BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902025e24287

Article

Composition of food supplements containing melatonin available in Portugal

Beatriz Vieira Araújo[1], Fátima Rato[2], João Paulo Capela[3]

[1,3]FP-I3ID, Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal, [2]Centro de Informação Antivenenos (CIAV), Portugal, [3]UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal, [3]Associate Laboratory i4HB - Institute for Health and Bioeconomy, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

Melatonin straddles the boundary between food supplements and medicine. In Portugal, its classification is contingent upon a critical dosage threshold of 2 mg. This study aimed to detail the composition of melatonin-containing food supplements, available in Portugal based on their labels, and report the number of potential intoxications. Data was collected from 44 food supplements, and the difference in active ingredients was revealed towards the 16 approved medicines. Data on melatonin intoxication cases from 2018 to 2022 were obtained from the Portuguese Poisons Information Center (CIAV). Melatonin supplements, available in tablets, capsules, gummies, powders, or sprays, exhibited a recommended daily dose ranging from 1 to 1.95 mg. Only 20% contained melatonin alone, while the majority included plant extracts and vitamins. The absence of clinical studies supporting the efficacy of melatonin combined with plant extracts in these formulations raises concerns about their evidence-based effectiveness. Medicines contain 2 to 3 mg of melatonin per tablet, either immediate or modified release. Melatonin intoxication occurs mainly in children, with a higher prevalence between the first year of life and the age of four. Food supplements containing melatonin and plant extracts should be more carefully studied, including the potential adverse effects.

Keywords: Melatonin. N-acetyl-5-methoxytryptamine. Dietary supplement. Medicine. Intoxication.

Abbreviations list

5-HTP	5-Hydroxytryptophan
CIAV	Poisons Information Center (from the Portuguese "Centro de Informação Antivenenos")
DDD	Defined Daily Dose
GABA	Gamma-Aminobutyric Acid
INFARMED	National Authority of Medicines and Health Products (from the Portuguese "Autoridade Nacional do Medicamento e Produtos de Saúde, I.P")

INTRODUCTION

Melatonin, N-acetyl-5-methoxytryptamine, is a widely recognized molecule and is commonly referred to as the "sleep hormone". Chemically, it is an indolic compound, being a ubiquitous substance in nature an amphiphilic antioxidant with lipophilic properties, which allows it to enter cells, compartments, or body fluids (Minich *et al.*, 2022; Samanta, 2022). Melatonin is known in vertebrates for its role in regulating circadian rhythms, particularly the sleep cycle in humans (Megha *et al.*, 2024; Wurtman, 2020). Currently, it is recognized as a

***Correspondence:** J. P. Capela Faculdade de Ciências da Saúde, Universidade Fernando Pessoa, Rua Carlos da Maia 296, 4200-150 Porto, Portugal E-mail: joaoc@ufp.edu.pt ORCID https://orcid.org/0000-0003-2607-1264

multifaceted molecule possessing an array of functions covering areas such as immune regulation, antioxidant, anti-inflammatory effects, anti-aging action, potential anti-cancer properties, as well as possible neuroprotective effects, among others (Gunata, Parlakpinar, Acet, 2020; Martin Gimenez *et al.*, 2022; Minich *et al.*, 2022; Rivara *et al.*, 2015). Studies have shown that through its interaction with monoaminergic neurotransmitters, melatonin secretion and/or serum levels vary seasonally and chronologically, with a reduction in the hormone's production being observed, particularly in childhood and advanced age, which is often associated with pathological conditions (Martin Gimenez *et al.*, 2022; Ophoff *et al.*, 2018). This decrease in production or reduced expression of melatonin receptors often emphasizes the need for dietary supplementation with the hormone, or its clinical use to restore appropriate physiological levels and optimize its physiological functions (Erland, Saxena, 2017).

Melatonin's pharmacological effects are remarkable, particularly in the treatment of sleep disorders in humans, which has been widely documented. There is evidence to prove that the administration of exogenous melatonin anticipates the onset of sleep without altering its architecture, making it the first-line indication. The molecule exerts its action by inhibiting the chemical signals coming from the pathway that connects the retina to the pineal gland, thus stimulating the melatonin receptors (Megha *et al.*, 2024; Meng *et al.*, 2017; Rivara *et al.*, 2015; Samanta, 2022). This process is triggered by the absence of light, predominantly at night, reaching its peak plasma concentration between 03:00 and 04:00 in the morning (Gunata, Parlakpinar, Acet, *et al.*, 2020). In general, its effect on sleep is believed to be a consequence of mechanisms that include an increase in sleep propensity, increasing the amplitude of circadian clock oscillations via MT_1 receptors, while at the same time synchronizing the circadian clock via MT_2 receptors (Kostoglou-Athanassiou, 2013; Wurtman, 2020). Although most of melatonin's actions are receptor-mediated, other functions can occur independently, with melatonin interacting directly with intra- or extracellular molecules (Rivara *et al.*, 2015). However, despite the extensive research carried out to date, the results of clinical studies have been equivocal, making it a molecule of great controversy in the scientific community, remembering that melatonin is an active field of research, and discoveries are emerging all the time (Givler *et al.*, 2023).

