ORIGINAL ARTICLE

Nanoemulsion Formulation and Evaluation of *Terminalia chebula* Fruit to Improve Bioavailability

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Abstract

Terminalia chebula is a reputed medicinal plant with various therapeutic characteristics; however, it is limited by poor solubility and permeability, leading to low bioavailability. A novel nanoemulsion-based formulation was developed and evaluated to improve the aforementioned properties. The nanoemulsion was prepared using oil in water method with appropriate surfactants and cosurfactants to increase the solubility and stability of bioactive compounds in *T. chebula* fruit extract. To explore its properties, the formulation was characterized for parameters such as particle size, zeta potential, polydispersity index, and stability under different conditions. *In vitro* release studies indicated a considerably enhanced dissolution rate as against that of conventional extracts, the presence of augmented bioavailability was further corroborated through the enhanced pharmacokinetics parameters in the *in vivo* studies. This approach upholds a real strategy to maximize therapeutic efficacy associated with *T. chebula* substances, pointing toward their use in developing effective herbal medicine.

Key words: Bioavailability enhancement, herbal medicine, nanoemulsion, pharmacokinetics, *Terminalia chebula*

INTRODUCTION

Background of *Terminalia chebula* and its medicinal properties

India contains a great legacy of plant-based knowledge for well-being. Utilizing herbal treatments is, as of now, on the rise globally.[1] The importance of medicinal plants for the purpose of disease treatment is given importance by ancient Indian systems of medicine such as Ayurveda and Siddha.[2] The Chief of Traditional Medicine of the World Health Organization, in his report issued in 1993, stated that traditional medicine primarily based on plants is the mainstay of about 80% of human society.[3] In India, it is reported that 70% of the population are using traditional medication for primary health care. Annual revenues from herbal medicine listings made by these major firms are approximately US$300 million when compared to US$2.5 billion accrued from traditional pharmaceuticals in the present time.[4] *T. chebula* Retz. is a tropical and subtropical tree belonging to the family *Combretaceae* (Syn, apathy), reaching d medium to large size, and is found throughout northern India to the UP and Bengal. In southern India, however, it is usually found in Tamil Nadu, Karnataka, and the southern part of Maharashtra. The tree is called black myrobalans in English and harad in Hindi.[5] The family Terminaliaceae contains over 250 species and is found throughout the world's tropical climates.[6] For the Tibetans, the fruit produced from the tree *T. chebula* is considered the "king of medicines," two Ayurvedic druggists do not dispute, and also appreciated by other ethnomedicine practitioners. This plant is referred to by different names in various parts of India, including, but not limited to - Telugu - Kari Kayi, Nall karaka, Tamil - Kadakkai, English - Black Myrobalan, and Hindi - Chhoti Har. According to the ethnomedicinal studies [Table 1], *T. chebula* retz. exhibits numerous medicinal

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benefits in all its parts. The infusion of fresh leaves is used to treat bacterial and fungal infections and as a vermicidal/medicinal agent. Dried entire plants are used for fever, coughing, asthma, urinary tract ailments, parasites, arthritis, and even certain types of poisonous scorpions and liver. Homeopathic roots have many uses, including using them as an astringent, a purgative, a stomachic, a laxative, and in the management of wounds.[7] Fruits for antimicrobial activities and activities against *Escherichia coli* stemming barks are used to treat cardiovascular diseases and related symptoms including hypertension, high cholesterol levels, and sexual performance enhancement. Therapeutic properties of *T. chebula* have been documented, including hypocholesterolaemia, anti-inflammation, anti-allergy, anti-microbial, anti-oxidant, and so on. These characteristics can be attributed to the phytochemicals found in the fruit, particularly phenolics like flavonoids.[8]

Many of the bioactive compounds in *T. chebula*, such as tannins, flavonoids, and phenolic acids, have poor solubility in water. This limits their dissolution in the gastrointestinal (GI) tract, a critical absorption factor.[9] Once absorbed, compounds often undergo significant metabolism in the liver (first-pass metabolism),[10] which can drastically reduce the concentration of active compounds reaching the systemic circulation. Certain compounds in *T. chebula* may exhibit poor permeability across the intestinal lining, leading to reduced absorption.[11] The bioactive compounds in *T. chebula* can be unstable, especially in the stomach's harsh environment (acidic pH) or due to enzymatic degradation.[12] This instability can lead to the breakdown of compounds before they are absorbed. Even when absorbed, the compounds might be rapidly excreted from the body, limiting their therapeutic efficacy. This occurs particularly for water-soluble compounds, which can be quickly excreted through the kidneys.[13] The tannins and polyphenols present in *T. chebula* can form complexes with proteins or other compounds in the gut, hindering their absorption. For instance, some polyphenols may bind with dietary proteins or enzymes, making them less available for uptake. Even if the compounds are absorbed, the challenge remains in delivering them effectively to their target tissues or organs, as they may not accumulate in the desired areas in therapeutic concentrations.[14]

