Cosmetics **2015**, *2*, 342-354; doi:10.3390/cosmetics2040342

OPEN ACCESS

cosmetics

ISSN 2079-9284

www.mdpi.com/journal/cosmetics

Review

Nanocarriers for Delivery of Antioxidants on the Skin

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Academic Editor: Martina Meinke

Received: 14 August 2015 / Accepted: 8 October 2015 / Published: 10 October 2015

Abstract: Skin is protected from the harmful effects of free radicals by the presence of an endogenous antioxidant system. However, when exposed to ultraviolet (UV) radiation, there is an imbalance between pro-oxidants and antioxidants, leading to oxidative stress and photoaging of the skin. It has been described that free radicals and other reactive species can cause severe damage to cells and cell components of the skin, which results in skin aging and cancer. To prevent these actions on skin, the use of topical antioxidant supplementation is a strategy used in the cosmetics industry and these antioxidants act on quenching free radicals. There are many studies that demonstrated the antioxidant activity of many phytochemicals or bioactive compounds by free radical scavenging. However, many bioactive substances are unstable when exposed to light or lose activity during storage. The potential sensitivity of these substances to light exposure is of importance in cosmetic formulations applied to skin because photo-degradation might occur, reducing their activity. One strategy to reduce this effect on the skin is the preparation of different types of nanomaterials that allow the encapsulation of the antioxidant substances. Another problem related to some antioxidants is their inefficient percutaneous penetration, which limits the amount of the active ingredient able to reach the site of action in viable epidermis and dermis. In this sense, the encapsulation in polymeric nanoparticles could enhance the permeation of these substances. Nanocarriers offers several advantages over conventional passive delivery, such as increased surface area, higher solubility, improved stability, controlled release, reduced skin irritancy, and protection from degradation. The different nanocarrier systems used in cosmetics include nanolipid delivery systems such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), nanoemulsions

(NEs), nanoparticles (NP) suspension, and polymer NPs, among others. In this review, we present the different types of nanomaterials used in cosmetic formulations to obtain the best effect of antioxidants applied onto the skin.

Keywords: skin; antioxidants; nanocarriers; nanovesicles

1. Introduction

The skin is the outer barrier of the body, and it is exposed to various exogenous sources of oxidative stress, including ultraviolet radiation and pollutants. As a response to these oxidative attacks, reactive oxygen species (ROS) and other free radicals are generated in the skin [1].

Skin is protected from the harmful effects of free radicals due to the presence of an endogenous antioxidant network consisting of a variety of lipophilic (e.g., vitamin E, ubiquinones, carotenoids) and hydrophilic (e.g., vitamin C, uric acid, and glutathione) substances, and it is responsible for the balance between pro-oxidants and antioxidants. As the first defense, ROS are reduced by antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as endogenous and exogenous small molecules, such as glutathione and vitamins C and E [2]. When biomolecules are oxidized, they are repaired or replaced by biological protective systems. Nevertheless, biomolecules are gradually oxidized in an irreversible manner, and accumulation of these biomolecules over time alters biological functions, eventually leading to aging and age-related diseases [3].

When exposed to UV radiation, there is an imbalance between pro-oxidants and antioxidants, leading to oxidative stress and photoaging of the skin [4]. The constant action of UV rays on the skin depletes the antioxidants present in the skin over time. Antioxidants present in the *stratum corneum* are susceptible to UV exposure and a single suberythemal dose can deplete their concentration to almost half [5].

Some studies have also demonstrated that visible and near-infrared (VIS/NIR) lights induce the development of free radicals in skin [6,7]. For this reason, sunscreen with an effect in the whole solar spectrum should contain UVB and UVA filters for the UV range, physical filters for the entire range, as well as antioxidants for the infrared (IR) range [8,9].

An impairment of the balance between oxidants and antioxidants, due to an increased exposure to exogenous sources of ROS, has been defined as “oxidative stress” and involves oxidative damage of lipids, proteins, and DNA. Topical administration of antioxidants is regarded as an interesting strategy in reducing ROS-induced skin damage since it may improve skin antioxidant status [1].

2. Antioxidants

Of the various enzymatic and non-enzymatic antioxidants present in the skin, vitamin E homologue, also known as α-tocopherol (tocopherol), is considered the most active, lipid-soluble, membrane-bound antioxidant. Tocopherol acts primarily by two mechanisms; as an antioxidant, it will donate one of its electrons to a free radical, thereby stabilizing it. In addition, tocopherol is known to slow down the process of collagen breakdown [5].

When the endogenous antioxidants are insufficient to reduce oxidative stress, then antioxidants from different sources can be applied to the skin in different cosmetic formulations.

Retinol has been intensively investigated to study the physiology and function of skin. Retinol is stored in the skin as retinyl ester or is converted into retinoic acid. Retinoic acid is the biologically active retinoid; however, retinol is less irritating and produces similar effects as retinoic acid. This quality makes retinol more favorable for use in cosmetic products. Although trans-retinol is extensively used in the cosmetic industry, there is insufficient information on its quantitative penetration and distribution within the different layers of the skin [10].

