Melatonin and vitamin D as potential synergistic adjuvants for cancer therapy (Review)

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Received August 12, 2024; Accepted October 8, 2024

DOI: 10.3892/ijo.2024.5702

Abstract. Significant advancements have been made in cancer therapy; however, limitations remain with some conventional approaches. Adjuvants are agents used alongside primary treatments to enhance their efficacy and the treatment outcomes of patients. Modern lifestyles contribute to deficiencies in melatonin and vitamin D. Limited sun exposure affects vitamin D synthesis, and artificial light at night suppresses melatonin production. Both melatonin and vitamin D possess anti-inflammatory, immune-boosting and anticancer properties, rendering them potential adjuvants of interest. Studies suggest melatonin and vitamin D supplementation may address antioxidant imbalances in lip, oral and pharyngeal cancers. Moreover, promising results from breast, head and neck, brain, and osteosarcoma research indicate potential for tumor growth inhibition, improved survival, and a better quality of life of patients with cancer. The radioprotective properties of melatonin and vitamin D are another exciting area of exploration, potentially enhancing radiotherapy effectiveness while reducing side effects. For its part, the sleep-promoting effects of melatonin may indirectly benefit patients with cancer by influencing the immune system. Thus, the prevalence of vitamin D and melatonin deficiencies highlights the importance of supplementation, as lower levels can worsen side-effects from cancer treatments. The present review explores the potential of combining melatonin and vitamin D as synergistic adjuvants for cancer therapy. These agents have shown promise individually in cancer prevention and treatment, and their combined effects warrant investigation. Therefore, large-scale controlled trials are crucial to definitively determine the optimal dosage, safety and efficacy of this combination in improving the lives of patients with cancer.

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Key words: melatonin, vitamin D, cancer, treatment, synergistic actions

1. Introduction

Connecting cancer with melatonin and vitamin D (VitD). Cancer is a devasting disease that affects millions of individuals worldwide annually (1). Current cancer treatments include surgical removal accompanied by chemo- and radiotherapy, immunotherapy, and the use of molecular inhibitors (2). Despite the technological advances being made in early detection and successful therapy, achieving remission, the risk of cancer recurrence often persists. Under specific circumstances, dormant residual cancer cells can reactivate their aggressive state to disseminate tumor cells from the primary lesion to

distant organs emerging as a recurrent disease (3). The etiology and plasticity of cancerous states have recently been revisited concerning epigenetic and gene regulation landscapes in addition to the conditions of entropy and attractor states (4). Under the influence of genetic mutations, epigenetic modifications and microenvironmental perturbations, tumor cell phenotypes dynamically change over time, thereby favoring intratumor heterogeneity (5). This may confer adaptability to cancer cells due to therapy resistance, metastasis, and clonal evolution. Cancer cell fitness includes a multitude of evolutionary and ecological features that determine cell fate and tumor behavior (6). A more precise recognition of this classification system holds promise for clinicians to personalize therapeutic interventions according to the evolvability of the cancer of a patient.

The use of functional adjunctive agents with antitumor activities and high tolerability, whose formation has been reported even in early life forms (7), such as melatonin and VitD represents an additional opportunity for cancer treatment. There is a plethora of evidence demonstrating that melatonin and VitD participate at different levels in complex signaling pathways and biological functions of cancer, most of which will be addressed in the present review. For instance, melatonin has been documented to counteract tumor development and growth via several physiological, molecular and atomic mechanisms in addition to alleviating the adverse effects of chemo- and radiotherapy in a number of types of cancer (8-11). As regards VitD, previous *in vitro* and *in vivo* studies have disclosed its immunomodulatory and antitumor properties (12-14). Similar to melatonin, VitD has been shown to exert anti-angiogenic, antiproliferative (15) and anti-inflammatory effects on cancer cells (16). What is of great value is the association of their serum levels with the cellular state; in other words, high levels of melatonin and VitD are strongly associated with reduced incidence rates of various malignancies and vice versa (17-21). Taken together, this evidence should encourage some clinical trials using melatonin and VitD as adjuvant therapy or even protective agents alone. The present review comprehensively evaluates individual mechanistic aspects whereby melatonin and VitD function in the context of cancer, with particular focus on their synergistic effects preventing cancer progression (Fig. 1).

2. General aspects of melatonin and its major association with cancer

Molecular pathways involved in the synthesis and action of melatonin. Melatonin (N-acetyl-methoxytryptamine) is an indoleamine produced at night by the pineal gland, but also by 'perhaps' all organismal cells in a continuous non-circadian manner (22). It is synthesized from the 5-hydroxytryptophan, which is catalyzed to serotonin by the enzyme aromatic L-amino acid decarboxylase (23). Serotonin is then converted into N-acetylserotonin by the alkylamine N-acetyltransferase, a rate limiting enzyme for melatonin synthesis. The final stage of melatonin biosynthesis occurs with the participation of the enzyme acetylserotonin O-methyltransferase and S-adenosyl methionine, a coenzyme involved in methylation reactions (24).

Due to its chemical structure and low molecular weight, melatonin easily crosses the cell membrane and interacts with multiple intracellular components. Melatonin exerts its effects through membrane G protein-coupled receptors (MT1 and MT2), as well as via cytosolic MT3 and calmodulin. Notably, melatonin is not a direct ligand for nuclear receptors (RZR/RORα) as previously documented (25). A recent study utilizing functional assays demonstrated that melatonin and its metabolites are promising candidates for interacting with both aryl hydrocarbon receptor and peroxisome proliferator-activated receptor γ. Their docking scores, comparable to those of the receptors' natural ligands, suggest a potential role in modulating these signaling pathways (26). The widespread detection of MT1 and MT2 receptors in various tissues underscores the broad spectrum of melatonin's activity, encompassing the blood vessels, adipocytes, liver, kidneys, retina, ovaries, testes, mammary glands, gallbladder, immune cells, cardiovascular system, brain sites and skin (26,27). There are also receptor-independent actions of melatonin by directly interfering with intracellular substrates of cancer cells. Of note, a myriad of internal regulatory mechanisms has already been proposed for a number of types of cancer, such as ovarian, breast and pancreatic cancer (18,28-30).

Another key site for melatonin synthesis and metabolism is the skin (31), particularly the mitochondria of skin cells. Under ultraviolet radiation, melatonin can be converted into different photoproducts without the involvement of enzymatic activities (32). Notably, metabolites, including N-acetyl-N2-formyl-5-methoxykynuramine (AFMK), 6-hydroxymelatonin (6-OHM), 2-hydroxymelatonin and 4-hydroxymelatonin (4-OHM) can be produced in the epidermis through UVB-induced non-enzymatic transformations of melatonin to maintain homeostasis through multiple mechanisms of action. The pathways for melatonin metabolism, including the indolic and kynurenine pathways, vary based on cell type and function. For example, in melanocytes, keratinocytes and fibroblasts, melatonin is transformed into AFMK and 5-methoxytryptamine, whereas in melanoma cells, 6-OHM and AFMK are produced endogenously (33).

While the central circadian clock regulates melatonin secretion, melatonin itself can also influence both the central circadian clock and peripheral oscillators in various tissues and organs, establishing it as a circadian rhythm marker (34). Melatonin levels typically increase at night and decrease during the day. Increased levels of melatonin during nighttime can signal to the cells and organs in the body that it is night, aiding in organizing target organs and organ systems into appropriate homeostatic metabolic rhythms (35). Consequently, exposure to light at night (LAN) may disrupt circadian rhythms and melatonin production (36), potentially contributing to the development, promotion and progression of cancers. Concurrently, although melatonin levels are generally lower in cancer cells (37), advanced tumors may still produce melatonin, potentially altering body homeostasis and conferring a protective effect following therapeutic interventions (38).

Mechanisms through which melatonin inhibits cancer growth and metastasis. Melatonin has long been reported to influence a variety of physiological processes in cancer and it would be a difficult task to mention all of them in detail.

