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Phytomelatonin: a potential phytotherapeutic intervention on COVID-19-exposed individuals

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Abstract
Phytomelatonin is a pleiotropic molecule that originated in higher plants with many diverse actions and is primarily an antioxidant. The recent identification and advancement of phytomelatonin unraveled the potential of this modulatory molecule being considered a new plant hormone, suggesting its relevance in treating respiratory infections, including COVID-19. Besides, this molecule is also involved in multiple hormonal, physiological, and biological processes at different levels of cell organization and has been marked for its ability to cross the blood-brain barrier and prominent antioxidant effects, reducing mitochondrial electron leakage, up-regulating antioxidant enzymes, acting as a free radical scavenger, and interfering with pro-inflammatory signaling pathways as seen in mood swings, body temperature, sleep, cancer, cardiac rhythms, and immunological regulation modulators. However, due to its diversity, availability, affordability, convenience, and high safety profile, phytomelatonin has also been suggested as a natural adjuvant. This review discussed the origin, content in various plant species, processes of extraction, and detection and therapeutic potentials of phytomelatonin in treating COVID-19-exposed individuals.

Keywords: Phytomelatonin, Antioxidant, Anti-inflammatory, Phytotherapeutic, COVID-19-exposed individuals

Over the years, discovering potential medicinal plants and concurrent screening of their biological activities has increased significantly, intending to provide useful information to enable patients and physicians to make rational decisions [1]. These medicinal plants can be in the form of plant extract (either as standardized extracts or in pure form). They have paved the way to a wide range of opportunities in drug discoveries due to their unlimited availability/unaltered diversity of their chemical constituents [2,3]. Melatonin is a ubiquitous biological molecule with a wide array of biological activities in plants, animals, unicellular organisms, and fungi. Melatonin plays vital regulatory roles in sleep, body temperature balance, locomotory activities, circadian rhythms, immune system, and retinal physiology [4,5]. In 1958, the bovine pineal gland was the first source of melatonin. It was isolated and identified as N-acetyl-5-methoxy tryptamine [6]. At physiological concentrations, melatonin has been shown to have good antioxidant capacity [7,8]. It has been employed as an anti-cancerous agent to decelerate cancerous cells’ growth rate [9,10]. Phytomelatonin is a term used to refer to melatonin from plant origin.

In this review, we presented the origin of phytomelatonin, its content in various plant species. Additionally, we went further to give an overview of the extraction, detection, and isolation of melatonin form using notable instruments and the pro-inflammatory mediators in patients living with COVID-19 which could be coupled with the anti-inflammatory and antioxidant effects of phytomelatonin for therapeutic intervention in COVID-19 individuals.
1. Origin of phytomelatonin

A widespread molecule named melatonin was discovered in living organisms previous years ago. This molecule is also involved in multiple hormonal, physiological, and biological processes at different levels of cell organization. It has been marked for its ability to cross the blood-brain barrier and prominent antioxidant effects, reducing mitochondrial electron leakage, up-regulating antioxidant enzymes, acting as a free radical scavenger, and interfering with pro-inflammatory signaling pathways \[11\]. Phytomelatonin (N-acetyl-5-methoxytryptamine) is related to an indoleamine derivative of the amino acid tryptophan chemically (Fig. 1). The compound of melatonin of animal origin or obtained by chemical synthesis is called melatonin, while plant origin is termed phytomelatonin \[12\]. In 1993, Van Tassel and his group in a congress communication described how they identified the endogenous phytomelatonin in higher plants by Gas chromatography by Mass spectrophotometer and Radio immune assay in a flowering plant named ivy morning glory (Pharbitis nil L.) and tomato fruits (Solanum lycopersicum L.) \[13\]. In 1995, Dubbels and his companions measured the levels of phytomelatonin in five edible plants in extracts of Nicotiana tabacum L. using Radio Immune Assay (RIA) and High-performance Liquid Chromatography-Mass Spectrometer (HPLC-MS) \[7\]. Later on, the Japanese group quantified the presence of melatonin in large quantities of edible plants by RIA and HPLC with Fluorescent detection \[14\].

Furthermore, the Czech research group detected phytomelatonin in Chenopodium rubrum L. using Liquid chromatography with mass identification LC/MS/MS. Quantitative analysis of phytomelatonin in many plants has been carried out previously by many researchers, and to date, the presence of this molecule in all plants has gained acceptance \[15\]. While low levels (pg to ng/g) of phytomelatonin are found in most plant tissues generally, higher levels are detected in leaves and medicinal plants \[16,17\].

Melatonin of plant origin is termed phytomelatonin, and that of synthetic or animal origin is melatonin, but structurally, melatonin and phytomelatonin are the same molecules. Melatonin was discovered to be naturally produced as tryptophan in cell species with mitochondria (either in plants, animals, unicellular organisms, and fungi). In plants, melatonin abundance varies. Several studies have documented the occurrence of phytomelatonin in medicinal herbs, fruits, wild plants, and vegetables, with a higher occurrence in aromatic plants and leaves than in seeds. However, as documented previously in decreasing order, the trend for its occurrence was leaves > seeds > roots > flowers > fruits, even though the data are missing in some plant organs \[18\]. Still, its highest levels have been found in reproductive organs, especially in seeds, because reproductive functions well in plant species survival. This plant has generated a wide range of metabolic, physiological, and cellular responses. It also acts as a biostimulator, plant growth regulator and reduces secondary oxidative stress in plants \[17,19,20\]. Phytomelatonin is an interesting compound due to its outstanding actions at the cellular and physiological levels, especially its protective effect in plants exposed to diverse stress situations. Simultaneously, its vegetable origin offers many opportunities because it is a natural compound \[17\]. The use of phytomelatonin in cosmetics and dietary derivatives has been documented. As an anti-tumor agent, it prevents residual synthetic by-products from being incorporated during tumor treatments. The consumption of melatonin (synthetic or phytomelatonin) plays a crucial role in some critical aspects of human bodily actions leading to beneficial effects on diseases and disorders, sleep regulation, immune, body temperature, mood, food intake patterns, locomotor activity, and circadian rhythms, among others \[18,21,22\].

