Review

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Does melatonin as an antioxidant and anticancer agent potentiate the efficacy of curcumin?

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ABSTRACT

Melatonin is a hormone that exhibits many bioactivities such as antioxidant, anti-inflammatory, anti-carcinogenic, anti-diabetic, neuroprotective, and anti-aging activity. In addition, melatonin has been used to strengthen the effect of drugs or agents used for treatment in many different disease models such as cancer, tumor, bacterial infection, autoimmune diseases, and gastrointestinal diseases. According to recent studies, curcumin is used as a pigment and powerful antioxidant and anti-inflammatory agent with therapeutic potential against various cancers. Melatonin and curcumin have been used in different models of disease or injury: such as Alzheimer's disease treatment, testicular tissue preservation, bladder cancer treatment, gastric mucosal damage, and prevention of nephrotoxicity. This review covers published literature studies on the effects of comparison or combined use of melatonin and curcumin as anticancer and antioxidant agents and it reveals whether melatonin potentiates the effect of curcumin when used together.

Keywords: Melatonin, curcumin, antioxidant, anticancer, apoptosis

INTRODUCTION

Melatonin

Melatonin is a hormone with strong antioxidant properties secreted from the cells of the pineal gland called pinealocytes, effective in determining biorhythm and the circadian rhythm.[1] Apart from its antioxidant activity, it displays many bioactivities such as anti-inflammatory properties, enhancing immunity, creating anti-carcinogenic effects, cardiovascular protection, protection against diabetes and obesity, and neuroprotective and anti-aging activity.[2] It has been noted that melatonin is also found in the leaves, fruits, and seeds of plants. Melatonin, whose secretion is adjusted according to the length of the night, is the hormone responsible for giving the body information about the light and dark cycle. The main physiological functions of melatonin are hormonal however, it may also exhibit autocrine or paracrine properties in the retina or intestine.[3] Today, the role of melatonin in human physiology and the treatment of many diseases has been proven. However, many functions and effects of melatonin still await discovery. According to the study by Reiter et al.[4] melatonin seems to reduce the toxic effect on the tissue and increase the effectiveness of the active substance with which it is used together. In addition, melatonin has been used to strengthen the effect of a drug or agent used for treatment in many different disease models such as cancer, tumor, bacterial infection, autoimmune diseases, and gastrointestinal diseases. As a result of the research of Qi et al.[5] it was noted that melatonin had an inhibitory effect on ferric nitrilotriacetate Fe-NTA-induced oxidative DNA damage. Liu et al.[6] reported in their study that melatonin was also effective on cerebral I/R. Melatonin prevents the harmful effects of free oxygen radicals formed in the tissue during reperfusion in the renal ischemia-reperfusion model. Apoptosis is seen especially in proximal tubule epithelial cells in renal ischemia-reperfusion injury, and melatonin has been shown to have a protective effect on renal tubular dysfunction.[7] Guzel Tanoglu et al.[8] reported that in an experimental chronic pancreatitis rat model, melatonin has shown to have protective properties, improving inflammation, oxidative stress, and pancreatic fibrosis. Another study shows that melatonin modulates by reversing the adverse effects of diabetes on NK-cell activity, which has a protective function in inflammatory and immunological processes.[9] Sapmaz et al.[10] investigated the effects of melatonin, oxytetracycline, and N-acetylcysteine on ovarian follicle reserves and surface epithelium in autologous intraperitoneal ovarian transplantation in

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rats. It was concluded that oxytetracycline and melatonin may be more effective than N-acetylcysteine in protecting against oxidative stress during ovarian transplantation. Melatonin is used for the prevention and treatment of several cancers e. g. breast cancer, gastric cancer, prostate cancer, colorectal cancer.[11]

Curcumin

Curcumin turmeric is a compound obtained from the rhizome of the Curcuma longa plant, which is widely used as a spice in Asia and is also used as a pigment.[12] Curcumin is an easily available antioxidant substance, inexpensive and available all over the world. It is considered a therapeutic agent used in a variety of foods in traditional and complementary medicine. Curcumin, which is widely consumed in traditional recipes in the Indian Subcontinent, South Asia, and Japan, is a potent anti-inflammatory agent against various cancers, according to recent studies.[13]

