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PHYLLANTHUS PLANTS IN PHOTOPROTECTION: A BROAD SPECTRUM OF MOLECULAR MECHANISMS

Ivette María Menéndez-Perdomo[1,2], Ángel Sánchez-Lamar[1*]

1. ***Department of Plant Biology, Faculty of Biology, University of Havana, 25St, 455 between I and J, CP 10400, Havana, Cuba***
2. ***Current address: Department of Biological Sciences, University of Calgary, 2500 University Drive NW, Calgary, AB T2N 1N4, Canada.***

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ABSTRACT

During the past few decades, there has been an increased scientific interest to prevent or amend the consequences of human exposure to the detrimental effects of sunlight ultraviolet (UV) radiation. Environmental UV radiation cause direct and indirect DNA damage, inducing mutations, and triggering associated diseases, such as skin cancer. Many photoprotection strategies are currently available, as this has become a core issue on public healthcare. In this context, many phytocomponents had shown photoprotective properties in different experimental models. Plants in the genus *Phyllanthus* (Phyllanthaceae) are widely used in traditional medicine by ethnics from all over the world, and recent investigations support their genoprotective activity against UV radiation. In the present review, we summarize UV-related DNA photodamages and several strategies for its prevention such as the use of phytocomponents. We update the current knowledge concerning the photoprotective properties of several *Phyllanthus* species, putting emphasis on studies carried out in the last decade. We examine different molecular mechanisms described to date, from antioxidant activity to DNA repair modulation, and critically discuss the state of art and perspectives in the use of these plants as a new and promising strategy in photoprotection.

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Introduction

The extent of ultraviolet (UV) radiation reaching the Earth's surface has important (beneficial and detrimental) implications on human health [60,78]. The main terrestrial UV component of sunlight corresponds to UV-B (280-315 nm) and UV-A (315-400 nm) wavelengths, since UV-C (100-280 nm) is completely absorbed by the stratospheric oxygen. Subject to the ozone layer depletion, as well as to variations in cloud cover, air pollutants, and surface albedo (all of which are influenced by climate change), the future of humans' UV radiation exposure remains uncertain [50]. Even though natural UV radiation affecting human health correspond to UV-A (approximately 95%) and UV-B (the remaining 5%), it is important to notice that there are artificial UV sources used in medicine and for cosmetic purposes, which can emit in the UV-C waveband [24], hence humans could be exposed to the harmful effects of all UV spectrum.

Long-term exposures to UV exert negative effects, mainly in the directly-exposed organs: the eyes and the skin. Cataracts, pterygium, squamous cell carcinoma of the cornea and conjunctiva, erythema, hyperpigmentation, photoaging, photoimmunosuppression, and photocarcinogenesis are among the main human diseases related to UV rays [60, 63]. Major UV radiation adverse effects are due to its genotoxicity, through direct photochemical and indirect ROS-mediated pathways, which produce mutagenic DNA damage leading to different disorders. Consequently, this phenomenon has had an enormous

Corresponding Author: Ángel Sánchez-Lamar, E-mail: alamar@fbio.uh. cu

impact on public healthcare, increasing the attention toward the field of photoprotection [91]. In this context, plants had arisen as a promising source of natural photoprotective agents [1,70], which could exert their action through topical or oral administration [33].

Plants belonging to the genus *Phyllanthus* (Phyllanthaceae) are well known for their medicinal properties, mostly as part of Ayurveda, the olden Indian System of Medicine [76]. The aqueous extracts obtained from different *Phyllanthus* species exert genoprotective activity against chemical and physical mutagens, and recent investigations support their UV-photoprotective properties [49, 66, 89].

In this review, we present an up-dated discussion of *Phyllanthus* plants photoprotective properties, focused in the genoprotective capacity on this genus. Possible molecular mechanisms responsible for such activity are discussed and future perspectives outlined.