Furthermore, several phytomelatonin-rich extracts of plant antioxidants such as simple phenols, flavonoids, tocopherols, ascorbic acid, carotenoids, and others, might be significant for maintaining a proper cell redox balance. In some experimental studies, it was proven that after consuming melatonin-containing food, the melatonin concentration in human serum could significantly increase. Also, some phytomelatonin rich foods have been analyzed. A general healthy effect in antioxidant status and increase in plasma melatonin levels, and increased sleep quality parameters were recorded \[23–26\]. Researchers have discovered many aromatic and medicinal plants and edible plants, including the herbs roots, leaves, fruits, and seeds of a considerable variety of plant species contains melatonin which has been classified and has used in ethnomedicine to treat numerous diseases of the central and peripheral nervous system (Table 1) \[5,15,27\]. In medicine, laboratory synthesized melatonin generated above 80% yield is often used, most commonly available in many forms such as pills, chewable, and liquids. Consumption of natural melatonin-rich edible medicinal herbs and foods, such as pineapple, banana, strawberry, carrot, onion, tomato, thyme, cucumber, cabbage, corn, as well as synthetic melatonin, has many benefits in human health.

![Fig. 1. Melatonin biosynthesis pathway.](image-url)
of melanin in the living pineal gland at night [30]. Their position was based on their findings that the decrease of NAT activity of more than 10-fold did not cause a corresponding reduction in melatonin production. Also, NAS is found in vast molar excess compared with melatonin within 1 h of lights-off. In addition, NAT protein levels increase throughout the night, while melatonin output approaches peak levels within 3 h of lights-off. Also, continuous increase of NAS over consecutive circadian cycles within the same animals in vivo did not cause a rise in melatonin output [31]. In addition, the synthesis of melatonin is continuous, though the peak of its production and subsequent release from the pineal gland occurs only at night. About 30 g of melatonin is reported to be synthesized per day in an adult, while the maximal concentration in the blood is achieved in the mid-dark period [32].

One of the significant issues with phytomelatonin quantification in plants has been the great variability of biosynthetic complexity compared to animals [33]. The melatonin biosynthetic pathway has been clearly determined in animals, including mammals, where melatonin biosynthesis is under the successive regulation of four enzymes [17]. Melatonin can be metabolized in living tissues via enzymatic or non-enzymatic pathways. In plants, melatonin is converted to 2-hydroxy melatonin (2-OH) M, unlike mammals, where melatonin metabolism is established differently [34]. Kim et al. [35] and Slowinski et al. [31] indicated that 6-hydroxy melatonin (6-OH) M, N1 - acetyl-2 formyl-5 methoxykynuramine (AFMK), and 5-methoxytryptamine (5-MT) are metabolites of melatonin in skin cells [36]. These products are usually obtained via two pathways: kynuric and indolic pathways. The 6-hydroxy melatonin and (5-MT) are the major and minor metabolites via the indolic pathway, respectively, while N1 - acetyl-N2 - formyl-5 methoxykynuramine was detected in the kynuric pathway [37]. AFMK is the only antioxidant that can donate two electrons for reduction, unlike other antioxidants. This compound is more active biologically than its parent compound (melatonin) since it can serve as an antioxidant and modulate cutaneous cancerous cells' proliferation (anti-carcinogenic). It can be easily detected when the skin is under environmental stress like UV exposure [37,38]. In addition to the fact that abiotic factors mainly modulate melatonin biosynthesis in plants, tryptophan is transformed into 5-hydroxytryptophan by tryptophan 5-hydroxylase to produce serotonin [16]. Besides, 5-hydroxytryptamine is generated from tryptamine, obtained from tryptophan via an alternative pathway catalyzed by the same enzymes. This additional pathway indicates that the action of enzymes in plants to produce serotonin varies from that observed in animals. The first pathway occurs mainly in mammals, whereas the second one occurs in plants. Another pathway not seen in animals is associated with tryptamine, acting as a substrate of serotonin N-acetyltransferase, forming N-acetyltryptamine, which can be hydroxylated to form N-acetylsertotonin [17,33].

Proper extraction and difficulty in recovering phytomelatonin from plant extracts, for example, walnut, because of its implications in human consumption was the initial challenge to phytomelatonin quantification as its level varies from plant to plant [39–41]. Organic solvents such as chloroform, methanol, or ethyl acetate are generally used to extract melatonin from liquid nitrogen-treated plants. However, low recovery rates have been reported with aqueous extraction [42] due to the amphiphatic nature of melatonin molecules, organic solvents with direct sample extraction procedures (without homogenization of fresh tissues) are highly suggested [15]. Extraction, purification, and determination of melatonin from higher plants with different methods have been carried out previously by different researchers. Simpler extraction solvents-phosphate-buffered saline, ethanol [27], 10% Na2CO3 [3], or potassium phosphate buffer have been employed by many

