## *Mini Review*

# The Role of Natural Plants with Incorporation of Tocopherols, Ubiquinone and Tocotrienols in Nanoemulsion Formulation: A Mini Review

Noreen Ang Azlan[1*], Vitalis Ronald Eden[1,2]

[1]Faculty of Allied Health Sciences, IJN College, 145, Jalan Tun Razak, 50400 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia
[2]Faculty of Pharmacy, Lincoln University College, Wisma Lincoln, No. 12-18, Jalan SS 6/12, 47301 Petaling Jaya, Selangor, Malaysia

**ABSTRACT**

Natural oils and fatty acids are frequently employed as key components in nanoemulsion formulations to enhance permeability in various pharmaceutical and cosmetic products. Their inclusion contributes to the formulation's ability to improve the absorption and bioavailability of active ingredients. The use of these natural oils and fatty acids in nanoemulsions is valued for their compatibility with biological systems, providing a versatile and effective means to enhance the delivery. The natural plant-based derivatives in nanoemulsion are favoured due to their safety, efficacy, and cost-effectiveness with potential therapeutic benefits. Furthermore, incorporating natural oils and fatty acids into nanoemulsion enhances the absorption rate of bioactive content, thereby amplifying their effectiveness. Combining both tocotrienols and ubiquinone in nanoemulsions is a common practice as potent antioxidants and stabilizers in formulations. Furthermore, it may enhance the permeability of active ingredients by facilitating their absorption and bioavailability. This integration represents a highly promising strategy for the foreseeable future. Meanwhile, the interest of nanotechnology has grown significantly, as evidenced by the growing number of publications in this field. This innovative technology holds the potential for long-term viability in cosmetic formulations, offering businesses the opportunity to stay relevant by providing consumers with cutting-edge and effective cosmeceutical products.

**Keywords:** Nanoemulsion, Skin delivery, Tocotrienols, Ubiquinone, Natural oils, Fatty acids

***Corresponding author:***
*Noreen Ang Azlan,*
*Faculty of Allied Health Sciences,*
*145, Jalan Tun Razak, 50400 Kuala Lumpur,*
*Wilayah Persekutuan Kuala Lumpur, Malaysia*
*Email: noreen@ijn.com.my*

*Received: 06 Feb 2024; accepted: 15 April 2024*
*Available online: 30 April 2024*
*http://doi.org/10.24191/IJPNaCS.v7i1.05*

## 1.0 Introduction

The largest organ in the human body is the skin, and its primary role is to safeguard against external elements, such as invading microorganisms, temperature fluctuations, exposure to ultraviolet (UV) rays, and to prevent the loss of water and electrolytes from our body (1). The outermost layer of the skin structure is known as the stratum corneum, playing a critical role as a robust barrier for transdermal applications or topical due to the complex biological structure of the human skin. The densely packed cells made of protein bricks and lipid mortar within the stratum corneum serve as the main barricade that limits the permeability of any forms of drugs including its active ingredients (2).

Exposure to the sun induces various changes in the human skin, leading to the development of skin wrinkles and influencing both the visual aspects and physiological of skin layers linked with the aging process (3). Therefore, any disruption to the function of skin protection becomes noticeable through changes in the integrity of the stratum corneum. This is commonly associated with an increase in water loss on the transepidermal human skin leading to reduction of membrane hydration (4). As a result, precautions like skin repair treatments, UV protection and skin rejuvenation are applied at the outer layer of the skin to mitigate such occurrences. Diverse treatments are available for the regeneration of human skin, and within the contemporary cosmeceutical product landscape, nano-sized emulsions have emerged as noteworthy contributors to this industry.

## 2.0 Nanotechnology

Nanotechnology is a scientific discipline focused on altering and reducing the active components into smaller particles called nanometre, measuring about 1 – 100 nm scale. This manipulation results in new properties for the materials, providing the ability to control various factors that impact the diffusion of ingredients through the skin (5).

Recently, nanotechnology has demonstrated success in improving drug bioavailability, active ingredients solubility and its stability during processing and storage (6). Meanwhile, lipid-based nano-preparations, derived from various natural sources that become part of the human nourishment, have shown superiority over polymeric nanoparticles. The main advantage of this includes preserving and prolong its shelf life and improve the biological mechanisms of the payloads (7). In addition, the choice of this type of nanoparticles depends on the low manufacturing expenditure, potency to improve stability profile of nanoparticles, ease of scale-up and option for components adjustments, thus, making nanoparticles among the best colloidal carriers.

Nanoemulsion is capable of improving the stability and solubility of bioactive compounds by increasing membrane diffusion to improve its therapeutic effects and its bioavailability as carrier (8). Moreover, nanoemulsions offer versatility in formulation whereby it can be formulated with various types of oils such as mineral oils, essential oils, triacylglycerol oils and flavour oils. Notably, oils with distinct fatty acid compositions yield significantly varied rates of lipid digestion and affect the bioavailability of bioactive for instance, long-chain triglycerides demonstrate a slower digestion rate compared to medium or short-chain triglycerides. Nevertheless, they contribute to higher bioaccessibility of carotenoids, emphasizing the impact of lipid composition on the absorption and utilization of bioactive compounds (9).