DNA photodamage

The major biological harm of UV radiation is due to its genotoxic effects, generating DNA direct and indirect damage. Bipyrimidine photoproducts are the main UV induced DNA lesions [11]. All UV wavelengths are involved in the generation of *cis-syn*cyclobutane pyrimidine dimers (CPDs), predominantly TT, through a [2π + 2π] photocycloaddition between the 5,6-pyrimidine bonds of adjacent pyrimidines. Although CPDs are the main DNA photolesion (80-90 %) and responsible for the vast majority of mutagenic events induced by UV radiation, UVB and UV-C also produce to a lesser extent pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), which could be further converted into its Dewar valence isomer (DEWs) under UV-A radiation (λ = 320 nm).

The higher yields of CPDs and 6-4PPs are found under irradiation around 260 nm (in correspondence with the absorption spectrum of DNA) and their distribution is similar in isolated and cellular DNA, with a frequency decreasing in the order: TT > TC > 6-4TC > CT > CC > 6-4TT [56]. Among other structural factors (such as nucleosome positioning), photoproducts formation strongly depends on the DNA sequence, and some base modifications may interfere in their photoreactivity. For instance, daylight UV induces CPDs preferentially at methylated cytosines, in 5´-CG-3´ (mCpG) sequences which are hotspots of mutations, and hence called solar UV signatures [38].

UV-A radiation could also generate DNA oxidative damage through indirect photosensitized mechanisms, and around 100 different base lesions and 2deoxyribose modifications have been identified so far [13]. The production of the radical singlet oxygen ($^1O_2$) anion, through the Type II photosensitization pathway, specifically induces the formation of 8-oxo-7,8dihydroguanine (8-oxoG). This is the main biomarker of DNA oxidative damage (also generated as the central product of the one-electron oxidation in Type I photosensitization mechanism), and one of the many oxidized products generated by hydroxyl radical (˙OH), which reacts without specificity with all components of DNA [12]. Reactive oxygen species (ROS) can also interact with cellular nucleotide pools, producing oxidized nucleotides such as 8-oxodGTP, that could later be used in DNA synthesis. The formation of 8-oxo-G and 8-oxo-dGTP constitute pre-mutagenic lesions since modified guanine generally pairs with adenine, generating the characteristic UV-A-induced oxidative stress-mediated mutations G→T and A→C transversions, respectively [69].

Although the oxidative properties of UV-A play a significant role, formation of CPDs by all UV wavelengths is the major event in the onset of mutations leading to tumorogenesis [63, 71]. Crosslinking of adjacent pyrimidines in DNA molecule produces distortion of the double helix which eliminates base stacking and its corresponding persistent length, generating a more flexible DNA helix around the lesion. The severity of DNA helix distortions correlates with the photoproduct´s repair efficiency: the most destabilizing 6-4PPs are also the most efficiently removed and repaired photolesion [14, 57].

Multiple repair pathways such as direct reversal by DNA photolyases (not present in humans), base excision repair (BER), nucleotide excision repair (NER), and translesion synthesis (TLS) are used to remove, repair, and bypass UV lesions. During replication unrepaired photoproducts, whether CPDs or 6-4PPs, are able to obstruct DNA synthesis. The stall and collapse of the replication fork at the damage site could cause DNA double strand breaks and result in cell death [8]. One solution to overcome this problem is the bypass of UV lesions during replication through TLS, which introduces mutations to a high frequency [93]. The miscoding properties of deaminated cytosine-containing CPDs is the cause of the characteristic UV signature mutations: C→T base substitution at bipyrimidine sites and CC→TT tandem base substitution [10].

A great volume of evidence for the implication of photoinduced damage to DNA in carcinogenicity is provided by the link between increased incidence of skin cancer and certain unusual human genetic disorders like xeroderma pigmentosum, which are characterized by defective NER mechanism or TLS and cell´s UV hypersensitivity [52]. Photocarcinogenesis follows a multistep model in which UV-induced DNA damage leads to mutations resulting in activation of oncogenes or silencing of tumor-suppressor genes such as *p53*. Both types of skin cancers, non-melanoma and melanoma, have been strongly associated with the above described genotoxic effects of UV sunlight exposure [63,79].

