Melatonin's role as a co-adjuvant treatment in colonic diseases: A review

Eduardo Esteban-Zubero, Laura López-Pingarrón, Moisés Alejandro Alatorre-Jiménez, Purificación Ochoa-Moneo, Celia Buisac-Ramón, Miguel Rivas-Jiménez, Silvia Castán-Ruiz, Ángel Antoñanzas-Lombarte, Dun-Xian Tan, José Joaquín García, Russel J. Reiter

PII: S0024-3205(16)30684-1
DOI: doi: 10.1016/j.lfs.2016.11.031
Reference: LFS 15097

To appear in: *Life Sciences*

Received date: 9 October 2016
Revised date: 17 November 2016
Accepted date: 30 November 2016

Please cite this article as: Eduardo Esteban-Zubero, Laura López-Pingarrón, Moisés Alejandro Alatorre-Jiménez, Purificación Ochoa-Moneo, Celia Buisac-Ramón, Miguel Rivas-Jiménez, Silvia Castán-Ruiz, Ángel Antoñanzas-Lombarte, Dun-Xian Tan, José Joaquín García, Russel J. Reiter , Melatonin's role as a co-adjuvant treatment in colonic diseases: A review. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Lfs(2016), doi: 10.1016/j.lfs.2016.11.031

Melatonin's role as a co-adjuvant treatment in colonic diseases: a review

Eduardo Esteban-Zubero[a*], Laura López-Pingarrón[b], Moisés Alejandro Alatorre-Jiménez[c], Purificación Ochoa-Moneo[b], Celia Buisac-Ramón[d], Miguel Rivas-Jiménez[b], Silvia Castán-Ruiz[d], Ángel Antoñanzas-Lombarte[b], Dun-Xian Tan[c], José Joaquín García[a], Russel J. Reiter[c*].

[a] Department of Pharmacology and Physiology, University of Zaragoza. Calle *Domingo Miral* s/n, 50009. Zaragoza, Spain.

[b] Department of Medicine, Psychiatry and Dermatology, University of Zaragoza. Calle *Domingo Miral* s/n, 50009. Zaragoza, Spain.

[c] Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio. 7703 Floyd Curl Drive, San Antonio, TX 78229, USA.

[d] Primary Care Unit, Sector Zaragoza III, Avenida San Juan Bosco 5, 50009. Zaragoza, Spain.

Running title: Melatonin and gastrointestinal diseases

* Authors to whom correspondence should be addressed; E-Mails: eezubero@gmail.com (E.E.Z.), reiter@uthscsa.edu (R.J.R.).

No conflict of interest shown in the realization of this writing and any comments are received. All authors agree with the work done and have collaborated actively in its development.

Word count: 4293

Table and figure count: 1 table, 2 figures

Abbreviations:

Melatonin receptors (MT2), serotonin (5-HT), and cholecystokinin B (CCK2), irritable bowel syndrome (IBS), constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), enterochromaffin cells (EC), gastrointestinal (GIT), nitric oxide synthase (NOS) nuclear factor kappaB (NF-κB), inducible NOS (iNOS), interleukins (IL), tumor necrosis factor alpha (TNF-α), reactive nitrogen species (RNS), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GRd), catalase (CAT), glutathione (GSH), corticotropin releasing factor (CRF), 6-Hydroxymelatonin sulphate (6-OHMs), Crohn‟s disease (CD), ulcerative colitis (UC), colitis-associated colon carcinogenesis (CACC), Nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), quinone oxidoreductase (NQO-1), Kelch-like ECH-associated protein 1 (Keap1), hydroxyindole-O-methyltransferase (HIOMT), homocysteine (HCY), lipid peroxidation (LPO), myeloperoxidase activity (MPO), Melatonin (MEL), malondialdehyde (MDA), prostaglandin E2 (PGE_2), matrix metallopeptidase (MMP), pentraxin-3 (PTX-3).

Author contributions:

E.E.Z.: Wrote the article, analysed data, review. L.L.P.: Review, M.A.A.J.: Review. P.O.M.: Review. C.B.R.: Review. M.R.J.: Review. S.C.R.: Review. A.A.L.: Review. D.X.T.: Review. J.J.G: Review. R.J.R.: Review, English support.

Abstract: Melatonin is produced in the pineal gland as well as many other organs, including the enterochromaffin cells of the digestive mucosa. Melatonin is a powerful antioxidant that resists oxidative stress due to its capacity to directly scavenge reactive species, to modulate the antioxidant defense system by increasing the activities of antioxidant enzymes, and to stimulate the innate immune response through its direct and indirect actions. In addition, the dysregulation of the circadian system is observed to be related with alterations in colonic motility and cell disruptions due to the modifications of clock genes expression. In the gastrointestinal tract, the activities of melatonin are mediated by melatonin receptors (MT2), serotonin (5-HT), and cholecystokinin B (CCK2) receptors and via receptor-independent processes. The levels of melatonin in the gastrointestinal tract exceed by 10-100 times the blood concentrations. Also, there is an estimated 400 times more melatonin in the gut than in the pineal gland. Gut melatonin secretion is suggested to be influenced by the food intake. Low dose melatonin treatment accelerates intestinal transit time whereas high doses may decrease gut motility. Melatonin has been studied as a co-adjuvant treatment in several gastrointestinal diseases including irritable bowel syndrome (IBS), constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), Crohn‟s disease, ulcerative colitis, and necrotizing enterocolitis. The purpose of this review is to provide information regarding the potential benefits of melatonin as a co-adjuvant treatment in gastrointestinal diseases, especially IBS, Crohn‟s disease, ulcerative colitis, and necrotizing enterocolitis.

Keywords: Gastrointestinal diseases; Crohn‟s disease; melatonin; ulcerative colitis; irritable bowel syndrome; necrotizing enterocolitis.

1. Introduction:

Gastrointestinal melatonin is produced by enterochromaffin cells (EC) of the digestive mucosa where its concentrations may exceed those in the blood [1]. One of melatonin‟s characteristics is its high lipophilicity allowing it to diffuse into deeper layers through the mucosa and submucosa, to act on the muscularis mucosae or the myenteric plexus. The amount of gastrointestinal (GIT) melatonin is estimated to be at least 400 times greater than in the pineal gland [2]. Its secretion from the EC cells may be influenced by food intake [3], its actions in the GIT are mediated by membrane receptors including (MT2), serotonin (5-HT) receptors, and its capacity of activate sympathetic neurons through the brain-gut connection system, and its antioxidant actions [4-8]. Melatonin produces smooth muscle relaxation by stimulating 5-HT4 receptors, whereas it may also cause smooth muscle contraction by acting on 5-HT3 receptors. 5-HT also modulates visceral sensation [6, 9]. Moreover, it was observed recently that melatonin may inhibit the activity of the serotonin transporter, which controls the reuptake of 5-HT by intestinal epithelial cells, and inhibits NK2 receptor-triggered 5-HT release by acting at a MT3 melatonin receptor located in the cells of the mucosal layer [10]. Low dose melatonin is also observed to accelerate intestinal transit time while high doses may decrease GIT motility by interacting with cholecystokinin B receptor (CCK2) and 5-HT3 receptors, present on the vagal afferent fibers inducing, via this means, vago-vagal inhibitory reflexes [3, 4]. Those findings are supported by melatonin‟s modulatory role on gastric emptying due to its capacity to alleviate the inhibitory effect of the lipid related ileal break [11].

Other roles related to motility regulation by melatonin have been suggested. The indoleamine reduces the nitrergic component of the smooth muscle inhibitory junction potential through a direct inhibition of nitric oxide synthase (NOS) activity at enteric synapses. Melatonin may also block nicotinic channels, or interact with Ca^{2+}-activated K^{+} channels generating an inhibitory effect through an apamin-sensitive reaction [12, 13]. Melatonin also modulates acetylcholine-induced contractions of intestinal strips by an extracellular calcium dependent pathway [14]. In addition, melatonin may reverse lipopolysaccharide-induced motility

disturbances, which involves a reduction in lipid peroxidation and an increase of mitogen-activated protein kinase activation, nuclear factor kappaB (NF-κB) activation, inducible NOS (iNOS) expression, and finally nitrite production [15]. Finally, melatonin regulates myoelectric activity by relaxing the bowel during phasic contractions [16].

Antinociceptive effects of melatonin have been reported, but the mechanisms are not well defined. A recent study suggested that these actions of melatonin were probably not directly at the level of the GIT since luzindole (a non-specific MT1 and MT2 receptor antagonist), or naltrexone (a non-specific opioid receptor antagonist), blocked the antinociceptive actions; this suggested viscero-motor response and modulation of lumbosacral spinal neuronal activity [17].

Gastrointestinal melatonin may also modulate the immune response by inhibiting macrophage activity through the reduction of NF-κB levels, COX-2 and iNOS activity; also, it modulates secretion elicited by prostaglandin E2 and regulates gene expression of proinflammatory cytokine levels including interleukins (IL-1), tumor necrosis factor alpha (TNF-α) and IFN-γ [18, 21]. In addition, gastrointestinal melatonin has antioxidant effects [22, 23], reduces prostaglandin degradation by prostaglandin reductase and limits gastric lesions and hydrochloric acid secretion [22-24]; it also antagonizes 5-HT actions, which are related to gastric ulcer formation [3].

Melatonin and its metabolites function as free radical scavengers and neutralize superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH) [25-29], a highly reactive oxygen species (ROS)[30], as well as nitric oxide (NO·) and the peroxynitrite anion ($ONOO^{\cdot-}$) [31, 32], which are reactive nitrogen species (RNS) [33]. In addition, the indoleamine stimulates the cellular antioxidant defense system increasing mRNA levels and the activities of several important antioxidant enzymes including superoxide dismutase (SOD, which catalyzes the conversion of $O_2^{\cdot-}$ to H_2O_2) and glutathione peroxidase (GPx) and glutathione reductase (GRd) [34-36]. Catalase (CAT) is also stimulated by melatonin and causes direct breakdown of

H_2O_2 to O_2 and H_2O [37, 38]. Moreover, the indoleamine inhibits iNOS, an enzyme involved in NO· generation [39]. Melatonin also promotes the synthesis of another important antioxidant, glutathione (GSH) [40] and it synergizes with other classic antioxidants to reduce oxidative damage [41]. Finally, melatonin chelates transition metals thereby reducing the formation of the highly toxic ·OH which significantly limits the number of essential molecules that are oxidatively mutilated [42, 43].

Herein, we summarize the protective actions of melatonin against several gastrointestinal diseases, including irritable bowel syndrome, Crohn‟s disease, ulcerative colitis, and necrotizing enterocolitis. To the authors‟ knowledge, this is the first review related to these subjects.

2. Irritable bowel syndrome:

Irritable bowel syndrome (IBS) is a common disorder (prevalence reported between 10-20%) characterized by recurrent abdominal pain or discomfort, in combination with disturbed bowel habits in the absence of identifiable organic cause [44]. IBS is 3-fold more prevalent in women than in men, and in the postmenopausal period this number increases to 6-fold. This may be a consequence of drop in melatonin secretion preceded by the rise in follicle-stimulating hormone (FSH) concentration in postmenopausal women [45, 46]. Its pathophysiology has been associated with abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction, mucosal inflammation, and intestinal microbiota imbalance [47, 48]. Moreover, corticotropin releasing factor (CRF) is released during stress, and stimulates colonic motor activity via either central [49, 50] or peripheral CRF receptors [51] resulting in colon hyperkinesis. Depending of the IBS predominant symptoms, there are two clinical types: constipation predominant IBS (IBS-C) and diarrhea-predominant IBS (IBS-D). IBS-D is associated with reduced 5-HT reuptake, while IBS-C is related with lack of 5-HT release [9].

Sleep disorders are also present in 26–55% of IBS patients [52] and are related to rapid eye movement (REM) sleep modifications [53]. In addition, the severity of IBS symptoms is observed to vary with the quality of the previous night"s sleep [54]. It is suggested that sleep disorders are a result of an increase in the activity of the kynurenine pathway (a tryptophan metabolite) (Figure 1) with a reduction in the serotonin/melatonin pathway [55-57]. This theory was considered since some studies reported reduced ratios of kynurenine/tryptophan in IBS patients [58]. One human study observed increased cortisol levels with a reduced melatonin/tryptophan ratio in IBS [58]. The mechanisms responsible for the sleep disorders in IBS patients remain unexplained.

