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Citrus Flavonones into nanotechnology-based formulations to skin treatment

Flavononas cítricas en formulaciones basadas en nanotecnología para el tratamiento de la piel

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Resumen

Introducción: Las flavononas muestran una aplicación potencial en el tratamiento de trastornos de la piel, cuyo rendimiento puede mejorarse mediante el uso de nanoportadores lipídicos y poliméricos. En esta revisión, se analiza un enfoque reciente con respecto a los nano-portadores que contienen naringina, naringenina, hesperidian o hesperitina para aplicación cutánea.

Método: Esta revisión aborda las publicaciones de los últimos 6 años sobre nanosistemas que contienen flavononas cítricas para aplicaciones cutáneas. Los artículos se seleccionaron mediante la búsqueda en base de datos Scopus de nanosistemas que contienen hesperidina, hesperitina, naringina o naringenina para aplicación cutánea, artículos de investigación escritos en inglés y publicados entre 2018 y 2023, y abordando la penetración de la piel o evaluación biológica.

Resultados: La mayoría de los artículos emplearon sistemas lipídicos como nano-portadores. La naringenina fue la flavonona más utilizada. En relación con los beneficios para la piel, se destacan la mejora de la cicatrización de heridas, el tratamiento de la dermatitis atópica y las enfermedades relacionadas con el estrés oxidativo. A pesar de los probables beneficios, el desarrollo de nanomedicinas de origen vegetal es complejo, lo que impone limitaciones al desarrollo de nuevos productos farmacéuticos. Además, se han demostrado el potencial de las flavononas en el tratamiento del cáncer de piel.

Conclusiones: Se emplean portadores lipídicos, poliméricos y nanohíbridos para administrar flavanonas. Debido a sus actividades antioxidantes y antiinflamatorias, las flavanonas tienen aplicaciones potenciales en el tratamiento de diferentes trastornos de la piel. Por lo tanto, existe una aplicación prometedora de las flavanonas para mejorar la salud humana, principalmente con su carga en nanoportadores.

Palabras clave: sistemas de liberación de fármacos; nanopartículas; flavonoides; Citrus

Abstract

Introduction: Flavonones show potential application in the treatment of skin disorders, whose performance may be improved by using lipid and polymeric nanocarriers. In this review, a recent approach regarding nanocarriers containing either naringin, naringenin, hesperidin or hesperitin for skin application are discussed.

Method: This review approaches the publications from the last 6 years about nanosystems containing Citrus flavonones for cutaneous applications. The articles were selected by searching in Scopus database for nanosystem containing either hesperidin, hesperitin, naringin or naringenin for cutaneous application, research articles written in English and published between 2018 and 2023, and reporting about skin penetration or biological evaluation.

Results: Majority of reports employed lipid systems as nanocarriers. Naringenin was the most used flavonone. In relation to skin benefits, improved wound healing, atopic dermatitis treatment and stress oxidative-related diseases are highlighted. Despite the probable benefits, the development of plant-based nanomedicines is complex, which imposes limitations on the development of new pharmaceutical products. Further, the potential of flavonoids in the treatment of skin cancer has been shown.

Conclusions: Lipid, polymeric and nanohybrid carriers are employed to deliver flavanones. Due to their antioxidant and anti-inflammatory activities, flavanones bear potential applications in the treatment of different skin disorders. Therefore, there is a promising application of flavanones to the improvement of human health, mainly with their loading into nanocarriers.

Keywords: drug delivery systems; nanoparticles; flavonoids; Citrus

Highlights

Although flavonones have beneficial effects in both cosmetic and medicinal treatments, they have low bioavailability and solubility. In that regard, nanotechnological formulations have been proposed to improve their efficacy.

This report is an overview of the most recent contributions on flavanones into nanosystems since there are few reports addressing these compounds into drug delivery systems for skin delivery.

This report could be useful in directing further research. Mainly to chronic skin diseases, more effective treatments are important to improve patients quality of life.