### Table 1

| Common name | Scientific name | Plant organ | Reference |
|-------------|----------------|-------------|-----------|
| Apple       | Malus domestica (Borkh) | Fruit | [14] |
| Asparagus   | Asparagus officinalis (L.) | Shoot | [14] |
| Onion Bulb  | Allium cepa (L.) | Bulb | [14] |
| Cucumber    | Cucumis sativus (L.) | Fruit | [14] |
| Banana      | Musa paradisiaca (L.) | Fruit | [20] |
| Morning glory| Pharbitis nil (Choisy) | Shoot | [51] |
| Almond      | Prunus amygdalus (Batsch.) | Seeds | [19] |
| Cabbage     | Brassica oleracea (L.) | Leaf | [14] |
| Tomato      | Lycopersicon esculentum (Mill.) | Fruch | [89] |
| Dat         | Avana sativa (L.) | Seeds | [14] |
| Corn        | Zea mays (L.) | Seeds | [14] |
| Curcuma     | Curcuma aeruginosa (Roxb.) | Root | [90] |
| Ginger      | Zingiber officinale (Roscoe) | Root | [14] |
| Grape vine  | Vitis vinifera (L.) | Fruit | [91] |
| Sunflower   | Helianthus annuus (L.) | Seeds | [92] |
| White radish| Raphanus sativus (L.) | Root | [90] |
| St. John’s wort | Hypericum perforatum (L.) | Leaf | [93] |
| Walnut      | Juglans regia (L.) | Seed | [91] |
| Burmese grape| Baccarea rumiflora Lour. | Leaf | [94] |
| Feverfew    | Tanacetum parthenium (L.) | Leaf | [95] |
| Pomegranate | Punica granatum (L.) | Fruit | [39] |
| Strawberry  | Fragaria x ananassa (Duch.) | Fruit | [42] |
| Orange juice| Citrus sinensis | Fruit | [41] |
| Feverfew    | Tanacetum parthenium (L.) | Flower | [95] |
| Water hyacinth | Eichhornia crassipes (Marth.) | Flower | [15] |
| Sweet cherries | Prunus cerasus L. | Fruit | [92] |
| Grapevine   | Vitis vinifera (L.) | Fruit | [92] |
| Barley      | Hordeum vulgare (L.) | Seeds | [14] |
| Poppy       | Papaver sommerfera (L.) | Seeds | [92] |
| Turnup      | Brassica campestris (L.) | Root | [92] |
| Flax        | Linum usitatissimum (L.) | Seeds | [92] |
| Anise       | Pimpinella anisum (L.) | Seeds | [92] |
| Alfalfa     | Medicago sativum | Seeds | [92] |
| Black mustard | Brassica nigra (L.) | Seeds | [92] |
| White mustard| Sinapis alba (L.) | Seeds | [92] |
| Coriander   | Coriandrum sativum (L.) | Seeds | [92] |
| Wolf berry  | Lycium barbarum | Seeds | [92] |
| Fenugreek   | Trigonella foenum-graecum (L.) | Seeds | [92] |
| Taficisee   | Festuca arundinacea | Seeds | [14] |
| Java bean   | Senna tora (L.) | Leaf | [94] |
| Fennel      | Foeniculum vulgare (Gilb.) | Seeds | [92] |
| Cherry      | Prunus cerasus (L.) | Fruit | [15] |
| Poppy       | Papaver sommerfera (L.) | seed | [92] |
| Celery      | Apium graveolens | Seed | [92] |
| Wolf berry  | Lycium barbarum | Seed | [92] |
| Milk thistle| Silium marianum | Seeds | [92] |
| Bitter lemon| Moneridica charantia(L) | Leaf | [94] |
| Black pepper| Piper nigrum (L.) | Leaf | [94] |
| Pineapple   | Ananas comosus (Sticht.) Merril. | Fruit | [14] |
| Wild strawberry | Fragaria ananassa (Duch.) | Fruit | [93] |
| Rice        | Oriza sativa japonica (L.) | Seeds | [14] |
| Carrot      | Daucus carota | Root | [14] |
| Beet        | Beta vulgaris (L.) | Root | [20] |

2. Synthesis, extraction, detection, and isolation of melatonin from plants

Melatonin is usually synthesised and secreted by the pineal gland, in which the synthesis is affected by circadian rhythm. During the synthesis of melatonin, the acetylation of serotonin by the enzyme arylalkylamine N-acetyltransferase (AANAT) to generate N-acetyl serotonin (NAS) has been considered as the rate-limiting step [29]. NAS is then methylated into melatonin by hydroxyindole-O-methyltransferase. On the other hand, arylalkylamine N-acetyltransferase does not determine the rate of synthesis of serotonin from tryptophan [37,38]. In addition, the synthesis of melatonin is continuous, though the peak of its production and subsequent release from the pineal gland occurs only at night. About 30 g of melatonin is reported to be synthesized per day in an adult, while the maximal concentration in the blood is achieved in the mid-dark period [32].
The most suggested methods for quantifying and detecting phytomelatonin are liquid chromatography with time-of-flight/mass spectrometry (LC-TOF/MS), liquid chromatography, and identification by mass spectrometry (LC-MS/MS). Multiple reaction monitoring (MRM) and LC-MS/MS with positive electro spray ionization (ESI+) is widely used. Due to cross-reactivity with coextractives, some methods like RIA or ELISA present serious problems during the extraction of melatonin in plants [23,39,42].

There is still much controversy over the stability of melatonin in plants, irrespective of the growing evidence of its importance in plant life. However, a very highly sensitive but less specific method such as LC with electrochemical or fluorometric detection is also outstanding if supplemented by identification by LC-MS/MS [43–49]. Some researchers have used acetone-, Tricine-based extraction mixtures, sometimes including antioxidants, HClO₄, or the chelator EDTA to extract melatonin from plants, while some suggested the use of potent hydroxyl radical scavengers (acetone, Tris/HCl, or Tricine/NaOH buffer) with added antioxidants [13,15,45,50]. Melatonin in plants can be converted to a volatile derivative and quantified by GC-MS. CG-MS, Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been used to identify melatonin in plants [13,51]. Furthermore, a more sensitive technique like HPLC with electrochemical detection, Gas chromatography-mass spectrometry (GC-MS) or LC-MS/MS is often used and in higher plants and algae [15,42,52] even though it is low in specificity — many compounds with similar oxidation potentials may have same retention times to melatonin [52].

3. Molecular immune pathogenesis of COVID-19

The immune system is an essential part of the body system, ensuring that the body is protected from diseases. Typically, immunity is categorized into innate and adaptive immunity. Innate immunity, otherwise called natural immunity, is the first line of defense against invading pathogens [53]. Innate immunity includes cellular defenses such as macrophages, lymphoid cells, dendritic cells, neutrophils, natural killer cells, and epithelial barriers such as skin surface and mucous membrane. Other components of the innate immune system include soluble mediators such as mannose-binding lectin, c-reactive proteins, kinins, and surfactant covering the respiratory passages; pattern recognition receptors; NOD-like receptors (NLRs), C-type lectin receptors (CLRs), toll-like receptors (TLRs), RIG-I-like receptors (RLRs), among others [54]. When COVID-19 virus enters the cells, the viral antigen is probed by the antigen presentation cells (APC) through the help of the major histocompatibility complex (MHC). The antigen is recognized by virus-specific cytotoxic T lymphocytes (CTLs) [55]. However, the antigen presentation activates the body’s humoral and cellular immunity as directed by B and T cells specific to the virus.

