Commentary

Current state of the natural melatonin: The phytomelatonin market

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ABSTRACT

Melatonin is a dietary supplement substance widely distributed in the global market and its therapeutic use has been significantly expanded from its original use to target the jet-lag. In this report, we have discussed the current situation of the natural melatonin market, an "*alternative melatonin"* to chemically synthesized melatonin, with exclusive characteristics and possibilities, to focus on a more selective, eco-friendly market that orients its consumption to natural and healthy products. The different possibilities obtained melatonin from genetically modified organisms to phytomelatonin which are extracted from algae/microalgae or medicinal plants are discussed.

Keywords: Melatonin, phytomelatonin, nutraceuticals, phytogenics, dietary supplement, Jet-lag, medicinal plants

1. THE GLOBAL MELATONIN MARKET

The melatonin is globally marketed with USA, Canada, Japan, South Korea, Australia, New Zealand and Europe as the major consumers. In some countries it is classified as a dietary or food supplement substance, which greatly favors its marketing. In Europe and Asia-Pacific, melatonin is not allowed to be marketed freely, and it is strictly regulated to the dosage limit (around 2 mg dose). In North America, there are no limitations in terms of dosage of melatonin products, and preparations of up to 10 mg/capsule or more can be found (1). Melatonin sales in the USA increased more than 1300% from 2003 to 2018 (from $62 million to $821 million). The number of people taking melatonin increased 5-fold in this country between 2000 and 2017. The consumption of synthetic melatonin in the world was about 4,000 tons in 2019, which was calculated to be worth approximately $1.3 billion, growing between 2013 and 2019 by 15%, and having an estimated yearly additional increase of $98.5 million until 2023. The global melatonin market is expected to witness significant growth, exceeding $217.9 million additional increase per year by 2033. This growth can be attributed to the growing popularity of dietary supplements (2, 3). There are estimates of growth in the production of synthetic melatonin due to its possible implementation in new food and beverage lines as nutraceuticals, which is being considered by the USA Food & Drug Administration (FDA). This production of synthetic melatonin is controlled by a half-dozen of countries.

Currently, almost all amounts of melatonin used for medical or industrial applications are generated by chemical synthesis (4). One of the serious shortcomings of the chemically synthesized products is the potentially presented unwanted by-products generated during the chemical reactions. Precursor molecules or intermediates for melatonin synthesis are usually by-products that are unintentionally present in the final preparation of melatonin.

In organisms, melatonin is synthesized from tryptophan (5–7) In animals and humans, the tryptophan is derived from the diet and during the process of melatonin synthesis, it is first converted to the intermediate 5-hydroxytryptophan; leading to the formation of serotonin which subsequently enables the biosynthesis of melatonin. In plants, melatonin (phytomelatonin) is also synthesized from tryptophan, which comes from the chorismic acid, a precursor to aromatic amino acids, that is transformed through the anthranilate/indole pathway to tryptophan. In the case of plants, tryptophan is mostly transformed into tryptamine which, after being hydroxylated, gives rise to serotonin, which either generates melatonin through *N*-acetylserotonin or 5-methoxytryptamine. Some differences in the pathway and enzymes involved can be found between animals, plants, fungi and bacteria (8–12).

2. STRATEGIES FOR BIOLOGICAL MACRO-PRODUCTION OF MELATONIN

With the aim of obtaining natural melatonin from a biological source, avoiding the unwanted byproducts generated during the chemical synthesis, many efforts have been made to "biologically produce" relevant amounts of melatonin from microorganisms and also from plants or microalgae. Obtaining natural melatonin should be an alternative and healthy goal with exclusive market possibilities (13–15).