6-Hydroxymelatonin sulphate (6-OHMs) is a hepatic metabolite of melatonin that is excreted in the urine. Urinary levels of 6-OHMs over a 24-hour period correlate well with plasma melatonin levels [59]. Human studies reported increased levels of 6-OHMs in premenopausal and postmenopausal women afflicted with IBS-C or IBS-D [60]. The authors did not observed significant statistical differences between IBS-C symptoms in premenopausal and postmenopausal females and the excretion of 6-OHMs, but a slight increase in levels of metabolite excretion was observed in patients with moderate symptoms. 6-OHMs, concentrations were found to be higher in postmenopausal women affected with IBS-D than in premenopausal females with a large increase in women with exacerbated symptoms. These results support the theory that melatonin levels in IBS women are lowered after menopause [61, 62]. Salivary melatonin levels, which are also well correlated with melatonin plasma concentrations [63], are reduced in IBS patients. The salivary melatonin concentrations increase if melatonin is orally administered [63].

Physicians usually treat IBS with antispasmodics, psychopharmacological treatments, psychotherapy, and newer drugs such as linaclotide, prucalopride, tegaserod, and lubiprostone, but disparate results are observed [64]. Antagonists of the serotonin 5-HT3 receptor are usually used in patients affected with IBS-D, whereas the partial agonist of serotonin 5-HT4 receptor alleviates symptoms of IBS-C [65, 66]. It is suggested that melatonin treatment may play an

important role in the regulation of intestinal motility by inhibiting nicotinic channels in the neurons of the submucosal plexus to regulate the cholinergic transmission and relax muscle contraction through an interaction with small conductance K^+-channels [12, 67], or by inhibiting the activity of 5-HT and CRF, which are increased in IBS patients [68].

Water avoidance stress generates motility disorders and increases fecal output [69]. In one study it was also observed that melatonin (10 mg/kg i.p.) attenuated the fecal output and reduced the dry weight of the stool. Furthermore, 5-HT serum levels were depressed in melatonin-treated animals suggesting that the modulatory effect may be mediated through the 5-HT pathway. Melatonin also was observed to lower the amplitude of spontaneous contractions of colonic smooth muscle strips as well as ACH-induced and KCl-mediated contractions. This was presumed to be due to an interaction between melatonin and Ca^{2+}-activated calmodulin preventing the latter from activating myosin light-chain kinase and inducing a reduced muscle contraction [70]. K^+-induced contractions are attributed to a Ca^{2+} effect [71]. Melatonin may have reduced the influx of calcium.

Oral melatonin (3 mg) treatment has been also observed to significantly increase colonic transit time of healthy subjects [72]. A similar effect was observed in IBS patients, as in previous studies [63, 68], suggesting a predominant beneficial effect of melatonin in IBS-C patients.

In reference to abdominal pain, it was observed that 3 mg of melatonin given orally for 2 weeks significantly reduced the discomfort with a tendency towards a greater reduction of abdominal distension, stool frequency, and total bowel symptoms. The authors also observed that rectal distension pressure and volume thresholds, which induce the sensations of urgency and pain, were significantly decreased [73]. Similar beneficial effects were obtained in a study in which melatonin improved the quality of life due to the modulation of colonic symptoms including pain severity and frequency, bloating, bowel habit dissatisfaction, and life interference. Extracolonic IBS symptoms such as headache, lethargy, nausea, early satiety, or

urinary disturbances were also improved [74]. Chojnacki et al. [62], in a recent study in postmenopausal women, observed that melatonin therapy significantly reduced pain and abdominal bloating in IBS-C patients. The authors did not find similar results in IBS-D patients or modifications in colonic transit time in either IBS-C or IBS-D subjects. In their study, researchers gave melatonin twice daily (in the morning and in the evening). Thus, they deduced that melatonin administration in a divided dose may be more effective because of melatonin‟s short half-life (30−60 min.) [75]. IBS patients usually have symptoms during the day and rarely at night.

3. Crohn's disease

Inflammatory bowel diseases (IBD) include Crohn‟s disease (CD) and ulcerative colitis (UC), both chronic inflammatory disorders of the gastrointestinal tract which are characterized by a relapsing and remitting course [76]. In the United States, CD incidence is estimated to be 6-8 per 100,000, with a prevalence of 100-200 per 100,000 [77]. IBD is a result of a miscommunication between the gut microbiota and the intestinal mucosal immune system, resulting in the failure of mucosal homeostasis. The integrity of the epithelial barrier, determined by genetic defects, and the presence of triggering environmental factors are also required to generate chronic inflammation [78]. A genetic polymorphism is not sufficient alone to generate the inflammatory phenotype of IBD [79]. Smoking is observed to be protective for UC and harmful for CD [80]. Moreover, drugs, stress, and dietary habits are also related with IBD pathogenesis [81]. Two recent studies show that melatonin in the gut microbiome may relate to melatonin‟s beneficial actions in patients with IBD [82, 83].

Like UC, there exists a relationship between sleep quality and colon disease activity. A poor sleep quality and fatigue are common in clinically active disease compared with inactive disease patients [84, 85]. This effect is more pronounced in those patients with CD compared with UC patients. In addition, it was observed that CD patients with impaired sleep have a two-

fold greater risk of active disease in 6 months, whereas no such relationship has been described in UC patients [86]. Furthermore, symptoms activity is increased in the mornings following a poor night of sleep, and this effect is also more usual in CD patients [87]. However, the relationship between sleep disorders and CD and UC diseases are poorly understood [88]. Figure 2 summarizes these relations.

Melatonin treatment for CD is rare. We found a single article related to the effects of melatonin (3 mg) in a CD patient [89]. The authors observed disease activation after melatonin treatment in a single previously inactive patient. 24 hours after stopping melatonin treatment, the symptoms abated. The authors suggested that melatonin may have activated a number of cytokines (i.e., IL-2 and IL-12) which could have exacerbated the symptoms. This presumption is based on the findings that Th1 and Th17 pathways appear to predominate in the inflamed mucosa of CD patients, whereas Th2 and Th17 factors are abundant in UC [90]. Moreover, it is known that Th1 increases the IFN-γ production in CD [91], and CD patients exhibit elevated lamina propria IL-12 production as compared to controls [92]. Melatonin promotes a Th1-response by increasing IL-12 and IFN-γ levels [93, 94]. The observations of Calvo and co-workers [89] require additional studies in a larger population of CD patients.

JAK kinase family is associated with intracellular signaling, which is initiated by the action of various cytokines. When JAK kinase activity is blocked, this cascade is suspended [95]. Usual treatments such as tofacitinib inhibit JAK1 and JAK3 [96]. A recent study suggested that Neu-P11 (piromelatine, N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-4-oxo-4H-pyran-2 carboxamide), a novel melatonin (MT1/MT2) and 5-HT1A/1D receptor agonist [97] protected the cells via activation of the JAK2 survival pathway [98]. A recent meta-analysis determined that a JAK2 rs10758669 polymorphism was significantly associated with CD and UC susceptibility [99]. Moreover, it is known that the activation of JAK2 in IL-R receptor results in the phosphorylation of STAT3 in activated macrophages and dendritic cells [100]. In IBD, JAK2/STAT3 pathway interferes with Th1, Th2, and Th17 cells [101, 102].

SMAD7 and SMAD2 also act as inhibitors of TGF-β1 and were found to be upregulated in CD [103, 104]. New CD treatments such as mongersen inhibits SMAD7 expression thereby restoring TGF-β1 levels; this leads to the suppression of inflammatory cytokine production [104]. Melatonin also inhibits SMAD6 and SMAD7 expression, but facilitates SMAD2 activation [105]. In addition, miR-200b prevents this effect by targeting SMAD2, but its levels are inversely correlated with the TGF-β1 levels in IBD [103]. Recent studies showed that failure of the integrity of the intestinal epithelial barrier may be an early event in the natural history of IBD; this allows for the uncontrolled influx of bacterial products into the lamina propria and the propagation of proinflammatory mucosal responses [106].

TGF-β and IL-6 are also important inducers of Th17 cells producing IL-17 and IL-22. IL-23 interacts with differentiated Th17 cells and causes "stabilization" and/or expansion of Th17 cells [107-109]. In vitro, the addition of melatonin suppresses the polarization of human T helper cells into the Th17 lineage [110]. However, IL-23p19 deficient mice exhibit increased numbers of regulatory T cells (Foxp3+ T cells) [111, 112] and, because of this, CD may develop because of the observed important role of Th1 pathway which causes an 40-fold greater IFN-γ production compare to that induced by IL-17 production [113, 114].

4. Ulcerative colitis:

The incidence of UC is estimated to be 9-12 per 100,000, with a prevalence of 205-240 per 100,000 [77]. Moreover, approximately 20 percent of people with UC have a close relative with IBD [115]. Like CD, the integrity of the epithelial barrier, genetic polymorphisms, and the presence of triggering environmental factors are required to generate the chronic inflammation [78]. Moreover, the incidence of colon cancer is increased in patients with UC, and the risk of colitis-associated colon carcinogenesis (CACC) augments with increased extent and duration of UC [116]. As stated above, Th2 and Th17 pathways are predominant in UC [90]. In addition, IBD-specific changes in the gut microbiota play an important role in UC disease and, because of

that, antibiotics or probiotics may be not effective in some cases [117]. However, probiotics like VSL#3 have high efficacy in preventing the development or recurrence of pouchitis in patients with UC who have undergone ileal-pouch-anal anastomosis [118]. The epithelial barrier also plays an important role in UC and treatment with phosphatidylcholine may restore barrier function and ameliorate intestinal inflammation [119]. Molecules such as tofacitinib, which inhibits JAK1 and JAK3, and several cytokines [78], are effective anti-inflammatory treatments in UC due to inhibition of the differentiation of effector lymphocytes of the Th2 and Th17 types [120]. Elevated IL-4, IL-13, and TGF-β levels are associated with the Th2 pathway [90, 121]. Vedolizumab is a humanized monoclonal antibody with anti-efficacy inflammatory effects on the gut without affecting trafficking of other sites [122]. Etrolizumab also has demonstrated beneficial effects against UC disease [123].

The number of myenteric neurons is reduced in patients affected with UC disease [124]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a protective factor for different cells and tissues against inflammation and oxidative stress [125]. Nrf2 deficiency is observed to increase oxidative stress and inflammatory processes through an increased production of COX-2, iNOS, IL-1β, IL-6, and TNF-α. Furthermore, in these situations, decreased expression of antioxidant/phase II detoxifying enzymes such as heme oxygenase-1 (HO-1), quinone oxidoreductase (NQO-1), UDP-glucuronosyltransferase 1A1, and GST Mu-1 is observed [126]. It is known that, under oxidative stress conditions, Nrf2 is released from its repressor Kelch-like ECH-associated protein 1 (Keap1) and transforms into its activated form; this results in an activation of antioxidants or detoxifying enzymes [127]. Several studies reported that melatonin regulates Nrf2 expression [128-130]. In rats, Nrf2 expression is reduced in UC [131]. In this study, melatonin upregulated Nrf2 expression thereby ameliorating the histopathological disturbances, including the preservation of myenteric neurons, which play an important role in the regulation of motility and sensitivity of the intestine.

EC proliferation, hydroxyindole-O-methyltransferase (HIOMT) expression (an enzyme involved in melatonin synthesis), and increased urine excretion of 6-OHMs is apparent in the

acute phases of ulcerative proctitis and UC. Consequently, the augmentation of melatonin secretion may have a beneficial effect in anti-inflammatory and defense mechanisms [132]. Melatonin levels are typically lower in active patients than in patients in remission [133].