In the European Union "Supplements" and "Medicines" obey different legislation. "Supplements" include Food Supplements regulated by Directive 2002/46/EC and are classified as food. There is no centralized pre-market authorization for these supplements, and the EU Member States can notify the placing of a food supplement on the market, with specific guidelines dictated by the regulatory authority of the country of origin (Thakkar *et al.*, 2020; Tuft *et al.*, 2023). Melatonin falls into this category, becoming a borderline product between food supplements and medicines, and is widely marketed in both forms. Food legislation allows the use of pharmaceutical drugs as ingredients in food supplements, which can occasionally make product categorization difficult. As a result, it is possible to find both a medicine and a food supplement on the market containing the same main substances, but falling into different categories, which subjects them to different requirements and obligations before the authorities. In the EU, melatonin can be marketed as an over-the-counter product if used in doses lower than 2 mg for immediate-release formulations. However, this is not the situation in several EU countries, such as Denmark, the Czech Republic, Slovenia, and in a non-EU country Switzerland, where the selling of melatonin as a food supplement requires a prescription (Skrzelowski *et al.*, 2021).

Melatonin is normally intended to be administered orally but undergoes an extensive first-pass metabolism. The drug displays a poor and variable bioavailability with studies reporting a range from 3% to 56% (Tordjman *et al.*, 2017; Vasey *et al.*, 2021). Alternative administration routes, other than oral with higher bioavailability, have been studied including transdermal and intranasal (Zetner, Andersen, Rosenberg, 2016). Following oral absorption peak plasma concentrations are reached after 60 minutes, and the half-life after intravenous administration was determined to be lower than 6 minutes (Esposito *et al.*,

2019; Tordjman *et al.*, 2017). 6-sulfatoxymelatonin (6-SM), is the main metabolite, is inactive and excreted via the urinary route (Tordjman *et al.*, 2017).

Considering all these factors, the study aimed to describe the composition of food supplements available in Portugal along with approved medications, in order to reveal the difference in their composition of active ingredients. Moreover, we detailed the number of potential intoxications notified to the Portuguese Poisons Information Center (from the Portuguese "Centro de Informação Antivenenos - CIAV") involving melatonin, from 2018 to 2022, and evaluated the potential risk of melatonin products.

Methods

A survey of food supplements containing melatonin available on the Portuguese market sought out at local points of sale, including websites, food supplements consisting of melatonin, or its synonym N-acetyl-5-methoxytryptamine. The research carried out between September 2022 and March 2023, resulted in a total of 44 supplements, the information contained in the supplement was thoroughly analyzed and grouped by consulting websites, as well as physical points of sale, such as parapharmacies and pharmacies including other places selling supplements. Following this data collection, we detailed the composition of active ingredients contained in food supplements by analyzing the labels.

Medicines containing melatonin that are currently approved in Portugal were also researched. It was also carried a brief analysis of data on sales of melatonin-containing medicines in Portugal over the last 10 years, according to the National Authority of Medicines and Health Products (from the Portuguese "Autoridade Nacional do Medicamento e Produtos de Saúde, I.P"– INFARMED).

To determine the number of potential instances involving melatonin intoxication, an analysis of cases reported to CIAV from 2018 to 2022 was conducted.

RESULTS

Medicines containing melatonin approved in Portugal

Currently, according to the INFARMED website, there are 16 medicines containing melatonin approved in Portugal. These are listed in Table I, as well as the daily dose recommended for insomnia treatment. In the European Union, prescription drugs containing melatonin include Circadin® (Neurim Pharmaceuticals) and Slenyto® (Neurim Pharmaceuticals). Circadin® was the first melatonin receptor agonist medicine approved in the European Union by the European Medicines Agency (EMA) in 2007. Its therapeutic indication is monotherapy, for the short-term treatment of primary insomnia characterized by poor sleep quality in patients aged 55 and over. Slenyto® is formulated as prolonged-release tablets containing 1 and 5 mg of melatonin and is indicated for the treatment of insomnia in patients aged 2 to 18 with autism spectrum disorder and/or Smith-Magenis syndrome. Of note, some approved medicines are not being sold in Portugal. Medicines containing melatonin are presented as immediate and prolonged-release pharmaceutical forms.

