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REVIEW

Serotonin and Melatonin: Plant Sources, Analytical Methods, and Human Health Benefits

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Abstract
Over the last few years, an increasing interest in the scientific research of natural antioxidant molecules from plants capable to attenuate, or even prevent, stress oxidative-related disorders, such as diabetes, inflammatory, and neurological pathologies has been observed. Serotonin and melatonin are two of these molecules, being widely found in Mediterranean foodstuffs, fruits, vegetables, and medicinal herbs. The consumption of foods containing both antioxidants can raise their physiologic concentrations in blood and, consequently, enhance antioxidant defenses, improve mood, and treat sleep disorders, depression, and anxiety. Currently, there exist several analytical methods suitable for the determination of melatonin and serotonin in fruits and edible plants. Among them, the most used include chromatographic techniques and immunological assays. This work aims to present a comprehensive overview of the biosynthesis of these indolamines in nature, the most common techniques used to detect and quantify both compounds in fruits, vegetables, medicinal herbs, and other food sources, as well as to address their health benefits, particularly their antioxidant, neuroprotective, and sleep-promoting effects.

Keywords Analytical methods · Biosynthesis · Tryptophan · Indolamines · Health benefits · Plant sources

Introduction

It is widely recognized that the daily intake of fruits and vegetables is imperative to maintain good health. In fact, there are already several epidemiological, clinical, and experimental published studies that have reported a positive relationship between their intake and a lower incidence of cancer, diabetes, neurodegenerative diseases, and cardiovascular disorders (Burkhardt et al. 2001; Garcia-Parrilla et al. 2009; Feng et al. 2014). Furthermore, dietary programs, such as the "Five-a-day" campaign, have been introduced to increase the consumption of both fruits and vegetables, and consequently their bioactive constituents, since many of them exhibit health protective effects (Moussaoui and Bendriss 2015).

Indeed, fruits and vegetables possess a wide variety of bioactive compounds, including micronutrients (vitamins and minerals), macronutrients (carbohydrates, proteins, fatty and organic acids), and secondary metabolites (non-colored and colored phenolics, volatile compounds, carotenoids, serotonin, and melatonin, *inter alia*). Serotonin and melatonin have been gaining great scientific interest due to their remarkable antioxidant, immune-active, hormonal, and neurological properties (Rayne 2010). Additionally, they have also been recognized as being involved in the modulation of many behavioral and neurophysiological processes, including mood, depression, sleep, wakefulness, energy balance, sexual maturation, perception, aggression, impulsivity, cognition, circadian rhythms, body temperature, neuroendocrine function, and antioxidant defenses (Chen et al. 2003; Anisimov et al. 2006; Garrido et al. 2009; González-Gómez et al. 2009; Nawaz et al. 2015).

Serotonin and melatonin are largely present in foodstuffs, including in leaves, stems, roots, flowers, seeds, and derivative products, varying at significant concentrations (Dubbels et al. 1995; Badria 2002; Rayne 2010). Particularly, while melatonin is widely found in feverfew (*Tanacetum parthenium* L., Asteraceae), tomatoes, bananas, cucumbers, and sunflower seeds, serotonin is mainly present in pineapples and walnuts (Dubbels et al. 1995; Manchester et al. 2000; Chen et al. 2003; Erland et al. 2016). However, there are still difficulties in the identification and quantification of melatonin and serotonin in edible plants since melatonin is a direct

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and non-receptor-mediated antioxidant that reacts quickly with free radical species and with other food components, while serotonin is an unstable compound that is severely affected by temperature, pH, and metal ions (Huang and Mazza 2011a). In addition to these factors, the analysis of both requires highly sensitive analytical methods since they are present in different concentrations among plants. In addition, it is also difficult to choose the right extraction solvent to obtain the greatest recovery and the best accurate results due to their amphiphilic character or dual lipophilic and hydrophilic properties, of melatonin (Huang and Mazza 2011a). Therefore, the analysis of both compounds requires highly sensitive analytical techniques, being recommended the use of organic solvents and short periods of sonication to extract both indolamines from matrixes for their detection and quantification (Erland et al. 2016).

Search Strategy

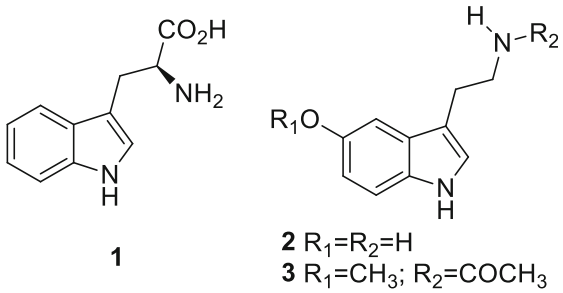
In this comprehensive and critical review, the main sources of melatonin and serotonin in the plant kingdom, the current analytical methods used to determine the contents of both compounds in fruits, edible plants, and other food sources, as well as their main benefits for human health, were summarized. The literature search was conducted in several electronic databases (PubMed, SciELO, Google Scholar, Springer, Scopus, and Web of Science) from database inception to November 2020. The search procedure was based on the keywords "melatonin" and/or "serotonin" combined with multiple terms (tryptophan, biosynthesis, food sources, analytical methods, health benefits, health-promoting properties, antioxidant properties, neurological protection, anticancer activity, anti-ageing effects, anti-obesity effects, sleep promotion) using the Boolean operators AND and OR. Reference lists of the identified papers were also analyzed, and additional research was traced online. Inclusion criteria were articles related to the biological potential of both indolamines (melatonin and serotonin). The search was performed in November 2020.

Discussion

Biosynthesis

The main secondary metabolites of tryptophan (**1**) in plant tissues are auxin, glucosinolates, phytoalexins, alkaloids, and indolamines, which are responsible for the maintenance of many physiological processes (Murch et al. 2000). Within indolamines, serotonin (**2**) and melatonin (**3**) assume highlight roles in plants defense, acting as protective agents against pathogens, free radical species, and abiotic and biotic stressors (Yu et al. 2018). Moreover, both compounds also stimulate plant growth, germination, xylem sap exudation from roots, flowering, and ion permeability (Kang et al. 2007; Arnao and Hernández-Ruiz 2015). Contrary to the plant kingdom, animals cannot synthesize tryptophan, which is obtained through the diet (Iriti and Faoro 2006).

The discovery of serotonin (**2**) was made independently by different researchers. First in Italy, during the 1930s, Vittorio Erspamer extracted a substance from enterochromaffin cells in the gastrointestinal tract responsible for smooth muscle contraction, designating it as enteramine. Years later, in 1952, the same researcher noticed that the extracted substance was the same isolated from serum after blood clotting by Green and Page in 1948 and decided to designate it as serotonin (Whitaker-Azmitia 1999).



