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Original Article

Efficient *Euphorbia hirta* Phytosomes for *in vitro* Antiasthmatic Activity

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ABSTRACT

Background: The purpose of this study was to assess the antiasthmatic activity of *Euphorbia hirta* extract and *Euphorbia hirta* phytosomes in an *in vitro* anti-asthmatic model. **Materials and Methods:** The phytosomes were tested for entrapment efficiency, solubility studies, and *in vitro* drug release. The *in vitro* goat tracheal chain preparation paradigm was used to test the *Euphorbia hirta* extract and *Euphorbia hirta* phytosomes. **Results:** Histamine-induced contraction in an isolated goat tracheal chain revealed that both *Euphorbia hirta* extract and *Euphorbia hirta* phytosomes decreased histamine's contractile effect. The entrapment efficiency was observed well at 60°C and a 1:2 ratio of extract: phospholipids. The solubility studies and *in vitro* drug release studies depicted a rise in the lipophilic nature of extract by formulating it in the form of phytosomes. The antiasthmatic activity of the extract and phytosomes increased as the concentration was raised. **Conclusion:** The presence of phytochemicals such as flavonoids, glycosides, and saponine may play a role in the antiasthmatic activity observed. Moreover, enhanced lipophilicity might have enabled phytosomes to show a better antiasthmatic profile as compared to extract.

Keywords: *Euphorbia hirta* extract, Phytosomes, Solubility, Antiasthmatic activity, *in vitro* drug release, lipophilicity

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INTRODUCTION

Asthma affects more than 20 million people in the United States and more than 60 million people worldwide. In developed countries, it affects between 5 and 10% of the population.

It is a condition in which the bronchial tubes swell and become congested, making breathing difficult. Bronchial asthma is the most frequent debilitating symptom among several respiratory disorders that affect humans. Various approaches are used in the current medical care of asthma. Unfortunately, these methods have certain unintended consequences. There are many herbs available in India that are used in traditional medicine to treat asthma.[1]

Euphorbia hirta is a member of the Euphorbiaceae family and the Euphorbia genus. It's a reddish or purplish-colored, slender-stemmed, annual hairy plant with many branches from the base to the top and spreads up to 40 cm in height. Afzelin (I), Quercitrin (II), and Myricitrin (III), as well as kaempferol, gallic acid, and protocatechuic acid are the major components.[2] According to a literature assessment of the *Euphorbia hirta* plant, it has a variety of actions and is listed in Ayurveda. *Euphorbia hirta* is found in hotter places in Australia and India and can be seen along the sides of roads.[3] Chemical components such as alkaloids, glycosides, Saponins, and flavonoids have been discovered in ethanol extract.[4]

Polar herbal compounds like phenolics, are highly active *in vitro* but poorly absorbed *in vivo* due to several variables, including their large molecular size, gastrointestinal breakdown, and poor lipid solubility, all of which restrict their bioavailability.[5]

It is possible to improve the efficacy of phytoactive or plant extracts by compounding them to suitable formulations to increase bioavailability and solve solubility difficulties, hence improving the therapeutic efficacy.[6] Although many formulation strategies (e.g., emulsions, liposomes, and nanoparticles) have been used to improve the bioavailability of phytoconstituents and extracts, their restricted drug loading of them in such dosage forms can be a major concern.[7-9]

Plant extracts or bioactive is complexed with phospholipids, primarily phosphatidylcholine, to form phytosomes, which are lipid compatible molecular complexes.[6] The technology deals with the conversion of water-soluble phytoconstituents into lipid-based complexes.[10] Phospholipids, particularly phosphatidylcholine, are used as lipid phase to render phytoconstituents lipid friendly. The phytosome technology has gained prominence in the cosmeceutical, pharmaceutical, and nutraceutical industries in recent years as it can be developed in powder, tablets, emulsions, gels, solutions, and lotions, capsules. Phytosomes are recognized for their increased stability due to a chemical interaction between phospholipid molecules and phytoconstituents. Phosphatidylcholine has various medicinal characteristics in addition to acting as a carrier, giving it a synergistic effect when employed in the preparation of phytosomes. Phospholipids are key vehicles that have two fat-soluble tails and a water-soluble head, giving them aqueous as well as lipid solubility and thus serving as excellent emulsifiers.[11] The phospholipids consist of a unique structural component that is equivalent to lipid components of the human cell membrane allowing them to be compatible with the mammalian physiological system. They also act as a promising carrier system for increasing the bioavailability of extracts or phytoconstituents that are poorly absorbed.[12]

