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Saffron Floral Bioresidues and Medicinal Herbs as Natural Phytomelatonin Sources for the Treatment of Anxiety and Insomnia

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Abstract— *Modern lifestyle challenges, including chronic stress and the pervasive disruption of circadian rhythms, have triggered a global surge in sleep disorders and a subsequent demand for natural phytotherapeutic alternatives. While the melatonin market has experienced an unprecedented expansion, with U.S. sales shoot up by over 1300%, it remains almost exclusively dominated by chemical synthesis. However, shifting consumer preferences toward sustainable and "clean-label" products have positioned phytomelatonin as a superior nutraceutical candidate. This plant-derived indoleamine, chemically identical to human melatonin, exhibits potent antioxidant, anti-aging, and immunomodulatory properties, acting as a pleiotropic regulator in both plants and mammals. Despite recent advances in microbial bioengineering for melatonin production, metabolic hurdles in industrial scale-up persist, driving the urgent search for novel botanical raw materials. This study investigates the potential of saffron floral residues as a sustainable supply of phytomelatonin for sedative and sleep-inducing applications. Using LC coupled to fluorescence detector, endogenous phytomelatonin levels were quantified and compared across a selection of traditional sedative plants, including valerian, St. John's wort, lemon balm, German and Moroccan chamomiles, among others. Our findings suggest that saffron bioresidues, currently considered an agricultural byproducts, represent a viable and high-value raw material for the phytotherapeutic industry. This research supports the valorization of saffron floral waste to meet the escalating global demand for natural treatments against anxiety and insomnia, providing a robust quantitative basis for its clinical and commercial application.*

Keywords— ***anxiety, botanicals, dietary supplements, health product, herbs, melatonin, phytomelatonin, phytotherapy, sleep disorder***

I. INTRODUCTION

In the contemporary era, the relentless pace of modern life and the pervasive disruption of natural light/dark cycles, often exacerbated by blue light exposure and shift work, have led to a global surge in stress-related pathologies. Consequently, there is a burgeoning demand for medicinal herbs and phytotherapeutic supplements to manage anxiety, nervousness, and various sleep disturbances. This trend reflects a significant shift in consumer and clinical preference toward natural alternatives, seeking to minimize

the secondary effects often associated with conventional sedative-hypnotics while fostering a greater societal acceptance of botanical medicine (Alanazi et al., 2023; L. Li et al., 2024; Mihai et al., 2025; Okeke et al., 2021).

Within this pharmacological framework, phytomelatonin has emerged as a molecule of paramount interest. First identified in higher plants in 1995, this indoleamine (*N*-acetyl-5-methoxytryptamine) is chemically identical to the melatonin produced by the human pineal gland. Beyond its role as a simple plant signaling molecule, phytomelatonin exhibits pleiotropic functions, acting as a master physiological regulator and a potent endogenous antioxidant, both in mammals and plants (Arnao et al., 2022; Arnao & Hernández-Ruiz, 2019; Cano et al., 2024c).

Extensive research has unveiled its therapeutic potential across a broad spectrum of clinical applications. Investigations into its antitumor, immunomodulatory, and antidepressant properties suggest that it may serve as a versatile scaffold for future drug development. Furthermore, its efficacy in synchronizing circadian rhythms makes it a primary candidate for treating insomnia and jet lag, as well as managing complex metabolic and depressive disorders. Currently classified as a high-value nutraceutical, its capacity to scavenge free radicals and mitigate oxidative stress bestows it with remarkable anti-aging properties, offering a holistic approach to enhancing cellular longevity and systemic well-being (Agathokleous et al., 2019; Ahn et al., 2014; Andronachi et al., 2025; Arora & Ivanovski, 2017; Dehdari Ebrahimi et al., 2023; Mayo et al., 2005).

The widespread use of melatonin against sleep disorders and other problems, such as jet lag, has been added to other therapeutic applications with proposals against aging (anti-aging), stress and anxiety, also as an activating molecule of the immune system, against acute metabolic syndrome and also as an anti-cancer adjuvant, among others, in most cases without a medical prescription (Anghel et al., 2022; Boga et al., 2019; Carrascal et al., 2018; Castejón-Castillejo et al., 2025; Francesca et al., 2018; Gonciarz et al., 2026; Griffin & Marignol, 2018; Haldar et al., 2014; C. Li et al., 2022; Okeke et al., 2021).

