

Review

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Review

Would Be Rutin a Feasible Strategy for Environmental-Friendly Photoprotective Samples? A Review from Stability to Skin Permeability and Efficacy in Sunscreen Systems

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Abstract: Rutin, a flavonoid compound found in various plants, has gained attention for its potential applications in the cosmetic industry due to its antioxidant, anti-inflammatory, and potential photoprotective properties. Our review explored the use of rutin (rutoside, 3-O-rutinoside-quercetin) in cosmetics/dermocosmetics, focusing on its physicochemical properties and stability, cutaneous permeability, and efficacy in sunscreen systems, involving in vitro tests and the current state of clinical trials. Rutin's ability to scavenge free radicals, prevent peroxidation, and reduce vascular fragility makes this flavonoid a promising ingredient for photoprotection. Studies have shown that rutin can enhance the sun protection factor (SPF) of sunscreen formulations, especially when combined with organic UV filters. The encapsulation of rutin in nanostructures has also been investigated to improve its applicability. Overall, rutin shows potential as a safe and effective ingredient in cosmetic/dermocosmetic formulations, offering protection against the harmful effects of UV radiation and oxidative stress on the skin.

Keywords: rutoside; labsphere; sunscreens; UV filters; sun protection factor

1. Introduction

Several bioactive substances are obtained from natural products of plant origin, finding applications in feeding, cosmetic, and medicinal products. Among the most widely used classes are flavonoids, comprising more than 8,000 identified substances, and being broadly recognized for their properties, including antioxidant, anti-inflammatory, and anti-cancer, among several others. One of the well-recognized subgroups of the flavonoid class are the flavonols (quercetin, mercetin, rutin *etc.*) [1–5]. Rutin (rutoside, 3-O-rutinoside-quercetin), also known as vitamin P, is a yellow and odorless pigment in the form of needle crystals [6–8]. This compound has free radical scavenging capacity and can also prevent peroxidation promoted by metal ions, being a metal chelator [9,10]. Moreover, it exhibits broad bioactivity, such as reducing vascular fragility, reducing hypertension, and possessing anti-inflammatory and antioxidant activities [7,11–13].

Rutin was detected in 1842 in the *Ruta graveolens* (common rue or herb-of-grace) and it was later isolated from *Caparis spinosa* (caper bush). It was classified as rutinic acid, since it is soluble in alkaline media, practically insoluble in water, and slightly soluble in alcohols. Its molecular structure

($C_{27}H_{30}O_{16}$) was elucidated in 1896 (**Figure 1**), with the discovery of the link between the sugars (glucose and rhamnose) in the quercetin molecule [1,6,14,15].

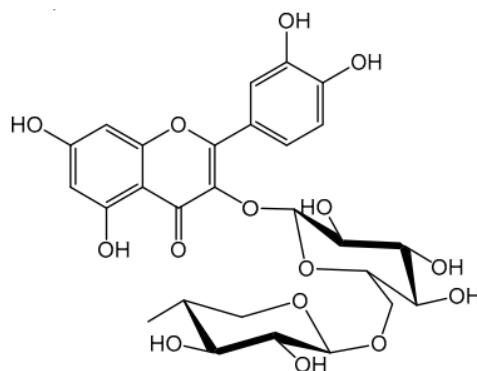


Figure 1. Chemical structure of rutin [16].

The molecular structure of rutin shows aromatic rings and structures capable of resonance. Thus, rutin can become an ally in photoprotection, being able to interact with the ultraviolet (UV) radiation, with the potential to improve the efficacy of sunscreen products [17–19]. Furthermore, it is known that much of the skin damage caused by UV radiation is related to free radicals formed during to UV exposure [20–25]. Therefore, considering the antioxidant capacity of rutin, it is believed that it can confer additional protection from oxidative damage to the skin caused by sun exposure, justifying its application in multifunctional photoprotective formulations [26–29]. It is still worth highlighting that this bioactive compound is biocompatible, therefore, possessing a suitable profile to be used in cosmetic formulations [20,30–34]. For this review, we explored the potential of rutin in the development of photoprotective formulations, discussing its physicochemical and functional properties, such as its antioxidant, anti-inflammatory, and photoprotective effects. We also examined the physicochemical stability of cosmetic preparations containing rutin and its cutaneous permeability, highlighting its relevance to Cosmetology. Additionally, we argued the efficacy of rutin in sunscreen systems, both *in vitro* and *in vivo*, also exploring the use of nanotechnology.