2.1. Obtaining melatonin from microorganisms.

In 2016, the Danish Novo Nordisk Co., using genetically modified organisms (GMO) with different genes from *Rattus norvegicus, Lactobacillus ruminis, Pseudomonas aeruginosa, Homo sapiens, Schistosoma mansoni, Bos Taurus,* and *Salmonella enterica*, constructed a recombinant melatonin synthetic pathway in a strain of *Saccharomyces cerevisiae* containing heterologous genes encoding several melatonin biosynthesis enzymes and co-factors supporting pathway (16). Table 1 shows some of the characteristics and yield of this strategy (Table 1, #1). More recently, a new focus on *in vitro* melatonin biosynthesis has been proposed. A polyamine acetyltransferase (PAA1), a homolog of the human arylalkylamine *N*-acetyltransferase (AANAT) of *S. cerevisiae* was cloned and overexpressed in *E. coli*, showing a specific activity lower, with a broader of substrates preference and lesser substrate specificity than the reference mammalian AANT, obtaining negligible amounts of melatonin (17, 18).

Also Novo Nordisk Co. assaying a new system for producing biological melatonin from recombinant cultures of GMO *Escherichia coli* strain, with a TDC gene from *Candidatus Koribacter versatilis*, a SNAT gene from *Streptomyces griseofuscus*, and a human ASMT gene, and several tryptophan-transporter genes, relevant amounts of melatonin were generated suppling cultured cells with mineral salts, vitamins and antibiotics, in addition to glucose as the sole carbon contribution (19). In this case, the cultured cells generated up to 1 g/L of melatonin, doubling when the culture was supplied with exogenous tryptophan (Table 1, #2).

The Quantum Nutrition Lab Company (TX, USA) markets a product rich in melatonin from the culture of lactic acid bacteria, mainly from *Lactobacillus spp., Bifidobacterium spp.,*

Enterococcus sp. and *Streptococcus thermophilus.* The product (Table 1, #3) contains around 8 mg of melatonin (20).

Symphony Natural Health Co. (Australia) produces a widely marketed product, Herbatonin®, it appears as the first plant-based melatonin (Table 1, #4). In its formulation, according to the data released by the company, three components are cited: (100:1 extracts of *Oryza sativa, Medicago sativa* and *Chlorella pyrenoidosa*). The two plants used (rice and alfalfa) and the green algae contained very low melatonin levels in its natural form (around ng/g DW), so it is staggering to get pills of up to 3 mg of melatonin. It seems that melatonin was obtained by culturing *Chlorella* cells, and possibly feeding with precursors such as tryptophan, in a similar way as in *Achillea millefolium* (21), although there are no published data on the method. Also, in cultured green algae products, the possible presence of cyanotoxins due to cyanobacteria contamination (blue-green algae) would be controlled.

Table 1. Biologically synthesized melatonin and phytomelatonin from microorganisms and plants with their brands or producers.

#	Brand/Producers	Biological origin	Concentration	Ref.
1	Novo Nordisk Co.	*S. cerevisiae* (GMO)	14.5 mg/L	(16)
2	"	*E. coli* (GMO)	1-2 g/L	(19)
3	Melatonin Cultured Quantum Nutrition Lab	*Lactobacillus* & others	0.015%	(20)
4	Herbatonin Symphony Natural Health Co.	*Chlorella* Rice Alfalfa	1%	(30)
5	Sleep Support Tru2U Co. New Zeland	Tart cherries	0.003%	(31)
6, 7	Somnatural/Nutraland USA	St. John's Wort	?	(32)
8, 9	Phyto-Melatonin Peak Health Co. USA	St. John's Wort & feverfew	51 µg/pill	(33, 34)
10	"	Tomatoes	54 mg/g	-
11	Phytomelatonin-UMU[1]	Valerian root	0.1-0.2%	(27)
12	Phytomelatonin-UMU-*Bioriex*[1]	MAPs	0.8-1%	(29)

[1]*UMU: University of Murcia, Spain.*

2.2. Obtaining phytomelatonin from plants.

Phytomelatonin, from plants or algae, is found at very low endogenous levels (pg or ng/g of plant) (22–24). Therefore, obtaining extracts rich in phytomelatonin will require starting materials (raw material) with medium-high levels to be commercially interesting.

