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Self-Nanoemulsifying Drug Delivery Systems for Natural Bioactives: A Sustainable Approach to Nanoformulation

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Abstract

Natural bioactive compounds are widely recognised for their antioxidant, anti-inflammatory, anticancer, and cardioprotective benefits. Despite these advantages, many of them face significant challenges when translated to clinical applications, mainly because they dissolve poorly in water, degrade easily, and display limited absorption after oral intake. This review highlights recent progress in employing Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) as a strategy to overcome these limitations. SNEDDS are carefully designed blends of oils and surfactants that, upon entering the gastrointestinal tract, spontaneously disperse into fine nano-sized droplets. This rapid formation of nanoemulsion supports improved solubilisation, protection from degradation, and enhanced uptake through intestinal and lymphatic pathways. Evidence from preclinical and clinical studies indicates that incorporating natural bioactives into SNEDDS leads to notable improvements in pharmacokinetics and overall therapeutic effect. Formulations developed using this approach have demonstrated superior antioxidant capacity, stronger anti-inflammatory actions, and beneficial effects on neurological and cardiometabolic health when compared to their non-encapsulated forms. Additionally, the adaptability, safety profile, and environmentally conscious design of SNEDDS make them suitable candidates for use in pharmaceutical products as well as functional and nutraceutical preparations. Overall, SNEDDS is a promising system for increasing the delivery and bioavailability of natural compounds. SNEDDS can enhance the preventive and therapeutic potential of these bioactive agents by enhancing solubility, stability, and absorption. Their role in the further development of nutraceuticals could lead to the better management of chronic diseases, such as neuropathic pain, and to the long-term condition and the well-being sustainability.

Major Findings: Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) offer a practical and effective strategy to improve the delivery of natural bioactive compounds. By enhancing their solubility, stability, and absorption in the body, SNEDDS can help maximize both preventive and therapeutic benefits. This approach shows strong potential in advancing nutraceuticals for better management of chronic conditions such as neuropathic pain, ultimately supporting long-term health and overall well-being.

Keywords: Bioavailability Enhancement, Formulation, Natural Bioactives, Nutraceuticals, Self-Nanoemulsifying Drug Delivery Systems, Sustainable

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1. Introduction

The vast and varied array of natural bioactive compounds. These remarkable substances found abundantly in nature that significantly affect various physiological processes and yield a positive impact on overall health, nutrition, and the quality of life holds tremendous promise for diverse therapeutic applications and advancements in healthcare[1]. Numerous examples of these compounds can be

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categorised, including but not limited to carotenoids, flavonoids, phenolic acids, phytosterols, saponins, terpenes, vitamins, and waxes[2]. However, the development and widespread utilisation of these beneficial compounds are frequently hindered by various challenges, such as instances of low solubility in both water and lipid matrices, low stability during storage conditions, and low bioavailability from food sources. This is often due to the presence of complex matrices or potential degradation that can occur along the digestive tract after food intake[3]. To address these challenges, Self-Nanoemulsifying Drug Delivery Systems (SNEDDSs) emerge as a promising and innovative solution for enhancing the effective delivery of natural bioactives. These systems are designed to improve bioavailability, increase the diversity of possible bioactive substances that can be utilised, and allow for the precise tailoring of mixtures of bioactives to match specific health needs[4]. SNEDDSs consist of isotropic mixtures that combine oil, surfactant, co-surfactant, and drug components. These mixtures have the remarkable ability to spontaneously form nanoemulsions when they come into contact with aqueous media, which ultimately facilitates the solubilization of poorly soluble Active Pharmaceutical Ingredients (APIs) and natural bioactive compounds, thereby improving their effectiveness for therapeutic use[5].

SNEDDSs have been developed with a large number of semi-synthetic and synthetic drug candidates and poorly soluble natural bioactive compounds. The preparations, characterisation, bioavailability, and pharmacokinetic estimation, release, behaviour in lipid digestion, permeation, and mechanism clarification- a broad range of experimental circumstances and formulations, as well as active ingredients, are covered in the literature of such formulations. The development of effective SNEDDS formulations, therefore, is a big challenge. Nevertheless, the discovery of effective bioactive compounds still has a large research opportunity, which is to systematically couple the promising bioactive compounds with appropriate SNEDDS formulations. Such an investigation may enable the development of oils, surfactants, and co-surfactants of enhanced compatibility, improved drug loading, improved solubility, extended stability, or bio-accessibility due to extended retention in the gut. The accurate recognition of essential properties of natural bioactive compounds and the following options in the SNEDDS formulation space would contribute to this objective.

2. Fundamentals of Self-Nanoemulsifying Drug Delivery Systems

SNEDDS consist of isotropic mixtures of oils, surfactants, co-surfactants, and active ingredients. These systems can spontaneously form nano-emulsions when introduced to aqueous media during gastrointestinal transit. Nano-emulsions are kinetically stable dispersions of oil in water that generally have a mean droplet size of less than 200 nm[6]. SNEDDS significantly enhance the oral bioavailability of poorly soluble natural bioactives, making them highly valuable in pharmaceutical applications. Detailed information on various classes of SNEDDS, their therapeutic targets, essential physicochemical properties, and the diverse range of bioactive compounds involved will greatly assist researchers and formulators in the selection of suitable candidate systems for effective drug delivery.

