Journal of Applied Pharmaceutical Science Vol. 10(1), pp 116-123, January, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.101016
ISSN 2231-3354

Comparison of the photoprotective effect between hydrolyzed and aglycones flavonoids as sunscreen: A systematic review

Yessica Andrea Monsalve-Bustamante, Miguel Angel Puertas-Mejia, Juan Camilo Mejia-Giraldo*
Grupo de Investigación en Compuestos Funcionales, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia UdeA, Medellin, Colombia.

ARTICLE INFO

Received on: 09/09/2019
Accepted on: 09/11/2019
Available online: 03/01/2020

Key words:
Systematic review, polyphenols, flavonoids, photoprotection, skin, natural sunscreen.

ABSTRACT

Currently, there is growing evidence of the role of polyphenols as protection agents against ultraviolet radiation (UVR), both in plant and animal cells, especially flavonoids, which are considered beneficial compounds that increase photoprotection of sunscreen formulations. The objective of this systematic review is to analyze if there is an increase in photoprotection of the hydrolyzed forms of polyphenols, specifically of flavonoids, such as quercetin and kaempferol, with respect to their corresponding glycosides, which are present in polar extracts of aerial parts of plants. Following the PRISMA guidelines, the systematic review was carried out in three electronic databases (Science Direct, Pubmed, and Embase) to identify the main articles that evaluated the effect of polyphenols against UVR protection. From a total of 1,230 research articles found, 21 met the inclusion parameters, of which 13 studies evaluated extracts isolated from different plants, and one study evaluated an agroindustrial residue. In all the cases, the main constituents were characterized as flavonoid compounds, including some of the compounds of interest of this revision. The effect of the pure compounds rutin and quercetin, as photoprotection enhancers, was evaluated in seven articles. Although a conclusive answer to the objective question of this systematic review could not be obtained, all the studies confirmed the biological activity of the polyphenols as photoprotector.

INTRODUCTION

Since in 1820, Widmark discovered the role played by sunlight in skin burns, it has been working on various strategies that can minimize the harmful effect of solar radiation on humans. Since then, the damage caused to living beings by exposure to ultraviolet radiation (UVR) has been studied, which has led to a desire to develop increasingly effective and safe substances that evolve the history of sunscreens (Urbach, 2001). The effects of UVR on the skin are diverse, and depend mainly on the duration of the exposure and the wavelength. In this sense, one of the acute effects of the UVR on the skin, specifically the UVB (290–320 nm), consists in sunburn (erythema), which if severe enough, can produce blisters and destruction of the superficial layers of the skin, with secondary infection and systemic effects, similar to a first- or second-degree heat burn. Furthermore, UVA radiation (320–400 nm) produces tanning, thickening of the stratum corneum, epidermis, and dermis, local and systemic immunosuppression, photokeratitis, and photoconjunctivitis, among others. In addition, the chronic changes due to UVR produce photoaging, induction of pre-malignant changes and malignant skin tumors, and so on (Kuchel *et al*., 2003; Samaniego *et al*., 2017).

Therefore, to prevent the effects of UVR exposure, topical sunscreens have been developed, with active ingredients that absorb or scatter radiation in the harmful UV range (wavelengths of 290–400 nm) that reaches the earth's surface (Food and Drug Administration, 2012). In addition, these compounds must have attributes, such as photostability greater than 80% and must not penetrate the skin where they may cause adverse effects. Commercial sunscreens contain chemical filters (organic substances, which absorb UVA and UVB radiation) or physical filters (inorganic substances, which reflect or disperse UVA and UVB radiation) and mostly present a combination of both (Schalka and Reis, 2011; Serpone *et al*., 2007).

**Corresponding Author*
Juan Camilo Mejia-Giraldo, Grupo de Investigación en Compuestos Funcionales, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia UdeA, Medellin, Colombia. E-mail: juan.mejia8 @ udea.edu.co

In this regard, several studies have demonstrated that plant extracts have various biological properties, such as antioxidant, anti-inflammatory, immunomodulatory, antimutagenic, and photoprotective, which have been justified by the presence of polyphenolic compounds (De Oliveira-Júnior *et al*., 2017; Greul *et al*., 2002). Polyphenols are important compounds in plants, which constitute a wide variety of secondary metabolites that include flavonoids, phenolic acids, tannins, lignans and coumarins, among others (Costa *et al*., 2015; Dai and Mumper, 2010). Then, based on their chemical structure, phenolic compounds act as scavenger of reactive oxygen species (ROS), which are produced in excess under oxidative stress. In addition, polyphenols play an important role as sunscreens and protect plants against high exposure to UVR (Agati *et al*., 2013; Agati and Tattini, 2010; Bendová *et al*., 2007; Jansen *et al*., 1998).

Within the phenolic compounds, the flavonoids constitute a large and diverse group of secondary metabolites in the plants, with their basic structure of C6–C3–C6 ring represented, mainly by the glycosides of quercetin and kaempferol, which accumulate in the plants in the which fulfill a large number of functions (Agati *et al*., 2013; Gitelson *et al*., 2017; Harborne and Williams, 2000). Thereby, flavonoids perform a determining role mainly as a defense mechanism against the harmful effects of UVR in plants, and consequently improve the photosynthetic resistance against UVA and UVB radiation from solar spectrum. In addition, as mentioned, they act as free radical scavengers, with characteristics that could benefit current sunscreens, with a summing or synergic effect on their photoprotective potential (Agati *et al*., 2011; 2013; Nagula and Wairkar, 2019). Consequently, this review aims to determine the role of quercetin and kaempferol in photoprotection, analyzing the studies carried out in plant extracts during the last 20 years. The main objective was to analyze relevant information where the aglycone form of such polyphenols is studied and their role in terms of photoprotection and photostability with application in humans, in comparison to their corresponding glycosides.