The melatonin market has experienced an unprecedented surge in recent decades. In the United States, sales skyrocketed by over 1300% between 2003 and 2018, rising from $62 million to $821 million, while the consumer base expanded five-fold from 2000 to 2017. On a global scale, synthetic melatonin production reached approximately 4,000 tons in 2019, with a market valuation of $1.3 billion. This sector grew by 15% between 2013 and 2019, maintained a steady annual increase of $98.5 million through 2023, and is projected to witness further growth exceeding 217.9 million annually by 2033. This trajectory is largely driven by the rising popularity of dietary supplements and the potential integration of melatonin into new food and beverage lines as nutraceuticals, a move currently under consideration by the US-FDA. Currently, the global melatonin market is supplied almost exclusively by chemical synthesis, with the industrial production highly concentrated dominated by a mere half-dozen companies (Cano et al., 2024b; Future Market Insights, 2024; Market Analysis Report, 2021; Mordor Intelligence, 2021; Research and Markets, 2024).

However, driven by a growing consumer shift toward natural and sustainable alternatives, the concept of phytomelatonin, melatonin derived from botanical sources, was introduced as a viable proposal several years ago. More recently, the field has evolved with the development of engineered microbial platforms. These genetically modified microorganisms have been highly optimized for large-scale melatonin biosynthesis within industrial bioreactors, providing a sophisticated and scalable pathway for pharmaceutical-grade production, although it has not yet been taken to industrial production due to some problems in the metabolic bioengineering used (Arnao & Hernández-Ruiz, 2018a; Arnao & Hernández-Ruiz, 2018b; Blask et al., 2004; Cano et al., 2024b; Choi, 2019; Francesca et al., 2018; Johns et al., 2013; Meng et al., 2017; Pereira et al., 2020; Sangsopha et al., 2020; Tresguerres et al., 2014).

In the continuous search for new raw materials as a source of phytomelatonin, the object of the study is to estimate the endogenous levels of phytomelatonin in saffron floral residues for its use as a new raw material to applied in phytotherapy as possible sedative and sleep-inducing agent. In addition, its content is measured and compared with different medicinal plants with sedative action such as valerian, St. John's wort, and chamomile, among others. For the analysis of phytomelatonin, liquid chromatography technique with fluorescence detection (LC-FL) was used as a sensitive and precise tool.

II. MATERIALS AND METHODS

Chemicals

Acetonitrile, ethyl acetate, methanol and several reagents used were obtained from Sigma-Aldrich Co. (Madrid, Spain). Melatonin as standard (99%) was provided by ThermoFisher Scientific Chemicals (Waltham, MA, USA). Pure water was used (Milli-Q Corp, Merck, Darmstadt, Germany).

Plant Material

All the herbs were obtained from the local distributor *Murciana de Herboristería* (Cobatillas-Murcia, Spain) in

the form of powder, with particles (0.2 mm ∅), stored at room temperature in the dark. Floral bioresidues of *Crocus sativus*, which include petals, stamens and styles were sourced from a local saffron productor in *Tomelloso* (Toledo, Castilla-La Mancha, Spain), which were cultivated according "Requirements Established by the Protected Designation of Origin Denomination (DOCM-*Azafrán de La Mancha*). Using traditional procedures, workers manually separated the stigmas from the rest of the saffron flowers, which retained all other parts (tepals, stamens, and styles) (DOCM-10, 1999). The floral bioresidues, in the form of wet biowaste, were desiccated at 50 ºC and crushed using a Microtron-MB550 (Kinematica AG, Germany).

Phytomelatonin analysis

The phytomelatonin content in the different organs of the plants studied was determined by LC-FL, following the methodology previously established (M.B. Arnao & Hernández-Ruiz, 2009; Cano et al., 2024a). Briefly, samples (0.2 g DW) were put in PVPP tubes containing ethyl acetate(5mL). After continuous shaking during 15 h at 4 °C in darkness, tissues was removed after washed with same solvent (0.5 mL). The different samples were centrifuged at 4,000 xg for 10 min (Sorvall RC 5B Plus, DuPont, Wilmington, DE, USA) and decanted into new tubes. Each eluent was dried under vacuum using a SpeedVac (ThermoSavant SPD111V, Thermo Fisher Scientific) connected to an RVT400 refrigerated vapor trap. The residue was reconstituted in 1 mL of acetonitrile via vortex mixing, filtered (0.2 μm ∅ PTFE), and injected into the LC-FL system.

