Review Article

Therapeutic Opportunities in Colorectal Cancer: Focus on Melatonin Antioncogenic Action

Hucong Wu,1,2 Jiaqi Liu,1,2 Yi Yin,1,2 Dong Zhang,1 Pengpeng Xia,1,2 and Guoqiang Zhu1,2

1College of Veterinary Medicine, Yangzhou University, Yangzhou 225009, China
2Jiangsu Co-Innovation Center for Prevention and Control of Important Animal Infectious Diseases and Zoonoses, Yangzhou 225009, China

Correspondence should be addressed to Guoqiang Zhu; yzgqzhu@yzu.edu.cn

Received 21 July 2019; Accepted 31 August 2019; Published 17 September 2019

Guest Editor: Guoku Hu

Copyright © 2019 Hucong Wu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Colorectal cancer (CRC) influences individual health worldwide with high morbidity and mortality. Melatonin, which shows multiple physiological functions (e.g., circadian rhythm, immune modulation, and antioncogenic action), can be present in almost all organisms and found in various tissues including gastrointestinal tract. Notably, melatonin disruption is closely associated with the elevation of CRC incidence, indicating that melatonin is effective in suppressing CRC development and progression. Mechanistically, melatonin favors in activating apoptosis and colon cancer immunity, while reducing proliferation, autophagy, metastasis, and angiogenesis, thereby exerting its antitumor function. This review highlights that melatonin can be an adjuvant therapy and be beneficial in treating patients suffering from CRC.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and a major cause of cancer-related mortality around the world [1–3]. Multiple factors are associated with the occurrence and the development of CRC, including genetic makeup, population aging/gender, dietary behaviors, poor physical activity, and smoking [4–6]. According to the clinical situations of the patients with CRC, the status of CRC treatments (e.g., surgical therapy, radiotherapy, chemotherapy, targeted therapy, and immunotherapy) develops rapidly [7]. Even though different and novel therapies are available, in almost >25% of patients with metastatic cancer systemic therapy remains the treatment option [8]. For example, treating CRC by conducting chemotherapy causes cytotoxicity and agents resistance (e.g., 5-FU, capecitabine, cetuximab, and panitumumab) which calls for the development of more effective and novel alternative agents and/or adjuvants [9, 10]. Fortunately, melatonin is under consideration for its low toxicity and high efficacy.

Melatonin (a natural substance derived from tryptophan, and for its synthesis, refer to [11, 12]), which was initially isolated from the bovine pineal gland, shows a wide distribution from bacteria to humans [13–15]. Interestingly, melatonin also has turned out to be found in other tissues, such as lymphocytes, Harderian gland, liver, and gastrointestinal tract [16–19]. Melatonin is highly pleiotropic and regulates numerous physiological functions including circadian rhythms [20], antioxidative protection [21, 22], immune modulation [12, 23], and, with particular relevance to this article, antioncogenic and oncostatic actions [24, 25].

Given melatonin could be produced in the gastrointestinal tract, in which the total level of melatonin is ~400 times than those in the pineal gland [26], and the protective effects of melatonin in the gastrointestinal tract (e.g., enhancing immune functions of the gut, reducing peristalsis [17], and altering intestinal microbiota community [27, 28]), and the antitumor function of melatonin, it is not surprising that melatonin could inhibit the gastrointestinal cancers including colon [29, 30]. Actually, the circadian rhythm change of blood melatonin is disordered in patients with CRC and melatonin disruption elevates the CRC incidence in humans [31, 32]. Previous studies confirmed that melatonin blocks colon carcinogenesis [33, 34]. Moreover, CGP
52608 (functions as a ligand for melatonin nuclear RZR/ROR receptor) could promote colon cancer cell apoptosis [35], and CGP 55644 (a RZR/ROR receptor antagonist) lowers the efficacy of melatonin in blocking colon tumor proliferation [36]. Altogether, these aforementioned results suggest that melatonin may inhibit CRC development and progression in humans.

Here, firstly, we summarize the cross-link between melatonin disorder and CRC occurrence; thereafter, we discuss several potential mechanisms (e.g., suppression of cancer cell proliferation, autophagy, metastasis and angiogenesis, and activation of apoptosis and cancer immunity) by which melatonin limits CRC development and progression.