Current Photoprotection Strategies

Nowadays, there is an increased search for compounds able to avoid, reduce, and/or abolish the UV radiation-induced genotoxicity, particularly its mutagenic effects. Antimutagens are classified into desmutagens or bioantimutagens, depending on their action mechanism [9]. The former acts before the occurrence of DNA damage, interacting physically, chemically or

biochemically with the mutagen; meanwhile, the latter acts after the DNA has been damaged, interfering with biological functions such as DNA replication and repair.

Photoprotection is a preventive and therapeutic strategy, which also occurs naturally. Human skin is regularly exposed to intense environmental UV radiation and consequently it has a number of intrinsic protective mechanisms to avoid its detrimental effects: hair, pigmentation, *stratum corneum*, antioxidant enzymes, DNA repair mechanisms, cell-cycle arrest, TLS, apoptosis, and removal of mutated cells by the immune system [68]. Some of these protective responses can be induced by UV radiation itself, providing additional protection against subsequent exposures. Regardless of natural strategies, there are plenty of other alternative methods to improve personal photoprotection [91]. One approach is to avoid sunlight by seeking shade and reducing the time of exposure, especially at midday sun. Another tactic is the use of proper clothing and accessories such as umbrellas, hats, and sunglasses.

Furthermore, topical protective filters (for UV-A and/or UV-B spectrum) are currently among the most suitably used methods of sunscreen, but not without controversy. Sunscreens usually contain compounds that reflect or scatter UV photons (physical blockers), or absorb them (chemical and biological filters), as well as substances with antioxidant properties to reduce the photo-oxidative damage that results from UV-induced ROS. Nevertheless, no preparation containing UV filters can provide a 100 % protection [82]. Beyond the prevention or absorption of UV radiation, newer possibilities are emerging, such as creams that repair UV-induced DNA damage –containing DNA repair enzymes such as DNA photolyase and T4 endonuclease encapsulated in liposomes– and compounds that activate the tanning pathway, such as melanocyte-stimulating hormone, favoring endogenous photoprotective mechanisms [33].

Additionally, systemic photoprotection could be achieved through the oral administration of antioxidant substances, which constitutes a novel approach to improve the response to UV-induced oxidative damage, complementing the above described strategies for skin care. Oral photoprotection has several advantages: less expensive, ease use, and their performance is not affected by external conditions such as swimming, types of vestment or sweating [21].

Phytophotoprotection

Natural products are of great interest in drug discovery, due to their large structural and chemical diversity, permitting the identification of lead molecules of interest for the development of new therapeutic agents [70]. Increasing published studies concerning the biological effects of phytocomponents against UV radiation in many experimental models validate them as an emerging photoprotection strategy (phytophotoprotection). Plants are a promising source of natural photoprotective agents, since they had a forced exposure to intense sunlight UV radiation and a rich secondary metabolism to overcome its damaging effects in many different ways, including the synthesis of UV-absorbing molecules [67] and antioxidant metabolites [22].

Compounds with aromatic rings can absorb UV rays, especially at a wavelength range of 200-400 nm; therefore, several botanical substances with UV absorption have been used to substitute/reduce the quantity of synthetic sunscreen agents: green tea polyphenols, grape seed proanthocyanidins, milk thistle silymarins, propoliscinnamic acids, algae mycrosporine-like amino acids and terpenes, and lichen polyphenols [70]. Also, plant-derived antioxidants could be used topically in sunscreens (such as hydroxicinnamic acids, anthocyanins, tannins, polyphenols: green tea polyphenols, genistein, silymarion, equol, quercentin, apigenin, resveratrol), as well as taken orally (carotenoids, genistein, and green tea polyphenols) [21,33]. In addition, most of these substances also act as anti-inflammatory and immunomodulatory agents, which provide further protection against the damaging effects of UV radiation exposure [59].