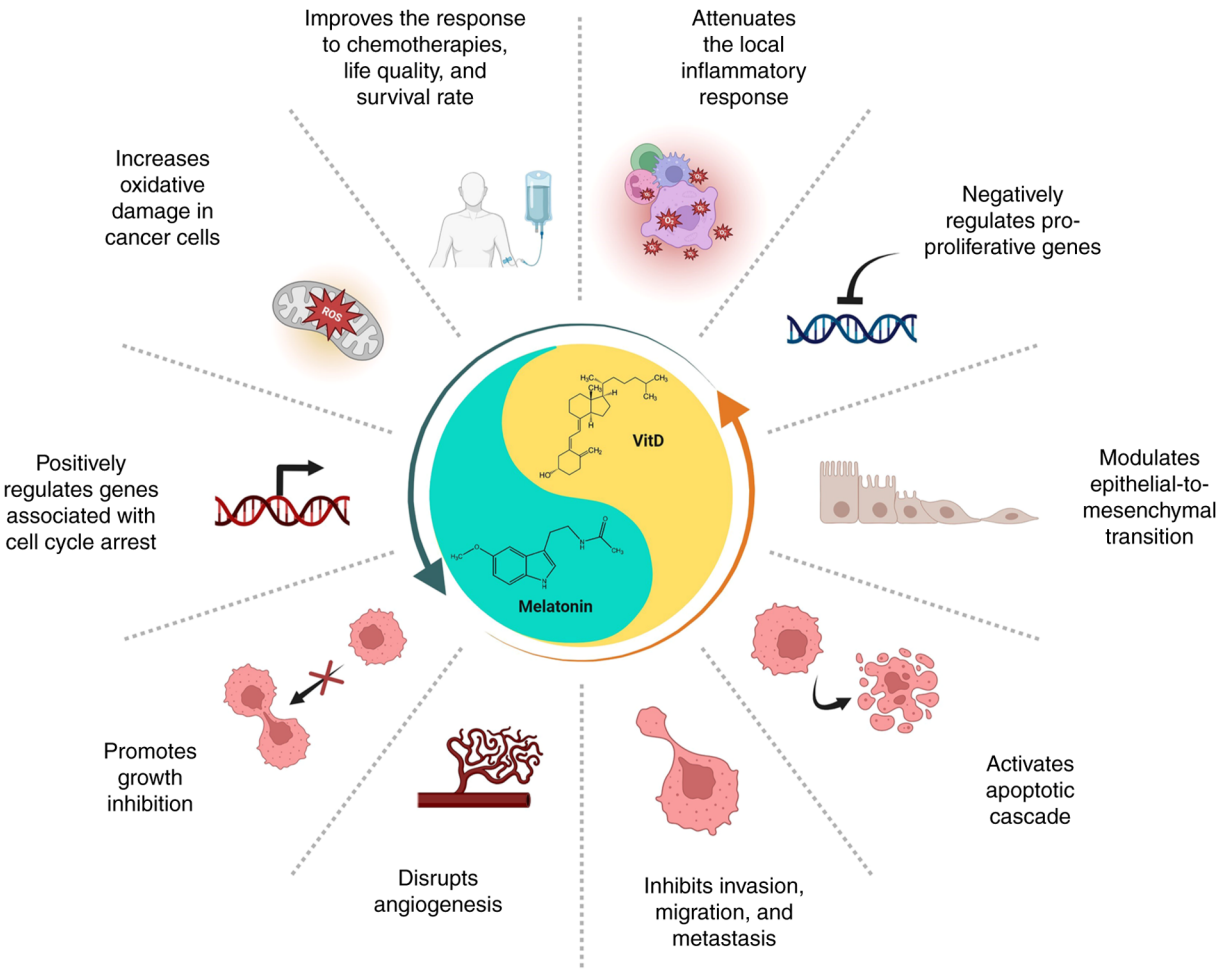

Figure 1. Antitumor activities of melatonin and vitamin D as regards different cancer hallmarks.

There is no consensus on how and why melatonin behaves distinctively on various oncogenic molecules and culture medium conditions; its effects may be dependent on specific concentrations or dosages, cell type or animal models, exposure time, routes, and period of treatment. Reiter *et al* compiled the molecular mechanisms by which melatonin restrains cancer at the initiation, progression and metastasis stages (39); in general, vast evidence exists pointing to melatonin as a regulator of DNA damage and inhibitor of oncogenic signaling pathways related to tumor progression and metastasis. In this scenario, melatonin largely intervenes in the hallmarks of cancer, including fundamental actions in genomic instability, sustained proliferative signaling, resistance to apoptosis, replicative immortality, dysregulated metabolism, inflammation, angiogenesis, tissue invasion and metastasis (40). The anticancer effects of melatonin target common pathways shared with a majority of established anti-cancer agents, suggesting that indoleamine exhibits pleiotropic characteristics akin to other antineoplastic drugs in terms of their mechanisms of action.

Some of these mechanisms of action include the regulation of major intracellular pathways, such as mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) and protein kinase B (AKT/PKB) signaling. Critical mediators affected by melatonin encompass cyclins, nuclear factor-κB (NF-κB), heat shock proteins (HSPs) and c-Myc, which are potential targets for cancer drugs (41). Additionally, melatonin also exerts its anticancer effects by inducing epigenetic modifications, DNA damage, and mitochondrial and endoplasmic reticulum alterations in neoplastic cells. The regulation of these mediators by melatonin mitigates tumor growth and invasiveness through modulation of differential expression of genes, protein secretion and activity, angiogenic factors, in addition to regulating structural molecules involved in metastasis. The role of melatonin in different cancer types has recently been documented and differentially expressed genes strongly linked to cancer hallmarks have been identified (42). Interconnecting gene subsets have exhibited a close association among breast, hepatocellular, prostate and oral cancers, as well as neuroblastoma and osteosarcoma, in terms of alterations in melatonin-related signaling pathways. Some of these genes have been already shown to be regulated by miRNAs potentially targeted by melatonin in a variety of cancers (43). Understanding the role of melatonin in intricate molecular signaling at the gene level is crucial for guiding appropriate therapeutic interventions.

As a considerable number of reviews that summarize the anticancer effects of melatonin are currently available, the present review focuses on the general aspects involving the aforementioned cancer categories which reinforce the use of the indole in clinical settings.

Table I. Major results regarding genomic instability in cancer and the role of melatonin.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
ECC (Ehrlich carcinoma cells)	Ascites	10^{-9}, 10^{-6} and 10^{-3} M melatonin for 24 h *in vitro* assays; 50 mg/kg b.w. for 7-21 days, orally	Melatonin reduced DNA synthesis and delayed the progression of cells from G_0/G_1 phase to S-phase of the cell cycle, also depressed the aneuploidy status in mice	(46)
Leukocytes	N.A.	A single oral dose of 100 mg melatonin to healthy human volunteers. Blood collected 1-2 h after melatonin ingestion	Melatonin effectively promoted radioprotection against ionizing radiation-induced DNA damage in human lymphocytes	(51)

N.A., not applicable.

Genomic instability in cancer and the role of melatonin. Cancer initiation is often associated with chromosomal instability by creating aneuploidy nuclei due to the failures in cell cycle checkpoint machinery (44). This is associated with the poor prognosis of patients as a result of metastasis, therapeutic resistance and inflammatory signaling by introducing double-stranded DNA into the cytosol (45). A previous study demonstrated that the oral supplementation of melatonin (50 mg/kg body weight) in mice with Ehrlich carcinoma promoted a reduction in the aneuploidy status associated with reduced DNA synthesis and delayed progression of cells to S-phase of the cell cycle (46). Melatonin is considered to protect DNA functioning as an antioxidant molecule capable of increasing the activity of other antioxidants, stimulating glutathione synthesis, inhibiting pro-oxidative processes, and enhancing the activity of the mitochondrial electron transport chain (47).

It has been recently documented the role of melatonin acting in different DNA repair systems, especially by preventing DNA from damage and ameliorating its repair processes (48). Of note, melatonin, including its metabolites (AMK, AFMK, c3-OHM, 4- and 6-OHM) regulate a variety of DNA repair pathways having a more precise effect on the factors governing the repair of double-stranded DNA breaks by homologous recombination (HR) and non-HR mechanisms. By preventing DNA oxidative damage, melatonin may act by activating antioxidant enzymes, inhibiting metal-induced DNA damage and pro-oxidative enzymes, protecting against non-radical DNA oxidation, and boosting DNA repair machinery (49). When used as a chemical adjuvant, melatonin has revealed various radio-protective and radio-sensitive effects following ionizing radiation in many cancer types (48,50-52). These actions indicate the potential of melatonin as a tumor initiation protector in addition to avoiding the deleterious side effects arising from radiotherapy (Table I).

Cell proliferation and apoptosis in melatonin-treated cancers. Sustained proliferative signaling and resistance to apoptosis represent a common characteristic of cancers by which they can develop and progress. There is vast literature available demonstrating that melatonin effectively alters the expression pattern of proteins and active signaling pathways related to the cell cycle of different types of cancer cells (Table II). For instance, *in vitro* studies have documented anti-proliferative actions of melatonin (varying from nano to millimolar concentrations) by arresting the cell cycle in the G1 phase, delaying G1/S transition and preventing the mitosis of breast cancer (MCF-7 cells) (53), ovarian cancer (SKOV-3 cells) (28), melanoma (SK-MEL-1 cells) (54), osteosarcoma (hFOB 1.19) (55) and glioma (C6 cells) (56).

Mechanistically, melatonin affects the cell cycle mainly through the inhibition of cyclin-dependent kinases (CDKs), CDK inhibitors (CDI) and cyclins (for further details please see the compiled information in the review by Targhazeh *et al* (57). In ovarian cancer cells (OVCAR-429 and PA-1), melatonin has been shown to promote a delay in the G1 phase by downregulating CDK2/4 gene expression and its protein levels (58). Similarly, Liu *et al* (55) revealed a significant reduction in the expression of CDK1/4 in osteosarcoma by melatonin (1 mM), and this was responsible for the prevention of ERK activation. Other studies have also reported the role of melatonin in inhibiting the expression of CDK2 in neuroblastoma (59), CDK4/6 in hepatocellular carcinoma (60) and CDK4 in non-small lung cancer cells (61). Melatonin is further able to inversely regulate the expression of cyclins, thus affecting the proliferation of cancer cells. In colon cancer cells, melatonin (10 μM) has been shown to cause a marked reduction in both the cyclins A and E (62), whereas in osteosarcoma, it significantly downregulated cyclin B1 and D1 (63). Another study revealed that melatonin completely abolished the growth of breast cancer cells induced by estradiol by suppressing cyclin D1 possibly interfering with G1 to S transition (64). By combining melatonin with other chemotherapeutics, an effective downregulation of cyclin D1, A and B was observed varying in pancreatic ductal carcinoma (65), breast cancer (66), and lung cancer cells (61).