The LC-FL system comprised an in-line degasser, a binary pump, an autosampler, a thermostatted column oven, and a Jasco FP-2020-Plus fluorescence detector ($\lambda_{ex} = 280$ nm, $\lambda_{em} = 350$ nm). Separation was performed on a Waters XBridge C18 column (5 μm, 100×2.1 mm; Sigma-Aldrich, Barcelona, Spain) kept at 36 °C. Isocratic elution was carried out at 0.5 mL/min using 85% solvent A (0.1% formic acid in Milli-Q water) and 15% solvent B (0.1% formic acid in methanol). Data were processed with Jasco ChromNAV (v.1.09.03), and target identification was confirmed via on-line spectral comparison of the phytomelatonin peak with a melatonin standard using Jasco Spectra Manager.

Statistical analysis

Data were analyzed using SPSS (IBM Corp., Armonk, NY, USA). One-way ANOVA followed by Tukey's multiple range test was used to assess significant differences among groups. Results represent the mean phytomelatonin content (ng/g DW ± SE) derived from three independent experiments."

III. RESULTS AND DISCUSSION

Table 1 shows the quantification of phytomelatonin in the floral bioresidues of *Crocus sativus* and in others medicinal plants. The data revealed significant variability in their contents. The plants analyzed can be ordered in decreasing order according to their phytomelatonin content. Three groups can be distinguished: i) with phytomelatonin content greater than 1000 ng/g DW; ii) with contents between 100 and 1000 ng DW, and iii) contents less than 100 ng/g DW (Table 1).

St. John's Wort roots showed the highest concentration, with 2.36 µg/g DW, followed by Valerian roots, whose concentration was 1.56 µg/g DW. The floral bioresidues of *Crocus sativus*, which include petals, stamens and styles, showed similar levels to valerian roots and spearmint leaves, with about 1.17 µg/g DW. On the other hand, German chamomile (leaves) showed significantly lower levels of 61.3 ng/g DW, while leaves of Moroccan chamomile recorded the lowest phytomelatonin content, with 11.4 ng/g DW. Melissa (lemon balm) that is extensively used in herb supplements as restfulness and sleep improves showed a very low amount of phytomelatonin.

Phytomelatonin levels in plant samples typically show high variability, which depends heavily on origin, variety, cultivation methods, and preservation techniques, in addition to the extraction and analytical procedures used. Likewise, although our quantified phytomelatonin levels generally fall within literature ranges, they differ substantially and tend to be markedly lower than values reported in other studies (Arnao et al., 2023; Arnao & Hernández-Ruiz, 2018a), possibly due to the variability in the sample sources and the quantification methodology applied, since methods with overestimation of phytomelatonin have been commonly used (Cano et al., 2024a).

From the plants studied in Table 1, interesting data can be extracted. The selected plants have a direct and proven relationship with sleep induction or stress relief. Thus, Valerian is the sedative plant par excellence; it reduces sleep onset latency and improves deep sleep quality (HMPC-EMA, 2016). St. John's wort is mainly used for mild or moderate depression; by improving mood and regulating serotonin, it usually indirectly improves sleep in people with anxiety or sadness, but it is not a quick "sedative" like valerian (Chung & Deng, 2020). Lemon Verbena is one of the best options of this new batch. It has a mild sedative effect and is excellent for "digestive stress" (when your nerves go to your stomach); it helps to induce rest, especially if insomnia is accompanied by stomach heaviness or mild anxiety. Lemon thyme is not a powerful

sedative like valerian, but in an infusion before going to sleep it provides a feeling of well-being and respiratory "cleanliness" that helps you rest better; its citrus aroma has a relaxing effect on mood. Lemon balm (Melissa) is very effective in reducing anxiety, restlessness and insomnia of nervous origin (Borrás et al., 2021). German chamomile is a potent sedative, containing apigenin, a flavonoid that binds to GABA receptors in the brain in a similar way to some anxiolytic drugs, but much more gently; it is ideal for inducing sleep and calming generalized anxiety. Moroccan chamomile is a digestive tranquilizer, less potent than German chamomile, but it is excellent for relaxing the enteric nervous system (the "brain" of the stomach) (El Mihyaoui et al., 2022, 2023).