MATERIALS AND METHODS

Materials

The investigation paid attention to the fruits of *T. chebula*, which were collected in the months of February and March from the forests of Bhandara, India.[15] The fruits were then washed with distilled water to get rid of dirt, and all the chemicals used for analysis were obtained from Merck and Sigma-Aldrich. After cleaning, stems and other unnecessary materials were cut off. The Japanese electric mill cut the fruit into powder to achieve uniformity in particle size for better quantity incorporation into the muffin mixture. The Harad powder was then packed in airtight containers and stored at 37°C to protect its active ingredients for later analysis.[16] Harad powder was added to the muffin formulations to assess its nutritional and functional qualities. This research was conducted to integrate age-old components with contemporary food items, particularly the medicinal properties of Harad in functional bakery products.

Chemicals and reagents used in nanoemulsion formulation of *T. chebula* fruit

1. Oil phase: Essential oils (such as olive oil, coconut oil, or sunflower oil) to dissolve hydrophobic compounds from *T. chebula* extract
2. Medium-chain triglycerides (oil) for enhanced solubility and emulsification properties
3. Surfactants and cosurfactants: Tween 80 (Polysorbate 80): A non-ionic surfactant widely used to stabilize nanoemulsion. Span 20 (Sorbitan monolaurate): Another common surfactant that can be used with Tween 80 to form stable emulsions.[17] Lecithin: A natural surfactant derived from soy or egg, stabilizes emulsions. Polyethylene glycol (PEG) derivatives (e.g., PEG-400 or PEG-600) are co-surfactants to enhance stability. Transcutol (diethylene glycol monomethyl ether) is a co-surfactant to improve drug solubility.
4. Aqueous phase: Deionized or distilled water is the main aqueous medium in the nanoemulsion system. Glycerol is used as a humectant to enhance the viscosity and stability of the aqueous phase.
5. Emulsifying agents: Sodium lauryl sulfate an emulsifying agent that helps form small droplets within the emulsion.[18] Pluronic F-127: A non-ionic triblock copolymer often used to stabilize nanoemulsion.
6. Stabilizers and antioxidants: Ascorbic acid (Vitamin C) or tocopherol (Vitamin E) act as antioxidants, protecting the bioactive compounds from oxidation. Citric acid to maintain the pH and stabilize the nanoemulsion formulation.
7. *T. chebula* extract: *T. chebula* extract, which contains tannins, flavonoids, and other bioactive compounds, is the core functional ingredient for which the nanoemulsion is designed.[19]
8. Organic solvents (optional): Ethanol or methanol may extract the bioactive compounds from *T. chebula* and in the initial stages of nanoemulsion preparation to dissolve hydrophobic substances.
9. pH adjusters: Sodium hydroxide or hydrochloric acid may be used to adjust the pH of the formulation, ensuring stability and optimal release of the active compounds.

Drying process of *T. chebula*

A technique was required that can be used to minimize the sulfonation at higher temperatures during drying, which is important to make possible the proper retention of vitamin C

Table 1: Difference between nanoemulsion and traditional formulations

Aspect	Nanoemulsion formulation	Traditional formulation (powder, extracts, tablets)
Particle size	Nano-sized droplets (20–200 nm)	Larger particles (microns to millimeters)
Solubility	Enhanced solubility, especially for hydrophobic compounds	Limited solubility, especially for hydrophobic components
Absorption	Rapid and efficient absorption through gastrointestinal barriers	Slower and less efficient absorption
Bioavailability	Higher bioavailability (Cmax, AUC)	Lower bioavailability
Onset of action (Tmax)	Faster onset (lower Tmax) due to quicker absorption	Slower onset (higher Tmax)
Distribution	Enhanced tissue penetration and targeting due to small particle size	Less effective tissue distribution
Therapeutic efficacy	Improved therapeutic efficacy due to better absorption and distribution	May require higher doses to achieve therapeutic levels
Stability	Improved therapeutic efficacy due to better absorption and distribution	Potential degradation of active compounds in storage and GI tract
Elimination	Prolonged circulation time, slower elimination	Faster elimination, leading to shorter action duration
Side effects	Potential for reduced side effects due to targeted delivery	Higher doses may increase the risk of side effects
Dosing	Lower doses required due to increased bioavailability	Higher doses required to achieve the same effects