2. Physicochemical Stability of Cosmetic Preparations Containing Rutin

The development of cosmetic formulations requires the rigorous selection of raw materials, careful technological processes, and validation of the analytical methodology used to determine the active substance(s), ensuring the quality (physical, physicochemical, chemical, microbiological, and toxicological aspects), safety, efficacy, acceptance, and adherence of the final product by the consumer [35–37].

Several extrinsic and intrinsic factors influence the stability of formulations:

- (i) extrinsic factors—external conditions to which cosmetic products are exposed, such as temperature, light, oxygen, humidity, packaging materials, microorganisms, and movements, among others;
- (ii) intrinsic factors—related to the nature of the formulation and the interactions among the components, leading mainly to physical and chemical incompatibilities [38,39].

Stability studies of cosmetic products aim to provide information indicating the relative stability of a product under various exposure conditions until the end of its shelf life. These studies should guide the development procedures, including the selection of formulation components, presentation form, alternative packaging materials, and confirmation of the estimated shelf life [38–40].

Preliminary Stability Evaluation (PSE) involves numerous formulations and tests applying extreme conditions of temperature, gravity, and humidity to select those with the best physicochemical stability. Typically, preparations undergo centrifugation and thermal stress tests. PSE allows the formulator to choose which formulas, among several tests from the development stage, are apparently stable [38–40]. Velasco and collaborators developed 14 oil-in-water (O/A)

emulsions, containing 5.0% w/w of the commercial extract of *Trichilia catigua* Adr. Juss (and *Ptychopetalum olacoides* Benthham, as a source of rutin. The PSE facilitated the identification of signs of instability in certain samples, such as phase separation, color alteration, and creaming [41]. Formulations showing modifications after the test should be rejected, or possible modifications for improved stability should be investigated. Those showing better performance are subjected to Accelerated Stability Testing.

The Accelerated Stability Test acts as a guide in predicting the stability of a product under harsh storage conditions in a shortened timeframe. Samples are stored under extreme temperature and light conditions: 22.0 ± 0.5 °C (room temperature); 5.0 ± 0.5 °C; under temperature cycles ranging from -10 ± 0.5 °C to $+45 \pm 0.5$ °C; -10 ± 0.5 °C; exposed to indirect or direct sunlight; in oven under 37.0 ± 0.5 °C to 50.0 ± 0.5 °C. They are carefully evaluated after the tests, and the best-performing samples are selected for sequential testing in the Normal Stability Test [39]. The parameters evaluated include appearance, color, odor, pH value, and apparent viscosity, indicating possible physical and physicochemical changes.