2. Melatonin Disruption and CRC Incidence

The fluctuation of melatonin level in day and night is associated with the circadian rhythms and highly affects individual development and health [37]. Indeed, melatonin disruption is closely correlated with CRC. Epidemiologic surveys showed that the CRC incidence increased significantly in humans who have ever performed rotating shift work and/or worked at night [38–40]. Besides, Kvetcnaia [41] found that the level of melatonin was increased in male patients with CRC; however, the amplitude of rhythm and secretion of melatonin in patients with CRC was significantly lowered [42, 43]. Likewise, constant illumination could cause crypt foci aberrance and promote the rodent colon cell proliferation [29]. Experimental study also reported that the melatonin concentration of serum in female rats with colon cancer was elevated compared with controls [44].

Collectively, these findings indicate that melatonin disruption is related to the elevation of CRC incidence and melatonin could be of high potential to modulate CRC development and progression.

3. Melatonin in CRC Cell Proliferation, Apoptosis, and Autophagy

Excessive proliferation of malignant tumors always favors in tumor progression; thus, it is meaningful to develop agents with high efficacy to inhibit CRC cell proliferation to limit CRC development and progression. The colon 38 is a transplanteable adenocarcinoma originally induced in the colon of C57BL/6 mice by 1,2-dimethylhydrazine. Indeed, melatonin can inhibit murine colon 38 cancer cell proliferation [36] and reduce the multiplicity of colon tumors induced by 1,2-dimethylhydrazine (DMH) in rats [45]. Mechanistically, melatonin mainly inhibits cancer cell proliferation via (1) decreasing DNA synthesis and (2) promoting cell differentiation. It has been shown that the utilization of melatonin was significantly correlated with reduced DNA synthesis in colon cancer cells [46, 47]. Moreover, melatonin could increase the number of highly differentiated cells to inhibit DMH-induced colon carcinoma cell proliferation [48].

The imbalance between the apoptosis and proliferation leads to malignancy development; therefore, it is another strategy to inhibit CRC development and progression by promoting cancer cell apoptosis. Actually, melatonin could induce Caco-2 cells [49] and human CRC cell apoptosis [34, 50]. 2-Hydroxymelatonin (a main melatonin metabolite in plants) could also increase CRC cell apoptosis [51]. Mechanistically, melatonin activates apoptosis through altering cell cycle program by increasing G1-phase arrest [34]. Intriguingly, it was shown that melatonin significantly contributed to 5-FU (a chemotherapeutic agent) inhibition of cell proliferation by activating apoptosis and cell cycle arrest [52]. Besides, endothelin-1 (ET-1), a peptide that serves as a survival factor in colon cancer, can promote proliferation while inhibiting apoptosis in carcinoma cells; melatonin was found to induce apoptosis by reducing ET-1 expression, thereby limiting the development and progression of colon cancer [53].

The overproliferating cancer cells compete for nutrients during the process of carcinogenesis, indicating that cancer cells may alter their metabolic states to survive. Indeed, autophagy could allow cancer cells to survive under stress (e.g., nutrients deprivation) [54]. Interestingly, melatonin can promote or inhibit autophagy (probably due to the antioxidant activity of melatonin) under specific conditions [55–58]. A series of autophagy-related proteins, such as microtubule-associated protein 1 light chain 3B (LC3B), p62, and Beclin-1, have been employed as markers of autophagy. [59] Previous study showed that melatonin treatment decreased the progression of colitis-associated colon carcinogenesis (CACC) by downregulating the process of autophagy as revealed by the expression pattern of various autophagy markers such as Beclin-1, LC3B-II/LC3B-I ratio, and p62. Melatonin intervention ameliorated inflammation and oxidative stress to inhibit autophagy, thereby blocking the progression of colitis-associated colon carcinogenesis [60].

Summarily, the inhibition of proliferation/autophagy and the activation of apoptosis could contribute to the antioncogenic effects of melatonin in inhibition of CRC.