Introduction

Citrus fruits are a rich source of flavonoids, which are found in all parts of the plant body. In plant metabolism, these compounds provide protection against ultraviolet radiation, defense against pathogens. Also, flavonoids play a role as signaling molecules[(1)]. More than a hundred flavonoids have been identified in citrus fruits, mainly flavonones. Glycosylated flavonones are more abundant than aglycone forms. The three most common aglycones are hesperetin, naringenin and eriodictyol. Glycoside flavonones are classified into rutinoside flavonones and neohesperidoside flavonones. Rutinoside flavanones include hesperidin (hesperitin rutinoside), narirutin (naringenin rutinoside), and eriocitrin (eriodictyol rutinoside) while neohesperidoside flavonones include neohesperidin (hesperitin neohesperidoside), naringin (narigenin neohesperidoside) and neoeriocitrin (eriodictyol neohesperidoside). Hesperidin and narutin are found in higher contents in sweet oranges, mandarins, tangors and lemons. Neohesperidoside flavones are related to bitter taste in some citrus species of which neohesperidin and neoeriocitrin highlights. Both are mostly found in grapefruit and sour oranges. On the other hand, hesperidin is the most abundant flavonoid in orange juice and its concentration can vary between 31 and 122 mg L^{-1} depending on the cultivar[(1-3)].

Plant phytochemicals are increasingly employed in the development of skin care products[(4)], including flavonoids, with several health benefits, where antioxidant activity is one of the most important properties[(5)]. In *Citrus* species, flavonones are a valuable class of flavonoids due to anti-inflammatory and anti-tumor activity. Therefore, these compounds may be applied in the treatment of various skin disorders[(6)]. As nanotechnology improves formulations performance, plant compounds have been loaded into nanosystems[(7)] to increase their solubility[(8,9)] and their skin penetration[(10)]. Hence, this review aims to arrange the current knowledge and state of the art of flavanones loaded in nanocarriers for cutaneous application, with an approach about limitations and challenges to be overcome in the development of phyto-nanomedicines.

Methods

The selection of articles was performed on a search for original articles covering flavanones in nanosystems for topical application, in the Scopus database. The articles were selected by searching for the terms: *flavonoids AND nano* AND skin*. A total of 300 articles were retrieved. Then, a second search was conducted for each flavanone by “searching within results” option of Scopus database, as shown in Figure 1.

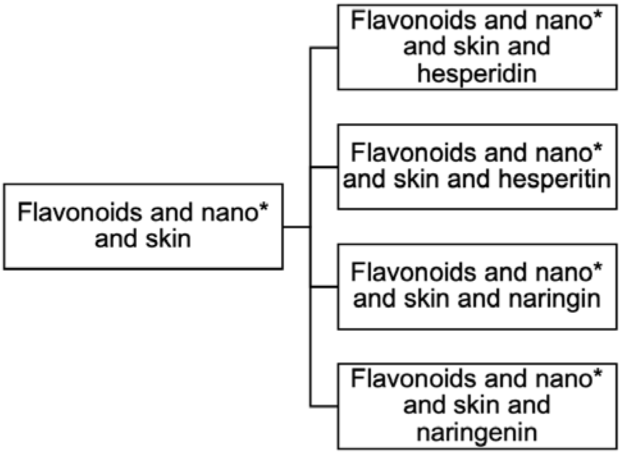

Figure 1. Schematic representation of the search for articles in the Scopus database.

The following inclusion criteria were employed:

1) a nanosystem containing either hesperidin, hesperitin, naringin or naringenin for cutaneous application; 2) articles written in english and published between 2018 and 2023; 3) reports approaching skin penetration or biological evaluation, 4) research articles.

The exclusion criteria included:1) articles prior to 2013; B) review articles, books, conference reviews, book chapters and conference papers reports; C) reports that do not address the use of flavanones in nanosystems, D) reports articles approaching solely with physicochemical characterization or optimization of nanoformulations.

Results

A total of 15 articles were selected after applying the inclusion criteria. Table 1 summarizes the flavonones loaded-nanocarriers for skin delivery, with emphasis to wound healing(11-16). Naringenin(11,12,17-20) and hesperidin(13-16,21) were the most encapsulated flavanones. Regard to nanocarrier, lipid carriers(12,17,19,22-24) are the most important ones.

Table 1. Flavonones in nanoformulations for skin delivery.