Polyphenols are a group of chemical molecules characterized by the presence of phenol units in their molecular structure and are the most abundant antioxidants present in fruits and vegetables. The efficiency of polyphenols as antioxidant compounds greatly depends on their chemical structure. Flavonoids, a class of polyphenols, are the most potent antioxidants present in plants, and catechin is an example of this class found abundantly in green tea extracts. Resveratrol, another polyphenol that is considered to be an important antioxidant from the family of stilbene, is abundantly found in the skin of grapes, nuts, and berries [11]. Resveratrol shows geometric isomerism, but only trans-resveratrol presents several biological effects, such as anticancer, anti-aging, and antioxidant activities. It is an interesting drug to be incorporated in dermal products. Resveratrol has poor oral bioavailability, short half-life, and is extensively metabolized in the body [12].

Curcumin is another polyphenol that gives color to the rhizomes of *Curcuma longa*. It is most commonly used in traditional medications and cosmetics. Studies have shown that curcumin is also poorly absorbed in the gastrointestinal tract [13]. Curcumin is a potent free radical scavenger quenching superoxide anions, singlet oxygen, and hydroxyl radicals and inhibiting lipid peroxidation [14].

Quercetin, coenzyme Q10, and vitamin C, among others, are the most used antioxidants for topical application. Supplementing skin with topical antioxidants may strengthen antioxidant capacity and thus reduce reactive oxygen species-induced skin damage. A good candidate for a topical antioxidant should fulfill two conditions: (i) the candidate should permeate through the *stratum corneum* and (ii) reach the deeper cutaneous layers without significant leakage into systemic circulation [15].

The attributes of different polyphenols and other antioxidants make them excellent candidates for skin treatment; however, in some cases, their poor water solubility makes their application difficult. On the other hand, there are good antioxidants such as vitamin C used in cosmetics and dermatological preparations because of their favorable effects on skin. However, vitamin C has a poor chemical stability in heterogeneous systems and may undergo dismutation reactions [16]. One strategy to avoid this type of inconveniences is the formulation of these antioxidants as nano using different nanocarriers.

3. Nanocarriers

Nanocarriers have emerged as a promising drug delivery system offering several advantages over conventional passive delivery, such as increased surface area, higher solubility, improved stability, controlled release of active ingredients, reduced skin irritancy, protection from degradation, increased drug loading, and improved permeation of actives into the skin [17].

In this sense, Lohani *et al*. have reviewed the use of nanotechnology in cosmetics and its advantages [18]. There are different types of nanoparticles: (a) liposomes consisting of spherical

self-closed vesicles of colloidal dimensions, in which the phospholipid bilayers sequester part of the solvent in which they freely float into their interior, and the lipid bilayer is mainly composed of natural or synthetic phospolipids; (b) nanocapsules that consist of vesicular systems that are made up of polymeric membranes in which an inner liquid core is encapsulated at the nanoscale level (10 nm to 1000 nm); (c) solid lipid nanoparticles which consist of submicron colloidal carriers composed of physiological lipid dispersed in water or in aqueous solution of surfactant; (d) nanocrystals which are aggregates composed of several hundreds to thousands of atoms that combine into a cluster (10–400 nm) and are used for the delivery of poorly soluble actives; (e) niosomes which are nonionic surfactant vesicles devised by using nonionic surfactants and have high entrapment efficiency, improved chemical stability, and enhanced penetration. Niosomes have the advantage of accommodating hydrophilic, lipophilic, and amphiphilic drug moieties. They are less toxic and expensive than liposomes but they have disadvantages such as aggregation and leaking of the entrapped drug (Figure 1).