TABLE I - Medications containing melatonin with Marketing Authorization in Portugal issued by Medicine's National Authority- INFARMED

Commercial name (Generic drug)	Unit Dose/pharmaceutical form	Recommended dose for insomnia therapy/day	Commercialization
Circadin	2 mg/extended-release tablet	2mg	Marketed
Melatonin Generis (GMP)	2 mg/extended-release tablet	2mg	Not sold
Melatonin Noxarem	3 mg/conventional tablet	3mg	Not sold
Melatonin Noxarem	5 mg/conventional tablet	3mg	Not sold
Melatonin Pharma Nord	3 mg/film-coated tablet	3mg	Marketed
Teva Melatonin (GMP)	2 mg/extended-release tablet	2mg	Marketed
Slenyto (PMP)	1 mg/extended-release tablet	2mg	Marketed
Slenyto (PMP)	5 mg/extended-release tablet	2mg	Marketed
Neurim Melatonin	2 mg/extended-release tablet	2mg	Not sold
Melatonin Bluefish (GMP)	2 mg/Extended-release film-coated tablet	2mg	Not sold
Adaflex	0.5 mg/tablet	0.5-2mg	Not sold
Adaflex	1 mg/tablet	0.5-2mg	Not sold
Adaflex	2 mg/tablet	0.5-2mg	Not sold
Adaflex	3 mg/tablet	0.5-2mg	Not sold
Adaflex	4 mg/tablet	0.5-2mg	Not sold
Adaflex	5 mg/tablet	0.5-2mg	Not sold

Footnote: The data was retrieved from the INFOMED database (https://extranet.infarmed.pt/INFOMED-fo/) on 27/03/2024. Generic Medicinal Product (GMP), Pediatric Medical Product (PMP)

Sales of melatonin-containing Medicines in Portugal 2012-2022

We collected the data from prescribed medicines dispensed in community pharmacies in Portugal from 2012 to 2022, according to data supplied by INFARMED Table II. There is a clear upward trend in both melatonin sales and DDD consumption over time, with notable annual fluctuations that reflect the dynamics in consumer preferences. The data revealed that sales vary from a low of 4 packs of melatonin (2012) to a high of 30 packs (2016). A similar pattern observed in DDD consumption agrees with a low use of these medicines that require a prescription.

TABLE II - Melatonin medicines annual consumption (in Defined Daily Dose - DDD) and packaging quantities (per year) from 2012 to 2022

DCI	2012 Packaging	2013 Packaging	2014 Packaging	2015 Packaging	2016 Packaging	2017 Packaging	2018 Packaging	2019 Packaging	2020 Packaging	2021 Packaging	2022 Packaging
Melatonin	4	7	8	8	30	25	12	6	5	26	24
Consumed DDD	84	147	168	168	630	525	252	126	105	546	504

Footnote: The data pertains to prescribed medications dispensed in community pharmacies in Continental Portugal from 2012 to 2022. Medications related to hospital environments are not included. The data has been collected based on information provided by the Shared Services of the Ministry of Health in Portugal (SPMS).

Defined daily dose (DDD), as defined by the World Health Organization, is the average daily maintenance dose of a medicine in its main indication intended for use in adults.

Food supplements containing melatonin available in Portugal

Research into the melatonin-containing food supplements in the Portuguese market led us to compile information on 44 different products Table III. The products revealed a diverse and complex panorama, where various associations between ingredients were identified. The melatonin in the food supplements is in a recommended daily dose that varies between a minimum of 1 mg and a maximum of 1.95 mg, thus not exceeding the limit allowed in food supplements. Available in a variety of pharmaceutical formulations, including tablets, capsules, gummies, powders, or sprays, most supplements are designed in tablet form.

TABLE III - Qualitative and quantitative composition of different dietary supplements containing melatonin available in Portugal

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
1	Melatonin plus (Vidaceleiro)	Pill (1 per day, before bed)	1.90 mg	-	(1.1 mg) Vitamin B1 (1.4 mg) Vitamin B6 (2.5 µg) Vitamin B12	-	-
2	Melatonin+ (Bional)	Capsule (1 per day, 30-60 min before bedtime)	1.90 mg	(100 mg) Extract from Poppy California, aerial parts	(1.4 mg) Vitamin B6 (200 µg) Vitamin B9 (2.5 µg) Vitamin B12	(75 mg) Magnesium	-

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
3	Vectidorm (Nutergia laboratory)	Capsule (2 per day, 30 minutes before bed)	1.0 mg	(50 mg) Eschscholzia extract (50 mg) Passionflower extract	(6 mg) Vitamin B5 (1.4 mg) Vitamin B6 (200 µg) Vitamin B9 (2.5 µg) Vitamin B12	(140 mg) Magnesium	(100 mg) Cherry Juice Powder
4	Melatonin (Solgar)	Pill (1 per day, at bedtime)	1.90 mg	-	-	-	-
5	Melatonina Gotas (Vidaceleriro)	Oral solution (12 drops per day, before bed)	1.95 mg/12 drops (daily total)	(20 mg) Passionflower	-	-	-
6	Melatonina Pura (Esi)	Oral solution (14 drops per day, 30 min before bed)	1.9 mg/14 drops (daily total)	-	-	-	-
7	Melatonina Pura (Esi)	Microtablet (1 per day, at bedtime)	1.9 mg	-	-	-	-
8	Melatonina (Sovex)	Capsule (1 per day, always at the same time, 1-2 hours before bed)	1 mg	-	-	-	-
9	Melatonina (Novohorizonte)	Orodispersible tablet (1 per day, at bedtime)	1.95 mg	-	-	-	-
10	Sono Express (Aquilea)	Sublingual spray (1 spray per day, before bed)	1.0 mg/spray (daily total)	-	-	-	-
11	Melatonat Forte (Natiris)	Capsule (1 per day, 1-2 hours, before bed)	1.94 mg	-	(1.4 mg) Vitamin B2	-	(300 mg) Tryptophan
12	Melatonina Plus Active (Naturmil)	Pill (1 per day, before bed)	1.95 mg	-	(1.1 mg) Vitamin B1 (1.4 mg) Vitamin B6 (2.5 µg) Vitamin B12	-	-
13	Melatonin Power Sleep (Goldnutrition)	Capsule (1 per day, 1 hour before bed)	1.9 mg	(100 mg) Dry extract of Valerian, root Griffonia simplicifolia dry extract, root	-	-	(50 mg) 5-HTP
14	Melatonox (Dietmed)	Pill (1 per day, before bed)	1.95 mg	50 mg Valerian, root	-	-	(150 mg) Tryptophan