Our research group has previously determined the stability profile of two emulsified systems containing 5.0% w/w of a commercial extract, standardized in total flavonoids quantified as rutin, through the Normal Stability Test [42]. The systems differed in the absence or presence of 2.0% w/w of soy lecithin as an additional tensioactive. The total analysis period was 90 days, with tests on the 3rd, 7th, 15th, 30th, 60th, and 90th days. The storage conditions were: 40.0 ± 0.5 °C; exposure to indirect and direct sunlight at room temperature (24.0 ± 2.0 °C); and 5.0 ± 0.5 °C. The evaluated parameters were the organoleptic characteristics, pH value, apparent viscosity (cP), and total flavonoid content, expressed as rutin equivalents, remaining in the samples ($\mu\text{g/mL}$) [42]. The quantification of rutin was performed through UV spectrophotometry at 361.0 nm [43–45]. In the storage conditions at 24.0 ± 2.0 °C and 5.0 ± 0.5 °C (refrigerator), the samples showed reduced degradation of rutin content compared to the levels determined after their preparation. The sample without soy lecithin exhibited a reduction in the bioactive compound of 3.36% in the room temperature condition and 0.68% in the refrigerator after 90 days of storage. Although there was a variation in the pH value in the refrigerator condition, the concentration of total flavonoids was considered satisfactory, indicating that the pH value change in the range of -13.8% to -5.2% did not increase rutin degradation. For the sample with soy lecithin, at the end of the 90-day analysis, the percentage reduction was 6.38% and 1.31% for the room temperature and refrigerator conditions, respectively. In the oven condition (40.0 ± 0.5 °C), after 90 days, rutin deteriorated to a greater extent due to the temperature effect, indicating chemical degradation of the active substance for both samples. There was a reduction of 34.16 and 35.12% in the rutin concentration for the system without and with lecithin, respectively [41]. Considering that the evaluation of the stability of emulsified systems is usually conducted empirically, the protocol used in this work has advantages by systematically establishing experimental assays and objective criteria for the acceptance/rejection of samples in a short period [42–46].

Overall, flavonoids are sensitive to the presence of metals, UV radiation, temperature, and hydrolysis, which is accelerated directly and proportionally to the temperature increase [47–49]. Bilia and collaborators evaluated the stability of flavonoids, as a dry extract with or without the addition of a mixture of ascorbic acid and citric acid, under storage conditions at room temperature and in an oven for periods of 90 and 45 days [50]. The researchers found the flavonoids stable and observed that the presence of the antioxidants did not affect the stability of the dry extract. Thus, it can be suggested that the absence of a vehicle or cosmetic form containing water contributes to the stability and content of flavonoids. This highlights the importance of a careful selection of pharmaceutical adjuvants (starting materials) to favor the chemical stability of rutin. Therefore, another interpretation for the justification of the high kinetics of rutin deterioration in the presence or absence of lecithin could be the inadequate concentration of, for example, the chelating/sequestering agent sodium heptanoate at 0.1% w/w [41]. Banov and coworkers evaluated the stability of gels and emulsions containing *Ginkgo biloba* L. extract, standardized in total flavonoid content, and the chelating/sequestering agent EDTA Na. The results found the suitability of this agent in maintaining

the quantified levels of total flavonoids by the Normal Stability Test, at a concentration of 0.1% w/w and under oven conditions (40.0 ± 0.5 °C) [51].

Additionally, Nishikawa and coworkers developed hydroalcoholic gel systems (10.0% w/w cereal alcohol) based on polyvinyl alcohol with 0.05% w/w rutin [52]. The authors aimed to obtain a suitable vehicle containing the bioactive compound for facial application as a peel-off mask. The samples differed by the absence or presence of EDTA Na₂ at 0.1% w/w. The stability study was conducted for 45 days, and the samples were stored at 22.0 ± 2.0 °C, 5.0 ± 0.5 °C, and at 40.0 ± 0.5 °C. The quantitative content of rutin was determined by first-order derivative spectrophotometry at 410.0 nm [43,53]. The authors found that the presence of the chelating agent, at the employed concentration, improved the stability of rutin in the peel-off mask under room (22.0 ± 2.0 °C) and low-temperature storage conditions. In the sample without EDTA Na₂, the bioactive compound degraded under all storage conditions. It was also observed that the pH value of both samples tended to decrease when stored at 40.0 ± 0.5 °C. However, as also noted by Velasco and collaborators, it did not interfere with the chemical stability of rutin [41]. Thus, Nishikawa and coworkers (2007) concluded that the chelating agent increased the stability of the bioactive compound in hydroalcoholic gel systems when stored at room and low temperatures [52]. In the storage conditions of 40.0 ± 0.5 °C, the presence of EDTA Na₂ did not inhibit rutin degradation, contrary to the findings of Banov and coworkers mentioned above [51], reinforcing that higher water contents in the vehicle intended to incorporate rutin should require additional care in the selection and concentration of pharmaceutical adjuvants..