MATERIALS AND METHODS

This systematic review included the articles from three databases: Pubmed, Science Direct, and Embase, since 1998 to the end of October 2018.

Search terms

According to the research question, three main themes were identified: "skin,, "photoprotection," and "polyphenols"; the latter were specified as "rutin," "quercetin," and "kaempferol"; also included are the terms "glycosides OR glucosides," "hydrolysis of glycosides OR glucosides," and the keywords "photoprotection OR fotoprotector" are used to formulate a search strategy that is applied in all the searches on the databases. Further relevant studies were identified through manual searches of reference lists. Studies have been first screened by title, then by abstract, and finally by reading of the full text.

Inclusion and exclusion criteria

Besides the search terms, articles were selected based on certain inclusion and exclusion criteria. The first one, peer reviewed journal articles were being included, whereas reviews, editorial material, meeting abstracts, letters, retracted publications, and book chapters were excluded. To be incorporated, the studies had to explore and assess at least one type of polyphenol or plant extract where photoprotection to be evaluated with application in humans. The language of the articles included was only English.

Quality evaluation

The quality of the studies selected was assessed in a systematic form. The quality score is composed of five items, and each item is allocated 0, 1, or 2 points for each category: quantification of flavonoids or polyphenols, characterization of extracts, photoprotection tests *in vitro*, *ex vivo*, and *in vivo,* in humans or animals. In total, each study can be awarded a maximum of 10 points.

Parameters evaluation of quality

Test of polyphenols and flavonoids

- If no polyphenols or flavonoids quantification test is performed: 0 points
- If a test of quantification of polyphenols or flavonoids is carried out: 1 point
- If polyphenols and flavonoids are quantified: 2 points

Chemical characterization of molecules of interest

- If the polyphenols are not characterized: 0 points
- If at least one specific molecule of interest is characterized: 1 point
- If they characterize or work with more than one molecule of our interest (rutin, quercetin, kaempferol): 2 points

Photoprotection tests in vitro

- If *in vitro* photoprotection tests are not carried out: 0 points
- If *in vitro* photoprotection tests are carried out: 1 point
- If *in vitro* photoprotection and photostability tests are carried out: 2 points

Photoprotection tests ex vivo

- If *ex vivo* photoprotection tests are not carried out: 0 points
- If *ex vivo* photoprotection tests are carried out: 1 point
- If *ex vivo* photoprotection and cytotoxicity or dermotoxicity tests are carried out: 2 points

Photoprotection tests in vivo *in humans or animals*

- If *in vivo* photoprotection tests are not carried out in humans or animals: 0 points
- If *in vivo* photoprotection tests are carried out on animals: 1 point
- If *in vivo* photoprotection tests are carried out in humans: 2 points

Quality ranges

High: 8–10 points
Average: 4–7 points
Low: 0–3 points

Data extraction

The quantitative and qualitative data were extracted from all the included publications: authors, year of publication, country of origin, information about the objectives, and main findings of each study. The analysis of the information was carried out by three experts in the subject, who evaluated the reproducibility and the risk of bias in each phase of the review.

RESULTS

Selection of studies

The search of the information in databases resulted in the identification of a total of 1,230 records (research papers that met the selection criteria) from the initial searches, the reference lists and the elimination of duplicate records. After the exhaustive selection of the studies, 21 final studies were included. Figure 1 shows the flowchart of the present study with the inclusion and exclusion criteria. All studies were in the English language and were published between January 1998 and October 2018.

Characteristics of the studies

Among the articles included and analyzed, 13 of them evaluated the photoprotective effect of the plant extracts (Aquino *et al.*, 2002; Bonina *et al.*, 2002; 2000; Costa *et al.*, 2015; De Oliveira-Júnior *et al.*, 2017; Gajardo *et al.*, 2016; Mejía-Giraldo *et al.*, 2015; 2016a; 2016b; Puertas-mejía *et al.*, 2015; Reis Mansur *et al.*, 2016; Silva *et al.*, 2016; Velasco *et al.*, 2008), one study evaluated polyphenols in an agroindustrial waste (Mandalari *et al.*, 2013), and seven of the studies evaluated rutin and quercetin pure in photoprotective formulations (De Oliveira *et al.*, 2015; Graziola *et al.*, 2016; Kamel and Mostafa, 2015; Kostyuk *et al.*, 2018; Peres *et al.*, 2015; Tomazelli *et al.*, 2018; Vicentini *et al.*, 2010). For the analysis of polyphenols, tests were carried out as total polyphenol content (TPC) or flavonoid content, antioxidant capacity by different methods, and in plant extracts their main compounds were chemically characterized. In addition, different *in vitro, ex vivo*, and *in vivo* photoprotection and photostability tests were carried out. Table 1 describes the main characteristics of each study, including the year of implementation, country, objectives, polyphenols, and the species of the plant used.

Results of individual studies

All studies promote the photoprotective capacity of polyphenols. A common denominator was the incorporation of these polyphenols into cosmetic formulations for the tests of interest, in which their effect was compared with antioxidants,