Phosphatidylcholine consists of dual-functional groups of which the phosphatidyl moiety is lipophilic, whereas the choline moiety is hydrophilic. The phosphatidylcholine molecule's choline head binds to the phytoconstituents, and the lipid-soluble phosphatidyl part, which includes the body and tail, wraps the choline-attached material. As a result, the phytoconstituents form a molecular complex with the help of phospholipids which is lipid-compatible and referred to as the phytophospholipid complex.[13] Researchers have made significant efforts to investigate phytosome technology, and studies have shown that phytosome complexes have enhanced bioavailability and therapeutic efficiency in areas such as antioxidant, anticancer, anti-inflammatory, anti-aging, and anti-wrinkle, skin disorders, and wound healing. As a result, phytosome compositions are comparatively safe and are suggested for cosmeceutical and pharmaceutical applications. These complexes also improve the permeability of extract across the membrane.[6]

Euphorbia hirta has been studied for its anti-asthmatic properties. It was also interesting to see if *Euphorbia hirta* in phytosome form may improve the anti-asthmatic impact. As a result, we set out to make a *Euphorbia hirta* phytosome complex and examine its anti-asthmatic properties.

MATERIALS AND METHODS

Euphorbia hirta extract (EHE) was received as a gift sample from Amsar Goa Pvt. Ltd., Goa, India. Phosphatidylcholine was purchased from MOLYCHEM. Quercetin was obtained from Natural remedies Pvt. Ltd, Bangalore, India. All the organic solvents were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. All the reagents used were of analytical grade.

Methods

Preparation of phyto-phospholipids complex

The antisolvent precipitation method was used for the preparation of phytosomes. In a round bottom flask, a suitable amount of soy-lecithin and *Euphorbia hirta* extract (1:2 ratio) were placed and dissolved by adding dichloromethane (20 ml). The mixture was subjected to reflux condensation for 2 hr at a temperature of about 60°C. All the organic phase was evaporated at the end of the operation, leaving a thin film on the round bottom flask's wall. The mixture was concentrated. To obtain the precipitate, n-Hexane (20 ml) was carefully added with continuous stirring. The precipitated mass was filtered, collected, and kept overnight in vacuum desiccators. The dried precipitate was crushed and screened through a #100 mesh sieve. The obtained complex was stored at room temperature.[6]

Encapsulation efficiency

An indirect method was used to determine EHP's encapsulation efficiency (EE percent). The samples were ultracentrifuged for 60 min at 5,000 rpm. The free drug concentration in the supernatant was estimated using the calibration curve at 338.5 nm, and the entrapped extract was calculated using the following equation as the difference between the total amount of the extract added to the preparation and the amount of unentrapped extract (Jasco's V 730).

$$\% \text{ Encapsulation efficiency} = (\text{added drug conc.}) - (\text{free drug conc.})/(\text{added drug conc.}) * 100$$

Solubility analysis

Using the approach previously described the solubility of EHE and EHP was examined.[14-15] 10 mL water or n-octanol were obtained in sealed glass containers, and an excess amount of EHE or EHP was added, holding the temperature at roughly 27°C. After mixing for 24 hr, the above mixtures were placed away for a time. After that, the mixtures were centrifuged at 1500 rpm for 25 min. The supernatant was separated and filtered using a membrane filter (0.45). After adequate dilutions, the material was evaluated using a UV–visible spectrophotometer. (Jasco's V 730).

In vitro dissolution studies

The *in vitro* release of EHE and EHP was investigated using the method previously described.[16] A dialysis membrane capable of retaining molecules up to 12000 kDa (Dialysis Membrane-50, Average diameter 14.3 mm, Average flat width 24.26 mm, pore size 2.4 nm, and approximate capacity 1.61 mL/cm; ANALAB FINE CHEMICALS, India) was used to make the sample dialysis bags. The membrane had been cleaned properly. The 200 mg EHE or 200 mg equivalent EHP was placed in the dialysis bag and knotted. In a beaker, the generated bags were suspended in phosphate-buffered saline (PBS, 200 mL, pH 7.4) with (Tween® 20, 1% w/v). The dissolving media was agitated at 50 revolutions per minute while the temperature was held at 37°C.

Particle size analysis and zeta potential

Dynamic light scattering (DLS) was used to evaluate the particle size and zeta potential of EHP using a Zetasizer (Malvern Instruments Ltd., UK). The phytosomal complex was suspended in deionized water. Each measurement was done in triplicate, and the results are shown as mean standard deviation.