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
15	Dormy Fast (Maxpowerline)	Capsule (1 per day, 2 hours before bed)	1.9 mg	(50 mg) Passiflora flower and leaf (50 mg) Dry extract of California poppy, aerial parts (25 mg) Dry extract of Bitter Orange, flower (25 mg) Linden dry extract, flower	-	-	(100 mg) GABA
16	Stresscalm Sleep (Natiris)	Capsule (1 per day, 30 minutes before bed)	1.94 mg	(100 mg) Passiflora dry extract (70 mg) Eschscholzia dry extract (40 mg) Valerian dry extract	-	-	-
17	Boas Noites (Eladiet)	Double-layer tablet (1 per day, 30 minutes before bed)	1.85 mg	(100 mg) Valerian dry extract, root (100 mg) Passiflora dry extract, flower (50 mg) Poppy dry extract California, aerial parts	(16 mg) Vitamin B3 (1.4 mg) Vitamin B6	-	(100 mg) GABA
18	Ansioplant Noite (Chi)	Capsule (1 per day, 30 minutes before bed)	1.9 mg	(180 mg) Woodruff (100 mg) Passionflower	-	-	(50 mg) L-Glycine
19	Ansioval Noite (Farmodiética)	Pill (1 per day, at bedtime)	1.9 mg	(65 mg) Passionflower (65 mg) Valerian (65 mg) Calamintha nepeta (32 mg) Orange (32 mg) Hops	-	-	-
20	Ansioval Gotas (Farmodiética)	Oral solution (2 drops per day, 30 minutes before bedtime)	mg/2 drops (daily total)	-	(0.23 mg) Vitamin B6	-	-
21	Ansiotina Noite (Phytogold)	Pill (1 per day, 1 hour before bed)	1.0 mg	(100 mg) Passiflora dry extract (20 mg) Lemon balm dry extract (100 mg) Poppy dry extract California (50 mg) Valerian dry extract	-	-	-

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
22	Rianima Noite (Fitofarmattivi)	Capsule (2 per day, at bedtime)	1.0 mg	(140 mg) Passionflower dry extract (140 mg) Poppy dry extract California (100 mg) Valerian dry extract (2 mg) Black Pepper dry extract (100 mg) Griffonia simplicifolia dry extract (100 mg) Evening Primrose Dry extract	-	-	(50 mg) L-Theanine (40 mg) Lavender Essential Oil (40 mg) Lavender Essential Oil (40 mg) Marjoram Essential Oil (40 mg) Vetiver Essential Oil (20 mg) Agrimony (20 mg) Vervain
23	Dorminatur Gummies (Esteve)	Gum (1 per day, 1 hour before bed)	1.0 mg	-	(0.7 mg) Vitamin B6	-	Coconut Vegetable Oil
24	Flavia Nocta (Effik)	Capsule (1 per day, before bed)	1.0 mg	-	(7.5 µg) Vitamin D (1.4 mg) Vitamin B6 (200 µg) Folic Acid (2.5 µg) Vitamin B12	(56.25 mg) Magnesium (120 mg) Calcium	Refined Flaxseed Oil Vegetable Oils
25	Arkosono Forte (Arkopharma)	Double-layer tablet (1 per day, before bed)	1.9 mg	(150 mg) Valerian extract, underground organs (100 mg) Passionflower extract, aerial parts (160 mg) California Poppy extract, aerial parts	(0.7 mg) Vitamin B6	-	-
26	Arkosueño (Arkopharma)	Oral solution (4 drops per day, 30 minutes before bed)	1.0 mg/4 drops (daily total)	-	-	-	-
27	Arkosono Sleepgummies (Arkopharma)	Gum (1-2 per day, 1 hour before bed)	1.9 mg	(95 mg) Melissa extract, leaf (25 mg) California Poppy extract, aerial parts (20 mg) Linden Blossom Powder	(1.4 mg) Vitamin B6	-	-
28	Sono Instant (Aquilea)	Sachet (1 per day, 30 minutes before bed)	1.95 mg	(100 mg) Lemon Balm extract, leaves, and branches (100 mg) Passionflower extract, aerial parts (50 mg) California Poppy extract, aerial parts	-	-	-