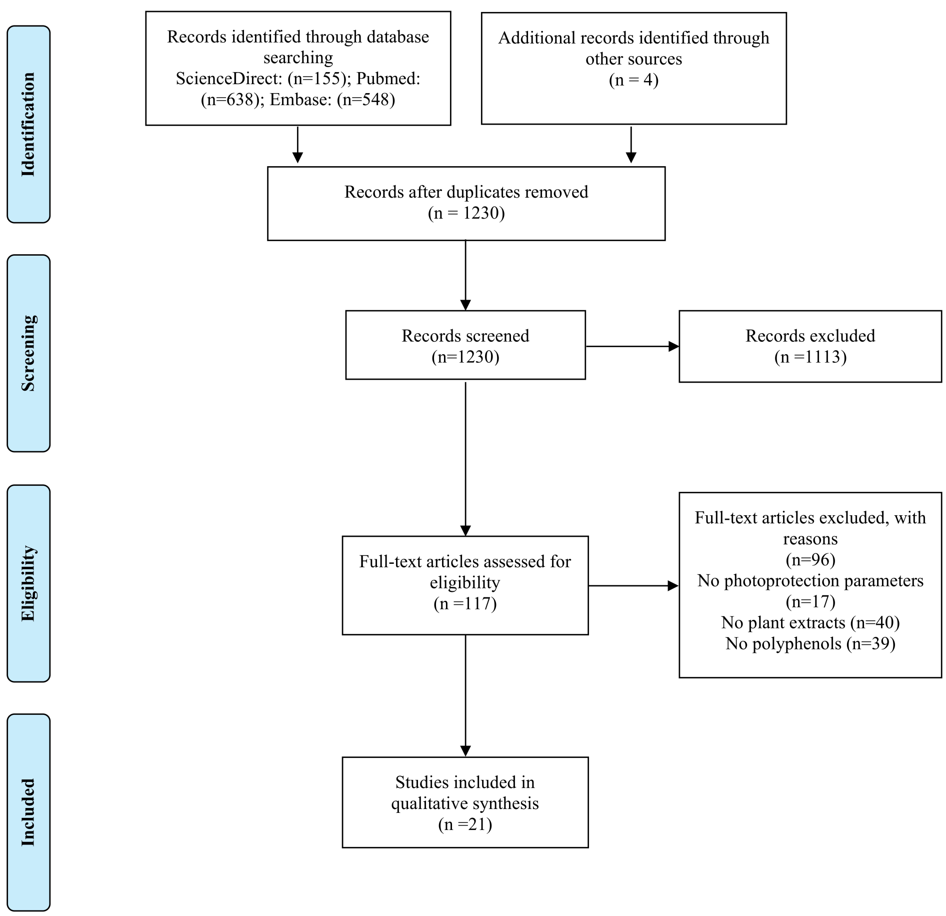

Figure 1. Flowchart of selection of studies.

Table 1. Summary of the main characteristics of the studies evaluated.

Ref	Year	Country	Objective	Polyphenols	Species
(Kostyuk *et al*., 2018)	2018	Belarus	Propose a panel of *in vitro* methods for the preselection of natural photoprotective substances with high photostability and low phototoxicity.	Rutin Quercetin	Does not apply, pure compounds
(Tomazelli *et al*., 2018)	2018	Brazil	To evaluate the SPF of the rutin by *in vitro* and *in vivo* methods, comparing sunscreen formulations containing 0.1 % (w/w) rutin, 3.0 % (w/w) avobenzone and 8.0 % (w/w) octyldimethyl PABA with a similar preparation free of active substances.	Rutin	Does not apply, pure compounds
(De Oliveira-Júnior *et al*., 2017)	2017	Brazil	To evaluate the photoprotective effect of cosmetic formulations containing hydroalcoholic extract of *N. variegate*.	Quercetin	*Neoglaziovia variegata*
(Gajardo *et al*., 2016)	2016	Chile	To investigate SPF and the antioxidant properties of *Parastrephia lepidophyla Cabr., Fabiana squamata Phil., Ephedra chilensis K.Presl., Lampaya medicinalis Phil., Baccharis tola Phil., And compact Azorella Phil*.	Quinic caffeic acid, apigenin-di-C-hexoside (vicenin II), apigenin-C-hexoside-C-pentoside, rutin pentoside, quercetin-dihexoside, dicaffeic quinic acid (isomer), caffeine	*Parastrephia lepidophyla* Cabr., *Fabiana squamata* Phil., *Ephedra chilensis* K.Presl., *Lampaya medicinalis* Phil., *Baccharis tola* Phil., and *Azorella compacta* Phil.
(Graziola *et al*., 2016)	2016	Brazil	To investigate the use of flavonoid rutin as an alternative to glutaraldehyde to cross-link gelatin microparticles.	Rutin	Does not apply, pure compounds
(Silva *et al*., 2016)	2016	Brazil	To evaluate the photoprotective capacity of the crude extract of *S. purpurea L.* peel, against UVA and UVB rays *in vitro* and its incorporation into a sunscreen formulation as an active principle.	HHDP-allioil-glucose, Galoil-bis-HHPD-glucose, rutin, Quercetin	*Spondias purpurea*
(Mejía-Giraldo *et al*., 2016b)	2016	Colombia	To evaluate the photoprotective, photostability and antioxidant activity of leaf extracts of *B. antioquensis*, as well as its phenolic composition.	Quercetin, rutin, kaempferol, chlorogenic acid	*Baccharis antioquensis*
(Reis Mansur *et al*., 2016)	2016	Brazil	To develop a photoprotective oil-in-water emulsion of *Bauhinia microstachya var.*	kaempferol-3-O- ramnoside, astragalina-2 ", 6" -di-O-digalato	*Bauhinia microstachya* var. *massambabensis* Vaz, Fabaceae
(Mejía-Giraldo *et al*., 2016a)	2016	Colombia	To evaluate the photoprotective and antioxidant capacity *in vitro* and correlate it with the content of polyphenol and anthocyanin in nine plants.	Polyphenols	*Sphagnum meridense, Calamagrostis effusa, Lycopodiella alopecuroides, Morella parvifolia, Baccharis antioquensis, Pentacalia pulchella, Castilleja fissifolia, Hesperomeles ferruginea and Hypericum juniperinum*
(De Oliveira *et al*., 2015)	2015	Brazil	To develop and evaluate the effectiveness of sunscreens containing benzophenone-3 or avobenzone with and without rutin.	Rutin	Does not apply, pure compounds
(Costa *et al*., 2015)	2015	Brazil	To investigate the potential of the ethanol extract of *M. taxifolia* as an active ingredient in a photoprotective formulation with sunscreen (UVA-UVB).	Quercetin	*Marcetia taxifolia*
(Peres *et al*., 2015)	2015	Brazil	Investigate the synergistic effect of rutin associated with organic UV filters.	Rutin	Does not apply, pure compounds
(Kamel and Mostafa, 2015)	2015	Egypt	Development of rutin nanoparticulate photoprotective preparations.	Rutin	Does not apply, pure compounds
(Puertas-Mejía *et al*., 2015)	2015	Colombia	To evaluate the *in vitro* UVR absorption capacity of extracts from three plants belonging to the Ericaceae family and compare them with their antioxidant capacity.	Polyphenols	*Bejaria aestuans, Cavendishia pubescens* y *Cavendishia bracteata*
(Mejía-Giraldo *et al*., 2015)	2015	Colombia	To evaluate the photoprotective and antioxidant capacity of *Sphagnum meridense* extract. In addition, try different extraction procedures to evaluate their effects on the excretion of phenolic compounds.	Polyphenols	*Sphagnum meridense*
(Mandalari *et al*., 2013)	2013	Italy	To evaluate the antioxidant and photoprotective effect of blanch water, a by-product of the almond processing agroindustry.	Naringenin-7-O-glucoside and kaempferol-7-O-rutinoside.	*Agua blanch*
(Vicentini *et al*., 2010)	2010	Brazil	Consider the histological aspects to evaluate the photoprotective effect in vivo of a w/o microemulsion containing quercetin against the skin damage induced by UVB radiation.	Quercetin	Does not apply, pure compounds
(Velasco *et al*., 2008)	2008	Brazil	To develop delivery systems of bioactive sunscreen containing rutin, *Passiflora incarnata L.* and *Plantago lanceolate* extracts, associated or not with organic and inorganic UV filters.	Rutin, Polyphenols	*Passiflora incarnata* L. and *Plantago lanceolata* extracts