4. Melatonin in CRC Metastasis, Angiogenesis, and Immunity

The cancer metastasis leads to the majority of cancer deaths because the advanced tumors are prone to invasion, migration, and metastasis, complicating the surgery and reducing its effectiveness [61, 62]. Melatoninˈs efficacy on migration in colonic cells has been well established. Accumulating evidence suggests that melatonin can inhibit cancer metastasis [63, 64]. It was shown that melatonin also significantly contributed to 5-FU inhibition of colon cancer cell migration [52]. Liu et al. [65] reported that melatonin decreased RKO colon cancer cell migration involving the p38/MAPK (mitogen-activated protein kinase) signaling pathway. Likewise, Zou et al. [66] also found that melatonin reduced human CRC cell proliferation and migration via the inactivation of p38 MAPK signaling. Moreover, melatonin has been suggested to decrease the depth of colon cancer invasion in vivo [48].

Angiogenesis serves an important role not only in physiological processes, but also in pathological conditions,
including cancer [67, 68], and it favors in promoting aggressive tumor activity (e.g., tumor growth, metastasis, and invasion) [69]. Actually, the antioncogenic effects of melatonin in the suppression of CRC angiogenesis have also been investigated. Melatonin could destabilize hypoxia-inducible factor (HIF)-1α and/or suppress HIF-1α transcriptional activity in colon cancer cell [70], resulting in a reduction in the expression of vascular endothelial growth factor (VEGF), which functions as the most important angiogenesis growth factor that promotes cancer progression [71, 72]. Additionally, ET-1, a survival factor in colon cancer, is associated with the activation of angiogenesis [73]. Melatonin could also block the release of ET-1 from CRC cells, leading to inhibit angiogenesis, thereby limiting the CRC development and progression [53].

The cross-link between cancer and immune system plays a crucial role in the modulation of cancer development and progression [74, 75]. Melatonin has immune system activation property (e.g., altering macrophage and/or T-cell polarization and function) [12, 23]. Notably, circadian disturbances induce selective proinflammatory responses in the rat colonic mucosa, suggesting that melatonin may modulate cancer immunity to inhibit CRC development [76]. Indeed, melatonin is effective in restraining neoplastic growth in various tumors and cancers, including CRC, by enhancing TH cell immune response by producing interleukin (IL)-2, IL-10, and interferon-gamma (IFN-γ) [77]. Previous study demonstrated that melatonin exposure could decrease mitotic and apoptotic indices in the colonic adenocarcinomas and lower the expression of inflammatory mediators like nuclear factor-κB (NF-κB), tumor necrosis factor (TNF)-α, IL-1β, and STAT3 in the epithelial malignancies [33]. Besides, melatonin was confirmed to enhance splenic zone expansion and augment CD8⁺ lymphocytes and Fas-positive cell proliferation in DMH-induced colon carcinogenesis of rats [78].

Collectively, the published results document that melatonin blocks metastasis and angiogenesis and augments cancer immunity, thereby inhibiting CRC development and progression.

5. Concluding Remarks

CRC is a prevalent cancer all over the world. Melatonin disruption has been reported in patients suffering from CRC, which heralds that melatonin could be a promising agent to block CRC development and progression. Mechanistically, melatonin mainly inhibits CRC cell proliferation and autophagy, metastasis, and angiogenesis, while promoting apoptosis and enhancing cancer immunity (Figure 1). Given the mechanisms of melatonin are carried out by various other means (e.g., epigenetic modulation), and cancer development always accompany with epigenetical alteration, it is of great interest to investigate whether melatonin could inhibit CRC progression through epigenetic modification. Additionally, intestinal microbiota are closely associated with the CRC onset [79–81]; it is also interesting to study that melatonin affects CRC development that involves in shifting intestinal microbiota structure in the future.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Hucong Wu, Jiaqi Liu, and Yi Yin contributed equally to this work.

Acknowledgments

This work was partially supported by Grant nos. 2017YFD0500203, 2017YFD 0500105, and 2016YDF0500905 from the National Key Research and Development Program of China, grants from the Chinese National Science Foundation Grant (Nos. 31672579, 30571374, 30771603, 31092136, 31270171), and a project funded by the Priority
Academic Program of Development Jiangsu High Education Institution and it grants from the Yangzhou Science and Technology Bureau International Cooperation Project (YZ2018154).