In this study we introduced other plants given their relevant endogenous level of phytomelatonin and possibilities such as relaxing plants: Spearmint is not generally classified as a sedative plant, although it may induce a mild digestive tranquilizing effect; Catnip, in humans, acts as a mild sedative and antispasmodic. It is usually used to relieve nervous tension and help in cases of mild insomnia, especially if there is physical restlessness (Boachon et al., 2018; Kenefick, 2012). Spearmint and catnip showed significant amounts of phytomelatonin (Table 1).

Table 1. Content of phytomelatonin in several medicinal plants, including saffron floral bioresidues.

Common name	***Scientific name***	**Organ**	**Phytomelatonin content** (ng/g DW ±SE)
St. John's Wort	*Hypericum perforatum*	R	2,365.8 ±138.9
Valerian	*Valeriana officinalis*	R	1,560.3 ±83.2
Saffron floral bioresidues	*Crocus sativus*	F	1,170.5 ±68.7
Catnip	*Nepeta cataria*	L	230.7 ±12.8
Lemon verbena	*Aloysia citriodora*	L	239.4 ±18.3
Lemon thyme	*Thymus citriodorus*	L	205.1 ±11.9
Spearmint	*Mentha spicata*	L	125.1 ±7.7
German chamomile	*Matricaria chamomilla*	L	61.3 ±2.7
		F	16.3 ±1.2
Lemon balm	*Melissa officinalis*	L	24.8 ±2.1
Moroccan chamomile	*Cladanthus mixtus*	L	11.4 ±1.0
		F	9.7 ±0.8

*R: roots; L: leaves; F: flowers.

Generally, in botanical preparations with phytotherapeutic activity related to anxiety and sedative capacity and even sleep improvement, three extracts of the plant's valerian, lemon balm and passionflower (*Passiflora incarnata)* are usually combined. A common practice is to mix these three botanicals with synthetic melatonin, such as biphasic tablets (Castejón-Castillejo et al., 2025). In the case of passionflower, there are no data on the identification of phytomelatonin in *Passiflora sp.*, and our analyses have given negative results in the phytomelatonin determination in all the samples tested (data not shown). However, passionflower is very rich in flavonoids such as chrysin, vitexin and isovitexin. These compounds bind to GABA receptors in the brain, acting similarly to a natural relaxant (Araújo et al., 2025). Although the plant does not contain phytomelatonin, studies in animals demonstrate that the *Passiflora* extract administration can increased the levels of endogenous melatonin in the blood (Kim et al., 2020).

The new component assayed from saffron floral bioresidues showed an interesting phytomelatonin content (1.17 µg/g DW) and also can be used as enrichment of nutraceutical foods due their interesting polyphenolic profile (Maestre-Hernandez et al., 2025; Maestre-Hernández et al., 2023). According to the data presented in this study, saffron floral waste could be applied as a natural raw of phytomelatonin,

focused on obtaining herbal supplements aimed at improving sleep and anxiety.

IV. CONCLUSIONS

The floral bioresidues of *Crocus sativus* analyzed showed relevant levels of phytomelatonin, like that detected in Valerian roots. In these 10 species analyzed, the order in terms of phytomelatonin content would be: St. John's Wort > valerian > saffron floral biowaste > catnip > lemon verbena > lemon thyme > spearmint > German chamomile > lemon balm > Moroccan chamomile. It suggests the possible application of saffron floral bioresidues as a raw material rich in phytomelatonin and its use to relieve symptoms associated with nervousness and anxiety. These data highlight the interest in the role of phytomelatonin for the management of emotional and sleep disorders from phytotherapy. Thus, herbal combinations focus on anxiety, and sleep improvement should be formulated considering both their phytomelatonin levels and other natural bioactive agents, such as flavonoids. Finally, a key consideration for the nutraceutical industry is the exclusive use of botanical sources with sufficient phytomelatonin to replace synthetic melatonin in dietary supplements. While recent literature reviews this transition (Arnao et al., 2023; Cano et al., 2024b), several innovative prototypes developed by our group stand out as viable candidates for this natural shift.

AUTHOR CONTRIBUTIONS

Conceptualization, M.B.A.; methodology, J.H.R., and A.C.; formal analysis, AB.M.H., A.E.M. and S.K.; software, S.K., A.E.M. and A.C.; validation, AB.M.H., A.C. and J.H.R.; investigation, AB.M.H., A.E.M. and S.K.; data curation, AB.M.H., S.K., M.B.A., A.C. and J.H.R.; writing original draft preparation, A.E.M. and M.B.A.; writing review and editing, M.B.A.; visualization, M.B.A., A.C. and J.H.R.; funding acquisition, M.B.A. All authors have read and agreed to the published version of the manuscript.