(*Continued*)

Table 1. (Continued)

Ref	Year	Country	Objetive	Polyphenols	Species
(Aquino *et al*., 2002)	2002	Italy	To evaluate the antioxidant effect *in vitro* and the photoprotective activity *in vivo* of an ethanolic leaf extract of *Culcitium reflexum* H.B.K.	Rutin, quercetin-3-O-D-galactopyranoside-4-O-D-glucopyranoside, quercetin-3-O-D-glucopyranoside, isorhamnetin-3-O-D-galactopyranoside, quercetin and kaempferol.	*Culcitium reflexum*
(Bonina *et al*., 2002)	2002	Italy	To evaluate the antioxidant effect *in vitro* and the photoprotective activity *in vivo* of a lyophilized extract of *Capparis spinosa L*. obtained by methanolic extraction of the flowering buds.	Quercetin, Kaempferol	*Capparis spinosa*
(Bonina *et al*., 2000)	2000	Italy	To evaluate the antioxidant effect *in vitro* and the photoprotective effect on the skin of three freeze-dried extracts obtained from the juice of the leaves of *S. telephium L*.	Quercetin, Kaempferol	*Sedum telephium*

SPF: Sun Protection Factor

UV filters, and polyphenols, such as quercetin and rutin or their additive; evaluating its possible applicability as sunscreens. Table 2 describes the main findings of the individually studies.

Evaluation of the quality of the studies

The evaluation of the quality of each study based on the inclusion and exclusion criteria was indicated in Table 3, according to the selected characteristics. The total average score was 4.6 ± 1.2. Thus, for articles where extracts were analyzed, an average quality of 4.5 ± 1.3 was presented and for studies evaluating specific polyphenols, such as rutin, quercetin, or kaempferol, an average quality of 4.9 ± 1.0 was found. Although it is not an excellent quality, in relation to the parameters defined by our self, these results indicated a sufficient level of quality to examine the conclusions in a valid way.

DISCUSSION

Summary of results

The main objective of the research was to carry out a systematic review of the evidence about the effect of hydrolyzed polyphenols, such as quercetin and kaempferol, on photoprotection and photostability, determining if they are better or not regarding these characteristics in comparison to their glycosides. It should be noted that none of the articles evaluated could find an analysis that may solve the propose question. However, in the research described by Kostyuk *et al*. (2018), the rutin is compared with its respective aglycone quercetin, finding better values for quercetin in some of analyzes carried out (Kostyuk *et al*., 2018). Nevertheless, all the analyzed papers showed that the photoprotective effect of plant extracts rich in polyphenols, especially flavonoids and their additive and synergistic effects when mixed with commercial sunscreens improve significantly the SPF and photostability of these formulations (Peres *et al*., 2015; Tomazelli *et al*., 2018).

Explanation of the results

Previous studies have proven that the photoprotective capacity of vegetable extracts is due to the presence of polyphenols, and especially flavonoids, such as rutin, quercetin, kaempferol, among others (Aquino *et al*., 2002; Costa *et al*., 2015; Gajardo *et al*., 2016; Mejía-Giraldo *et al*., 2016b; Silva *et al*., 2016). In addition, some authors have demonstrated that polyphenols could avoid the damage induced by the UVR, through mechanisms, such as capture and inactivation of ROS. It also increases its photostability, due to an additive effect produced by high polyphenolic antioxidant capacity and a co-active effect, so that antioxidants do not absorb radiation (Greul *et al*., 2002).