Curcumin has been used in many different studies as an antioxidant, anti-inflammatory, and anticancer agent. In the review prepared by Trujillo et al.[14] it was shown in the chronic kidney failure model that curcumin exerts a therapeutic effect. In this study, the renoprotective effect of curcumin was collected under the following headings: It helps inhibition of mitochondrial dysfunction, weakening of the inflammatory response, protection of antioxidant enzymes, and prevention of oxidative stress. The information presented in this article identifies curcumin as a promising molecule against kidney damage. In a review on curcumin doses prepared by Shoba et al.[15], it was stated that curcumin is safe at high doses e. g. 12 g/day in humans, 2 g/kg in rats and does not show any undesirable effects. As a result of all these studies, curcumin is a substance suitable for use as an antioxidant and anticancer agent in many diseases because it is not toxic even at high doses and is an easily accessible active substance.

ANTIOXIDANT POTENTIALS OF MELATONIN AND CURCUMIN

Nervous System

Alzheimer's disease: Melatonin is known as the sleep-regulating hormone and has a neuroprotective effect. Because of this neuroprotective feature, melatonin has been used as a therapeutic agent in many diseases of the brain Alzheimer's disease AD, Huntington's Disease HD. AD is a neurodegenerative disease that is seen in memory and cognitive impairments and develops with a sleep disorder. Sleep disturbance SD is a disease also seen in AD patients and has been shown to increase memory, behavioral and cognitive complications.[16] AB peptide, which is one of the important factors in the etiology of AD, accumulates in the brain of AD patients as a result of production and clearance imbalance. Researchers speculate that this leads to the formation of neurotoxic Aβ oligomers.[17] Melatonin hormone levels have been observed to decrease in the preclinical stages of AD, so it can be said that melatonin deficiency occurs in AD.

Studies are carried out to prevent or delay the onset of neurodegenerative diseases with the use of curcumin. These diseases include Alzheimer's disease, stroke, Huntington's disease, Parkinson's disease, Multiple Sclerosis, Prion disease, Down syndrome, anxiety, autism, Amyotrophic lateral sclerosis, depression, and aging. In one study, Z-CM-I-1, one of the curcumin and melatonin hybrid compounds with potential therapeutic effects for AD, was used in an APP/PS1 transgenic AD model. As a result of this in vivo study, it was shown that this hybrid compound exhibited functional properties on AD pathologies.[18] In another study, Chojnacki et al.[19] designed hybrid compounds of two natural products, curcumin, and melatonin, these hybrid compounds were synthesized and biologically characterized. It has been stated that optimization of a new hybrid structure named 5-4-hydroxyphenyl-3-oxo-pentanoic acid 2-5-methoxy-1H-indol-3-yl-ethyl-amide can be effective on AD by strengthening it.

In another study, unsaturated anionic membranes made of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine POPC and 1,2-dimyristoyl-sn-glycero-3-phospho-L-serine DMPS in Alzheimer's disease used. In this way, it is aimed to delay the progression of Alzheimer's disease. As a result of this study, in which melatonin, acetylsalicylic acid ASA, and curcumin substances were used to examine the membrane active molecule, researchers think that the progression of Alzheimer's disease can be delayed by changing the anionic unsaturated lipid membrane properties.[20] In one study, Espargaró et al.[21] reported an in vitro cell-based assay to evaluate the potential anti-aggregation activity of putative Aβ aggregation inhibitors. In this study, which analyzed the anti-Aβ aggregation activity of rosmarinic acid, melatonin, o-vanillin, curcumin, apigenin, and quercetin it was stated that curcumin had an inhibitory effect.