Nanoemulsions can be formulated with triacylglycerol oils, flavor oils, essential oils and mineral oils. Oils with different fatty acid compositions have been shown to give significantly different lipid digestion rates as well as bioactives. Long chain triglycerides have shown to be digested more slowly than medium or short chain triglycerides; however, they lead to a higher bioacessibility of carotenoids (10). The bioaccesibility of certain lipophilic compound like coenzyme Q10 can be improved with the utilization of nanoemulsion (11). Additionally, nanoemulsions are also important in incorporation of small molecule surfactants with other stabilizers that facilitate the formation of small mixed micelles possessing the advantage of easily penetrating through the mucus layer, thus enhance the bioavailability of encapsulated compounds (12).

The lipid droplets present in nanoemulsions can serve as a non-polar solvent to bioactive compounds present in plant-based products. Therefore, the lipid droplets that act as a carrier helps in extraction and dispersion of hydrophobic compounds that enhance the bioavailability and potentially provide health benefits (13). One crucial feature seen is their capacity and capability to maintain the condition of the nanoparticles drug in proper storage condition (14). The smaller particles lipid bilayer known as liposomes has been shown to be able to integrate high amount of both hydrophobic and hydrophilic drugs due to their natural components of phospholipids and cholesterols (15). According to Shakeri *et al*. (16) the liposomes found in the nanoparticles serve as a guard to defend the loaded drugs and facilitate the penetration through biological membranes of the cells effortlessly. Nanoemulsions shown in Fig. 1 is an example of small droplet of nanoemulsion that can be established in nano formulation with lipid-based colloidal and to stabilize the incorporation of several surfactants.

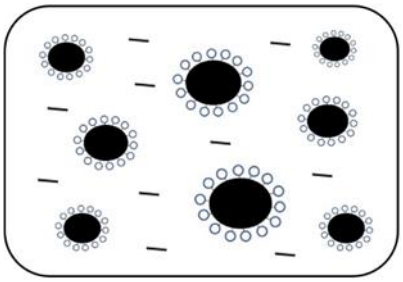

**Figure 1:** Droplet of Nanoemulsion

Antimisiaris *et al.* (17) reported that the stability of the main phases in colloidal state, which refers to the oil and water immiscible phases, can be established for various types of formulations, including water-in-oil and oil-in-water (Fig. 2).

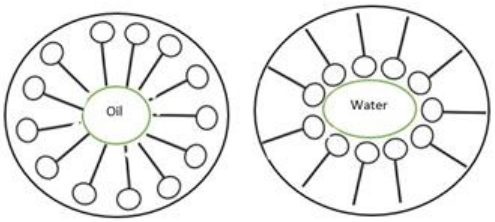


**Figure 2:** Oil-in-Water & Water-in-oil Nanoemulsion

Nanoemulsions present various mainly to improve the bioaccessibility of nutraceutical and low solubility drugs, to enhance bioavailability and increase solubility in a straightforward and easy manufacturing process. Thus, nanoemulsions can be classified as having protection properties to synthetic and natural active ingredients that focus on the defence against hostile storage environments including exposure to light, fluctuating temperatures, degradation of product and unpredictable pH variations (18).

Tarhan and Spotti (19) stated that the importance of the nanomedicines began to rise especially in pharmaceutical industry to explore the adverse effects associated with treatment duration and therapeutic outcomes of bioactive materials in

nanotechnology. In this case, nanotechnology offers great opportunity of growth in pharmacoeconomic especially in diagnostic and therapeutic products. The surge in market size of nutraceuticals and nanomedicines in global industry is expected to increase two-fold within eight years and predicted to rise approximately to USD 964 billion by the end of 2030 (20). Ashfaq *et al.* (21) added that in water-in-oil structure, the water droplet is designed in nanosized particles with the hydrophilic head fronting the water and hydrophobic tail projected facing the oil. Whilst, in the oil-in-water structure, the hydrophilic head directed towards the water and the hydrophobic tail on the oil droplets.

Correspondingly, the systems that classified into water-in-oil or oil-in-water involving double nanoemulsions structure making the dispersion systems more complex which carries various uses in numerous fields, providing distinct attributes including consisting multilayers of emulsions mechanisms (22). Nanoemulsions are also recognized for their exceptional stability against unstable colloidal aspects, such as flocculation creaming, sedimentation and coalescence. Ultimately, nanoemulsions has the capability to increase the stability and its effectiveness in various applications to ensure the prolonged shelf life of products based on nanoemulsions systems (23).

### *2.1 Plant extract*

Natural plant active ingredients and extracts derived from its fruits, leaves, flower, roots and seeds hold a significant value as cosmetic ingredients in ancient Egypt and China. These natural components played a crucial role in the beauty regimens of individuals in these cultures, serving various cosmetic and skincare purposes. The historical use of plant extracts underscores the enduring significance of natural ingredients in beauty practices (24). Table 1 shows the herbaceous plants used in nanoemulsion and its pharmacological benefits.