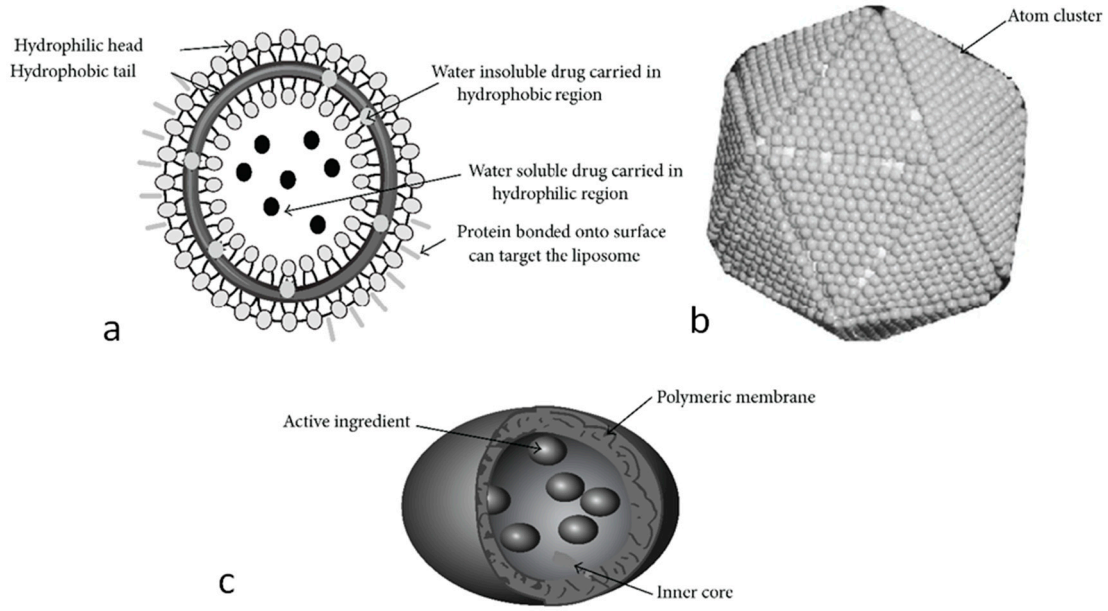

Figure 1. Examples of different types of nanoparticles. (**a**) Liposome showing a phospholipid bilayer surrounding an aqueous interior; (**b**) solid lipid nanoparticle; (**c**) nanocapsule loaded with an active ingredient [18].

Many lipid nanocarrier products available on the market are for cosmetic applications. Nanostructured lipid carriers (NLCs) belonging to the second generation of lipid nanoparticles are stable to leakage and have high drug loading capacity [19]. Lipid-based nanosystems that have been investigated for topical applications include solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and nanoemulsions (NE) [20]. SLN are composed of lipids that are solid at ambient temperature, whereas NLC are mixtures of solid and liquid lipids. Some of the advantages of SLN and NLC include the use of physiological lipids in the composition, the avoidance of organic solvents, the possibility to produce concentrated lipid suspensions, and the availability of established scale-up processes [21]. Topical application of SLN- and NLC-based systems have been studied with various active compounds such as vitamin E, vitamin A, and retinoic acid, among others [22].

3.1. Nanocarriers for Resveratrol Administration

Recently, an extensive review of the nanoformulations with resveratrol has been published [23] with special focus on the application of resveratrol as a cancer therapy. In this sense, nano-sized formulations are additionally advantageous in cancer therapeutics due to the enhanced permeability and retention (EPR) effect by which these molecules accumulate preferentially in cancer tissues as was postulated.

For the application on skin, resveratrol-loaded solid lipid nanoparticles (SLN) have been developed and the cellular uptake, transport, and internalization in keratinocytes have been studied [24]. The particles readily crossed the cell membrane in as little as 15 min and, in comparison with resveratrol in solution, the SLN-encapsulated drug exhibited greater intracellular delivery, solubility, and stability. SLN were able to protect resveratrol from photo degradation, enhance its uptake in porcine ear skin, and improve its anti-lipoperioxidative activity, appearing as a promising delivery system [25].

Liposomes and niosomes can increase the residence time of the drug in the *stratum corneum* and epidermis, reducing the systemic absorption of the drug. The advantages of niosomes over liposomes are their higher chemical stability and their low cost. Niosomes loaded with resveratrol showed higher delivery of resveratrol in deeper layers of the skin compared to liposomes; then they are better as carriers of resveratrol. Niosomes have been prepared with different proportions of polyglyceryl-3 dioleate (PLU) or glycerol monooleate (PEC) and cholesterol. In particular, niosomes composed by 30 mg/mL of PEC and 30 mg/mL of cholesterol (PEC-niosomes 30:30) allowed the highest amount of resveratrol to be accumulated in the *stratum corneum* as is shown in Figure 2 [26]. Another study has demonstrated the efficacy of [27].

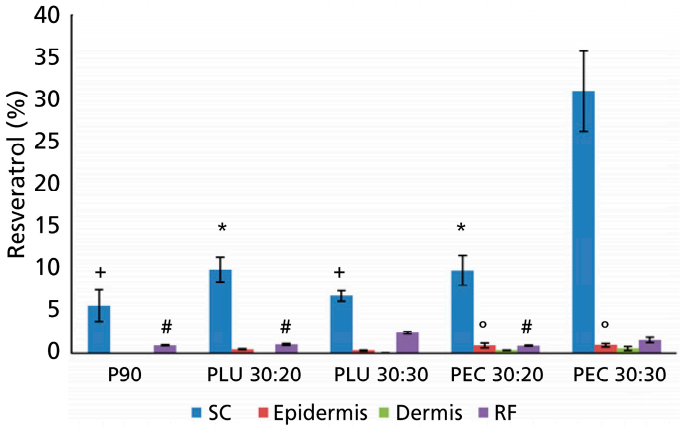

Figure 2. Percentage of resveratrol accumulated in *stratum corneum* (SC), epidermis, dermis, and receptor fluid (RF) applied onto the skin into P90-liposomes and PLU- or PEC-niosomes. Each value is the mean ± SD of six experimental determinations. No statistical differences ($P > 0.05$) were found in samples labelled with the same symbol (*, +, #, °). Reproduced with permission from [26], published by Royal Pharmaceutical Society, 2013.

Another possibility is the simultaneous encapsulation of resveratrol with curcumin in lipid-core nanocapsules, as has been proposed recently. Skin penetration studies showed an increased delivery of resveratrol into deeper skin layers upon co-delivery in comparison to the encapsulation of one individual polyphenol. The authors demonstrated that the interaction of curcumin with the lipid bilayers of the

stratum corneum facilitated the penetration of the less lipophilic resveratrol across the skin barrier into the epidermis and dermis [28].

