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Self-Nanoemulsifying Drug Delivery Systems of Herbal Oils with Flavonoids: Emerging Therapeutic Strategies for Obesity

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Abstract

Obesity is a complex chronic condition that affects over a billion people worldwide, contributing to a growing burden of metabolic disorders, including diabetes, cardiovascular disease, and insulin resistance. Natural bioactive compounds such as flavonoids and herbal oils have attracted considerable attention for their ability to regulate lipid metabolism, reduce inflammation, and improve overall metabolic health. However, the therapeutic potential of these compounds is often limited by poor water solubility, resulting in low oral bioavailability and reduced clinical efficacy. Self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as an innovative solution, offering improved solubility, stability, and absorption of poorly water-soluble compounds. This review highlights the development and application of SNEDDS for key flavonoids including quercetin, myricetin, naringenin, and luteolin, demonstrating their ability to enhance plasma exposure, modulate lipid profiles, and improve insulin sensitivity in preclinical obesity models. Similarly, herbal oils such as flaxseed, olive, pomegranate seed, Nigella sativa, and gamma-linolenic acid-rich oils have been successfully incorporated into SNEDDS, showing hypolipidemic, antioxidant, and anti-inflammatory effects. Importantly, combining flavonoids with herbal oils in a single SNEDDS formulation remains largely unexplored, offering significant potential for synergistic therapeutic outcomes. By bridging traditional herbal wisdom with modern nanotechnology, these advanced delivery systems provide a promising strategy to develop safe, effective, and patient-friendly interventions for obesity and associated metabolic disorders. This review emphasizes the importance of further research into combined flavonoid-herbal oil SNEDDS to fully harness their therapeutic potential.

Keywords: Obesity, Flavonoids, Herbal Oils, Self-nanoemulsifying drug delivery system (SNEDDS),bioavailability, nanoemulsion

Introduction

Obesity is a chronic complex disease and when a person's weight exceeds what is standardized to be healthy for their height, they are said to be obese[1]. According to a recent Lancet study, over 1 billion people worldwide suffer from obesity as of 2022.Since 1990, the prevalence of adult obesity has more than doubled globally, and among children and adolescents, it has quadrupled[2].

One of the most researched substances due to its many advantageous benefits is flavonoids, which can be used to treat obesity,neoplasia, diabetes, hypertension, and cardiovascular disease.What makes flavonoids particularly fascinating is how researchers have beginning to understand exactly how they work in our bodies, with numerous studies pointing to their capacity to activate AMPK, a critical cellular energy regulator that could hold the key to better obesity therapies[3].In the kingdom of plants, flavonoids are extensively dispersed and are utilized for defense and growth. Two benzene rings and a heterocyclic pyrone ring define their structural makeup.The present work is focused on describing the molecular mechanisms underlying the metabolic impact of flavonoids in obesity and obesity-related diseases [4].

Despite their therapeutic potential, many herbal compounds face a fundamental challenge - they simply don't dissolve well in water, which makes it difficult for our bodies to absorb them effectively after we take them orally. Fortunately, pharmaceutical scientists have developed clever solutions using nanotechnology, creating tiny delivery vehicles like lipid nanoparticles and liposomes that can carry these stubborn compounds safely to where they're needed in the body [5].

What makes SNEDDS particularly attractive to pharmaceutical scientists is their elegant simplicity - they're relatively easy to make, remain stable over time, and can be scaled up for commercial production without losing their effectiveness [6].These innovative delivery systems work through a sophisticated interplay of mechanisms: they help drugs dissolve better in the digestive system, stay in the body longer, trigger natural digestive processes, and make it easier for therapeutic compounds to cross intestinal barriers. SNEDDS technology works through multiple complementary pathways in the body - it helps drugs bypass the liver's initial screening process, encourages absorption through lymphatic channels, and prevents the intestines from pumping therapeutic compounds back out before they can do their job [7].

These formulations work like a pharmaceutical magic trick - they start as a simple mixture of oils and emulsifiers, but the moment they contact the watery environment of our digestive system, they instantly transform into tiny, perfectly formed nanoparticles. The merger between ancient herbal wisdom and cutting-edge nanotechnology has already begun to bear fruit, with several promising products making their way from laboratory benches to pharmacy shelves [8].The secret lies in their incredibly small size - these droplets are so tiny that they create an enormous surface area relative to their volume, giving poorly soluble drugs many more opportunities to dissolve and be absorbed by the body. As we look toward the future of medicine, nanoemulsions are emerging as a game-changing technology that could dramatically improve how we deliver treatments and, ultimately, how patients respond to therapy[9].