The utilization of these plant-based derivatives used as a composition in external skincare and cosmetic products is regarded as more effective, harmless, and cost saving compared to artificial alternatives (25). The preference for natural ingredients is often associated with the perceived benefits of plant compounds, such as potential therapeutic properties and lower risk of adverse effects (26). Additionally, the appeal of using sustainable and eco-friendly resources contributes to the popularity of plant-based skincare formulations. The external application, also facilitated by nanotechnology transporters, commonly known as nano-carriers, can enhance the rate of absorption of plant-based containing bioactive mixtures to targeted areas on the human body (27). Table 2 shows different types of commonly found natural oils in the ecosystem and the types of fatty acids to be incorporated in the formulation of nanoemulsion.

These various natural oils can be found in nature and harvested; for instance, avocado oil, canola oil, chia seeds oil, coconut oil, fish oil, flaxseeds oil, nuts oil, olive oil, hemp seed oils, and palm kernel oil, soya oil, vegetable oil and walnuts oil. These natural oils are also composed of different forms of structure, namely short chain fatty acids, medium chain fatty acids and long chain fatty acids. The oils can be harvested and collected through specific processes to obtain their oil. They can be utilized as a component in nanoemulsion formulation to improve its stability and enhance the shelf life of a nanoemulsions product under stressful conditions for a long period of time. The topical delivery systems can use minute droplet contains plants active ingredients normally carries high lipid and low water solubility. In the target areas, particularly the external skin

of human, this system serves dual purpose, by protecting the chemical and physical deprivation of active ingredients, thus enhancing the release and regulating its rate of absorption (28). Moreover, nano-carriers enhance the spreadability of skincare products, improving the overall application experience of cosmetic formulations. This heightened spreadability can increase user satisfaction, encouraging greater adherence to skincare routines among the public (29).

**Table 1:** Herbaceous Plants used in Nanoemulsion and its Pharmacological Benefits

| Herbaceous Plants | Pharmacological Benefits |
|---|---|
| Amaranth Oil | Antimicrobial |
| Avocado Oil | Hypercholesterolemia |
| Buckwheat | Antioxidant and Anti-Inflammatory |
| Chia Mucilage | Cosmetic Ingredient and Texturizing Agent |
| Grape Seed Polyphenols | Antioxidant and Anti-Inflammatory |
| Linseed Oil | Anti-Inflammatory |
| Neem Oil | Antibacterial and Anti-Haemorrhoid |
| Phytosterols & Phytostanols | Hypocholesterolaemia |
| Soybean Glycitein | Antioxidant and Anti-Aging |
| Tocotrienols | Anti-Inflammatory and Antioxidant |

**Table 2:** Natural Oils and Types of Fatty Acids in Nanoemulsions

| Natural Oils | Structure of Fatty Acids |
|---|---|
| Avocado Oil | LCFA |
| Canola Oil | SCFA |
| Chia Seeds Oil | SCFA |
| Coconut Oil | MCFA |
| Fish Oil | LCFA |
| Flax Seeds Oil | SCFA |
| Hemp Seeds Oil | SCFA |
| Nuts Oil | LCFA |
| Olive Oil | LCFA |
| Palm Kernel Oil | MCFA |
| Soya Oil | LCFA |
| Vegetable Oil | LCFA |
| Walnuts Oil | SCFA |

**short chain fatty acid (SCFA), medium chain fatty acid (MCFA), long chain fatty acid (LCFA)*

*2.2 Tocopherols*

The increase in the rate of reactive oxygen species (ROS), or free radicals, within living organisms, originating from processes such as aging, has the potential to result in apoptosis or cell death (30). This outcome arises due to the detrimental impacts of ROS levels on essential cellular structures, including deoxyribonucleic acid, ribonucleic acid, proteins, and lipids (31). Antioxidants is a preventive measure to shield cells from an excess of ROS, with the goal of slowing down cellular aging and preventing cell death. Antioxidants work to counteract the detrimental effects of ROS, contributing to the preservation of cellular health and functionality over time (32). Tocopherols form a family of natural and artificial derivatives with D-alpha-tocopherol, generally referred to as vitamin E, being the most widely recognized member. These compounds are preferentially accumulated and

absorbed in the cells of the human body (33). These molecules consist of two primary structural elements namely the chromanol head, which incorporates a benzodihydropyran with the group of alcohol and the tail of phytyl that composed of repetitions of saturated units of isoprenoid (34). Meanwhile, D-alpha-tocopherol, leveraging its antioxidant role, operates by detecting peroxyl radicals in the cells. It possesses the capability to protect the fats or lipids exist in the related phase of food products and those within the membranes of living cells from auto-oxidation (35). Yang *et al.* (36) suggested that in order to enhance its stability throughout the production and its storage, D-alpha-tocopherol must be combined with the nanocarriers formulation. Pereira *et al.* (37), Ren *et al.* (38*)* and Xu *et al.* (39) emphasized that the utilization of various forms of nanocarriers able to boost antioxidant properties in the products and at the same time preserving their nourishing value.