The co-encapsulation of resveratrol and curcumin in niosomal systems affected the entrapment efficiency values, with respect to the formulations containing the single antioxidant. The *in vitro* percutaneous permeation of the antioxidants appeared to be controlled and improved with respect to the corresponding free solutions used as the control. Moreover, the antioxidant combinations resulted in a promoted ability to reduce free radicals due to a synergic antioxidant action and, for this reason, these niosomal formulations showed potential in the transdermal delivery of antioxidant molecules and may be useful in the cosmeceutical field [29].

3.2. Nanocarriers for Vitamin C

Vitamin C has been used in cosmetic products due to its biological activity as a non-enzymatic soluble antioxidant. Vitamin C can protect biomolecules against oxidative degradation through its ability to scavenge and reduce reactive oxidizing molecules and free radicals. However, vitamin C is unstable and can be easily oxidized under aerobic conditions, the rate of which is increased with increasing heat of UV light levels [30]. In order to avoid this oxidation, many derivatives of vitamin C have been introduced, including various esters, such as ascorbylpalmitate (AP) and retinylascorbate, bis(Lascorbicacid-3,3′)phosphate, and L-ascorbic acid 2-phosphate. AP has been the more popular ester, used as an antioxidant additive in cosmetic products because of its improved stability and better skin penetration in comparison to vitamin C. The deceleration in the AP degradation has been obtained by encapsulation of AP into microemulsions, bilayer vesicles, polymeric nanoparticles, and solid lipid nanoparticles [31]. To increase the stability of AP, it is possible to make a nanocarrier with an antioxidative property, attaching the natural dietary antioxidant curcumin onto poly(vinyl alcohol) (PV(OH)), a nontoxic, biocompatible, and biodegradable hydrophilic polymer. The obtained curcumin-grafted PV(OH) polymer (CURPV(OH)) was then fabricated into a nanocarrier and AP was encapsulated into the CUR-PV(OH) nanocarrier. The stability of the encapsulated AP was evaluated and it demonstrated better stability compared to free AP, as can be observed in Figure 3 [32].

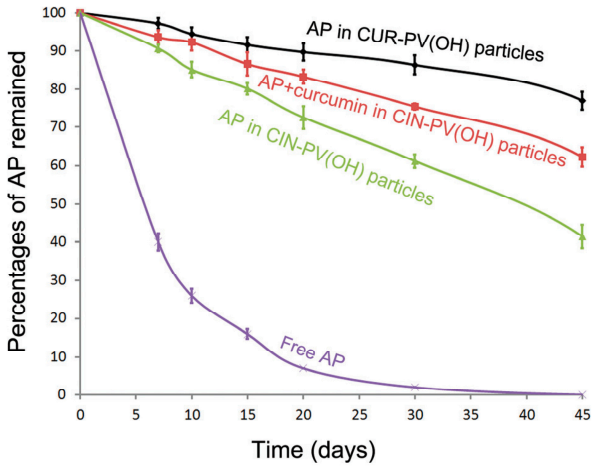

Figure 3. Stability of dry free AP (unencapsulated AP), or AP encapsulated in different nanocarriers, after storage at 30 °C under light-proof conditions with normal air exposure. Reproduced with permission from [32], published by Wiley Periodicals, Inc., 2013.

3.3. Nanocarriers for Quercetin Delivery

Quercetin has been demonstrated as the flavonoid with the highest antioxidant activity, characterized by multiple mechanisms. Moreover, the topical application of quercetin decreases skin damage induced by exposure to UV radiation [33]. However, the skin protective activity of quercetin is insufficient due to its poor percutaneous penetration that limits the amount of the compound reaching the site of action in the epidermis [34]. Different formulations of quercetin have been developed based on microemulsions, encapsulation in lipid nanoparticles, and silica nanoparticles in order to enhance its penetration in the skin. Results of this study demonstrated that the emulsion containing silica nanoparticles was the only vehicle which could significantly enhance the *in vivo* penetration of quercetin into the human *stratum corneum*, with the advantage that the silica particles were confined in the upper layers, limiting the potential toxicological risks [35]. This study was performed in humans in real conditions, considering the reported differences between human and animal skin and the alterations observed in excised human skin when the studies are performed *in vitro* [36].

Nanostructured lipid carriers of quercetin have been developed using a solvent (chloroform/acetone)-based emulsification technique and evaluated for topical delivery [37]. One of the major disadvantages of a manufacturing method involving the use of organic solvents can be toxicological issues arising from solvent residues. For this reason, a solvent-free, solid lipid-based nanosystem of quercetin using a probe ultrasonication process has been developed. This process showed, using *in vitro* permeation studies with full thickness human skin, higher amounts of quercetin to be localized within the skin compared to a control formulation with particles in the micrometer range. Such an accumulation of quercetin in the skin is highly desirable since the efficacy of quercetin in delaying ultra-violet radiation-mediated cell damage and eventual necrosis mainly occurs in the epidermis [38].