Melatonin has also been shown to exert a positive effect on CDI (tumor suppressors) in different cancer types. In HepG2 liver cancer cells, melatonin promotes the high expression of the p21 protein, which negatively reduces cell proliferation by

Table II. Major results regarding cell proliferation and apoptosis in melatonin-treated cancers.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
MCF-7	Human breast carcinoma	10^{-9} M melatonin during 0-40 h	Melatonin added to the culture medium, increase the duration of the cell cycle from 20.36 to 23.48 h.	(53)
SKOV-3	Human ovarian cancer	1.6, 3.2 and 4.0 mM melatonin for 48 h	Melatonin induced cell cycle arrest by reducing DNA content in the S and G2/M phases.	(28)
SK-MEL-1	Human melanoma	0.1, 0.3 and 1.0 mM melatonin for 24, 48 and 72 h	Melatonin at 1 mM significantly arrested the cell cycle in the G1 phase (after 24 h) and in the S and G2-M phase (after 48-h incubation period).	(54)
hFOB 1.19	Normal human fetal osteoblastic cell line	1 nM to 1.0 mM melatonin for 24 h	Melatonin significantly increased the fraction of cells in G0/G1 phase, while simultaneously reducing the proportion of cells in the G2/M phase rather than the S phase.	(55)
C6	Glioma cells	1 nM to 1.0 mM melatonin 48 and 72 h *in vitro* assays	Melatonin inhibiting cell progression from G0/G1 to S phase of the cell cycle.	(56)
B65	Neuroblastoma cell line	0.1 to 1 mM melatonin for 24 h	Melatonin increased the percentage of cells in the G1 phase of the cell cycle. It also downregulated the transcriptional activity of cdk4, cdk2 and cyclin D1.	(59)
Bel7402, SMMC-7721	Human hepatocellular carcinoma	0.2 to 2 mM melatonin for 48 and 72 h	Combined treatment with melatonin and sorafenib enhanced the cell cycle arrest of cancer cells at the G0/G1 phase. It also upregulated p27, and downregulated p-AKT, c-myc, cyclin D1 and CDK4/6 protein expression.	(60)
H1975 and HCC827	Non-small-cell lung cancer and hepatocellular carcinoma	0.1 to 10 mM melatonin for 24 and 48 h	Melatonin treatment significantly increased the sub-G1 populations in H1975 cells. Melatonin downregulated the survivin, p-Bad, Bcl-xL and Bcl-2 levels, but did not affect the evels of Mcl-1.	(61)
HCT116	Human colorectal adenocarcinoma	10 μM melatonin for a 12-h period in 2 days	Melatonin exposure for 48 h induced cell cycle arrest at the G1 phase. Melatonin also markedly reduced the expression of cyclin A and cyclin E at 48 h after the second treatment.	(62)
MG-63	Osteosarcoma	1 nM to 10 mM melatonin for 24, 48, or 72 h	Melatonin significantly increased the fraction of cells in the G0/G1phase, reducing the proportion in the S and G2/M phases of the cell cycle by the downregulation of cyclin D1, CDK4, cyclin B1 and CDK1.	(63)
OVCAR-429 and PA-1	Ovarian cancer	400, 600 and 800 μM melatonin for 24,48 and 72 h	Melatonin promoted the accumulation of the treated cells in the G1 phase with the downregulation of CDK 2/4.	(57)

Table II. Continued.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
LNCaP	Prostate cancer	0.25 to 3.0 mM melatonin for 6, 12, 24 and 48 h	Melatonin markedly activated Bax expression and decreased Bcl-2 expression in a dose- and time-dependent manner. Melatonin also increased the expression of p53, p21 and p27.	(84)
Ovarian tissue	Rat ovarian cancer	200 μg melatonin/ 100 g body weight per day for 60 days	Melatonin therapy promoted apoptosis along with the upregulation of p53, BAX and cleaved caspase 3.	(72)
PANC-1	Human pancreatic carcinoma	10^{-9} and 10^{-12} M melatonin for 24 and 48 h	Melatonin interfered with the Bax/ Bcl-2 protein balance and promoted caspase-9 expression. These effects were reversed by treatment with the melatonin receptor antagonist, luzindole.	(77)
HL-60	Human leukemia	1 nM, 1 μM and 1 mM for 1, 6, 12, 24, 48 and 72 h	Melatonin at 1 mm induced a significant increase in caspase-3 and -9 activities, and also evoked cell death by mitochondrial membrane depolarization and permeability transition pore induction.	(82)
RAMOS-1	Human leukemia	2 mM melatonin for 12, 24, 48 and 72 h	Apoptotic effect of melatonin was associated with cell-cycle arrest, the activation of caspase-3, the downregulation of Bcl-2, mitochondrial membrane depolarization and cytochrome *c* release.	(83)
HepG2	Human hepatocellular carcinoma	2 and 4 mM melatonin for 24 and 48 h	Melatonin increased the transcriptional activity of the forkhead-responsive element FoxO3a which binds to a specific sequence in the Bim promoter, leading to apoptosis.	(85)
HepG2 and SMMC-7721	Human hepatocellular carcinoma	10^{-3} to 10^{-9} M melatonin for 24 and 48 h	Melatonin promoted apoptosis and the downregulation of XIAP and survivin levels. Melatonin also reduced the expression of COX-2 and inhibited AKT activation.	(86)

FoxO3a, forkhead box class O3a; COX-2, cyclooxygenase 2; XIAP, X-linked inhibitor of apoptosis.

increasing G2/M arresting (67). An augmentation in the expression of p21wafl, p16, p21 and p27KIP1 levels by melatonin was also evidenced in breast, colorectal and ovarian cancer cells, respectively (58,62,68). p53 is another target by which melatonin may exert tumor-suppressive effects, acting by altering both protein expression and phosphorylation. The concentration of p53 protein was identified at high levels after melatonin treatment in hepatoma (69), breast (68), prostate (70), cervical and endometrial (71) cancer cells, and further in animal models of ovarian carcinoma (72) and hepatocellular carcinoma (73). These melatonin-mediated increases in p53 levels are regulated by different signaling mechanisms [e.g., p38 MAPK, sirtuin (SIRT)1, MT1/2 receptors, MDM2/MDMX/p300] (57).

As a 'smart killer' molecule, melatonin can induce anti-apoptotic effects in healthy cells while triggering pro-apoptotic signals in cancer cells. Bizzarri *et al* (74) compiled the extensive molecular mechanisms of the pro-apoptotic actions of melatonin; it can activate the intrinsic and extrinsic apoptotic pathways depending on cancer cell type, particularly through the increase in the p53/MDM2 ratio and decrease of SIRT1. Cancer cells evade apoptosis by overexpressing anti-apoptotic molecules, whereas under expressing pro-apoptotic messages thus resisting apoptosis (75). There is a multitude of studies that document a reduction of B-cell lymphoma-2 (Bcl-2) levels and the upregulation of Bax and caspases (pro-apoptotic proteins) by melatonin treatment in different cancer models as outlined

by Rubio *et al* (76), Leja-Szpak *et al* (77), Xu *et al* (78) and Chuffa *et al* (79).

Although the mitochondria are strongly involved in apoptosis, they also participate in other types of cell death, such as necrosis, autophagy, necroptosis, ferroptosis and pyroptosis (80,81). Mitochondria are involved in the control of the intrinsic pathway by releasing and activating some pro-apoptotic factors (e.g., cytochrome *c* and caspase activators). Experimental data concerning major apoptotic pathways and mitochondrial processes have been demonstrated based on melatonin treatment. In leukemia HL-60 cells, it has been shown that melatonin induces apoptosis with a significant increase in caspase-3 and -9 levels accompanied by the depolarization of the mitochondrial membrane and the augmentation of the mitochondrial permeability transition pore (82). Another study using HL-60 cells revealed activation of the Bcl-2 members (Bid and Bax) followed by the release of cytochrome c from mitochondria (76). In lymphoblastic RAMOS-1 cells, melatonin lowered the mitochondrial membrane potential resulting in the release of cytochrome *c* and the activation of apoptosis (83).

Alternative pathways whereby melatonin indirectly regulates cancer cell apoptosis include MAPK, forkhead box class O3a (FoxO3a), cycloxygenase-2 (COX-2) and NF-κB signaling (57). Melatonin is capable of increasing p38 MAPK and extracellular signal-regulated kinase (ERK) thereby triggering apoptosis in prostate cancer LNCaP cells (84); this activated pathway in turn increases Bax and Bad in addition to cytochrome *c* and caspase-9. The activation and nuclear translocation of FoxO3a is mediated by melatonin in HepG2 cells, which leads to apoptosis through an increase in the pro-apoptotic protein Bim and Fas ligand (85). Melatonin has also the ability to overcome apoptosis resistance of HepG2 and SMMC-7721 cells by promoting downregulation of survivin and XIAP (anti-apoptotic members); these mechanisms were associated with reduced expression of COX-2 and AKT activation (86).