3. Cutaneous Permeability of Rutin: Relevance to Cosmetology and Photoprotection

Bioactives must reach the site of action in sufficient concentration for their effectiveness. Therefore, rutin, when formulated in different cosmetic forms, should be mainly available on the outer layers of the skin, its target tissue, to satisfactorily exert its protective effects [33,54]. Experiments on the release of active ingredients provide data on the behavior of the active component in semi-solids, supporting characterization and comparison of formulations, evaluation of production quality, and batch-to-batch uniformity. Therefore, they are essential to compare the performance of products under development with those available on the market [54]. In vitro penetration studies offer advantages such as cost-effectiveness, rapid results acquisition, experiment condition control, and the ability to assess a greater number of assays and replicas, among others. The ideal situation would be to use human skin as a model; however, the limited availability of this type of material, the need to submit the experiment to an Ethics Committee, and the difficulties and costs associated with storage and viability restrict its use [54]. As alternatives to human skin, researchers use experimental animal skin, synthetic membranes, and three-dimensional cultures, such as reconstructed epidermis. There is an interest in using snake shed skin as a substitute model for human skin, and researchers have evaluated its applicability in permeation studies, finding favorable responses [54].

Baby and coworkers developed emulsions containing 5.0% w/w rutin, differing in the presence of urea, isopropanol, and/or propylene glycol at 2.5 or 5.0% w/w (concentrations and combinations defined according to a two-levels experimental factorial design) [54,55]. The authors evaluated the release profile and, subsequently, the skin penetration of the bioactive compound in vertical diffusion cells for 6 hours, using cellulose acetate membrane and a biomembrane model (shed skin from *Crotalus durissus* snake). Rutin content in the receptor compartment was quantified by spectrophotometry at 410.0 nm [54]. Rutin dissolution was found to be a limiting factor in the diffusion process (zero-order model) [55]. Nonetheless, higher amounts of released and accumulated rutin over time were found with propylene glycol addition (5.0% w/w). Since the presence of propylene glycol showed a tendency to be more suitable in favoring the release of rutin from the investigated sample, this formulation was selected for further studies with shed skin from *Crotalus durissus*, as a model biomembrane. Even though the spectrophotometric method used in this investigation had a limit of quantification value equal to 0.308 µg/mL, no penetration of rutin through the model biomembrane was observed over 6 hours. The authors attributed this behavior to the reduced logP of rutin (-0.69), since similar results were reported in other permeation studies of

flavonoids using human and pig skins [56]. Valenta, Nowack, and Bernkop-Schnürch observed the penetration of rutin through rat skin and suggested that it interacted with the membrane model, in agreement with the results obtained in snake shed skin [53].

In a study of the penetration of quercetin and its 3-O-acyl esters through abdominal human skin, the authors proposed the duration of the experiment as an extremely relevant factor [57]. In their opinion, the diffusion assay should be conducted for, at least, 22 hours, as only after long time intervals did the identification and quantification of quercetin in the receptor fluid of the diffusion cells possible. To verify if the experiment's duration in this research was appropriate, Baby and collaborators conducted a diffusion assay for 52 hours [54]. Despite not being able to detect rutin in the receptor compartment after this interval, they were successful in quantifying the rutin retained in the model membrane, finding 0.931 ± 0.039 $\mu\text{g}/\text{mg}$ after just 6 hours, thus confirming that rutin is significantly retained in shed snake skin.

The association of rutin with nanostructures has been used to aid the penetration of this active ingredient into deeper layers of the skin to improve the action of this compound [8,58–60]. In vitro studies using nanostructures such as nanocrystal, glycosomal, and microencapsulated nanostructured lipid carriers showed permeability enhancement of the active ingredient, demonstrating the potential of these nanocarriers for bioactive delivery [61–64]. Encapsulation in ethosomes was also found to improve rutin penetration *ex vivo*, which was attributed to the characteristics of the nanostructure, since these malleable vesicles can facilitate the passage of the active ingredient to deeper layers of the skin [20]. These studies indicated that the use of rutin in nanostructures should be considered in the development of photoprotective formulations.