Currently, serotonin (**2**) is known as a biogenic monoamine, similar to epinephrine, norepinephrine, dopamine, and histamine (Mohammad-Zadeh et al. 2008). In plants, serotonin was first identified in *Mucuna pruriens* (L.) DC. legume in 1954 (Bowden et al. 1954). Presently, it is identified in ~42 plant species from 20 different families, being widely distributed in leaves, stems, roots, fruits, and seeds. Its synthesis occurs in plants via two different pathways (Fig. 1) (Ramakrishna et al. 2011). Tryptophan (**1**) is catalyzed into tryptamine by tryptophan decarboxylase (TDC), followed by its catalysis by tryptamine 5-hydroxylase (T5H) action that hydroxylates the C-5 position of tryptamine (Pelagio-Flores et al. 2011), forming serotonin (**2**). Tryptamine is also the precursor of indole acetic acid, serving the indole-3-acetaldehyde as an intermediate product (Nawaz et al. 2015). In animals, T5H originates serotonin (**2**) by hydroxylating tryptophan to form 5-hydroxytryptophan (5-HTP), which is subsequently decarboxylated by decarboxylase, originating serotonin (Fig. 1) (Ramakrishna et al. 2011). Curiously, in *Hypericum perforatum* L., Hypericaceae, serotonin synthesis occurs via 5-hydroxytryptophan, as in animals (Nawaz et al. 2015). In a first step, tryptophan (**1**) undergoes hydroxylation by the action of tryptophan hydroxylase (TPH) that adds a hydroxyl group to position 5 of tryptophan, being converted into T5H. Then, T5H is decarboxylated by aromatic L-amino acid decarboxylase (AAAD), forming serotonin (Fig. 1) (Mohammad-Zadeh et al. 2008).

In plants, serotonin (**2**) is normally detected in the vascular parenchyma cells of plants (Ramakrishna et al. 2011). In rice,

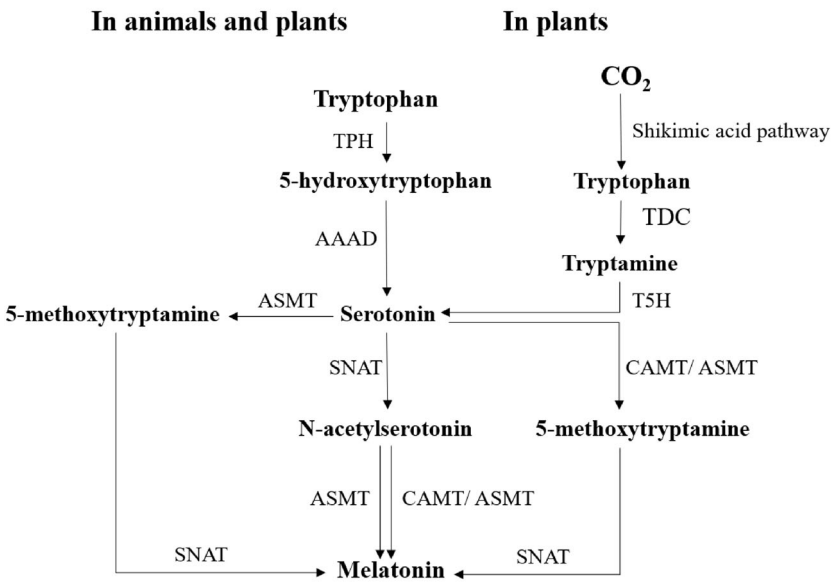


Fig. 1 Comparison of the conversion of L-tryptophan to serotonin and melatonin in animals and plants. TPH, tryptophan hydroxylase; AAAD, aromatic L-amino acid decarboxylase; SNAT, serotonin *N*-acetyltransferase; ASMT, *N*-acetylserotonin *O*-methyltransferase; TDC, tryptophan decarboxylase; T5H, tryptamine-5-hydroxylase; CAMT, caffeic acid *O*-methyltransferase

higher concentrations were reported in companion and xylem cells (Kang et al. 2007), while in bananas, higher contents were found in its vascular bundle walls (Kimura 1968). Additionally, reports stated that serotonin can also be accumulated in protein bodies of cotyledons of embryos of *Juglans regia* L., Juglandaceae, while their vacuoles are being formed (Grobe 1982). Alternatively, in animals, serotonin (**2**) is synthesized and stored predominantly in the central nervous system, particularly in presynaptic neurons (serotonergic and catecholaminergic neurons and in the pineal gland) (Mohammad-Zadeh et al. 2008). Outside the central nervous system, serotonin synthesis only occurs in enterochromaffin cells and platelets, being both ones responsible to store about 90–95% of the total body's serotonin (Mohammad-Zadeh et al. 2008).

In relation to the serotonin catabolism in plants, it is recognized by the scientific community that serotonin: (i) can be catabolized by hydroxytryptamine acetyltransferase, originating *N*-acetylserotonin that will be then methylated and will form melatonin (**3**); (ii) suffers dihydroxylation in its 5-hydroxyindolylacetic acid leading to the formation of indoleacetic acid, which is the main indole compound of plants; or finally (iii) undergoes methylation, giving rise to many alkaloids, such as bufotenine, bufotenidine, psilocin, and psilocybin (Ramakrishna et al. 2011). Moreover, the indole nucleus of serotonin can be condensed with secologanin, generating alkaloids as reserpine, yohimbane and yohimbine, and vinblastine, which in turn, when ingested by humans, may cause paranoid states and psychic disorders (Ramakrishna et al. 2011).

Melatonin (**3**) was discovered by Lerner in 1960. He isolated and characterized it from the bovine pineal gland. Its name appears associated with its ability to lighten fish, reptiles, and amphibians' skin (Arnao and Hernández-Ruiz 2006). In humans, in addition to being produced and secreted by the pineal gland, evidence has revealed that melatonin is also synthesized by the retina, gastrointestinal tract, ovaries, bone marrow, Harder's gland, platelets, lymphocytes, megakaryocytes, and skin at varying rates and dependent of the organ (Iriti and Faoro 2006; Favero et al. 2014).

Furthermore, melatonin has also the ability to cross all morphological barriers (Aguilera et al. 2015) and it is present in all body fluids, tissues, and cellular compartments, including saliva, urine, and cerebrospinal, preovulatory follicular, seminal and amniotic fluids, bile, and breasting milk (Favero et al. 2014). This indolamine is not exclusive to vertebrates, being also present in unicellular and simple multicellular organisms without a pineal gland, including alga, bacteria, fruit fly (*Drosophila melanogaster*), and locust (*Locusta migratoria*) (Badria 2002).

In plants, melatonin was discovered in 1993 by van Tassel and O'Neill who detected its presence in tomato fruits (*Solanum lycopersicum* L., Solanaceae). Two years later, the same authors also reported its presence in Japanese morning glory (*Ipomoea nil* (L.) Roth, Convolvulaceae), by radioimmunoassay (RIA) and gas chromatography coupled to mass spectrometry (GC-MS). Currently, melatonin is largely identified in fruits, vegetables, and cereals, ranging from pg/g to multiple μg/g of tissue (Tan et al. 2007), being its content higher in plants than in animals (Nawaz et al. 2015).