SNEDDS can be further classified into distinct categories, including micro-emulsions, nano-emulsions, or various emulsion formulations based on the size of the initial droplets before their dispersion in a system[7]. In terms of bioactive selection guidelines, the percentage of drug loading which is measured by the weight of the total formulation serves as a primary estimate of the potential effectiveness of these systems. This drug loading percentage takes precedence over considerations of solubility enhancement, underscoring its importance in formulation development[8]. Typically, the solubility enhancement target established for these formulations remains below a factor of 100-fold. This limitation is crucial because the concentration levels of the major active ingredients found in various biocides, including compounds like flavonoids, carotenoids, as well as natural "green" waste materials, and bioactive phenolic compounds or essential oils derived from spices, tend to fall well within that range of 100-fold or less[9]. Furthermore, the prior statements regarding SNEDDS also imply the multitude of activities that natural bioactive compounds can exert, either independently or in conjunction with the formulated lipids and other components present in the mixtures[10].

3. Natural Bioactives: Profiles and Therapeutic Potential

Natural bioactives are remarkable bioactive phytochemicals found abundantly in a variety of sources such as plants, fruits, vegetables, tea, spices, herbs, and various marine organisms[11]. These natural compounds are known to exhibit a wide range of therapeutic activities that can be beneficial for health and wellness[12]. Among these bioactives, some notable examples include curcumin, resveratrol, quercetin, catechins, and essential fatty acids like eicosapentaenoic and docosahexaenoic acids[13]. The physicochemical properties of specific natural bioactives, along with their specific therapeutic targets and applications, depend on the class of natural components. The diverse bioactive compounds demonstrate remarkable effects, including anti-inflammatory, antitumor, antioxidant, cardioprotective, and neuroprotective properties that can significantly contribute to disease prevention and health promotion[14]. Despite these benefits, the bioactives often face challenges such as low aqueous solubility, poor chemical stability across various pH environments, and rapid degradation when exposed to light and heat[15]. These limitations highlight the importance of incorporating these bioactive compounds into advanced formulations. For instance, SNEDDS offer a promising strategy to enhance the bioavailability of these beneficial nutrients, ensuring their therapeutic potential can be realized effectively[16].

Natural bioactives are an array of essential compounds found in various food sources that confer numerous health benefits to individuals. These compounds can be classified into two main categories: the active substances, which are capable of triggering physiological effects through interaction with biological receptors, and the inactive compounds, which serve an important role by neutralising harmful substances that could be detrimental to health[1]. Among the active compounds, there are numerous notable examples, including polyphenols such as flavonoids, alkaloids, terpenoids, phytosterols, organosulfur compounds, and organonitrogen compounds. These compounds exhibit a range of significant properties, encompassing anti-inflammatory effects, antioxidant capabilities, anticancer activities, antihypertensive functions, antidiabetic characteristics, and anti-obesity effects[17]. Several remarkable bioactive compounds have attracted considerable attention due to their health-promoting properties, including resveratrol, which is known for its heart-protective effects[18]; curcumin, widely recognized for its powerful anti-inflammatory and antioxidant properties[19]; genistein, which is noted for its potential in cancer prevention[20]; Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), both of which are crucial omega-3 fatty acids with notable benefits for brain and heart health[21]. A plethora of studies have been conducted that establish their potential roles in treating and managing major diseases effectively[22]. To enhance the bioavailability of these vital compounds, innovative micro and nano delivery systems have been extensively developed and utilised. These systems include liposomes, which are small vesicles that can encapsulate bioactive compounds; antioxidative or anti-inflammatory emulsions designed to stabilise and protect these compounds[23]; nanocrystals that facilitate better absorption[24]; and SNEDDS, which are advanced formulations aimed at improving the delivery and efficacy of bioactive compounds in the body[25].

4. Formulation Strategies for SNEDDS with Natural Bioactives

Formulation strategies for SNEDDS with natural bioactives integrate design principles, selection criteria, and optimisation approaches to pair bioactives with SNEDDS. Companion sections on lipid choice and surfactant/co-surfactant combinations, loading and stability considerations, and process parameters further illuminate these critical formulation issues.

Formulation strategies aimed at enhancing the solubility of natural bioactives within SNEDDS encompass a comprehensive array of design principles, selection criteria, and optimisation approaches that are crucial for effectively pairing bioactives with these advanced delivery systems[26]. As has been summarised in earlier sections of this discussion, to achieve maximum therapeutic benefit, bioactives must be loaded at their maximum solubility within the SNEDDS. Furthermore, it is critical to minimise their degradation when subjected to gastric or intestinal fluids during the digestive process. Compounding this complexity, many bioactive compounds exhibit limited solubility in the lipid and surfactant systems employed

in the formulation. Subsequent sections discussing the selection of lipids, surfactant–co-surfactant combinations, as well as considerations related to drug loading, stability, and manufacturing parameters, further highlight the critical formulation challenges that must be addressed[27]. Effective development of SNEDDS, therefore, requires careful optimisation of these factors to enhance the delivery and bioavailability of natural bioactives, ultimately contributing to improved therapeutic outcomes.

4.1 Lipid Choice and Surfactant/Co-surfactant Combinations

SNEDDSs are isotropic mixtures of natural and synthetic oils, surfactants, and co-surfactants with a high drug loading capacity. SNEDDS have been proposed as a promising strategy to deliver natural bioactives, due to the preservation of their therapeutic effect, complementary mechanisms of action, and a wide spectrum of targets. Natural bioactives include substances derived from plants, animals, and minerals that possess pharmaceutical properties such as anti-inflammatory, antioxidant, and anticancer effects. Cadmium and lead are examples of heavy metals accumulated in the human body through various routes and lead to several diseases. SNEDDS formulations containing curcumin and α-tocopherol have an ameliorating effect on cadmium and lead-induced toxicities in the liver, kidneys, hematopoietic system and sexual organs[28], thus SNEDDS are considered as a promising system to deliver natural bioactives to protect human health from heavy metals. Figure 1 for the schematic presentation of SNEEDS formulation.