Flavonones	Nanocarrier	Application	Reference
Naringenin	Solid lipid nanoparticles	Atopic dermatitis	(17)
	Polymeric nanoparticles	Sunscreen	(18)
	Nanofiber	Wound healing	(11)
	Microemulsion	Skin anti-aging	(19)
	Nanoemulsion	Wound healing	(12)
	Nanohybrid hydrogel	Skin cancer	(20)
Naringin	Elastic Liposomes	Sunscreen	(22)
		Skin inflammatory diseases	(23)

Flavonones	Nanocarrier	Application	Reference
Hesperitin	Elastic Liposomes	Topical antioxidant	(24)
Hesperidin	Nanocrystal	Skin anti-aging	(21)
	Nanofiber	Wound healing	(13)
	Hybrid nanoparticles		(14)
	Silver nanoparticles		(15)
	Dendrimer		(16)

Flavonones were applied for cosmetic or therapeutic purposes. In cosmetics, naringenin is the most important one. In this sense, association of physical sunscreens nanoparticles and naringenin nanoparticles improved photoprotection[18] due to the ultraviolet scattering ability of lipid nanoparticles. Sunscreen use is essential for preventing skin diseases such as skin cancer[25]. Besides, both hesperidin and naringenin had anti-aging activity. Hesperidin nanocrystals were able to chelate copper and zinc, important cofactors of enzymes related to skin aging[21]. In other report, sericin gel bearing naringenin microemulsions reduced ultraviolet radiation-induced wrinkles[19].

About therapeutic purpose, flavonones in nanosystems are used for atopic dermatitis[17] and for wound healing[11–13,15,16,26]. In the treatment of inflammatory skin diseases, naringenin may be employed to reduce inflammatory markers[27,28]. Thereby, solid lipid nanoparticles containing linoleic acid, cyclosporine and naringenin were able to reduce inflammation due to the anti-inflammatory synergistic of these compounds[17]. Likewise, naringenin loaded in liposomes reduced skin edema indicating its anti-inflammatory activity[23]. Beyond that, liposomes improved hesperitin ability to scavenge reactive oxygen radicals. As several skin diseases increase free radicals, an antioxidant approach would be very useful[24].

Besides, both naringenin[11,12] and hesperidin[13-16] are designed for wound healing, mainly hesperidin[13-16]. In that regard, nanoemulsions[12], dendrimers[16], silver nanoparticles[15] and nanofibers[11,13] promoted wound contraction[11-13,16] and reduction of inflammatory cells[12,13,15]. Further, a greater cell migration and a greater expression of beta Fibroblastic Growth Factor (bFGF) was detected for hydrogels containing silver nanoparticles in which hesperidin was employed as a reducing agent. A greater cell migration and expression of bFGF are indicative of a better healing and improved re-epithelialization, respectively[15].

Furthermore, a nanohybrid hydrogel bearing metallic nanoparticles, cysteine complexed with chitosan, naringenin, and cellulose, improved anti-cancer ability over skin cancer cell line regarding naringenin. Although naringenin itself had cytotoxic effect, it was lower than nanohybrid[20]. Then, the naringenin loaded into nanotechnological formulations may be interesting in the treatment of cancer.

Discussion

Nanocarriers employed for flavanones encapsulation include inorganic and organic ones[7,15]. Although the most employed nanocarriers are organic[12,17,18,19,21,22,29], silver nanoparticles stand as an inorganic nanocarrier employed mainly due to their antibacterial activity on wound healing[15]. Among organic nanoparticles, elastic liposomes[22,24], solid lipid nanoparticles[17], nanoemulsions[12], microemulsions[19], polymeric nanoparticles[18], nanocrystals[21], hybrid systems[14,20] were employed to load either hesperidin, hesperitin, naringenin or naringin. Lipid carriers are widely used due to their biocompatibility with biological tissues. Among them, elastic liposomes improve drug penetration into skin[30]. In that regard, hesperitin loaded in proposomal gels had a higher in vitro release regarding to non-nanotechnological hesperidin gels. Proposomes are liposomes containing polyethylene glycol, as an agent promoting skin permeation[24]. Moreover, ethosomes emulsions bearing ethanol and naringin had an improved skin deposition. The increased in vitro release and increased skin retention of nanotechnological formulations is a desired effect that directly correlates to formulation efficacy[22].