As shown in Fig. 1, melatonin (**3**) can be biosynthesized by plants and animals from tryptophan and serotonin involving different enzyme-mediated metabolic pathways (Favero et al. 2014). In addition, the microorganisms' decomposition can

also release melatonin to the soil, being this one absorbed by plant roots. The major metabolite of melatonin degradation, known as N_1-acetyl-N_2-formyl-5-methoxykynuramine (AFMK), was identified in some aquatic plants, as a result of enzymatic and non-enzymatic conversions (Tan et al. 2007).

Sources in Plants

As mentioned before, serotonin (**2**) and melatonin (**3**) are largely identified in the plant kingdom, varying from plant to plant and from pg to ng/g of tissue (Stege et al. 2010). Additionally, their levels also differ within the tissues and/or organs of the same plant and are seriously influenced by the time of harvest and environmental changes that the plants are subjected during their growth and development, such as pH and temperature variations and the possible presence of metal ions in the soil (Arnao and Hernández-Ruiz 2015).

In plants, serotonin (**2**) is found in roots, leaves, fruits, and seeds (Pelagio-Flores et al. 2011). It was first described in 1959 by Sidney Udenfriend and colleagues in peel and pulp of banana, pulp of plantain, tomato, plum, avocado, and eggplant. They also described that, during the ripening process, serotonin concentrations (μg/g) in bananas' peel are three times higher than in the pulp. The obtained values are in line with those reported by Adão and Glória (2005) who also reported that its levels in banana did not differ significantly up to the 14th day of storage, decreasing significantly afterward, varying from 49.9 to 56.7 μg/g during the ripening and decreased to 12 μg/g during the fruit's senescence. More recently, Erland and Collaborators (Erland et al. 2016) also reported the presence of serotonin in banana shoots and roots.

Melatonin (**3**) was only described for the first time outside the animal kingdom in the early 1990s, first in the dinoflagellate algae *Gonyaulax polyedra*, and later, in bacteria, fungi, insects, and plants (Johns et al. 2013). Currently, melatonin has already been identified in roots, leaves, bulbs, fruits, and seeds of more than 140 plant species (Hernández-Ruiz and Arnao 2008a; Ye et al. 2017). Generally, seeds and leaves present the highest level of melatonin, followed by roots, flowers, and finally by fruits (Arnao and Hernández-Ruiz 2006). Furthermore, Mediterranean foodstuffs, such as olive oil, grape wine, and walnuts, as well as medicinal plants, such as Chinese herbs, feverfew, and St. John's Wort also possess high levels of melatonin (Johns et al. 2013). Chen et al. (2003) reported melatonin levels of 108 Chinese medicinal herbs, using SPE and HPLC-FD on-line with MS. Sixty-four of these herbs contain melatonin with contents higher than 10 ng/g of dry weight (dw) and 39 had levels greater than 100 ng/g of dw. Given their high content of melatonin, these herbs are traditionally used to treat oxidative stress–related diseases. For example, yinyanghuo (*Epimedium brevicornum* Maxim., Berberidaceae) (melatonin 1105 ng/g of dw) and sangbaipi (cortex of *Morus alba* L., Moraceae) (melatonin 1110 ng/g of dw) are typically used to slow the aging process, while sangye (leaves of *M. alba*) (melatonin 1510 ng/g of dw) is used to protect against irradiation damage from UV or radiotherapy (Chen et al. 2003).

Melatonin is also present in beer (94.5 ± 6.70 pg/g of dw) (Kocadağli et al. 2014), being its level directly linked to the alcoholic degree of this drink, probably due to the solubility of melatonin in alcohol. So, drinks with higher alcoholic graduation have a higher content of melatonin (Maldonado et al. 2009). Additionally, the Gramineae family, which includes rice, barley, sweet corn, oat, and tall fescue (Hernández-Ruiz et al. 2005) and pistachio kernels also present high amounts of melatonin (Oladi et al. 2014).

Additionally, it is also true that there exists a direct relationship between the quantity of melatonin (**3**) and its precursor serotonin (**2**) (Udenfriend et al. 1959), being verified an increase of melatonin levels during the plant maturation and without light (Reiter et al. 2007; Hernández-Ruiz and Arnao 2008b). For example, the roots of young lupine plants presented the highest melatonin content, followed by their leaves, hypocotyls, and cotyledons with values that increased during their development (12–14 ng/g of fresh weight (fw)) (Hernández-Ruiz and Arnao 2008b). In contrast, old barley leaves revealed a lower level of melatonin (8 ng/g of fw) than lupine plants, possibly due to their senescence and the fact that they are more exposed to the light than the latter ones (Hernández-Ruiz and Arnao 2008b). Serotonin (**2**) and melatonin (**3**) were also identified in sweet cherry cultivars (*Prunus avium* L., Rosaceae), being their levels a characteristic of each cultivar (González-Gómez et al. 2009).

Melatonin (**3**) presence was also described in tart cherries (*Prunus cerasus* L.), particularly in the varieties "Montmorency" (13.45 ng/g of fw) and "Balaton" (2.06 ng/g of fw). Interestingly, though "Balaton" had significantly lower levels of melatonin than "Montmorency," it presents higher concentrations of other antioxidants (*e.g.*, polyphenols) than "Montmorency" cherries (Wang et al. 1997). Its levels also did not vary according to the harvesting time (Burkhardt et al. 2001). Additionally, Özen and Ekşi (2016), through LC-MS, reported that serotonin content of sour cherry concentrate ranged between 1.07 and 1.38 ng/ml, while no melatonin was detected in the studied juices. The same was reported by Kirakosyan et al. (2009), and their explanation for the lack of melatonin in sour cherries is due to its instability, being easily degraded during the processing and storage of the samples. Melatonin was also found in wheat. Particularly, its content in purple wheat (4 μg/kg) was significantly higher ($p > 0.05$) than that found in purple wheat with heat-stressed (2 μg/kg). Additionally, no serotonin (**2**) was found in purple wheat, probably since its amount was below the limit of HPLC detection (0.1 μg/mg) or due to its conversion into melatonin (**3**) before analysis (Hosseinian et al. 2008).

Furthermore, *Cantharellus cibarius* Fr., Cantharellaceae, one of the most highly valued and commonly harvested edible mushrooms also present serotonin and melatonin in their composition, with scores of 17.61 ± 0.455 and 20.49 ± 0.670 mg/100 g dw for serotonin, and 0.11±0.006 0.01±0.006 mg/100 g dw for melatonin (Muszyńska et al. 2013). On the other hand, and although potato vegetables present neither serotonin nor melatonin in their composition, Erland et al. (2016) identified melatonin in potato shoots (40.05 ng/g of fw), using UPLC-MS analysis.