Huntington's disease: Huntington's disease HD is seen as a result of the disorder in the sleep-wake order and the lack of motor ability accompanying the disturbance of circadian behavior. Changes in melatonin levels have been noted in diseases Huntington's disease, multiple sclerosis, and cerebral ischemia in which severe ischemia occurs and, as a result, neuronal cells die within minutes. This shows the potential of melatonin to be therapeutic for these diseases. Neurodegenerative diseases cannot be completely cured with any drug today, treatments are often used to reduce the severity of disease symptoms. As an example, curcumin is preferred in HD to stop the progression of neurodegeneration. This antioxidant works

by targeting the reduction of oxidative and inflammatory stresses, metal ion chelation, and transcriptional changes. In a study looking at the effect of melatonin and curcumin in a Drosophila model of HD, mRNA expression of the genes of the transcriptional feedback TF loop, which creates rhythmicity for approximately 24 hours, was examined to examine the circadian timing. As a result of this study, researchers thought that melatonin and curcumin could be potential therapeutic agents for the treatment of HD in humans.[22]

Hippocampus: The hippocampus is the brain region that manages various functions of the body. It has been shown in various studies such as Alzheimer's Disease, and Parkinson's Disease that the lower region of the hippocampus is particularly affected by ischemia.[23] In vivo studies have reported that curcumin has the potential to increase the expression of various detoxifying enzymes e. g. glutathione-S-transferase, superoxide dismutase, GSH reductase and decrease glutathione in the brain.[23] In a study conducted by creating a chronic Gulf War Illness rat model, the effectiveness of melatonin was examined to improve cognitive and mood function with antioxidant, anti-inflammatory, and pro-cognitive effects. In this study, it was shown that melatonin increases neurogenesis in the hippocampus and decreases synapse loss.[24]

In light of these studies, it can be said that melatonin and curcumin have neuroprotective effects. However, there is a need for further studies on the mechanisms of neuroprotective effects in the brain. In a study where melatonin and curcumin were used together, the effects of treatment with these antioxidant substances on oxidative stress parameters, SIRT2, Bcl-2, and Bax expression in the hippocampus were investigated. It has been stated that melatonin can reduce cell apoptosis in the hippocampus by decreasing oxidative stress and SIRT2 expression and increasing Bcl-2 expression.[25]

Sciatic nerve crush injury: The aim of another study examining peripheral nerve injury, which is one of the acute clinical problems, in rats was to compare the effects of melatonin and curcumin on sciatic nerve crush injury repair. As a result of the study, it was stated that these two antioxidant substances accelerate nervous recovery and help treat nerve injury.[26]

Fetal rhombencephalic neurons: Antonio et al.[27] examined the effects of --epigallocatechin-3-gallate, polyphenol, curcumin, resveratrol, melatonin, and α-lipoic acid against ethanol-related apoptosis in fetal rhombencephalic neurons in vitro and investigated the potential neuroprotective effects of these antioxidant substances. As a result of this study, the researchers stated that these antioxidant substances can exert neuroprotection against ethanol-related apoptosis in fetal romencephalic neurons.

Neurodegeneration and depression: Olfactory bulbectomized is an established disease of depression and cognitive decline. In the study by Borre et al.[28] an experimental method consisting of zinc, melatonin, curcumin, piperine, eicosapentaenoic acid EPA, 20:5, n-3, docosahexaenoic acid DHA, 22:6, n-3, uridine, and choline, the diet, was administered to olfactory bulbectomized rats. The findings in rats on this diet were as follows: reduction in glutamate excitotoxicity, potent antioxidant/anti-inflammatory effect, and improved synaptogenesis. In rats fed this diet, decreased cognitive and behavioral deficits were noted. At the end of this study, in which more than one disease etiology was investigated at the same time, Borre et al.[28] say that the development of neurodegenerative and depressive disorders and accompanying cognitive deficits can be prevented with this diet.