References

[1] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, “Global cancer statistics, 2012,” CA: A Cancer Journal for Clinicians, vol. 65, no. 2, pp. 87–108, 2015.

[2] L. Roncucci and F. Mariani, “Prevention of colorectal cancer: how many tools do we have in our basket?,” European Journal of Internal Medicine, vol. 26, no. 10, pp. 752–756, 2015.

[3] V. Stigliano, L. Sanchez-Mete, A. Martayan, and M. Anti, “Early-onset colorectal cancer: a sporadic or inherited disease?,” World Journal of Gastroenterology, vol. 20, no. 35, pp. 12420–12430, 2014.

[4] J. Zhu, Z. Tan, K. Hollis-Hansen, Y. Zhang, C. Yu, and Y. Li, “Epidemiological trends in colorectal cancer in China: an ecological study,” Digestive Diseases and Sciences, vol. 62, no. 1, pp. 235–243, 2017.

[5] C. M. Johnson, C. Wei, J. E. Ensor et al., “Meta-analyses of colorectal cancer risk factors,” Cancer Causes & Control, vol. 24, no. 6, pp. 1207–1222, 2013.

[6] E. J. Kuipers, W. M. Grady, D. Lieberman et al., “Colorectal cancer,” Nature Reviews Disease Primers, vol. 1, no. 1, p. 25, 2015.

[7] Y. Zhang, Z. Chen, and J. Li, “The current status of treatment for colorectal cancer in China,” Medicine, vol. 96, no. 40, article e8242, 2017.

[8] A. Mehta and B. M. Patel, “Therapeutic opportunities in colon cancer: focus on phosphodiesterase inhibitors,” Life Sciences, vol. 230, pp. 150–161, 2019.

[9] D. Cunningham, Y. Humblet, S. Siena et al., “Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer,” New England Journal of Medicine, vol. 351, no. 4, pp. 337–345, 2004.

[10] E. Van Cutsem, M. Peeters, S. Siena et al., “Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer,” Journal of Clinical Oncology, vol. 25, no. 13, pp. 1658–1664, 2007.

[11] D.-X. Tan, R. Hardeland, K. Back, L. C. Manchester, M. A. Alatorre-Jimenez, and R. J. Reiter, “On the significance of an alternate pathway of melatonin synthesis via 5-methoxytryptamine: comparisons across species,” Journal of Pineal Research, vol. 61, no. 1, pp. 27–40, 2016.

[12] W. Ren, G. Liu, S. Chen et al., “Melatonin signaling in T cells: functions and applications,” Journal of Pineal Research, vol. 62, no. 3, article e12394, 2017.

[13] R. Dubbels, R. J. Reiter, E. Klenke et al., “Melatonin in edible plants identified by radioimmunoassay and by high performance liquid chromatography-mass spectrometry,” Journal of Pineal Research, vol. 18, no. 1, pp. 28–31, 1995.

[14] M. A. Tosches, D. Bucher, P. Vopalensky, and D. Arendt, “Melatonin signaling controls circadian swimming behavior in marine zooplankton,” Cell, vol. 159, no. 1, pp. 46–57, 2014.

[15] D.-X. Tan, X. Zheng, J. Kong et al., “Fundamental issues related to the origin of melatonin and melatonin isomers during evolution: relation to their biological functions,” International Journal of Molecular Sciences, vol. 15, no. 9, pp. 15858–15890, 2014.

[16] D. Acuña-Castroviejo, G. Escames, C. Venegas et al., “Extrapineal melatonin: sources, regulation, and potential functions,” Cellular and Molecular Life Sciences, vol. 71, no. 16, pp. 2997–3025, 2014.

[17] G. A. Bubenik, “Gastrointestinal melatonin: localization, function, and clinical relevance,” Digestive Diseases and Sciences, vol. 47, no. 10, pp. 2336–2348, 2002.

[18] A. Conti, S. Conconi, E. Hertens, K. Skwarlo-Sonta, M. Markowska, and G. J. M. Maestroni, “Evidence for melatonin synthesis in mouse and human bone marrow cells,” Journal of Pineal Research, vol. 28, no. 4, pp. 193–202, 2000.