Polyphenols from green tea (*Camellia sinensis*), importantly its catechin constituents like (-) epigallocatechin-3-gallate (EGCG), protect against many of the damaging effects of UV radiation, including skin cancer [1]. Acting by a variety of cellular, molecular, and biochemical mechanisms, these phytocomponents have shown *in vitro* reduction of UV-mediated DNA damage through an IL-12 dependent functional NER mechanism [51]; *in vivo* inhibition of UV-induced H_2O_2 and NO in human skin [40]; modulation of epigenetic targets, enhancing the expression of tumor suppressor genes, such as p53 [65]. among many others. Milk thistle (*Silybum marianum*) is an important medicinal plant, containing as active principle a mix of flavonoids named silymarin, found to decrease UV radiation-induced apoptotic cell death of epidermal cells through repair of damaged DNA and protecting the skin against all the stages of photocarcinogenesis [41]. Curcumin, obtained from the plant *Curcuma longa* employed in ayurvedic and Chinese traditional medicine, promotes apoptosis in UV irradiated cells [23]. Fruit extract from *Punica granatum* (rich in anthocyanins, tannins, and ellagitannins), possess a strong antioxidant activity and has shown *in vitro* and *in vivo* reduction of UV-mediated formation of CPD and 8-oxodG [2,3].

Genus *Phyllanthus*

Phyllanthus L., was described for the first time in 1737 by Linneus, as the largest genus of the family Phyllanthaceae. It comprises approximately 1270 species, being one of the world´s largest plant genera [37]. According to recent molecular phylogenetic studies based on chloroplast and nuclear DNA sequence data, it includes the subgenus *Conami*, *Cyclanthera*, *Emblica*, *Eriococcus*, *Gomphidium*, *Isocladus*, *Kirganelia*, *Phyllanthodendron*, *Phyllanthus*, and *Xylophylla* [39]. *Phyllanthus* plants possess a remarkable diversity of growth forms (annual and perennial herbaceous, arborescent, climbing, floating, aquatic, pachycaulous, and phyllocladous), widely distributed in tropical and subtropical regions of the planet. Many species

are employed as ornamental plants, due to the attractiveness of its flowers and leaves, although their major significance relies in their multiple ethnomedicinal properties.

In folk medicine (Indian Ayurveda System, Traditional Chinese Medicine, and other practiced by several ethnics from Asia, Latin America, Africa, and Australia), the infusion of leaves, fruits, barks, and roots of many *Phyllanthus* species has been used. Since ancient times, plants of this genera, have been used for the treatment of kidney and urinary bladder disturbances, intestinal infections, hypertension, sexually transmitted disorders, malaria, diabetes, hepatitis B, and many others ailments [76]. Preclinical and clinical studies carried out with the extracts and purified compounds from these plants support most of their reported uses in folk medicine for the treatment of a wide variety of pathological conditions. Species such as *P. amarus*, *P. emblica*, *P. niruri*, and *P. urinaria* are among the most investigated, exhibiting a broad pharmacological spectrum as antiviral, antimicrobial, and anti-inflammatory properties [7, 26, 43, 61, 80, 92].

P. emblica [19], *P. amarus*, *P. niruri*, *P. urinaria* [64], *P. acidus* [16], *P. virgatus* [36], and *P. orbicularis* [75] have been highlighted because of its antioxidant benefits, attributed to many components like rutin, quercetin-3-O-glucoside (flavonoids), phyllanthin (lignan), amariin, repandusinic acid A, corilagin, phyllanthusiin A, B, C, geraniin (ellagitannins), 2,4-di*tert*butilphenol and 2-6 di-*sec*butilphenol (phenols).

Phyllanthus spp. anticancer properties have been well established. *P. emblica* fruit extract chemopreventive potential against skin carcinogenesis has been reported in Swiss albino mice [72]. In a series of interesting studies in human skin melanoma MeWo cells, Tang *et al*. had proved growth inhibition capacity of *P. amarus*, *P. niruri*, *P. urinaria*, and *P. watsonii*, aqueous and methanolic extracts, which exert such effect through modulation of cell cycle and induction of apoptosis via caspases activation [86]; affect cancerrelated signaling pathways by down-regulation of NFκB, Myc/Max, and MAPK/ERK, and up-regulation of MAPK/JNK [84]; and exert antimetastatic effects by matrix metalloproteinases inhibition [85].