Sleep deprivation plays an important role in UC by downregulating gene expression. These disturbances are reduced after using melatonin (10 mg/kg i.p.) [134]. In addition, microvascular thrombosis and oxygen free radical-induced injury are known to be important in UC pathogenesis [135, 136]. UC is a Th2 and Th17-like disease associated with increased IL-13 production [137]. IL-17 levels are also elevated in UC due to Th17 activity, but its levels are lower in CD [114]. IL-13, IL-4, and TGF-β levels are also increased in an oxazolone-colitis model; however, IFN-γ levels remain normal [138, 139]. IL-13 is the most important cytokine involved in UC disease. As a result, treatments such as IFN-β are effective in this illness through a reduction in IL-13 levels [121]. Unlike in CD, melatonin may be effective in the treatment of UC via its capacity of attenuate IL-13 levels [140]. In addition, elevated homocysteine (HCY) concentrations stimulate vascular smooth muscle cell proliferation, increase collagen formation and deposition, lead to vascular stenosis and accelerate thrombosis [141, 142]. UC patients have increased plasma and intestinal mucosal levels of HCY [143-145] with reduced levels of melatonin [132]. HCY inhibits GPx levels, decreases NO· bioavailability, and generates H_2O_2 [146]. However, a relationship between melatonin and HCY levels was not observed [132].

Melatonin has been studied as a UC adjuvant treatment. Melatonin benefits against UC syndrome are summarized in table 1. The findings indicate melatonin may reverse the macro- and microscopic lesions. This relates to melatonin‟s capacity to limit lipid peroxidation (LPO), myeloperoxidase activity (MPO), reduce inflammatory cytokine levels, and stimulate antioxidant enzymes; these are all oxidative stress markers and are modified during UC [54, 164]. Moreover, STAT-3, an important mediator in IBD, is elevated during UC since this disease is associated with elevated levels of IL-6, which induces STAT3 [165, 166]. NF-κB is important for the inflammatory process; low levels of peroxides induce its activation whereas

some antioxidants reduce its translocation [167, 168]. NF-κB upregulates the expression of TNF-α, IL-1β, iNOS, and COX-2 [169]. Elevated pentraxin-3 (PTX-3) levels, an acute phase protein related to C-reactive protein, is present during inflammatory conditions [170], and a reduction of PTX-3 gene activity results in an inflammatory process in the vascular wall with augmented macrophage accumulation [171]. Moreover, PTX-3 is involved in immune defense in inflamed colon tissue, in particular, in crypt abscess lesions of patients with UC [172]. As summarized in table 1, melatonin reportedly attenuates inflammatory processes thereby alleviating colitis.

Melatonin treatment also significantly enhances expression of Nrf2 and NQO-1, while decreasing matrix metalloproteinase-9 [158]. All these are markers of oxidative stress [173-175]. MMPs mediate cellular infiltration, cytokine activation, cell migration, tissue damage, remodeling and repair [176]. TNF-α stimulates MMP-9 expression while melatonin reduces the levels of this cytokine [147].

From the findings summarized in table 1, one report indicates a detrimental effect of melatonin (1-2 mg/kg) in the evolution of the lesions, levels of TNF-α and MPO activity as well as the hydroxyproline production, an indicator of fibrosis [144]. This latter parameter may be of special interest because fibrosis is a major complication of IBD [177]. These differential effects may be a consequence of diurnal variations of melatonin binding sites during the day [178], with a maximal affinity of the receptors detected in the evening [179]. It is also known that the capacity of melatonin to stimulate gene expression of antioxidant enzymes controls biorhythms [180]. This is consistent with observations in a gastric model of damage that involved ischemia–reperfusion, where melatonin clearly diminished the number and severity of the ulcers in animals treated late in the afternoon while no protection was detected when treatments were applied in the morning [181]. Perhaps the articles with the greatest importance in table 1 are the human studies, which yielded good results when melatonin was used in addition to mesalazine; this suggests a new therapeutic option for this disease.

Melatonin benefits against colitis-associated colon carcinogenesis (CACC) have been uncovered. In a mouse model, melatonin (1 mg/kg) reduced inflammatory markers (MPO, IL-17, IL-6, TNF-α, NF-Kβ, STAT-3, and COX-2), oxidative stress markers (TBARS), autophagy markers (including Beclin-1, LC3B-II/LC3B-I ratio and p62), and DNA damage. Conversely, Nrf2, HO-1, and NQO-1 expression were elevated by melatonin. The benefits of melatonin were also reflected at the histopathological level with a decrease of tumor frequency and dysfunction of calcium-activated calcium channels. The findings indicate that reduced inflammation and oxidative stress due to melatonin intervention in mice inhibits autophagy and prevents CACC malfunctions [182].

5. Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is the most common neonatal gastrointestinal emergency requiring surgical intervention [183, 184]. The prevalence of the disorder is about 7% among infants with a birth weight between 500 and 1500 g, and the estimated rate of death is between 20 and 30% [185].The pathogenesis of NEC is likely multifactorial, including immature gut function, impaired intestinal barrier, disturbed gastrointestinal motility, and circulatory factors [186]. Platelet-activating factor, intestinal toll-like receptors, TNF-α, interleukins (IL-1β, IL-6, IL-8, IL-10, IL-12), lipopolysaccharide, nitric oxide (NO), and oxygen-derived free radicals may also play pivotal roles in NEC pathogenesis [187-191]. In a preterm infant study [192], the authors measured non-protein bound iron (a marker of potential oxidative stress risk), and markers of free radical damage (advanced oxidation protein products and total hydroperoxides) in the cord blood and observed these were significantly higher in babies with NEC than in healthy infants. Moreover, they reported that toll-like receptor-4 is a crucial component of NEC vulnerability [193].

Human neonates, especially those born prematurely, have an incompletely developed system to detoxify free radicals [194]. Thus, treatments that modulate antioxidative defense and

anti-inflammatory protection including hyperbaric oxygen [195], medical ozone [196], N-acetylcysteine [197], and glutamine alone or in conjunction with arginine [198] have been studied. Melatonin, a molecule that clearly upregulates these systems, ameliorated oxidative stress by reducing MDA levels, an index of lipid peroxidation [199], protein carbonyl content, TNF-α, and IL-1β levels, and stimulated SOD and GPx activities in a rat model of NEC [200]. Melatonin treatment combined with PGE1 [201], a cytoprotective agent in the gastrointestinal system mucosa, had a preventive effect against bacterial invasion and reduced inflammation and tissue injury [2020, 203]. Each provided preventive effects individually but melatonin was more effective in reducing MDA levels and elevating SOD and GPx activities. These results were also reflected at histopathological level. The best results were observed using melatonin and PG concurrently.

6. Conclusions:

IBD and IBS patients exhibit poor sleep quality and reduced levels of melatonin. Moreover, gender and aging are important risk factors for individuals suffering with IBS, with women exhibiting this disease more frequently than men. In IBS-C, melatonin improves life quality and decreases pain. In IBS-D patients the benefits of melatonin are much less apparent possibly because 5-HT receptors play a different role in this pathology. IBD has more similarities to UC, since Th2 and Th17 are involved in both and melatonin has beneficial effects by modulating these pathways. Recent studies also suggest that melatonin may be effective in preventing the progression of colitis-associated colon carcinogenesis due to its capacity to attenuate the induction of autophagy. In contrast, Th1 and Th17 are the major pathways involved in CD, and melatonin increases Th1 activity which induces more injury in the affected tissues. More studies are necessary to identify the potential beneficial effects of melatonin in these illnesses. The potential of melatonin as a treatment for these conditions should be pursued because the usual treatments are not often effective and may have negative secondary effects.

Melatonin may be effective when given in combination with the routinely-used drugs, if for no other reason than, to reduce the side effects of those medications.

7. Acknowledgements:

This work was supported by grants from the „Gobierno de Aragón" (Aging and Oxidative Stress Physiology, Grant No. B40) and from the „Instituto de Salud Carlos III" (RD12/0043/0035). Special acknowledgment also is given to the Department of Cellular and Structural Biology of University of Texas Health Science Center at San Antonio for hosting E.E.Z. during the preparation of this review.

8. References:

[1] C.Q. Chen, J. Fichna, M. Bashashati, Y.Y. Li, M. Storr, Distribution, function and physiological role of melatonin in the lower gut, World J. Gastroenterol. 17 (2011) 3888-3898.

[2] M. Soták, L. Mrnka, J. Pácha J, Heterogeneous expression of melatonin receptor MT1 mRNA in the rat intestine under control and fasting conditions, J. Pineal Res. 41 (2006) 183-188.

[3] G.A. Bubenik, Gastrointestinal melatonin: localization, function, and clinical relevance, Dig. Dis. Sci. 47 (2002) 2336-2348.

[4] F. Drago, S. Macauda, S. Salehi, Small doses of melatonin increase intestinal motility in rats, Dig. Dis. Sci. 47 (2002) 1969-1974.

[5] O. Kasimay, B. Cakir, E. Devseren, B.C. Yegen, Exogenous melatonin delays gastric emptying rate in rats: role of CCK2 and 5-HT3 receptors, J. Physiol. Pharmacol. 56 (2005) 543-553.

[6] M. Manocha, W.I. Khan WI, Serotonin and GI Disorders: An Update on Clinical and Experimental Studies. Clin. Transl. Gastroenterol. 26,3:e13 (2012). doi: 10.1038/ctg.2012.8.

[7] P.C. Konturek, T. Brzozowski, S.J. Konturek, Gut clock: implications for circadian rhythms in the gastrointestinal tract, J. Physiol. Pharmacol. 62 (2011) 139-150.

[8] R.J. Reiter, D.X. Tan, J.C. Mayo, J. Leon, D. Bandyopadhyay Neurally-mediated and neurally-independent beneficial actions of melatonin in the gastrointestinal tract, J. Physiol. Pharmacol. 54 (Suppl 4) (2003) 113-125.

[9] S. Mozaffari, S. Nikfar, M. Abdollahi, Metabolic and toxicological considerations for the latest drugs used to treat irritable bowel syndrome, Expert Opin. Drug Metab. Toxicol. 9 (2013) 403-421.

[10] N. Matheus, C. Mendoza, R. Iceta, J.E. Mesonero, A.I. Alcalde, Melatonin inhibits serotonin transporter activity in intestinal epithelial cells, J. Pineal Res. 48 (2010) 332-339.

[11] T.M. Martín, F. Azpiroz, J.R. Malagelada, Melatonin as a modulator of the ileal brake mechanism, Scand. J. Gastroenterol. 40 (2005) 559-563.

[12] C. Barajas-Lopez, A.L. Peres, R. Espinosa-Luna, C. Reyes-Vázquez, B. Prieto-Gómez, Melatonin modulates cholinergic transmission by blocking nicotinic channels in the guinea-pig submucous plexus, Eur. J. Pharmacol. 312 (1996) 319-325.

[13] M. Storr, P. Koppitz, A. Sibaev, D. Saur, M. Kurjak, H. Franck, V. Schusdziarra, H.D. Allescher, Melatonin reduces non-adrenergic, non-cholinergic relaxant neurotransmission by inhibition of nitric oxide synthase activity in the gastrointestinal tract of rodents in vitro. J. Pineal Res. 33 (2002) 101-108.

[14] E. Velarde, A.L. Alonso-Gómez, C. Azpeleta, E. Isorna, M.J. Delgado, Melatonin attenuates the acetylcholine-induced contraction in isolated intestine of a teleost fish, J. Comp. Physiol. B. 179 (2009) 951-959.

[15] D. De Filippis, T. Iuvone, G. Esposito, L. Steardo, G.H. Arnold, A.P. Paul, G. De Man Joris, Y. De Winter Benedicte, Melatonin reverses lipopolysaccharide-induced gastro-intestinal motility disturbances through the inhibition of oxidative stress, J. Pineal Res. 44 (2008) 45-51.

[16] A. Merle, P. Delagrange, P. Renard, D. Lesieur, J.C. Cuber, M. Roche, S. Pellissier, Effect of melatonin on motility pattern of small intestine in rats and its inhibition by melatonin receptor antagonist S 22153, J. Pineal Res. 29 (2000) 116-124.