Ex-vivo studies on goat trachea

Fresh goat trachea was taken straight from the butcher in an oxygenated Krebs-Henseleit solution shortly after the animal was slaughtered. Three rings were knotted one over the other in succession after the individual rings were separated to make a tracheal chain. Krebs-Henseleit solution was kept at 37±1°C in an organ tube, and the carbogen was bubbled (1 bubble/sec). In the organ tube, the tracheal chain was hung. The oxygen delivery tube was attached to the lower end of the chain, while the frontal writing lever was attached to the other end. The frontal writing lever was linked to the tip of a sketch pen, and white plain paper was rolled across Sherrington's spinning drum. The tracheal chain was relaxed under 400 g strain for 45 min, with the bathing solution changing every 15 min. In the absence and presence of a 100 µg/ml aqueous solution of EHE and EHP, concentration-response curves (CRC) for acetylcholine and histamine were measured. Finally, the CRC of acetylcholine and histamine was displayed as a percentage of the maximum contractile response.[17]

RESULTS

a. Encapsulation efficiency

Encapsulation efficiency was found to be affected by the extract: phospholipid ratio (X1, w: w) and reaction temperature (X2,°C). The findings displayed encapsulation efficiency of about 95.22 ± 4.56 percent in a formulation formed with a 1:2 extract: phospholipid ratio and a reaction temperature of 60°C. Several methods for preparing phytosomes were tried, with the antisolvent precipitation method proving to be the most successful.

Solubility studies

The results of the solubility studies are shown in Table 1. The aqueous solubility of pure EHE was high (86.50 µg/ml), whereas the n-octanol solubility was low (2.544 µg/ml). The following data point to EHE having a hydrophilic nature. EHP's solubility was reduced by almost 2 times in distilled water (42.56 mg/ml) but was found to be higher by 11 times in n-octanol (23.33 µg/ml) when compared to pure EHE ($p < 0.001$). Solubility investigations predicted that the phytosomes produced would become more lipophilic. According to the findings, the extract encapsulated in phytosomes achieved a perfect combination of

Table 1: Solubility analysis of EHE and EHP in distilled water and n-octanol.

Sample	Aqueous solubility (mg/ml) [a]	n-octanol solubility (mg/ml) [a]
EHE	86.50 ± 1.26	2.544 ± 0.068
EHP	42.56 ± 1.10	23.33 ± 0.062

a Data expressed as mean ± Std. Dev.; $n = 3$

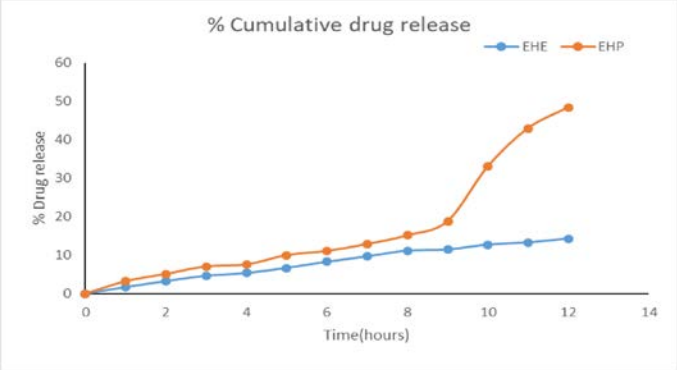

Figure 1: *In vitro* release study of EHE and EHP.

hydrophilic and lipophilic characters. As a result, the findings supported the idea that phytosomes' higher lipophilic nature assisted them in breaking through a moderately lipophilic barrier.

In vitro dissolution studies

A comparison of the dissolving behavior of EHE and EHP is shown in Figure 1. At the conclusion of the seven-hour, the results of EHE and EHP *in vitro* release were approximately equal (20 percent). EHP's drug release rose considerably as the test proceeded, compared to EHE. The release of EHP (33%) was nearly double that of EHE (13%) after 10 hr, indicating a considerable difference ($p < 0.05$). Following this point, EHE showed a moderate increase in dissolution behaviour, reaching around (14%), but EHP continued to show a large increase in dissolution pattern (48%) and revealed a very significant difference ($p < 0.001$) at the end of 12 hr.