[19] N. T. Raikhlin, I. M. Kvetnoy, and V. N. Tolkachev, “Melatonin may be synthesised in enterochromaffin cells,” Nature, vol. 255, no. 5506, pp. 344-345, 1975.

[20] R. J. Reiter, “Melatonin: the chemical expression of darkness,” Molecular and Cellular Endocrinology, vol. 79, no. 1–3, pp. C153–C158, 1991.

[21] B. Poeggeler, R. J. Reiter, D.-X. Tan, L.-D. Chen, and L. C. Manchester, “Melatonin, hydroxyl radical-mediated oxidative damage, and aging: a hypothesis,” Journal of Pineal Research, vol. 14, no. 4, pp. 151–168, 1993.

[22] R. Hardeland, “Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance,” Endocrine, vol. 27, no. 2, pp. 119–130, 2005.

[23] Y. Xia, S. Chen, S. Zeng et al., “Melatonin in macrophage biology: current understanding and future perspectives,” Journal of Pineal Research, vol. 66, no. 2, article e12547, 2019.

[24] S. M. Hill, T. Frasch, S. Xiang, L. Yuan, T. Duplessis, and L. Mao, “Molecular mechanisms of melatonin anticancer effects,” Integrative Cancer Therapies, vol. 8, no. 4, pp. 337–346, 2009.

[25] G. Favero, E. Moretti, F. Bonomini, R. J. Reiter, L. F. Rodella, and R. Rezzani, “Promising antineoplastic actions of melatonin,” Frontiers in Pharmacology, vol. 9, p. 1086, 2018.

[26] G. A. Bubenik, “Thirty four years since the discovery of gastrointestinal melatonin,” Journal of Physiology and Pharmacology, vol. 59, pp. 33–51, 2008.

[27] W. Ren, P. Wang, J. Yan et al., “Melatonin alleviates weanling stress in mice: involvement of intestinal microbiota,” Journal of Pineal Research, vol. 64, no. 2, article e12448, 2018.

[28] J. Yin, Y. Li, H. Han et al., “Melatonin reprogramming of gut microbiota improves lipid dysmetabolism in high-fat diet-fed mice,” Journal of Pineal Research, vol. 65, no. 4, article e12524, 2018.

[29] V. Kannen, T. Marini, D. L. Zanette et al., “The melatonin action on stromal stem cells within pericryptal area in colon cancer model under constant light,” Biochemical and Biophysical Research Communications, vol. 405, no. 4, pp. 593–598, 2011.

[30] J. Wang, W. Guo, W. Chen et al., “Melatonin potentiates the antiproliferative and pro-apoptotic effects of ursolic acid in colon cancer cells by modulating multiple signaling pathways,” Journal of Pineal Research, vol. 54, no. 4, pp. 406–416, 2013.

[31] V. N. Anisimov, I. A. Vinogradova, A. V. Panchenko, I. G. Popovich, and M. A. Zabezhinski, “Light-at-night-induced circadian disruption, cancer and aging,” Current Aging Science, vol. 5, pp. 170–177, 2012.

[32] V. N. Anisimov, “Light pollution, reproductive function and cancer risk,” Neuroendocrinology Letters, vol. 27, pp. 35–52, 2006.

[33] T. Tanaka, Y. Yasui, M. Tanaka, T. Tanaka, T. Oyama, and K. W. Rahman, “Melatonin suppresses AOM/DSS-induced large bowel oncogenesis in rats,” Chemico-Biological Interactions, vol. 177, no. 2, pp. 128–136, 2009.
[34] Y. Hong, J. Won, Y. Lee et al., “Melatonin treatment induces interplay of apoptosis, autophagy, and senescence in human colorectal cancer cells,” *Journal of Pineal Research*, vol. 56, no. 3, pp. 264–274, 2014.

[35] K. Winczyk, M. Pawlikowski, and M. Karasek, “Melatonin and RZR/ROR receptor ligand CDP 52608 induce apoptosis in the murine colorectal cancer,” *Journal of Pineal Research*, vol. 31, no. 2, pp. 179–182, 2001.

