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## REVIEW ARTICLE

## Melatonin in traditional Mediterranean diets

**Abstract:** Compared with other industrialized countries, the lower incidence of chronic-degenerative disorders in Mediterranean populations has been emphasized in recent decades. The health-promoting effects arising from Mediterranean dietary habits have been attributed to the large intake of plant foodstuffs rich in bioactive phytochemicals, such as melatonin.

Recently, it has been suggested that melatonin present in edible plants may improve human health, by virtue of its biological activities and its good bioavailability. Plant melatonin, besides contributing to optimize the physiological functions regulated, in humans, by endogenous melatonin, may be involved in nutritional therapy to reduce the risk of cancer, cardiovascular and neurodegenerative diseases in western populations. In this view, the presence of melatonin in some Mediterranean foods and beverages adds a new element to the hypothesis of health benefits associated to Mediterranean dietary patterns, although the available data are still preliminary and incomplete.

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**Key words:** beer, grape, Mediterranean diet, melatonin, olive oil, tomato, wine

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## Introduction

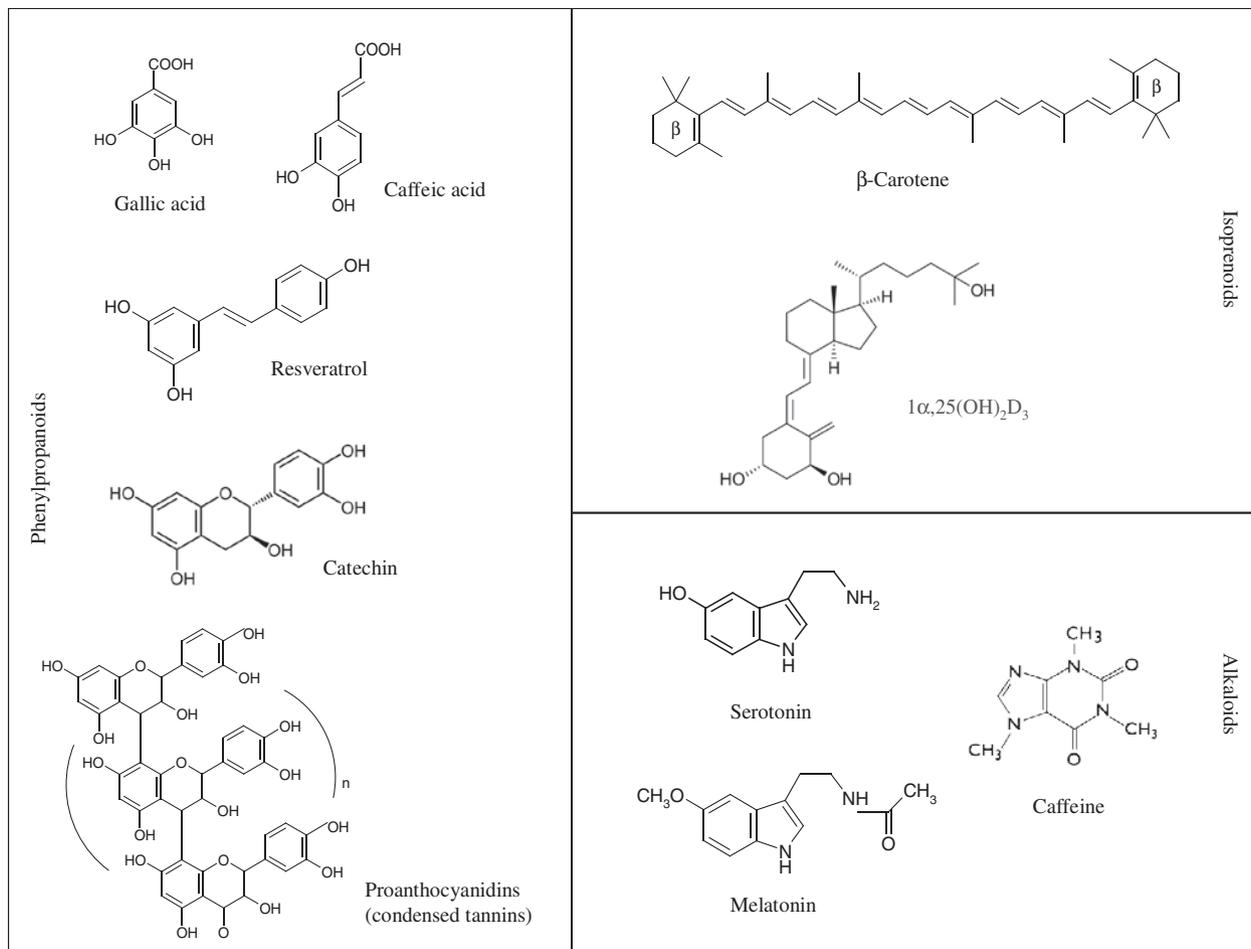
In the Mediterranean basin, different traditional dietary patterns have developed in each geographical subarea (southern Italy and France, Spain, Greece, Turkey, northern Africa and Middle East), and, hence, a unique Mediterranean diet does not exist. Traditionally, these dietary habits originated in areas where olive (*Olea europaea* L.) and grapevines (*Vitis vinifera* L.) were cultivated, where olive oil and wine are produced and regularly consumed [1]. Besides these foodstuffs, other main components of Mediterranean diets include whole grains, fruits, vegetables, legumes, nuts; yogurt and ricotta as dairy products; fish and white meat as a protein source [2]. Additionally, dietary styles proper to Mediterranean countries are somehow similar to the alimentary habits that determined the nutritional evolution of the genus *Homo* after the advent of agriculture, about 10,000 years ago. In this view, since the Neolithic period, phytochemicals entered the diet, and *Homo* experienced the health benefits arising from plant food consumption [3, 4]. Currently, Mediterranean diets, rich in fruits and vegetables, are correlated with a low incidence of the chronic-degenerative disorders common in western populations, and compelling evidence points out the reduced risk of cancer, cardiovascular and neurodegenerative diseases in Mediterranean populations compared with other industrialized countries [5–7].