Reactive oxygen species (ROS), dysregulated metabolism and the interference of melatonin in cancer cells. ROS play a crucial significant role in the etiopathogenesis of cancer. ROS are signal transducers involved with angiogenesis, apoptosis, ferroptosis, necroptosis, autophagy, cell migration and invasion and proliferation (87). An increasing number of studies has explored immunotherapies and anticancer agents that lead to ROS generation or inhibition and disrupt oxidative stress balance (e.g., natural extracts and nutraceuticals); thus, targeting cancer with effective design of ROS-mediated therapies in clinical trials is expected (88). Notably, while the production of ROS can result in DNA damage and cancer initiation, a massive production of ROS inhibits tumor growth via basically two mechanisms: i) Blocking cell proliferation by altering signaling pathways associated with cell cycle and biosynthesis of nucleotides and ATP; and ii) activating ferroptosis and apoptotic signaling related to endoplasmic reticulum stress, mitochondria and the p53 pathway (88). Through this perspective, a newly proposed mechanism of action of melatonin inducing ROS generation in cancer cells reiterates its clinical use as an anti-neoplastic therapeutic (89). Florido *et al* (89) emphasized the role of melatonin in SIRT signaling, AKT pathways and the anti-Warburg effect; of particular interest is the melatonin-mediated ROS production via the activation of reverse electron transport (RET) in the mitochondria of cancer cells. This finding was particularly evidenced in head and neck squamous cell carcinoma (Cal-27 and SCC-9 cell lines) treated with 0.5 or 1 mM melatonin, and also in mice with Cal-27 tumor xenografts (89). In these experimental models, melatonin led to increased mitochondrial activity, thus inducing ROS-dependent mitochondrial uncoupling via RET in addition to increasing the membrane potential and CoQ10 H2/CoQ10 ratio associated with mitochondrial ROS.

The induction of oxidative stress can also be regulated by SIRT3 and hypoxia-inducible factor-1α (HIF-1α) activities. As SIRT3 activates superoxide dismutase 2 (SOD2), an antioxidant enzyme, its suppression substantively increases ROS-mediated oxidative damage (90). In HeLa cancer cells, melatonin has been shown to induce oxidative stress by inhibiting SIRT3/SOD2 activities, which potentially stimulates the release of cytochrome *c*, resulting in apoptosis (91). Otherwise, a high SIRT3 activity has been found to be associated with the apoptosis of lung cancer cells by elevating ROS production due to an increase in oxidative phosphorylation (92). In this case, melatonin-induced SIRT3 contributes to the deacetylation of pyruvate dehydrogenase followed by the enhancement of mitochondrial complex I and IV activities, finally inducing ROS while reversing the Warburg-type metabolism. Melatonin has been proven not only to reverse the Warburg effect via SIRTs and ROS production, but also by inhibiting HIF-1α (93). The activation of HIF-1 stimulates mitochondrial pyruvate dehydrogenase kinase, which in turn prevents pyruvate from entering the mitochondria and its conversion to acetyl coenzyme A by pyruvate dehydrogenase complex. Notably, melatonin directly or indirectly inhibits HIF-1 in cancer cells (94), thereby favoring the reversal of the Warburg effect while inducing ROS generation and apoptosis (11,95). These anti-Warburg effects of melatonin are presented in Table III.

Inflammation and angiogenesis in the context of melatonin in cancer. The association between inflammation and cancer progression has been widely documented. Several factors serve as crucial targets that can be adjusted to regulate the detrimental effects of inflammation, including COX-2, NF-κB, TNF-α, prostaglandins and inducible nitric oxide synthase (iNOS). Melatonin has been shown to have the ability to reduce these inflammatory mediators through multiple signaling pathways in various types of cancer, such as hepatocellular carcinoma, ovarian, pulmonary and breast cancer (60,96-98). Studies have indicated that attenuating the local inflammatory response through NF-κB inhibition can help restrict tumor expansion (39,99). Melatonin has been frequently observed to modulate NF-κB translocation into the nucleus and its binding to DNA (96,100,101). These actions may be pertinent to the ability of melatonin to impede tumor progression, as they could influence the redox status and immune microenvironment of the tumor.

Hypoxia (low levels of O_2) is linked to metastatic disease and increased mortality due to its capacity to promote the development of blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis), enabling cancer cells to evade the adverse tumor microenvironment and spread to secondary sites (102). HIF-1 and vascular endothelial growth factor (VEGF) are

Table III. Major results regarding metabolism and the interference of melatonin in cancer cells.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
Various cell lines	Various types of cancer	0.5, 1 and 2 mM melatonin in combination or not with shikonin for 6 or 24 h	Melatonin potentiates the cytotoxic effects of shikonin on cancer cells by inducing oxidative stress via inhibition of the SIRT3/SOD2-AKT pathway	(91)
HCT116	Human colon cancer	1 mM melatonin for 16 h under hypoxic conditions	Under hypoxia, melatonin suppressed HIF-1 transcriptional activity, leading to a decrease in VEGF expression	(94)

SIRT3, sirtuin 3; SOD2, superoxide dismutase 2; VEGF, vascular endothelial growth factor; HIF-1, hypoxia-inducible factor-1.

pivotal factors that mediate the angiogenic process. There is a plethora of experimental studies proving the anti-angiogenic role of melatonin in different tumors (33,103-105). Among the actions of melatonin, it commonly inhibits the expression of VEGF and its receptors (VEGFRs) at the protein and gene levels, in addition to the HIF-1α activity (106). Some of these actions of melatonin are summarized in Table IV.

Tissue invasion, metastasis and the role of melatonin in cancer. Evidence suggests that disseminated cells interact with a variety of proteins and cells to colonize other sites (107). In doing this, a metastatic cell loses cell-to-cell contact to invade tissue and promote intravasation, transportation, and extravasation to the secondary tumor site (108). Cell adhesion molecules play pivotal roles in cellular processes, and melatonin has been shown to inhibit cancer invasion by influencing the expression of tight and adherent junction proteins. For instance, melatonin treatment modulates epithelial-to-mesenchymal transition by increasing epithelial markers (e.g., E-cadherin expression), while decreasing mesenchymal markers (e.g., N-cadherin, Snail and vimentin) in different cancer types (109-111); the mechanisms related to these regulations involved the participation of ERK1/2 and NF-κB pathways. Concurrently, melatonin upregulated occludin expression, a transmembrane protein in tight junctions, inhibiting the migration of human lung adenocarcinoma cells (112). Additionally, melatonin is capable of regulating integrin expression, thereby inhibiting the invasion of glioma, prostate and breast cancer cells (113-115).

Extracellular matrix (ECM) remodeling is another essential mechanism occurring in the tumor microenvironment, and changes in ECM stiffness and degradation contribute to tumor growth and progression (116). Several factors, including integrin signaling, cancer associated fibroblasts (CAFs), the TGF pathway and MMPs are featured as key players (116). An endless body of evidence has mentioned the role of melatonin in regulating ECM. Of note, melatonin has been shown to inhibit chondrosarcoma cell proliferation, migration and anoikic resistance by suppressing MMP7 expression via miR-520f-3p activity (117). In addition, melatonin indirectly reduces gastric cell proliferation and invasion through the inhibition of ROS and CAFs followed by a consecutive reduction of MMP2 and MMP9 in the CAFs; these effects have been proven to be involved in NF-κB signaling (118). The inhibition of melatonin-induced MMPs associated with the invasive potential of cancer has been further documented in chondrosarcoma (118), liver (119), ovarian (120), renal (121), glioblastoma (122) and bladder cancer cells (123). The anti-metastatic effects of melatonin on different types of cancer are presented in Table V.

Clinical trials for the melatonin-based prevention and treatment of cancers. There is credible evidence demonstrating the use of melatonin in clinical trials. A previous systematic review of randomized controlled trials of melatonin in 643 patients suffering from solid tumors revealed a reduced risk of mortality at 1 year (relative risk, 0.66; 95% confidence interval, 0.59-0.73; I^2, 0%; heterogeneity, P<0.56); treatment with melatonin had no adverse events and the majority of the effects were dose- and cancer type-dependent (124). A few years later, the same research group evaluated 21 clinical trials associating the use of melatonin with chemotherapy, radiotherapy, supportive care and palliative care on the 1-year survival of patients with solid tumors (125). They observed improvements in complete and partial response to treatment in addition to the stabilization of disease. Notably, melatonin combined with chemotherapy decreased the mortality rate of patients while ameliorating all chemotherapy-related side-effects.