3.4. Nanocarriers for Coenzyme Q10 Delivery

Coenzyme Q10 (CoQ10) is the only lipophilic cellular antioxidant endogenously synthesized in humans. It is a cofactor in the mitochondrial respiratory chain and it is essential to transfer free electrons from complexes I and II to complex III during oxidative phosphorylation and ATP synthesis. CoQ10 acts as an antioxidant in the skin with 10-fold higher levels in the epidermis than in the dermis. It has been used in cosmetics due to its ability to reduce photo-aging *in vivo*, which could be attributed to the capacity to increase production of basal membrane components, fibroblast proliferation, and protection against oxidative damage [39]. The difficulty of CoQ10 in reaching the deeper layers of the skin determines its inclusion in different carriers. In this sense, liposomes, lipid nanoparticles, solid nanoparticles, and nanostructured lipid carriers (NLC) are more often used for this purpose [40]. Among them, nanostructured lipid carriers have been used successfully for dermal delivery of CoQ10 due to its highly lipophilic character [41], but the possible interference with intracellular biochemical processes should be investigated. It has been recently demonstrated that ultra-small lipid nanoparticles promote the penetration of coenzyme Q10. In this publication, the cell viability and the efficiency of these nanocarriers were examined in HaCaT cells [42].

Recent study demonstrated that nanostructured lipid carriers induced some subtle cytotoxic effects and they did alter the redox state level on human dermal fibroblasts under normal and oxidative conditions, but genotoxicity was not observed. The use of reduced CoQ10 decreased these effects because CoQ10 is a highly active antioxidant and maintains mitochondrial functionality. Then the use of antioxidants could be considered when preparing NLC for cosmetic delivery purposes in order to prevent undesirable effects on cells by the carrier systems used. The geno- and cytotoxicity should be evaluated, especially under conditions which closely mimic their normal usage [43].

3.5. Nanocarriers for Other Antioxidants

Curcumin is a major phytopolyphenolic compound consisting of three curcuminoids derived from turmeric (Curcuma longa) rhizomes, a spice commonly used in curries and other South Asian cuisine, and in both Ayurvedic and Chinese medicine for the treatment of skin diseases and wound healing, among other applications. Curcumin is a potent free radical scavenger quenching superoxide anions, singlet oxygen, and hydroxyl radicals and inhibiting lipid peroxidation. However, upon exposure to sunlight, free curcumin degrades rapidly, reducing its antioxidant capacity. To avoid this effect, one strategy is to encapsulate it into biodegradable, safe, inexpensive, and commercially available polymeric nanospheres, which offers protection from photo-degradation and retains its antioxidant capacity [14].

Tocopherol is considered the most active, lipid-soluble, membrane-bound antioxidant present in the skin. However, the constant bombardment of UV rays on the skin depletes the antioxidants present in the skin over time and a decreasing gradient of tocopherol from the deeper to the outermost layers of the stratum corneum has been reported in the literature. In order to protect the skin from oxidative stress, tocopherol should be supplemented topically to replenish the antioxidants in the upper layers of the skin [44].

Synthetically available tocopherol is a highly viscous skin irritant and light-sensitive liquid. This property makes it difficult to incorporate tocopherol in topical/cosmetic formulations. Therefore, tocopherol acetate, a prodrug ester, is used in most of the anti-aging formulations available on the market [45]. Another option is to formulate tocopherol into nanocarriers to produce a non-irritant, stable, and cosmetically appealing aqueous formulation. The results confirmed that nanostructured lipid carriers (NLC) induced a higher release of tocopherol than nanoemulsions; thus, NLC are promising nanocarriers for cosmetic delivery [5].

Finally, alpha lipoic acid (ALA) is a naturally occurring fatty acid with potent antioxidant activity which exists in the mitochondria of all kinds of prokaryotic and eukaryotic cells. ALA is known as a network antioxidant due to its ability to regenerate/recycle itself as well as other antioxidants, such as vitamins C and E, so that they can continue destroying free radicals [46]. There available data of formulations containing 5% ALA producing a dramatic reduction in facial lines in cases associated with photo-aging, and for this reason, this compound has gained the attention of cosmetologists and dermatologists. One of the strategies to formulate this compound is as cubosomes, which are discrete, submicron, nanostructured particles of bicontinuous cubic liquid crystalline phase which are able to incorporate large amounts of drugs or actives [47]. A recent study has demonstrated that the formulation of ALA in cubosome dispersion has excellent results in reducing facial lines with almost

complete resolution of fine lines in the periorbital region and upper lip area and an overall improvement in skin color and texture in most volunteers [48]. Table 1 shows different studies demonstrating that the use of nanoformaulation enhances the skin delivery of antioxidants.

Table 1. Different nanoformulations that enhance the skin delivery of different antioxidants and other advantages demonstrated by different methods.