3.1. Inflammatory mediators in COVID-19

Inflammation is a protective approach employed by higher organisms in response to stimuli from harmful agents such as microbial infection, tissue injury, and other uncomfortable conditions [56]. Inflammatory stimuli are recognized by the host cells via a specialized transmembrane receptor known as pattern recognition receptors (PRRs). Pattern recognition receptors are germline-encoded receptors that detect cellular damage and the presence of pathogens [56,57]. Acute inflammation has been regarded as an essential part of innate immunity. Acute lung inflammation is a complex pathophysiological mechanism involving various inflammatory mediators such as chemokines and cytokines [53].

3.2. Cytokine storm in COVID-19

Acute respiratory distress syndrome has been regarded as the primary cause of death during COVID-19 infection. An essential mechanism of action of acute respiratory distress syndrome is the cytokine storm. Cytokine storm is a fatal unregulated systemic inflammatory response that arises due to the release of large amounts of pro-inflammatory cytokines such as IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb, and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 by the immune effector cells during SARS-CoV infection [55]. Normally, a cytokine storm activates a violent attack by the immune system on the body leading to ARDS and multiple organ failure which then, causes death in severe cases [58].

3.3. Mechanism of action of inflammatory mediators in COVID-19

The early induction of IL-10 consequent to SARS-CoV-2 infection during the initiation phase in the lung has been reported to indicate a negative feedback mechanism that could provide a countermeasure to inflammation resulting from other pro-inflammatory mediators (Fig. 2) [59]. Activation of pro-inflammatory cytokine and T cell activation and proliferation by IL-10 have been reported responsible for the lethal immunopathological situation observed in COVID-19 patients [60]. However, the increase in endogenous IL-10 production has been thought to activate the immune system and thus enhance the release of other pro-inflammatory mediators of cytokine storm and exacerbate viral-sepsis linked hyper inflammation [60]. Another critical interleukin implicated in COVID-19 is IL-6. IL-6 receptors are present in most immune cells. Thus, IL-6 functions as an activator of immune cell proliferation and differentiation [61]. Due to the significant role played by Interleukins in the pathogenesis of COVID-19 immunopathological condition, possible inhibitors of these pro-inflammatory mediators are being investigated. Under normal conditions, the concentration of circulating IL-6 levels is low, at the range of 1–5 pg/mL, while during COVID 19 infection, it increases uncontrolled [60]. IL-6 proliferation is activated by SARS-CoV-2 or other immune cells [62]. Specifically, CD4+ T lymphocytes differentiate into pathogenic Th1 cells readily, thereby releasing granulocyte colon-stimulating factors and other pro-inflammatory cytokines that facilitate a high expression of IL-6 [60].

4. Anti-inflammatory and antioxidant effect of phytomelatonin in the respiratory level

The scope of the impact of phytomelatonin in humans is broad. Its relevance in respiratory organ and tissue affliction is at its peak since the emergence of the COVID-19 pandemic. Phytomelatonin roles have been seen in mood swings, body temperature, sleep, cancer, cardiac rhythms, and immunological regulation modulators, as well as antioxidant property [18].

4.1. Anti-inflammatory effect

Different biochemical mechanisms impact the anti-inflammatory qualities of phytomelatonin. A protein deacetylator identified as silent mating type information regulation 2 homolog 1, also known as sir2uin-1 (SIRT1) is known to mediate the remedial properties of phytomelatonin. Phytomelatonin can inhibit HMGCR protein, limiting the partitioning of the macrophages in the direction of the pro-inflammation area [63]. A typical example of the impact of melatonin on the up-regulation of SIRT1 was seen in the lung injury induced by exposure to heavy metal chromium [64].
Pro-fibrotic and pro-inflammatory cytokines are usually regulated on the administration of phytomelatonin by inhibiting the nuclear factor-Kappa beta (NF-κβ) and reducing the activity of matrix metalloproteinases-3 (MMP-3) [65]. This has been seen in occasions of acute respiratory diseases and acute lung infections [4]. To shield the lungs from an intending injury, increasing NF-E2-related factor 2 (Nrf2) activities is vital. From the studies of Ahmadi & Ashrafizadeh [66], phytomelatonin escalates the activities of NF-E2-related factor 2. It has been documented and advocated that this compound decreases the mobility of fibroblasts as a result of the curtailed activity of chloride channels which are usually regulated by protein kinase C [67]. Pneumonitis and Lung fibrosis have been known to be impaired by phytomelatonin and its metabolites [68]. They play a role such as the regulation of pro-fibrogenic and inflammatory mechanisms that are involved in the development of pulmonary fibrosis. This mechanism regulation of platelet-derived growth factor, renin-angiotensin system, impaired caveolin 1 function, interleukin 17A, and vascular endothelial growth factor prevents damage to the lung caused by contraction of fibrous tissues at wound sites that in turn distorts the tissue [69].

Phytomelatonin has had positive impacts at the pulmonary level, as observed in different studies. The expression of hypoxia-inducible factor-1α (HIF-1α) and nuclear factor-κB (NF-κB) in low oxygen conditions leads to pulmonary hypertension has been recorded to be inhibited by melatonin. It has repressed the proliferation of pulmonary artery smooth muscle and the level of some phosphorylated kinases elicited by hypoxia [70]. It was also observed that in the process that the plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), heat shock protein 70 extracellular (Hsp70e), and vascular endothelial growth factor (VEGF) were appreciably decreased [71]. These findings put forward that phytomelatonin also has an anti-inflammatory impact at the pulmonary level. A study using an animal model (mice and rats) investigated the effect of melatonin on pulmonary injury caused by ischemia. It was discovered that this compound could prevent the activation of NF-κB and JNK and also boost the activation of Nrf2. It also limited the expression of some inflammatory biomarkers (TNF-α, IKK-γ, interleukin-1β) and apoptotic markers such as Bcl-2-associated X protein (Bax/Bcl-2) and cleaved caspases (CASP3). These mechanisms all together lead to the reduction of programmed cell death of lung cells due to ischemia [72]. When there are surplus fluids in the lungs, it is called pulmonary edema. Exposure to drugs, pneumonia, toxins, and a heart condition can also lead to this phenomenon. This fluid accumulates in the lungs’ air sacs and makes it strenuous to breathe, which can lead to respiratory failure [73]. Administration of phytomelatonin has been seen to alleviate this condition by several mechanisms, some of which are inhibiting NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3), which is also responsible for an inflammatory form of cell death releasing pro-inflammatory cytokines IL-1β, responsible for the inflammation of airways during this pathology [74].