This approach aids in preserving the efficacy of D-alpha-tocopherol and extends its protective effects on food constituents. Loading D-alpha-tocopherol in oil-in-water nanoemulsions provides several advantages, primarily focused on enhancing the vitamin's chemical stability and preventing auto-oxidation (40). Incorporating this formulation has the potential to enhance the oral bioavailability and antioxidant properties of D-alpha-tocopherol when used in food products or pharmaceutical formulations (41). Because of its high lipophilicity, D-alpha-tocopherol is well-suited for loading into nanoemulsions. The nanocarriers known to be typically generated within the nanometric scale, typically ranging from 20 to 300 nm (42). Furthermore, they exhibit transparency and kinetic stability. The transparency of nanoemulsions also credited to their tiny size of molecules and possessing narrow polydispersity (43). Besides, nanoemulsions possess the benefit of being able to reduce the potential adverse event of toxics occurrence having biodegradable and physiological lipids composition (44). This attribute improves the safety profile of nanoemulsions, rendering them appropriate for a range of applications, including pharmaceutical and food formulations (45).

Earlier studies have revealed that the inclusion of D-alpha-tocopherol in nanoemulsions not only safeguards the vitamin from degradation but also improves its bioavailability (46). This dual effect positions nanoemulsions as a promising delivery system for D-alpha-tocopherol, ensuring both its stability and enhanced absorption and availability in the body. The inherent stability of emulsified nanodroplets is attributed to their tiny size particles, offering resistance against sedimentation, creaming, accumulation and flocculation of nanoemulsion products. This characteristic significantly contributes to the overall stability and functionality of emulsions across various applications (47). Overall, tocopherols can be utilized for diverse purpose in nanoemulsions leveraging their antioxidant properties and potential health advantages.

### *2.3 Ubiquinone*

Coenzyme Q10 (CoQ10), also known as ubiquinone, serves a crucial role in cellular energy production. It also acts as an antioxidant (48). Due to its highly lipophilic nature, the topical and oral bioavailability of CoQ10 is notably low. Various efforts have been undertaken to enhance its absorption, and recent technological advancements highlight that encapsulating CoQ10 in nanoemulsions leads to a significantly improved bioavailability (49).

The application of CoQ10 has seen further enhancement with the introduction

of novel CoQ10 double nanoemulsions, incorporating tocopherols and CoQ10 into individual nanodroplets (50). The concentration of CoQ10 in these nanoemulsions has been elevated through the development of a supersaturated CoQ10 nanoemulsion (51). CoQ10 forms a fascinating group of lipid-soluble compounds found in the plasma and inner membranes of the majority of eukaryotic cells (52). They comprise of a substituted quinone headgroup connected to an isoprenoid chain whose length varies depending on the species (53). In humans, the chain consists of ten isoprenoid units, leading to the designation of human ubiquinone as ubiquinone-10 (UQ-10), or simply, Q10.

Q10 participates in various facets of cellular metabolism, notably within the mitochondrial respiration chain, where it assumes a crucial function in facilitating the transport of electrons and protons across lipid membranes (54). Additionally, in its fully reduced form, ubiquinol, Q10 serves as a potent antioxidant, safeguarding membrane lipids from peroxidation (55). Coenzyme Q10, is present in extramitochondrial structures and the mitochondria. It can occur in various distinct oxidation forms namely the fully oxidized, known as ubiquinone, the half-reduced forms that referred to as ubisemiquinone, and lastly the ubiquinol that has fully reduced state (56). Indeed, ubiquinone has the potential to play a pro-oxidant role. This is attributed to the fact that the unstable ubisemiquinone, one of its oxidation states, has the potential to react with molecular oxygen, resulting in the formation of superoxide radicals.

Consequently, the pro-oxidant activity becomes a significant factor in comprehending the intricate and versatile role of CoQ10 in cellular processes (57). Thus, incorporating ubiquinone in nanoemulsions help in enhancing the bioavailability and delivery making it one of the valuable components for wide range pharmaceutical products, cosmetics and nutritional supplements due to its unique health benefits and distinctive properties.

### *2.4 Tocotrienols*

Malaysia's palm oil industry plays a substantial role in contributing to the country's economic growth. Presently, Malaysia holds the position of the second-largest producer of palm oil in the world trailing only behind Indonesia (58). The rapid expansion of the Malaysian palm oil industry has been evident over the past few decades, paralleling the growth of the palm oil plantation sector within the country. This industry not only functions as a crucial driver of Malaysia's economy but also holds global significance in the production and supply of palm oil—a versatile commodity with diverse applications in various sectors worldwide (59).

Palm oil extracted from the *Elaeis guineensis* tree stands out as the most abundant source of a specific type of vitamin E, namely tocotrienols. Tocotrienols represent a less well-known form of vitamin E. This study focuses on vitamin E due to its involvement in numerous essential metabolic processes (60). In the context of palm oil, vitamin E primarily comprises tocotrienols, constituting approximately 70% of its total content. This unique composition makes palm oil a valuable natural source of tocotrienols, emphasizing its significance in nutritional and health-related studies (61).