Novelty

While researchers have created many SNEDDS carrying either plant compounds or oils separately, there's a clear gap in the literature where no one has explored combining flavonoids with herbal oils in the same delivery system, especially for treating metabolic diseases like obesity[10].For example, quercetin-loaded SNEDDS showed dramatically better absorption than regular quercetin and offered superior protection against heart problems linked to metabolic disorders, yet this work focused solely on the flavonoid without exploring potential synergistic effects with herbal oils[11].When formulated pomegranate seed oil into SNEDDS, it became over 14 times more effective at blocking fat-digesting enzymes compared to the plain oil, showing excellent promise for obesity treatment—though no studies have yet combined such oils with flavonoids in the same formulation[12].This review highlights a significant research gap, as no study has yet combined specific flavonoids with herbal oils in SNEDDS for obesity management. By addressing this gap, we explore the untapped potential of such formulations to harness synergistic therapeutic effects while overcoming the bioavailability limitations of individual components.

Method of preparation

The preparation of self-nanoemulsifying drug delivery systems (SNEDDS) generally follows a systematic process in which lipid-based excipients are combined with surfactants and co-surfactants to form isotropic mixtures. Upon exposure to aqueous fluids, these mixtures spontaneously generate nanoemulsions that improve the solubility and absorption of poorly water-soluble compounds [13]. This approach has particular relevance for bioactive flavonoids and herbal oils that exhibit therapeutic potential in obesity management.

The first step in developing SNEDDS is the selection of an appropriate oil phase. Oils act not only as solvents for poorly soluble compounds but may also serve as active ingredients themselves. For example, herbal oils rich in omega-3 fatty acids or medium-chain lipids have been investigated both for their solubilizing properties and for their inherent hypolipidemic effects, making them particularly suitable for obesity-related applications [14].

After oil selection, surfactants and co-surfactants are introduced in carefully optimized ratios to ensure rapid and uniform emulsification. High-HLB surfactants such as polysorbates are often paired with co-solubilizers like polyethylene glycols or Transcutol P to enhance dispersibility. In many cases, ternary phase diagrams are constructed to identify the self-emulsifying region and guide the choice of excipient ratios [15].

In addition to conventional liquid SNEDDS, solid forms have been developed to improve stability, handling, and patient compliance. These are typically produced by converting liquid SNEDDS into free-flowing powders through techniques such as adsorption onto porous carriers, spray drying, or melt granulation. Such solidified systems retain their self-emulsifying properties when reconstituted and are regarded as a step toward translating laboratory formulations into clinically viable dosage forms [16].

Observation

Self-nanoemulsifying drug delivery systems (SNEDDS) and nanoemulsions have emerged as promising strategies to enhance the solubility, stability, and oral bioavailability of natural therapeutics such as flavonoids and herbal oils, which often face formulation challenges due to poor water solubility. Flavonoids including quercetin, naringenin, myricetin, and luteolin have been successfully incorporated into SNEDDS or nanoemulsion systems. In vivo studies demonstrate that quercetin SNEDDS significantly improved plasma exposure and positively modulated lipid profiles in high-fat diet animal models, highlighting its potential in obesity management [17]. Similarly, naringenin SNEDDS enhanced oral absorption and showed improvements in insulin resistance and lipid metabolism in rats, demonstrating efficacy against metabolic dysfunction [18]. Myricetin SNEDDS exhibited rapid self-emulsification, nanoscale droplet formation, and significantly higher plasma concentrations, suggesting potential benefits in modulating obesity-associated metabolic parameters [19]. Luteolin nanoformulations have also been explored in preclinical models of metabolic syndrome, improving lipid and glucose homeostasis and reducing adipose inflammation, which are closely linked to obesity management [14].

Table 1: Flavonoids for SNEDDS Applications

Flavonoid	SNEDD Study Type	Animal Model / Study Type	Key Observations	Reference
Quercetin	SNEDDSformulation, in vivo rats	High-fat diet rats	Improved plasma exposure; reduced lipid accumulation; enhanced oral bioavailability	[17]
Naringenin	SNEDDSformulation, in vivo rats	High-fat diet / insulin resistance rats	Enhanced oral absorption; improved lipid metabolism; reduced insulin resistance	[18]

Myricetin	SNEDDSformulation, in vivo rats	Rats (bioavailability study)	Rapid self-emulsification; nanoscale droplets (20–40 nm); significantly higher plasma concentration	[19]
Luteolin	Nanoformulation	Preclinical metabolic syndrome models	Improved lipid and glucose homeostasis; reduced adipose inflammation	[14]