The prophylactic effects of melatonin in reducing the toxicity of chemotherapy and radiotherapy have been widely documented (40,126,127). Ma *et al* (106) highlighted that melatonin plays a protective role in mitigating mitochondrial damage induced by chemotherapeutic drugs. These protective effects of melatonin against the harmful effects induced by various chemotherapeutic categories and agents encompass anthracyclines, alkylating agents, platinum compounds, antimetabolites, mitotic inhibitors and molecular-targeted agents. By combining melatonin with other chemotherapeutic agents used to treat 250 patients with metastatic solid cancers (104 patients with lung cancer, 77 patients with breast cancer; 42 patients with gastrointestinal tract neoplasms, and 27 patients with head and neck cancers), Lissoni *et al* (128) observed a significant tumor regression rate in patients who underwent melatonin (20 mg/day orally every day) and chemotherapy compared to those receiving chemotherapy alone. In addition, the administration of adjunctive melatonin further reduced cardiotoxicity, neurotoxicity, thrombocytopenia, stomatitis and asthenia. Hence, the potential advantages of

Table IV. Major results regarding inflammation and angiogenesis in the context of melatonin in cancer.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
Ovarian tissue	Rat ovarian cancer	200 μg melatonin/100 g body weight per day for 60 days	Melatonin significantly decreased the expression of IkBα, NFκB p65, TRIF and IRF-3, which are implicated in TLR4-mediated signaling	(96)
H1299 and A549	Human lung cancer	1 mM melatonin for 48 h associated or not with berberine	Melatonin improved the antitumor activity of berberine by stimulating caspase/Cyto C and inhibiting AP-2β/hTERT, NF-κB/COX-2 and Akt/ERK signaling pathways	(97)
MDA-MB-361	Human breast cancer	0.1 to 1.0 mM melatonin for 72 h	Melatonin inhibited COX-2 expression and PGE2 production, abrogated p300 histone acetyltransferase activity and p300-mediated NF-κB acetylation, thereby blocking NF-κB binding and p300 employment to COX-2 promoter	(98)
HepG2	Human hepatocellular carcinoma	1 mM melatonin for 24 and 48 h under normoxic and hypoxic conditions	Melatonin reduced the expression of proangiogenic proteins VEGF and HIF-1α in cells treated with 1 mM melatonin for 24 h in both normoxic and hypoxic conditions	(103)
Renal tissue	Mouse renal adeno-carcinoma	1 mM melatonin for 16 h under hypoxic conditions with or without luzindole (1 μM) for *in vitro* studies and *in vivo* with 20 mg melatonin/kg body weight per day for 7 days	Melatonin inhibited tumor growth and blocked tumor angiogenesis in mice and diminished the expression of the HIF-1α protein	(33)

TRIF, TIR-domain-containing adapter-inducing interferon-β; IRF-3, interferon regulatory factor 3; TLR4, Toll-like receptor 4; COX-2, cyclo-oxygenase 2; HIF-1, hypoxia-inducible factor-1.

melatonin appear noteworthy; thus, it may be reasonable to consider implementing melatonin therapy in the early stages of cancer with the prospect of enhanced benefits. Research has demonstrated that the anticancer effects of melatonin are not tissue-specific, and its therapeutic and preventive properties have been reported in cancers originating from various tissues (129). In addition to augmenting the therapeutic effects of other anticancer drugs, melatonin improves the sleep and quality of life of patients with cancer. Although further research is warranted to fully establish the indole as an ally in the clinical setting, evidence suggests its potential benefits and warrants further exploration. For more detailed information on the particular effectiveness of melatonin in specific cancer types in human trials, please consult the review by Talib *et al* (129).

3. Vitamin D and cancer

Metabolic pathways involved in the production and action of VitD. VitD plays a critical role in the metabolism of calcium and phosphorus, which are essential for bone health and various other biological functions. Pathologies due to VitD deficiency are characterized by hypocalcemia, hypophosphatemia, and dental and skeletal alterations. For several decades, it has been shown that VitD, in addition to maintaining bone and tooth health, has antioxidant, anti-inflammatory and immunomodulatory properties, as well as stimulating the growth of hematopoietic tissue (130-136). The two main inactive precursors of VitD are VitD2 and VitD3. VitD2 (ergocalciferol) can be derived from dietary sources (20%), and some of its hydroxy-derivatives may be produced in several types of cells (137), while VitD3 (cholecalciferol) is produced when the cholesterol precursor, 7-dehydrocholesterol located in the epidermis, is exposed to the UVB radiation (80%) (138-140). Both undergo the same activation process (141), and synthesized VitD is transported by binding to VitD binding protein (DBP) in serum. However, there is a greater amount of knowledge available about the synthesis and action of 1,25(OH)2 D3 (calcitriol), as the active form of VitD (142). To activate both forms, they must be metabolized, and the liver is the organ where hydroxylation to 25OHD3 (calcifediol) mainly occurs. In the liver, the microsomal and mitochondrial 25-hydroxylase

Table V. Major results regarding tissue invasion, metastasis and the role of melatonin in cancer.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
GBC-SD	Human gallbladder cancer	0.25, 0.50, 1.00, 2.00 and 3.00 mM for 24 or 48 h	Melatonin increased the protein levels of the epithelial marker, E-cadherin, while the expression levels of the mesenchymal markers, N-cadherin, Snail and vimentin decreased	(109)
MGC80-3 and SGC-7901	adenocarcinoma	0.1, 0.5 and 1.5 mM for 24 h	Melatonin reduced cell invasion and migration, increased E-cadherin and β-catenin expression, and downregulated fibronectin, vimentin, Snail, MMP-2 and MMP-9 expression	(110)
A549	Human lung adenocarcinoma	0.1, 0.5, 0.75, 1.0, 2.5 and 5.0 mM melatonin for 12 and 24 h or 7 days	Melatonin inhibits the migration by down-regulation of the expression of osteopontin and myosin light chainkinase and upregu-lation of occludin involving in JNK/MAPK pathway	(112)
C4-2 and LNCaP	Human o steoblastic prostate cancer	1, 0.3 and 1.0 mM 0melatonin for 24 and 48 h under normoxic and hypoxic conditions	Melatonin inhibits FAK, c-Src, and NF-κB transcriptional activity via the melatonin MT1 receptor, which inhibits integrin α2β1 expression	(114)
U251	Human glioma	1 nM and 1.0 mM melatonin for 12 and 24 h under normoxic and hypoxic conditions	Melatonin suppressed the migratory and invasive capacity by reducing the phospho-rylation of FAK and Pyk2, and decreasing expression of alphav beta 3 (αvβ3) integrin	(115)
JJ012 and SW1353	Human chondrosarcoma	0.1, 0.3 and 1 mM melatonin for 18 and 24 h or 1, 2, 3, and 4 days	Melatonin reduced MMP-7 synthesis by promoting increased levels of miR-520f-3p expression, which were downregulated in human chondrosarcoma tissue samples	(117)
SKOV-3 and CSC	Human ovarian carcinoma	1 to 10 mM melatonin for 24, 48 or 72 h with or without luzindole	Melatonin decreased genes related with EMT including ZEB1, ZEB2, Snail and vimentin, whereas increase E-cadherin; melatonin also decreased MMP-9 expression and inhibited PI3K and MAPK	(120)
Achn, Caki-1, and HL-60	Human renal adenocarcinoma and human leukemia	0.5 to 2 mM melatonin for 24 and 48 h	Melatonin transcriptionally inhibited MMP-9 by reducing p65- and p52-DNA-binding activities	(121)
HT1197, HT1376, T24, and	Human bladder carcinoma	1 mM melatonin for 24 h or 10 days	Melatonin treatment suppressed the growth, migration, and invasion through downregu-lating ZNF746-regulated MMP-9/MMP-2 signaling	(123)

MMP, matrix metalloproteinase; EMT, epithelial-mesenchymal transition; ZEB, zinc finger E-box binding homeobox.

enzymes, CYP2R1 and CYP27A1 respectively, convert VitD to 25OHD3 (141,142). CYP27A1 is widely distributed in different tissues with the highest levels found in the liver and muscles, while CYP27R1 is mainly expressed in the liver, skin and testes (143). Finally, in the kidneys, there are transmembrane proteins, megalin and cubilin (144), which function as DBP receptors in the proximal renal tubules where a mitochondrial oxidase as CYP27B1, also known as 1α-hydroxylase, acts on 25OHD3 to synthesize 1,25(OH)2 D3 (145). This is considered the most potent metabolite of VitD, which mediates many of its hormonal actions (135). Notably, new pathways of VitD activation by CYP11A1 have also been established, with the production of various hydroxy-derivatives *in vivo* and their presence in human serum (146-149).

As previously mentioned, VitD metabolites are transported in the blood bound mainly to DBP (85-88%), a transport protein homologous to albumin and α-fetoprotein (150) produced mainly in the liver. 25OHD3 is the form that predominates in the circulation, and it is used as a clinical marker to determine VitD status, by identifying reserve levels. Moreover, the concentration in serum is very similar to the levels of VitD stored in adipose and muscle tissue (151,152). The average concentration in blood is 30 ng/ml, and it has a half-life of 15 days (153). Under normal conditions, the concentration of DBP is markedly higher than the concentrations of VitD metabolites, and the affinity of DBP for 25OHD3 is markedly greater than that of 1,25(OH)2D3; thus, in physiological situations, a very low percentage of 25OHD3 and 1,25(OH)2 D3 is free in the blood (154).

Mechanisms by which VitD may inhibit cancer growth and metastasis. The majority of the effects of 1,25(OH)2 D3 are mediated primarily by its binding to the VitD receptor (VDR), which is a member of the superfamily of nuclear receptors with homology to the receptors for retinoic acid (RXR), thyroid hormone, sex hormones and adrenal steroids. VDR is a phosphoprotein and the binding of 1,25(OH)2D3 induces phosphorylation on serine residues, stabilizing the receptor and setting the stage for a cascade of multiple events that intricately modulate cancer pathways (155,156). Within the cancer cell, VDR can be located both in the cytosol and in the nucleus, influencing genomic and non-genomic signaling pathways that play crucial roles in cancer growth and metastasis (157,158).

Genomic actions of VitD to counteract cancer development and progression to metastasis. Once 1,25(OH)2 D3 and other VitD hydroxy-derivatives (159-163) cross the target cell membrane, they bind to the cytoplasmic VDR and this complex binds the RXR, increasing the affinity for specific DNA sequences known VitD response elements located in the promoter regions of target genes (164,165). Following this interaction, several coactivators (e.g., SRC-1, SRC-2, SRC-3, P300 and CBP, RIP140, etc.) and corepressors (e.g., NCoR and SMRT, HDACs, etc.) influence the transcription of different genes involved in the control of cancer (166,167). The genomic mechanisms of VitD are not immediate, since a time interval is necessary to obtain the functional proteins that mediate the anticancer actions.