Antioxidant	Nanoformulation	Methods	Advantages	Reference
Resveratrol	Solid lipid nanoparticles	*In vitro* photo-degradation *In vitro* porcine skin	Protection from photo-degradation Enhance uptake in skin	Carloti *et al.* 2012 [25]
Resveratrol	Fosfolipid vesicels	DPPH radical scavenging activity assay	Increase efficiency and stability of carriers	Caddeo *et al.* 2013 [27]
Resveratrol + curcumin	Lipid-core nanocapsules	*In vitro* static Franz diffusion cell human skin	Increase delivery of resveratrol into skin	Friedrich *et al.* 2015 [28]
Resveratrol + curcumin	Niosomes	*In vitro* static Franz diffusion cell rabbit skin DPPH radical scavenging activity assay	Increase delivery of resveratrol into skin Increase antioxidant activity	Tavano *et al.* 2014 [29]
Q10	Ultra small nano-structured lipid carrier (NLC)	*In vitro* static Franz diffusion cell porcine skin	Increase delivery of Q10 into skin	Schwarz *et al.* 2013 [42]
Q10	Ultra-small lipid nanoparticles (usNLC)	*In vitro* human keratinocyte cell line HaCaT	Strongest reduction of the radical formation and non-toxic	Lohan *et al.* 2015 [42]
Quercetin	Solid lipid nanosystems	*In vitro* static Franz diffusion cell human skin	Higher amounts of quercetin within the skin	Bose *et al.* 2013 [38]
Quercetin	Colloidal silica emulsion	*In vivo* human penetration assay	Enhance penetration into *stratum corneum* in human	Scalia *et al.* 2012 [35]

4. Conclusions

The administration of antioxidants to skin is fundamental to reduce aging and to achieve protective effects on the skin. However, their stability is not always enough to guarantee their effects on skin and their delivery into deeper layers of skin is not always possible. Different nanocarriers have been proposed with the objective to increase the stability and the delivery of them into the skin in order to obtain their highest activity. The type of nanocarrier varies depending on the antioxidant under consideration and this should be taken into account when formulating different cosmetic products based on these antioxidants. Another important aspect to consider is the potential genotoxicity and/or cytotoxicity of the nanocarriers, especially under conditions similar to the normal usage in cosmetic formulations. Lastly, this should be evaluated and considered before formulating any cosmetic based on these nanocarriers.

Acknowledgments

The authors acknowledge financial support from the Ministerio de Economía y Competitividad, Spain and FEDER, European Union (Project MAT2012-38047-C02-01).

Author Contributions

The two authors participated in the search of information to write this review and participated in its redaction.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Dreher, F.; Maibach, H.I. Protective effects of topical antioxidants in humans. *Curr. Probl. Dermatol.* **2001**, *29*, 157–164.
2. Yoshihisa, Y.; Honda, A.; Zhao, Q.L.; Makino, T.; Abe, R.; Matsui, K.; Shimizu, H.; Miyamoto, Y.; Kondo, T.; Shimizu, T. Protective effects of platinum nanoparticles against UV-light-induced epidermal inflammation. *Exp. Dermatol.* **2010**, *19*, 1000–1006.
3. Bokov, A.; Chaudhuri, A.; Richardson, A. The role of oxidative damage and stress in aging. *Mech. Ageing Dev.* **2004**, *125*, 811–826.
4. Montenegro, L.; Sinico, C.; Castangia, I.; Carbone, C.; Puglisi, G. Idebenone-loaded solid lipid nanoparticles for drug delivery to the skin: *In vitro* evaluation. *Int. J. Pharm.* **2012**, *434*, 169–174.
5. Abla, M.J.; Banga, A.K. Formulation of tocopherol nanocarriers and *in vitro* delivery into human skin. *Int. J. Cosmet. Sci.* **2014**, *36*, 239–246.
6. Zastrow, L.; Groth, N.; Klein, F.; Kockott, D.; Lademann, J.; Renneberg, R.; Ferrero, L. The missing link—Light-induced (280–1600 nm) free radical formation in human skin. *Skin Pharmacol. Phys*. **2009**, *22*, 31–44.
7. Darvin, M.E.; Haag, S.F.; Meinke, M.C.; Sterry, W.; Lademann, J. Determination of the influence of IR radiation on the antioxidative network of the human skin. *J. Biophotonics* **2011**, *4*, 21–29.
8. Meinke, M.C.; Syring, F.; Schanzer, S.; Haag, S.F.; Graf, R.; Loch, M.; Gersonde, I.; Groth, N.; Pflücker, F.; Lademann, J. Radical protection by differently composed creams in the UV/VIS and IR spectral ranges. *Photochem. Photobiol*. **2013**, *89*, 1079–1084.
9. Arndt, S.; Haag, S.F.; Kleemann, A.; Lademann, J.; Meinke, M.C. Radical protection in the visible and infrared by a hyperforin-rich cream—*In vivo versus ex vivo* methods. *Exp. Dermatol*. **2013**, *22*, 354–357.
10. Melot, M.; Pudney, P.D.; Williamson, A.M.; Caspers, P.J.; van der Pol, A.; Puppels, G.J. Studying the effectiveness of penetration enhancers to deliver retinol through the stratum cornum by *in vivo* confocal Raman spectroscopy. *J. Control. Release* **2009**, *138*, 32–39.
11. Kohen, R. Skin antioxidants: Their role in aging and in oxidative stress—New approaches for their evaluation. *Biomed. Pharmacother.* **1999**, *53*, 181–192.

