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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.

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/unmatched 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 anticancerous 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.

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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 antitumor 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,

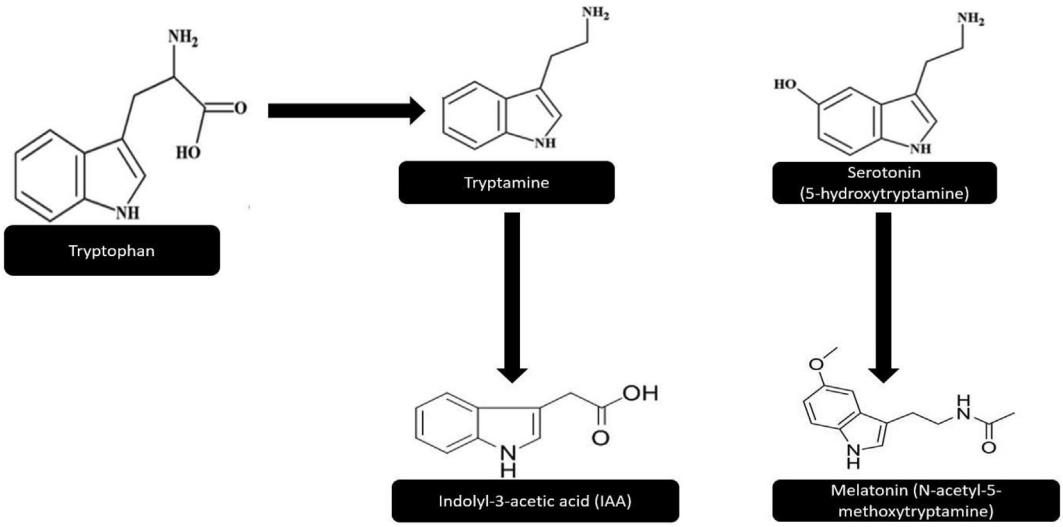

Fig. 1. Melatonin biosynthesis pathway.

Table 1
Phytomelatonin content of some aromatic/medicinal plant species.

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.).*	Fruit	[89]
Oat	*Avena 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	*Baccaurea ramiflora Lour.*	Leaf	[94]
Fever few	*Tanacetum parthenium (L.)*	leaf	[95]
Pomegranate	*Punica granatum (L.)*	Fruit	[39]
Strawberry	*Fragaria x ananassa (Duch.)*	Fruit	[42]
Orange juice	*Citrus sinensis (L.)*	Fruit	[41]
Feverfew	*Tanacetum parthenium (L.)*	Flower	[95]
Water hyacinth	*Eicchornia crassipes (Marth.)*	Flower	[15]
Sweet cherries	*Prunus cerasus L.*	Fruit	[15]
Grapevine	*Vitis vinifera (L).*	Fruit	[92]
Barley	*Hordeum vulgare (L.)*	Seeds	[14]
Poppy	*Papaver somniferum (L.)*	Seeds	[92]
Turnip	*Brassica compestris (L.)*	Root	[92]
Flax	*Linum usitatissimum (L.)*	Seeds	[92]
Anise	*Pimpinela anisum (L.)*	Seeds	[92]
Alfalfa	*Medicago sativum (L.)*	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]
Tall fescue	*Festuca arundinacea*	Seeds	[14]
Java bean	*Senna tora (L.)*	Leaf	[94]
Fennel	*Foeniculum vulgare (Gilib.)*	Seeds	[92]
Cherry	*Prunus cerasus (L.)*	Fruit	[15]
Poppy	*Papaver somniferum (L.)*	seed	[92]
Celery	*Apium graveolens (L.)*	Seed	[92]
Wolf berry	*Lycium barbarum*	Seed	[92]
Milk thistle	*Silybum marianum (L.)*	Seeds	[92]
Bitter lemon	*Momordica charantia.(L)*	Leaf	[94]
Black pepper	*Piper nigrum (L.)*	Leaf	[94]
Pineapple	*Ananas comosus (Stickm.) Merill.*	Fruit	[14]
Wild strawberry	*Fragaria ananassa (Duch.)*	Fruit	[95]
Rice	*Oryza sativa japonica (L.)*	Seeds	[14]
Carrot	*Daucus carota*	Root	[14]
Beet	*Beta vulgaris (L.)*	Root	[20]

ginger, etc. is necessary to avoid the presence of unwanted residual compounds generated during the process of synthetic melatonin process, and their human health associated risks [11,18,28].

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 melatonin 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 Slowminiski et al. [31] indicated that 6-hydroxy melatonin (6-OH) M, N1 -acetyl-N2 - 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-acetylserotonin [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 plants [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 amphipathic 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% Na_2CO_3 [6], or potassium phosphate buffer have been employed by many

authors [5,14,15]. 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 electrospray 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, $HClO_4$, 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 (e.g., pentafluoropropionyl – 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, LC-MS are 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 immune, otherwise called natural immunity, is the first line of defense against invading pathogens [53]. Innate immunity has a fast response system but lacks antigen specificity. Thus, it does not provide lifetime immunity [53]. The human innate immune system 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 (PPRs) such as 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 rapidly, thereby releasing granulocyte colony-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 sirtuin-1 (SIRT1) is known to mediate the remedial properties of phytomelatonin. Phytomelatonin can inhibit HMGB1 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 SITR1 was seen in the lung injury induced by exposure to heavy metal chromium [64].