Analysis in Plants

There are several analytical methods able to identify and quantify serotonin (**2**) and melatonin (**3**) in fruits, vegetables, and in other foods. The chosen one needs to take into account the instability of serotonin and melatonin in the matrices, as well as the presence of other constituents (Paredes et al. 2009; Huang and Mazza 2011a; Ramakrishna et al. 2011).

Normally, samples are prepared using liquid-liquid extraction, solid-phase extraction, or microextraction by packed sorbent. These sample preparation techniques are the best for the clean-up of plant tissue samples containing serotonin and melatonin. Then, their analyses have been preferably done by high-performance liquid chromatography (HPLC) coupled to a mass spectrometer (HPLC-MS) or to an electrochemical detector (HPLC-ECD) (Garcia-Parrilla et al. 2009; González-Gómez et al. 2010; Huang and Mazza 2011b; Ramakrishna et al. 2012; Özen and Ekşi 2016; Ye et al. 2017). Table S1 shows the main sources of serotonin (**2**) and melatonin (**3**), in addition to the methods applied to their determination.

Extraction Techniques

The first challenge to analyze serotonin (**2**) and melatonin (**3**) levels in plants is to find the most appropriate methodology to extract these target analytes and clean-up the samples, given that several factors (*e.g.*, type and volume of the solvent, temperature, and pH) may influence the efficiency of the process (Oladi et al. 2014). However, regardless of the specific extraction procedure, it is recommended the stirring of fresh and unmixed samples with organic solvents (*e.g.*, MeOH, $CHCl_3$, or EtOAc), instead of water, because the use of water reduces recovery rates of melatonin (**3**) owing to its amphiphilic character (Çalişkan et al. 2017). Additionally, ultrasonic treatment of samples for a short period of time should also be applied in the extraction process, since its use can increase extraction yields by about 20% (Aguilera et al. 2015).

Recent studies indicate that the optimal conditions for serotonin (**1**) and melatonin (**3**) extraction include sonication and use of methanol as solvent, followed by total evaporation. MeOH is recommended since it does not require extra cleaning steps, unlike other organic solvents, and can be directly injected in a reversed-phase column (Erland et al. 2016). Particularly, for serotonin extraction, Pelagio-Flores et al. (2011) suggest continuous stirring for 3 h with MeOH, followed by total evaporation with nitrogen; however, additional steps may be required to further increase serotonin extraction, such as acetylation of the mixture with acetic anhydride, addition of CH_2Cl_2 and sonication, followed by heating at 75 °C and evaporation. For melatonin extraction, Stege et al. (2010) recommend ultrasonication (200 W, 7 min) at 15 °C using MeOH. Erland and co-workers (Erland et al. 2016) recommended the sonication of samples on ice using as extraction solvent a mixture of MeOH and 4% CH_3CO_2H in water (50:50, v/v), followed by centrifugation (2 min at 13,000 rpm). Additionally, and considering the instability of melatonin, Setyaningsih et al. (2012) developed a microwave-assisted extraction (MAE) method for this analyte, using rice grains as a matrix; the solvent used was pure MeOH, and the optimal conditions were 15 min of sonication at 1000 W, and 175 °C. Although it was previously reported that high temperatures can lead to degradation of melatonin, the authors of this work verified that the extraction of melatonin increases more than the degradation at 175 °C. In fact, heating (until 175 °C) and sonication enable extraction yields around 60%. To support the findings, they reported values concerning melatonin extraction 50 times superior to those of Hattori et al. (1995) (54.17 ± 13.48 against 1 ± 0.06 ng/g). Finally, and if the detection of indolamines will be done by radioimmunoassay (RIA), organic solvents are also evaporated until dryness to avoid antibody denaturalization (Garcia-Parrilla et al. 2009).

Clean-up Techniques

After extraction of serotonin (**2**) and melatonin (**3**), samples are commonly purified previously to the instrumental analysis by the application of liquid-liquid extraction and solid-phase extraction techniques (Ye et al. 2017). Relatively to these two sample clean-up techniques, and despite their cost, solid-phase extraction use is preferred, mainly due to the presence of other compounds in matrices, such as carbohydrates, lipids, and phenolics that can induce false results because of their polarity (Feng et al. 2014). In fact, solid-phase extraction is more selective than liquid-liquid extraction, allowing a better retaining of the target compounds in the sorbent, and consequently, a higher concentration of them in the eluate (Huang and Mazza 2011a). Normally, samples are first washed with Milli-Q water to remove the most hydrophilic compounds and then eluted with MeOH (Erland et al. 2016). Another alternative is to use microextraction by packed sorbent. This process is faster and cheaper than conventional solid-phase extraction, but it is only applicable to small sample volumes (Mercolini et al. 2012).

Analytical Methods

Nowadays, the most used techniques to detect and quantify serotonin (**2**) and melatonin (**3**) include immunological assays, such as RIA and enzyme-linked immunosorbent assay (ELISA), and liquid chromatography (HPLC) methods coupled to different detection systems, *e.g.*, HPLC-MS, HPLC-ECD, HPLC-UV, HPLC-DAD, or HPLC-FD, and gas chromatography (GC-MS) (Huang and Mazza 2011a; Nawaz et al. 2015). Among them, the results of ELISA and RIA are not considered accurate, since the various compounds present in plants can cross-react with antibodies and enzymes, overestimating the real values of both indolamines. To prove that, Van Tassel and O'Neill (2001) compared the melatonin level in tomatoes by RIA and GC-MS and verified that the values obtained by RIA were about 6- to 100-fold superior. Relatively to the other techniques, HPLC and GC-MS are both considered accurate and sensitive; however, HPLC is the recommended one since, unlike GC-MS, it does not require derivatization (Huang and Mazza 2011a).

HPLC-ECD Analysis

Electrochemical detection (ECD) coupled with HPLC is usually based on an isocratic-mobile phase and requires reversed-phase C_{18} columns, with dimensions of 100–250 mm × 2–4.6 mm. Commonly, the aqueous phase is acidified, and the organic phase is composed of MeOH or CH_3CN. Additionally, it is applied a potential of 850 mV, in order to provide greater sensitivity for the detection of both compounds. In these conditions, serotonin (**2**) will elute first than melatonin (**3**). Despite being widely used, this method is not specific, leading to erroneous detection and quantification results because plants contain several compounds with oxidation potentials and retention times similar to compounds **2** and **3** (Huang and Mazza 2011a). This analytical system was first used by Fuhrberg et al. (1996) for the determination of melatonin (**3**) in brown alga (*Pterygophora californica* Rupr.); the applied conditions are described in Table S2. In recent years, HPLC-ECD also enabled the detection of serotonin and/or melatonin in barley (*Hordeum vulgare* L., Poaceae), canary grass (*Phalaris canariensis* L. Poaceae), hypocotyls, oat (*Avena sativa* L., Poaceae), wheat (*Triticum aestivum* L., Poaceae), white lupine (*Lupinus albus* L., Fabaceae) (Hernández-Ruiz et al. 2004, 2005), walnuts (*Juglans regia* L., Junglandaceae) (Reiter et al. 2005), and in tart (*Prunus cerasus* L., Rosaceae) (Burkhardt et al. 2001) and sweet cherries (*Prunus avium* L.) (Rosado et al. 2017) (Table S2).