Kidney

Kidney ischemia-reperfusion injury: Ischemia is a condition in which oxygen cannot reach an organ in the body for any reason. With the disappearance of ischemia, the blood flow entering the organ is called reperfusion. Renal ischemia/reperfusion injury increases the risk of mortality and morbidity and causes permanent damage to the organ, especially due to the oxidative stress it causes during the reperfusion phase. In a study investigating how renal ischemia-reperfusion damage affects the ovaries as a distant organ in rats and the effects of melatonin, curcumin, and combined melatonin-curcumin treatments on ischemia-reperfusion; It has been stated that all treatments partially preserve the histological structure. However, especially melatonin treatment appears to be more effective than curcumin treatment.[29]

Nephrotoxicity: In a study investigating the effect of the combination of melatonin and curcumin on cisplatin-induced nephrotoxicity in rats, the following results were found: According to the report of Ali et al.[30] when curcumin and melatonin were given together, tumor necrosis factor-alpha, cystatin C, uric acid, phosphorus in plasma and creatinine in urine and creatinine clearance values improved. It has been stated that the renal platinum concentration decreases much more when these two active substances are given together than when they are given separately.

Acute kidney injury: In another study investigating the effects of cisplatin on the kidney, they stated that thanks to the antioxidant properties of amifostine, curcumin, and melatonin, they could be a promising agent in the treatment of malignant tumors and the prevention of acute kidney disease caused by cisplatin.[31]

Renal oxidative damage: In another study investigating the antioxidant effect of curcumin, quercetin, melatonin, and resveratrol on ferric nitrilotriacetate Fe-NTA

induced oxidative kidney damage in rats, the amount of lipid peroxidation induced by Fe-NTA was found to be significantly suppressed by these antioxidant substances.[32]

Testis

Testicular tissue preservation: In the study by Muratoglu et al.[33] the effect of melatonin and curcumin on testicular tissue in rats was investigated. According to the results of this study, the total testes/body weight ratio of the group given melatonin in rats decreased significantly compared to the control group. In addition, a significant increase in glutathione levels was noted in rats treated with curcumin compared to rats in the control group. It was noted that the number of apoptotic cells determined by the TUNEL method decreased significantly in the group treated with melatonin and curcumin. However, it was stated that melatonin and curcumin treatment significantly increased the Johnsen score.

Bone

Rapid maxillary expansion: In another study, researchers used the rat model to investigate the effects of curcumin and melatonin on new bone formation following rapid maxillary enlargement. According to the results of this study, the researchers stated that new bone formation was accelerated in rats treated with curcumin and melatonin.[34]

Liver

Age-related liver injury: In a study of the age-related carbonyl content of the liver modeled in mice, the effects of melatonin and curcumin were examined. The results of this study, which was performed separately in young 1 month and old 18 months mice, showed that protein carbonyl formation in the liver of old mice increased compared to young mice, but the use of melatonin and curcumin decreased this value.[35]

Cold hepatic ischemia-reperfusion: In another study on the effect of multi-drug donor preconditioning MDDP: Curcumin, simvastatin, N-acetylcysteine, erythropoietin, pentoxifylline, melatonin, glycine, and methylprednisolone on cold ischemia-reperfusion injury in a rat liver perfusion model, MDDP inhibited inflammation. and it is stated that it can completely prevent parenchymal damage. Researchers say that this MDDP, in which melatonin and curcumin are used together, can be used in clinical liver transplantation.[36]

Stomach

Gastric mucosal damage: In gastric mucosal damage, a disease associated with extracellular matrix degradation in which matrix metalloproteinases play a role, conditions such as remodeling of connective tissues and loss of tissue integrity are seen. The same situation is observed in gastric ulcers, which is one of the inflammatory diseases. In gastric ulceration, reactive oxygen species are formed and transcription and translation of metalloproteinases are decreased.[37] In a study to determine the mechanism of suppression of the activity of metalloproteinases by reactive oxygen species in acute ulceration disease and also to examine some antioxidants including melatonin and curcumin during healing, it was noted that melatonin blocked the formation of reactive oxygen species, protein oxidation, mucosal cell disruption and down-regulation of metalloproteinases. In vitro studies have shown that suppression of metalloproteinase activity by H_2O_2 is blocked by melatonin and curcumin. As a result of these studies, the researchers emphasized that melatonin and curcumin inhibit H_2O_2-mediated inactivation and down-regulation of the expression of metalloproteinases at the onset of ulceration.[37]