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
29	Sono (Aquilea)	Double-layer tablet (1 per day, 30 minutes before bed)	1.95 mg	(50 mg) Valerian extract (100 mg) Passionflower extract (100 mg) California Poppy extract, aerial parts	-	-	-
30	Sono Forte (Aquilea)	Trilayer tablet (1 per day, 30 minutes before bed)	1.95 mg	(5.3 mg) Black Pepper extract, fruit (30.6 mg) Gryphonia extract, seeds (100 mg) Passionflower extract, aerial parts (100 mg) California Poppy extract, aerial parts (100 mg) Lemon Balm extract, leaves (100 mg) Valerian extract, root	(1.4 mg) Vitamin B6 (5 µg) Vitamin D	-	-
31	Stillnoite (Sanofi)	Pill (1 per day, before bed)	1.0 mg	(340 mg) Passionflower extract, aerial parts (81 mg) Melissa extract, leaves (8.4 mg) California Poppy extract, aerial parts	(0.42 mg) Vitamin B6	-	-
32	Angelicalm Noite (Uriach)	Capsule (1 per day, before bed)	1.95 mg	(100 mg) Passionflower extract, plant (130 mg) Valerian extract, root	-	-	-
33	Angelicalm Rapid (Uriach)	Spray (5 sprays per day, before bed)	1.95 mg/5 sprays (daily total)	(20 mg) Passionflower extract, aerial parts (30 mg) Valerian extract, root	-	-	-
34	Serenum (Tecnilor)	Coated tablet (1 per day, before bed)	1.9 mg	(240 mg) Valerian extract, root (125 mg) California Poppy extract, plant (100 mg) Chamomile extract, flower (50 mg) Hops dry extract, fruit (50 mg) Passionflower extract, aerial parts	-	(100 mg) Magnesium (40 mg) Calcium	-
35	Advancis Passival Gotas (Gmp)	Oral solution (2 drops per day, 30 minutes before bed)	1 mg/2 drops (daily total)	-	(0.23 mg) Vitamin B6	-	-
36	Advancis Passival Sono (Gmp)	Tablet (1 per day, before bed)	1.9 mg	(65 mg) Passionflower extract, aerial parts (65 mg) Valerian extract, root (65 mg) Calamintha nepeta extract, aerial parts (32 mg) Hops extract, inflorescence (32 mg) Orange Tree extract, flower	-	-	-

N	Supplement (producer/commercial representative)	Pharmaceutical form (Recommended daily total)	Melatonin	Plant extracts	Vitamins	Minerals	Other constituents
37	Melamil Tripto (Humana)	Oral solution (0.5 mL, once a day, 30 minutes before bed)	1 mg	-	(1.4 mg) Vitamin B6	-	(20 mg) L-Tryptophan
38	Melamil (Humana)	Oral solution (4 drops, once a day, 30 minutes before bed)	1 mg/4 drops (daily total)	-	-	-	-
39	Melatonina (Wells)	Tablet (1 per day, before bed)	1 mg	-	(36 mg) Vitamin B3 (9.6 mg) Vitamin B6	-	-
40	Valdispertnoite (Vemedia)	Coated extended-release tablet (1 per day, 15 min before bedtime)	1 mg	-	Vitamin B3 Vitamin B6	-	-
41	Valdispertnoite Rapid (Vemedia)	Orodispersible tablet (1 per day, before bed)	1.9 mg	-	-	-	-
42	Valdispertnoite Total (Vemedia)	Capsule (1 per day, 30 minutes before bed)	1 mg	(50 mg) Poppy extract California, plant (50 mg) Lavender essential oil	-	-	-
43	Win-Fit Melatonina (Ampliphar)	Chewable tablet (1 per day, at bedtime)	1.5 mg	(6 mg) Lavender extract (6 mg) Rosemary extract	-	-	(15 mg) 5-HTP
44	Zzzquil natura (Vicks)	Gum (1 per day, 30 minutes before bed)	1 mg	(30 mg) Valerian extract, root (10 mg) Chamomile extract, flower (10 mg) Lavender extract, flower	(1.4 mg) Vitamin B6 Vitamin C	-	-

Footnote: The quantities of melatonin and other constituents correspond to the values found on the label for each pharmaceutical form, concerning the recommended daily dose. (5-HTP: 5-Hydroxytryptophan; GABA: Gamma-Aminobutyric Acid)

It was found that only nine (20%) supplements were characterized by the presence of melatonin alone, namely supplements 4, 6, 7, 8, 9, 10, 26, 38, and 41. Most supplements are made up of plant extracts, with Valerian, California Poppy, and Passionflower being the most frequent ingredients associated with melatonin in their formulations. According to the therapeutic indications on the label of these supplements, the dosage amount is defined according to the claimed effect. The information provided below is taken directly from the labels of the supplements analyzed, following the authorized health claims for Melatonin, as described in Commission Regulation (EU) No. 432/2012 dated May 16, 2012. According to these labels, the therapeutic indications for using melatonin include the relief of subjective symptoms of time difference, with a recommended minimum dose of 0.5 mg before bedtime on the first day of travel and in subsequent days after arrival at the destination. On the other hand, by taking 1 mg of the hormone right before bed, melatonin is also said to assist shorten the amount of time it takes to fall asleep.