Genoprotective effects of *Phyllanthus* plants

Phyllanthus species are also recognized by its antigenotoxic properties against chemical and physical mutagens. In murine experimental models, *P. emblica* significantly inhibited the toxicity caused by benzopyrene, lead, aluminium, and arsenic [25, 45, 58, 77]. *P. amarus* showed antimutagenic effects against 2-aminofluorene, 2aminoanthracene, and 4-nitroquinolone-1-oxide and prevented *in vivo* DNA single strand breaks caused by dimethylnitrosamine [83]; reduced the cyclophosphamide-induced toxicity in mice [42]; and exerted genoprotection against aflatoxin B1 toxicity in human lymphocyte culture and bone marrow cells of Albino mice [4]. *P. orbicularis* aqueous extract exhibit antimutagenic effects against H_2O_2 [30, 73, 75] and several aromatic amines [28,29], *P. amarus*, *P. emblica*, *P. niruri*, and *P. orbicularis* had shown radioprotective effects against γ radiation in different experimental models [5,31,35,44,81,87], associated to the presence of flavonoids (rutin and quercetin-3-O-glucoside) and ellagitannins (geraniin, amariin, repandusinic acid, corilagin, and phyllanthusin).

***Phyllanthus* as photoprotectors: a wide range of molecular mechanisms**

An ideal chemopreventive agent for humans should have little or no toxicity; antimutagenic and anticarcinogenic activities; a known mechanism of action; capability of oral consumption; affordable low cost; and human acceptance [1]. Plant metabolites are among the most promising group of compounds that can be exploited as ideal chemopreventive agents to prevent, delay or completely halt the process of photocarcinogenesis.

Several species of *Phyllanthus* have been focus of photoprotection studies in the last decade (Table 1) and increasing data unveil them as a promising source for genoprotective compounds.

Phyllanthus emblica (Amla) is regularly used in Ayurveda because of its fruits high polyphenol content crediting its antioxidant capability. *P. emblica* was shown to reduce UV-induced erythema, having excellent free-radical quenching ability, chelating capability to iron and copper, as well as MMP-1 and -3 inhibitory activity [20]. In addition, *P. emblica* protects human skin fibroblasts against oxidative stress and shows type I collagen promoting and anti-collagenase effects on primary mouse fibroblast cells in a dose-dependent manner, suggesting its natural anti-aging properties [18, 32]. The active compound 1-O-Galloyl-β-D-glucose (β-glucogallin) obtained in the fruit water extract, showed a dose-dependent decrease in UV-B induced cytotoxicity and ROS generation in mouse fibroblast cells up to 90% and 80%, respectively, as well as a 55% in UV-B induced melanogenesis in mouse melanoma cells, encouraging its usage as a potent photoprotective plant product for sunscreen applications due to its significant free radical scavenging activity [48]. Moreover, this extract showed protection from UV-B induced ROS generation and subsequent collagen damage in normal human dermal fibroblasts [49]. In the mentioned study, it was proved that *P. emblica* fruit aqueous extract has grater antioxidant potency when compared with ascorbic acid, suggesting that the combination of various gallates such as β-glucogallin and mucic acid contributes to its UV-B protection efficacy. Recently, it was developed a cream containing an Amla derived methanol extract in a phospholipid complex that enhanced the delivery of its polyphenols into the skin, to be used as antioxidant cosmetic formulation for photoprotection [62].

Raja and coworkers demonstrate that a non-genotoxic *P. niruri* leaf aqueous extract inhibit chromosomal aberrations induced by UV-B in mouse bone marrow cells, possible through its free radical scavenging activity. Approximately a 40% of protection was achieved when the extract (750 mg/Kg body weight) was administrated to the animals 24 hours prior UV light exposure [66].

However, phytocomponents responsible for the observed antioxidant/genoprotective activity of the extract remain to be elucidated. Skin antiaging nanocreams based in *P. niruri* [47] and *P. urnaria* [46] extracts have been reported, for which UV absorption and ROS scavenger capabilities are supported.