Formulation strategies for SNEDDS containing natural bioactives consist of systematic specifications related to bioactives and SNEDDS design. Lipid systems (liquid, semi-solid, or solid), surfactants, and co-surfactants were compared based on their solubility toward several bioactives, emulsification efficiency, and compatibility with excipients. The quantity of natural bioactives was selected in connection with the desired solubility enhancement and stability under typical gastric and intestinal conditions, whereas the balance of the system needed to keep a suitable emulsification ability and remain inside the same natural origin category. Characteristics of systemic transformation during digestion and various *in vitro* digestion models are of increasing interest for investigation. Simulated dissolution and intestinal conditions were linked to the time evolution of droplet size and digestion profiles, and changes in lipid digestion continued to modify the bioactive solid-state within the evaluation time span[29].

4.2 Drug Loading, Solubility, and Stability Considerations

SNEDDS can further enhance the oral bioavailability of natural bioactives, which often suffer from poor solubility and stability. Natural bioactives encapsulated within SNEDDS formulations remain soluble and stable in simulated gastric fluid for extended periods of time. Besides maintaining a stable and soluble form of the drug, an optimal

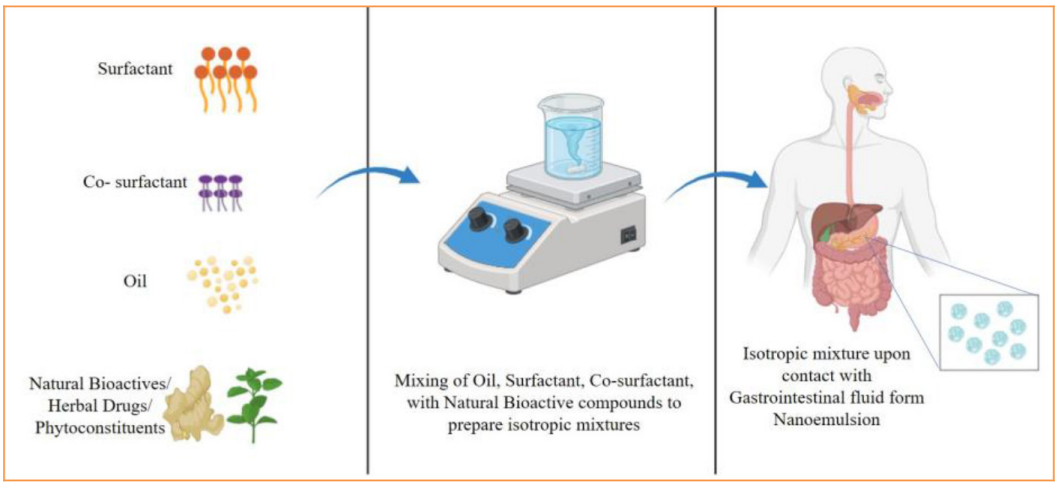


Figure 1. Schematic presentation of SNEDDS constituents, isotropic mixture, and mechanism of forming self-nano emulsion upon contact with Gastrointestinal fluids.

formulation acts as a solubilization vehicle that can magnify the drug's inherent solubility by orders of magnitude. Continuous improvement of drug solubility and stability ensures that the bioactive compound can persist in gastric and intestinal digestion media long enough to allow its efficient delivery to the target site[30]. Certain natural bioactives are prone to degradation under simulated gastrointestinal conditions, leading to the formation of insoluble degradation products. In such cases, it is crucial to retain bioactive integrity and avoid or minimise degradation and subsequent precipitation. Natural bioactives are encapsulated within lipid or surfactant systems at concentrations that greatly exceed their equilibrium solubility in aqueous media. To achieve optimum loading without compromising the benefits of the self-emulsifying system, it is important to select natural bioactives with substantial loading capacities that do not adversely affect self-emulsifying performance[5].

4.3 Process Parameters and Quality Attributes

Process parameters are closely linked to the quality attributes of self-nanoemulsifying systems. The size and stability of nanoemulsions are influenced by the homogenization speed and duration, the absence or presence of organic solvents, and temperature during the preparation. After homogenization, either the temperature is maintained above or brought back to a predetermined value without undue delay[31]. The effect of temperature on globule size is generally investigated at a fixed homogenization time and speed.

Based on the composition of the SNEDDS, multiple chemical tests can evaluate the physicochemical stability of the formulations over time. The UV–Visible (UV–Vis) absorption spectrum is commonly used to check the degradation of active compounds, such as curcumin and carotenoids, in different surfactants, co-surfactants, and oils[16]. The degree of discolouration is also an indicator of the photodegradation of active compounds under UV irradiation[32]. A particle size measurement, such as Dynamic Light Scattering (DLS), can reveal whether emulsion coalescence or significant phase separation has occurred[33]. The relative viscosity and pH, which are less affected by chemical structure, are essential quality attributes of semi-solid formulations.

5. Biopharmaceutics of SNEDDS-encapsulated Bioactives

Microencapsulation has emerged as an effective technique to enhance the stability and bioavailability of natural bioactives. However, the physicochemical properties of Polylactic-Co-Glycolic Acid (PLGA), such as low glass transition temperature (unfavourable equilibrium) and solubility in common organic solvents, limit its applicability[34]. SNEDDS provide a promising alternative to microencapsulation to improve bioactivity. This is due to the efficient solubilisation of polar bioactives, improved spatiotemporal and bio-efficiency of delivery, and the ease of formulating solid and semi-solid lipid formulations.