[17] A. Mickle, M. Sood, Z. Zhang, G. Shahmohammadi, J.N. Sengupta, A. Miranda, Antinociceptive effects of melatonin in a rat model of post-inflammatory visceral hyperalgesia: a centrally mediated process, Pain 149 (2010) 555-564.

[18] A. Carrillo-Vico, R.J. Reiter, P.J. Lardone, J.L. Herrera, R. Fernández-Montesinos, J.M. Guerrero, D. Pozo, The modulatory role of melatonin on immune responsiveness, Curr. Opin. Investig. Drugs 7 (2006) 423-431.

[19] Q. Mei, J.P. Yu, J.M. Xu, W. Wei, L. Xiang, L. Yue, Melatonin reduces colon immunological injury in rats by regulating activity of macrophages, Acta Pharmacol. Sin. 23 (2002) 882-886.

[20] L. Mrnka, M. Hock, M. Rybová, J. Pácha, Melatonin inhibits prostaglandin E2- and sodium nitroprusside-induced ion secretion in rat distal colon, Eur. J. Pharmacol. 581 (2008) 164-170.

[21] Mozaffari S, Rahimi R & Abdollahi M (2010) Implications of melatonin therapy in irritable bowel syndrome: a systematic review. Curr Pharm Des 16, 3646-3655.

[22] D. Bandyopadhyay, K. Biswas, U. Bandyopadhyay, R.J. Reiter, R.K. Banerjee Melatonin protects against stress-induced gastric lesions by scavenging the hydroxyl radical, J. Pineal Res. 29 (2000) 143-151.

[23] G. Klupińska, T. Poplawski, J. Drzewoski, A. Harasiuk, R.J. Reiter, J. Blasiak, J. Chojnacki, Therapeutic effect of melatonin in patients with functional dyspepsia, J. Clin. Gastroenterol. 41 (2007) 270-274.

[24] T. Brzozowski, P.C. Konturek, K. Zwirska-Korczala, S.J. Konturek, I. Brzozowska, D. Drozdowicz, Z. Sliwowski, M. Pawlik, W.W. Pawlik, E.G. Hahn, Importance of the pineal gland, endogenous prostaglandins and sensory nerves in the gastroprotective actions of central and peripheral melatonin against stress-induced damage, J. Pineal Res. 39 (2005) 375-385.

[25] R.J. Reiter, D.X. Tan, M.J. Jou, A. Korkmaz, L.C. Manchester. S.D. Paredes, Biogenic amines in the reduction of oxidative stress: melatonin and its metabolites, Neuro. Endocrinol. Lett. 29 (2008) 391-398.

[26] S. Burkhardt, R.J. Reiter, D.X. Tan, R. Hardeland, J. Cabrera, M. Karbownik, DNA oxidatively damaged by chromium (III) and H_2O_2 is protected by the antioxidants melatonin, N1-acetyl-N2-formyl-5-methyoxykynuramine, resveratrol and uric acid, Int. J. Biochem. Cell Biol. 33 (2001) 775-783.

[27] R.J. Reiter, D.X. Tan, M.D. Maldonado, Melatonin as an antioxidant: physiology versus pharmacology, J. Pineal Res. 39 (2005) 215-216.

[28] L.C. Manchester, A. Coto-Montes, J.A. Boga, L.P. Andersen, Z. Zhou, A. Galano, J. Vriend, D.X. Tan, R.J. Reiter, Melatonin: an ancient molecule that makes oxygen metabolically tolerable, J. Pineal Res. 59 (2015) 403-419.

[29] R.J. Reiter, J.C. Mayo, D.X. Tan, R.M. Sainz, M. Alatorre-Jimenez, L. Qin, Melatonin as an antioxidant: under promises but over delivers, J. Pineal Res. 61 (2016) 253-278.

[30] T. Finkel, N.J. Holbrook, Oxidants, oxidative stress and the biology of ageing. Nature 408 (2000) 239–247.

[31] A. Galano, D.X. Tan, R.J. Reiter, Melatonin as a natural ally against oxidative stress: a physicochemical examination, J. Pineal Res. 51 (2011) 1-16.

[32] R.J. Reiter, D.X. Tan, A. Galano, Melatonin: exceeding expectations, Physiology (Bethesda) 29 (2014) 325-333.

[33] R.P. Patel, J. McAndrew, H. Sellak, C.R. White, H. Jo, B.A. Freeman, V.M. Darley-Usmar, Biological aspects of reactive nitrogen species, Biochim. Biophys. Acta 1411, (1999) 385-400.

[34] L.R. Barlow-Walden, R.J. Reiter, M. Abe, M. Pablos, A. Menendez-Pelaez, L.D. Chen, B. Poeggeler, Melatonin stimulates brain glutathione peroxidase activity, Neurochem. Int. 26 (1995) 497-502.

[35] Y. Okatani, A. Wakatsuki, K. Shinohara, C. Kaneda, T. Fukaya, Melatonin stimulates glutathione peroxidase activity in human chorion, J. Pineal Res. 30 (2001) 199-205.

[36] M.I. Pablos, R.J. Reiter, G.G. Ortiz, J.M. Guerrero, M.T. Agapito, J.I. Chuang, E. Sewerynek, Rhythms of glutathione peroxidase and glutathione reductase in brain of chick and their inhibition by light, Neurochem. Int. 32 (1998) 69-75.

[37] R.J. Reiter, D.X. Tan, C. Osuna, E. Gitto, Actions of melatonin in the reduction of oxidative stress: a review, J. Biomed. Sci. 7 (2000) 444–458.

[38] C. Rodriguez, J.C. Mayo, R.M. Sainz, I. Antolín, F. Herrera, V. Martín, R.J. Reiter, Regulation of antioxidant enzymes: a significant role for melatonin, J. Pineal Res. 36 (2004) 1-9.

[39] D. Pozo, R.J. Reiter, J.R. Calvo, J.M. Guerrero Inhibition of cerebellar nitric oxide synthase and cyclic AMP production via complex formation with calmodulin, J. Cell Biochem. 65 (1997) 430-442.

[40] Y. Urata, S. Honma, S. Goto, S. Todoroki, T. Iida, S. Cho, K. Honma, T. Kondo, Melatonin induces gamma-glutamylcysteine synthetase mediated by activator protein 1 in human vascular endothelial cells, Free Radic. Biol. Med. 27(1999) 838-847.

[41] E. Gitto, D.X. Tan, R.J. Reiter, M. Karbownik, L.C. Manchester, S. Cuzzocrea, F. Fulia, I. Barberi, Individual and synergistic antioxidative actions of melatonin: studies with vitamin E, vitamin C, glutathione and desferrioxamine (desferoxamine) in rat liver homogenates, J. Pharm. Pharmacol. 53 (2001) 1393-1401.

[42] M. Valko, H. Morris, M.T. Cronin, Metals, toxicity and oxidative stress, Curr. Med. Chem. 12 (2005) 1161-1208.

[43] A. Galano, M.E. Medina, D.X. Tan, R.J. Reiter, Melatonin and its metabolites as copper chelating agents and their role in inhibiting oxidative stress: a physiochemical analysis, J. Pineal Res. 58 (2015) 107-116.

[44] A.P. Hungin, P.J. Whorwell, T. Tack, F. Mearin, The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects, Aliment. Pharmacol. Ther. 17 (2003) 643-650.

[45] Y. Okatani, N. Marioka, A. Wakatsuki, Changes in nocturnal melatonin secretion in perimenopausal women: correlation with endogenous estrogen concentrations, J. Pineal Res. 20 (2000) 111-118.

[46] E. Walecka-Kapica, J. Chojnacki, A. Stępień, P. Wachowska-Kelly, G. Klupińska, C. Chojnacki, Melatonin and female hormone secretion in postmenopausal overweight women, Int. J Mol. Sci. 16 (2015) 1030-142.

[47] E. Malinen, T. Rinttilä, K. Kajander, J. Mättö, A. Kassinen, L. Krogius, M. Saarela, R. Korpela, A. Palva Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR, Am. J. Gastroenterol. 100 (2005) 373-382.

[48] S.J. Konturek, P.C. Konturek, I. Brzozowska, M. Pawlik, Z. Sliwowski, M. Cześnikiewicz-Guzik, S. Kwiecień, T. Brzozowski, G.A. Bubenik, W.W. Pawlik, Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT), J. Physiol. Pharmacol. 58 (2007) 381-405.

[49] V. Martinez, Y. Tache, Role of CRF receptor 1 in central CRF-induced stimulation of colonic propulsion in rats, Brain Res. 893 (2001) 29–35.

[50] Y. Tache, V. Martinez, M. Million, L. Wang, Stress and the gastrointestinal tract. III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors, Am. J. Physiol. Gastrointest. Liver Physiol. 280 (2001) G173–G177.

[51] Y. Tache, M.H. Perdue, Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function, Neurogastroenterol. Motil. 16 Suppl 1 (2004) 137–142.

[52] R. Fass, S. Fullerton, S. Tung, E.A. Mayer Sleep disturbances in clinic patients with functional bowel disorders, Am. J. Gastroenterol. 95 (2000) 1195-2000.

[53] J.J. Thompson, S. Elsenbruch, M.J. Harnish, W.C. Orr, Autonomic functioning during REM sleep differentiates IBS symptom subgroups, Am. J. Gastroenterol. 97 (2002) 3147-3153.

[54] M. Jarrett, M. Heitkemper, K.C. Cain, R.L. Burr, V. Hertig, Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome, Dig. Dis. Sci. 45 (2000) 952-959.

[55] P. Fitzgerald, M. Cassidy Eugene, P. Scully, S. Barry, M.M. Quigley Eamonn, F. Shanahan, J. Cryan, G. Dinan Timothy, Tryptophan catabolism in females with irritable bowel syndrome: relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity, Neurogastroenterol. Motil. 20 (2008) 1291-1297.

[56] G. Clarke, P. Fitzgerald, J.F. Cryan, E.M. Cassidy, E.M. Quigley, T.G. Dinan, Tryptophan degradation in irritable bowel syndrome: evidence of indoleamine 2,3-dioxygenase activation in a male cohort, BMC Gastroenterol. 9, 6 (2009). doi: 10.1186/1471-230X-9-6.

[57] P.J. Kennedy, A.P. Allen, A. O'Neill, E.M. Quigley, J.F. Cryan, T.G. Dinan, G. Clarke, Acute tryptophan depletion reduces kynurenine levels: implications for treatment of impaired visuospatial memory performance in irritable bowel syndrome, Psychopharmacology (Berl) 232 (2015) 1357-1371.

[58] M.M. Heitkemper, C.J. Han, M.E. Jarrett, H. Gu, D. Djukovic, R.J. Shulman, D. Raftery, W.A. Henderson, K.C. Cain, Serum Tryptophan Metabolite Levels During Sleep

in Patients With and Without Irritable Bowel Syndrome (IBS), Biol. Res. Nurs. 18 (2016) 193-198.

[59] T. Pääkkönen, T.M. Mäkinen, J. Leppäluoto, O. Vakkuri, H. Rintamäki, L.A. Palinkas, J. Hassi, Urinary melatonin: a noninvasive method to follow human pineal function as studied in three experimental conditions, J. Pineal Res. 40 (2006) 110-115.

[60] M. Wisniewska-Jarosinska, J. Chojnacki, S. Konturek, S. Konturek, T. Brzozowski, J. Smigielski, C. Chojnacki Evaluation of urinary 6-hydroxymelatonin sulphate excretion in women at different age with irritable bowel syndrome, J. Physiol. Pharmacol. 61 (2010) 295-300.

[61] P. Radwan, B. Skrzydło-Romańska, K. Radwan-Kwiatek, B. Burak-Czapiuk B & Strzemecka J (2009) Is melatonin involved in the irritable bowel syndrome? J Physiol Pharmacol 60 (Suppl. 3), 67–70.

[62] C. Chojnack, M. Wiśniewska-Jarosińska, G. Kulig, I. Majsterek, R.J. Reiter, J. Chojnacki, Evaluation of enterochromaffin cells and melatonin secretion exponents in ulcerative colitis, World J. Gastroenterol. 19 (2013) 3602-3607.