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The original dataset is available from the corresponding author upon request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

[1] Agathokleous, E., Kitao, M., & Calabrese, E. J. (2019). New insights into the role of melatonin in plants and animals. *Chemico-Biological Interactions*, *299*, 163–167. http://www.sciencedirect.com/science/article/pii/S0009279718315369

[2] Ahn, J. H., Park, J. H., Kim, I. H., Lee, J.-C., Yan, B. C., Yong, M. S., Lee, C. H., CHoi, J. H., Yoo, K.-Y., Hwang, I. K., Moon, S. M., Shin, H.-C., & Won, M.-H. (2014). Comparison of arylalkylamine N-acetyltransferase and melatonin receptor type 1B immunoreactivity between young adult and aged canine spinal cord. *Journal of Veterinary Science*, *15*(3), 335–342. https://doi.org/10.4142/jvs.2014.15.3.335

[3] Alanazi, H. H., Elasbali, A. M., Alanazi, M. K., & El Azab, E. F. (2023). Medicinal Herbs: Promising Immunomodulators for the Treatment of Infectious Diseases. *Molecules*, *28*(24), Article 24. https://doi.org/10.3390/molecules28248045

[4] Andronachi, V.-C., Simeanu, C., Matei, M., Radu-Rusu, R.-M., & Simeanu, D. (2025). Melatonin: An Overview on the Synthesis Processes and on Its Multiple Bioactive Roles Played in Animals and Humans. *Agriculture*, *15*(3), Article 3. https://doi.org/10.3390/agriculture15030273

[5] Anghel, L., Baroiu, L., Popazu, C. R., Pătraș, D., Fotea, S., Nechifor, A., Ciubara, A., Nechita, L., Muşat, C. L., Stefanopol, I. A., Tatu, A. L., & Ciubara, A. B. (2022). Benefits and adverse events of melatonin use in the elderly (Review). *Experimental and Therapeutic Medicine*, *23*(3), 219. https://doi.org/10.3892/etm.2022.11142

[6] Araújo, P. C., Ramos, C. C., & de Oliveira, D. B. (2025). Investigation into the Sleep-Promoting Effects of the Traditional Use of Passionflower (Passiflora spp.), Chamomile (Matricaria chamomilla L.) and Mulungu (Erythrina spp.) in Brazil. *Drugs and Drug Candidates*, *4*(1), Article 1. https://doi.org/10.3390/ddc4010011

[7] Arnao, M. B., Cano, A., & Hernández-Ruiz, J. (2022). Phytomelatonin: An unexpected molecule with amazing

performances in plants. *Journal of Experimental Botany*, *73*(17), 5779–5800. https://doi.org/10.1093/jxb/erac009

[8] Arnao, M. B., Giraldo-Acosta, M., Castejón-Castillejo, A., Losada-Lorán, M., Sánchez-Herrerías, P., El Mihyaoui, A., Cano, A., & Hernández-Ruiz, J. (2023). Melatonin from Microorganisms, Algae, and Plants as Possible Alternatives to Synthetic Melatonin. *Metabolites*, *13*(1), Article 1. https://doi.org/10.3390/metabo13010072

[9] Arnao, M. B., & Hernández-Ruiz, J. (2009). Assessment of different sample processing procedures applied to the determination of melatonin in plants. *Phytochemical Analysis*, *20*, 14–18.

[10] Arnao, M. B., & Hernández-Ruiz, J. (2018a). Phytomelatonin, natural melatonin from plants as a novel dietary supplement: Sources, activities and world market. *Journal of Functional Foods*, *48*, 37–42. https://doi.org/10.1016/j.jff.2018.06.023

[11] Arnao, M. B., & Hernández-Ruiz, J. (2019). Melatonin: A New Plant Hormone and/or a Plant Master Regulator? *Trends in Plant Science*, *24*(1), 38–48. https://doi.org/10.1016/j.tplants.2018.10.010

[12] Arnao, M. B., & Hernández-Ruiz, J. (2018b). Phytomelatonin versus synthetic melatonin in cancer treatments. *Biomedical Research and Clinical Practice*, *3*, 1–6. https://doi.org/10.15761/BRCP.1000170