In addition to the nutritional information on the label or in the description on websites, some food supplements sometimes contain the following warnings: “Food supplements should not be used as a substitute for a varied, balanced diet and a healthy lifestyle”, “Do not exceed the recommended daily intake”, “Keep out of reach and sight of children”, “Medical or nutritional

advice is recommended", and "Pregnant women, infants, and children are not recommended to use this product". Including warnings on the label plays a crucial role in making consumers aware of the appropriate use of the product, thus enabling informed decision-making, and should be complemented by advice from health professionals, especially pharmacists.

Melatonin-related poisonings reported to the Portuguese Poisons Information Center

The number of reported intoxications suspected to involve melatonin are summarized in Table IV. The data shows that melatonin poisoning occurs mainly in children, with a higher prevalence between the first year of life and the age of four. Also, it is noticeable that the number of reports increased dramatically from 2020 onwards. The overwhelming majority of cases occur accidentally owing to easy access to the drug, mainly due to children's propensity for more attractive galenic forms such as gummies. Some cases occur due to medication errors, such as dosage or time of administration. In addition, there are some cases, albeit rare, of intentional ingestion, mainly among the 10-17 age group. In general, intoxications are of low severity, and referral to the hospital is only necessary for unusual circumstances, particularly in smaller children, to keep them under medical monitoring until symptoms resolve.

TABLE IV - Cases notified to the CIAV suspected to involve melatonin, from 2018 to 2022, in Portugal

	2018	2019	2020	2021	2022
Total	7	23	116	146	113
Adults (≥18)	2	11	38	37	31
Children (1 - 17)	5	12	78	109	82
1-4 years	1	6	61	72	60
5-9 years	2	2	10	9	8
10-15 years	2	2	4	16	9
16-17 years	0	2	3	9	5

Footnote: The information presented is primarily sourced from the Portuguese Poisons Information Center (CIAV). They refer exclusively to cases of melatonin-suspected poisoning reported to that center in Portugal.

DISCUSSION

The data on medicines sales, that require a prescription, reveal a low number of medicines sold. Overall, the observation of low use of melatonin-containing medicines suggests the possibility that consumers predominantly opt for food supplements not regulated by INFARMED, which can be acquired without the need for a prescription. Empirically, this clearly shows a growing preference for dietary supplements over prescription drugs. Regretfully, we do not possess supplement sales statistics, nor are we aware of any possibility of obtaining solely melatonin supplement sales in Portugal. The correlation between medicine sales and consumer preferences highlights the direct influence of consumer choices, which underscores the importance of understanding the motivations behind this behavior. Importantly, we cannot assume that consumers only are acquiring melatonin-containing food supplements for sleep disorders, as there are many other potential uses including the important antioxidant

properties (Bonomini *et al.*, 2018; Minich *et al.*, 2022). Therefore, correlating medicines sales, which are only approved for sleep disorders, with those of dietary supplements may have limitations. However, it is crucial to recognize that the Portuguese market is part of a broader regulatory framework in the European Union, sharing common standards and guidelines. In this context, the local preference for food supplements raises pertinent questions about indiscriminate access and safety, considering the high heterogeneity in over-the-counter melatonin-containing formulations in Portugal, which may reflect similar trends in other EU countries (Skrzelowski *et al.*, 2021).