GI: Gastrointestinal

and total flavonoid content (TFC) from dry fruit of *T. chebula* when used to prepare nanoemulsion.

Harvesting and preparation

Roast the matured fruit of *T. chebula* for maximum bioactive content. Wash the fruits thoroughly with clean water and slice them into smaller pieces to simplify drying.

Extraction of bioactive compound

Given that the process of extracting bioactive compounds from medicinal plants plays an important role in curating consumer herbal products, modern, "evolutionary" extraction technologies are way better than the earlier ones when it comes to the extraction of active ingredients. In producing herbal products, extraction is one of the most crucial processes because it influences the qualitative and quantitative parameters of total active ingredients in examined samples.[20] Considering the variety of plant species and different physiologically active substances, screening methods must be simple and exhaustive [Figure 1]. Only Suitable extraction methods can facilitate the separation, identification, and characterization of the physiologically active substances. Physiologically active substances extracted from biological materials depend on several parameters, such as extraction methods and devices, starting materials, and extraction solvents. Various methodologies for extraction need to be applied in different situations to appreciate the degree of selectivity of extraction from different natural resources. In recent years, conducting extraction processes of phenolic compounds from natural sources has become attractive. The particular uses, the location where the separation techniques were employed, and relevant bioactive compounds are some of the matters that should be looked into.[21]

Nanoemuision formulation

Components of the nanoemulsion

Oil phase

The oil phase in a nanoemulsion can be derived from various sources. In the case of *T. chebula*, it contains nutrients such as protein, amino acids, minerals, and vitamin C. In addition, specific compounds found in *T. chebula* contribute to its therapeutic properties. For example, quercetin is a flavanol recognized for its antitonicity and anti-inflammatory effects. Terchebin: It is a terpenoid that is examined for possible antitumor and anti-inflammatory properties [Figure 2].

Aqueous phase (water)

Water forms the continuous phase in nanoemulsion. It surrounds the oil droplets and provides the medium for dispersing hydrophilic compounds. Imagine it as the gentle embrace that holds the oil droplets together.[22]

Surfactants (emulsifiers)

Surfactants are essential for stabilizing nanoemulsion. They have both hydrophilic (water-loving) and hydrophobic

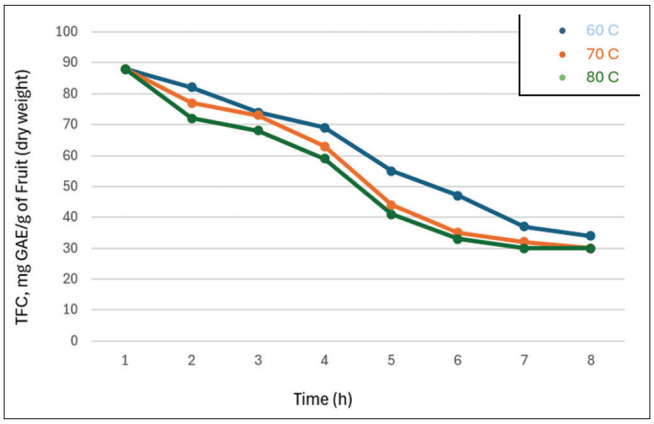

Figure 1: Variation in total flavonoid content *Terminalia chebula* fruit during drying at different temperature

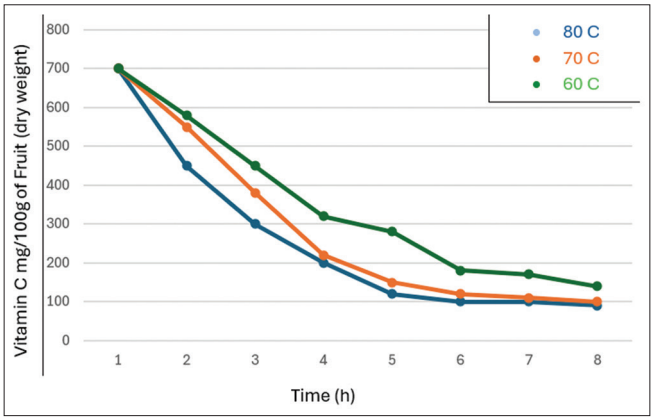

Figure 2: Variation in vitamin C *Terminalia chebula* fruit during drying at different temperature