Early investigation revealed that tocotrienols exhibit better antioxidant properties compared to tocopherols (62). Meanwhile, several studies have provided evidence of tocotrienols demonstrating significant dermatological benefits, particularly in the treatment of skin inflammation and melasma (63, 64, 65,). Furthermore, numerous studies done by

Chong *et al.* (66); Jiang (67); Gensler & Magdaleno (68); Kosmadaki & Gilchrest (69); Hasan (70) reported that tocotrienols also contain anti-cancer properties, inducing the potency of neuroprotective and cardioprotective in *in-vitro* studies. The study also suggested that tocotrienol-rich nanoemulsions are able to help in wound closure, healing and recovery by improving the migration and proliferation of cell particularly keratinocytes (71). Hence, tocotrienols can be seen as an important composition in nanoemulsion as it improves the stability and prolong shelf life of the pharmaceuticals, nutraceuticals and functional products.

## 3.0 Conclusion

Nanoemulsions are poised to be a central area of research and development in the future, offering promising applications. However, several challenges need to be addressed before nanoemulsions can gain widespread acceptance in the pharmaceutical market. Scaling up nanoemulsion manufacturing poses financial considerations, and the exploration of nontoxic solvents for formulation remains a priority. Additionally, expanding the toxicity database for various excipients used in nanoemulsion synthesis is a critical aspect that requires attention. Overcoming these hurdles will be essential to harness the full potential of nanoemulsions and integrate them effectively into mainstream pharmaceutical applications. Indeed, despite advancements, there remain numerous areas within the field of delivering bioactive through the skin that warrant further investigation.

Furthermore, the use of natural oils and fatty acids in nanoemulsion may enhance penetration, particularly by facilitating transport across the highly structured lipid-rich stratum corneum (SC) membrane, requires a deeper exploration of formulation variables in nanoemulsion and the manufacturing processes involved in delivering active compounds through the skin barrier. The complexities of these processes and their influence on effective delivery are intricate and not yet fully understood. Therefore, additional study is imperative to gain a comprehensive understanding of the present work.

Delving into these unexplored aspects will contribute to refining and optimizing the delivery systems, ensuring their efficacy and safety. This ongoing study is crucial for advancing the field and unlocking the full potential of bioactive delivery through the skin and at the same time able to investigate the potential benefits of natural oils and fatty acids to be used in the nanoemulsions.

## Authorship contribution statement

**NAA**: Conceptualization, methodology, data analysis, review and supervision; **VRE:** Data evaluation, writing original draft**,** editing manuscript.

## Acknowledgement

The authors would like to express their sincere gratitude to Dr. Hariyati Shahrima binti Abdul Majid, Senior Lecturer, IJN College, Kuala Lumpur for providing guidance and support in the process of writing this review article.

## Conflict of Interest

The authors declare that there is no conflict of interest in the current work.

## References

1. Che Marzuki NH, Wahab RA, Abdul Hamid M. An overview of nanoemulsion: Concepts of development and cosmeceutical applications. Biotechnol Biotechnol Equip. 2019 Jan 1;33(1):779-97.

2. Menon GK, Cleary GW, Lane ME. The structure and function of the stratum corneum. Int J Pharm. 2012 Oct 1;435(1):3-9.

3. Van Tran V, Nguyen TL, Moon JY, Lee YC. Core-shell materials, lipid particles and nanoemulsions, for delivery of active anti-oxidants in cosmetics applications: Challenges and development strategies. Chem Eng J. 2019 Jul 15; 368:88-114.

4. Ribeiro AS, Estanqueiro M, Oliveira MB, Sousa Lobo JM. Main benefits and applicability of plant extracts in skin care products. Cosmetics. 2015 Apr 10;2(2):48-65.

5. Santos AC, Morais F, Simões A, Pereira I, Sequeira JA, Pereira-Silva M, Veiga F, Ribeiro A. Nanotechnology for the development of new cosmetic formulations. Expert Opin Drug Deliv. 2019 Apr 3;16(4):313-30.

6. Huang Q, Yu H, Ru Q. Bioavailability and delivery of nutraceuticals using nanotechnology. J Food Sci. 2010 Jan;75(1): R50-7.

7. Üner M. Preparation, characterization and physico-chemical properties of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC): their benefits as colloidal drug carrier systems. Pharmazie. 2006 May 1;61(5):375-86.

8. Ting P, Srinuanchai W, Suttisansanee U, Tuntipopipat S, Charoenkiatkul S, Praengam K, Chantong B, Temviriyanukul P, Nuchuchua O. Development of chrysin loaded oil-in-water nanoemulsion for improving bioaccessibility. Foods. 2021 Aug 18;10(8):1912.

9. Qian C, Decker EA, Xiao H, McClements DJ. Nanoemulsion delivery systems: Influence of carrier oil on β-carotene bioaccessibility. Food Chem. 2012 Dec 1;135(3):1440-7.