[63] S. Shirakawa, S. Tsuchiya, Y. Tsutsumi, Time course of saliva and serum melatonin levels after ingestion of melatonin, Psychiatry Clin. Neurosci. 52 (1998) 266–267.

[64] C.W. Hammerle, C.M. Surawicz, Updates on treatment of irritable bowel syndrome, World J. Gastroenterol. 14 (2008) 2639-2649.

[65] W.D. Chey, Tegaserod and other serotonergic agents. What is the evidence?, Rev. Gastroenterol. Disord. 3 (2003) S35- S40.

[66] V. Andersen, M. Camilleri, Irritable bowel syndrome: recent and novel therapeutic approaches, Drugs 66 (2006) 1073-1088.

[67] M. Storr, V. Schusdziarra, H.D. Allescher, Inhibition of small conductance K+ -channels attenuated melatonin-induced relaxation of serotonin-contracted rat gastric fundus, Can. J. Physiol. Pharmacol. 78 (2000) 799-806.

[68] G.H. Song, K.A. Gwee, S.M. Moochhala, K.Y. Ho, Melatonin attenuates stress-induced defecation: lesson from a rat model of stress-induced gut dysfunction, Neurogastroenterol. Motil. 17 (2005) 744-750.

[69] W. Tan, W. Zhou, H.S. Luo, C.B. Liang, H. Xia, The inhibitory effect of melatonin on colonic motility disorders induced by water avoidance stress in rats, Eur. Rev. Med. Pharmacol. Sci. 17 (2013) 3060-3067.

[70] J.H. Han, I.H. Chang, S.C. Myung, M.Y. Lee, W.Y. Kim, S.Y. Lee, S.Y. Lee, S.W. Lee, K.D. Kim, A novel pathway underlying the inhibitory effects of melatonin on isolated rat urinary bladder contraction, Korean J. Physiol. Pharmacol. 16 (2012) 37-42.

[71] A. Semercioöz, R. Onur, A. Ayar, I. Orthan, The inhibitory role of melatonin on isolated guinea-pig urinary bladder: an endogenous hormone effect, B.J.U. Int. 94 (2004) 1373-1376.

[72] W.Z. Lu, G.H. Song, K.A. Gwee, K.Y. Ho, The effects of melatonin on colonic transit time in normal controls and IBS patients, Dig. Dis. Sci. 54 (2009) 1087-1093.

[73] G.H. Song, P.H. Leng, K.A. Gwee, S.M. Moochhala, K.Y. Ho, Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study, Gut 54 (2005) 1402-1407.

[74] L. Saha, S. Malhotra, S. Rana, D. Bhasin, P. Pandhi, A preliminary study of melatonin in irritable bowel syndrome, J. Clin. Gastroenterol. 41 (2007) 29-32.

[75] M. Gonciarz, Z. Gonciarz, W. Bielanski, A. Mularczyk, P.C. Konturek, T. Brzozowski, S.J. Konturek, The effects of long-term melatonin treatment on plasma liver enzymes

levels and plasma concentrations of lipids and melatonin in patients with nonalcoholic steatohepatitis: a pilot study, J. Physiol. Pharmacol. 63 (2012) 35-40.

[76] R.B. Stein, G.R. Lichtenstein, Medical therapy for Crohn's disease: the state of the art, Surg. Clin. North. Am. 81 (2001) 71-101.

[77] N.J. Talley, M.T. Abreu, J.P. Achkar, C.N. Bernstein, M.C. Dubinsky, S.B. Hanauer, S.V. Kane, W.J. Sandborn, T.A. Ullman, P. Moayyedi, American College of Gastroenterology IBD Task Force, An evidence-based systematic review on medical therapies for inflammatory bowel disease, Am. J. Gastroenterol. 106 Suppl 1 (2011) S2-25; quiz S26.

[78] A. Kaser, S. Zeissig, R.S. Blumberg, Inflammatory bowel disease, Annu. Rev. Immunol. 28 (2010) 573–621.

[79] A. O'Toole, J. Korzenik, Environmental triggers for IBD, Curr. Gastroenterol. Rep. 16, 396 (2014). doi: 10.1007/s11894-014-0396-y

[80] G.C. Parkes, K. Whelan, J.O. Lindsay, Smoking in inflammatory bowel disease: impact on disease course and insights into the aetiology of its effect, J. Crohns Colitis 8 (2014)., 717–725.

[81] A.N. Ananthakrishnan, Epidemiology and risk factors for IBD, Nat. Rev. Gastroenterol. Hepatol. 12 (2015) 205–217.

[82] J.K. Paulose, J.M. Wright, A.G. Patel, V.M. Cassone, Human gut bacteria are sensitive to melatonin and express endogenous circadian activity, PLoS One 11:e0146643 (2016). doi: 10.1371/journal.pone.0146643.

[83] J.K. Paulose, V.M. Cassone, The melatonin sensitive circadian clock of the enteric bacterium enterobacter aerogenes, Gut Microbes 7 (2016) 1-4.

[84] T. Ali, M.F. Madhoun, W.C. Orr, D.T. Rubin, Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients, Inflamm. Bowel Dis. 19 (2013) 2440-2243.

[85] L.A. Graff, I. Clara, J.R. Walker, L. Lix, R. Carr, N. Miller, L. Rogala, C.N. Bernstein, Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors, Clin. Gastroenterol. Hepatol. 11 (2013) 1140-1146.

[86] A.N. Ananthakrishnan, M.D. Long, C.F. Martin, R.S. Sandler, M.D. Kappelman Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis, Clin. Gastroenterol. Hepatol. 11 (2013) 965-971.

[87] Z. Ranjbaran, L. Keefer, A. Farhadi, E. Stepanski, S. Sedghi, A. Keshavarzian, Impact of sleep disturbances in inflammatory bowel disease, J. Gastroenterol. Hepatol. 22 (2007) 1748-1753.

[88] P.J. Parekh, E.C. Oldfield Iv, V. Challapallisri, J.C. Ware, D.A. Johnson DA Sleep disorders and inflammatory disease activity: chicken or the egg?, Am. J. Gastroenterol. 110 (2015) 484-488.

[89] J.R. Calvo, J.M. Guerrero, C. Osuna, P. Molinero, A. Carrillo-Vico, Melatonin triggers Crohn's disease symptoms, J. Pineal Res. 32 (2002) 277-278.

[90] W. Strober, I.J. Fuss IJ, Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases, Gastroenterology 140 (2011) 1756–1767.

[91] I.J. Fuss IJ M. Neurath, M. Boirivant, J.S. Klein, C. de la Motte, S.A. Strong, C. Fiocchi, W. Strober, Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn‟s disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5, J. Immunol. 157 (1996) 1261–1270.

[92] D.B. Graham, R.J. Xavier, From genetics of inflammatory bowel disease towards mechanistic insights, Trends Immunol. 34 (2013) 371–378.

[93] S. Garcia-Mauriño, M.G. Gonzalez-Haba, J.R. Calvo, M. Rafii-El-Idrissi, V. Sanchez-Margalet, R. Goberna, J.M. Guerrero Melatonin enhances IL-2, IL-6, and IFN-gamma production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes, J. Immunol. 159 (1997) 574-581.

[94] S. García-Mauriño, D. Pozo, A. Carrillo-Vico, J.R. Calvo, J.M. Guerrero, Melatonin activates Th1 lymphocytes by increasing IL-12 production, Life Sci. 65 (1999) 2143-2150.

[95] M. Coskun, M. Salem, J. Pedersen, O.H. Nielsen, Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. Pharmacol. Res. 76 (2013) 1–8.

[96] L. Vuitton, S. Koch, L. Peyrin-Biroulet, Janus kinase inhibition with tofacitinib: changing the face of inflammatory bowel disease treatment, Curr. Drug Targets 14 (2013) 1385–1391.

[97] P. He, X. Ouyang, S. Zhou, W. Yin, C. Tang, M. Laudon, S. Tian, A novel melatonin agonist Neu-P11 facilitates memory performance and improves cognitive impairment in a rat model of Alzheimer' disease, Horm. Behav. 64 (2013) 1–7.

[98] I. Buendia, V. Gómez-Rangel, L. González-Lafuente, E. Parada, R. León, I. Gameiro, P. Michalska, M. Laudon, J. Egea, M.G. López, Neuroprotective mechanism of the novel melatonin derivative Neu-P11 in brain ischemia related models, Neuropharmacology 99 (2015) 187-195.

[99] J.X. Zhang, J. Song, J. Wang, W.G. Dong, JAK2 rs10758669 polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis, Inflammation 37 (2014) 793-800.

[100] C. Parham, M. Chirica, J. Timans, E. Vaisberg, M. Travis, J. Cheung, S. Pflanz, R. Zhang, K.P. Singh, F. Vega, W. To, J. Wagner, A.M. O'Farrell, T. McClanahan, S. Zurawski, C. Hannum, D. Gorman, D.M. Rennick, R.A. Kastelein, R. de Waal Malefyt, K.W. Moore, A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R, J. Immunol. 168 (2012) 5699-5708.

[101] L. Durant, W.T. Watford, H.L. Ramos, A. Laurence, G. Vahedi, L. Wei, H. Takahashi, H.W. Sun, Y. Kanno, F. Powrie, J.J. O'Shea, Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis, Immunity 32 (2010) 605-615.

[102] G.L. Stritesky, R. Muthukrishnan, S. Sehra, R. Goswami, D. Pham, J. Travers, E.T. Nguyen, D.E. Levy, M.H. Kaplan, The transcription factor STAT3 is required for T helper 2 cell development, Immunity 34 (2011) 39-49.

[103] Y. Chen, Y. Xiao, W. Ge, K. Zhou, J. Wen, W. Yan, Y. Wang, B. Wang, C. Qu, J. Wu, L. Xu, W. Cai, miR-200b inhibits TGF-β1-induced epithelial-mesenchymal transition and promotes growth of intestinal epithelial cells, Cell Death. Dis. 4:e541 (2013). doi: 10.1038/cddis.2013.22.

[104] G. Monteleone, F. Pallone, Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn's Disease, N. Engl. J. Med. 372:2461 (2015). doi: 10.1056/NEJMc1504845.

[105] T. Hara, F. Otsuka, N. Tsukamoto-Yamauchi, K. Inagaki, T. Hosoya, E. Nakamura, T. Terasaka, M. Komatsubara, H. Makino, Mutual effects of melatonin and activin on induction of aldosterone production by human adrenocortical cells, J. Steroid Biochem. Mol. Biol. 152 (2015) 8-15.

[106] L. Pastorelli, C. De Salvo, J.R. Mercado, M. Vecchi, T.T. Pizarro, Central role of the gut epithelial barrier in the pathogenesis of chronic intestinal inflammation: lessons

learned from animal models and human genetics, Front. Immunol. 4: 280 (2013). doi: 10.3389/fimmu.2013.00280.

[107] M. Veldhoen, R.J. Hocking, C.J. Atkins, R.M. Locksley, B. Stockinger, TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells, Immunity 24 (2006) 179–189.

[108] I.I. Ivanov, L. Zhou, D.R. Littman, Transcriptional regulation of Th17 cell differentiation, Semin. Immunol. 19 (2007) 409–417.

[109] M.J. McGeachy, Y. Chen, C.M. Tato, A. Laurence, B. Joyce-Shaikh, W.M. Blumenschein, T.K. McClanahan, J.J. O'Shea, D.J. Cua, The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo, Nat. Immunol. 10 (2009) 314–324.

[110] M.F. Farez, I.D. Mascanfroni, S.P. Méndez-Huergo, A. Yeste, G. Murugaiyan, L.P. Garo, M.E. Balbuena Aguirre, B. Patel, M.C. Ysrraelit, C. Zhu, V.K. Kuchroo, G.A. Rabinovich, F.J. Quintana, J. Correale, Melatonin contributes to the seasonality of multiple sclerosis relapses, Cell 162 (2015) 1338– 1352.

[111] A. Izcue, S. Hue, S. Buonocore, C.V. Arancibia-Cárcamo, P.P. Ahern, Y. Iwakura, K.J. Maloy, F. Powrie, Interleukin-23 restrains regulatory T cell activity to drive T cell-dependent colitis, Immunity 28 (2008) 559–570.