Bioactives such as curcumin, resveratrol, quercetin, and Epigallocatechin Gallate (EGCG) have been encapsulated in SNEDDS. The various bioactives have their physicochemical properties (indicated by log P values, pKa values) and therapeutic targets (sudden coronary death, liver-related disorders, obesity, diabetes, and microbial infections)[4]. SNEDDS can enhance the bioavailability and improve the pharmacological activities of bioactives through lymphatic uptake, interaction with transporters or the microbiota, and other mechanisms. The bioavailability of curcumin equipped with SNEDDS has been reported to increase up to 11-fold. SNEDDS-designed curcumin delivery significantly mitigates gouty arthritis without causing toxicity at the tested concentrations. Such works highlight the great promise, versatile adaptability, and broad potential therapeutic applications of bioactives delivered via SNEDDS formulation[6].

5.1 In Vitro Release and Digestive Fate

In vitro dissolution testing is widely performed within controlled laboratory environments to predict drug release. Unfortunately, standard dissolution equipment is ill-suited for simulating Gastrointestinal (GI) digestive fluids. Studies elucidating the fate of SNEDDS under simulated GI conditions are conspicuously rare. Dissolution testing performed in media designed to mimic prevailing gastric and intestinal conditions shows a clear distinction between SNEDDS-formulated compounds and their coarse forms[26]. Deployment of selected lipids in a digestible SNEDDS formulation further elevates the performance differential compared

to coarse excipient systems. GI digestion entails the generation of emulsified lipids and the detergent-like activity of Free Fatty Acids (FFA) released from triglyceride lipids. Supplementation of non-digestible components fails to completely abrogate the elevated release of non-polar compounds observed from digestible formulations.

Full-filling a key role in drug delivery, the gut interfaces with dietary components and physicochemical properties of bioactive compounds to shape absorption rates[16]. Gastric residence time varies broadly depending on formulation type and physicochemical attributes; therefore, therapeutically-relevant concentrations of active bioactives must be neighbouring gut secretions for subsequent intestinal absorption steps.

Influencing Cmax, Tmax, AUC, and inter-subject variability, the dynamic interplay between confinement and metabolic processes establishes the pharmacokinetic profile. The intended bioactive aim asks whether an oral dosage form meets the prerequisites for pharmacokinetic comparisons[35]. At the pharmacokinetic screening stage, drug-release-dissolution capabilities established during early formulation screening helps grounded the selection of appropriate dosage forms.

5.2 Permeation and Bioavailability Enhancement

Permeation and bioavailability enhancement. The formation of nanoemulsions can aid in improving the oral bioavailability of drugs like coenzyme Q10, vitamin E, halofantrine, and cyclosporine A, with the overall process being governed by several factors[36]. The enrichment of permeation through the Nanoemulsifying Drug Delivery System (NEDDS) can be explained through various transporters, lymphatic uptake, and a subsequent reduction of first-pass metabolism[16]. This is further elucidated by specific changes in pharmacokinetic properties such as Cmax, Tmax, AUC, and variability between subjects; for instance, higher AUC values stemming from the same dose level and lower Tmax values for separate administered bioactive compounds.

5.3 Pharmacokinetic Implications

Oral bioavailability is a major hurdle for many natural bioactives, leading to low plasma concentrations and high interindividual variability. The incorporation of bioactives into SNEDDS formulations can provide a strategic approach to overcome these challenges by improving the pharmacokinetic profile. With the formation of the emulsion in the gastrointestinal tract, it is anticipated that SNEDDS-encapsulated natural bioactives exhibit a higher Cmax, a shorter Tmax, a larger AUC, and a reduced inter-individual variability in plasma concentration compared to the unformulated bioactives[37]. To properly study these pharmacokinetic implications, bioactivity confirmation is essential after the chosen dosage form in preclinical studies, as not all natural bioactives exhibit identical bioactivity following a similar dosage regimen. Moreover, comparing the pharmacokinetic profiles of the formulation and the free drug in the same study incurs a common pitfall[38]. If a bioactive is incorporated into a SNEDDS formulation, the respective base of the formulation is essential for understanding the bioavailability enhancement provided by the emulsifying composition, as it already undergoes a significant elimination process during the gastrointestinal tract. A preformulation study is therefore suggested to select the appropriate dosage according to the physicochemical properties of the bioactive and its metabolic pathway, ensuring that the comparison is done at a similar dosing level in terms of molar concentration instead of mass[16].

6. Biological Activities and Therapeutic Applications

SNEDDSs can synergistically enhance the water solubility, stability, and intestinal absorption of various classes of natural bioactives, including polyphenols, terpenes, alkaloids, and phytoextracts. Correspondingly, the SNEDDS-encapsulated bioactives exhibit a range of biological activities and therapeutic targets, which are summarised in this section. Several SNEDDS-encapsulated bioactives demonstrate potent anti-inflammatory and antioxidant effects by inhibiting relevant pathways, biomarkers, and mediators. Quercetin and curcumin, for instance, effectively inhibit the production of the pro-inflammatory cytokine IL-6 in LPS-induced macrophage cells[39]. Similarly, curcumin inhibits the expression of inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenas (COX)-2 in RAW 264.7 macrophages, while also blocking the NF-kB pathway in LPS-stimulated

microglial cells. Anthocyanins and isoflavones show comparable anti-inflammatory activities[16].