The respiratory infection experienced in cases of COVID-19 is greatly related to what is today known as the cytokine storm or hypercytokinemia. A hyperinflammatory response significantly characterizes this. During this scenario, a violent production of pro-inflammatory cytokines such as TNF-α and IL-1β spiking or accelerates the generation of free radicals. In extreme situations, it can
lead to pronounced COVID-19 signs such as fever, dry cough from a lung injury, and breathing difficulty, leading to death in long-term cases [7]. Usually, in a healthy condition, the body produces its melatonin for inflammatory purposes. It is usually produced using Acetyl coenzyme A (obtained in mitochondrion from pyruvate during glycolysis by pyruvate dehydrogenase complex) as a cofactor for the enzyme (arylalkylamine N-acetyltransferase) required in the rate-limiting step. But in the course of the COVID-19 infection, a Warburg effect improves ATP production and macrophage activity leading to an exacerbated cytokine production [75]. This is mediated by the transcription factor HIF-1α (hypoxia-inducible factor-1α) and the serine/threonine kinase, mTOR (mammalian target of rapamycin), thereby limiting the production of the endogenous melatonin. When phytomelatonin is administered, it represses these mediators, allowing the pyruvate dehydrogenase complex to activate, producing acetyl CoA in the mitochondria and making it available for the continuous production of endogenous melatonin. This, with the administered phytomelatonin, works together to relieve the COVID-19 symptoms [7].

4.2. Antioxidant effect

Phytomelatonin, as seen in recent studies, has displayed relevant synergistic actions with other antioxidants such as vitamin C, vitamin D3, vitamin E, glutathione, and some antioxidant enzymes such as catalase, lipooxygenase, glutathione peroxidase, and reductase, including superoxide dismutase that alters cytokine storm and oxidative stress with impaired acute respiratory distress syndrome (ARDS) secondary to coronavirus disease [76]. Recent findings have also stipulated that increased levels of phytomelatonin have increased the serum antioxidant activity in the blood. It has also inhibited the activity of pro-oxidants [18]. Ji et al. [77] investigated the impact of melatonin on inhaling an environmental pollutant of particulate matter 2.5 μm that leads to chronic cough in a pig. The study uncovered that the oxidative stress caused by the chronic cough from the inhalation of the particulate matter was reduced. Melatonin was used to manage infants with respiratory conditions, and it was seen to instigate antioxidant activities in the lung easing their ailment [78]. Melatonin and its metabolites have also been reported to offer various photoprotective properties, including protecting melanocytes from UVB-induced oxidative stress and DNA damage, serving as local antioxidants under oxidative stress conditions caused by multiple environmental factors and inducing the expression of antioxidative enzymes in melanocytes [79,80].

Severe acute respiratory syndrome (SARS) leads to the development of oxidative stress. This stress leads to low-density lipoproteins (LDL) oxidation, signaling the Toll-like receptor 4 (TLR4)/NF-kB, thereby activating the surplus production of interleukins-6 alveolar macrophages. This causes acute liver injury. The TLR4 serves as a target for melatonin [81]. Cavalcante et al. [82] suggested that the administration of this compound suppressed oxidative stress in patients with chronic obstructive pulmonary disease. Some of the cytokines impacts are pronounced through the exacerbated generation of reactive oxygen species such that by suppressing the signaling molecules that produce the cytokines, melatonin indirectly reduces the damage caused by the generated radicals, thereby acting as an antioxidant. These studies suggest that melatonin can combat the stress-induced from an acute lung injury.

5. Phytomelatonin prospects in COVID-19 treatment

The global transmission of COVID-19, specifically with the outrageous increase in the number of exposed individuals and targeting drugs for new therapeutic purposes, is the cost-effective and invaluable approach to treating or preventing the disease. Recent studies described COVID-19 as a methodologic infectious disease jolting variegated cell types, tissues, and organs. Therefore, apprehension of the multiplex synergy between the virus and other diseases is paramount to discerning COVID-19-related complications and recognizing treatment drugs. Findings from recent studies have used novel artificial intelligence and other platforms to identify possible drugs for COVID-19 treatment and have proposed phytomelatonin as a promising adjuvant [83]. Likewise, Slominski et al. [84] reported the anti-inflammatory potential of active hydroxyl forms of vitamin D in treating COVID-19 diseases respiratory distress (ARDS). Besides, very recent findings indicate that inflammation is a major feature in COVID-19 patients. Therefore, it is suggested that excessive inflammation, and defective immune system, considerably contribute to the pathogenesis of COVID-19. However, the potential benefits of phytomelatonin use as anti-oxidation, anti-inflammation, immune response regulation that has frequently manifested in respiratory disorders through drug discovery trials could be successive in COVID-19 induced viral infections [85]. The presence of phytomelatonin in large doses in many plant species has opened the door to its use as a natural adjuvant. The biosynthesis of phytomelatonin differs from that in animals, including humans, and its regulation by environmental factors is the basis of the large variability in the phytomelatonin levels observed in plants [17]. Therefore, large doses of phytomelatonin would be beneficial to use in the treatment of COVID-19 infections. Phytomelatonin is synthesized in large quantities, readily available, inexpensive, easily self-administered, and has a very high safety profile [7]. Phytomelatonin has been characterized as a safe adjuvant, but its application in COVID-19 is imprecise. The recent studies on the application of phytomelatonin in humans have indicated its effectiveness and immunity in COVID-19 exposed individuals [85]. For instance, the analysis of patients' data from the COVID-19 registry revealed that melatonin usage was associated with a nearly 30 percent reduced likelihood of testing positive for COVID-19 after adjusting for age, race, employment history, and various disease comorbidities [86].