ANTICANCER POTENTIALS OF MELATONIN AND CURCUMIN

Nervous system

Pc12 cells: Cellular oxidative stress and changes in redox metabolisms play a role in the etiology and pathology of many diseases, including cancer. Antioxidant therapies have proven beneficial in controlling these diseases. 4-hydroxynonenal 4-HNE, a byproduct of lipid peroxidation, induces oxidative stress in PC12 cells by damaging mitochondrial redox metabolism. In a study investigating the effects of 4-HNE on mitochondrial respiratory functions and apoptosis in the PC12 cell line, the effects of curcumin and melatonin were also compared. As a result of this study, researchers stated that melatonin and curcumin have a protective effect on mitochondrial functions.[38]

Bladder

Bladder cancer: Melatonin has been used in many different studies to increase the effect of the active substance it is applied together. In one study, researchers examined whether the effect of curcumin on bladder cancer cells would be altered when used with melatonin. According to the results of the research, melatonin increased the anti-proliferation, anti-migration, and pro-apoptotic activities of curcumin. The combination of melatonin and curcumin has been noted to exert an inhibitory effect against the growth of bladder cancer.[39]

Prostate

Prostate cancer: Rodriguez-Garcia et al.[40]'s study, in which curcumin, resveratrol, melatonin, and silibinin were used, investigated their effects on prostate cancer cells. As a result of the study, the researchers noted that

melatonin and silibinin inhibited cell growth. In addition, curcumin and resveratrol have been shown to induce apoptosis in prostate cancer cells.

CONCLUSION

Unlike many substances with antioxidant properties, melatonin has a high inducible capacity to scavenge free radicals, even under stressful conditions. Melatonin has secondary and tertiary metabolites, which can neutralize too many toxic oxygen derivatives. An antioxidant substance can usually scavenge 1 reactive oxygen derivative, while melatonin can scavenge 10 reactive oxygen derivatives. In addition, melatonin has been used as a second active substance in many studies, because melatonin strengthens the antioxidant, anti-inflammatory, and anti-carcinogenic effects of the other active substance. Melatonin is used as a therapeutic agent against many diseases due to its properties and a substance naturally found in the body.

Like melatonin, curcumin is an active ingredient with antioxidant properties. In addition, it is frequently used in various chronic inflammatory diseases with its anti-inflammatory properties. In addition, curcumin, which has anti-carcinogenic properties, is also used to prevent/treat cancer. If we look at curcumin from a biological point of view, its non-toxicity even at high doses and long-term use ensures its safe use in in vivo studies. In addition, curcumin, which releases the active free thiol group in the target tissue, inhibits the growth of cells. This ensures that fast-growing tissues such as cancer are kept under control. In addition to these properties, the low half-life of curcumin can be considered an obstacle to its use. Researchers continue to work towards overcoming this obstacle. In light of all this information, we can say that the treatment of curcumin for various chronic inflammatory diseases or cancer is promising.

The ability of melatonin to potentiate the effect of a second antioxidant has also been shown in various studies when used together with curcumin (**Tables 1**, **2**, and **3**). In this review, studies in which melatonin and curcumin, which have antioxidant and anticarcinogenic properties, were compared or used together, were compiled. As a result of all studies, it can be said that these two active substances are more effective when used together, creating a synergistic effect, compared to their separate use. However, the articles published in the literature on the combined use of these two active substances are limited. We think more studies should be done with the combination of melatonin and curcumin, and this combination has a clear path to preventing and treating diseases.

Table 1. The antioxidant effects of melatonin and curcumin in various in vitro and in vivo nervous system studies at IRI