Natural bioactives exhibiting anticancer and neuroprotective potentials include curcumin, apigenin, berberine, and resveratrol. Resveratrol, for example, inhibits the growth of human cancer cell lines, with efficacy varying by cell type[40]. Curcumin treatment induces apoptosis in ovarian cancer cells via P53 activation, whereas its protective effects against neurodegeneration in animals are mediated through the Notch signalling pathway[41]. The cancerous cell lines HCT116, PC-12, and HepG2 also show sensitivity to berberine, which activates target proteins involved in cell cycle regulation, DNA repair, and apoptosis[42]. Curcumin-loaded SNEDDS further enhances protection against glucose/glutamate-induced toxicity in PC12 cells and MPP+-induced toxicity in a *C. elegans* Parkinson model.

Cardiovascular and metabolic benefits associated with bioactives such as flavonoids, curcumin, and DL-3-n-butylphthalide include improvements in lipid profiles, glycemic control, blood pressure, and endothelial function[43]. Curcumin and the flavonoids luteolin and naringin lower triglycerides and total cholesterol, whereas flavonoids and phenolic extracts from various fruits inhibit α-glucosidase. Curcumin-loaded SNEDDS triggered a >2-fold decrease in total cholesterol and >3-fold decrease in triglycerides compared with the unformulated compound[44]. As well, quercetin, resveratrol, and catechins derived from fermented green tea reduce blood pressure. DL-3-n-butylphthalide enhances cerebral blood flow and alleviates vascular inflammation in cerebral ischemia-reperfusion injury[45].

6.1 Anti-inflammatory and Antioxidant Effects

Natural bioactives with various biological activities hold great promise for maintaining health and preventing the onset of chronic diseases. Their activities and the concomitant physiological mechanisms can serve as a basis for the development of effective nutraceuticals. Despite this, many natural bioactives, including carotenoids, polyphenols, and essential fatty acid-rich oils, have low solubility in the Gastrointestinal (GI) tract or poor chemical stability during GI transit, resulting in low oral bioavailability and limited therapeutic potential. SNEDDS have attracted considerable interest as a means of improving the oral delivery of such bioactives[46].

A range of pathways, biomarkers, and experimental models has been used to evaluate, respectively, the anti-inflammatory and antioxidant effects of bioactive compounds. SNEDDS-encapsulated agents capable of ameliorating inflammation and oxidative stress have emerged as nutraceuticals and are under study as therapeutics for diseases such as diabetes, cancer, and neurodegeneration.

6.2 Anticancer and Neuroprotective Potentials

Several natural extracts with anticancer activity have been encapsulated in SNEDDS, including curcumin from *Curcuma longa*[47], botulinic acid from Betula alba (Kaps *et al.,* 2021), quercetin from diverse sources, and pentacyclic triterpenoids from various plant families[48]. Curcumin formulations can also enhance antidiabetic and anti-inflammatory activities. Esculin from *Aesculus hippocastanum* further improves the anti-inflammatory profile of curcumin[49]. Varieties of α-, β-, and γ-sterols, resveratrol from *Vitis vinifera*, and β-sitosterol from diverse plants also augment the anticancer effects of curcumin. SNEDDS have also been combined with polymeric nanoparticles for co-delivery of curcumin and resveratrol to address challenges in separate encapsulation. The neuroprotective activity of curcumin in Parkinson's disease models has been enhanced through SNEDDS, leading to greater transcription of neuroprotection-related genes than free curcumin. Bioavailability, tissue localisation, and neighbourhood interactions are vital for anticancer and neuroprotective therapeutic action and can be improved through bioavailability-modulating SNEDDS.

6.3 Cardiovascular and Metabolic Benefits

Natural bioactives have been examined for a variety of cardiovascular and metabolic-related benefits. Recently, the cardiovascular effects of resveratrol, curcumin, and green tea catechins have been investigated, highlighting their potential. Resveratrol has been found to have various effects on lipid profiles through different pathways, helping to decrease body weight and glycaemia while regulating glucose and insulin metabolism. Curcumin has shown anti-hyperglycaemic activity *in vitro* and in animal studies, while also ameliorating triglyceride levels, total cholesterol, and LDL cholesterol in diabetic rats. Green tea catechins have displayed beneficial

effects on blood pressure and endothelium-dependent vasodilation in subjects with metabolic syndrome.

Regarding the prevention and treatment of metabolic syndrome, several natural bioactives have been identified. For instance, resveratrol has been reported to reduce body weight, adipocyte differentiation, and lipogenesis, leading to improved glycaemic control. Curcumin can also inhibit adipocyte differentiation and is involved in the regulation of glucose metabolism and transport. L-carnitine is associated with enhanced glucose homeostasis, increased energy expenditure, and reduced fat mass. In particular, the most evaluated compound, curcumin, has shown anti-hyperglycaemic activity through the improvement of glucose homeostasis and modulation of insulin sensitivity[50].

7. Safety, Tolerability, and Regulatory Considerations

Despite their beneficial effects, many natural bioactives are cytotoxic at higher doses. Regulatory authorities generally consider supplements made from natural substances to have a lower risk than synthetic compounds. Nonetheless, they still require toxicological evaluations to establish safe use levels[36]. The safety of excipients commonly included in SNEDDS formulations for bioactives has been documented; the considerations are therefore focused on the bioactives themselves, the expected dose per SNEDDS unit, potential Drug-Drug Interactions (DDIs), stability under storage and use conditions, and regulatory expectations.

Toxicity data, such as the Maximum Tolerated Dose (MTD) and No-Observed-Adverse-Effect-Level (NOAEL), are essential to derive dosage limits and open registration avenues for novel combinations that exhibit advantageous pairing properties[33]. When addressing the food and health supplement supply segment, especially natural bioactives, to supplement existing formulations, bioavailability enhancement at validated concentrations, product stability, and a simple, fast method of residue determination are crucial specifications.