(oil-loving) parts. By adsorbing at the oil-water interface, surfactants prevent droplets from coalescing. They're like molecular matchmakers, ensuring oil and water stay happily mixed.

Co-surfactants (co-solvents)

Co-surfactants are substances that assist surfactants in decreasing interfacial tension and increasing stability further. They improve the emulsifying properties.[23] Think of them as the loyal companions, helping to further the cause of the surfactants in the emulsification process.[24]

Characterization of nanoemulsion

Evaluation of droplet size, polydispersity index (PDI), and zeta potential

The optimized NE systems droplet size distributions and PDIs were evaluated in triplicate measurement using dynamic light scattering techniques with a Particle Size Analyzer (Horiba). Each sample was diluted with distilled water in a 1:100 ratio before the analysis. Zeta potentials for the optimized NE systems were performed using Laser Doppler anemometry by Zetasizer (Horiba) apparatus.[25] Before the analysis, each sample (100 µL) was diluted with distilled water at 1:100.

pH and viscosity determination

The nanoemulsion pH was estimated using a digital pH meter on a 2 g preparation dissolved in 20 mL distilled water for each sample, whereby each was replicated thrice, and the average pH was calculated. Viscosity was measured with a Brookfield viscometer using the number 2 spindle rotating at room temperature. Readings were taken at 10, 20, 50, and 100 rpm, and the corresponding viscosity values were recorded. The digital pH meter was employed for the pH analysis of the nanoemulsion after 2 g of the formulation was mixed with 20 mL of distilled water. Each sample was done three times, and pH was averaged from the three replicates. Viscosity was measured using a Brookfield viscometer with a number 2 spindle at room temperature. Readings were taken at 10, 20, 50, and 100 rpm, and their corresponding viscosity values were recorded.

Thermodynamic stability study

The centrifugal evaluation was carried out for ready-to-use emulsions containing *T. chebula* NEs.[26] During this quality-control process, which consisted of implementations due to phase separations, drug precipitations, or changes in color, control of NEs for signs of physical instabilities was made to eliminate those NEs from any further studies and characterization. The compositions were spun at 5000 rpm for 30 min and then checked for any occurrence of phase separation, creaming, or cracking.

Drug content

Weighing samples was followed by placing them in methanol and vertexing. The solutions were filtered using Whatman filter paper and analyzed by ultraviolet (UV)-visible spectroscopy.

pH

A digital pH meter was used to measure the pH value. 0.5 g of the nanoemulgel was dispersed in 50 mL of distilled water, then stored at 25°C.[27]

Viscosity

The monkeys were housed with the help of optimized *T. chebula* nanoemulgel systems, which were then subjected to evaluation of viscosities at the ambient room temperature using the Brookfield viscometer.

Spread ability study

This apparatus consists of a wooden block with a pulley attached at one end, used to assess the spreadability of gels through their "slip" and "drag" behavior.[28] To evaluate the spreadability of nanoemulgel, 1 g of gel is applied to a 1 cm diameter dot on a glass slide, with a second slide placed on top. A 100 mg

weight is placed on the upper slide for 5 min, causing the gel to spread as indicated by the increase in the gel's diameter.[29] The spreadability is determined by measuring the time in seconds for the two sides to separate, using the following equation to quantify the nanostructured lipid carrier gel's spreadability.[30]

Evaluation parameters and analytical methods for nanoemulgel formulation

Evaluating the thermodynamic stability of the nanoemulgel involves centrifuging the emulsion at 5000 rpm for 30 min. This process helps identify physical instabilities such as phase separation, drug precipitation, creaming, or cracking. For drug content analysis, a weighed sample is dissolved in methanol and vortexed. The resulting solution is then filtered using Whatman filter paper, and the filtrate is analyzed using UV-visible spectroscopy to quantify the drug content, ensuring uniformity across batches. To assess pH, 0.5 g of the nanoemulgel is dispersed in 50 mL of distilled water and stored at 25°C. A digital pH meter measures the pH, with stability over time being crucial. Viscosity is measured using a Brookfield viscometer at room temperature to ensure consistency and uniformity. The spreadability study employs an apparatus with a wooden block and pulley for "slip" and "drag" analysis, evaluating the spread behavior of 1 g of the nanoemulgel.