Antioxidant potentials	Type of tissue/ Disease	Dose	Outcome	In vivo/ In vitro	Study
Nervous system	Alzheimer's Disease	Concentrations of 5 mol% (drug-to-peptide ratio)	Melatonin did not change the structural parameters of the membranes and did not impact the size or extent of peptide clusters Curcumin made membranes softer and thinner Curcumin reduced the volume fraction of cross-β sheets by ~70%	Unsaturated anionic membranes	Khondker et al.[20]
	Huntington's Disease	Melatonin (50, 100, or 150 µg) or curcumin (10 µM) in the diet commencing from the larval stage	Both melatonin (100 µg) and curcumin reestablished the 24-h pattern in mRNA expression of Period and Timeless to normal (control) levels, and significantly improved both locomotion ability and eclosion behavior of HD flies	the Drosophila model	Khyati et al.[22]
	Hippocampus	Melatonin (10 mg/kg/day, s.c. for 30 days), Curcumin (30 mg/kg/day, i.p. for 30 days)	Melatonin and curcumin significantly decreased MDA and SIRT2 expression in the hippocampus ($p < 0.05$) A significant increase in the GSH levels of curcumin-treated group and melatonin-treated group Melatonin, but not curcumin, significantly increased the Bcl-2 expression of the hippocampal region. There was a significant correlation between SIRT2 and MDA levels ($p < 0.05$).	Rats	Keskin-Aktan et al.[25]
	Sciatic Nerve Crush Injury	IP injections of curcumin (100 mg/kg) and melatonin (10 mg/kg) over two periods of light (9:00 a.m.) and dark (9:00 p.m.) for 4 weeks	No statistically significant difference was identified between dark and light curcumin groups while curcumin groups displayed better results than did melatonin groups Dark melatonin group displayed better results than the light melatonin	Rats	Moharrami Kasmaie et al.[26]
	Fetal Rhombencephalic Neurons	1 µM melatonin, 1 µM curcumin	Co-treatment of these cultures with melatonin and curcumin prevented ethanol-associated apoptosis	Cultures of fetal rhombencephalic neurons	Antonio et al.[27]
	Neurodegeneration and Depression	Dietary treatment (containing melatonin and curcumin) started 2 weeks before olfactory bulbectomized surgery, continuing for 6 weeks in total	The experimental diet reduced hippocampal atrophy and decreased the peripheral immune activation in the olfactory bulbectomized rats The ameliorating effects of the diet on the olfactory bulbectomized-induced changes were comparable to those of the NMDA receptor antagonist, memantine, a drug used for the management of Alzheimer's disease	Rats	Borre et al.[28]

Table 2. The antioxidant effects of melatonin and curcumin in various in vitro and in vivo studies at IRI

Antioxidant potentials	Type of tissue/ Disease	Dose	Outcome	In vivo/ In vitro	Study
Kidney	Nephrotoxicity	Curcumin (200 mg/kg) or melatonin (10 mg /kg) given singly by oral gavage for eight consecutive days prior to CP injection and four days thereafter	Curcumin and melatonin were given together, the ameliorative effect was augmented in some of the measured indices e.g. tumor necrosis factor alpha, cystatin C, uric acid, phosphorus in plasma and, urine creatinine and creatinine clearance Renal platinum concertation was reduced more with curcumin than that with melatonin, while the reduction was maximized when both melatonin and curcumin were given.	Rats	Ali et al.[30]
	Acute Kidney Injury	Oral CMN at 200 mg/kg/day dissolved in freshly prepared corn oil over a total of 5 days, 5 mg/ kg/day melatonin dissolved with saline solution IP for 5 days	Curcumin and melatonin reduced the increases in serum urea and serum creatinine levels following cisplatin administration ($p < 0.05$) Curcumin and melatonin reduced the levels of TNS, HPS, NF-κB/p65, 8-OHdG, and caspase-3 expressions ($p < 0.05$)	Rats	Mercantepe et al.[31]
Testis	Testicular Tissue Preservation	Melatonin (10 mg/kg, s.c.); Curcumin (30 mg/kg, i.p.)	Melatonin treatment for aged rats significantly decreased paired total testicular/body weight ratio compared to aged control group ($p < 0.05$) Curcumin treatment for aged rats significantly increased GSH level compared to the aged control group ($p < 0.05$)	Rats	Muratoğlu et al.[33]
Bone	Rapid Maxillary Expansion (RME)	Melatonin 75 mg/d/kg and Curcumin 150 mg/d/kg by intraperitoneal injection during the whole study period	Serum bone alkaline phosphatase levels in the melatonin group were statistically (P=.007) higher than in the expansion group Serum glutathione peroxidase and catalase activities in the curcumin and melatonin groups were significantly higher than in the expansion group (P=.007 and P=.021, respectively) Inflammatory cell infiltration, new bone formation and capillary intensity parameters did not demonstrate statistically significant differences between the groups (P=.865, P=.067 and P=.055, respectively) The immunohistochemical findings revealed that IL-1, IL-6 and TNF-α H scores showed considerable differences between the groups (all P < .001) The highest IL-1, IL-6 and TNF-α H scores were found in the expansion groups rather than in the other groups (P < .001)	Rats	Cesur et al.[34]
Liver	Age-related Liver Injury	Melatonin (10 mg/kg body weight) and curcumin (90 mg/ kg body weight) in dimethyl sulfoxide intraperitoneally.	Protein carbonyls of liver have been found to be significantly higher in 18-month-old mice as compared to 1-month-old mice The carbonyl content in 1- and 18-month-old mice decreases significantly upon administrations of melatonin and curcumin	Mice	Dkhar et al.[35]
Stomach	Gastric Mucosal Damage	Melatonin (60 mg/kg bw) curcumin (60 mg/kg bw) intraperitoneally (ip) 30 min before indomethacin treatment	Melatonin and curcumin offered gastroprotection in vivo by upregulation of suppressed MMP-2 expression and activity at the level of secretion and synthesis Antioxidants reversed the suppression of MMP-2 expression by upregulation of MT1-MMP and downregulation of TIMP-2	Rats	Ganguly et al.[37]