[112] P.P. Ahern, C. Schiering, S. Buonocore, M.J. McGeachy, D.J. Cua, K.J. Maloy, F. Powrie Interleukin-23 drives intestinal inflammation through direct activity on T cells, Immunity 33 (2010) 279–288.

[113] M.A. Kleinschek, K. Boniface, S. Sadekova, J. Grein, E.E. Murphy, S.P. Turner, L. Raskin, B. Desai, W.A. Faubion, R. de Waal Malefyt, R.H. Pierce, T. McClanahan, R.A. Kastelein, Circulating and gut- resident human Th17 cells express CD161 and promote intestinal inflammation, J. Exp. Med. 206 (2009) 525-534.

[114] A. Sakuraba, T. Sato, N. Kamada, M. Kitazume, A. Sugita, T. Hibi, Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn‟s disease, Gastroenterology 137 (2009) 1736-1745.

[115] K.A. Head, J.S. Jurenka, Inflammatory bowel disease Part 1: ulcerative colitis--pathophysiology and conventional and alternative treatment options, Altern. Med. Rev. 8 (2003) 247-283.

[116] T. Jess, C. Rungoe, L. Peyrin-Biroulet, Risk of colorectal cancer in patients with ulcerative colitis: A meta-analysis of populationbased cohort studies, Clin. Gastroenterol. Hepatol. 10 (2012) 639–645.

[117] C.T. Peterson, V. Sharma, L. Elmen, S.N. Peterson, Immune homeostasis, dysbiosis and therapeutic modulation of the gut microbiota, Clin. Exp. Immunol. 179 (2015) 363–377.

[118] S.D. Holubar, R.R. Cima, W.J. Sandborn, D.S. Pardi, Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database Syst Rev 6 CD001176 (2010). doi: 10.1002/14651858.CD001176.pub2.

[119] W. Stremmel, U. Merle, A. Zahn, F. Autschbach, U. Hinz, R. Ehehalt, Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis, Gut 54 (2005) 966–971.

[120] W.J. Sandborn, S. Ghosh, J. Panes, I. Vranic, C. Su, S. Rousell, W. Niezychowski, Study A3921063 Investigators, Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis, N. Engl. J. Med. 367 (2012) 616-624.

[121] P.J. Mannon, R.L. Hornung, Z. Yang, C. Yi, C. Groden, J. Friend, M. Yao, W. Strober, I.J. Fuss, Suppression of inflammation in ulcerative colitis by interferon-β-1a is accompanied by inhibition of IL-13 production, Gut 60 (2011) 449-455.

[122] B.G. Feagan, P. Rutgeerts, B.E. Sands, S. Hanauer, J.F. Colombel, W.J. Sandborn, G. Van Assche, J. Axler, H.J. Kim, S. Danese, I. Fox, C. Milch, S. Sankoh, T. Wyant, J. Xu, A. Parikh, GEMINI 1 Study Group, Vedolizumab as induction and maintenance therapy for ulcerative colitis, N. Engl. J. Med. 369 (2013) 699-710.

[123] S. Vermeire, S. O'Byrne, M. Keir, M. Williams, T.T. Lu, J.C. Mansfield, C.A. Lamb, B.G. Feagan, J. Panes, A. Salas, D.C. Baumgart, S. Schreiber, I. Dotan, W.J. Sandborn, G.W. Tew, D. Luca, M.T. Tang, L. Diehl, J. Eastham-Anderson, G. De Hertogh, C. Perrier, J.G. Egen, J.A. Kirby, G. van Assche, P. Rutgeerts P, Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial, Lancet 384 (2014) 309-318.

[124] N. Bernardini, C. Segnani, C. Ippolito, R. De Giorgio, R. Colucci, M.S. Faussone-Pellegrini, M. Chiarugi, D. Campani, M. Castagna, L. Mattii, C. Blandizzi, A. Dolfi, Immunohistochemical analysis of myenteric ganglia and interstitial cells of Cajal in ulcerative colitis, J. Cell. Mol. Med. 16 (2012) 318–327.

[125] G. Jena, P.P. Trivedi, A review of the use of melatonin in ulcerative colitis: experimental evidence and new approaches. Inflamm. Bowel. Dis. 20 (2014) 553–563.

[126] T. Sprong, G. Peri, C. Neeleman, A. Mantovani, S. Signorini, J.W. van der Meer, M. van Deuren, Pentraxin 3 and C-reactive protein in severe meningococcal disease, Shock 31 (2009) 28-32.

[127] B. Harder, T. Jiang, T. Wu, S. Tao, M. Rojo de la Vega, W. Tian, E. Chapman, D.D. Zhang, Molecular mechanisms of Nrf2 regulation and how these influence chemical modulation for disease intervention, Biochem. Soc. Trans. 43 (2015) 680–686.

[128] I. Crespo, B.S. Miguel, A. Laliena, M. Alvarez, J.M. Culebras, J. González-Gallego, M.J. Tuñón, Melatonin prevents the decreased activity of antioxidant enzymes and

activates nuclear erythroid 2-related factor 2 signaling in an animal model of fulminant hepatic failure of viral origin, J. Pineal Res. 49 (2010) 193–200.

[129] L. Zhou, D. Zhao, H. An, H. Zhang, C. Jiang, B. Yang B, Melatonin prevents lung injury induced by hepatic ischemia-reperfusion through anti-inflammatory and anti-apoptosis effects, Int. Immunopharmacol. 29 (2015) 462–467.

[130] D. Wang, Y. Wei, T. Wang, X. Wan, C.S. Yang, R.J. Reiter, J. Zhang, Melatonin attenuates (-)- epigallocatehin-3-gallate-triggered hepatotoxicity without compromising its downregulation of hepatic gluconeogenic and lipogenic genes in mice, J. Pineal Res. 59 (2015) 497–507.

[131] B. Shang, H. Shi, X. Wang, X. Guo, N. Wang, Y. Wang, L. Dong, Protective effect of melatonin on myenteric neuron damage in experimental colitis in rats, Fundam. Clin. Pharmacol. 30 (2016) 117-127.

[132] C. Chojnacki, M. Wisniewska-Jarosinska, E. Walecka-Kapica, G. Klupinska, J. Jaworek, J. Chojnacki, Evaluation of melatonin effectiveness in the adjuvant treatment of ulcerative colitis, J. Physiol. Pharmacol. 62 (2011) 327-334.

[133] M. Chen, Q. Mei, J. Xu, C. Lu, H. Fang, X. Liu, Detection of melatonin and homocysteine simultaneously in ulcerative colitis, Clin. Chim. Acta 413 (2012) 30-33.

[134] S.H. Chung, Y.S. Park, O.S. Kim, J.H. Kim, H.W. Baik, Y.O. Hong, S.S. Kim, J.H. Shin, J.H. Jun, Y. Jo, S.B. Ahn, Y.K. Jo, B.K. Son, S.H. Kim, Melatonin attenuates dextran sodium sulfate induced colitis with sleep deprivation: possible mechanism by microarray analysis, Dig. Dis. Sci. 59 (2014) 1134-1141.

[135] R.K. Cross, K.T. Wilson, Nitric oxide in inflammatory bowel disease, Inflamm. Bowel Dis. 9 (2003) 179-189.

[136] S. Danese, L. Motte Cd Cde, C. Fiocchi, Platelets in inflammatory bowel disease: clinical, pathogenic, and therapeutic implications, Am. J. Gastroenterol. 99 (2004) 938-945.

[137] I.J. Fuss, F. Heller, M. Boirivant, F. Leon, M. Yoshida, S. Fichtner-Feigl, Z. Yang, M. Exley, A. Kitani, R.S. Blumberg, P. Mannon, W. Strober, Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis, J. Clin. Invest. 113 (2014) 1490–1497.

[138] M. Boirivant, I.J. Fuss, A. Chu, W. Strober, Oxazalone colitis: A murine model of T helper cell type 2 colitis treatable with antibodies to interleukin 4, J. Exp. Med. 188 (1998) 1929-1939.

[139] F. Heller, I.J. Fuss, E.E. Nieuwenhuis, R.S. Blumberg, W. Strober, Oxazalone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells, Immunity 17 (2002) 629-638

[140] L.L Zhou, W. Wei, J.F. Si, D.P. Yuan, Regulatory effect of melatonin on cytokine disturbances in the pristane-induced lupus mice, Mediators Inflamm. (2010). pii: 951210. doi: 10.1155/2010/951210.

[141] K. Perez-de-Arce, R. Foncea, F. Leighton, Reactive oxygen species mediates homocysteine-induced mitochondrial biogenesis in human endothelial cells: modulation by antioxidants, Biochem. Biophys. Res. Commun. 338 (2005) 1103–1109.

[142] P.E. Lazzerini, P.L. Capecchi, E. Selvi, S. Lorenzini, S. Bisogno, M. Galeazzi, F. Laghi Pasini, Hyperhomocysteinemia, inflammation and autoimmunity, Autoimmun. Rev. 6 (2007) 503-509.

[143] P. Zezos, G. Papaioannou, N. Nikolaidis, K. Patsiaoura, A. Papageorgiou, T. Vassiliadis, O. Giouleme, N. Evgenidis, Low-molecular-weight heparin (enoxaparin) as

adjuvant therapy in the treatment of active ulcerative colitis: a randomized, controlled, comparative study, Aliment. Pharmacol. Ther. 23 (2006) 1443-1453.

[144] P. Zezos, G. Papaioannou, N. Nikolaidis, T. Vasiliadis, O. Giouleme, N. Evgenidis, Hyperhomocysteinemia in ulcerative colitis is related to folate level, World J. Gastroenterol. 11 (2005) 6038–6042.

[145] Y. Erzin, H. Uzun, A.F. Celik, S. Aydin, A. Dirican, H. Uzunismail, Hyperhomocysteinemia in inflammatory bowel disease patients without past intestinal resections: correlations with cobalamin, pyridoxine, folate concentrations, acute phase reactants, disease activity, and prior thromboembolic complications, J. Clin. Gastroenterol. 42 (2008), 481–486.

[146] S.J. Heydrick, N. Weiss, S.R. Thomas, A.P. Cap, D.R. Pimentel, J. Loscalzo, J.F. Keaney jr, L-Homocysteine and L-homocystine stereospecifically induce endothelial nitric oxide synthase-dependent lipid peroxidation in endothelial cells, Free Radic. Biol. Med. 36 (2004) 632-640.

[147] S. Cuzzocrea, E. Mazzon, I. Serraino, V. Lepore, M.L. Terranova, A. Ciccolo, A.P. Caputi, Melatonin reduces dinitrobenzene sulfonic acid-induced colitis, J. Pineal Res. 30 (2001) 1-12.

[148] W.G. Dong, Q. Mei, J.P. Yu, J.M. Xu, L. Xiang, Y. Xu, Effects of melatonin on the expression of iNOS and COX-2 in rat models of colitis, World J. Gastroenterol. 9 (2003) 1307-1311.

[149] J.H. Li, J.P. Yu, H.G. Yu, X.M. Xu, L.L. Yu, J. Liu, H.S. Luo, Melatonin reduces inflammatory injury through inhibiting NF-kappaB activation in rats with colitis, Mediators Inflamm. 2005 (2005) 185-193.

[150] Q. Mei, J.M. Xu, L. Xiang, Y.M. Hu, X.P. Hu, Z.W. Xu, Change of nitric oxide in experimental colitis and its inhibition by melatonin in vivo and in vitro, Postgrad. Med. J. 81 (2005) 667-672.

[151] E. Marquez, S. Sánchez-Fidalgo, J.R. Calvo, C.A. la de Lastra, V. Motilva, Acutely administered melatonin is beneficial while chronic melatonin treatment aggravates the evolution of TNBS-induced colitis, J. Pineal Res. 40 (2006) 48-55.

[152] E. Mazzon, E. Esposito, C. Crisafulli, L. Riccardi, C. Muià, P. Di Bella, R. Meli, S. Cuzzocrea, Melatonin modulates signal transduction pathways and apoptosis in experimental colitis, J. Pineal Res. 41 (2006) 363-373.