Flavanones would bring benefits in the treatment of several skin disorders such as atopic dermatitis skin aging because of its antioxidant ability. In addition, skin health maintenance could also be achieved as well as the prevention of aging-related diseases[31,32]. Beyond that, use of sunscreen goes beyond an aesthetic purpose, as it prevents the development of skin cancer[33]. Moreover, the improved wound healing is of importance mainly in diabetic patients whose healing ability is compromised[34]. For wound healing purposes, nanofibers are worthed, nanometric-sized structures[35] resembling biological tissues[36].

Hybrid systems are obtained by a mixture of different types of particles. Then, a hybrid may be a nanoparticle system formed by both polymers and lipids[14]. Also, a nanohybrid may be a mixture of inorganic and organic nanoparticles[20]. Hybrid systems are a trend in nanotechnology systems as they can present better performance than non-hybrid nanotechnology systems[14,20].

As previously mentioned, naringenin shows cytotoxic effect. However, this effect is concentration-dependent. In the development of formulations designed for cancer treatment, the use of naringenin in higher concentrations is desirable as changes in cell viability were shown naringenin in higher concentrations is desirable as changes in cell viability were shown[37]. In this sense, nanofibers bearing higher naringenin contents reduced cell viability of human carcinoma-derived cell culture[11]. On the other hand, the antioxidant[14] and wound contraction ability[16] of hesperidin loaded in nanocarriers also relies on hesperidin content. Unlike cancer, in both cases, it is important to maintain cell viability. Therefore, flavonones may be used for cancer or not-cancer disorders. Nevertheless, it is required to better establish the ideal dose in for each skin disorder treatment.

Current limitation and challenges on development of plant-based nanomedicines

The majority of flavonones have been applied to cosmetics, as their development and regulatory issues are less complex than pharmaceuticals products. For pharmaceuticals based on plants, aspects related to the environmental factors must be considered as they have influence on the phytochemicals composition. The development of nanotechnology products is challenging because there is still a lack of international standards regarding quality, safety, and efficacy. Beyond that, characterization may require several different assays which may have an impact on the consumer price. Furthermore, conventional toxicity tests may be not suitable for nanoproducts. Therefore, new safety tests would be important. With regard to nano phytomedicine, the challenge is even greater as there is the combination of challenges in the development of phytomedicines with the challenges of nanomedicines development[38].

In addition, plant ingredients are often employed as extracts and therefore have a complex composition, which also hinders product development. Use of isolated and synthetic flavonones partially reduces this difficulty, mainly about analytical aspects[38]. As to flavonones in nanodelivery systems, most studies employed synthetic bioactives[11,12,24,13,15,17-20,22,23]. However, synthetic compounds may have different chemical composition than natural ones which may impact the therapeutic effect. Also, another relevant issue is the flavonoid content. Because they are used as alternative therapies, there is no standardization in relation to the dose.

Lastly, other citrus flavonoids show potential skin health benefits[6]. There is a trend to evaluate flavonoids for the treatment of other skin disorders. Since there is a growing number of skin cancer cases[39], it is desirable the development of topical treatments designed to treat actinic keratosis and superficial basal cell carcinoma[40]. Flavonoids activity over melanoma has been investigated mainly in cell culture. Thus, there is a need for further investigations on new treatments for this type of cancer. Also, reports are also directed for non-dermatological applications including treatment of cardiovascular and neurological diseases[6]. These potential drugs may be loaded in drug delivery systems aiming to develop more effective treatments. Nevertheless, there is still a need to overcome the highlighted challenges in order to more effective drugs become available worldwide.

Conclusions

Flavanones have been loaded in different nanocarriers, with emphasis to lipids, polymeric and hybrid ones. The majority of applications are aimed at treating skin diseases. However, anti-aging activity and sunscreen properties has been reported for naringenin and naringin. Furthermore, anti-inflammatory, antitumoral and wound healing effects must be highlighted which makes flavanones interesting to inflammatory skin diseases, cancer and wound healing treatments. Therefore, there is a promising application of flavanones to the improvement of human health, despite their low solubility and low skin permeability. Hence, their loading into nanocarriers may enable an improved efficacy treatment.

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