## Phytochemistry of Mediterranean diets

From a phytochemical point of view, Mediterranean diets are based on an array of plant secondary metabolites: phenylpropanoids (or phenolic compounds), isoprenoids and alkaloids [8, 9]. Phenylpropanoids comprise mainly hydroxybenzoates, hydroxycinnamates and polyphenols, the latter in turn including flavonoids (with anthocyanins), stilbenes (resveratrol) and proanthocyanidins (or condensed tannins); among isoprenoids, carotenoids (tetraterpenes, C<sub>40</sub>) and vitamin D (triterpenes, C<sub>30</sub>) represent important molecules, whereas alkaloids comprise a series of very diversified metabolites, from purinic alkaloids, i.e., caffeine, theobromine and theophylline in coffee, cacao and tea, respectively, to indolic compounds, such as indolamines (serotonin and melatonin) (Fig. 1) [10–13].

## Melatonin in animals and plants

In vertebrates, the essential amino acid L-tryptophan is the precursor of 5-methoxyindoles, or indolamines/tryptamines, including melatonin (N-acetyl-5-methoxytryptamine), through the intermediate serotonin (5-HT, 5-hydroxytryptamine) and the activity of hydroxyindole-O-methyltransferase (HIOMT) [14]. In mammals, melatonin is synthesized in the pineal gland, predominantly during the night-time, although it can be also produced in other



**Fig. 1.** Main bioactive phytochemicals of Mediterranean diets. Phenylpropanoids consist of hydroxybenzoates (gallic acid), hydroxycinnamates (caffeic acid), stilbenes (resveratrol), flavonoids (catechin) and proanthocyanidins (or condensed tannins); stilbenes, flavonoids and proanthocyanidins are in turn grouped in polyphenols. Among isoprenoids, triterpenes (1 $\alpha$ ,25-dihydroxy-vitamin D<sub>3</sub> or calcitriol) and tetraterpenes ( $\beta$ -carotene) include important vitamins, whereas alkaloids comprise indolamines (serotonin and melatonin) and methylxanthines (caffeine).