[153] V. Nosál'ová, M. Zeman, S. Cerná, J. Navarová, M. Zakálová, Protective effect of melatonin in acetic acid induced colitis in rats, J. Pineal Res. 42 (2007) 364-370.

[154] E. Esposito, E. Mazzon, L. Riccardi, R. Caminiti, R. Meli, S. Cuzzocrea, Matrix metalloproteinase-9 and metalloproteinase-2 activity and expression is reduced by melatonin during experimental colitis, J. Pineal Res. 45 (2008) 166-173.

[155] A. Akcan, C. Kucuk, E. Sozuer, D. Esel, H. Akyildiz, H. Akgun, S. Muhtaroglu, Y. Aritas, Melatonin reduces bacterial translocation and apoptosis in trinitrobenzene sulphonic acid-induced colitis of rats, World J. Gastroenterol. 14 (2008) 918-924.

[156] G. Tahan, R. Gramignoli, F. Marongiu, S. Aktolga, A. Cetinkaya, V. Tahan, K. Dorko, Melatonin expresses powerful anti-inflammatory and antioxidant activities resulting in complete improvement of acetic-acid-induced colitis in rats, Dig. Dis. Sci. 56 (2011) 715-720.

[157] H.G. Sayyed, R.J. Jaumdally, N.K. Idriss, D.A. El Sers, A. Blann, The effect of melatonin on plasma markers of inflammation and on expression of nuclear factor-kappa beta in acetic acid-induced colitis in the rat, Dig. Dis. Sci. 58 (2013) 3156-3164.

[158] P.P. Trivedi, G.B. Jena, Melatonin reduces ulcerative colitis-associated local and systemic damage in mice: investigation on possible mechanisms, Dig. Dis. Sci. 58 (2013) 3460-3474.

[159] F. Esiringü, F. Tuğcu-Demiröz, F. Acartürk, Ş. Coşkun Cevher, F. Bircan, S.M. Sarı Kılıçaslan, Investigation of the effect of intracolonic melatonin gel formulation on acetic acid-induced colitis, Drug Deliv. Jul 25 (2015) 1-9. [Epub ahead of print]

[160] P.P. Trivedi, G.B. Jena, K.B. Tikoo, V. Kumar, Melatonin modulated autophagy and Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis, Mol. Carcinog. 55 (2016) 255-67

[161] S. Tasdemir, H. Parlakpinar, N. Vardi, E. Kaya, A. Acet, Effect of endogen-exogenous melatonin and erythropoietin on dinitrobenzene sulfonic acid-induced colitis, Fundam. Clin. Pharmacol. 27 (2013) 299-307.

[162] S. Mann, Melatonin for ulcerative colitis?, Am. J. Gastroenterol. 98 (2003) 232-233.

[163] M.D. Maldonado, J.R. Calvo. Melatonin usage in ulcerative colitis: a case report, J. Pineal Res. 45 (2008) 339-340.

[164] C.L. Chang, P.H. Sung, C.K. Sun, C.H. Chen, H.J. Chiang, T.H. Huang, Y.L. Chen, Y.Y. Zhen, H.T. Chai, S.Y. Chung, M.S. Tong, H.W. Chang, H.H. Chen, H.K. Yip, Protective effect of melatonin-supported adipose-derived mesenchymal stem cells against small bowel ischemia-reperfusion injury in rat, J. Pineal Res. 59 (2015) 206-220.

[165] W.W. Lin, M. Karin, A cytokine-mediated link between innate immunity, inflammation, and cancer, J. Clin. Invest. 117 (2007) 1175–1183.

[166] J. Mudter, M.F. Neurath, Il-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance, Inflamm. Bowel. Dis. 13 (2007) 1016–1023.

[167] M.S. Byun, K.I. Jeon, J.W. Choi, J.Y. Shim, D.M. Jue, Dual effect of oxidative stress on NF-kappakB activation in HeLa cells, Exp. Mol. Med. 34 (2002) 332–339.

[168] J. Macdonald, H.F. Galley, N.R. Webster, Oxidative stress and gene expression in sepsis, Br. J. Anaesth. 90 (2003) 221–232.

[169] I.M. Verma, Nuclear factor (NF)-kappaB proteins: therapeutic targets, Ann. Rheum. Dis. 2 (2004) 57–61.

[170] G.D. Norata, P. Marchesi, V.K. Pulakazhi Venu, F. Pasqualini, A. Anselmo, F. Moalli, I. Pizzitola, C. Garlanda, A. Mantovani, A.L. Catapano, Deficiency of the long pentraxin PTX3 promotes vascular inflammation and atherosclerosis, Circulation 120 (2009) 699-708.

[171] A.S. Savchenko, A. Inoue, R. Ohashi, S. Jiang, G. Hasegawa, T. Tanaka, T. Hamakubo, T. Kodama, Y. Aoyagi, T. Ushiki, M. Naito, Long pentraxin 3 (PTX3) expression and release by neutrophils in vitro and in ulcerative colitis, Pathol. Int. 61 (2011) 290-297.

[172] K. Ganguly, P. Kundu, A. Banerjee, R.J. Reiter, S. Swarnakar, Hydrogen peroxide-mediated downregulation of matrix metalloprotease-2 in indomethacin- induced acute gastric ulceration is blocked by melatonin and other antioxidants, Free Radic. Biol. Med. 41 (2006) 911-925.

[173] H.J. Kim, M. Zheng, S.K. Kim, J.J. Cho, C.H. Shin, Y. Joe, H.T. Chung, CO/HO-1 Induces NQO-1 Expression via Nrf2 Activation, Immune Netw. 11 (2011) 376-382.

[174] Q. Ma, Role of nrf2 in oxidative stress and toxicity, Annu. Rev. Pharmacol. Toxicol. 53 (2013) 401-426.

[175] T.O. Khor, M.T.Huang, K.H. Kwon, J.Y. Chan, B.S. Reddy, A.N. Kong, Nrf2-deficient mice have an increased susceptibility to dextran sulfate sodium-induced colitis, Cancer Res. 66 (2006) 11580-11584.

[176] J.D. Mott, Z. Werb, Regulation of matrix biology by matrix metalloproteinases, Curr. Opin. Cell Biol. 16 (2004) 558–564.

[177] F.F. di Mola, P. Di Sebastiano, A. Gardini, P. Innocenti, A. Zimmermann, M.W. Büchler, H. Friess, Differential expression of connective tissue growth factor in inflammatory bowel disease, Digestion 69 (2004) 245-253.

[178] M.T. Albarrán, S. López-Burillo, M.I. Pablos, R.J. Reiter, MT. Agapito, Endogenous rhythms of melatonin, total antioxidant status and superoxide dismutase activity in several tissues of chick and their inhibition by light, J. Pineal Res. 30 (2001) 227-233.

[179] T. Brzozowski, K. Zwirska-Korczala, P.C. Konturek, S.J. Konturek, Z. Sliwowski, M. Pawlik, S. Kwiecien, D. Drozdowicz, M. Mazurkiewicz-Janik, W. Bielanski, W.W. Pawlik, Role of circadian rhythm and endogenous melatonin in pathogenesis of acute gastric bleeding erosions induced by stress, J. Physiol. Pharmacol. 58 Suppl 6 (2007) 53-64.

[180] J.L. Esparza, M. Gómez, M. Rosa Nogués, J.L. Paternain, J. Mallol, J.L. Domingo, Melatonin reduces oxidative stress and increases gene expression in the cerebral cortex and cerebellum of aluminum-exposed rats, J. Pineal Res. 39 (2005) 129-136.

[181] J. Cabeza, C. Alarcón-de-la-Lastra, M.J. Martín, J.M. Herrerias, V. Motilva, Diurnal variation in the protective effect of melatonin against gastric injury caused by ischemia-reperfusion, Biol. Rythms Res. 33 (2002) 319–332.

[182] P.W. Lin, B.J. Stoll, Necrotising enterocolitis, Lancet 368 (2006) 1271-1283.

[183] M.C. Henry, R.L. Moss, Neonatal necrotizing enterocolitis, Semin. Pediatr. Surg. 17 (2008) 98-109.

[184] J. Neu, W.A. Walker, Necrotizing enterocolitis, N. Engl. J. Med. 364 (2011) 255-264.

[185] W. Hsueh, M.S. Caplan, X.W. Qu, X.D. Tan, I.G. De Plaen, F. Gonzalez-Crussi, Neonatal necrotizing enterocolitis: clinical considerations and pathogenetic concepts, Pediatr. Dev. Pathol. 6 (2003) 6-23.

[186] M.S. Caplan, D. Simon, T. Jilling, The role of PAF, TLR, and the inflammatory response in neonatal necrotizing enterocolitis, Semin. Pediatr. Surg. 14 (2005) 145-151.

[187] R. Zamora, N.S. Bryan, P. Boyle, C. Wong, A.B. Milsom, R. Jaffe, M. Feelisch, H.R. Ford, Nitrosative stress in an animal model of necrotizing enterocolitis, Free Radic. Biol. Med. 39 (2005) 1428-1437.

[188] K.L. Schnabl, J.E. Van Aerde, A.B. Thomson, M.T. Clandinin, Necrotizing enterocolitis: a multifactorial disease with no cure, World J. Gastroenterol. 14 (2008) 2142-2161.

[189] S. Perrone, M.L. Tataranno, S. Negro, S. Cornacchione, M. Longini, F. Proietti, V. Soubasi, M.J. Benders, F. Van Bel, G. Buonocore, May oxidative stress biomarkers in cord blood predict the occurrence of necrotizing enterocolitis in preterm infants?, J. Matern. Fetal Neonatal Med. 25 Suppl 1 (2012) 128-131.

[190] E. Gitto, L. Marseglia, S. Manti, G. D'Angelo, I. Barberi, C. Salpietro, R.J. Reiter, Protective role of melatonin in neonatal diseases. Oxid Med Cell Longev 2013 (2013) 980374.

[191] L. Marseglia, G. D‟Angelo, S. Manti, S. Aversa, R.J. Reiter, P. Antonuccio, A. Centorrino, C. Romeo, P. Impellizzeri, E. Gitto, Oxidative stress-mediated damage in newborns with necrotizing enterocolitis: a possible role of melatonin, Am. J. Perinatol. 32 (2015) 905-909.

[192] C.P. Sodhi, M.D. Neal, R. Siggers, S. Sho, C. Ma, M.F. Branca, T. Prindle Jr, A.M. Russo, A. Afrazi, M. Good, R. Brower-Sinning, B. Firek, M.J. Morowitz, J.A. Ozolek, G.K. Gittes, T.R. Billiar, D.J. Hackam, Intestinal epithelial Toll-like receptor 4

regulates goblet cell development and is required for necrotizing enterocolitis in mice, Gastroenterology 143 (2012) 708-718.

[193] O.D. Saugstad, Mechanisms of tissue injury by oxygen radicals: implications for neonatal disease, Acta Paediatr. 85 (1996) 1–4

[194] P.P. Trivedi, G.B. Jena, K.B. Tikoo, V. Kumar, Melatonin modulated autophagy and Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis, Mol. Carcinog. 55 (2016) 255-267.

[195] A. Guven, G. Gundogdu, B. Uysal, H. Cermik, M. Kul, S. Demirbag, H. Ozturk, S. Oter, Hyperbaric oxygen therapy reduces the severity of necrotizing enterocolitis in a neonatal rat model, J. Pediatr. Surg. 44 (2009) 534-540.

[196] A. Guven, G. Gundogdu, S. Vurucu, B. Uysal, E. Oztas, H. Ozturk, A. Korkmaz, Medical ozone therapy reduces oxidative stress and intestinal damage in an experimental model of necrotizing enterocolitis in neonatal rats, J. Pediatr. Surg. 44 (2009) 1730-1735.

[197] R. Ozdemir, S. Yurttutan, F.N. Sarı, B. Uysal, H.G. Unverdi, F.E. Canpolat, O. Erdeve, U. Dilmen, Antioxidant effects of N-acetylcysteine in a neonatal rat model of necrotizing enterocolitis, J. Pediatr. Surg. 47 (2012) 1652-1657.