Table 3. The anticancer effects of melatonin-curcumin in various in vitro and in vivo studies at IRI

Anticancer potentials	Type of tissue/ Disease	Dose	Outcome	In vivo/ In vitro	Study
Nervous system	PC12 cells	25 μM curcumin for 16 h / 100 μM melatonin for 16 h.	Curcumin and melatonin treatments maintained the mitochondrial redox and respiratory functions without a marked effect on ROS production and cell viability	PC12 cell line	Raza et al.[38]
Bladder	Bladder Cancer	Appropriate dosage	Combinational treatment enhanced the repression of nuclear translocation of NF-κB and their binding on COX-2 promoter via inhibiting IKKβ activity, resulting in inhibition of COX-2 expression Combined treatment with curcumin and melatonin induced cell apoptosis in bladder cancer through enhancing the release of cytochrome c from the mitochondrial intermembrane space into the cytosol	Human bladder cancer cell lines T24, UMUC3 and 5637	Shrestha et al.[39]
	Bladder Cancer	10 mg/kg melatonin and 30 mg/ kg curcumin by intraperitoneal injection each day	Combinational treatment enhanced the repression of nuclear translocation of NF-κB and their binding on COX-2 promoter via inhibiting IKKβ activity, resulting in inhibition of COX-2 expression. Combined treatment with curcumin and melatonin induced cell apoptosis in bladder cancer through enhancing the release of cytochrome c from the mitochondrial intermembrane space into the cytosol	Mice	Shrestha et al.[39]
Prostate	Prostate Cancer	Curcumin (1.6–25 μM), melatonin (0.062–1 mM)	These compounds affect differently one of the main intracellular redox regulator, the thioredoxin system. Exposure to curcumin promoted TRX1 oxidation and altered its subcellular location. Conversly, melatonin only worked as cytostatic agents, reducing ROS levels and showing preventive effects against TRX oxidation.	Human androgen-dependent epithelial prostate cancer cells (LNCaP)	Rodriguez-Garcia et al.[40]

HIGHLIGHT KEY POINTS

Melatonin has been used as a second active substance in many studies because melatonin strengthens the antioxidant, anti-inflammatory, and anti-carcinogenic effects of the other active substance.

The treatment of curcumin for various chronic inflammatory diseases or cancer is promising.

The ability of melatonin to potentiate the effect of a second antioxidant has also been shown in various studies when used together with curcumin (**Tables 1**, **2**, and **3**).

Melatonin and curcumin are more effective when used together, creating a synergistic effect, compared to their separate use.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer reviewed.

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