Over the past two decades, our research group has studied the genoprotective properties of Cuban endemic specie *Phyllanthus orbicularis* Kunth used in folk medicine, with proved antiviral activity [6, 94, 27]. The aqueous extract obtained from *P. orbicularis* did not exert genotoxicity in different *in vitro* and *in vivo* experimental models [15, 73, 74, 90], and exhibits potent antioxidant activity [30, 73, 75]. Phytochemical characterization had revealed the presence of flavonoids, tannins, antocianidins, coumarins, gallic acidderivates, catechin, epicatechin, rotocatechuic acid, and others [34].

P. orbicularis aqueous extract protected against UV-B (≥ 0.1 mg/mL) and UV-C (≥ 0.5 mg/mL) induced plasmid DNA damage [90]. Transmittance quantification revealed that for 0.1 mg/mL, the extract blocked around 50% of UV radiation and all of it for higher concentrations, thus the photoprotective effect assessed in the above *ex vivo* experimental model suggests that there are some phytocomponents in the extract capable of absorb UV radiation, inhibiting bipyrimidine photoproducts formation. It is also possible that antioxidant components were able to decrease the ROS induced by UV-B, in a synergic UV absorption/antioxidant photoprotective mechanism. Recently, it was demonstrated that *P. orbicularis* aqueous extract protect DNA from primarily damage induced by UVC light in *E. coli* cells, with no significant genotoxic response [89]. Moreover, the protective effect non associated to UV absorption (1 µg/mL, which permitted the passage of more than 90% UV-B radiation) was tested in DNA repair proficient (MRC5-SV) and deficient (XP4PA, complementation group XPC) human cell lines under UV light, through clonogenic assay and apoptosis induction by flow cytometry [88]. *P. orbicularis* extract enhanced the removal of CPD from genomic DNA in a time-dependent manner, possibly by means of modulation of NER repair system effectiveness, suggesting the bioantimutagenic capacity of this extract against UV radiation.

Recently, we focused our attention in extending the search for photoprotective activity to other Cuban endemic *Phyllanthus* species with antioxidant properties.

We assessed the non-genotoxic *P. chamaecristoides*, *P. microdictyus*, and *P. williamioides* aqueous extracts [53] for its photoprotective capacity against UV-C artificial light at two levels: structural DNA damage and gene mutations [54]. *P. chamaecristoides* extract showed the highest free radicals scavenging capacity (IC_{50} = 0.032 mg/mL), higher than reported under the same conditions for other *Phyllanthus* species with known antioxidant properties [17, 19]. All the extracts showed DNA photoprotection as they significant diminish SOS response, which could be due in part to its antioxidant properties, as well as a possible enhancement of DNA repair system [54]. In the same study, *P. chamaecristoides* and *P. microdictyus* extracts were highly bioantimutagenic (relative mutation frequency RMF ≤ 5%), diminishing UVC-induced DNA damage in *Caulobacter crescentus* cells three and five times, respectively. According to the results, the underlying molecular mechanisms could also implicate TLS polymerases inhibition and/or apoptosis induction. The referred plant extracts (1-1000 µg/mL) permitted the passage of most of UV-C radiation, indicating low absorption, thus they did not exert their photoprotective action through desmutagenic mechanisms. Interestingly, for the three aqueous extracts at 1 mg/mL about 100% (*P. chamaecristoides* and *P. williamioides*) and 50% (*P. microdictyus*) of UV-B absorption was detected [54]. This result suggests that some desmutagenic effects may occur for longer UV wavelengths exposure probably based in the extracts antioxidant capabilities.

Table 1: Summary of *Phyllanthus* species with reported photoprotective activity in the last decade, extract composition, main studies performed, and molecular mechanisms suggested.