HPLC-FD Analysis

The principle of HPLC combined with a fluorescence detector (HPLC-FD) is based on the excitation and emission wavelengths. It is more sensitive than HPLC-ECD, providing lower limits of detection and quantification. For serotonin (**2**), the excitation and emission wavelengths used for detection are 295 and 330 nm or 340 and 445 nm, while melatonin (**3**) is detected at 280 and 340–350 nm or 245 and 380 nm, respectively (Huang and Mazza 2011a). Focusing on elution modes, there are no studies about the simultaneous detection of both compounds **2** and **3** by application of HPLC-FD in a single run. Usually, both compounds are identified in separated runs, and although the gradient elution provides better separation peaks, the isocratic-, linear-, or step-gradient elution is normally applied for serotonin (excitation and emission wavelengths of 295 and 330 nm and 340 and 445 nm, respectively), while isocratic elution alone is used for melatonin detection (280 and 340–350 nm and 245 and 380 nm regarding excitation and emission wavelengths, respectively) (Huang and Mazza 2011a). Furthermore, this technique requires the use of degassed solvents that do not cause background fluorescence to affect sensitivity. The aqueous phase is normally composed of H_2O acidified to pH values between 2.8 and 5.5. On the other hand, the organic phase is composed of either MeOH/EtOH (3:2, v/v) or CH_3CN (Swartz 2010; Feng et al. 2014).

This technique allowed serotonin identification in fruits, leaves, and tubers of potato (*Solanum tuberosum* L., Solanaceae) (Engström et al. 1992), in banana (*Musa acuminata* Colla × *Musa balbisiana* Colla, Musaceae) (Adão and Glória 2005), and in hazelnut and spinach leaves (Lavizzari et al. 2006), as described in Table S2. Concerning melatonin's identification using HPLC-FD, Pape and Lüning (2006) quantified this compound in tomatoes (*Lycopersicon esculentum* Mill., Solanaceae), ginger (*Zingiber officinale* Roscoe, Zingiberaceae), and in the marine green macroalga (*Ulva lactuca* L.) (Table S2), while Hernández-Ruiz and Arnao (2008b) quantified it in white lupine (*Lupinus albus* L., Fabaceae) and barley (*Hordeum vulgare* L., Poaceae) (Table S2).

HPLC-UV Analysis

The HPLC coupled with ultraviolet detection (HPLC/UV) is one of the most widely used analytical techniques to determine serotonin (**2**) and melatonin (**3**) in plants due to its accuracy and being a cheaper instrumentation than the MS detector. The spectra of each compound may be also obtained using a DAD in the range of 254 to 600 nm with a maximum absorbance at 280 nm (Hosseinian et al. 2008). The mobile phases are composed of acidic H_2O, adjusted with weak acids (CF_3CO_2H or CH_3CO_2H), and MeOH, or CH_3CN (Huang and Mazza 2011a). Kang and Back (2006) identified the presence of serotonin in pepper's (*Capsicum annuum* L., Solanaceae) leaves, stems, fruits, flowers, and roots, while Afreen et al. (2006) detected melatonin in seed, leaf, stem,

and root of Chinese licorice (*Glycyrrhiza uralensis* Fisch, Fabaceae) plants. Applying a gradient elution, it was also possible the detection of both melatonin and serotonin in purple wheat, in a single run (Hosseinian et al. 2008). The applied conditions are summarized in Table S2.

HPLC-MS Analysis

HPLC coupled to mass spectrometry (HPLC-MS) provides lower limits of detection, as well as higher sensitivity, reproducibility, and specificity (Ye et al. 2017). Nevertheless, sometimes during the analysis of less abundant metabolites in complex matrices occurs the "matrix-effect" due to the co-elution of compounds and chemicals. In these situations, an ionization reduction occurs, and consequently, analyte peak areas are not reliable. To minimize these drawbacks, it is necessary to optimize the analytical conditions. Nowadays, it is known that it is preferable to use an acidic aqueous mobile phase, and the application of a gradient elution to avoid the co-elution of compounds and to increase ionization efficiency and, thus, to improve HPLC resolution (Huang and Mazza 2011a).

Different mass analyzers can be applied, being the triple quadrupole (QqQ) the most frequently used because it allows ion fragmentation in a positive ion mode, by adding a proton to the ion source (Huang and Mazza 2011b). Nevertheless, and although possesses lower limited quantitation capabilities to detect the number of ions in only one spectrum since its dynamic range (10^4-10^5) is smaller when compared to QqQ analyzers (10^8), the TOF analyzer is also useful, particularly in situations of qualitative identification and *m/z* differentiation of similar ions (Huang and Mazza 2011b).

Regarding ionization, and although several techniques can be applied, electrospray ionization (ESI) is the most employed (Cao et al. 2006; Huang and Mazza 2011a). This method was used to detect melatonin (**3**) in tart (Kirakosyan et al. 2009) and sweet cherry fruits (Huang and Mazza 2011b), purple wheat (Hosseinian et al. 2008), jujubes, raspberries, wolfberries, and herbal remedies (Chen et al. 2003), as well as in barley (*Hordeum vulgare* L., Poaceae) and white lupine (*L. albus*) (Hernández-Ruiz and Arnao 2008b). The conditions used for analyses are described in Table S2.

HPLC-HRMS Analysis

High-performance liquid chromatography-high resolution mass spectrometry (HPLC-HRMS) is the latest and the most innovative detection technique. HMRS is 5 to 10 times faster than the conventional MS, allowing to switch positive-to-negative polarities while allowing the detection and quantification of acidic and basic compounds, as well as isobaric compounds (the same *m/z* but different elemental compositions) of complex matrices, in a unique run (Campmajó et al. 2019). Gomez et al. (2012) already resorted to this technique to detect the presence of melatonin (**3**) in grapes and wines (Table S2).

Chemiluminescence and Spectrophotometry Analysis

Furthermore, a chemiluminescence assay was proposed to identify melatonin in fruits and vegetables (Lu et al. 2002). Its principle is based on the ultra-weak chemiluminescence emitted after the reaction of melatonin (**3**), hydrogen peroxide (H_2O_2), and CH_3CN, under alkaline conditions. Although this assay is simple, convenient, and economical to do, it presents low sensitivity and requires the use of completely purified samples because the existence of other compounds leads to the formation of singlet oxygen species and undesirable cross-reactions that will originate dubious results. Therefore, these results need an additional confirmation by chromatographic techniques (Garcia-Parrilla et al. 2009).