RESULTS

Drying methods

Consider the following methods to balance efficiency and the preservation of bioactive compounds such as Vitamin C and TFC.

Shade drying

Spread the sliced fruits thinly on a clean surface in a shady, well-ventilated area, avoiding exposure to direct sunlight to minimize the decomposition of heat-sensitive compounds such as Vitamin C. This usually takes 7–14 days, depending on humidity conditions.

Drying in the oven (at a low temperature): dry cuts for thermal degradation at 40–50°C. Depending on how thick and moist the fruit slices are, this method usually takes 12–24 h. The temperature must always be monitored to avoid over-drying.

Lyophilization (freeze-drying) is critical in preserving Vitamin C and TFC. Freeze fruits at −40°C and apply vacuum to sublimate ice, preventing bioactive loss.

Preparation of nanoemulsion

Nanoemulsion of *T. chebula* was formulated using a high-energy emulsification technique guided by specific weight ratios obtained from phase diagrams. Initially, oil and surfactant (Smix) phases were mixed continuously with a mechanical stirrer, followed by the slow addition of purified water to create a coarse emulsion. This emulsion was then processed with a sonicator probe generating over 20 kHz sound waves, compressing it into manometer-sized droplets (5–500 nm). Various batches were prepared by varying the amounts of oil, surfactant, and cosurfactant to assess their effects on droplet size, PDI, zeta potential, and stability of the formulations. Figure 3 shows nanoemulsion preparation and characterization.

Stability evaluation

The evaluation of *T. chebula's* stability implies assessing the analytical scales or methods for assessing the bioactive profile effectiveness of heat and humidity, light, and time. *T. chebula* comprises several active phytoconstituents, including tannins, flavonoids, and phenolic acids in its conventional medicinal applications. The significance of these tests lies in the proof that active features of the extract not change over time, which is vital in formulating effective and stable modern allopathic or Ayurvedic preparations [Table 2].

Advantages of nanoemulsion over non-emulsified extract

Nanoemulsion improve bioavailability due to small droplet sizes and encapsulation, which aids in the controlled release of drugs and protection from degradation of bioactive agents, leading to better and longer therapeutic effects and stability in living systems.

Comparative analysis between nanoemulsion and traditional formulation

Nanoemulsions enhance drug solubility, stability, and bioavailability compared to traditional formulations. Their

Table 2: Example of stability test result for *Terminalia chebula* nanoemulsion

Test	Initial	After 3 months (25°C)	After 3 months (40°C)
Particle size (nm)	120±5 nm	122±7 nm	130±10 nm
Polydispersity index (PDI)	0.25	0.26	0.29
Zeta potential (mV)	−32 mV	−30 mV	−28 mV
pH	4.7	4.6	4.5
Visual appearance	Clear, no separation	Clear, no separation	Slight turbidity

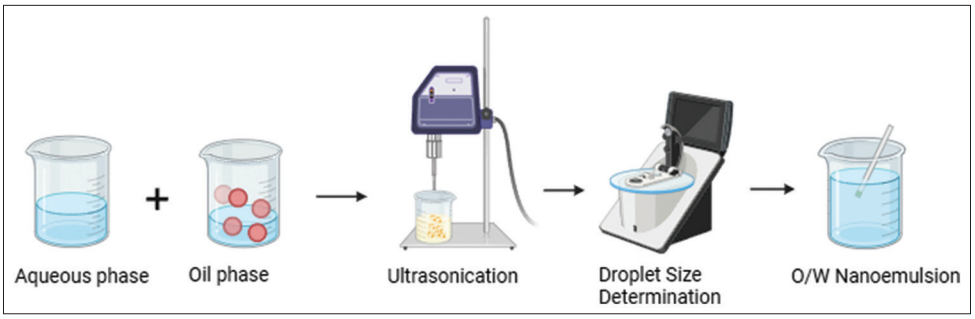

Figure 3: Procedure of nanoemulsion preparation and characterization

smaller droplet size improves absorption and targeted delivery, reducing dosage and side effects. Traditional formulations, though simpler and cost-effective, often suffer from poor solubility and lower efficacy. Nanoemulsions offer a superior alternative for efficient therapeutic delivery.