10. Yaghmur A, Glatter O. Characterization and potential applications of nanostructured aqueous dispersions. Adv Colloid Interface Sci. 2009 Mar 1; 147:333-42.

11. Li M, Du C, Guo N, Teng Y, Meng X, Sun H, Li S, Yu P, Galons H. Composition design and medical application of liposomes. Eur J Med Chem. 2019 Feb 15; 164:640-53.

12. Degrou A, Georgé S, Renard CM, Page D. Physicochemical parameters that influence carotenoids bioaccessibility from a tomato juice. Food Chem. 2013 Jan 15;136(2):435-41.

13. Mustafa IF, Hussein MZ. Synthesis and Technology of Nanoemulsion-Based Pesticide Formulation. Nanomaterials. 2020 Aug 17;10(8):1608.

14. Cho HT, Salvia-Trujillo L, Kim J, Park Y, Xiao H, McClements DJ. Droplet size and composition of nutraceutical nanoemulsions influences bioavailability of long chain fatty acids and Coenzyme Q10. Food Chem. 2014 Aug 1; 156:117-22.

15. Soares S, Sousa J, Pais A, Vitorino C. Nanomedicine: principles, properties, and regulatory issues. Front Chem. 2018:360.

16. Shakeri S, Ashrafizadeh M, Zarrabi A, Roghanian R, Afshar EG, Pardakhty A, Mohammadinejad R, Kumar A, Thakur VK. Multifunctional polymeric nanoplatforms for brain diseases diagnosis, therapy and theranostics. Biomedicines. 2020 Jan 13;8(1):13.

17. Antimisiaris SG, Marazioti A, Kannavou M, Natsaridis E, Gkartziou F, Kogkos G, Mourtas SJ. Overcoming barriers by local drug delivery with liposomes. Adv Drug Deliv Rev. 2021 Jul 1; 174:53-86.

18. Ashfaq R, Rasul A, Asghar S, Kovács A, Berkó S, Budai-Szűcs M. Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. Int J Mol Sci. 2023 Oct 30;24(21):15764.

19. Tarhan O, Spotti MJ. Nutraceutical delivery through nano-emulsions: General aspects, recent applications and patented inventions. Colloids Surf B Biointerfaces. 2021 Apr 1; 200:111526.

20. Augustin, M.A.; Sanguansri, L. Challenges and Solutions to Incorporation of Nutraceuticals in Foods. Annu Rev Food Sci Technol. 2015, 6, 463–477.

21. Ashfaq R, Rasul A, Asghar S, Kovács A, Berkó S, Budai-Szűcs M. Lipid Nanoparticles: An Effective Tool to Improve the

Bioavailability of Nutraceuticals. Int J Mol Sci. 2023 Oct 30;24(21):15764.

22. Madkhali OA. Perspectives and prospective on solid lipid nanoparticles as drug delivery systems. Molecules. 2022 Feb 24;27(5):1543.

23. Lee CH, Huang GC, Chen CY. Bioactive compounds from natural product extracts in Taiwan Cosmeceuticals-Mini review. Biomed Res. 2017 Jan 1;28(15):6561-6.

24. Kupikowska-Stobba B, Kasprzak M. Fabrication of Nanoparticles for Bone Regeneration: New Insight into Applications of Nanoemulsion Technology. J Mater Chem B. 2021;9(26):5221-44.

25. Antonopoulou I, Varriale S, Topakas E, Rova U, Christakopoulos P, Faraco V. Enzymatic synthesis of bioactive compounds with high potential for cosmeceutical application. Appl Microbiol Biotechnol. 2016 Aug; 100:6519-43.

26. Adekunle KF. A Review of Vegetable Oil-Based Polymers: Synthesis and Applications. Open J Polymer Chem. 2015;5(3):34-40

27. Saewan N, Jimtaisong A. Natural products as photoprotection. J Cosmet Dermatol. 2015 Mar;14(1):47-63.

28. Ahsan H. The biomolecules of beauty: Biochemical pharmacology and immunotoxicology of cosmeceuticals. J Immunoassay Immunochem. 2019 Jan 2;40(1):91-108.

29. Santos AC, Morais F, Simões A, Pereira I, Sequeira JA, Pereira-Silva M, Veiga F, Ribeiro A. Nanotechnology for the development of new cosmetic formulations. Expert Opin Drug Deliv. 2019 Apr 3;16(4):313-30.

30. Lagoa R, Silva J, Rodrigues JR, Bishayee A. Advances in phytochemical delivery systems for improved anticancer activity. Biotechnol Adv. 2020 Jan 1; 38:107382.

31. Nakazawa T, Miyanoki Y, Urano Y, Uehara M, Saito Y, Noguchi N. Effect of vitamin E on 24 (S)-hydroxycholesterol-induced necroptosis-like cell death and apoptosis. J Steroid Biochem Mol Biol. 2017 May 1; 169:69-76.