organs, such as retina, gastrointestinal tract, lymphocytes and bone marrow cells. Conversely, light at night has an inhibitory effect on pineal melatonin biosynthesis which is initiated by the uptake of tryptophan from the circulation into pinealocytes [15]. Once synthesized, melatonin is not stored in the pineal cells, but it is released into the bloodstream with a circadian rhythm, from which it reaches other body fluids, including urine, saliva, cerebrospinal fluid, bile, semen and amniotic fluid [16, 17]. The circadian rhythm of melatonin secretion is generated by the biological clock, situated in the suprachiasmatic nucleus of the hypothalamus, via a neuronal pathway that begins in the retina and involves the retinohypothalamic tract [18]. In mammals, melatonin acts in part via membrane receptors MT<sub>1</sub> and MT<sub>2</sub> [19]. Physiological processes regulated by melatonin presumably via a receptor-mediated mechanism include the control of the sleep/wake cycle, modulation of reproductive function and bone metabolism [20]. Apart from these receptor-mediated processes, melatonin and its metabolites exert a series of receptor-independent functions, mainly because of their powerful antioxidant activity

[21–23]. Melatonin can directly scavenge free radical species (both ROS, reactive oxygen species and RNS, reactive nitrogen species) and stimulating the activity of antioxidant enzymes [24].

Although, at present, no orthologues of the gene encoding the enzyme HIOMT has been discovered in plants, the latter reportedly also synthesize melatonin [25]. It is possible that, in plants, other aspecific methyltransferases catalyse the 5-methoxylation of serotonin in the biosynthetic pathway of melatonin. Outside the Animal Kingdom, melatonin was discovered, for the first time, in the dinoflagellate alga *Lingulodinium polyedrum* (Stein) J. D. Dodge 'sin. *Gonyaulax polyedra* Stein' [26]. Since then, it was detected in higher plants, including food plants and medicinal herbs, where the physiological and pathophysiological function of melatonin is still unclear. Because of its structural similarity with the plant growth hormones of the auxin family, a hormone-like role has been putatively attributed to melatonin in some plant species, as well as an action in delaying flowering, preventing chlorophyll degradation, protecting against

Table 1. Melatonin content in Mediterranean commodities assessed by both immunological and chromatographic techniques

Foodstuffs	Melatonin content	References
Grape berries (skin)	5–96 pg/g	[20]
Spanish wines	50–80 pg/mL	[22]
Italian wines	0.4–0.5 ng/mL	[21]
Beer	52–170 pg/mL	[34]
Extra virgin olive oil (D. O.)	71–119 pg/mL	[25]
Tomato berries (pericarp, mature red stage)	2.8 ng/g	[32]
Tomato berries (loculi, mature red stage)	3.4 ng/g	[32]
Tomato berries (seeds, mature red stage)	66.5 ng/g	[32]

oxidative damage, abiotic stresses, pathogens and environmental pollution [25, 27, 28].

### Melatonin in the main components of Mediterranean diets

Among plant foods where melatonin has been identified, there are important Mediterranean products, namely grape, wine, olive oil, tomato and beer. In different Italian and French grape cultivars employed in wine-making (Nebbiolo, Sangiovese, Barbera, Marzemino, Croatina, Merlot, Cabernet Sauvignon and Cabernet Franc), melatonin content of berry skin tissues ranged from 5 to 96 pg/g (Table 1). Interestingly, open field treatment with benzo-thiadiazole, a functional analogue of the plant hormone salicylic acid which is able to activate the plant's own defence mechanisms against pathogens, elicited a twofold rise of melatonin content in Merlot cultivar [29]. As expected, soon after, melatonin was reported in Italian and Spanish wines, ranging around 0.4–0.5 ng/mL [30] and 50–80 pg/mL, respectively (Guerrero, personal communications) (Table 1). Interestingly, red wines showed a higher melatonin content than white wines or distillate beverages, such as whisky, gin, vodka and rum (Guerrero, personal communications). In any case, besides cultivar, environmental factors, agricultural practices, vintage and wine-making procedures may influence the melatonin levels in wine [31]. Similarly, differences may arise from the analytical techniques (immunological versus chromatographic) employed for melatonin analysis in food matrices [32, 33]. After its detection in grape products, melatonin has been also identified in olive oil [34] and in purslane, a commonly used salad ingredient in the Mediterranean region [35]. In particular, the melatonin content of extra virgin olive oil registered designations of origin (D. O.) was almost twofold higher than the levels measured in the other refined oils analysed, ranging from 71 to 119 pg/mL (Table 1) [34].

