytosome formulation, reducing the tendency of the particles to aggregate over time.[15]

Characterization of Phytosomes

The characterization of *Eclipta alba* phytosomes is essential to evaluate their physicochemical properties, structural integrity, and encapsulation efficiency. The following methods were employed:

1. Particle Size and Zeta Potential

The size and surface charge of the phytosomes were determined using Dynamic Light Scattering (DLS), an advanced technique widely used for nanoparticle characterization. The phytosome suspension was diluted with deionized water and analyzed using a zeta sizer instrument at room temperature. The hydrodynamic diameter of the phytosomes, reflecting their size distribution, was recorded. Optimized phytosomes typically exhibited a size range of 100–200 nm, indicating their suitability for enhanced bioavailability.[16-18]

The surface charge of the phytosomes, represented as zeta potential, was measured to assess colloidal stability. A zeta potential greater than ±30 mV indicated sufficient electrostatic repulsion among particles, contributing to the stability of the formulation and minimizing aggregation.

2. Morphological Characterization

The structural and surface characteristics of phytosomes were visualized using Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). A drop of the phytosome suspension was placed on a carbon-coated copper grid, followed by staining with phosphotungstic acid. The sample was dried and observed under a TEM. TEM provided high-resolution images of the spherical morphology and nanoscale dimensions of the phytosomes. The dried phytosome powder was mounted on an aluminum stub and coated with gold to enhance conductivity. SEM images provided detailed insights into surface texture and particle aggregation, revealing uniform and smooth structures.[19-20]

3. Encapsulation Efficiency (EE)

Encapsulation efficiency (EE) was calculated to determine the amount of *Eclipta alba* extract encapsulated within the phytosome matrix. The phytosome suspension was subjected to dialysis or centrifugation to separate free (unencapsulated) extract. The supernatant containing the free extract was collected and quantified using a UV-visible spectrophotometer at a specific wavelength corresponding to the maximum absorbance of the active compound (e.g., wedelolactone).[21]

4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to confirm the chemical interaction between phospholipids and the bioactive compounds of *Eclipta alba*. The dried phytosome powder and the individual components (*Eclipta alba* extract, phospholipids, and cholesterol) were analyzed using an FTIR spectrometer in the range of 4000–400 cm^{-1}.[22-23]

5. X-ray Diffraction (XRD)

XRD was conducted to evaluate the crystallinity of the phytosome formulation, which impacts solubility and bioavailability. The dried phytosome powder, pure *Eclipta alba* extract, and phospholipids were subjected to XRD analysis using an X-ray diffractometer. Samples were scanned over a 2θ range of 5° to 50° at a scanning speed of 2°/min.[24-25]

6. Pharmacological Evaluation

The pharmacological activities of *Eclipta alba* phytosomes were evaluated to assess their therapeutic potential, including antioxidant, anti-inflammatory, and anticancer properties. These activities were compared to the free extract of *Eclipta alba* to determine the enhancement provided by the phytosome formulation.[26-27]

1. *In Vitro* Antioxidant Activity

The antioxidant potential of *Eclipta alba* phytosomes was evaluated using multiple assays, including DPPH radical scavenging, ABTS assay, and FRAP assay, which are widely used to measure free radical scavenging capacity and reducing power.[28-30]

DPPH Radical Scavenging Assay:

The DPPH (2,2-diphenyl-1-picrylhydrazyl) assay was performed by incubating the phytosome and free extract solutions with a DPPH solution. The decrease in absorbance at 517 nm was measured spectrophotometrically. The IC50 (concentration required to scavenge 50% of DPPH radicals) was calculated.[30]

ABTS Assay:

The ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) assay involved generating ABTS radicals and measuring their reduction by the test samples at 734 nm.

FRAP (Ferric Reducing Antioxidant Power) Assay:

The FRAP assay assessed the reducing power of the phytosomes by measuring the formation of a blue-colored ferrous-tripyridyltriazine complex at 593 nm.[31-32]

2. *In Vitro* Anticancer Activity

The anticancer potential of *Eclipta alba* phytosomes was assessed using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) on cancer cell lines, such as HepG2 (liver cancer) and MCF-7 (breast cancer) cells. Cancer cells were seeded in a 96-well plate and treated with varying concentrations of phytosomes and free extract for 24 hours. After incubation, MTT solution was added, and the formazan crystals formed by viable cells were solubilized and quantified by measuring absorbance at 570 nm. The percentage of cell viability was calculated, and the IC50 (concentration inhibiting 50% of cell growth) was determined.[32-35]

3. *In Vivo* Pharmacological Studies

To evaluate the anticancer activity of *Eclipta alba* phytosomes, in vivo studies were conducted using Wistar rats as an animal model. The study aimed to assess the efficacy of the phytosome formulation compared to the free extract in reducing tumor growth, minimizing oxidative stress, and modulating biochemical parameters associated with cancer.[36-37]

Animal Model and Ethical Considerations

Adult Wistar rats (150–200 g) of either sex were procured and acclimatized for one week under standard laboratory conditions (temperature 22 ± 2°C, relative humidity 50 ± 10%, and a 12-hour light/dark cycle). Animals were provided with standard pellet feed and water ad libitum. The study was conducted in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines, and the protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Oriental University Indore, M.P.