32. Ashfaq R, Rasul A, Asghar S, Kovács A, Berkó S, Budai-Szűcs M. Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. Int J Mol. Sci. 2023 Oct 30;24(21):15764.

33. Farahin AW, Yusoff FM, Basri M, Nagao N, Shariff M. Use of microalgae: Tetraselmis tetrathele extract in formulation of nanoemulsions for cosmeceutical application. J Appl Phycol. 2019 Jun 15; 31:1743-52.

34. Puglia C, Santonocito D. Cosmeceuticals: Nanotechnology-based strategies for the delivery of phytocompounds. Curr Pharm Des. 2019 Jun 1;25(21):2314-22.

35. Isnaini N. Preparation and Investigation of Antioxidant, Antibacterial and Antityrosinase Potentials of O/W Nanoemulsions Containing Extract of Tamarindus indica L. Fruit Pulp. Doctoral dissertation, Hat Yai, Thailand: Prince of Songkla University. 2018. PSU Knowledge Bank.

36. Yang S, Liu L, Han J, Tang Y. Encapsulating plant ingredients for dermocosmetic application: An updated review of delivery systems and characterization techniques. Int J Cosmet Sci. 2020 Feb;42(1):16-28.

37. Pereira AB, da Silva AM, Barroca MJ, Marques MP, Braga SS. Physicochemical properties, antioxidant action and practical application in fresh cheese of the solid inclusion compound γ-cyclodextrin· quercetin, in comparison with β-cyclodextrin· quercetin. Arab J Chem. 2020 Jan 1;13(1):205-15.

38. Ren G, Sun Z, Wang Z, Zheng X, Xu Z, Sun D. Nanoemulsion formation by the phase inversion temperature method using polyoxypropylene surfactants. J Colloid Interface Sci. 2019 Mar 22; 540:177-84.

39. Xu L, Wang X, Liu Y, Yang G, Falconer RJ, Zhao CX. Lipid nanoparticles for drug delivery. Adv NanoBiomed Res. 2022 Feb;2(2):2100109.

40. Ferreira-Nunes R, da Silva SM, de Souza PE, de Oliveira Magalhães P, Cunha-Filho M, Gratieri T, Gelfuso GM. Incorporation of Eugenia dysenterica extract in microemulsions preserves stability, antioxidant effect and provides enhanced cutaneous permeation. J Mol Liq. 2018 Sep 1; 265:408-15.

41. Algahtani MS, Ahmad MZ, Ahmad J. Nanoemulsion loaded polymeric hydrogel for topical delivery of curcumin in psoriasis. J Drug Deliv Sci Technol. 2020 Oct 1; 59:101847.

42. Gomaa E, Fathi HA, Eissa NG, Elsabahy M. Methods for preparation of nanostructured lipid carriers. Methods. 2022 Mar 1; 199:3-8.

43. Kaviyarasu K, Matinise N, Mayedwa N, Mongwaketsi N, Letsholathebe D, Mola GT, AbdullahAl-Dhabi N, Valan Arasu M, Henini M, Kennedy J, C. Maria Magdalane CM. Evaluation on La2O3 garlanded ceria heterostructured binary metal oxide nanoplates for UV/visible light induced removal of organic dye from urban wastewater. S Afr J Chem Eng. 2018 Dec 1;26(1):49-60.

44. Jovanović AA, Balanč BD, Ota A, Ahlin Grabnar P, Djordjević VB, Šavikin KP, Bugarski BM, Nedović VA, Poklar Ulrih N. Comparative effects of cholesterol and β-sitosterol on the liposome membrane characteristics. Eur J Lipid Sci Technol. 2018 Sep;120(9):1800039.

45. Kumar M, Bishnoi RS, Shukla AK, Jain CP. Techniques for formulation of nanoemulsion drug delivery system: a review. Prev Nutr Food Sci. 2019 Sep;24(3):225.

46. Gharibzahedi SM, Hernández-Ortega C, Welti-Chanes J, Putnik P, Barba FJ, Mallikarjunan K, Escobedo-Avellaneda Z, Roohinejad S. High pressure processing of food-grade emulsion systems: Antimicrobial activity, and effect on the physicochemical properties. Food Hydrocolloids. 2019 Feb 1; 87:307-20.

47. Soni H, Sharma S. Current update on nanoemulsion: a review. Sch Int J Anat Physiol. 2021;4(1):6-13.

48. Bansal T, Mustafa G, Khan ZI, Ahmad FJ, Khar RK, Talegaonkar S. Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs. Crit Rev Ther Drug Carr Syst. 2008;25(1).

49. Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm. 2008 Jun 24;358(1-2):285-91.

50. Yukuyama MN, Kato ET, de Araujo GL, Löbenberg R, Monteiro LM, Lourenco FR, Bou-Chacra NA. Olive oil nanoemulsion preparation using high-pressure homogenization and d-phase emulsification–A design space approach. J Drug Deliv Sci Technol. 2019 Feb 1; 49:622-31.