4. Rutin and Sunscreen Systems: In Vitro and In Vivo Efficacy Assessment

As previously discussed, rutin exhibits poor penetration/permeation through the skin, being retained within the stratum corneum and, therefore, being appropriate for topical formulations [54,65–67]. The observed superficial action profile of rutin, related to its aglycone counterpart, aligns with the desired characteristics of sunscreens, which ideally should remain predominantly at the application site's surface [57,61,63,64,68]. Other factors, combined with the stability of this bioactive compound in diverse topical vehicles, support the incorporation of rutin in dermocosmetic products designed to protect the skin from UVA and UVB radiation [12,54,65]. The structural resemblance of flavonoids with organic UV filters and the antioxidant properties inherent to polyphenolic compounds indicate the potential to prevent photooxidative stress in the skin. Additionally, the absorption spectra in the UV radiation region position this compound as a promising candidate for providing complementary or adjuvant photoprotective activity [4,14,69–72].

Velasco and coworkers showed based on reflectance spectrophotometry with an integrating sphere that the inclusion of rutin in photoprotective formulations, isolated or combined with octyl p-methoxycinnamate (UVB filter) and benzophenone-3 (UVA filter) in varying proportions, enhanced in vitro the sun protection factor (SPF) and protected against UVA radiation [14]. Notably, 0.1% w/w rutin increased the estimated SPF value from 7.34 ± 0.24 to 9.97 ± 0.18 , in the presence of octyl p-methoxycinnamate at 3.5% w/w and benzophenone-3 at 1.0% w/w, representing an increase of 2.63 units. Interestingly, the combination of rutin at 0.1% w/w with filters at maximum concentration (octyl p-methoxycinnamate at 7.0% w/w and benzophenone-3 at 2.0% w/w) did not result in a significant increase in the SPF value. The combination of rutin with organic UV filters, at various concentrations, resulted in a reduction of the critical wavelength (λ_c) and the UVA/UVB ratio. The photoprotective interaction between rutin and the UV filters was found to be concentration-dependent. Based on these results, it is plausible to suggest that an interaction occurred between the active ingredients, leading to a decrease in UVA protection that rutin has the potential to induce [14].

UVA radiation directly impacts the dermal compartment of the skin, and it is well-established that this radiation contributes significantly to skin photoaging [69,73–77]. The primary cumulative effects of UVA radiation (320–400 nm) include the generation of reactive oxygen species and alterations in tumor suppressor genes, such as p53. UVA radiation is further categorized into UVA II (320–340 nm) and UVA I (340–400 nm). It is known that UVA I radiation induces damage to dermal

fibroblasts, leading to the induction of cytokines, matrix metalloproteinases, and mutations in mtDNA [78–81]. In a complementary study, Baby and coworkers expanded upon the research to determine the in vitro anti-UVA I efficacy of the previously described photoprotectors [82]. The anti-UVA I efficacy was assessed through diffuse reflectance spectrophotometry with an integrating sphere, followed by mathematical treatment [83,84]. The outcomes indicated that formulations containing octyl p-methoxycinnamate at 3.5% w/w and benzophenone-3 at 1.0% w/w, and formulations with octyl p-methoxycinnamate at 7.0% w/w and benzophenone-3 at 2.0% w/w—representing a twofold increase in filter concentration—did not provide a directly proportional escalation in anti-UVA I protection. This observation persisted despite a substantial increase in SPF from 7.34 ± 0.24 to 14.63 ± 2.05 [14], a finding also supported by other studies that established that the SPF value is directly dependent on the concentration of filters utilized [84,85]. Contrastingly, Baby and coworkers found that increasing the proportion of UV filters did not inherently result in a proportional enhancement in protection against UVA radiation [82]. Samples with rutin at 0.1% w/w combined with filters at intermediate concentrations resulted in a modest increase in anti-UVA I protection, a phenomenon not replicated in samples with the doubled proportion of octyl p-methoxycinnamate and benzophenone-3. The authors attributed this behavior to the electronic stabilization-destabilization mechanism of UV filter molecules (resonant structures), influenced by the presence of rutin. However, given that the concentration of UV filters in the aforementioned samples was at least ten times higher than that of rutin, it can be proposed that the maximal proportions of octyl p-methoxycinnamate and benzophenone-3 may have hindered potential adjuvant photoprotective effect of rutin. In terms of the estimated anti-UVA efficacy, benzophenone-3 exhibited a limited contribution to the augmentation of its UV radiation-absorbing effects with the respective increase in concentration in the systems proposed by Velasco and coworkers, and Baby and coworkers [14,82].