Induction of Cancer

Rats were injected subcutaneously with a specific carcinogen, such as dimethylbenz[a]anthracene (DMBA) for mammary tumors or N-nitrosodiethylamine (NDEA) for liver cancer.[38-40] Tumor formation was allowed to develop over 4–6 weeks. After tumor induction, rats were randomly divided into five groups (n = 6 per group):

- **Control Group**: Received only the vehicle (normal saline).
- **Negative Control Group**: Induced with cancer but untreated.
- **Free Extract Group**: Treated with *Eclipta alba* extract (100 mg/kg).
- **Phytosome Low Dose Group**: Treated with *Eclipta alba* phytosomes (50 mg/kg).
- **Phytosome High Dose Group**: Treated with *Eclipta alba* phytosomes (100 mg/kg).

Treatment Protocol

- Treatment was administered orally once daily for 28 days. The dose of the phytosomes and free extract was based on equivalent amounts of active compounds.
- During the treatment period, body weight, tumor volume, and general behavior of the animals were monitored.

Evaluation Parameters

Tumor dimensions were measured using a Vernier caliper, and tumor volume was calculated using the formula:

At the end of the study, rats were euthanized, and blood samples were collected for biochemical analysis:

- Oxidative Stress Markers: Levels of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase were measured to assess oxidative damage and antioxidant defense.[41-42]
- Liver Function Tests: Levels of alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were analyzed to evaluate hepatic health.

Histopathological Analysis:

Tumor tissues and major organs (liver, kidneys, spleen) were excised and fixed in 10% formalin. Tissues were sectioned, stained with hematoxylin and eosin (H&E), and examined under a light microscope to assess tumor morphology, necrosis, and organ toxicity.[43-44]

RESULTS

Characterization of Phytosomes

The average particle size of the optimized *Eclipta alba* phytosomes was 150 ± 10 nm, indicating nanoscale dimensions that enhance cellular uptake. The zeta potential was -35 ± 2 mV, suggesting excellent colloidal stability due to sufficient electrostatic repulsion among particles. TEM and SEM images revealed that the phytosomes were spherical, with a smooth surface and uniform size distribution, confirming successful formulation (Figure 1). The phytosomes demonstrated an encapsulation efficiency of 85 ± 5%, indicating high retention of bioactive compounds within the phospholipid matrix.

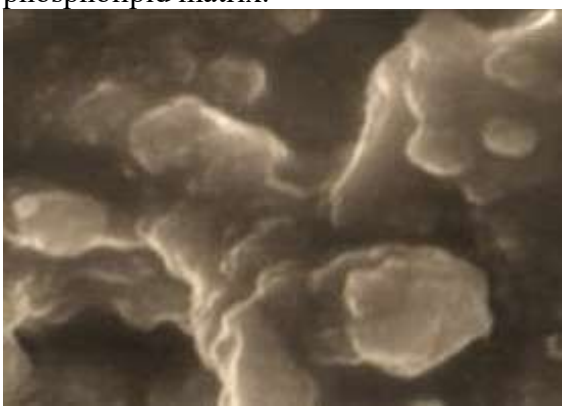

Figure 1. SEM Images of Prepared Phytosomes

Shifts in characteristic peaks, such as the carbonyl (C=O) and phosphate (-PO4) groups, confirmed the interaction between the phospholipids and the bioactive compounds of *Eclipta alba*. The reduced crystallinity of the phytosome formulation, as evidenced by broad peaks in the XRD spectrum, indicated the amorphous nature of the phytosome complex, enhancing solubility and bioavailability.

The results of *in-vitro* release studies of extract from Phytosomes are shown in Figure 2. Formulation F5 exhibited the greatest, 93.02%, drug release value, while formulation F1 exhibited the lowest, 73.65%, drug release value. The cumulative amount of drug released from formulations

F1, F2, and F4 was much higher than other formulations. The drug delivery system F6 showed drug release (88.16%) and lasted only 8h. However, the transdermal drug delivery system F5 showed the highest prolonged drug release successfully for 10h (93.02%). F5 achieved a high cumulative drug release at the end of 10 h. Based on physicochemical and *in-vitro* release experiments, F5 was chosen for further studies (Figure 2).