8. Challenges, Limitations, and Future Perspectives

Incorporating SNEDDS in developing nutraceutical formulations is a promising strategy for enhancing the oral bioavailability of poorly soluble and unstable food bioactive compounds. Nevertheless, SNEDDS formulation remains challenging, as several bioactive candidates lack the necessary solubility, emulsification capacity, or stability to compatible, high excipients[52]. Consequently, bioactive–SNEDDS combinations developed to date are scarce and rely on trial-and-error or time-consuming screening procedures. The industry-friendly approach of using readily available and cost-effective surfactants with low toxicity and high compatibility with both lipid mixtures and other excipients has been devoted negligible attention. Moreover, biopharmaceutical and pharmacokinetic databases on SNEDDS-encapsulated bioactives are limited; the existing knowledge of release mechanisms, digestion behaviour, and the influence of lipid digestion on bioavailability is inadequate for understanding the expected benefits and framing new studies[36].

9. Conclusion

Natural bioactives have gained prominence as preventive and therapeutic agents due to their safety and acceptability. Consequently, SNEDDS have emerged as a formulation technology to improve drug solubility, dissolution, and *in vivo* permeability. SNEDDS consist of isotropic mixtures of oil, surfactants, co-surfactants, and natural bioactives in selected proportions. They spontaneously form nanoemulsions in aqueous media through mild agitation, promoting improved bioactive delivery through various mechanisms. The therapeutic application of bioactives is limited by poor solubility, stability, and absorption. SNEDDS were found to be a suitable formulation approach to refine these bioactives. SNEDDS can enhance the delivery of tamoxifen (an anticancer agent), curcumin (an anti-inflammatory agent), and oridonin (an anti-infection agent) when paired with suitable excipients. Overall, SNEDDS offer a viable option for advancing the use of natural bioactives. Improving delivery systems does not fundamentally alter materials, thereby ensuring compliance with green or environmentally friendly tenure. New bioactive candidates can still be evaluated, sustaining research momentum.

10. References

1. Narayanankutty A, Famurewa AC, Oprea E. Natural bioactive compounds and human health. Molecules. 2024; 29(3):586. https://doi.org/10.3390/molecules29030586
2. Mohammadi-Cheraghabadi M, Hazrati S. Chapter 5 Terpenoids, steroids, and phenolic compounds of medicinal plants. In: Arora C, Verma D, Aslam J, Mahish P, editors. Phytochemicals in Medicinal Plants: Biodiversity, Bioactivity and Drug Discovery. Berlin, Boston: De Gruyter. 2023: pp. 105-130. https://doi.org/10.1515/9783110791891-005
3. Shahidi F, Pan Y. Influence of food matrix and food processing on the chemical interaction and bioaccessibility of dietary phytochemicals: a review. Crit Rev Food Sci Nutr. 2022; 62(9):2451-2470. https://doi.org/10.1080/10408398.2020.1852170
4. de Oliveira MC, Bruschi ML. Self-emulsifying systems for the delivery of bioactive compounds from natural origin. AAPS PharmSciTech. 2022; 23(5):123. https://doi.org/10.1208/s12249-022-02291-z
5. Gautam S, Kumar Singh A. Self-nanoemulsifying drug delivery system: a novel approach for improving bioavailability. Int J Pharm Sci Rev Res. 2014; 25(2):123-130. https://ijpsrr.com
6. Mounika M, Kumar Desu P, Vanitha K. A review on self-nanoemulsifying drug delivery system. Int J Pharm Sci Res. 2019; 10(5):2245-2254. https://doi.org/10.13040/IJPSR.0975-8232.10(5).2245-54
7. Divate MP, Bawkar SU, Chakole RD, Charde MS. Self-nano-emulsifying drug delivery system: a review. J Adv Sci Res. 2021; 12(3 Suppl 2):1-2. https://doi.org/10.55218/JASR.s2202112301
8. Shao Z, Yin T, Jiang J, He Y, Xiang T, Zhou S. Wound microenvironment self-adaptive hydrogel with efficient angiogenesis for promoting diabetic wound healing. Bioact Mater. 2022; 20:561-573. https://doi.org/10.1016/j.bioactmat.2022.06.018
9. Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, Bansal KK, Kurmi BD. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. Life (Basel). 2023; 13(5):1099. https://doi.org/10.3390/life13051099
10. Vaou N, Stavropoulou E, Voidarou C, Tsakris Z, Rozos G, Tsigalou C, Bezirtzoglou E. Interactions between medical plant-derived bioactive compounds: focus on antimicrobial combination effects. Antibiotics (Basel). 2022; 11(8):1014. https://doi.org/10.3390/antibiotics11081014
11. Riar CS, Panesar PS. Bioactive compounds and nutraceuticals: classification, potential sources, and application status. In: Bioactive Compounds and Nutraceuticals from Dairy, Marine, and Nonconventional Sources. Apple Academic Press. 2024: pp. 3-60. https://doi.org/10.1201/9781003452768-2
12. Sun W, Shahrajabian MH. Therapeutic potential of phenolic compounds in medicinal plants: natural health products for human health. Molecules. 2023; 28(7):2996. https://doi.org/10.3390/molecules28072996
13. Méndez L, Medina I. Polyphenols and fish oils for improving metabolic health: a revision of the recent evidence for their combined nutraceutical effects. Molecules. 2021; 26(2):385. https://doi.org/10.3390/molecules26020385
14. Wijesekara T, Xu B. Health-promoting effects of bioactive compounds from plant endophytic fungi. J Fungi (Basel). 2023; 9(3):314. https://doi.org/10.3390/jof9030314
15. Kurek M, Benaida-Debbache N, Elez Garofulić I, Galić K, Avallone S, Voilley A, Waché Y. Antioxidants and bioactive compounds in food: critical review of issues and prospects. Antioxidants (Basel). 2022; 11(4):742. https://doi.org/10.3390/antiox11040742
16. Salvia-Trujillo L, Martín-Belloso O, McClements DJ. Excipient nanoemulsions for improving oral bioavailability of bioactives. Foods. 2016; 5(4):47. https://doi.org/10.3390/nano6010017
17. Dar RA, Shahnawaz M, Ahanger MA. Exploring the diverse bioactive compounds from medicinal plants: a review. Phytopharma Journal. 2023; 3(2):15-25. https://doi.org/10.31254/phyto.2023.12307
18. Akgun-Unal N, Ozyildirim S, Unal O. The effects of resveratrol and melatonin on biochemical and molecular parameters in diabetic old female rat hearts. Exp Gerontol. 2023; 181:112292. https://doi.org/10.1016/j.exger.2023.112292
19. Peng Y, Ao M, Dong B, Jiang Y, *et al.* Anti-inflammatory effects of curcumin in the inflammatory diseases: status, limitations and countermeasures. Drug Des Dev Ther. 2021; 15:4503-4525. https://doi.org/10.2147/DDDT.S327378
20. Rasheed S, Rehman K, Shahid M, Suhail S, Akash MS. Therapeutic potentials of genistein: new insights and perspectives. J Food Biochem. 2022; 46(9):e14228. https://doi.org/10.1111/jfbc.14228
21. von Schacky C. Importance of EPA and DHA blood levels in brain structure and function. Nutrients. 2021; 13(4):1074. https://doi.org/10.3390/nu13041074
22. Anwar S, Alrumaihi F, Sarwar T, Babiker AY, Khan AA, Prabhu SV, Rahmani AH. Exploring the therapeutic potential of catalase: strategies in disease prevention and management. Biomolecules. 2024; 14(6):697. https://doi.org/10.3390/biom14060697
23. Kyriakoudi A, Spanidi E, Mourtzinos I, Gardikis K. Innovative delivery systems loaded with plant bioactive ingredients: formulation approaches and applications. Plants (Basel). 2021; 10(11):2361. https://doi.org/10.3390/plants10112361
24. Tian Z, Mai Y, Meng T, Ma S, *et al.* Nanocrystals for improving oral bioavailability of drugs: intestinal transport mechanisms