[13] Arora, H., & Ivanovski, S. (2017). Melatonin as a pro-osteogenic agent in oral implantology: A systematic review of histomorphometric outcomes in animals and quality evaluation using ARRIVE guidelines. *Journal of Periodontal Research*, *52*(2), 151–161. https://doi.org/10.1111/jre.12386

[14] Blask, D. E., Dauchy, R. T., Sauer, L. A., & Krause, J. A. (2004). Melatonin uptake and growth prevention in rat hepatoma 7288CTC in response to dietary melatonin: Melatonin receptor-mediated inhibition of tumor linoleic acid metabolism to the growth signaling molecule 13-hydroxyoctadecadienoic acid and the potential role of phytomelatonin. *Carcinogenesis*, *25*(6), 951–960. http://carcin.oxfordjournals.org/content/25/6/951.abstract

[15] Boachon, B., Buell, C. R., Crisovan, E., Dudareva, N., Garcia, N., Godden, G., Henry, L., Kamileen, M. O., Kates, H. R., Kilgore, M. B., Lichman, B. R., Mavrodiev, E. V., Newton, L., Rodriguez-Lopez, C., O'Connor, S. E., Soltis, D., Soltis, P., Vaillancourt, B., Wiegert-Rininger, K., & Zhao, D. (2018). Phylogenomic Mining of the Mints Reveals Multiple Mechanisms Contributing to the Evolution of Chemical Diversity in Lamiaceae. *Molecular Plant*, *11*(8), 1084–1096. https://doi.org/10.1016/j.molp.2018.06.002

[16] Boga, J. A., Caballero, B., Potes, Y., Perez-Martinez, Z., Reiter, R. J., Vega-Naredo, I., & Coto-Montes, A. (2019). Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. *Journal of Pineal Research*, *66*(1), e12534. https://doi.org/10.1111/jpi.12534

[17] Borrás, S., Martínez-Solís, I., & Ríos, J. L. (2021). Medicinal Plants for Insomnia Related to Anxiety: An Updated Review. *Planta Medica*, *87*(10–11), 738–753. https://doi.org/10.1055/a-1510-9826

[18] Cano, A., Hernández-Ruiz, J., & Arnao, M. B. (2024a). Common Methods of Extraction and Determination of Phytomelatonin in Plants. In F. J. Corpas & J. M. Palma (Eds.), *ROS Signaling in Plants: Methods and Protocols* (pp. 161–181). Springer US. https://doi.org/10.1007/978-1-0716-3826-2_11

[19] Cano, A., Hernández-Ruiz, J., & Arnao, M. B. (2024b). Current state of the natural melatonin: The phytomelatonin market. *Melatonin Research*, *7*(3), 242–248. https://doi.org/10.32794/mr112500179

[20] Cano, A., Hernández-Ruiz, J., & Arnao, M. B. (2024c). Role of Exogenous Melatonin in Plant Biotechnology: Physiological and Applied Aspects. *Critical Reviews in Plant Sciences*, *43*(6), 395–404. (world). https://www.tandfonline.com/doi/abs/10.1080/07352689.2024.2394002

[21] Carrascal, L., Nuñez-Abades, P., Ayala, A., & Cano, M. (2018). Role of melatonin in the inflammatory process and its therapeutic potential. *Current Pharmaceutical Design*, *24*(14), 1563–1588. http://www.eurekaselect.com/node/161582/article

[22] Castejón-Castillejo, A., Hernández-Ruiz, J., Cano, A., & Arnao, M. B. (2025). Synthetic Melatonin and/or Phytomelatonin Contents in Different Commercial Phytotherapeutic Supplements. *Nutraceuticals*, *5*(2). https://doi.org/10.3390/nutraceuticals5020009

[23] Choi, D. (2019). Effects of dietary supplement containing melatonin on reproductive activity in male golden hamsters. *Dev Reprod*, *23*(2), 101–110.