Health Benefits

It is well-known that, nowadays, there exists a great deal of interest in the ability of plant-derived compounds to improve human health due to their capacity to scavenge free radical species. At very low concentrations, reactive species act as second messengers in some signal transduction pathways. However, when they are overproduced, they damage DNA, lipids, and proteins and exacerbates many pathological conditions, including cancer, neurological disorders, and cardiovascular illnesses (Favero et al. 2014; Özen and Ekşi 2016). Despite the fact that there are insufficient conclusive studies available from clinical trials, there is evidence that the intake and subsequent incorporation of serotonin (**2**) and melatonin (**3**) in daily diets have a positive impact on reducing free radicals, decreasing pro-inflammatory markers, and attenuating depressive moods and sleep disorders and control disorders, such as irritability and aggressiveness, and also offering improvements in neurological and immune systems (Fig. 2).

Antioxidant Properties

Since ancient times in Asian traditional medicine, Chinese medicinal herbs are prescribed to retard the effects of aging and combat oxidative stress–related disorders, due to their richness in serotonin and melatonin (Chen et al. 2003). Nowadays, we know that both are potent free radical scavengers, being serotonin (**2**) more active due to its phenolic group. Deprotonation of a phenol to form a corresponding negative phenolate ion is easily achieved by **2** (Gülçin 2008). On the other hand, like melatonin which is not regenerated, it does not promote oxidative reactions or the formation of other oxidized species (Feng et al. 2014). Recent studies reported that both molecules showed effectiveness in *N,N*-dimethyl-*p*-

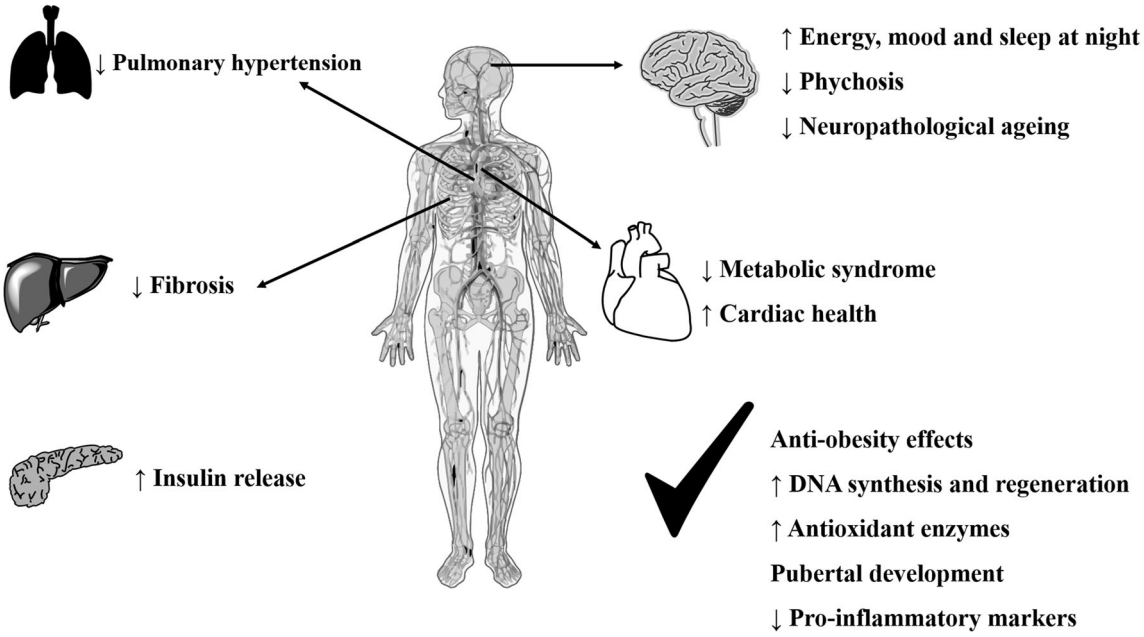


Fig. 2 A summary of main health benefits exhibited by serotonin and melatonin

phenylenediamine (DMPD) radical scavenging assay (73.5 and 127.4 μg/ml trolox equivalent for melatonin and serotonin at the concentration of 100 μg/ml), and in cupric ion ($Cu2^{+}$) reducing ability trial (14.41 and 116.09 μg/ml trolox equivalent for melatonin (**3**) and 100 μg/ml trolox equivalent for serotonin (**2**)) (Gülçin 2008).

Melatonin (**3**) also shows the capacity to inhibit lipid peroxidation and to quench superoxide and 1,1-diphenyl-2-picrylhydrazyl radicals and H_2O_2 species and chelate metals under *in vitro* conditions (Gülçin et al. 2002). Indeed, 50, 100, 250, and 500 μg of melatonin (**3**) showed the ability to inhibit in 41, 60, 86, and 97% the lipid peroxidation of linoleic acid, respectively, being more efficient than 500 μg of α-tocopherol that only inhibited in 34% the occurrence of this event (Gülçin et al. 2002). Gulcin et al. (2003) also demonstrated that 60 μg/ml of melatonin (**3**) was able to inhibit 95% of ferrous ions and to scavenge 83% of H_2O_2 species. On the other hand, α-tocopherol, β-hydroxy acid, and butylated hydroxytoluene at the same concentration exhibited lower rates of inhibition concerning the formation of the Fe^{2+}-ferrozine complex (58, 61, and 72%, respectively) and H_2O_2 species capture (48, 20, and 23%, respectively).

Melatonin (**3**) also acts as an antioxidant against peroxyl and hydroxyl ions, displaying to be more efficient than glutathione. In fact, 2 μM of melatonin had higher antioxidant activity against hydroxyl radicals than 8 μM of glutathione (Sofic et al. 2005). Additionally, serotonin (**2**) showed the ability to protect rat erythrocytes from senescence, increasing the antioxidant capacity of plasma and their lifespan, delaying hemolysis, and preventing lipid peroxidation at concentrations of 10 μM, 30 μM, and 100 μM (Amireault et al. 2013).

Regarding *in vivo* studies, Reiter et al. (2005) verified that the ingestion of walnuts with 3.5 ng/g of melatonin (**3**) by rats increased blood levels of this compound and, consequently, the antioxidant and ferric reduction capacities of blood. Additionally, Kitagawa et al. (2012) showed that the daily administration of melatonin in rats (10 mg/kg body weight), after 6 weeks of a diet containing 60% fructose that caused insulin resistance, improved this condition by attenuating the metabolic syndrome.