and influencing factors. AAPS PharmSciTech. 2021; 22(6):234. https://doi.org/10.1208/s12249-021-02041-7

25. Bravo-Alfaro DA, Ochoa-Rodriguez LR, Velasco-Rodriguez LC, Vega-Guerrero PE, Luna-Barcenas G, Garcia HS. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS): a thermodynamic and molecular approach and their potential applications in functional foods. Food Eng Rev. 2025; 17:1-38. https://doi.org/10.1007/s12393-025-09429-2
26. Morakul B, Teeranachaideekul V, Limwikrant W, Junyaprasert VB. Dissolution and antioxidant potential of apigenin Self-Nanoemulsifying Drug Delivery System (SNEDDS) for oral delivery. Sci Rep. 2024; 14(1):8851. https://doi.org/10.1038/s41598-024-59617-z
27. Samant BS, Kaliappan R. The use of surfactants in the extraction of active ingredients from natural resources: a comprehensive review. RSC Adv. 2025; 15(10):6597-6621. https://doi.org/10.1039/D5RA02072G
28. Mohsin K, Alamri R, Ahmad A, Raish M, *et al.* Development of self-nanoemulsifying drug delivery systems for the enhancement of solubility and oral bioavailability of fenofibrate, a poorly water-soluble drug. Drug Des Dev Ther. 2016; 10:3875-3885. https://doi.org/10.2147/DDDT.S114995
29. McClements DJ, Öztürk B. Utilisation of nanotechnology to improve the handling, storage and biocompatibility of bioactive lipids in food applications. Annu Rev Food Sci Technol. 2021; 12:181-202. https://doi.org/10.3390/foods10020365
30. Bhardwaj K, Sharma A, Kumar R, Tyagi V, Kumar R. Improving oral bioavailability of herbal drugs: a focused review of self-emulsifying drug delivery system for colon cancer. Curr Drug Deliv. 2024; 21(3):389-402. https://doi.org/10.2174/1567201820666230505113108
31. Jindal A, Saifi A, Kumar A, Chaudhary D. Quality-by-design (QbD) accredited rutin-loaded self-nanoemulsifying system of krill oil for improved dissolution rate, ameliorating human neuroblastoma and hyperlipidemia. Int J Biol Macromol. 2025; 290:145768. https://doi.org/10.1016/j.ijbiomac.2025.145768
32. Zhao Z, Cui X, Ma X, Wang Z. Preparation, characterisation, and evaluation of antioxidant activity and bioavailability of a Self-Nanoemulsifying Drug Delivery System (SNEDDS) for buckwheat flavonoids. Food Chem. 2020; 319:126515. https://doi.org/10.1016/j.foodchem.2020.126515
33. Eid AM, El-Enshasy HA, Aziz R, Elmarzugi NA. Preparation and evaluation of self-nanoemulsifying systems containing Swietenia oil and an examination of its anti-inflammatory effects. J Nanomed Nanotechnol. 2014; 5(5):1000224. https://doi.org/10.4172/2157-7439.1000224
34. Pateiro M, Gómez B, Munekata PE, Barba FJ, Putnik P, Kovačević DB, Lorenzo JM. Nanoencapsulation of promising bioactive compounds to improve their absorption, stability, functionality, and the appearance of the final food products. Molecules. 2021; 26(6):1547. https://doi.org/10.3390/molecules26061547
35. Zakaraya Z, Abu Assab M, Tamimi LN, Karameh N, Hailat M, Al-Omari L, Abu Dayyih W, Alasasfeh O, Awad M, Awad R. Pharmacokinetics and pharmacodynamics: a comprehensive analysis of the absorption, distribution, metabolism, and excretion of psychiatric drugs. Pharmaceuticals (Basel). 2024; 17(3):280. https://doi.org/10.3390/ph17030280
36. Jaiswal P, Aggarwal G. Bioavailability enhancement of poorly soluble drugs by SMEDDS: a review. J Drug Deliv Ther. 2013; 3(3):155-161. https://doi.org/10.22270/jddt.v3i3.498
37. Shahba AAW, Sherif AY, Elzayat EM, Kazi M. Combined ramipril and black seed oil dosage forms using Bioactive Self-Nanoemulsifying Drug Delivery Systems (BIO-SNEDDSs). Pharmaceuticals (Basel). 2022; 15(5):550. https://doi.org/10.3390/ph15050550