Considering in vivo studies, the use of rutin was evaluated by incorporating this bioactive into a photoprotective formulation containing butyl methoxydibenzoylmethane and octyl dimethyl PABA, resulting in an increase in the SPF of the formulation by around 70% concerning the formulation without the compound (*in vivo* SPF 12.4 with rutin and SPF 7.3 without rutin). This fact was attributed mainly to the anti-inflammatory activity of rutin that results in a reduction of erythema and consequently increases the photoprotective action [33]. Polyphenolic compounds present a diverse array of biological properties, encompassing antiallergic, anti-inflammatory, hepatoprotective, vasoactive, antithrombotic, antioxidant, free radical scavenging, antitumor, antibacterial, and antiprotozoal actions, among other [20,33,86,87] s. Considering the presence of polyphenols, studies were conducted to investigate the photoprotective properties of various plants, including Aloe, Helichrysum, Chamomile, Hamamelis, Cinnamomum, Camellia, Rosa, Ginkgo, and Polypodium, among others [88]. In a clinical study on the dorsal skin of rats, *Aronia melanocarpa* (black chokeberry), whose extract composition is rich in rutin and chlorogenic acid, significantly influenced the reduction of the severe effects of UVB radiation, such as erythema, excoriation, and scarring, after topical treatment for 7 days. Furthermore, it was clear that the extract reduced the thickening of the epidermis, and the degradation of fibroblasts and collagen, in addition to helping to reduce the inhibition of collagen production [89].

In this context, Velasco and coworkers developed sunscreens containing rutin and extracts of *Passiflora incarnata* L. and *Plantago lanceolata* associated or not with chemical (octyl p-methoxycinnamate and benzophenone-3) and physical filters (TiO_2) [90]. The extracts were chosen as potential bioactive compounds for sunscreens due to their phytochemical composition, which also includes polyphenolic compounds [91–94]. The authors standardized the concentration of the mentioned extracts in the samples based on their total flavonoid content, expressed in rutin, which was previously quantified [41–43]. The concentrations of *P. incarnata* L. and *P. lanceolata* extracts in the photoprotective formulations were 1.68 and 2.78% w/w, respectively, corresponding to 0.1% w/w of rutin. Chemical filters were incorporated at different concentrations [14,82], while TiO_2 was used at 1.0% or 2.0% w/w. The formulated samples exhibited a range of in vitro SPF values, spanning from 0.972 ± 0.004 (control, without active compounds) to 28.064 ± 2.429 (*P. lanceolata* extract at 2.78% w/w,

octyl p-methoxycinnamate at 7.0% w/w, benzophenone-3 at 2.0% w/w, and TiO₂ at 2.0% w/w). The best SPF values were observed in samples containing rutin (27.574 ± 2.055) or *P. lanceolata* extract (28.064 ± 2.429) combined with filters at their maximum concentrations, significantly higher than the SPF of the control (24.256 ± 3.276), clearly demonstrating the activity of rutin or *P. lanceolata* extract. Unexpectedly, the inclusion of *P. incarnata* L. extract led to a significant reduction in the SPF value when associated with octyl p-methoxycinnamate at 7.0% w/w, benzophenone-3 at 2.0% w/w, and TiO₂ at 2.0% w/w, resulting in a decrease of approximately four SPF units. A similar trend was observed for the combination of *P. lanceolata* extract with octyl p-methoxycinnamate at 3.5% w/w, benzophenone-3 at 1.0% w/w, and TiO₂ at 1.0% w/w, causing a reduction in anti-UVB efficacy by approximately seven SPF units. The authors justified this observed phenomenon by considering factors such as vehicle composition, the presence of inorganic filters, the quantitative composition of organic filters, and the phytochemical composition of *P. incarnata* L. and *P. lanceolata* extracts [90].