In male volunteers, it was also observed that the ingestion of melatonin (**3**) increases the plasma capacity for ferric reduction and oxygen radical elimination. Particularly, in a recent study with a 1-week washout period, each participant (n = 12) received a melatonin-rich juice from one kilogram of orange (400 ± 14 ml) or pineapple (500 ± 35 ml) and two whole bananas (190 ± 3 g), respectively. The obtained data revealed that the highest serum melatonin concentration was observed 120 min after banana consumption. In fact, this one increased from pineapple juice (146 *vs* 48 pg/ml, p = 0.002) to orange juice (151 *vs* 40 pg/ml, p = 0.005) and finally to banana fruit (140 *vs* 32 pg/ml, p = 0.008), respectively. It was observed too that the serum antioxidant capacity significantly increased concerning the ferric reducing ability of plasma (7–14% increase, $p \leq 0.004$) and the oxygen radical scavenging activity (6–9% increase, p = 0.002) after banana's consumption. These findings suggest that the consumption of fruits and their beverages rich in melatonin raise the serum melatonin concentrations and consequently the antioxidant capacity of the serum (Sae-Teaw et al. 2013).

Melatonin (**3**) also exerts antioxidant effects through synergistic actions with other antioxidants, such as ascorbic acid, vitamin E, and glutathione, enhancing the activity and gene

expression of glutathione peroxidase, glutathione reductase, and superoxide dismutase antioxidant enzymes (Kitagawa et al. 2012). This happens because melatonin can easily permeate all tissues and subcellular compartments due to its small size and amphipathic nature, and thereby provide antioxidant defenses where they are needed, with or without a receptor (*e.g.*, direct radical scavenging processes and hormonal actions, respectively) (Feng et al. 2014). It is very likely that both receptor-mediated and receptor-independent actions are cooperative (Burkhardt et al. 2001; Reiter et al. 2005; Favero et al. 2014; Feng et al. 2014;) and mediated by binding to G-protein-coupled melatonin membrane receptors (MT1, MT2, and MT3), diffuse in central nervous tissues and peripheral and steroidogenic tissues. Furthermore, melatonin directly reduces electrophilic radical species due to its electron-rich aromatic indole ring (Iriti and Faoro 2006; Favero et al. 2014; Aguilera et al. 2015).

Neuroprotection

There is growing evidence that serotonin (**2**) and melatonin (**3**) play important actions in the neurological system by inhibiting mitochondrial cell death pathways, increasing antioxidant defenses and activating survival signal pathways in stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Serotonergic axons are deteriorated in patients brains with neurodegenerative diseases; however, the administration of serotonin (**2**) showed to prevent the oxidation of 2-thio-5-nitrobenzoate by the chlorination of hypochlorous acid with the aryl and alkyl nitrogen atoms of serotonin, attenuating symptoms of these disorders, such as depression and anxiety (Gamelin et al. 2009; Kalogiannis et al. 2016). Another study by Muñoz-Castañeda et al. (2006) demonstrated that the exogenous administration of 5-hydroxytryptophan (300 mg/kg), a substrate that synthesizes serotonin (**2**) using tryptophan (**1**) as precursor in rat's brains, after the administration of *p*-chlorophenylalanine (a molecule that inhibits the synthesis of serotonin in the brain through the inhibition of tryptophan hydroxylase), increases serotonin brain levels in them. It was also found an increase in the contents of catalase, superoxide dismutase, and glutathione antioxidant enzymes.

Additionally, serotonin (**2**) may also be associated with cognitive processes, physical health, and mood. In general, low amounts of serotonin predispose healthy individuals to sadness and suboptimal physical and mental functioning, given the low synthesis of this indolamine in the right anterior cingulate cortex. High levels of serotonin are associated with happiness and better memory and learning capacities (Gamelin et al. 2009; Tang et al. 2019).

Sleep Promotion

Serotonin (**2**) and melatonin (**3**) are involved in the treatment of sleep disorders (Garrido et al. 2010). Pieces of evidence suggest that 1–1.5 ng/g of melatonin are sufficient to normalize blood melatonin levels in humans and to promote quiet nights (~200 pg/ml at the maximum night peak and below 10 pg/ml during the day) (González-Gómez et al. 2009; Vitalini et al. 2011). This fact was already evidenced in a work published by Lemoine et al. (2007). In this study, 35 middle-aged/elderly volunteers (with ages ranging from 55 to 75 years old) ate cereals enriched with tryptophan (**1**) for 3 weeks. In the first week, every participant ingested 22.5 mg tryptophan in 30 g of cereals per dose at breakfast and dinner. In the second week, volunteers consumed 30 g of tryptophan-enriched cereals (containing 60 mg of tryptophan) at breakfast and dinner. Finally, in the *post*-treatment week (third week), volunteers ingested their habitual diet, without cereals. Each participant wore a wrist actimeter that logged activity during the experiment. Urine was collected to examine melatonin and urinary metabolites of serotonin levels and to measure total antioxidant capacity. The consumption of cereals containing tryptophan increased sleep efficiency and period, immobile time, and decreased total nocturnal activity, sleep fragmentation index, and sleep latency. In addition, urinary 6-sulfatoxymelatonin and 5-hydroxyindoleacetic acid concentrations and urinary total antioxidant capacity increased, and there was also verified improvement in anxiety and depression symptoms (Bravo et al. 2013). Melatonin also showed to be able to raise restorative sleep in 29 male and 53 female patients aged 55 years and older when compared to the placebo (29 males and 59 females), without withdrawal symptoms upon discontinuation during 3 weeks of prolonged-release 2 mg of melatonin (Lemoine et al. 2007).

Recently, Tang et al. (2019) reported that the combination of venlafaxine (0.025 mg/l) with melatonin (1 μM) reduce depression behaviors in zebrafish by increasing exploration, exercise, and serotonin and norepinephrine levels, and by reducing irregular movements when compared to the control group (Tang et al. 2019). Indeed, the administration of exogenous melatonin appears to normalize physiologic and behavioral sleep patterns, delaying rhythms, and decrease nocturnal core body temperature, facilitating sleep (Sofic et al. 2005).

Anticarcinogenic Activity

In addition to melatonin (**3**) being a potent antioxidant, it also shows anticarcinogenic and antitumor effects by stimulating apoptosis and anti-growth signaling and by inhibiting proliferation, angiogenesis, immune evasion, and dysregulated metabolism and inflammation, as reported by Mills et al. (2005) who investigated 643 patients with cancer between 1992 and 2003. In their meta-analysis work, they

revealed that the administration of large doses of melatonin (10–40 mg/day) reduces the risk of death at 1 year by 34%, being effective in reducing the proliferation of lung cancer cell lines in 100 patients. Additionally, another study using melatonin revealed that the intake of 20 mg of this per day is capable to promote tumor regression in 30 patients with renal cancer (Lissoni et al. 2000). The same dosage mentioned above also increased the survival at 1 year in 30 patients with brain glioblastoma (Lissoni et al. 1996). Moreover, Cho et al. (2011) reported that 1 mM of melatonin can reduce sphingosine kinase 1 (SPHK 1) activity, hypoxia-inducible factor (HIF)-1α, Akt/glycogen synthase kinase-3β signaling pathway, and vascular endothelial growth factor (VEGF) production in PC-3 cancer cell lines under hypoxia (Cho et al. 2011).