Herbal oils have been increasingly explored as self-nanoemulsifying drug delivery systems (SNEDDS) to improve the solubility, bioavailability, and therapeutic potential of their bioactive compounds in obesity and metabolic disorders. Flaxseed oil, rich in alpha-linolenic acid (ALA) and lignans, has been incorporated into SNEDDS formulations, showing promising hypolipidemic and anti-inflammatory effects, as well as improved insulin sensitivity in rodent models (20,21). Extra virgin olive oil, containing oleic acid and polyphenols such as hydroxytyrosol and oleuropein, has been formulated in SNEDDS to enhance absorption of lipophilic nutraceuticals, demonstrating antioxidant, cardioprotective, and lipid-lowering benefits in both clinical and preclinical studies (22,23,24,25). Pomegranate seed oil, a rich source of punicic acid, has been delivered via SNEDDS or nanoemulsions, preventing diet-induced obesity and insulin resistance in mice while exerting anti-inflammatory effects (26,27). Nigella sativa oil, which contains thymoquinone and unsaturated fatty acids, has shown improved oral bioavailability in SNEDDS formulations, reducing blood glucose, adiposity, and systemic inflammation in animal studies (28,29). Finally, gamma-linolenic acid-rich oils such as evening primrose and borage oil have been incorporated into SNEDDS to enhance stability and solubility, leading to improved lipid metabolism and reduced inflammatory markers in preclinical models (30,31). Collectively, these findings show the versatility of SNEDDS for delivering bioactive flavonoids and herbal oils in therapeutic strategies targeting obesity and related metabolic disorders.

Table 2: Herbal Oils for SNEDDS Applications

Herbal Oil	**Major Component**	**Therapeutic Properties**	**SNEDDS Applications**	**ClinicalEvidence**	**Reference**
Flaxseed Oil	Alpha-linolenic acid (ALA), lignans	Hypolipidemic, anti-inflammatory, improves insulin sensitivity	Incorporated into SNEDDS to enhance solubility, bioavailability, and lipid-lowering effect	Rodent studies: improved lipid profile, reduced body fat	[20],[21]
Olive Oil (Extra Virgin)	Oleic acid, polyphenols (hydroxytyrosol, oleuropein)	Cardioprotective, antioxidant, anti-inflammatory, mild hypolipidemic	Used in SNEDDS to improve absorption of lipophilic nutraceuticals	Clinical & preclinical evidence: reduces oxidative stress, improves lipid profile	[22],[23],[24],[25]

Pomegranate Seed Oil	Punicic acid (conjugated linolenic acid)	Anti-obesity, anti-inflammatory, improves insulin sensitivity	Incorporated into SNEDDS/nanoemulsion to enhance bioavailability	Mice studies: prevented diet-induced obesity and insulin resistance	[26],[27]
Nigella sativa Oil	Thymoquinone, unsaturated fatty acids	Hypoglycemic, anti-inflammatory, antioxidant, anti-obesity	SNEDDS formulations improve oral bioavailability of active compounds	Rodent studies: decreased blood glucose and adiposity	[28],[29]
Evening Primrose Oil, Borage Oil)	Gamma-linolenic acid (GLA)	Anti-inflammatory, improves lipid metabolism	SNEDDS used to enhance solubility and stability	Animal studies: improved lipid profile and inflammatory markers	[30],[31]

Result and Discussion

SNEDDS effectively enhance the solubility and bioavailability of flavonoids such as quercetin, naringenin, myricetin, and luteolin, improving plasma exposure and metabolic outcomes in preclinical obesity models [17–19,14]. Quercetin SNEDDS reduced lipid accumulation, while naringenin SNEDDS improved insulin sensitivity and lipid metabolism.

Herbal oils like flaxseed, olive, pomegranate seed, Nigella sativa, and gamma-linolenic acid-rich oils also show enhanced therapeutic effects when delivered via SNEDDS, including lipid-lowering, anti-inflammatory, and antioxidant activities [20–31].

Combining flavonoids with herbal oils in a single SNEDDS formulation presents an unexplored opportunity for synergistic benefits, addressing bioavailability limitations and potentially offering superior outcomes in obesity management.

SNEDDS are simple to prepare, stable, and scalable, with solidified forms improving patient compliance and translational potential. Overall, flavonoid-herbal oil SNEDDS represent a promising, novel strategy for obesity and metabolic disorders, warranting further investigation.

Conclusion

Self-nanoemulsifying drug delivery systems (SNEDDS) offer a promising solution to one of the biggest challenges in herbal and flavonoid therapeutics—their poor water solubility and limited oral absorption. By encapsulating bioactive flavonoids and herbal oils, SNEDDS not only improve bioavailability but also enhance the therapeutic effects of these natural compounds, particularly in managing obesity and metabolic disorders. Preclinical studies with flavonoids like quercetin, naringenin, myricetin, and luteolin, as well as herbal oils such as flaxseed, olive, pomegranate seed, and Nigella sativa, highlight significant improvements in lipid metabolism, insulin sensitivity, and anti-inflammatory activity.

Importantly, the combination of flavonoids with herbal oils in a single SNEDDS formulation remains largely unexplored, representing a novel strategy with potential synergistic benefits. The ease of preparation, stability, and

scalability of SNEDDS further support their translational potential for clinical applications. Overall, flavonoid-herbal oil SNEDDS stand out as a versatile, innovative, and promising approach for improving metabolic health, offering hope for more effective and patient-friendly interventions against obesity.

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