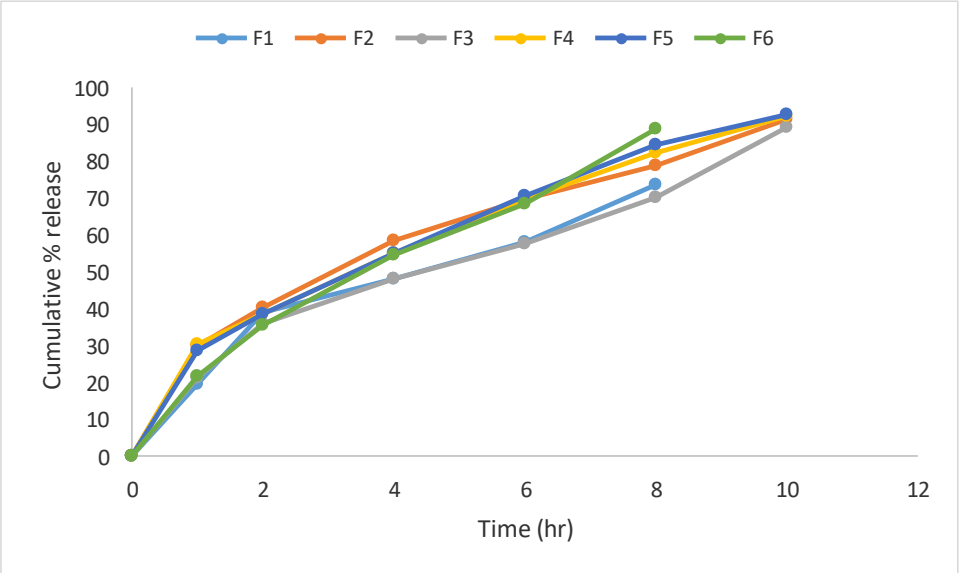

Figure 2. Release profiles of extract from different Phytosomes

In Vitro Antioxidant and Anti-inflammatory Activity

The phytosomes exhibited superior radical scavenging activity, with IC50 values of 12.5 µg/mL (DPPH assay) and 15 µg/mL (ABTS assay), compared to 25 µg/mL and 30 µg/mL, respectively, for the free extract. The FRAP assay demonstrated higher reducing power for the phytosomes, correlating with their potent antioxidant activity. The IC50 values for the phytosomes were 20 µg/mL (HepG2 cells) and 25 µg/mL (MCF-7 cells), significantly lower than the free extract (40 µg/mL and 50 µg/mL, respectively), indicating enhanced anticancer activity.

In Vivo Tumor Inhibition:

In Wistar rats, the phytosome high-dose group showed a 70% reduction in tumor volume, significantly higher than the free extract group (40% reduction). The phytosome low-dose group achieved a moderate inhibition rate of 55%. The inhibition of tumor growth correlated with enhanced oxidative stress markers and histopathological findings.

MDA levels in the phytosome-treated groups were significantly reduced (2.1 ± 0.2 nmol/mg protein) compared to the negative control (5.8 ± 0.5 nmol/mg protein). SOD and catalase activities were significantly higher in the phytosome groups, indicating improved antioxidant defense mechanisms.

Histopathology:

Tumor tissues from the phytosome-treated groups exhibited extensive necrosis and reduced cellular proliferation compared to the free extract group. No signs of toxicity were observed in the liver, kidneys, or spleen of the treated animals, confirming the safety of the phytosome formulation.

DISCUSSION

The results highlight the advantages of phytosome technology in enhancing the therapeutic efficacy of *Eclipta alba*. The reduced particle size and enhanced encapsulation efficiency of the phytosomes facilitated better solubility and cellular uptake of bioactive compounds. The

phytosome formulation exhibited significantly improved radical scavenging and reducing power compared to the free extract. This enhancement is attributed to the stabilization of bioactive compounds within the phospholipid matrix, preventing degradation and facilitating sustained release.

The enhanced in vitro cytotoxicity and in vivo tumor inhibition demonstrated by the phytosomes underscore their potential as an anticancer therapy. The improved anticancer activity is likely due to the increased bioavailability of wedelolactone and other flavonoids, which modulate key pathways in cancer progression, such as apoptosis and oxidative stress.

The absence of significant toxicity in major organs confirms the safety of the phytosome formulation, making it a promising candidate for therapeutic applications.

CONCLUSION

This study highlights the successful formulation and evaluation of *Eclipta alba* phytosomes, showcasing their potential to overcome the inherent limitations of low bioavailability and solubility of plant bioactives. By complexing the extract with phospholipids, the phytosome technology enhanced the delivery and therapeutic efficacy of key constituents such as wedelolactone and flavonoids. The phytosome formulation demonstrated superior antioxidant activity by effectively scavenging free radicals and reducing oxidative stress markers. Most notably, the in vivo anticancer studies revealed significant tumor growth inhibition, with improved oxidative balance and minimal systemic toxicity compared to the free extract.

The findings confirm the role of phytosomes in amplifying the pharmacological potential of herbal extracts, paving the way for their application in the development of effective, targeted, and safer phytopharmaceuticals. This approach not only advances the therapeutic use of traditional medicines but also addresses critical challenges in modern drug delivery systems. Future clinical studies are warranted to validate these results and establish the translational potential of *Eclipta alba* phytosomes for widespread healthcare applications.

DECLARATIONS:

Consent for Publication

Both authors give consent for the publication of research article.

Conflict of Interest

The authors affirm that there is no conflict of interest.

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Authors' Contributions

The authors confirm their contribution to the paper: study conception and design: Prachi Maheshwari; data collection: Vivek Daniel; analysis and interpretation of results: Prachi Maheshwari; draft manuscript: Vivek Daniel. Both authors reviewed the content and approved the final version of the manuscript.

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