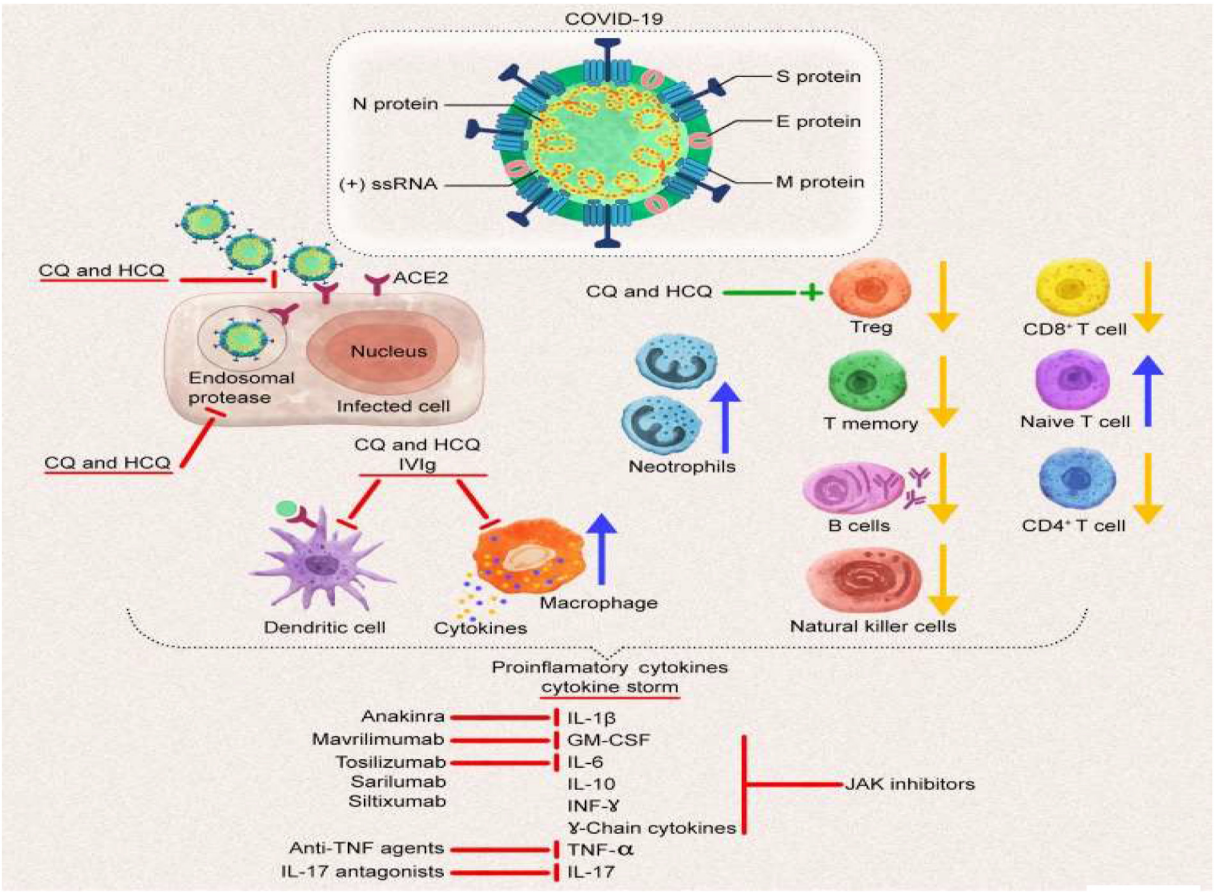

Fig. 2. Involvement of the immune system in COVID-19. Reproduced with permission from Tufan et al. [60].

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, lipoxygenase, 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 methodic 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 pathway 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 probity. 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.

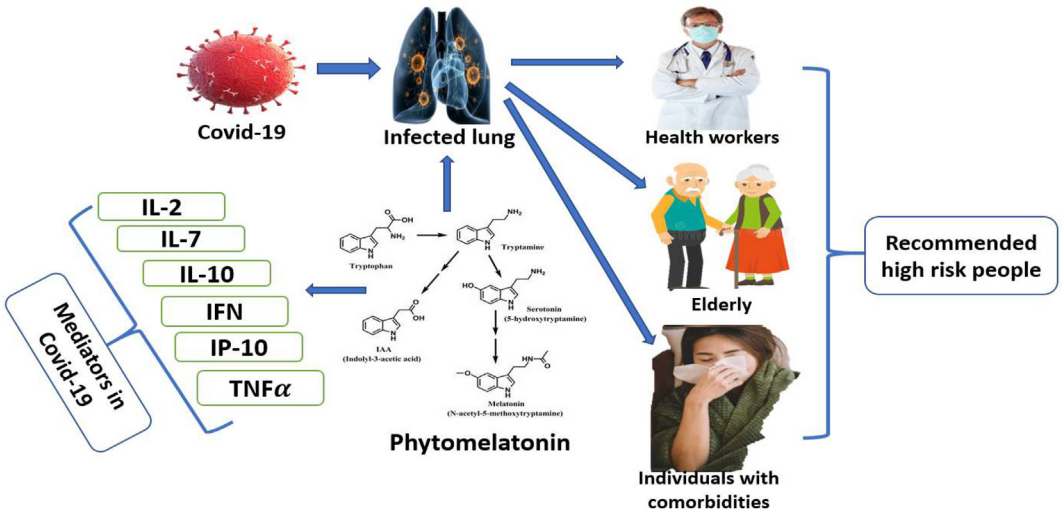

Fig. 3. Potential application of phytomelatonin on COVID-19-exposed individuals.

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.

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