[24] Chung, M.-H., & Deng, T.-S. (2020). Effects of circadian clock and light on melatonin concentration in Hypericum perforatum L. (St. John's Wort). *Botanical Studies*, *61*(1), 23. https://doi.org/10.1186/s40529-020-00301-6

[25] Dehdari Ebrahimi, N., Sadeghi, A., Shojaei-Zarghani, S., Shahlaee, M. A., Taherifard, E., Rahimian, Z., Eghlidos, Z., Azarpira, N., & Safarpour, A. R. (2023). Protective effects of exogenous melatonin therapy against oxidative stress to male reproductive tissue caused by anti-cancer chemical and radiation therapy: A systematic review and meta-analysis of animal studies. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1184745

[26] DOCM-10. (1999). *Specifications for the Saffron Protected by This Denomination of Origin, Which Includes Those Saffron Produced in a Defined Geographical Area of the Autonomous Community of Castilla-La Mancha.* Junta de Comunidades de Castilla—La Mancha (JCCM). https://docm.jccm.es/docm/verDisposicionAntigua.do?ruta=1999/02/19&idDisposicion=123061871701130333

[27] El Mihyaoui, A., Erbiai, E. H., Charfi, S., Pinto, E., Castillo, M. E. C., Hernández-Ruiz, J., Cano, A., Badoc, A., Lamarti, A., Esteves da Silva, J. C. G., & Arnao, M. B. (2023). Chemical Characterization and Several Bioactivities of Cladanthus mixtus from Morocco. *Molecules*, *28*(7), Article 7. https://doi.org/10.3390/molecules28073196

[28] El Mihyaoui, A., Esteves da Silva, J. C. G., Charfi, S., Candela Castillo, M. E., Lamarti, A., & Arnao, M. B. (2022). Chamomile (Matricaria chamomilla L.): A Review of Ethnomedicinal Use, Phytochemistry and Pharmacological Uses. *Life*, *12*(4), Article 4. https://doi.org/10.3390/life12040479

[29] Francesca, B., Borsani, E., Favero, G., Rodella, L., & Rezzani, R. (2018). Dietary melatonin supplementation could

be a promising preventing/therapeutic approach for a variety of liver diseases. *Nutrients*, *10*, 1135.

[30] Future Market Insights. (2024). *Melatonin Market*. https://www.futuremarketinsights.com/reports/melatonin-market

[31] Gonciarz, M., Wiatrak, B., Lombard, I., Konecki, Ł., & Sarbinowska, J. (2026). Therapeutic Potential of Melatonin in Gastrointestinal Cancers: Molecular Mechanisms, Preclinical Evidence and Clinical Implications. *Journal of Pineal Research*, *78*(1), e70101. https://doi.org/10.1111/jpi.70101

[32] Griffin, F., & Marignol, L. (2018). Therapeutic potential of melatonin for breast cancer radiation therapy patients. *International Journal of Radiation Biology*, *94*(5), 472–477. https://doi.org/10.1080/09553002.2018.1446227

[33] Haldar, C., Ghosh, S., & Singh, A. K. (2014). Phyto-melatonin: A Novel Therapeutic Aspect of Melatonin in Nature's Way. In V. Srinivasan, G. Gobbi, S. Shillcutt, & S. Suzen (Eds.), *Melatonin: Therapeutic Value and Neuroprotection* (Vols. 1–43, pp. 515–522). CRC Press.

[34] HMPC-EMA. (2016). European Union herbal monograph on Valeriana officinalis L., radix. *Herbal Medicinal Products Committee*, *EMA/HMPC/150848/2015*, 9.

[35] Johns, N. P., Johns, J., Porasupthana, S., Plaimee, P., & Sae-Teaw, M. (2013). Dietary intake of melatonin from tropical fruit altered urinary excretion of 6-sulfatoxymelatonin in healthy volunteers. *Journal of Agricultural and Food Chemistry*, *61*, 913–919.

[36] Kenefick, K. (2012, January 18). *Catnip and Its Effect on Cats, Dogs and Humans*. Promega Connections. https://www.promegaconnections.com/catnip-and-its-effect-on-cats-dogs-and-humans/

[37] Kim, G.-H., Kim, Y., Yoon, S., Kim, S.-J., & Yi, S. S. (2020). Sleep-inducing effect of Passiflora incarnata L. extract by single and repeated oral administration in rodent animals. *Food Science & Nutrition*, *8*(1), 557–566. https://doi.org/10.1002/fsn3.1341

[38] Li, C., Ma, D., Li, M., Wei, T., Zhao, X., Heng, Y., Ma, D., Anto, E. O., Zhang, Y., Niu, M., & Zhang, W. (2022). The Therapeutic Effect of Exogenous Melatonin on Depressive Symptoms: A Systematic Review and Meta-Analysis. *Frontiers in Psychiatry*, *13*, 737972. https://doi.org/10.3389/fpsyt.2022.737972