[36] K. Winczyk, M. Pawlikowski, J. M. Guerrero, and M. I. Karasek, “Possible involvement of the nuclear RZR/ROR-alpha receptor in the antitumor action of melatonin on murine colon 38 cancer,” *Tumor Biology*, vol. 23, no. 5, pp. 298–302, 2002.

[37] O. Pechanova, L. Paulis, and F. Simko, “Peripheral and central effects of melatonin on blood pressure regulation,” *International Journal of Molecular Sciences*, vol. 15, no. 10, pp. 17920–17937, 2014.

[38] C.-L. Lin, T.-C. Liu, Y.-N. Wang, C.-H. Chung, and W.-C. Chien, “The association between sleep disorders and the risk of colorectal cancer in patients: a population-based nested case-control study,” *In Vivo*, vol. 33, no. 2, pp. 573–579, 2017.

[39] K. Papantoniou, E. E. Devore, J. Massa et al., “Rotating night shift work and colorectal cancer risk in the nurses’ health studies,” *International Journal of Cancer*, vol. 143, no. 11, pp. 2709–2717, 2017.

[40] M.-E. Parent, M. El-Zein, M.-C. Rousseau, J. Pintos, and J. Siemiatycki, “Night work and the risk of cancer among men,” *American Journal of Epidemiology*, vol. 176, no. 9, pp. 751–759, 2012.

[41] T. V. Kvetnaia, “Melatonin for diagnosis of cancer and assessment of prognosis in elderly patients,” *Advances in Gerontology=Uspekhii Gerontologii*, vol. 12, pp. 132–142, 2003.

[42] R. Khoory and D. Stemme, “Plasma melatonin levels in patients suffering from colorectal carcinoma,” *Journal of Pineal Research*, vol. 5, no. 3, pp. 241–258, 1988.

[43] B. Kos-Kudla, Z. Ostrowska, A. Kozlowski et al., “Circadian rhythm of melatonin in patients with colorectal carcinoma,” *Neuroendocrinology Letters*, vol. 23, pp. 239–242, 2002.

[44] V. N. Anisman, I. M. Kvetnoy, N. K. Chumakova et al., “Melatonin and colon carcinogenesis,” *Experimental and Toxicologic Pathology*, vol. 51, no. 1, pp. 47–52, 1999.

[45] V. N. Anisman, I. G. Popovich, A. V. Shyltik et al., “Melatonin and colon carcinogenesis,” *Experimental and Toxicologic Pathology*, vol. 52, no. 1, pp. 71–76, 2000.

[46] P. T. Ryabikh, T. G. Nikolayeva, and N. B. Bodrova, “Effects of the biorhythm regulator melatonin on DNA synthesis in short-term human malignant tumors,” *Vestnik Rossiskoi Akademii Meditsinskikh Nauk*, vol. 8, no. 30–33, 2000.

[47] M. Farriol, Y. Venereo, X. Orta, J. M. Castellanos, and T. Segovia-Silvestre, “In vitro effects of melatonin on cell proliferation in a colon adenocarcinoma line,” *Journal of Applied Toxicology*, vol. 20, no. 1, pp. 21–24, 2000.

[48] V. Anisman, I. G. Popovich, and M. A. Zabezhinski, “Melatonin and colon carcinogenesis: I. Inhibitory effect of melatonin on development of intestinal tumors induced by 1,2-dimethylhydrazine in rats,” *Carcinogenesis*, vol. 18, no. 8, pp. 1549–1553, 1997.

[49] A. P. C. Batista, T. G. da Silva, A. A. C. Teixeira et al., “Ultrastructural aspects of melatonin cytotoxicity on Caco-2 cells in vitro,” *Micron*, vol. 59, pp. 17–23, 2014.

[50] C. W. Yun, S. Kim, J. H. Lee, and S. H. Lee, “Melatonin promotes apoptosis of colorectal cancer cells via superoxide-mediated ER stress by inhibiting cellular prion protein expression,” *Anticancer Research*, vol. 38, no. 7, pp. 3951–3960, 2018.