12. Hung, C.F.; Lin, Y.K.; Huang, Z.R.; Fang, J.Y. Delivery of resveratrol, a red wine polyphenol polyphenol, from solutions and hydrogels via the skin. *Biol. Pharm. Bull.* **2008**, *31*, 955–962.
13. Fang, J.Y.; Hung, C.F.; Chiu, H.C.; Wang, J.J.; Chan, T.F. Efficacy and irritancy of enhancers on the *in vitro* and *in vivo* percutaneous absorption of curcumin. *J. Pharm. Pharmacol.* **2003**, *55*, 593–601.
14. Suwannateep, N.; Wanichwecharungruang, S.; Haag, S.F.; Devahastin, S.; Groth, N.; Fluhr, J.W.; Lademann, J.; Meinke, M.C. Encapsulated curcumin results in prolonged curcumin activity *in vitro* and radical scavenging activity *ex vivo* on skin after UVB-irradiation. *Eur. J. Pharm. Biopharm.* **2012**, *82*, 485–490.
15. Marti-Mestres, G.; Mestres, J.P.; Bres, J.; Martin, S.; Ramos, J.; Vian, L. The *in vitro* percutaneous penetration of three antioxidant compounds. *Int. J. Pharm.* **2007**, *331*, 139–144.
16. Jurkovic, P.; Šentjurc, M.; Gašperlin, M.; Kristl, J.; Pecar, S. Skin protection against ultraviolet induced free radicals with ascorbylpalmitate in microemulsions. *Eur. J. Pharm. Biopharm.* **2003**, *56*, 59–66.
17. Abramovits, W.; Granowski, P.; Arrazola, P. Applications of nanomedicine in dermatology: Use of nanoparticles in variousthera pies and imaging. *J. Cosmet. Dermatol.* **2010**, *9*, 154–159.
18. Lohani, A.; Verma, A.; Joshi, H.; Yadav, N.; Karki, N. Nanotechnology-Based Cosmeceuticals. *ISRN Dermatol.* **2014**, *2014*, 843687.
19. Muller, R.H.; Petersen, R.D.; Hommoss, A.; Pardeike, J. Nanostructured lipid carriers (NLC) in cosmetic dermal products. *Adv. Drug Deliv. Rev.* **2007**, *59*, 522–530.
20. Schafer-Korting, M.; Mehnert, W.; Korting, H.C. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv. Drug Deliv. Rev*. **2007**, *59*, 427–443.
21. Mehnert, W.; Mader, K. Solid lipid nanoparticles: Production, characterization and applications. *Adv. Drug Deliv. Rev.* **2001**, *47*, 165–196.
22. Castro, G.A.; Coelho, A.L.; Oliveira, C.A.; Mahecha, G.A.; Orefice, R.L.; Ferreira, L.A. Formation of ion pairing as an alternative to improve encapsulation and stability and to reduce skin irritation of retinoic acid loaded in solid lipid nanoparticles. *Int. J. Pharm.* **2009**, *381*, 77–83.
23. Summerlin, N.; Soo, E.; Thakur, S.; Qu, Z.; Jambhrunkar, S.; Popat, A. Resveratrol nanoformulations: Challenges and opportunities. *Int. J. Pharm.* **2015**, *479*, 282–290.
24. Teskac, K.; Kristl, J. The evidence for solid lipid nanoparticles mediated cell uptake of resveratrol. *Int. J. Pharm.* **2010**, *390*, 61–69.
25. Carlotti, M.; Sapino, S.; Ugazio, E.; Gallarate, M.; Morel, S. Resveratrol in solid lipid nanoparticles. *J. Dispers. Sci. Technol.* **2012**, *33*, 465–471.
26. Pando, D.; Caddeo, C.; Manconib, M.; Fadda, A.M.; Pazos, C. Nanodesign of olein vesicles for the topical delivery of the antioxidant resveratrol. *J. Pharm. Pharmacol.* **2013**, *65*, 1158–1167.
27. Caddeo, C.; Manconi, M.; Faddda, M.A.; Lai, F.; Lanpis, S.; Diez-Sale, O.; Sinico, C. Nanocarriers for antioxidant resveratrol: Formulation approach, vesicle self-assembly and stability evaluation. *Colloids Surf. B*. **2013**, *11*, 327–332.
28. Friedrich, R.B.; Kann, B.; Coradini, K.; Offerhaus, H.L.; Beck, R.C.; Windbergs, M. Skin penetration behavior of lipid-core nanocapsules for simultaneous delivery of resveratrol and curcumin. *Eur. J. Pharm. Sci*. **2015**, *78*, 204–213.