Organic filters represent active compounds widely employed in diverse cosmetic formulations, particularly in sunscreens. These filters mitigate the impact of UV radiation on the skin by absorbing the radiation through the promotion of electrons from the lowest energy molecular orbital (LUMO) to a higher energy value (HOMO). Considering this mechanism, it is conceivable to propose that the phytochemical composition of extracts, with the presence of flavonoids as electronegative polyphenolic compounds, might have facilitated the stabilization of the filter system, augmenting the energy gap between LUMO and HOMO. As energy is inversely proportional to wavelength (nm), this could result in a reduction in intensity, causing a shift in the maximum wavelength to values below 290 nm, thereby leading to a decrease in SPF. Conversely, an opposing effect could have favored anti-UVA protection, potentially pushing the maximum wavelength beyond 320 nm, justifying improvements in the *in vitro* anti-UVA efficacy of bioactive photoprotectors [31,90].

From a practical standpoint, combining UV filters with bioactive compounds in a complex medium like an emulsion, a distinct photochemical profile emerged, deviating from that identified for isolated bioactive compounds. Consistent with the findings of Velasco and coworkers, Dondi and coworkers also discovered interactions in the associations between bioactive compounds and UV filters (such as octyl p-methoxycinnamate and avobenzone) and noted that these interactions were concentration- and media-dependent [90,95].

Considering the limited solubility of rutin in topical formulations and the possibility of negative interaction of bioactive compounds with organic filters, the encapsulation of rutin can be an interesting alternative to improve its benefits in photoprotective formulations, such as enhancing the photostability and safety of sunscreens. Also, by using rutin, the amount of chemical filters could be reduced in the formulation, which is an important approach to prevent adverse effects, toxicity, and also ecological impact [30,61,96–100].

The encapsulation of rutin in gelatin nanostructures (R-NC) was evaluated by Oliveira and collaborators, which demonstrated *in vitro* the photoprotective efficacy of this nanostructure creating a possible adjuvant UV filter with higher wavelength ranges in the UVB and UVA region concerning free rutin. The effect was attributed to the interaction of R-NC with the skin surface resulting in a protective film capable of reflecting and sequestering UV radiation [30]. Also, the formulation containing R-NC and the filters ethylhexyl dimethyl PABA, ethylhexyl methoxycinnamate and butyl methoxydibenzoylmethane resulted in 48% increase in the SPF determined *in vitro*, attributed to a synergistic effect among the components of the formulation. However, these results were not corroborated when evaluating *in vivo* the SPF of R-NC, since the nanostructures failed to enhance the SPF [32].

5. Conclusions

Among the flavonoids, the multifaceted properties of rutin (antioxidant, and anti-inflammatory, for instance) make it a promising candidate for inclusion in cosmetics/dermocosmetics, particularly in photoprotective products, combined with its biocompatibility (safety), relative stability, and low-cost. However, the successful incorporation of rutin into formulations requires careful consideration of its interactions with other components. *In vitro* and *in vivo* studies have demonstrated rutin's

ability to enhance the sun protection factor (SPF) of sunscreen systems, mainly by acting in synergy with some organic UV filters. Nonetheless, the efficacy of rutin in sunscreens can be influenced by its concentration, formulation composition, and interactions with other UV-active ingredients. Encapsulation/association of rutin in nanostructures has been explored as a strategy to improve its photoprotective properties, although further research is needed to optimize its efficacy *in vivo*. Overall, rutin shows potential as a bioactive compound for use in photoprotective formulations toward environmental-friendly sunscreens, i.e., with the maintenance or improvement of efficacy, while keeping or reducing the concentration of organic UV filters and also providing multibenefits for the cutaneous tissue.

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