Tart cherry skin extracts was possibly the first phytomelatonin commercialized product in New Zealand) (Table 1, #5). This product, although with very low phytomelatonin content, gained great popularity as an improvement of sleep quality and antioxidant status (25, 26).

In 2022, phytomelatonin obtained from St. John's wort (*Hypericum perforatum*) was commercialized by Nutraland Co. (Table 1, #6). The presence of naphthodianthrones (hypericin, and others), and their possible actions as anti-depressant agents must be considered. Other

companies (Purity Products, USA) have marketed similar St. John's wort-based products with non-credible doses of 3 and 10 mg of phytomelatonin by a pill (Table 1, #7).

Feverfew (*Tanacetum vulgare*) and St. John's wort (*Hypericum perforatum*) extracts are able to obtain pills containing 5 mg phytomelatonin. According to the producer, phytomelatonin is pure, at 100% (2 mg feverfew + 3 mg St. John's wort) (Table 1, #8). In other similar products, 1.02 mg of St. John's wort extract contained 1 mg of phytomelatonin (purity at 98.5%) (Table 1, #9), really extra-terrestrial plants.

The same company as in St. John's wort products, Nutraland, has also marketed Somato®, a condensed extract from tomatoes with considerable amounts of phytomelatonin (Table 1, #10). This product is surprising considering the very low concentration of phytomelatonin in tomatoes (~ng/g FW) and the lability of the molecule in extractive processes since it does not withstand high heat treatments. Normally, phytomelatonin-concentrated extracts around 0.7-1% are usual, but not 5.4% as is the case here. Curiously, this product presents highest phytomelatonin contents than lycopene.

Valerian roots *(Valeriana officinalis)* and valerian commercial product studies demonstrated the possible contribution of phytomelatonin as sedative and sleep improvement agent (27). Phytomelatonin-rich extracts from valerian roots can be obtained, but the high variability in the phytomelatonin content of raw sources will be an obstacle (Table 1, #11).

From an exclusive selection of medicinal-aromatic plants (MAPs), it led us to obtain phytomelatonin-rich extracts. However, through a natural elicitation process, MAPs can express and accumulate commercially interesting phytomelatonin contents up to 80-100 mg/kg DW (up to 100 times more phytomelatonin than the control plants), obtaining filtered extracts at the modest concentrated value of 0.8-1% (Table 1, #12) (28). So, the MAPs and their extracts (*Bioriex* product/UMU) have been characterized, containing natural antioxidants such as simple phenols, flavonoids, and carotenoids. Also, the *in vivo* melatonin-activity in specific bioassay that determines the ability of phytomelatonin-rich extracts to aggregate melanophores in fish were positively verified (29).

Another possibility for the industrial bio-production of phytomelatonin would be its biosynthesis from *in vitro* plant cells culture. This field is very little researched, with scarce data on the role of melatonin in plant cells growing *in vitro*. In this regard, a recent review can be consulted (35).

In conclusion, the possibilities of marketing products with natural melatonin are booming. So far, products obtained from GMOs do not seem to be commercialized, mainly due to the legal and social restrictions on the consumption of this type of product obtained by modified organisms. Until now, the most exploited route has been to obtain phytomelatonin, either produced by algae/microalgae, or from plant extracts. Phytomelatonin from plants, despite many doubts about the source of raw material, seems to be the most exploited option. Guaranteeing quality, natural product from organic and eco-friendly crops seems like the next challenge. Finally, we cannot fail to point out that this "alternative green melatonin" can in no case be similar in price to the abundant, cheap and globalized synthetic melatonin.

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More information in: *https://www.um.es/en/web/phytohormones/* accessed on 08/july, 2024 (Phytohormones and Plant Development Lab) and in *https://www.pbs-phytomel.com/* accessed on 20/October/2024.

AUTHORSHIP

All authors contributed equally to the writing of this paper.

CONFLICT OF INTEREST

Authors declare intellectual property on the *Bioriex* product manufactured by the University of Murcia and PBS-Phytomel Co, Spain.

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