29. Tavano, L.; Muzzalupo, R.; Picci, N.; de Cindio, B. Co-encapsulation of lipophilic antioxidants into niosomal carriers: Percutaneous permeation studies for cosmeceutical applications. *Colloids Surf. B Biointerfaces* **2014**, *114*, 144–149.
30. Austria, R.; Semenzato, A.; Bettero, A. Stability of vitamin C derivatives in solution and topical formulations. *J. Pharm. Biomed. Anal.* **1997**, *15*, 795–801.
31. Kristl, J.; Volk, B.; Gasperlin, M.; Sentjurc, M.; Jurkovic, P. Effect of colloidal carriers on ascorbylpalmitate stability. *Eur. J. Pharm. Sci.* **2003**, *19*, 181–189.
32. Janesirisakule, S.; Sinthusake, T.; Wanichwecharungruang, S. Nanocarrier with self-antioxidative property for stabilizing and delivering ascorbylpalmitate into skin. *J. Pharm. Sci.* **2013**, *102*, 2770–2779.
33. Casagrande, R.; Georgetti, S.R.; Verri, W.A., Jr.; Dorta, D.J.; dos Santos, A.C.; Fonseca, M.J. Protective effect of topical formulations containing quercetin against UVB-induced oxidative stress in hairless mice. *J. Photochem. Photobiol. B* **2006**, *84*, 21–27.
34. Kitagawa, S.; Tanaka, Y.; Tanaka, M.; Endo, K.; Yoshii, A. Enhanced skin delivery of quercetin by microemulsion. *J. Pharm. Pharmacol.* **2009**, *61*, 855–860.
35. Scalia, S.; Franceschinis, E.; Bertelli, D.; Iannuccelli, V. Comparative evaluation of the effect of permeation enhances, lipid nanoparticles and colloidal silica on *in vivo* human skin penetration of quercetin. *Skin Pharmacol. Physiol.* **2013**, *25*, 57–67.
36. Menon, G.K. New insights into skin structure: Scatching the surface. *Adv. Drug Deliv. Rev.* **2002**, *54*, S3–S17.
37. Guo, C.; Yang, C.; Li, Q.; Qi, T.; Xi, Y.; Liu, W.; Zhai, G. Development of a quercetin-loaded nanostructured lipid carrier formulation for topical delivery. *Int. J. Pharm.* **2012**, *430*, 292–298.
38. Bose, S.; Du, Y.; Takhistov, P.; Michniak-Kohn, B. Formulation optimization and topical delivery of quercetin from solid lipid based nanosystems. *Int. J. Pharm.* **2013**, *441*, 56–66.
39. Muta-Takada, K.; Terada, T.; Yamanishi, H.; Ashida, Y.; Inomata, S.; Nishiyama, T.; Amano, S. Coenzyme Q10 protects against oxidative stress-induced cell death and enhances the synthesis of basement membrane components in dermal and epidermal cells. *Biofactors* **2009**, *35*, 435–441.
40. Puglia, C.; Bonina, F. Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. *Expert Opin. Drug Deliv.* **2012**, *9*, 429–441.
41. Schwarz, J.; Baisaeng, N.; Hoppel, M.; Löw, M.; Keck, C.M.; Valenta, C. Ultra-small NLC for improved dermal delivery of coenzyme Q10. *Int. J. Pharm.* **2013**, *447*, 213–217.
42. Lohan, S.B.; Bauersachs, S.; Ahlberg, S.; Baisaeng, N.; Keck, C.M.; Müller, R.H.; Witte, E.; Wolk, K.; Hackbarth, S.; Röder, B.; *et al*. Ultra-small lipid nanoparticles promote the penetration of coenzyme Q10 in skin cells and counteract oxidative stress. *Eur. J. Pharm. Biopharm*. **2015**, *89*, 201–207.
43. Brugè, F.; Damiani, E.; Puglia, C.; Offerta, A.; Armeni, T.; Littarru, G.P.; Tiano, L. Nanostructured lipid carriers loaded with CoQ_{10}: Effect on human dermal fibroblast under normal and UVA-mediated oxidative conditions. *Int. J. Pharm.* **2013**, *455*, 348–356.
44. Mahamongkol, H.; Bellantone, R.A.; Stagni, G.; Plakogiannis, F.M. Permeation study of five formulations of alpha-tocopherol acetate through human cadaver skin. *J. Cosmet. Sci*. **2005**, *56*, 91–103.

45. Ben-Shabat, S.; Kazdan, Y.; Beit-Yannai, E.; Sintov, A.C. Use of alpha-tocopherol esters for topical vitamin E treatment: Evaluation of their skin permeation and metabolism. *J. Pharm. Pharmacol.* **2013**, *65*, 652–658.
46. Charles, S.T.; Reynolds, C.A.; Gatz, M. Age-related differences and change in positive and negative affect over 23 years. *J. Personal. Soc. Psychol.* **2001**, *80*, 136–151.
47. Wu, H.; Li, J.; Zhang, Q.; Yan, X.; Guo, L.; Gao, X.; Qui, M.; Jiang, X.; Lai, R.; Chen, H. A novel small odorranalectin-bearing cubosomes: Preparation, brain delivery and pharmacodynamics study on amyloid-b25-35-treated rats following intranasal administration. *Eur. J. Pharm. Biopharm.* **2012**, *80*, 368–378.
48. Sherif, S.; Bendas, E.R.; Badawy, S. The clinical efficacy of cosmeceutical application of liquid crystalline nanostructured dispersions of alpha lipolic acid as anti-wrinkle. *Eur. J. Pharm. Biopharm.* **2014**, *86*, 252–259.