Tomato (*Solanum lycopersicum* L., syn. *Lycopersicon esculentum* Mill.) is one of the first edible plants where melatonin has been identified [36], and in tomatoes the melatonin concentration varies with the developmental stage [37]. Although it is not a Mediterranean crop *sensu stricto*, tomato products represent main components of the Mediterranean dietary style. Tomato plant is native to the highlands of the west coast of South America, where it was

used by the Pre-Columbian cultures as early as 500 BC. By the end of 15th century, when the Spanish *conquistadores* reached the Yucatan area, tomato was an important crop among Aztecs and, at the beginning of 16th century, the explorer Cortés exported tomatoes to Europe. By 1540, the first cultivations were reported in the Mediterranean area, where the climate was optimal for growing [38–40]. Melatonin was detected in all tomato organs at different developmental stages [37, 41, 42]. In young leaf tissues, melatonin reached a maximum of 6 ng/g FW, whereas, in berries, its content increased gradually from the mature green stage, both in pericarp and locular tissues, up to 2.8 and 3.4 ng/g FW, respectively, at mature red stage (Table 1) [37]. A great variability in melatonin content of tomato berries has been also reported, with authors reporting 0.032, 0.5 and 0.3 ng/g [36, 43, 44]. Interestingly, seeds contained the highest amount of melatonin, 66.6 ng/g FW, as previously reported in seeds of other species, where it is probably involved in protection of susceptible germ tissues from oxidative stress (Table 1) [28, 37].

Recently, melatonin has been reported in different commercial beers [45]. Although the consumption of beer is common all over the world, it can be considered a traditional Mediterranean beverage, produced in ancient Egypt since the Dynastic Age, as described by Diodorus Siculus in his *Bibliotheca Historica* (20,4; 34,10) [46]. In all the beers analysed, melatonin was measured at concentration ranging from 51.8 to 169.7 pg/mL, and the more melatonin they contained, the higher their alcoholic degree, probably because of the solubility of melatonin in alcohol (Table 1) [45]. A possible source of melatonin in beer may be barley, where this molecule has been identified, although *Saccharomyces cerevisiae* Meyen is able to produce melatonin in presence of tryptophan [47, 48].

### Melatonin bioavailability

In a pioneering study, the bioavailability of melatonin from edible plants has been demonstrated, as well as the competitive binding of melatonin to melatonin receptors, in mammalian brain. In particular, feeding chicks with plant products rich in melatonin increased their serum melatonin levels, and, in rabbit brain, melatonin extracted from plants inhibited the binding of labelled melatonin to cell membrane receptors [43]. Because of its amphipathic properties, melatonin is able to cross the physiological barriers, such as the blood brain barrier, reaching target sites where it exerts its biological activities [49–51]. Furthermore, melatonin has been found in all cell compartments: membranes, cytoplasm, mitochondria and nucleus [52]. As regards Mediterranean food products, it was shown that, in humans, serum melatonin concentration increased significantly 1 hr after a single 100 mL red wine administration, from 10 to 12 pg/mL (Guerrero, personal communications). Likewise, both melatonin levels and total antioxidant status of serum samples from healthy volunteers raised 45 min after drinking beer [45]. In rats fed with 3 g of walnuts (*Juglans regia* L.), containing about 10.5 ng of melatonin, the serum concentration of the indole rose from 11.5 to 38.0 pg/mL, as well as the serum antioxidant capacity, measured with ferric reducing

antioxidant power, increased significantly [53]. In urine, excretion of 6-sulfatoxymelatonin has been reported as a biomarker of vegetable intake, inversely related to breast cancer risk [54].

## Conclusions

Although not abundant, the collective results suggest that melatonin present in plant foods may promote health benefits by virtue of its biological activities, and it may counteract pathological conditions related to carcinogenesis, diabetes, cardiovascular diseases, neurological disorders and ageing. Finally, it is noteworthy that the health-promoting effects ascribed to a dietary style are due to the assortment of foods and beverages constituting that diet, consumed with regularity and, in some cases, with moderation. Similarly, the health benefits attributed to a (plant) food or beverage do not depend on a single compound present in it (phenolic, carotenoid or other), but combination of phytochemicals has shown to enhance their bioactivities, by additive and synergistic effects.

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