Research into the composition of dietary supplements containing melatonin reveals the significant heterogeneity in formulations across different brands, illustrating the wide variety and availability of these products on a global scale. Notably, this diversity raises concerns about consumer safety, particularly exacerbated by the significant challenge associated with food supplements in general, underscoring the lack of stringent regulation and, at times, inadequate scientific evidence to substantiate various claims made by these products (Bailey, 2020). The analysis further discloses that comprehensive warnings are incorporated into all packaging to safeguard the integrity of the product, ensuring both stability and safety. Recommendations for storage methods emphasize the importance of minimizing exposure, favoring blister packs with an oxygen barrier over the traditional bottle format (Pranil, Moongngarm, Loypimai, 2020). This precaution assumes particular significance due to melatonin's susceptibility to degradation in the presence of air and light. The few, albeit rare, supplements that do not follow this pattern are mostly formulations intended for children or those who simply prefer alternative forms of intake. Apart from that, it is noteworthy that the recommended use of these supplements is specifically tailored to address sleep disorders, as explicitly indicated on their labels (Culnan, McCullough, Wyatt, 2019; Hartstein *et al.*, 2024). There is a lack of studies evaluating the efficacy, quality, and safety of these products. Also, the complexity of the associations between components in the formulations, makes it sometimes challenging to study how they operate. FDA evaluation of dietary supplements occurs at incidence-based intervals, focusing on potential concerns or adverse effects associated to these products until they are proven unsafe (Bailey, 2020; Givler *et al.*, 2023; Menczel Schrire *et al.*, 2022). In addition, the absence of strict manufacturing guidelines contributes to variations in dosage and composition, including some supplements with added vitamins. This scenario implies that the effects of consumption are not exclusively attributable to melatonin, but to the complexity of the mixtures present in these supplements (Bonomini *et al.*, 2018; Culnan, McCullough, Wyatt, 2019). These added components, predominantly plant extracts or parts of their roots, as observed in the supplements analyzed, are often incorporated due to their claimed hypnotic and sedative properties. It is known that the pharmacological effects are mainly mediated by the GABAergic system, which explains the promotion of these products as sleep aids. In this way, it is believed that the effects of the components present in the formulation, together with melatonin, are intended to be synergistic or have enhanced efficacy (Esposito *et al.*, 2019; Lemoine, Bablon, Da Silva, 2019). Furthermore, contrary to what is observed with medicines, substantial efforts need to be made to determine the ideal dose of melatonin for long-term supplementation and to improve the forms of administration, thus considering alternative routes, or administration by different forms of preparation, as observed in the supplements analyzed (Meng *et al.*, 2017; Zetner, Andersen, Rosenberg, 2016). The study on melatonin-containing medications revealed that immediate-release formulations are mainly used for sleep onset problems, while extended-release formulations are more effective for sleep maintenance problems. This distinction is attributed to the slower and more sustained absorption of extended-release melatonin, which delays and reduces the peak plasma concentration, unlike immediate-release formulations where melatonin is rapidly metabolized and eliminated (Skrzelowski *et al.*, 2021). However, both maintain melatonin levels within physiological standards along the plasma concentration curve during the night. The dose generally ranges from 2

to 3 mg per tablet and is adjusted according to different needs, considering the person's clinical history.

Overall, there was an increase in melatonin poisoning cases reported to the CIAV since 2020, coinciding with the year that the COVID-19 pandemic appeared (Beck *et al.*, 2021). Growing evidence suggests that the significant changes in people's daily routines due to the pandemic have contributed to the increase in sleep problems, also reflected in the increasing numbers of melatonin intoxications reported to the CIAV (Gasmi *et al.*, 2024; Lelak *et al.*, 2022). In particular, the substantial increase in poisonings, especially in children from 2020 to 2022, suggests a possible link with the significant increase in exposure, such as the presence of more children at home during the pandemic and the greater availability of melatonin supplements in chewable forms. This scenario highlights the importance of addressing issues related to the safety of childproof packaging and adjusting the dose of medicines and supplements, including melatonin (Bishop-Freeman *et al.*, 2022; Minich *et al.*, 2022). It is crucial to encourage consumers and healthcare professionals to report any adverse events related to melatonin products. Aggregating data from these reports can provide valuable insights into the need for implementing public health measures to raise awareness about the increase in pediatric melatonin intake (Esposito *et al.*, 2019; Lelak *et al.*, 2022).

Ultimately, when confronting the data on melatonin medicines sales with the notable increase in the number of intoxications, it would be expected an association between the increase in consumption and the subsequent increase in poisonings. However, it is not possible to estimate a causal relationship between the two factors as we lack data on sales of melatonin-containing supplements. This lack of correlation is exacerbated by the non-mandatory notification of supplements to regulatory bodies and the absence of monitoring requirements at the time of sale and after consumption, in contrast to the strict control observed for medicines.

CONCLUSION REMARKS

Consumers should be made aware by healthcare professionals of the various melatonin formulations available, their effective doses, and their potential adverse effects. In the case of supplements, several combinations with plant extracts have been identified, their mode of action is complex to understand and their therapeutic potential as well as adverse effects merit careful clinical studies.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

BVA: Collecting and organizing data, Writing - review & editing.

FR: Writing - review & editing.

JPC: Conceptualization, Writing – original draft.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGMENTS

This research was funded by national funds from Fundação para a Ciência e a Tecnologia (FCT), I.P., in the scope of the project UIDP/04378/2020 and UIDB/04378/2020 of the Research Unit on Applied Molecular Biosciences (UCIBIO) and the project LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy—i4HB.

REFERENCES

Bailey RL. Current regulatory guidelines and resources to support research of dietary supplements in the United States. Crit Rev Food Sci Nutr. 2020;60(2):298-309.

Beck F, Leger D, Fressard L, Peretti-Watel P, Verger P, Coconel G. Covid-19 health crisis and lockdown associated with high level of sleep complaints and hypnotic uptake at the population level. J Sleep Res. 2021;30(1):e13119.

Bishop-Freeman SC, Young KA, Labay LM, Beuhler MC, Hudson JS. Melatonin Supplementation in Undetermined Pediatric Deaths. J Anal Toxicol. 2022;46(8):808-16.

Bonomini F, Borsani E, Favero G, Rodella LF, Rezzani R. Dietary Melatonin Supplementation Could Be a Promising Preventing/Therapeutic Approach for a Variety of Liver Diseases. Nutrients. 2018;10(9).

Culnan E, McCullough LM, Wyatt JK. Circadian Rhythm Sleep-Wake Phase Disorders. Neurol Clin. 2019;37(3):527-43.