Particle size analysis and zeta potential

EHP displayed a mean diameter of 161.3 ± 58.3 nm with a PDI of 0.187 ± 0.02 which is shown in Figure 2. Because of their smaller size, EHP particles would have a larger surface area. The colloidal dispersion stability is envisioned by the zeta potential. The average zeta potential was -42.56 ± 3.5. The result was in the range of -20 to 30 mV, indicating that phytosomes had excellent stability at smaller particle sizes.

Antiasthmatic activity

In these tissue preparations, *Euphorbia hirta* extract and its phytosomes were both found to prevent the contractions caused by histamine. DRC was plotted using Acetylcholine (10 µg/ml) and histamine (5 ug/ml) at various dose levels. In goat tracheal chain preparation, *Euphorbia hirta* extract and phytosomes inhibited considerable contraction at a concentration of 100 µg/ml and 100 µg/ml equivalent with a dosage-dependent effect. When effects of EHP were compared with EHE, inhibition of contractions was observed more in the case of EHP.

DISCUSSION

The phytosomes prepared the with antisolvent precipitation method displayed good encapsulation efficiency. Particle size, according

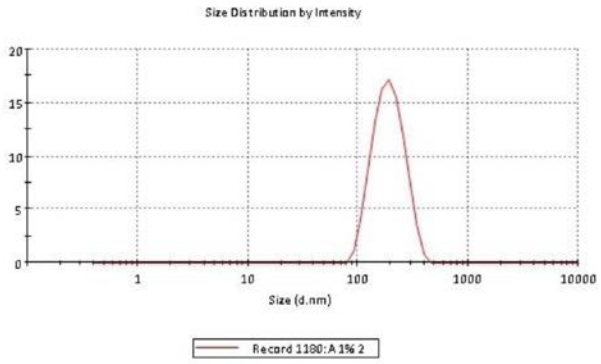

Figure 2: Particle size distribution of EHP.

Table 2: Effect of EHE and EHP (100 µg/ml) on the acetylcholine-induced contraction of isolated goat tracheal chain preparation.

Dose of Acetylcholine (10 µg/ml) (ml)	- ve log molar conc. of Acetylcholine	% Maximum contractions		
		Control	EHE	EHP
0.1	8.16	7.84 ± 0.52	4.56 ± 0.26	2.26 ± 0.65
0.2	7.86	18.22 ± 1.10	10.58 ± 0.88	8.86 ± 0.84
0.4	7.56	28.44 ± 1.46	20.56 ± 0.84	17.56 ± 0.64
0.8	7.26	46.28 ± 1.36	30.54 ± 0.42	27.86 ± 0. 85
1.6	6.96	68.18 ± 1.28	41.52 ± 1.22	38.24 ± 0.58
3.2	6.66	84.56 ± 0.66	56.12 ± 0.64	52.32 ± 0.54

to prior study, played a significant effect in sustaining drug release from the phospholipids complex as well as increasing the drug's oral absorption. Phytosomes' increased surface area may allow entrapped extract moieties to escape from the phytosome via a surface erosion and diffusion mechanism.[18] The narrow distribution of particle size of EPH was also indicated by the polydispersity index of 0.187 ± 0.02. EHP's zeta potential was around -42.56 ± 3.5 mV, indicating good stability (Figure 2).

EHE and EHP solubility in water and n-octanol showed a drop in aqueous solubility and a substantial increase in n-octanol solubility in the study. The findings indicated that the hydrophilic character of the extract was decreasing while the lipophilic nature of the extract was found more in phytosome formulation. The solubility of EHP in lipophilic phospholipids could be increased by integrating it into amphiphilic phospholipids. The amorphous structure of phytosomes may have contributed to the drug's extended-release at the end of the 12-hr period (Figure 1).

As seen in Tables 2 and 3, both acetylcholine and histamine caused a significant contraction of the goat trachea in our investigation. The contractile impact of acetylcholine and histamine was found to be greatly decreased ($p < 0.001$) in the presence of a modified physiological salt solution containing EHE (100 µg/ml) and EHP (100 µg/ml). Compared to the dose-response curves of these agonists alone, the dose-response curves of acetylcholine and histamine were moved to the right in the presence of EHE and EHP (Figures 3 and 4). The contraction of the goat trachea was significantly reduced in both EHE and EHP.

The trachea of a goat is thought to be a suitable tissue for studying agonists and antagonists such as acetylcholine and histamine. It is currently commonly used to assess the antiasthmatic properties of numerous test substances, including herbal formulations. It is simple to obtain, and the assembling process is similarly simple.[19] H1 histaminergic, M3

Table 3: Effect of EHE and EHP (100 µg/ml) on the histamine-induced contraction of isolated goat tracheal chain preparation.