38. Fazmiya MJ, Sultana A, Rahman K, Heyat MB, Sumbul, Akhtar F, Khan S, Appiah SC. Current insights on bioactive molecules, antioxidant, anti-inflammatory, and other pharmacological activities of *Cinnamomum camphora* Linn. Oxid Med Cell Longev. 2022; 2022:9354555. https://doi.org/10.1155/2022/9354555
39. Ranjbar S, Emamjomeh A, Sharifi F, Zarepour A, *et al.* Lipid-based delivery systems for flavonoids and flavonolignans: liposomes, nanoemulsions, and solid lipid nanoparticles. Front Nutr. 2023; 10:1125409. https://doi.org/10.3390/pharmaceutics15071944
40. Singh A, Singh J, Parween G, Khator R, Monga V. A comprehensive review of apigenin, a dietary flavonoid: biological sources, nutraceutical prospects, chemistry, pharmacological insights, and health benefits. Crit Rev Food Sci Nutr. 2025; 65(23):4529-4565. https://doi.org/10.1080/10408398.2024.2390550
41. Mohamadian M, Bahrami A, Moradi Binabaj M, Asgharzadeh F, Ferns GA. Molecular targets of curcumin and its therapeutic potential for ovarian cancer. Nutr Cancer. 2022; 74(8):2713-2730. https://doi.org/10.1080/01635581.2022.2049321
42. Almatroodi SA, Alsahli MA, Rahmani AH. Berberine: an important emphasis on its anticancer effects through modulation of various cell signalling pathways. Molecules. 2022; 27(20):6646. https://doi.org/10.3390/molecules27185889
43. Khan J, Deb PK, Priya S, Medina KD, Devi R, Walode SG, Rudrapal M. Dietary flavonoids: cardioprotective potential with antioxidant effects and their pharmacokinetic, toxicological, and therapeutic concerns. Molecules. 2021; 26(13):4021. https://doi.org/10.3390/molecules26134021
44. Subramanian P. Lipid-based nanocarrier system for the effective delivery of nutraceuticals. Molecules. 2021; 26(22):6761. https://doi.org/10.3390/molecules26226761

45. Gai Z, Hu S, Gong G, Zhao J. Recent advances in understanding dietary polyphenols protecting against hypertension. Trends Food Sci Technol. 2023; 138:58-70. https://doi.org/10.1016/j.tifs.2023.07.001
46. Józsa L, Vasvári G, Sinka D, Nemes D, *et al.* Enhanced antioxidant and anti-inflammatory effects of self-nano and microemulsifying drug delivery systems containing curcumin. Int J Pharm. 2022; 622:121858. https://doi.org/10.1016/j.ijpharm.2022.121858
47. Khan T, Gurav P. Phytonanotechnology: enhancing delivery of plant-based anticancer drugs. Front Pharmacol. 2018; 9:1307. https://doi.org/10.3389/fphar.2018.01307
48. Kaps A, Gwiazdoń P, Chodurek E. Nanoformulations for delivery of pentacyclic triterpenoids in anticancer therapies. Int J Mol Sci. 2021; 22(2):628. https://doi.org/10.3390/ijms22020628
49. Yan L, Zhang Y, Dai D, Li Y, Xiao W. Pharmacological activities of *Aesculus hippocastanum* and its bioactive constituents in hemostasis: A mechanistic review. Pharmacogn Mag. 2025; 21(3):727-737. https://doi.org/10.1177/09731296241299498
50. Nouri Z, Hajialyani M, Izadi Z, Bahramsoltani R, *et al.* Nanophytomedicines for the prevention of metabolic syndrome: a pharmacological and biopharmaceutical review. Pharmacol Res. 2020; 156:104754. https://doi.org/10.1016/j.phrs.2020.104754
51. Godase SS, Kulkarni NS, Dhole SN. A comprehensive review of novel lipid-based nano drug delivery. Curr Pharm Biotechnol. 2024; 25(8):678-690. https://doi.org/10.34172/apb.2024.012
52. Subramanian P. Lipid-based nanocarrier system for the effective delivery of nutraceuticals. Molecules. 2021; 26(22):6761. https://doi.org/10.3390/molecules26226761

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