These genomic effects of VitD exert a profound influence on pathways crucial to cancer cell proliferation. Through precise modulation of gene expression, VitD disrupts the delicate balance that sustains uncontrolled tumor growth (168). By downregulating pro-proliferative genes, such as CDK, c-Myc, EGFR, KRAS, NF-κB, etc. (16,168,169), and upregulating those associated with cell cycle arrest, including CDKN1A and CDKN1B, GADD45A, BTG2, IGFBP3, CDH1, PTEN, among others, VitD emerges as a potent genomic modulator, halting cancer cell to attenuate their ability to proliferate uncontrollably (170,171).

Among the main features of the genomic actions of VitD, is its ability to induce the apoptosis, or programmed cell death, of cancer cells. Through the targeted regulation of pro- and anti-apoptotic genes, including BCL2, BAX, caspases 3 and 8, p53, etc., VitD promotes the elimination of damaged or malignant cells (172). This genomic modulation not only impedes cancer development, but also serves as a critical barrier against the survival and dissemination of cells poised for metastasis (173).

The genomic influence of VitD also extends to pathways governing cellular differentiation. By favorably modulating gene expression associated with this process, VitD promotes a cellular environment that discourages the maintenance of a stem cell-like state in cancer cells (174). This not only impedes tumorigenesis, but also disrupts the acquisition of the aggressive traits necessary for metastatic progression (175).

In addition, the genomic actions of VitD extend to the inhibition of angiogenesis, which, as previously mentioned, constitutes a process vital for sustained tumor growth (176). Through the modulation of pro- and anti-angiogenic genes, such as VEGF, FGF-2, MMPs, ANGPT2, THBS1, among others, VitD disrupts the formation of new blood vessels that nourish tumors (177). Thus, this genomic interference serves as a strategic impediment to the establishment of a robust blood supply, critically hindering the expansion and metastatic potential of cancer cells.

In addition to its direct genomic actions, VitD engages in crosstalk with inflammatory signaling pathways, contributing to its inhibitory effect on cancer development (178). By modulating the expression of genes involved in inflammation and immune regulation, VitD creates an anti-inflammatory milieu that hampers the pro-tumorigenic environment often associated with chronic inflammation (179).

As is known, the genomic modulation by VitD tends to extend its protective influence to counteract metastatic pathways (180). By selectively up- or downregulating genes involved in cellular motility, extracellular matrix degradation and epithelial-mesenchymal transition, VitD exerts genomic control over the migration, invasion, and colonization of cancer cells intending to spread to distant sites (181). Therefore, VitD emerges as a potential guardian against the formidable challenge of metastasis, especially during advanced cancer stages.

Non-genomic actions of VitD in the battle against cancer and metastasis. One of the hallmark features of non-genomic actions of VitD in cancer inhibition is its ability to rapidly modulate cell signaling cascades. Through interactions with membrane-associated receptors, VitD orchestrates fast responses that impact cellular processes such as proliferation, survival and apoptosis (182). Hence, this non-genomic modulation serves as an immediate brake on the aberrant signaling often associated with cancer cells (183). These rapid responses have been studied for different steroids and can be induced by the binding of the hormone to a protein associated with the membrane (184), which involves a classic receptor such as VDR, but associated with the caveolae of the bilayer lipid, or a non-classical steroid receptor specific for rapid responses called membrane-associated rapid response steroid binding protein (185). The interaction of 1,25(OH)2 D3 with these receptors promotes the activation of signaling molecules, such as phospholipase C, increasing the synthesis of second messengers including inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 in turn stimulates the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm and DAG activates protein kinase C (PKC). Both Ca^{2+} and PKC regulate Ca^{2+} entry into the cell through voltage-gated channels (186). Thus, it is clear that VitD, in its non-genomic capacity, plays a crucial

role in maintaining cellular calcium homeostasis (187). Hence, by swiftly regulating calcium influx and efflux across the cell membrane, VitD contributes to the normalization of calcium levels, disrupting the signaling pathways that sustain uncontrolled cell growth (188). Additionally, some of the second messengers mentioned can also interact with the nucleus to modulate gene expression, whereby under certain circumstances, both genomic and non-genomic actions of VitD may collaborate to fight against cancer and metastasis (189).

Similar to genomic mechanisms, non-genomic pathways of VitD also extend to the inhibition of angiogenesis, albeit through rapid responses (179,190). By directly influencing endothelial cells and vascular smooth muscle cells, VitD disrupts the formation of new blood vessels crucial for tumor sustenance (191). This rapid interference with angiogenesis contributes to the containment of cancer growth and metastasis.

The non-genomic actions of VitD also have a profound effect on immune cells, influencing their functions in the tumor microenvironment (192). The rapid modulation of immune responses, such as enhanced phagocytosis and cytokine production, contributes to an antitumor environment. This rapid immune regulation represents a critical non-genomic strategy employed by VitD to inhibit cancer progression (132).

VitD also swiftly interferes with cellular processes involved in migration and invasion, essential steps in cancer metastasis. Through non-genomic mechanisms, VitD hampers the reorganization of the cytoskeleton and disrupts focal adhesion, thereby impeding the ability of cancer cells to migrate and invade surrounding tissues (193). A compilation of *in vitro* and *in vivo* studies related to the antitumor actions of VitD is presented in Table VI.

Evidence from animal and human studies on the effects of VitD in cancer treatment and prevention. Numerous animal studies have demonstrated that adequate VitD levels contribute to the suppression of tumor growth. Experimental models, ranging from mice to rats, consistently show a reduction in tumor size and incidence when VitD is administered (194-197). Animal experiments also suggest that VitD plays a role in inhibiting metastasis. Studies utilizing metastatic models demonstrate that VitD supplementation can impede the spread of cancer cells to distant organs, highlighting its potential as a modulator of metastatic pathways (198). Likewise, VitD has been implicated in the modulation of immune responses in animal studies. Enhanced immune surveillance and increased activity of immune cells contribute to a microenvironment less conducive to tumorigenesis (199).

Notably, epidemiological studies have consistently associated higher VitD levels with a reduced risk of developing certain types of cancer. Thus, populations with increased sun exposure or VitD supplementation tend to exhibit lower incidences of colorectal, breast and prostate cancers (200). Human studies have also explored the impact of VitD on cancer survival rates, as well as both the genomic and non-genomic effects of VitD in these patients. In this regard, some research suggests that patients with cancer with higher VitD levels at the time of diagnosis may experience improved outcomes and an increased overall survival. In fact, studies examining gene expression patterns indicate that VitD may influence key pathways associated with cell proliferation, apoptosis and differentiation (201-203). Emerging evidence even suggests that the VitD status may influence the response to cancer treatments such as chemotherapy, radiotherapy and immunotherapy. Therefore, patients with optimal VitD levels may exhibit better responses to therapeutic interventions (204-206).

As regards the prevention of cancer, some clinical trials have also explored the potential of VitD supplementation in reducing the risk of developing several types of cancer, including colorectal, breast and prostate cancer. In addition, findings from observational studies and meta-analyses have suggested an association between higher VitD levels and a lower incidence of developing certain types of cancer, such as pancreatic, colorectal, gastric, prostatic, liver, bladder and lung cancer (207,208).

Establishing the optimal VitD dosage for cancer prevention and treatment remains a challenge. The dose-response association is complex, and individual variations in metabolism and absorption add layers of intricacy to this value. Furthermore, the effects of VitD appear to be cancer-type specific (209). In this sense, while there is evidence to support its protective role in certain malignancies, the association with other cancer types remains less clear, highlighting the need for targeted research in diverse cancer types (210).

4. Synergistic effects of melatonin and vitamin D in cancer

Potential mechanisms by which melatonin and VitD interact to produce synergistic effects in the prevention and treatment of cancer. The authors have previously documented an inverse association between melatonin and VitD deficiencies with the pathogenesis of multiple diseases, including cancer (211). Since the synthesis of both VitD and melatonin tend to be depressed during aging, the proper functioning of some biological systems is disrupted resulting in excessive oxidative stress, inflammation, and mitochondrial malfunction. It is known that the mitochondria are the preferential site for both melatonin and VitD actions; thus, they may play cooperative roles in ensuring the maintenance of cellular homeostasis (211). Common signaling pathways associated with the mitochondrial functions regulated by melatonin and VitD include the downregulation of mTOR, FOXO1, iNOS, NF-κB and RAAS, as well as the upregulation of Klotho, SIRT-, AMPK, Nrf2 and HSP70. The regulatory events mediated by these targeted molecules in association with mitochondrial-related processes (e.g., apoptosis and resistance to chemotherapy) are promising biological mechanisms to be addressed in future or ongoing studies using melatonin and VitD as adjunctive agents.