The population with the most significant susceptibility to becoming infected and developing a severe COVID-19 infection involves the elderly and health workers, patients with hypertension, diabetes, and various cardiovascular pathologies. One feature common to these groups of people is their depressing night-time melatonin rise and exposure. The production of natural melatonin progressively decreases with increased age, and the lowest levels are found among the elderly. Impaired nocturnal melatonin secretion is also observed in hypertensive patients and night-time workers [87]. The pulmonary effects of phytomelatonin have been tested in adult animals, and it improved right ventricular function and reduced cardiac refitting in pulmonary hypertensive (PAH) rats, suggesting a pressure decrease in the pulmonary artery. Besides, phytomelatonin vitiated pulmonary hypertension by alienating the oxidative injury and restoring nitric oxide production in rats with chronic obstructive pulmonary disease.

Interestingly, the anti-inflammatory effects of phytomelatonin manifested in the restoration of vascular homeostasis in PAH mice and improved endothelial profluence. Finally, the direct vasodilator effects of phytomelatonin in pulmonary arteries and veins on adult animals have also been reported [88]. Based on the foregoing, it is pertinent to cipher that the use of phytomelatonin has great potential as a therapy for COVID-19-exposed individuals both at physiological and pharmacologic dosages (Fig. 3). Therefore, the search for and study of phytomelatonin as an adjuvant should be prioritized.
6. Conclusion

A large body of evidence has proven the multiple roles of melatonin in hormonal, physiological, and biological processes at different levels of cell organization. Therefore, it is imperative to evaluate its potentials since its sources are readily available and relatively cheap compared to other orthodox active ingredients in the current COVID-19 drugs, making it cost-effective. We, therefore, suggest that phytomelatonin, just like melatonin, will find extensive application in the management and possibly treatment of COVID-19-exposed individuals. The search for and study of phytomelatonin as an adjuvant should be prioritized.

Declaration of competing interest

The authors declare that they have no conflicting interest in the publication.

References

[1] Enechi OC, Okeke ES, Nwankwo NE, Nweke JE, Obior CP, Okoye CI, et al. Membrane stabilization, albumin denaturation, protease inhibition, and antioxidant activity as possible mechanisms for the anti-inflammatory effects of flavonoid-rich extract of *Peltophorum reticulatum* (DC.). K.Heyne (FREPP) stem bark. Trop J Nat Prod Res 2020;4:812–6.
[2] Okeke ES, Enechi OC, Nwankwo NE, Nwodo OFC. Evaluation of the phytochemical constituents and anti-inflammatory potential of *fagara zanthoxyloides* root-bark using in vivo and in vitro models. Pharmacologline 2019;2:212–24.
[3] Andong FA, Okwuonu ES, Melefa TD, Okoye CO, Nkemakolam AO, Hinsikayie FF, et al. The consequence of aqueous extract of tobacco leaves (*Nicotiana tabacum* L.) feed intake, body mass, and hematological indices of male wistar rats fed under equal environmental conditions. J Am Coll Nutr 2020;40:127–37. https://doi.org/10.1080/07315724.2020.1784471.
[4] Carrillo-Vico A, Lardone PJ, Manchester LC, Tan DX, Reiter RJ. Phytomelatonin: a pineal gland factor that lightens melanocytes. J Am Chem Soc 1958;80:2587. https://doi.org/10.1021/ja0143a096.
[5] Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W. Isolation of melatonin, the entrainment of the mammalian circadian clock. *Nature* 1995;376:137–8. https://doi.org/10.1038/376137a0.
[6] Paredes SD, Korkmaz A, Manchester LC, Tan DX, Reiter RJ. Phytomelatonin: a new plant hormone? *Biological Rhythm Research* 2008;3:825–7.
[7] Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A. Therapeutic algorithm for use of melatonin in patients with COVID-19. Front Med 2020;7:1–7. https://doi.org/10.3389/fmed.2020.00226.
[8] Bhavsar B, Farooq M, Bhatt A. The therapeutic potential of melatonin in neurological disorders. Recent Pat Endocr Metab Immune Drug Discov 2008;3:60–4. https://doi.org/10.2174/1877221087807003001.
[9] Srinivasan V, Cardinale DP, Srinivasan US, Kaur C, Brown GM, Spence DW, et al. Therapeutic potential of melatonin and its analogs in Parkinson’s disease: focus on sleep and neuroprotection. Ther Adv Neurol Disord 2011;4:297–317. https://doi.org/10.1177/1758285611401666.
[10] Wang JZ, Wang ZF. Role of melatonin in Alzheimer-like neurodegeneration. Acta Pharmacol Sin 2006;27:41–9. https://doi.org/10.1111/j.1745-7254.2006.00260.x.
[11] Salehi B, Sharopov F, Fokou P, Kobylinska A, Jonge L, Tadio K, et al. Melatonin in medicinal and food plants: occurrence, bioavailability, and health potential for humans. Cells 2019;8:681.https://doi.org/10.3390/cells8070681.
[12] Blask DE, Dauchy RT, Sauer LA, Krause JA. Melatonin uptake and growth prevention in rat hepatoma 7228CTC 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. Carcinogenesis 2004;25:951–60. https://doi.org/10.1093/carcin/bgh090.
[13] Van Tassel DL, O’Neill SD. Putative regulatory molecules in plants: evaluating melatonin. J Pineal Res 2001;31:1–7. https://doi.org/10.1034/j.1600-709X.2001.310101.x.
[14] Hattori A, Migita H, Igo M, Itoh M, Yamamoto K, Ohtani-Kaneko R, et al. Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. Biochem Mol Biol Int 1995;35:627–34.
[15] Kolár J, Macháčková I. Melatonin in higher plants: occurrence and possible functions. J Pineal Res 2005;39:333–41. https://doi.org/10.1034/j.1600-709X.2005.00276.x.
[16] Arnao MB, Hernández-Ruiz J. Is phytomelatonin a new plant hormone? *Agronomy* 2020;10. https://doi.org/10.3390/agronomy10010095.
[17] Arnao MB, Hernández-Ruiz J, Pineda-Vázquez F, Paredes SD, Reiter RJ. Phytomelatonin: searching for plants with high levels for use as a natural nutraceutical. *Nutr Rev*. 46. Elsevier B.V.; 2015. https://doi.org/10.1079/978-0-444-63462-7.00011-7.
[18] Arnao MB, Hernández-Ruiz J. The potential of phytomelatonin as a nutraceutical. *Molecules* 2018;23:1–19. https://doi.org/10.3390/molecules23010238.
[19] Mir AR, Faizan M, Bajguz A, Sami F, Siddiqui H, Hayat S. Occurrence and biosynthesis of melatonin and its exogenous effect on plants. *Acta Soc Bot Pol* 2020;89:1–23. https://doi.org/10.5586/absp.8922.
[20] Kołodziejczyk I, Bałabusta M, Szewczyk R, Posmyk MM. The levels of melatonin and its metabolites in conditioned corn (*Zea mays* L.) and cucumber (*Cucumis sativus* L.) seeds during storage. *Acta Physiol Plant* 2015;37:1–11. https://doi.org/10.1007/s11258-015-1850-7.
[21] Pérez-Llamas F, Hernández-Ruiz J, Cuesta A, Zamora S, Arnao MB. Development of a phytomelatonin-rich extract from cultured plants with excellent biochemical and functional properties as a synthetic alternative to synthetic melatonin. *Antioxidants* 2020;9:158. https://doi.org/10.3390/antiox9020158.
[22] Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, et al. Protective role of melatonin on retinal ganglionar cell: in vitro and in vivo evidences. *Life Sci* 2019;15:1689–99. https://doi.org/10.1016/j.lfs.2019.06.020.
[23] Águlera Y, Rebollo-Hernanz M, Herrera T, Cayuela LT, Rodríguez-Redondo P, De Pablo ALL, et al. Intake of bean sprouts influences melatonin and antioxidant capacity biomarker levels in rats. *Food Funct* 2016;7:1438–45. https://doi.org/10.1039/c6fo01538c.
[24] González-Flores D, Camero E, Garrido M, Ramírez R, Moreno D, Delgado J, et al. Urinary 6-sulfatoxymelatonin and total antioxidant capacity increase after the intake of a grape juice cv. Tempranillo stabilized with HHP. *Food Funct* 2012;3:34–9. https://doi.org/10.1039/c1fo00146c.
[25] Sae-Teaw M, Johns J, Johns NP, Subongkot S. Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by
healthy male volunteers. J Pineal Res 2013;55:58–64. https://doi.org/10.1111/j.1071-256X.2012.00125.x.