De Oliveira-Junior *et al*. (2017) found that after incorporation of Nv-HA (Hydro Alcoholic extract of *Neoglaziovia variegata*) into O/W emulsions, no photoprotective activity was presented for concentrations at 5.0% of Nv-HA (SPF = 0.008 ± 0.013) and 10.0% (SPF = 0.059 ± 0.057). However, the extracts were able to maximize the protective effect of the formulations that contained synthetic filters (5.43 ± 0.07 and 11.73 ± 0.04) extract concentrations of 0.5 and 1.0 % (v/v), respectively in a dose-response behavior. When compared to quercetin (SPF = 2.45 ± 0.13) and benzophenone-3 (SPF = 5.10 ± 0.15), the Nv-HA extract at 1.0%, showed the highest photoprotective effect. Likewise, the results propose that Nv-HA extract may be utilized as a coadjuvant or booster of chemical filters when added in a cosmetic sunscreen, reducing the necessary amount of synthetic filters, and therefore, lowering the risks of phototoxic reactions without affecting the photoprotective property of the formulation (De Oliveira-Júnior *et al*., 2017).

In addition, the molecules that prevent skin erythema produced by exposure to UVB, such as antioxidant and anti-inflammatory molecules, could significantly improve the UV protection of sunscreens, as demonstrated by Tomazelli *et al*. (2018) with the results of the *in vivo* SPF test, in which the formulation containing rutin, enhance the SPF by approximately 70%, compared to the rutin free formulation in a mixture with the UV filters (butylmethoxydibenzoylmethane and octyl dimethyl). This fact is evidence of the improvement in photoprotection efficiency, even at low concentration, decreasing significantly the formation of erythema, effects associated probably to its anti-inflammatory activity (Peres *et al*., 2015; Tomazelli *et al*., 2018). Similarly, the use of plant extracts mixed with chemical or physical sunscreens has shown that it can protect the skin more effectively against UV rays by preserving skin matrix damage against oxidative stress, and synergistically increasing the SPF of single filter formulations (De Oliveira-Júnior *et al*., 2017). Thus, Aquino *et al*. (2002) demonstrated that the beneficial

Table 2. Individual main findings.

Reference	Main findings
(De Oliveira-Júnior *et al*., 2017)	After evaluating the photoprotective activity of Nv-HA, the extract was incorporated into cosmetic formulations and its photoprotective efficacy was also investigated. Compared with quercetin (SPF= 2.45 ± 0.13) and benzophenone-3 (SPF= 5.10 ± 0.15), Nv-HA 1.0 % (SPF= 11.73 ± 0.04) the extract had the greatest photoprotective effect. Which suggests that the extract have a superior effect than the molecules alone.
(Costa *et al*., 2015)	All formulations containing *Marcetia taxifolia* extract had an SPF ≥ 6; with SPF values near to benzophenone-3 a chemical filter frequently used as a component of sunscreens. These results indicated the possibility of using these extracts as sunscreen in pharmaceutical preparations.
(Mejía-Giraldo *et al*., 2015)	The extract of *Sphagnum meridense* showed hopeful values of UVAPF of 2, UVA/UVB ratio of 0.697, critical wavelength (λc) of 384 nm and *in vitro* antioxidant capacity, similar values compared to common sunscreens.
(Mejía-Giraldo *et al*., 2016a)	The extracts of *P. pulchella* and *B. antioquensis* could be the origin of promising and photostable new ingredients for use in sunscreens. In addition, they may exert an antioxidant and photoprotective effect on the skin by reducing oxidative stress related with aging mechanisms.
(Reis Mansur *et al*., 2016)	Leaf extracts of *Bauhinia microstachya* var. *massambabensis* were integrated into O/W emulsions containing commercial photoprotectors, without contributing to photodegradation of the sunscreen, when exposed to UV radiation. All the formulations showed an adequate SPF and both plant extracts boosted the photoprotective result, as an improvement in the SPF in vivo; therefore, they could be considered safe for cosmetic use.
(Aquino *et al*., 2002)	The EIP of the crude extract of *Culcitium reflexum* H.B.K. leaves was compared with the TOC in a gel formulation, finding in the extract an EIP of 43.5 % and TOC of 21.7 %, demonstrating its possible applicability in photoprotection.
(Velasco *et al*., 2008)	It was found that broad-spectrum sun protection is achieved when the dried extract of *Passiflora incarnata* L. was in the presence of 7.0 % (w/w) of ethylhexyl methoxycinnamate, 2.0 % (w/w) benzophenone-3 and 2.0 % (w/w) of TiO_2. This shows additive effect of the extract in the increase of photoprotection in a system delivery.
(Gajardo *et al*., 2016)	The *Baccharis tola* extract has sun protection properties, as well as antioxidant and regenerative activities. Two cosmetic products were developed and subjected to several tests of quality control and stability tests, showing remarkable stability and absence of pathogenic microorganisms.
(Bonina *et al*., 2002)	When the extracts were compared with TOC, the EIP values were 59.6 % and 22.0 % for gel formulations of *Capparis spinosa* L. and TOC, respectively. This methanolic extract provides excellent photoprotection to UVB induced skin disturbance. Therefore, it could have important applications as a component in cosmeceutical products used in skin alterations, propitiated or sharpened by ROS and the overproduction of free radicals.
(Silva *et al*., 2016)	The crude shell extract of *Spondias purpurea* provided photoprotective activity against UVB (SPF 43.78 ± 0.19 in dilution of 50 mg/mL of ethanol) and UVA (this protection was comparated with rutin and benzophenone-3, used as patterns). The phenolic content was 28.68 ± 0.046 mg GAE/g and flavonoid content of 2.64 ± 0.005 mg EQ/g extract. The antioxidant activity showed inhibition percentage of 74.41, with EC_{50} 27.11 g/mL.
(Bonina *et al*., 2000)	The results obtained *in vitro* and *in vivo* test show that both the total freeze-dried juice and the freeze-dried lipophilic fraction of the leaves of *Sedum telephium* L., have photoprotective effects against induced skin alterations by the UVB rays.
(Mejía-Giraldo *et al*., 2016b)	The characteristics of *in vitro* photoprotection and the antioxidant activity of the extracts of *B. antioquensis* are demonstrated, as well as its broad-spectrum UVA-UVB protection with excellent sensory and photoprotective characteristics. Thus, it can be deduced that it is feasible to employ the extract of B. antioquensis as a natural ingredient with photoprotective and antioxidant properties.
(Puertas-Mejía *et al*., 2015)	According to results, the three plants evaluated *Bejaria aestuans, Cavendishia pubescens* and *Cavendishia bracteata* could be considered as a potential source of natural compounds with UV absorption due to the presence of polyphenols and anthocyanins in the extracts with the TPC value (from 15.29-27.35 mg GAE g^{-1} DS) and TAC value (0.36 - 3.31 mg C3GE g^{-1} DS) and its antioxidant capacity expressed as EC_{50} value. The EC_{50} values found were 2.64 E^{-04}, 1.96 E^{-04} and 3.75 E^{-04} mg μmol^{-1} DPPH of reaction medium in the reduction of DPPH.
(Mandalari *et al*., 2013)	The EIP of blanch water, a byproduct of the almond processing industry is compared to TOC in a gel formulation; giving the extrac an EIP of 50.5 % and TOC of 22.4 %; these results demonstrated an effect of Blanch Water against photooxidative damage *in vivo.*
(De Oliveira *et al*., 2015)	Rutin addition to UVA filters supplier antioxidant properties to the formulations and were considered safe for human use. It should be noted that rutin 0.1 % (w/w) plus benzophenone 6.0 % (w/w) increased the SPF from 24.3 ± 1.5 to 33.3 ± 2.9. Besides, the SPF enhanced after irradiation as was the case with the control. Nevertheless, this did not happen with blend of rutin and butyl methoxydibenzoylmethane.
(Graziola *et al*., 2016)	The SPF results of dispersions containing M0, MG or MR, free or in combination with commercial UV filters (benzophenone-3 and octyl methoxycinnamate) indicated that the microspheres (M0, MG or MR) 5.0 % (w/w) had no photoprotective impact *in vitro*, and presented no influence on the evaluated efficacy when mixed with UV filters. However, *in vivo* studies proved that these materials had excellent skin compatibility.
(Vicentini *et al*., 2010)	According to the analyzes carried out, it was found that ME + Q is a promising photochemoprotective agent with applicability in humans. This due to ME + Q managed to reduce the histological damage caused by UV radiation to which they were subjected in hairless mice.
(Kostyuk *et al*., 2018)	It was possible identify some photostable and nonphototoxic substances, principally phenylpropanoids and glycosylated flavonoids, with UVA + UVB physical, chemical and biological broad-spectrum protection.
(Peres *et al*., 2015)	The association of rutin and UVB filters enhanced notably the critical wavelengths of formulations, evincing a photoprotective improvement particularly in the UVA range, presenting this compound as a striking adjuvant for anti-UVB sunscreen.
(Kamel and Mostafa, 2015)	The evaluation of designed nanoemulsions demonstrated the improvement of photoprotection effect of the flavonoid rutin, when mixed with common physical sunscreen such as TiO_2.
(Tomazelli *et al*., 2018)	The rutin has proven to be an excellent antioxidant when mixed with UVA and UVB filters as Butyl methoxydibenzoylmethane (avobenzone) and Octyl dimethyl PABA, besides being stable and safe to use in sunscreen formulations.