In this regard, a complementary therapeutic strategy using melatonin and VitD has been highly recommended for patients with breast cancer (212). While *in vitro* studies hae revealed the capacity of melatonin to regulate the transcriptional activity of VDR in human breast cancer cells, higher levels of VitD have exhibited a negative regulation with melatonin secretion (211). Notably, Bizzarri *et al* (213) exposed estrogen-responsive rat breast cancer cells (RM4 line) to combined treatment with 1,25-dihydroxyvitamin D3 (VitD3, the active form of VitD) at low concentrations with melatonin (10^{-9} M). Melatonin markedly increased the sensitivity of RM4 cells to VitD3 and the combination treatment further enhanced

Table VI. Major results regarding the effects of vitamin D in various types of cancer.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
LS180 CRC	N.A.	10^{-7} M $1,25(OH)_2D_3$ for 3 h	During $1,25(OH)_2D_3$ activation the coactivator SRC-1 was correlated with VDR/RXR activity, while corepressors NCoR and SMRT were also recruited to activation of complexes near genes stimulated by $1,25(OH)_2D_3$	(167)
MM96L, Sk-Mel-28, 1205Lu, WM164, and C8161	Human melanoma	10 nM $1,25(OH)_2D_3$ for 24, 48 and 72 h	$1,25(OH)_2D_3$ inhibition of melanoma growth was dependent on PTEN and VDR; $1,25(OH)_2D_3$ also inhibited the PI3K-AKT-mTOR and RAS-ERK signaling pathways, while increasing caspase levels	(171)
HCT116	Human colorectal carcinoma	2.5, 5, 7.5, 10, 15, 20, 40 μM $1,25(OH)_2D_3$ for 24 h	Treatment with $1,25(OH)_2D_3$ exerted a dose-dependent effect on the expression of caspase-3, but did not have any effect on NF-κB expression	(172)
MCF-7 and MDA-MB-231	Human breast cancer	100 nM $1,25(OH)_2D_3$ for 24 and 48 h	Treatment with calcitriol ($1,25(OH)_2D_3$) increased the expression of TIMPs 1 and 2 and decreased MMPs 2 and 9); it also reduced the expression of VEGF, TGF-β1 and amphiregulin	(176)
4T1	Murine breast cancer	0.001 to 100 μM $1,25(OH)_2D_3$ for 12, 24 and 48 h for *in vitro* assays and 10 mg per kg-1 every 3 days for six times	MMP-2 and MMP-9 were downregulated by $1,25(OH)_2D_3$, while paxillin, a key component of the focal adhesion complex, was upregulated	(180)
MCF-7 and MDA-MB-231	Human breast cancer	0.5 and 1 μM $1,25(OH)_2D_3$ for 24 h	$1,25(OH)_2D_3$ impaired migration by increasing E-cadherin, and F-actin and reducing vimentin expression; it also induced apoptosis by decreasing mTOR expression and increasing AMPK activation	(193)
Fragment of human leiomyoma	Human leiomyoma in xenograft model	0.5 μg/kg/day or 1 μg/kg/day vitamin D for 21 or 60 days	$1,25(OH)_2D_3$ at 1 μg/kg for 60 days significantly reduced proliferation, collagen-I, plasminogen activator inhibitor 1 and TGF-β3 expression in the xenograft tissue; it also increased apoptosis in the animal model	(194)
EO771	Mouse breast adenocarcinoma	40 IU/day $1,25(OH)_2D_3$ per mouse seven times in 2 weeks	Vitamin D was able to modulate the tumor growth and the inflammation in the microenvironment by recruitment of $CD8^+$ cells; this effect was reversed in high-fat diet conditions	(195)
BT-474, MCF-7, T47D, MDA-MB 453, MDA-MB-231, MDA-MB-468, and A549	Human breast and lung cancer	7.78, 15.62, 31.25, 62.5, 125.0, 250, and 500.0 μM $1,25(OH)_2D_3$ for 24, 48, and 72 h	$1,25(OH)_2D_3$ induced cell growth arrest mediated by the upregulation of p53 and the downregulation of Bcl2 and cyclin-D1 expression levels; $1,25(OH)_2D_3$ also decreased cell migration and inhibited blood vessel growth *in vitro*	(196)

Table VI. Continued.

Cell lineage	Type of cancer	Dosage and period of treatment	Relevant effects	(Refs.)
MMTV-PyMT	Mouse breast cancer	10^{-10}, 10^{-9}, 10^{-8}, and 10^{-7} M $1,25(OH)_2D_3$ for 48 h for *in vitro* studies and 25 IU/kg or 1,000 IU/kg for *in vivo* studies for 10 weeks	Vitamin D treatment inhibited p-STAT3, Zeb1 and vimentin, and increased E-cadherin levels; epithelial-mesenchymal transition and CXCL12/CXCR4 signaling were favored for metastases in a condition of vitamin D deficiency (25 IU/kg)	(198)

N.A., not applicable; SRC-1, steroid receptor coactivator-1; VDR, vitamin D receptor; RXR, receptor for retinoic acid; TIMPs, tissue inhibitors of metalloproteinases; MMP, matrix metalloproteinase; ZEB, zinc finger E-box binding homeobox.

the release of TGF-β1 compared to either melatonin or VitD3 alone; increasing TGF-β1 secretion is considered to promote the growth inhibition of breast cancer cells and to activate the apoptotic cascade (213). To more completely understand the anti-proliferative effect of TGF-β1-dependent signaling on breast cancer cells, the same research group investigated the role of melatonin and VitD3 considering the activities of proteins involved with cell cycle, tumor suppression, and cell growth (214). Melatonin synergistically interacted with VitD3 to induce a complete cell growth arrest at 144 h following incubation. This TGF-β1-activated blockade was accompanied by increased levels of Smad4 and phosphorylated Smad3. Moreover, the combination of melatonin and VitD3 significantly reduced the Akt phosphorylation and MDM2 levels, with a consequent increase in the p53/MDM2 ratio. These events can be completely reversed by the addition of a monoclonal anti-TGF-β1 antibody to the culture medium, which reinforces the TGF-β1 dependence in downregulating critical molecules involved with cell growth (214). The main actions by which melatonin and VitD synergistically interact to exert antitumor effects are illustrated in Fig. 2.

In vivo and *in vitro* experiments have also documented that inflammation and oxidative processes represent the main mechanisms of carbon tetrachloride (CCl4)-induced liver cancer (71,215). For this reason, Özerkan *et al* (216) evaluated the hepato-protective activity of melatonin and VitD3 on CCl4-induced cytotoxicity in human hepatoma (HepG2 and Hep3B cell lines). Efficiently, the co-administration of melatonin (10^{-8} M) and VitD3 ($2.5x10^{-6}$ M) protected liver cells from oxidative damage by diminishing lipid peroxidation and augmenting glutathione levels similar to that of the control groups. Given that there are several means by which ROS compromise cancer cell survival, it is hypothesized that melatonin and VitD may synergistically act to intensify oxidative damage in a more advanced stage of cancer.

Evidence from studies on patients with cancer on the effects of the combined use of melatonin and VitD. According to the Clinical Practice Committee of The Society of Integrative Oncology, composed of leading researchers and clinicians, melatonin and VitD are among the supplements that have evidenced effectiveness against different types of cancer (217). Although clinical trials (Clinical trial no. NCT01965522) focusing on the potential benefits and realistic expectations of this combination are far from optimal, they are of significant value to ease the burden of patients afflicted with this disease.

The pathogenesis of lip, oral cavity and pharyngeal cancers (LOCP), which are categorized as rare neoplasms, is still unclear; however, it is considered to involve oxidative stress, the immune system and components of the extracellular matrix (217-219). Recently, a study conducted with 45 patients diagnosed with LOCP and classified according to their age (younger vs. older cancer groups) demonstrated the link between the serum levels of melatonin and VitD with the oxidant-antioxidant status of patients (218). Regardless of age, patients with LOCP exhibited a decrease in VitD and catalase levels in contrast to an increase in osteopontin and malondialdehyde levels. In the older LOCP group, melatonin levels were diminished in addition to the variations in the antioxidant status (218).

Previous clinical studies using melatonin and vitamins including VitD as therapy have been conducted on patients with breast, head and neck cancer. While in patients with breast cancer a significant tumor regression rate followed with no recurrence rate and a 5-year survival of 50% at stage IV was commonly observed (220), patients with head and neck cancer exhibited a greater response to therapy and an improved survival rate (221). More recently, a retrospective observational study by Di Bella *et al* (222) observed the effectiveness of treating patients with malignant anaplastic brain cancer with a combination of components (including melatonin and VitD) that exhibit anti-proliferative, cytostatic, antioxidant and anti-metastatic features. Notably, they observed the antitumor actions of the treatment and a longer survival rate of patients (5 to 8 years after commencing the therapy). Aligned with these findings, the same group retrospectively analyzed 15 cases of osteosarcomas treated with a multitherapy composed of melatonin and VitD, among other active principles, and observed an increased patient survival rate and life quality without overt toxicity compared to the standard therapy for osteosarcoma (223).