Dose of histamine (05 µg/ml) (ml)	- ve log molar conc. of histamine	% Maximum contractions		
		Control	EHE	EHP
0.1	8.16	9.17±0.25	5.96± 0.06	3.21±0.04
0.2	7.86	22.12±0.12	14.56 ± 0.08	9.52 ±0.06
0.4	7.56	31.17±0.05	20.66± 0.09	19.86±0.04
0.8	7.26	42.52±0.08	27.68 ±0.12	27.60±0.18
1.6	6.96	50.13±0.04	42.63 ±0.09	37.56±0.17
3.2	6.66	68.15±0.06	52.56 ± 0.12	48.58±0.04

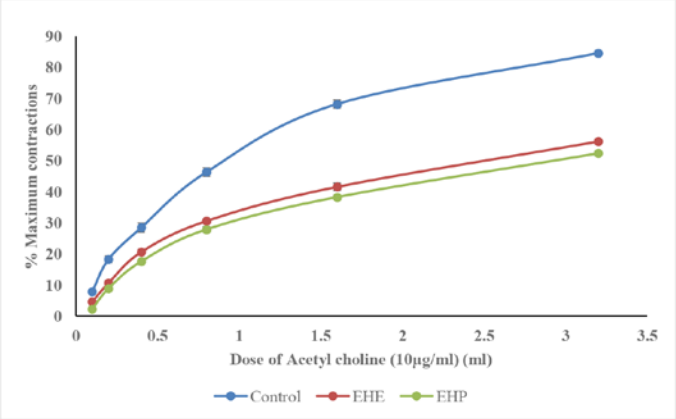

Figure 3: Effect of EHE and EHP (100 µg/ml) on the acetylcholine-induced contraction of isolated goat tracheal chain preparation.

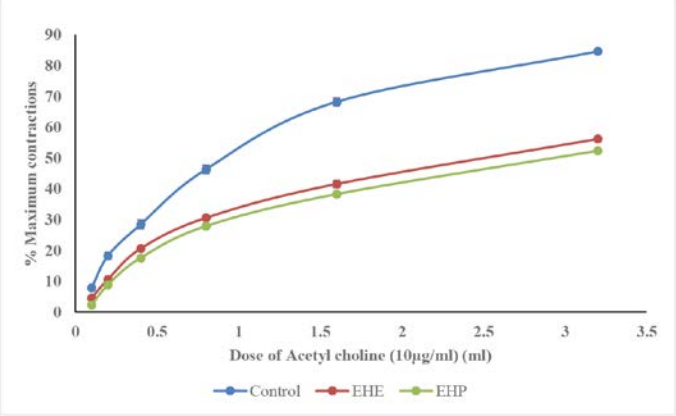

Figure 4: Effect of EHE and EHP (100 µg/ml) on the histamine-induced contraction of isolated goat tracheal chain preparation.

muscarinic, and B2 adrenergic receptors are found in the goat trachea.[20] It is hypothesized that if the agonist's dose-response curve shifts to the right in the presence of the test drug when compared to the agonist's dose-response curve alone, the test drug has antagonistic activity.[21]

The contractile action of acetylcholine and histamine was shown to be considerably reduced in the presence of a modified physiological salt solution containing EHE and EHP in our investigation. Furthermore, as compared to the dose-response curves of these agonists alone, the dose-response curves of acetylcholine and histamine were pushed to the right side (Figures 3 and 4). It could be predicted that EHE has anticholinergic and H1 receptor antagonistic properties due to its ability to block the effects of acetylcholine and histamine, respectively. Moreover, the anticholinergic and H1 receptor antagonistic properties were found to be enhanced in EHP.

CONCLUSION

In conclusion, the current investigation revealed that hydroalcoholic extract of *Euphorbia hirta*, as well as its phytosomes, had strong dose-dependent antiasthmatic action *in vitro* model, bolstering the plant's traditional use in asthma treatment. However, phyosomes being good in lipid content displayed better antiasthmatic action as compared to pure extract. The findings of solubility and *in vitro* dissolution supported the enhanced lipophilicity of phytosomes. More research is being carried out to isolate and describe the active component responsible for the Antiasthmatic Activity. In the future, the active constituent of the extract might be isolated and formulated into phytosomes for knowing its potential in antiasthmatic activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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