EIP: Erythema Inhibition Percentage; TOC: Tocopheryl Acetate, ME+Q: microemulsion + quercetin; UVAPF: UVA protection factor, Nv-HA: hydro alcoholic extract of Neoglaziovia variegate; gelatin microspheres (M0), gelatin microspheres crosslinked with glutaraldehyde (MG) or rutin (MR); GAE: Gallic acid equivalents; DS: Dry extract; C3GE: cyanidin-3-glucoside equivalents; PABA: *para*-aminobenzoic acid, SPF: Sun Protection Factor.

photoprotective effect of the extract of *Culcitium reflexum*, which could be related to its antioxidant activity *in vitro* and, in turn, to the content of biophenols, where the EIP (Erythema Inhibition Percentage) was 43.5 compared to 21.7 of the TOC (Tocopheryl Acetate) a recognized antioxidant agent (Aquino *et al*., 2002).

On the other hand, in the study described by Kostyuk *et al*. (2018) compares the photoprotective effect of quercetin and rutin. There, an SPF of 5.71 ± 0.12 and a UVA/UVB ratio of 1.5 were found for quercetin (10 %), while the values for the rutin (10%) were SPF of 3.44 ± 0.16 and UVA/UVB of 1.2, which demonstrated the

Table 3. Quality criteria.

Ref.	Test of polyphenols and/or total flavonoids	Molecules of interest	Photoprotection tests *in vitro*	Photoprotection tests *ex vivo*	Photoprotection tests in humans or animals *in vivo*	Total
(De Oliveira-Júnior *et al*., 2017)	2	2	1	0	0	5
(Costa *et al*., 2015)	1	2	1	0	0	4
(Mejía-Giraldo *et al*., 2015)	1	0	2	0	0	3
(Mejía-Giraldo *et al*., 2016a)	1	0	2	0	0	3
(Reis Mansur *et al*., 2016)	0	0	2	1	2	5
(Aquino *et al*., 2002)	1	2	1	0	2	6
(Velasco *et al*., 2008)	1	2	1	0	0	4
(Gajardo *et al*., 2016)	0	2	1	2	0	5
(Bonina *et al*., 2002)	1	2	1	0	2	6
(Silva *et al*., 2016)	2	2	2	0	0	6
(Bonina *et al*., 2000)	0	2	0	0	2	4
(Mejía-Giraldo *et al*., 2016b)	1	2	2	0	0	5
(Puertas-Mejía *et al*., 2015)	1	0	1	0	0	2
(Mandalari *et al*., 2013)	1	2	1	0	2	6
(De Oliveira *et al*., 2015)	0	2	2	0	2	6
(Graziola *et al*., 2016)	0	2	1	0	2	5
(Vicentini *et al*., 2010)	0	2	0	2	1	5
(Kostyuk *et al*., 2018)	0	2	2	2	0	6
(Peres *et al*., 2015)	0	2	2	0	0	4
(Kamel and Mostafa, 2015)	0	2	1	0	0	3
(Tomazelli *et al*., 2018)	0	2	1	0	2	5