Despite the administration of high doses of melatonin for cancer treatment being eight times higher than those used to treat insomnia and jet lag, there are no known side effects. It is only verified a tendency to produce sedation and sleepiness in some people. Therefore, melatonin is generally administered during the evening (Mills et al. 2005).

Immunoregulatory Properties

Serotonin (**2**) already proved to be able to decrease the interferon-gamma (IFN-γ)/IL-10 ratio. This fact was demonstrated by Kubera et al. (2005). In their study, blood samples were collected from twenty-six subjects (19 healthy volunteers, divided into two subgroups according to age (< 45 years *vs* ≥ 45 years), and seven depressed patients, and supplemented with serotonin (150 ng/ml, 1.5 μg/ml, and 15 μg/ml), *p*-chlorophenylalanine (PCPA; a serotonin depleting agent, 5 μM), flesinoxan (a serotonin agonist, 15 ng/ml and 1.5 μg/ml), *m*-chlorophenylpiperazine (mCPP; a 5-HT2A/2C agonist, 27 ng/ml, and 2.7 μg/ml), and ritanserin (a serotonin antagonist, 5 μg/ml and 5 μg/ml). The obtained data revealed that 150 ng/ml, 1.5 μg/ml, and 15 μg/ml concentrations of serotonin significantly decreased the IFN-γ/IL-10 ratio. On the other hand, 5 μM of PCPA suppressed the production of IFN-γ and IL-10. Flesinoxan at concentrations of 15 ng/ml and 1.5 μg/ml had no significant effects on the production of the above cytokines, while 5 μg/ml of ritanserin and 2.7 μg/ml of mCPP suppressed the IFN-γ/IL-10 ratio (Kubera et al. 2005).

Relatively to melatonin, this one is capable to reduce fibrosis, inflammation, and liver tissue injury in rats with cirrhosis at a concentration of 20 mg/kg, after 15 days of treatment. These effects are due to the capacity of melatonin to reduce the hepatosomatic and splenosomatic indices and to restore antioxidant enzyme concentrations, including nitric oxide radicals and tumor necrosis factor-alpha (TNF-α) levels (Colares et al. 2016).

Melatonin also offered protection in Wistar rats with ulcerative colitis induced by acetic acid. Initially, rats ($n = 32$) were divided into 4 groups. Acetic acid–induced colitis was performed in two of the groups, while the other two groups were intrarectally injected with saline solution. After that, one of the acetic acid–induced colitis groups and one of the control groups were treated, through intraperitoneal injection, with 100 mg/kg per day of melatonin. The other pair of groups again received the saline solution. After 4 days of treatment, the animals were sacrificed by cervical decapitation and their tissues were submitted to histopathological examination. It was observed that melatonin administration decreased TNF-α, interleukin (IL)-1β and IL-6, myeloperoxidase, and malondialdehyde levels and increased glutathione and superoxide dismutase levels (Tahan et al. 2011).

Anti-obesity and Anti-aging Effects

Additionally, serotonin (**2**) also showed to be able to control obesity (Cangiano et al. 1992). Previous observations have shown that oral administration of serotonin without dietary prescriptions causes anorexia, decreased food intake, and weight loss in obese subjects. To confirm these data and to verify whether adherence to dietary restriction can be improved by serotonin, 20 obese patients were randomly assigned to receive either 900 mg per day of serotonin or placebo. The study was double-blinded and lasted 12 weeks. No diet was prescribed during the first period, while during the second period, a diet of 5040 kJ per day was recommended. Significant weight loss and a reduction in carbohydrate intake were observed in serotonin-treated patients during both periods. A consistent presence of early satiety was also found. These findings suggest that serotonin may be safely used to treat obesity (Cangiano et al. 1992).

Furthermore, melatonin (**3**) exhibits anti-aging properties. In fact, in a designed experiment (50 animals per group), rats that were fed with melatonin during night time (2.5–3 mg/kg) presented a delay in age-related disorders, as well as an increased survival (Anisimov et al. 2006). Melatonin has also proven to be a protective agent against aging skin (Kleszczynski and Fischer 2012). In fact, HaCaT keratinocytes pre-incubated with amounts between 10^{-6} and 10^{-3} M of melatonin 30 min before ultraviolet (UV) irradiation at doses of 25 and 50 mJ/cm^2 revealed higher levels of cell survival when compared to cells that were not pre-incubated with this hormone (Fischer et al. 2006). Also, the application of 0.6 mg/cm^2 of melatonin dissolved in a nanocolloid gel carrier 15 min before UV exposure, in 20 healthy volunteers, showed to be efficient in suppressing UV erythema (Bangha et al. 1997).

Future Perspectives

Serotonin and melatonin are present in various Mediterranean foods, medicinal herbs, and fruits, such as apple, banana, pineapple, and strawberry. Additionally, it is possible to state that,

for melatonin and serotonin extraction, it is recommended short periods of agitation, sonication, and heating, using methanol as solvent. For sample purification, the use of SPE columns is the most preferred given its selectivity. Regarding the analytical methodologies to detect and quantify both indolamines, HPLC-MS and HPLC-HMRS are the better ones; however, due to their cost, HPLC-ECD and HPLC-UV/Vis are good alternatives. In addition, it is recommended the use of acidified mobile phases and gradient elution to improve peak separation. The use of immunological methods, namely RIA and ELISA, should be avoided because their results are overestimated due to the occurrence of cross-reactions between targeted and untargeted metabolites with the enzymes. Additionally, more in-depth studies are needed for a better understanding of the role of melatonin and serotonin in plants. Also, the creation of a standardized set of methodologies in order to provide additional homogeneous results and to promote more accurate and rapid comparisons between different studies is needed. It is also imperative to discover new pharmacological approaches, to clarify the bioavailability of both indolamines in humans, and to unravel the dose needed to promote more substantial health benefits before they can be used extensively in clinical area.

Conclusion

Smoking, ingesting alcohol, consuming too much coffee, and intaking some pharmaceutical drugs may interfere with the production of serotonin and melatonin, originating sleeping disorders, lower mood, depression, and aggressiveness. Consequently, melatonin and serotonin ingestion can attenuate or even prevent depressive states, cancer, type 2 diabetes, neurological ailments, and cardiovascular pathologies. These benefits are mainly due to their antioxidant effects and capacity to cross all morphological barriers, reducing not only reactive species but also proinflammatory markers. However, more depth studies are needed for the discovery of new pharmacological approaches, and to unravel the dose needed to promote more substantial benefits to human health.

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Author Contribution ACG researched prior studies, interpreted the results, and drafted the manuscript. ARN, GA, and LR contributed to the critical reading of the manuscript and performed the final revision of the same. All the authors have read the final manuscript and approved the submission.

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Declarations

Conflict of Interest The authors declare no competing interests.

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