[26] Meng YW, Pan XD, Chen F. Safety evaluation for highway expansion and upgrading based on access management. Adv Transp Stud 2015;2:55–64.

[27] Erland LAE, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J Clin Sleep Med 2017;13:698–701. https://doi.org/10.5005/jp-journal.org/12.17.06.

[28] Meng X, Li Y, Li Z, Zhou Y, Gan RY, Xu DP, et al. Dietary sources and bio-activities of melatonin. Nutrients 2017;9:1–64. https://doi.org/10.3390/nu9040367.

[29] Slominski AT, Kim TK, Kleszczyński K, Semak I, Janjetovic Z, Sweetman T, et al. Characterization of serotonin and N-acetylserotonin systems in the human epidermis and skin cells. J Pineal Res 2020;68:1–14. https://doi.org/10.1111/jpi.12622.

[30] Slominski A, Wortsman J, Tobin DJ. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. Faseb J 2005;19:176–94. https://doi.org/10.1096/fj.04-0279rev.

[31] Slominski A, Pisarchik A, Semak I, Fischer TW, Kim T, Hardeland R, et al. Melatonin, mitochondria, and the skin. Cell Mol Life Sci 2017;74:224691. https://doi.org/10.1007/s00018-017-2617-7.

[32] Kleszczyński K, Slominski AT, Steinhink K, Reiter RJ. Clinical trials for use of melatonin to fight against COVID-19 are urgently needed. Nutrients 2020;12: 1–12. https://doi.org/10.3390/nu12092561.

[33] Arnau MB, Hernández-Ruiz J. Functions of melatonin in plants: a review. J Pineal Res 2015;59:133–50. https://doi.org/10.1111/jpi.12253.

[34] Slominski AT, Semak I, Fischer TW, Kim T. Metabolism of melatonin in the skin: why is it important? Exp Dermatol 2016;25:563–8. https://doi.org/10.1111/exd.13208.

[35] Kim T, Kleszcyn K, Janjetovic Z, Sweetman T, Lin Z, Li W, et al. Metabolism of melatonin and biological activity of intermediates of melatonin pathway in human skin cells. Faseb J 2013;27:2742–55. https://doi.org/10.1096/fj.13-224691.

[36] Slominski AT, Semak I, Fischer TW, Kim T, Hardeland R, Reiter RJ, et al. Metabolism of melatonin in the skin: why is it important? Exp Dermatol 2018;26:563–8. https://doi.org/10.1111/exd.13208.

[37] Slominski AT, Zmięwski MA, Semak I, Kang T, Janjetovic Z, Slominski RM, et al. Melatonin, mitochondria, and the skin. Cell Mol Life Sci 2017;74:921–35. https://doi.org/10.1007/s00018-017-2567-7.

[38] Slominski AT, Hardeland R, Zmięwski MA, Slominski RM, Reiter RJ, Paur RS. Melatonin: a cutaneous perspective on its production, metabolism, and functions. J Invest Dermatol 2018;138:490–9. https://doi.org/10.1002/jid.20171.00202.

[39] Pape C, Lüning K. Quantification of melatonin in phototrophic organisms. J Pineal Res 2006;41:157–65. https://doi.org/10.1111/j.1600-0796.2006.00383.x.

[40] Hardeland R. Melatonin in plants and other phototrophs: advances and gaps concerning the diversity of functions. J Exp Bot 2015;66:627–46. https://doi.org/10.1093/jxb/erv386.