[51] Y. Yang, R. Zhou, S.-Y. Park et al., “2-Hydroxymelatonin, a predominant hydroxylated melatonin metabolite in plants, shows antitumor activity against human colorectal cancer cells,” *Molecules*, vol. 22, no. 3, p. 453, 2017.

[52] Y. Gao, X. Xiao, C. Zhang et al., “Melatonin synergizes the chemotherapeutic effect of 5-fluorouracil in colon cancer by suppressing PI3K/AKT and NF-kB/NOS signaling pathways,” *Journal of Pineal Research*, vol. 62, no. 2, article e12380, 2017.

[53] J. León, J. Casado, S. M. Jiménez Ruiz et al., “Melatonin reduces endothelin-1 expression and secretion in colon cancer cells through the inactivation of FoxO1 and NF-kB,” *Journal of Pineal Research*, vol. 56, no. 4, pp. 415–426, 2014.

[54] K. Sato, K. Tsuchihara, S. Fuji et al., “Autophagy is activated in colorectal cancer cells and contributes to the tolerance to nutrient deprivation,” *Cancer Research*, vol. 67, no. 20, pp. 9677–9684, 2007.

[55] Y. Guo, J. Wang, Z. Wang, Y. Yang, X. Wang, and Q. Duan, “Melatonin protects N2a against ischemia/reperfusion injury through autophagy enhancement,” *Journal of Huazhong University of Science and Technology [Medical Sciences]*, vol. 30, no. 1, pp. 1–7, 2010.

[56] A. Coto-Montes and C. Tomas-Zapico, “Could melatonin unbalance the equilibrium between autophagy and invasive processes?” *Autophagy*, vol. 2, no. 2, pp. 126–128, 2006.

[57] P. Kongsuphol, S. Mukda, C. Nopparat, A. Villarroel, and P. Goviratpong, “Melatonin attenuates methamphetamine-induced deactivation of the mammalian target of rapamycin signaling to induce autophagy in SK-N-SH cells,” *Journal of Pineal Research*, vol. 46, no. 2, pp. 199–206, 2009.

[58] C. Nopparat, J. E. Porter, M. Ebadi, and P. Goviratpong, “The mechanism for the neuroprotective effect of melatonin against methamphetamine-induced autophagy,” *Journal of Pineal Research*, vol. 49, no. 4, pp. 382–389, 2010.

[59] J. Gao and W. Wang, “Knockdown of galectin-1 facilitated cisplatin sensitivity by inhibiting autophagy in neuroblasticoma cells,” *Chemico-Biological Interactions*, vol. 297, pp. 50–56, 2019.

[60] P. P. Trivedi, G. B. Jena, K. B. Tikoo, and V. Kumar, “Melatonin modulated autophagy and Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis,” *Molecular Carcinogenesis*, vol. 55, no. 3, pp. 255–267, 2016.

[61] R. K. Thakur, V. K. Yadav, A. Kumar et al., “Non-metastatic 2 (NME2)-mediated suppression of lung cancer metastasis involves transcriptional regulation of key cell adhesion factor vinculin,” *Nucleic Acids Research*, vol. 42, no. 18, pp. 11589–11600, 2014.

[62] Q. Yuan, Z. Zhang, L. Feng, and Y. Jiang, “Upregulated long noncoding RNA LINCO1296 indicates a dismal prognosis for pancreatic ductal adenocarcinoma and promotes cell metastatic properties by affecting EMT,” *Journal of Cellular Biochemistry*, vol. 120, no. 1, pp. 552–561, 2019.

[63] N. D. N. Gonçalves, J. Colombo, J. R. Lopes et al., “Effect of melatonin in epithelial mesenchymal transition markers and invasive properties of breast cancer stem cells of canine and human cell lines,” *PloS one*, vol. 11, no. 3, Article ID e0150407, 2016.

[64] S. Zhang, Y. Qi, H. Zhang et al., “Melatonin inhibits cell growth and migration, but promotes apoptosis in gastric cancer cell line, SGC7901,” *Biotechnic & Histochemistry*, vol. 88, no. 6, pp. 281–289, 2013.
[65] Z. Liu, D. Zou, X. Yang et al., “Melatonin inhibits colon cancer RKO cell migration by downregulating rho-associated protein kinase expression via the p38/MAPK signaling pathway,” *Molecular Medicine Reports*, vol. 16, no. 6, pp. 9383–9392, 2017.