Mean: 4.6 ±1.2.

predominant absorption of quercetin in the UVA region. In addition, the photostability of both polyphenols was analyzed, finding the SPF of the rutin stable (SPF= 5.25 ± 0.13) against UV irradiation (66 % UVA and 33 % UVB) of 0–6.0 J/cm^2, while the quercetin passed from an SPF of 4.31 ± 0.10 to 3.16 ± 0.20 under the same conditions, demonstrating the photostability of the rutin (Kostyuk *et al*., 2018). This case is the only one that could be conclusive with respect to the research question, but because it is a single study and it is also not specific regarding the research topic, it could not be conclusive to answer the objective question of this review.

Finally, the analysis of this review showed us that there remains a broad field of research in terms of the photoprotective capacity of natural products and their applications in cosmetic formulations, and how it can support the evolution of sunscreens and to correct their possible adverse effects, through an improvement in their effectiveness, safety and photostability, which could be attributed to natural products modified with safe, affordable, and economical procedures.

CONCLUSION

This review attempted to systematically analyze the current evidence on the photoprotective effects of glycosylated polyphenols and aglycones. A total of 21 studies were included in this review, which 13 of them evaluated plant extracts, one article studied an industrial waste and seven analyzed rutin and quercetin in cosmetic formulations. The results and analysis of the scientific literature suggest that the studies included in this review provide evidence of the protective effect of natural products. However, there are no specific investigations that can determine whether hydrolyzed polyphenols, such as quercetin and kaempferol, could improve the photoprotective effect and photostability with respect to their glycosides, which leaves a gap in this field of phytochemical research.

ACKNOWLEDGMENTS

The authors acknowledge CODI-Universidad de Antioquia (Project No. CIQF 290) for financial support. Monsalve, Y.A., acknowledges master fellowship granted by SAPIENCIA-Alcaldía de Medellín. The authors would like to thank the International Passages Support Fund—Universidad de Antioquia.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Agati G, Biricolti S, Guidi L, Ferrini F, Fini A, Tattini M. The biosynthesis of flavonoids is enhanced similarly by UV radiation and root zone salinity in *L. vulgare* leaves. J Plant Physiol, 2011; 168:204–12.

Agati G, Brunetti C, Di Ferdinando M, Ferrini F, Pollastri S, Tattini M. Functional roles of flavonoids in photoprotection: new evidence, lessons from the past. Plant Physiol Biochem, 2013; 72:35–45.

Agati G, Tattini M. Multiple functional roles of flavonoids in photoprotection. New Phytol, 2010; 186:786–93.

Aquino R, Morelli S, Tomaino A, Pellegrino ML, Saija A, Grumetto L, Bonina F. Antioxidant and photoprotective activity of a crude extract of *Culcitium reflexum* H.B.K. leaves and their major flavonoids. J Ethnopharmacol, 2002; 79:183–91.

Bendová H, Akrman J, Krejčí A, Kubáč L, Jírová D, Kejlová K, Malý M. *In vitro* approaches to evaluation of Sun Protection Factor. Toxicol In Vitro, 2007; 21:1268–75.

Bonina F, Puglia C, Aquino RP, Sacchi A. In vitro antioxidant and in vivo photoprotective effects of a lyophilized extract of Capparis spinosa L. buds. J Cosmet Sci, 2002; 53:321–35.

Bonina F, Puglia C, Tomaino A, Saija A, Mulinacci N, Romani A, Vincieri F. In-vitro antioxidant and in-vivo photoprotective effect of three lyophilized extracts of Sedum telephium L. leaves. J Pharm Pharmacol, 2000; 5:1279–85.

Costa SCC, Detoni CB, Branco CRC, Botura MB, Branco A. In vitro photoprotective effects of Marcetia taxifolia ethanolic extract and its potential for sunscreen formulations. Revista Brasileira de Farmacognosia, 2015; 25:413–18.

Dai J, Mumper RJ. Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties. Molecules, 2010; 15:7313–52.

De Oliveira AC, Peres DAlmeida D, Mendes Rugno C, Kojima M, Sales de Oliveira Pinto CA. Functional photostability and cutaneous compatibility of bioactive UVA sun care products. J Photochem Photobiol B, 2015; 148:154–59.

De Oliveira-Júnior RG, Souza GR, Ferraz CAA, de Oliveira AP, Araújo CS, de Lima-Saraiva SRG, Reis SAGB, Gonçalves TM, Rolim LA, Rolim-Neto PJ, César FCS, Almeida JRGDS. Development and evaluation of photoprotective O/W emulsions containing hydroalcoholic extract of *Neoglaziovia variegata* (Bromeliaceae). Sci World J, 2017; 2017:5019458

Food and Drug Administration (FDA). Guidance for industry labeling and effectiveness testing: sunscreen drug products for over-the-counter human use-small entity compliance guide, Silver Spring-Maryland, Estados Unidos. 2012.

Gajardo S, Stowhas T, Salas F, Quispe C, Buc-calderon P, Benites J. Determination of sun protection factor and antioxidant properties of six Chilean Altiplano plants. Blacpma, 2016; 15:352–63.

Gitelson A, Chivkunova, O, Zhigalova, T, Solovchenko A. *In situ* optical properties of foliar flavonoids: implication for non-destructive estimation of flavonoid content. J Plant Physiol, 2017; 218:258–64.