[41] Jahanbani-Feshani A, Ostadi-Melashar A, Tabibzadeh M, Amarnawicz R. A comparative review on the extraction, antioxidant content and antioxidant potential of different parts of walnut (Juglans regia L.) fruit and tree. Molecules 2019;24:2133. https://doi.org/10.3390/molecules24112133.

[42] Burkhart S, Tan DX, Manchester LC, Hardeland R, Reiter R. Detection and quantification of melatonin and melatonin metabolites in balaton tart cherries (Prunus cerasus). J Agric Food Chem 2001;49:4896–902. https://doi.org/10.1021/jf0108117.

[43] Hardeland R, Pandi-Perumal S, Poeggeler B. Melatonin in plants—focus on a vertebrate night hormone with cytoprotective properties. Plant Sci 2007;170:32–45.

[44] Hernández-Ruiz J, Arnau MB. Distribution of melatonin in different zones of lupin and barley plants at different ages in the presence and absence of light. J Agric Food Chem 2008;56:10567–73. https://doi.org/10.1021/jf0802063.

[45] Ye T, Hao YH, Yu L, Shi H, Reiter RJ, Feng YQ. A simple, rapid method for determination of melatonin in plant tissues by UPLC coupled with high resolution orbitrap mass spectrometry. Front Plant Sci 2017;8:1–10. https://doi.org/10.3389/fpls.2017.00064.

[46] Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: potential use of melatonin as a treatment. J Pineal Res 2014;57:381–4. https://doi.org/10.1111/j.1071-256X.2014.00127.x.

[47] Erland LAE, Chattopadhyay A, Jones AMP, Saxena PK. Melatonin in plants and plant culture systems: variability, stability and efficient quantification. Front Plant Sci 2016;7. https://doi.org/10.3389/fpls.2016.01176.

[48] Albu C, Radu IE, Radu GL. Assessment of melatonin and its precursors content by a HPLC-MS/MS method from different Romanian wines. ACS Omega 2020;5:27254–60. https://doi.org/10.1021/acsomega.0c03463.

[49] Hernández-Ruiz J, Cano A, Arnau MB. Melatonin: a growth-stimulating compound present in plant tissues. Planta 2004;220:140–4. https://doi.org/10.1007/s00018-004-1317-3.

[50] Van Faassen M, Bischoff R, Kema IP. Relationship between plasma and salivary melatonin and cortisol investigated by LC-MS/MS. Clin Chem Lab Med 2015;53:1340–8. https://doi.org/10.1515/cclm-2015-0117.

[51] Koca Çalışkan U, Aka C, Bor E. Melatonin in edible and non-edible plants. Turk J Pharm Sci 2017;14:75–83. https://doi.org/10.4274/tips.33043.
Janjetovic Z, Jarrett SG, Lee EF, Duprey C, Reiter RJ, Slominski AT. Melatonin and its metabolites protect human melanocytes against UVB-induced damage: involvement of NF-E2-mediated pathways. Sci Rep 2017;7:1–13. https://doi.org/10.1038/s41598-017-01305-2.

Skobowiat C, Brozyña AA, Janjetovic Z, Jeayeng S, Oak ASW, Kim TK, et al. Melatonin and its derivatives counteract the ultraviolet B radiation-induced damage in human and porcine skin ex vivo. J Pineal Res 2018;65. https://doi.org/10.1111/jpi.12501.

Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, et al. Identification of oxidative stress and toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 2008;133:235–49. https://doi.org/10.1016/j.cell.2008.02.043.

De Matos Cavalcante AG, De Bruin PFC, De Bruin VMS, Nunes DM, Pereira EDB, Cavalcante MM, et al. Melatonin reduces lung oxidative stress in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study. J Pineal Res 2012;53:238–44. https://doi.org/10.1111/j.1600-079X.2012.00992.x.

Zhou Y, Hou Y, Shen J, Melha R, Kallianpur A, Culver DA, et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. PLoS Biol 2020;18:9–11. https://doi.org/10.1371/journal.pbio.3000970.

Simko F, Reiter RJ. Is melatonin deficiency a unifying pathomechanism of high risk patients with COVID-19? Life Sci 2020;256:117902. https://doi.org/10.1016/j.lfs.2020.117902.

Herrera EA, González-Candia A. Comment on melatonin as a potential adjuvant treatment for COVID-19. Life Sci 2020;253:117739. https://doi.org/10.1016/j.lfs.2020.117739.

Tan DX, Hardeland R, Manchester LC, Korkmaz A, Ma S, Rosales-Corral S, et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. J Exp Bot 2012;63:577–97. https://doi.org/10.1093/jxb/erz256.

Debnath B, Hussain M, Li M, Lu X, Sun Y, Qiu D. Exogenous melatonin improves fruit quality features, health promoting antioxidant compounds and yield traits in tomato fruits under acid rain stress. Molecules 2018;23:1–13. https://doi.org/10.3390/molecules23081868.

Murch SJ, Saxena PK. A melatonin-rich germplasm line of St John’s wort (Hypericum perforatum L.). J Pineal Res 2006;41:284–7. https://doi.org/10.1111/j.1600-079x.2006.00367.x.

Nawaz MA, Huang Y, Bie Z, Ahmed W, Reiter RJ, Niu M, et al. Melatonin: current status and future perspectives in plant science. Front Plant Sci 2016;6:1–13. https://doi.org/10.3389/fpls.2015.01230.

Xu L, Yue Q, Xiang C, Biao F, Yao Y. Melatonin promotes ripening of grape berry via increasing the levels of ABA, H2O2, and particularly ethylene. Hortic Res 2018;5. https://doi.org/10.1038/s41438-018-0045-y.

Kolář J, Johnson CH, Macháčková I. Exogenously applied melatonin (N-acetyl-5-methoxytryptamine) affects flowering of the short-day plant Chenopodium rubrum. Physiol Plantarum 2003;118:605–12. https://doi.org/10.1046/j.1399-3054.2003.00114.x.

Padumanonda T, Johns J, Sangkasat A, Tiyaworanant S. Determination of melatonin content in traditional Thai herbal remedies used as sleeping aids. DARU, J Pharm Sci 2014;22:6. https://doi.org/10.1186/2008-2231-22-6.