[39] Li, L., Wang, L., & Zhang, L. (2024). Therapeutic Potential of Natural Compounds from Herbs and Nutraceuticals in Alleviating Neurological Disorders: Targeting the Wnt Signaling Pathway. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/acs.jafc.3c07536

[40] Maestre-Hernandez, A. B., Kaabi, S., Cano, A., Hernandez-Ruiz, J., & Arnao, M. B. (2025). Phytochemicals and Biological Activities of Flowers of Crocus sativus L. (Saffron). In H. N. Murthy, *Bioactive Compounds in Edible Flowers* (1st ed., pp. 345–359). CRC Press. https://doi.org/10.1201/9781003645979-16

[41] Maestre-Hernández, A.-B., Vicente-López, J.-J., Pérez-Llamas, F., Candela-Castillo, M.-E., García-Conesa, M.-T., Frutos, M.-J., Cano, A., Hernández-Ruiz, J., & Arnao, M. B. (2023). Antioxidant Activity, Total Phenolic and Flavonoid Contents in Floral Saffron Bio-Residues. *Processes*, *11*(5), Article 5. https://doi.org/10.3390/pr11051400

[42] Market Analysis Report. (2021). *Melatonin Market Size, Share & Trends Analysis Report By Application, Regional Outlook, Competitive Strategies, And Segment Forecasts, 2019 To 2025*. https://www.grandviewresearch.com/industry-analysis/melatonin-market

[43] Mayo, J. C., Sainz, R. M., Tan, D. X., Hardeland, R., Leon, J., Rodriguez, C., & Reiter, R. J. (2005). Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages. *Journal of Neuroimmunology*, *165*(1), 139–149. http://linkinghub.elsevier.com/retrieve/pii/S0165572805001724?showall=true

[44] Meng, X., Li, Y., Li, S., Zhou, Y., Gan, R.-Y., Xu, D.-P., & Li, H.-B. (2017). Dietary Sources and Bioactivities of Melatonin. *Nutrients*, *9*(4), Article 4. https://doi.org/10.3390/nu9040367

[45] Mihai, M., Ciont, C., Pop, O.-L., Dumitras, D. E., Mihai, V. C., Morariu, I. D., & Pocol, C. B. (2025). European Consumer and Regulatory Trends in Medicinal Plant Food Supplements and Their Functional Properties: The Road from Farm to Fork. *Applied Sciences*, *15*(21). https://doi.org/10.3390/app152111605

[46] Mordor Intelligence. (2021). *Melatonin market—Growth, trends, covid-19 impact, and forecasts (2022—2027)*. https://www.mordorintelligence.com/industry-reports/melatonin-market

[47] Okeke, E. S., Ogugofor, M. O., Nkwoemeka, N. E., Nweze, E. J., & Okoye, C. O. (2021). Phytomelatonin: A potential phytotherapeutic intervention on COVID-19-exposed individuals. *Microbes and Infection*, 104886. https://www.sciencedirect.com/science/article/pii/S1286457921001088

[48] Pereira, N., Naufel, M. F., Ribeiro, E. B., Tufik, S., & Hachul, H. (2020). Influence of Dietary Sources of Melatonin on Sleep Quality: A Review. *Journal of Food Science*, *85*(1), 5–13. https://doi.org/10.1111/1750-3841.14952

[49] Research and Markets. (2024). *2024 Melatonin Market Outlook Report: Industry Size, Market Shares Data, Insights, Growth Trends, Opportunities, Competition 2023 to 2031*. 2024 Melatonin Market Outlook Report. https://www.researchandmarkets.com/reports/4834539/2024-melatonin-market-outlook-report-industry

[50] Sangsopha, J., Johns, N. P., Johns, J., & Moongngarm, A. (2020). Dietary sources of melatonin and benefits from production of high melatonin pasteurized milk. *Journal of Food Science and Technology*, *57*(6), 2026–2037. https://doi.org/10.1007/s13197-020-04236-5

[51] Tresguerres, I. F., Tamimi, F., Eimar, H., Barralet, J. E., Prieto, S., Torres, J., Calvo-Guirado, J. L., & Tresguerres, J. A. F. (2014). Melatonin dietary supplement as an anti-aging therapy for age-related bone loss. *Rejuvenation Research*, *17*(4), 341–346. https://doi.org/10.1089/rej.2013.1542