51. Hasan ZA, Idris Z, Gani SS, Basri M. In vitro safety evaluation of palm tocotrienol-rich fraction nanoemulsion for topical application. J Oil Palm Res. 2018 Mar 1; 30:150-62.

52. Zhang LW, William WY, Colvin VL, Monteiro-Riviere NA. Biological interactions of quantum dot nanoparticles in skin and in human epidermal keratinocytes. Toxicol Appl Pharmacol. 2008 Apr 15;228(2):200-11.

53. Xu Q, Liu X, Zhao J, Wang D, Wang Q, Li X, Yang Q, Zeng G. Feasibility of enhancing short-chain fatty acids production from sludge anaerobic fermentation at free nitrous acid pretreatment: role and significance of Tea saponin. Bioresour Technol. 2018 Apr 1; 254:194-202.

54. Arancibia C, Navarro-Lisboa R, Zúñiga RN, Matiacevich S. Application of CMC as thickener on nanoemulsions based on olive oil: Physical properties and stability. Int J Polym Sci. 2016 Dec 1;2016:833-42.

55. Atun S, Arianingrum R, Cahyaningsih L, Pratiwi FA, Kusumaningrum R, Khairuddean M. Formulation and Characterization of Quercitrin Nanoemulsion Isolated from Dendropthoe falcata and Its Antioxidant Activity Test. Rasayan J Chem. 2020 Jul;13(3):1347-56.

56. Arancibia C, Navarro-Lisboa R, Zúñiga RN, Matiacevich S. Application of CMC as thickener on nanoemulsions based on olive oil: Physical properties and stability. Int J Polym Sci. 2016 Jan 1;2016.

57. Aripin NF, Park JW, Park HJ. Preparation of vesicle drug carrier from palm oil-and palm kernel oil-based glycosides. Colloids Surf B Biointerfaces. 2012 Jun 15; 95:144-53.

58. Wang Y, Hekimi S. Understanding ubiquinone. Trends Cell Biol. 2016 May 1;26(5):367-78.

59. Linnane AW, Kios M, Vitetta L. Coenzyme Q10–Its role as a prooxidant in the formation of superoxide anion/hydrogen peroxide and the regulation of the metabolome. Mitochondrion. 2007 Jun 1;7: S51-61.

60. Boakye CH, Patel K, Singh M. Doxorubicin liposomes as an investigative model to study the skin permeation of nanocarriers. Int J Pharm. 2015 Jul 15;489(1-2):106-16.

61. Choudhury H, Zakaria NF, Tilang PA, Tzeyung AS, Pandey M, Chatterjee B, Alhakamy NA, Bhattamishra SK, Kesharwani P, Gorain B, Md S. Formulation development and evaluation of rotigotine mucoadhesive nanoemulsion for intranasal delivery. J Drug Deliv Sci Technol. 2019 Dec 1; 54:101301.

62. Gopalan Y, Shuaib IL, Magosso E, Ansari MA, Abu Bakar MR, Wong JW, Khan NA, Liong WC, Sundram K, Ng BH, Karuthan C. Clinical investigation of the protective effects of palm vitamin E tocotrienols on brain white matter. Stroke. 2014 May;45(5):1422-8.

63. Prasad K. Tocotrienols and cardiovascular health. Curr Pharm Des. 2011 Jul 1;17(21):2147-54.

64. Chong WT, Tan CP, Cheah YK, B. Lajis AF, Habi Mat Dian NL, Kanagaratnam S, Lai OM. Optimization of process parameters in preparation of tocotrienol-rich red palm oil-based nanoemulsion stabilized by Tween80-Span 80 using response surface methodology. PLoS One. 2018 Aug 24;13(8): e0202771.

65. Yamada Y, Obayashi M, Ishikawa T, Kiso Y, Ono Y, Yamashita K. Dietary tocotrienol reduces UVB-induced skin damage and sesamin enhances tocotrienol effects in hairless mice. J Nutr Sci Vitaminol. 2008;54(2):117-23.

66. Chong WT, Tan CP, Cheah YK, Lai OM. In-vitro and in-vivo evaluations of tocotrienol-rich nanoemulsified system on skin wound healing. PLoS One. 2022 May 25;17(5): e0267381.

67. Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic Biol Med. 2014 Jul 1; 72:76-90.

68. Gensler H. L., Magdaleno M. Topical vitamin e inhibition of immunosuppression and tumorigenesis induced by ultraviolet irradiation. Nutr Cancer. 1991 5; (2), 97–106.

69. Kosmadaki MG, Gilchrest BA. The role of telomeres in skin aging/photoaging. Micron. 2004 Apr 1;35(3):155-9.

70. Hasan ZA, Idris Z, Gani SS, Basri M. In vitro safety evaluation of palm tocotrienol-rich fraction nanoemulsion for topical application. J Oil Palm Res. 2018 Mar 1; 30:150-62.

71. Choi SJ, McClements DJ. Nanoemulsions as delivery systems for lipophilic nutraceuticals: Strategies for improving their formulation, stability, functionality and bioavailability. Food Sci Biotechnol. 2020 Feb; 29:149-68.