Erland LA, Saxena PK. Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med. 2017;13(2):275-81.

Esposito S, Laino D, D'Alonzo R, Mencarelli A, Di Genova L, Fattorusso A, et al. Pediatric sleep disturbances and treatment with melatonin. J Transl Med. 2019;17(1):77.

Gasmi A, Semenova Y, Noor S, Benahmed AG, Bjorklund G. Sleep, Dietary Melatonin Supplementation, and COVID-19. Curr Med Chem. 2024;31(11):1298-314.

Givler D, Givler A, Luther PM, Wenger DM, Ahmadzadeh S, Shekoohi S, et al. Chronic Administration of Melatonin: Physiological and Clinical Considerations. Neurol Int. 2023;15(1):518-33.

Gunata M, Parlakpinar H, Acet HA. Melatonin: A review of its potential functions and effects on neurological diseases. Rev Neurol (Paris). 2020;176(3):148-65.

Hartstein LE, Garrison MM, Lewin D, Boergers J, Hiraki BK, Harsh JR, et al. Factors contributing to U.S. parents' decisions to administer melatonin to children. Sleep Med. 2024;114:49-54.

Kostoglou-Athanassiou I. Therapeutic applications of melatonin. Ther Adv Endocrinol Metab. 2013;4(1):13-24.

Lelak K, Vohra V, Neuman MI, Toce MS, Sethuraman U. Pediatric Melatonin Ingestions - United States, 2012-2021. MMWR Morb Mortal Wkly Rep. 2022;71(22):725-9.

Lemoine P, Bablon JC, Da Silva C. A combination of melatonin, vitamin B6 and medicinal plants in the treatment of mild-to-moderate insomnia: A prospective pilot study. Complement Ther Med. 2019;45:104-8.

Martin Gimenez VM, de Las Heras N, Lahera V, Tresguerres JAF, Reiter RJ, Manucha W. Melatonin as an Anti-Aging Therapy for Age-Related Cardiovascular and Neurodegenerative Diseases. Front Aging Neurosci. 2022;14:888292.

Megha KB, Arathi A, Shikha S, Alka R, Ramya P, Mohanan PV. Significance of Melatonin in the Regulation of Circadian Rhythms and Disease Management. Mol Neurobiol. 2024.

Menczel Schrire Z, Phillips CL, Chapman JL, Duffy SL, Wong G, D'Rozario AL, et al. Safety of higher doses of melatonin in adults: A systematic review and meta-analysis. J Pineal Res. 2022;72(2):e12782.

Meng X, Li Y, Li S, Zhou Y, Gan RY, Xu DP, et al. Dietary Sources and Bioactivities of Melatonin. Nutrients. 2017;9(4).

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"?: A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. Nutrients. 2022;14(19).

Ophoff D, Slaats MA, Boudewyns A, Glazemakers I, Van Hoorenbeeck K, Verhulst SL. Sleep disorders during childhood: a practical review. Eur J Pediatr. 2018;177(5):641-8.

Pranil T, Moongngarm A, Loypimai P. Influence of pH, temperature, and light on the stability of melatonin in aqueous solutions and fruit juices. Heliyon. 2020;6(3):e03648.

Rivara S, Pala D, Bedini A, Spadoni G. Therapeutic uses of melatonin and melatonin derivatives: a patent review (2012 - 2014). Expert Opin Ther Pat. 2015;25(4):425-41.

Samanta S. Physiological and pharmacological perspectives of melatonin. Arch Physiol Biochem. 2022;128(5):1346-67.

Skrzelowski M, Brookhaus A, Shea LA, Berlau DJ. Melatonin Use in Pediatrics: Evaluating the Discrepancy in Evidence Based on Country and Regulations Regarding Production. J Pediatr Pharmacol Ther. 2021;26(1):4-20.

Thakkar S, Anklam E, Xu A, Ulberth F, Li J, Li B, et al. Regulatory landscape of dietary supplements and herbal medicines from a global perspective. Regul Toxicol Pharmacol. 2020;114:104647.

Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, et al. Melatonin: Pharmacology, Functions and Therapeutic Benefits. Curr Neuropharmacol. 2017;15(3):434-43.

Tuft C, Matar E, Menczel Schrire Z, Grunstein RR, Yee BJ, Hoyos CM. Current Insights into the risks of using melatonin as a treatment for sleep disorders in older adults. Clin Interv Aging. 2023;18:49-59.

Vasey C, McBride J, Penta K. Circadian Rhythm Dysregulation and Restoration: The Role of Melatonin. Nutrients. 2021;13(10).

Wurtman RJ. The pineal as a gland and melatonin as a hormone. Hormonal Signaling in Biology and Medicine. 2020. p. 107-18.

Zetner D, Andersen LP, Rosenberg J. Pharmacokinetics of Alternative Administration Routes of Melatonin: A Systematic Review. Drug Res (Stuttg). 2016;66(4):169-73.

Received for publication on 23rd April 2024
Accepted for publication on 17th July 2024
Associated Editor: Carmen Fávaro Tindade