Other effects of these biotherapeutic agents, have been used to treat a total of 28 patients with advanced non-small-cell-lung cancer (NSCLC) (stage IIIB or stage IV NSCLC) receiving cyclophosphamide as therapy. Patients who experienced a

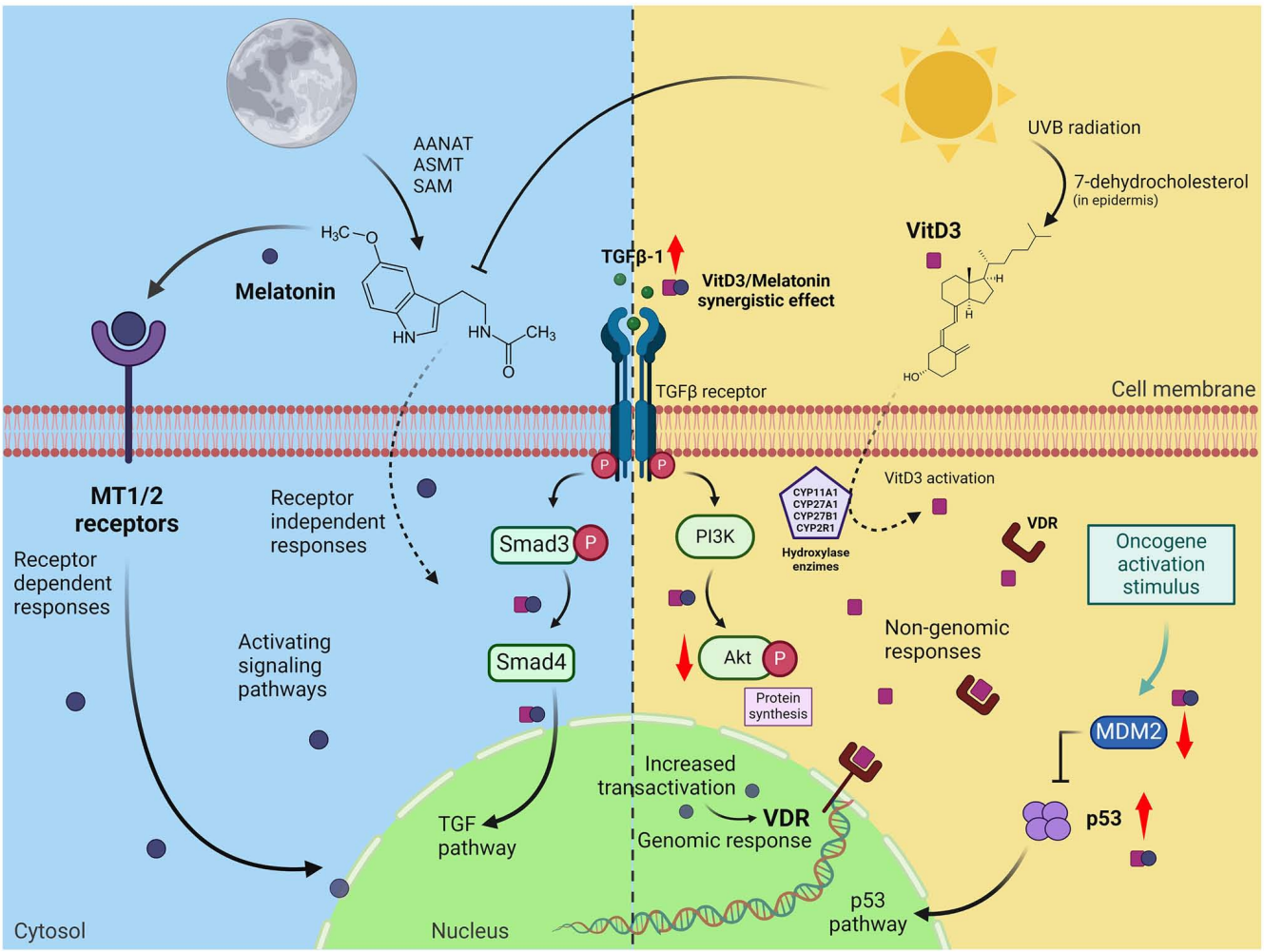

Figure 2. Illustration of the synthesis and potential synergistic effects of melatonin and VitD3 (cholecalciferol) in a cancer cell. During the night, melatonin is synthesized in the pineal gland from the precursor serotonin which is converted into N-acetyl-serotonin by AANAT. With the action of ASMT and SAM the final stage of melatonin production is achieved. Light inhibits the synthesis of melatonin, while increasing the levels of VitD3, which is activated with different tissue-specific hydroxylase enzymes. Melatonin can easily cross the cell membrane to act in a receptor independent response thus activating signaling pathways in the cytosol or mainly binding through their G protein-coupled receptors MT1 and MT2 to mediate numerous biological actions. The effects of VitD3 are primarily genomic and mediated by its interaction with nuclear VDR, and melatonin is documented to increase VDR transactivation. In the cytosol, VDR and VitD3 can trigger non-genomic responses by modulating various cell signaling cascades. Treatment with melatonin and VitD3 may act synergistically to inhibit cancer cell growth by increasing the levels of TGFβ-1, Smad4 and phosphorylated Smad3, thus enhancing the TGF pathway. This combination can also promote a reduction in Akt phosphorylation and MDM2 levels, thereby leading to an increase in p53 pathway and consequently causing tumor suppression and apoptosis. AANAT, alkylamine acetyltransferase; ASMT, acetyl-serotonin O-methyltransferase; SAM, S-adenosyl methionine; VDR, vitamin D receptor; TGFβ-1, transforming growth factor beta 1; Smad3, suppressors of mothers against decapentaplegic homolog 3; Smad4, suppressors of mothers against decapentaplegic homolog 4; MDM2, mouse double minute 2 homolog; p53, tumor protein p53.

low-performance status and prognosis benefited from the complementary therapy in terms of survival rate [(overall survival rate was 51.2% (at 1 year) and 21.1% (at 2 years)] and quality of life. The majority of patients improved their respiratory conditions (e.g., dyspnea and cough) and general symptoms such as fatigue, insomnia, and pain (224). Of note, 1 year later, Norsa and Martino (225) investigated the effect of the melatonin and VitD combination in patients with advanced-stage lung cancer in whom the disease had progressed following standard chemotherapy. Among the disease-related benefits, there were improvements in respiratory symptoms, which was even more evident in patients surviving for >95 days after commencing the protocol regimen.

Additionally, the radioprotective actions of melatonin and VitD, whose synthesis is dependent on appropriate light wavelengths, have been broadly recognized since various studies with animals and humans supported their protective effects against ionizing radiation (IR)-induced damage (226). In the course of the ever-growing use of IR in medical practice, a number of individuals are continuously exposed to different IR sources and doses, particularly patients undergoing radiotherapy. In this regard, melatonin and VitD show promise in selectively enhancing the sensitivity of cancer cells to radiotherapy, rendering them potential adjuncts to improve anticancer effects and therapeutic outcomes. Considering existing research on their antioxidant effects, these substances may be beneficial for protecting individuals exposed to radiation and those undergoing radiation treatments. However, further human studies are required to determine optimal and safe doses, which requires clinical trials for validation.

5. Conclusions and future perspectives

It is well-known that melatonin and VitD share similarities, with a significant impact on human health, acting through multiple systems due to their anti-inflammatory and anti-oxidant actions, immune enhancer responses and oncostatic properties. A notable and paradoxical fact concerning both agents is that VitD deficiency could be caused by 'low sunlight exposure', whereas a reduction in melatonin secretion occurs when a 'darkness deficiency' arises, among other conditions, from overexposure to artificial blue light (227). Previous research has shown the representation of low daytime UVB or high LAN exposure on circadian disruption and related disorders (e.g., cancer risk) (228). Although epidemiological investigations on the deleterious consequences of the combined suppression of VitD and melatonin are lacking, it appears likely that they negatively affect the physiology of cancerous cells or tissue, while protecting non-damaged cells.

As regards the central discussion of the present review, VitD and melatonin supplementation exhibit efficacy against several types of cancer. Clinical trials on this combination are still limited but are valuable in improving the quality of life of cancer patients. Specifically, human studies involving osteosarcoma, as well as lip, oral cavity, pharynx, breast, head, neck, brain and lung cancers are examples of these improvements. VitD and melatonin also have radioprotective potential, which could improve the effectiveness of radiotherapy and protect patients from its side-effects. The use of synthetic radioprotective compounds is restricted due to the occurrence of undesirable health consequences, particularly when higher doses are required for maximum radioprotection. Considering the prevalent deficiencies of melatonin and VitD in modern societies, supplementing with both substances would be crucial, given that such deficiencies may exacerbate the adverse effects of radiotherapy (e.g., ionizing radiation) and chemotherapy. In this sense, further studies are warranted to determine optimal doses when these agents are used in combination.

In addition to reducing the growth of cancer cells and improving the life quality of patients, this combination may improve sleep quality providing an indirect benefit on the cancer mediated by the connections between sleep and the immune system (229).

Finally, to determine the efficacy of both agents in ameliorating the life quality of patients with cancer, large controlled trials comparing the effects of combined therapy with melatonin and VitD with a single agent or even placebo are warranted, in order to investigate their potential synergistic effects. This intervention is easy to follow, since melatonin and VitD are inexpensive compounds and do not produce organic toxicity, dependence and/or chemoresistance.

Acknowledgements

The authors would like to thank Dr Vinícius Augusto Simão from the Department of Structural and Functional Biology, UNESP, São Paulo State University, Institute of Biosciences, Botucatu, São Paulo, Brazil, for his participation in the design and elaboration of the figures of the manuscript.

Funding

The present study work has been partially supported by grants from Instituto de Salud Carlos III (FIS PI22/01608) and the Ministerio de Ciencia e Innovación (PID2021-1230760B-100). The present study also received grant funding PICT 2020 Seria A 4000 from Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación (FONCyT), and Fundación Florencio Fiorini (Academia Nacional de Medicina, 2024).

Availability of data and materials

Not applicable.

Authors' contributions

All authors (RJR, LGDAC, VAS, VMMG, NDLH, DAS and WM) contributed equally to the conception and design of the review, with substantial input on the data, content analysis and interpretation, writing, and critical review of the article for its intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the re-viewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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