DISCUSSION

Nanoemulsion technology has gained attention for improving the solubility and stability of bioactive compounds, including those found in *T. chebula* (Haritaki). Water-in-oil nanoemulsion, with droplet sizes ranging from 20 to 200 nm, enhances the solubility and dispersion of compounds such as chebulinic acid, chebulagic acid, and gallic acid. Due to their hydrophilic and hydrophobic regions, this is achieved through their increased surface area and ability to solubilize both water-insoluble and water-soluble compounds.

One significant advantage of nanoemulsion is their protection of bioactive from degradation by heat, light, and oxygen, reducing photodegradation and oxidation. This protective effect extends shelf life and enhances stability by minimizing environmental damage. Nanoemulsion also improves bioavailability by promoting better absorption through the digestive tract. Their small droplet size enhances solubility and interaction with cell membranes, allowing more bioactive compounds to reach systemic circulation. In addition, nanoemulsion can be engineered for controlled and sustained release, preventing rapid degradation and ensuring prolonged therapeutic effects.

Potential applications include cosmetics and pharmaceuticals, where *T. chebula* extracts in nanoemulsion could provide anti-oxidant and anti-aging benefits. In functional foods and beverages, nanoemulsion can increase the bioavailability of therapeutic compounds, improving the effectiveness of supplements and functional foods.

Several mechanisms improve the absorption of *T. chebula* bioactive compounds when formulated as nanoemulsion, addressing challenges like low aqueous solubility and poor bioavailability, especially with compounds such as chebulagic acid, chebulinic acid, and gallic acid. A key factor is the increased surface area provided by nanoemulsion's small droplet size, which enhances the dissolution of bioactive matter and increases its contact with absorption surfaces. Encapsulation of hydrophobic bioactive in nano-sized oil droplets further boosts their solubility, leading to better absorption.

Surfactants and lipid carriers in nanoemulsion improve permeability, facilitating better passage of bioactive compounds across biological membranes. Nanoemulsion also promotes lymphatic absorption, bypassing first-pass liver metabolism, thereby reducing degradation and increasing systemic availability of bioactive. In addition, nanoemulsion often possess mucoadhesive properties, which prolong retention in the gut, giving more time for absorption. They also protect bioactive compounds from degradation in the GI tract, preserving their integrity. Facilitated endocytosis allows nano-sized particles to be directly absorbed by cells, further enhancing bioavailability.

Conventional formulations for enhancing the bioavailability of poorly water-soluble compounds use various approaches, each with strengths and limitations.

Solid dispersions enhance solubility by dispersing bioactive in a water-soluble matrix, improving dissolution. However, they face challenges like drug crystallization, inconsistent absorption, and limited protection from degradation during digestion.

Lipid-based formulations like self-emulsifying drug delivery systems solubilize bioactive in oils or surfactants, enhancing solubility and absorption of hydrophobic compounds. Yet, they are less effective in controlling release and protecting against environmental degradation, with performance highly dependent on the specific bioactive compound. Cyclodextrin complexation forms inclusion complexes to improve solubility but offers moderate bioavailability enhancement, limited by bioactive size and type. It doesn't provide controlled release or degradation protection. Micelles, colloidal dispersions, improve solubility but are sensitive to environmental conditions like pH and ionic strength, leading to premature release and reduced stability. These systems are less effective than more advanced technologies like nanoemulsion.

CONCLUSION

To summarize, the nanoemulsion development of *T. chebula* fruit extract proved to be a viable solution for enhancing

its bioavailability. The diminutive size of the droplet and the larger surface area created in the nanoemulsion system led to better solubility and dispersion of the active phytoconstituents, one of the critical issues herbal extracts face. Furthermore, the compound assisted in enhancing the stability of the bioactive compounds, thus preventing them from deteriorating for a more effective therapeutic outcome. The increased bioavailability is anticipated to improve the therapeutic activity of *T. chebula*, which is notorious for its antioxidant, anti-inflammatory, and antimicrobial activities. In conclusion, the research in question emphasizes that nanoemulsion drug delivery systems are quite useful for natural products, making incorporating herbal medicines into practice more effective.

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