[66] D.-B. Zou, X. Wei, R.-L. Hu et al., “Melatonin inhibits the migration of colon cancer RKO cells by down-regulating myosin light chain kinase expression through cross-talk with p38 MAPK,” *Asian Pacific Journal of Cancer Prevention*, vol. 16, no. 14, pp. 5835–5842, 2015.

[67] M. Ushio-Fukai and R. W. Alexander, “Reactive oxygen species as mediators of angiogenesis signaling. Role of NAD(P)H oxidase,” *Molecular and Cellular Biochemistry*, vol. 264, no. 1/2, pp. 85–97, 2004.

[68] R. N. Gacche and R. J. Meshram, “Targeting tumor micro-environment for design and development of novel anti-angiogenic agents arresting tumor growth,” *Progress in Biophysics and Molecular Biology*, vol. 113, no. 2, pp. 333–354, 2013.

[69] J.-H. Park, J. Yoon, and B. Park, “Pomolic acid suppresses HIF1α/VEGF-mediated angiogenesis by targeting p38-MAPK and mTOR signaling cascades,” *Phytomedicine*, vol. 23, no. 14, pp. 1716–1726, 2016.

[70] S.-Y. Park, W.-J. Jang, E.-Y. Yi et al., “Melatonin suppresses tumor angiogenesis by inhibiting HIF-1α stabilization under hypoxia,” *Journal of Pineal Research*, vol. 48, no. 2, pp. 178–184, 2010.

[71] M. V. Gelfand, N. Hagan, and A. Tata, “Neuropilin-1 functions as a VEGFR2 co-receptor to guide developmental angiogenesis independent of ligand binding,” *eLife*, vol. 3, p. 40, 2014.

[72] A. Abusnina, T. Keravis, Q. Zhou, H. Justiniano, A. Lobstein, and C. Lugnier, “Tumour growth inhibition and anti-angiogenic effects using curcumin correspond to combined PDE2 and PDE4 inhibition,” *Thrombosis and Haemostasis*, vol. 113, no. 2, pp. 319–328, 2015.

[73] I. A. Abdel-Gawad, H. M. Hassanein, N. A. Bahgat et al., “Study of endothelin-1 and vascular endothelial growth factor in patients with cancer colon,” *Journal of the Egyptian National Cancer Institute*, vol. 20, pp. 216–223, 2008.

[74] A. Toso, A. Revandkar, D. Di Mitri et al., “Enhancing chemotherapy efficacy in pten -deficient prostate tumors by activating the senescence-associated antitumor immunity,” *Cell Reports*, vol. 9, no. 1, pp. 75–89, 2014.

[75] B. Dong, L. J. Minze, W. Xue, and W. Chen, “Molecular insights into the development of T cell-based immunotherapy for prostate cancer,” *Expert Review of Clinical Immunology*, vol. 10, no. 11, pp. 1547–1557, 2014.

[76] L. Polidarová, P. Houdek, and A. Sumová, “Chronic disruptions of circadian sleep regulation induce specific proinflammatory responses in the rat colon,” *Chronobiology International*, vol. 34, no. 9, pp. 1273–1287, 2017.

[77] V. Srinivasan, S. R. Pandi-Perumal, A. Brzezinski, K. P. Bhatnagar, and D. P. Cardinali, “Melatonin, immune function and cancer,” *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, vol. 5, pp. 109–123, 2011.

[78] G. Kossoy, H. Ben-Hur, I. Popovich, M. Zabezhinski, V. Anisimov, and I. Zusman, “Melatonin and colon carcinogenesis. IV. Effect of melatonin on proliferative activity and expression of apoptosis-related proteins in the spleen of rats exposed to 1,2-dimethylhydrazine,” *Oncology Reports*, vol. 7, pp. 1401–1405, 2000.

[79] H. Tilg, T. E. Adolph, R. R. Gerner, and A. R. Moschen, “The intestinal microbiota in colorectal cancer,” *Cancer Cell*, vol. 33, no. 6, pp. 954–964, 2019.