Graziola F, Candido TM, De Oliveira CA, Peres DD, Issa MG, Mota J, Rosado C, Consiglieri VO, Kaneko TM, Robles Velasco MV, Baby AR. Gelatin-based microspheres crosslinked with glutaraldehyde and rutin oriented to cosmetics. Braz J Pharm Sci, 2016; 52:603–12.

Greul AK, Grundmann JU, Heinrich F, Pfitzner I, Bernhardt J, Ambach A, Biesalski HK, Gollnick H. Photoprotection of UV-Irradiated Human Skin: an antioxidative combination of vitamins E and C, carotenoids, selenium and proanthocyanidins. Skin Pharmacol Physiol, 2002; 15: 307–15.

Harborne JB, Williams CA. Advances in flavonoid research since 1992. Phytochemistry, 2000; 55:481–504.

Jansen MA, Gaba V, Greenberg BM. Higher plants and UV-B radiation: balancing damage, repair and acclimation. Trends Plant Sci, 1998; 3:131–5.

Kamel R, Mostafa DM. Rutin nanostructured lipid cosmeceutical preparation with sun protective potential. J Photochem Photobiol B, 2015; 153:59–66.

Kostyuk V, Potapovich A, Albuhaydar AR, Mayer W. Natural substances for prevention of skin photoaging: screening systems in the development of sunscreen and rejuvenation cosmetics. Rejuvenation Res, 2018; 21:91–101.

Kuchel JM, Barnetson RSC, Halliday GM. Nitric oxide appears to be a mediator of solar-simulated ultraviolet radiation-induced immunosuppression in humans. J Invest Dermatol, 2003; 121:587–93.

Mandalari G, Arcoraci T, Martorana M, Bisignano C, Rizz, L, Bonina FP, Trombetta D, Tomaino A. Antioxidant and photoprotective effects of blanch water, a byproduct of the almond processing industry. Molecules (Basel, Switzerland), 2013; 18:12426–40.

Mejía-Giraldo JC, Gallardo C, Puertas-Mejía MA. In vitro photoprotection and antioxidant capacity of *Sphagnum meridense* extracts, a novel source of natural sunscreen from the mountains of Colombia. Pure Appl Chem, 2015; 87:961–70.

Mejía-Giraldo JC, Henao-Zuluaga K, Gallardo C, Atehortúa L, Puertas-Mejía MA. Novel *in vitro* antioxidant and photoprotection capacity of plants from high altitude ecosystems of Colombia. Photochem Photobiol, 2016a; 92:150–7.

Mejía-Giraldo JC, Winkler R, Gallardo C, Sánchez-Zapata AM, Puertas-Mejía MA. Photoprotective potential of *Baccharis antioquensis* (Asteraceae) as natural sunscreen. Photochem Photobiol, 2016b; 92: 742–52.

Nagula RL, Wairkar S. Recent advances in topical delivery of flavonoids: a review. J Control Release, 2019; 296:190–201.

Peres DA, De Oliveira CA, Tokunaga VK, Mota J P, Rosado C, Consiglieri VO, Kaneko TM, Velasco MV, Baby AR. Rutin increases critical wavelength of systems containing a single UV filter and with good skin compatibility. Skin Res Technol, 2015; 22:325–33

Puertas-Mejía MA, Rincón-Valencia S, Mejía-Giraldo JC. Screening of UVA / UVB absorption and in vitro antioxidant capacity of *Bejaria aestuans, Cavendishia pubescens* and *Cavendishia bracteata* leaf extracts. Res J Med Plant, 2015; 9:435–41.

Reis Mansur MC, Guimarães Leitão S, Cerqueira-Coutinho C, Vermelho AB, Silva RS, Presgrave OAF, Leitão AAC, Leitão GG, Ricci-Júnior E, Santos EP. *In vitro* and *in vivo* evaluation of efficacy and safety of photoprotective formulations containing antioxidant extracts. Braz J Pharmacognosy, 2016; 26:251–58.

Samaniego Rascón D, Ferreira AD, Gameiro da Silva M. Cumulative and momentary skin exposures to solar radiation in central receiver solar systems. Energy, 2017; 137:336–49.

Schalka S, Silva dos Reis VM. Sun protection factor: meaning and controversies. An Bras Dermatol, 2011, 86:507–15.

Serpone N, Dondi D, Albini A. Inorganic and organic UV filters: their role and efficacy in sunscreens and suncare products. Inorganica Chim Acta, 2007; 360:794–802.

Silva RV, Costa SCC, Branco CRC, Branco A. *In vitro* photoprotective activity of the *Spondias purpurea* L. peel crude extract and its incorporation in a pharmaceutical formulation. Ind Crops Prod, 2016; 83:509–14.

Tomazelli LC, de Assis Ramos MM, Sauce R, Cândido TM, Sarruf FD, de Oliveira Pinto CAS, de Oliveira CA, Rosado C, Velasco MVR, Baby AR. SPF enhancement provided by rutin in a multifunctional sunscreen. Int J Pharm, 2018; 552:401–6.

Urbach F. The historical aspects of sunscreens. J Photochem Photobiol B, 2001; 64:99–104.

Velasco MV, Sarruf FD, Salgado-Santos IM, Haroutiounian-Filho CA, Kaneko TM, Baby AR. Broad spectrum bioactive sunscreens. Int J Pharm, 2008; 363:50–7.

Vicentini FT, Fonseca YM, Pitol DL, Iyomasa MM, Bentley MV, Fonseca MJ. Evaluation of protective effect of a water-in-oil microemulsion incorporating quercetin against UVB-induced damage in hairless mice skin. J Pharm Pharm Sci, 2010; 13:274–85.

How to cite this article:
Monsalve-Bustamante YA, Puertas-Mejia MA, Mejia-Giraldo JC. Comparison of the photoprotective effect between hydrolyzed and aglycones flavonoids as sunscreen: A systematic review. J Appl Pharm Sci, 2020; 10(1): 116–123.