Phyllanthus species	**Solvent (organ)**	**In vitro/in vivo studies**	**Molecular mechanism suggested**	**Ref.**
 P. chamaecristoides	Water (leaves and stems)	DPPH radical assay, survival assay, SOS Chromotest and RifR test in C. crescentus (UV-C)	Bioantimutagenic and free radical scavenging	(Menéndez-Perdomo et al. 2017)
 P. emblica	Water (fruit)	Neutral red uptake and ROS inhibition assay in Swiss mouse fibroblast; melanogenesis inhibition in mouse melanoma cells; ELISA, ROS inhibition assay, and immunocytochemistry in human fibroblasts (UV-B)	Free radical scavenging (β-glucogallin)	(Majeed et al. 2010) (Majeed et al. 2011)
	Methanol (plant powder)	SPF evaluation, DPPH radical assay, H2O2 scavenging assay (UV-B)	Free radical scavenging	(Pereira and Mallya 2015)

 P. microdictyus	Water (leaves and stems)	DPPH radical assay, survival assay, SOS Chromotest and RifR test in C. crescentus (UV-C)	Bioantimutagenic and free radical scavenging	(Menéndez-Perdomo et al. 2017)
 P. niruri	Water (leaves)	Chromosomal aberration assay in Swiss albino mice and Fenton test (UV-B)	Free radical scavenging	(Raja et al. 2011)
 P. orbicularis	Water (leaves and stems)	DNA breaks induction in plasmid DNA (UV-B and UV-C)	UV absorption	(Vernhes et al. 2013b)
		Clonogenic assay, DNA damage (CPD) removal quantification, and apoptosis induction in human fibroblasts (UV-B)	NER system enhancement	(Vernhes et al. 2013a)
		SOS Chromotest in E. coli (UV-C)	UV absorption + DNA repair enhancement (NER-independent)	(Vernhes et al. 2016)
 P. urinaria	Ethanol (plant powder)	DPPH radical assay (UV-B)	Free radical scavenging	(Mahdi et al. 2011)
 P. williamioides	Water (leaves and stems)	DPPH radical assay, survival assay, SOS Chromotest and RifR test in C. crescentus (UV-C)	SOS response modulation and free radical scavenging	(Menéndez-Perdomo et al. 2017)

Perspectives

The deleterious effects of UV solar radiation are accumulative, irreversible, and currently a major health concern worldwide. Exposure to UV radiation results in DNA damage, mutations, and ultimately lethal diseases, such as cancer. Thus, adequate photoprotection is an essential issue, and classical approaches such as avoidance of sunlight, shielding with clothing and the use of sunscreens, must be combined with novel ones like the enhancement of endogenous protective responses to UV light-damage using natural products.

In the 21st century, there was still an increased interest in using plant-derived agents in UV-induced damage prevention [1, 33, 55]. *Phyllanthus* plants have been shown to contain different combinations of secondary metabolites which render them with medicinal properties. In recent years, the interest in the plants of the genus *Phyllanthus* has increased and considerable progresses on their chemistry and pharmacological properties (both *in vitro* and *in vivo*) have been made [76]. Data strongly supports the idea that the plants belonging to the genus *Phyllanthus* have potential beneficial therapeutic actions in the management of UV-induced genotoxicity through a broad spectrum of molecular mechanisms. UV absorbance/blocking efficacy (desmutagenic effect) and/or inhibition and repair of UV-induced damages like pyrimidine dimers and oxidative stress (bioantimutagenic effects) have been reported for several species. Apoptosis induction, as an alternative photoprotective method, has been also suggested.

P. emblica, *P. niruri*, and *P. urinaria* antioxidant extracts are currently used as sunscreens formulations [46, 47, 62]. Nevertheless, the development of phytocomponents as new commercial photoprotective agents in sun-care products must be safe. To ensure protection efficacy the quantity of active constituents in natural products, compatibility, stability, and stability must be elucidated. Although there is enough literature discussing the antioxidant properties of *Phyllanthus* species that contributes to its UV-protection efficacy, there is still lacking information regarding the active constituents (and their molecular

mechanisms). *P. orbicularis* extract bioantimutagenic properties have been proved and suggested to enhance NER system in human fibroblast cells [88], but a deeper understanding of the molecular mechanism and the phytocomponents implicated in it is still needed. Likewise, further research should be carried out to shed more light into the detected antimutagenic properties of species such as *P. chamaecristoides*, *P. microdictyus*, and *P. williamioides* that seem to act by different pathways [54].

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