[198] M. Kul, S. Vurucu, E. Demirkaya, T. Tunc, S. Aydinoz, C. Meral, V. Kesik, F. Alpay, Enteral glutamine and/or arginine supplementation have favorable effects on oxidative stress parameters in neonatal rat intestine, J. Pediatr. Gastroenterol. Nutr. 49 (2009) 85-89.

[199] H. Jaeschke, Preservation injury: mechanisms, prevention and consequences, J. Hepatol 25 (1996) 774–780.

[200] A. Guven, B. Uysal, G. Gundogdu, E. Oztas, H. Ozturk, A. Korkmaz, Melatonin ameliorates necrotizing enterocolitis in a neonatal rat model, J. Pediatr. Surg. 46 (2011) 2101-2107.

[201] F. Cekmez, M. Cetinkaya, C. Tayman, F.E. Canpolat, I.M. Kafa, S. Uysal, T. Tunc, SÜ Sarıcı, Evaluation of melatonin and prostaglandin E1 combination on necrotizing enterocolitis model in neonatal rats, Regul. Pept. 184 (2013) 121-125.

[202] N.M. Davies, J. Longstreth, F. Jamali, Misoprostol therapeutics revisited, Pharmacotherapy 21 (2001) 60–73.

[203] B. Säfsten, M. Sjöblom, G. Flemström, Serotonin increases protective duodenal bicarbonate secretion via enteric ganglia and a 5-HT4-dependent pathway, Scand. J. Gastroenterol. 41 (2006) 1279-1289.

Figure 1: Kynurine and melatonin pathways. It is suggested that sleep disorders generated in patients affected of irritable bowel syndrome are a result of an increase in the activity of the kynurenine pathway with a reduction in the serotonin/melatonin pathway.

Figure 2: Sleep disruption increases ulcerative colitis and Crohn‟s disease disturbs. However, these alterations may also induce sleep disruption, generating a loop not well understood yet.

Studies	Model	Melatonin dose	Comments
Cuzzocrea et al., 2001 [147]	Dinitrobenzene sulfonic acid (DNBS)–induced colitis in rats	15 mg/kg i.p.	MEL ameliorated the disruption of the colonic architecture, reduced MPO activity, MDA levels, appearance of nitrotyrosine, PARS immunoreactivity, ICAM-1 expression, and the expression of P-selectin. Staining degree of COX-2 and iNOS were also reduced.
Dong et al., 2003 [148]	Acetic-acid (AA) or trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats	2.5, 5.0, 10.0mg/kg i.c.	MEL, in a dose-dependent manner, inhibit iNOS and COX-2 expression, decreased NO· and PGE_2 levels,
Li et al., 200 [149]	TNBS-induced colitis in rats	2.5, 5.0, 10.0mg/kg i.c.	MEL treatment, in a dose-dependent manner, reduced macro/microscopic lesions, TNF-α, and ICAM-1 protein expression, and NF-κB activation. MEL 10 mg/kg obtained similar results to 5-aminosalicylic acid (5-ASA) group.
Mei et al., 2005 [150]	TNBS-induced colitis in rats	2.5, 5.0, 10.0mg/kg i.c.	MEL, in a dose-dependent manner, attenuates macro/microscopic lesions, reduced MPO activity, MDA, and NO· levels.
Marquez et al.,2006 [151]	TNBS-induced colitis in rats	0,5 mg/kg, 1 mg/kg and 2 mg/kg i.p.	MEL, in a dose-dependent manner, attenuates macroscopic lesions, body weight loss, and fibrosis markers expression. TNF-α level and MPO activity were also reduced due to MEL effect. Detrimental effects were observed in long-term treated animals (21 days).
Mazzon et al., 2006 [152]	DNBS–induced colitis in rats	15 mg/kg i.p.	MEL attenuates macro/microscopic lesions, reduced the degree of the expression of JNK, attenuates TNF-α and IL-1β levels, and NF-κB, Bcl-2 and Bax expression.
Nosál'ová et al., 2007 [153]	AA-induced colitis in rats	5 mg/kg and 10 mg/kg i.p.or i.c.	In a dose-dependent manner, MEL reduced macroscopic lesions, increased GSH levels, and decreased MPO activity.
Esposito et al., 2008 [154]	DNBS–induced colitis in rats	15 mg/kg i.p.	MEL treatment reduced macro/microscopic lesions, MDA levels and TNF-α level. MEL also reduced MMP-2 and MMP-9 activities after DNBS-induced colitis.
Akcan et al., 2008 [155]	TNBS-induced colitis in rats	10 mg/kg i.p.	MEL treatment reduced macro/microscopic lesions, TNF-α level, MPO and caspase-3 activities, and bacterial translocation.
Tahan et al., 2010 [156]	AA-induced colitis in rats	100 mg/kg i.p.	AA produced macro/microscopic lesions, increased MPO activity, and increased MDA, IL-1β, IL-6, and TNF-α levels. MEL attenuates significant statistical all these disturbs. GSH and SOD activity were also increased.
Sayyed et al., 2013 [157]	AA-induced colitis in rats	10 mg/kg i.p. Groups: Pre-treatment during 15 days, treatment after 15 days, treatment after 4 weeks	MEL treatment reduced macro/microscopic lesions, and maintain body and colon weight. MEL also attenuates the positive staining of NF-κb, the increased PTX-3 and lipid peroxides serum levels, and the decreased thiols levels. These changes are present due to AA effect. MEL short treatment was the most effective group.
Trivedi and Jenna, 2013 [158]	Dextran sulfate sodium (DSS)-induced colitis in rats	2 mg/kg, 4 mg/kg, 8 mg/kg orally	MEL, in a dose-dependent manner, decreased UC activity, increased colon length, decreased MPO activity, NF-Kb, COX-2 and STAT3 levels, increased IL.6, IL-17 and TNF-α levels, reduced oxidative stress cytokine levels and DNA damage, and attenuates fibrosis.
Chung et al., 2014 [142]	DSS-induced colitis with sleep deprivation in rats	10 mg/kg i.p.	MEL not recovered weight loss, but prevented weight loss and gene modification due to DSS-induced colitis + sleep deprivation.
Esiringü et al., 2015 [159]	AA-induced colitis in rats	Intracolonic melatonin gel	MEL attenuates NO· levels and histological lesions, but any effects were showed in MDA and GSH levels.
Trivedi et al., 2015 [160]	DSS-induced colitis associated colon carcinogenesis	1 mg/kg i.p.	MEL reduced UC activity, tumor multiplicity, and progression of colon carcinogenesis, caused a significant decrease in NF-κB, COX-2, and STAT3 levels, attenuates oxidative stress, autophagy and DNA damage, and caused a significant increase in Nrf2, NQO-1, and HO-1 levels.
Shang et al., 2016 [130]	DNBS–induced colitis in rats	2.5 mg/kg i.p.	MEL ameliorated the histopathological disturbs caused by DNBS, reduced MDA SOD, and MPO levels. Nrf2 and HO-1 reduced expression due to DNBS was modified in MEL rats with an upregulation of its levels.
Tasdemir et al., 2011 [161]	DNBS–induced colitis in rats	MEL 5mg/kg i.p. + erythropoietin (EPO) (1000 IU/kg s.c.)	MEL groups obtained better results than EPO groups reducing histological injury, CD4 and CD8 expression. However, MEL + EPO groups showed better results than these antioxidants alone.
Mann, 2003 [162]	Human model	3 mg orally	UC activity was reduced during MEL treatment
Maldonado and Calvo, 2008 [163]	Human model	3 mg orally	MEL triggers UC symptoms. After 24-48h of the stop of melatonin consumption, UC activity ceased.
Chojnacki et al., 2011 [132]	Human model	5 mg orally	MEL reduced UC activity, c-reactive protein levels, and attenuates the decreased hemoglobin concentration in blood observed in non-melatonin treatment group.

Table 1: Studies related to melatonin‟s benefits in ulcerative colitis (UC). MEL, Melatonin, MPO; myeloperoxidase, MDA; malondialdehyde, iNOS; inducible nitric oxide synthase, NO·; nitric oxide, PGE_2; prostaglandin, E2; GSH, glutathione, MMP, matrix metallopeptidase; SOD, superoxide dismutase; PTX-3: pentraxin-3.

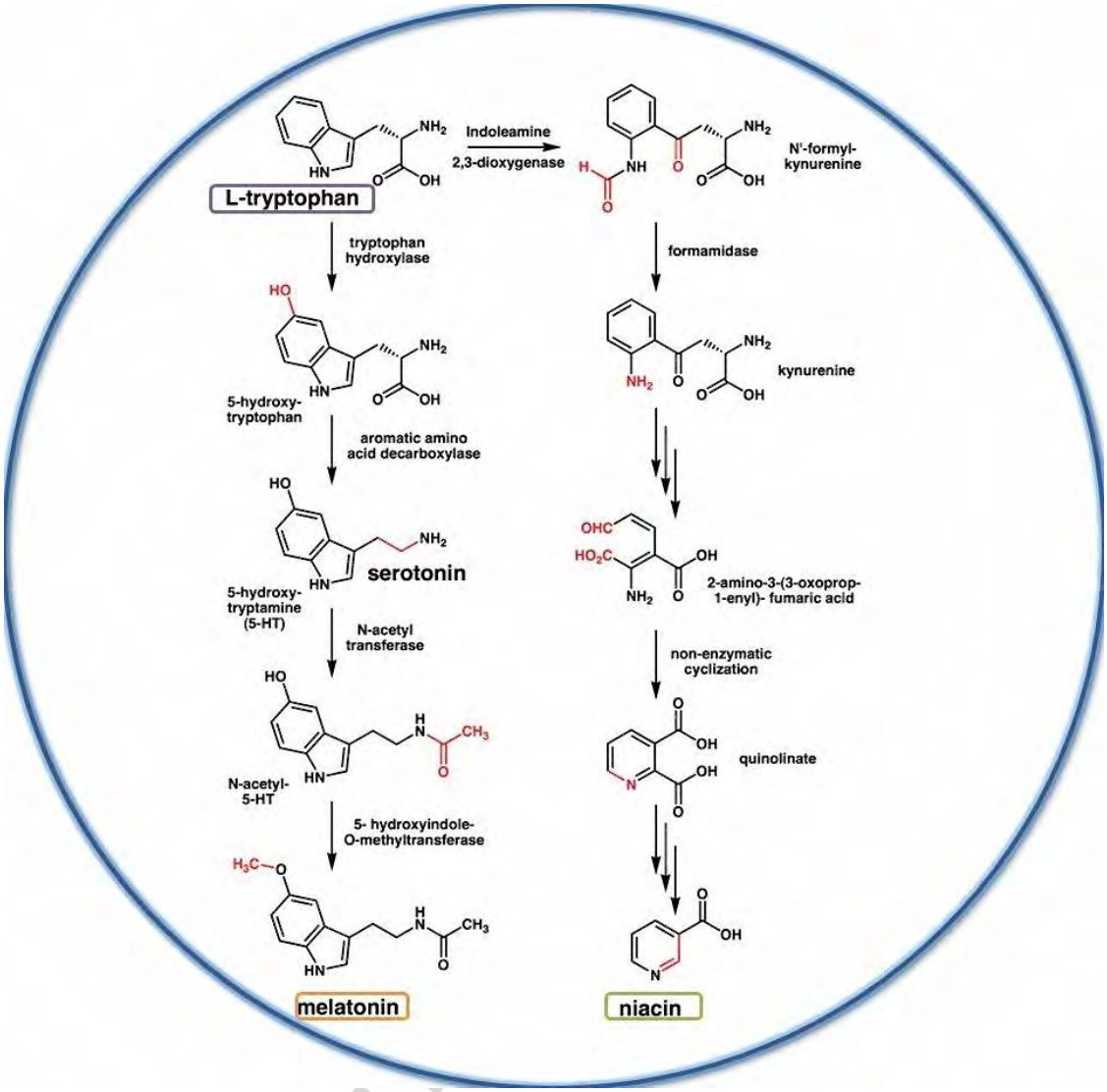


Figure 1

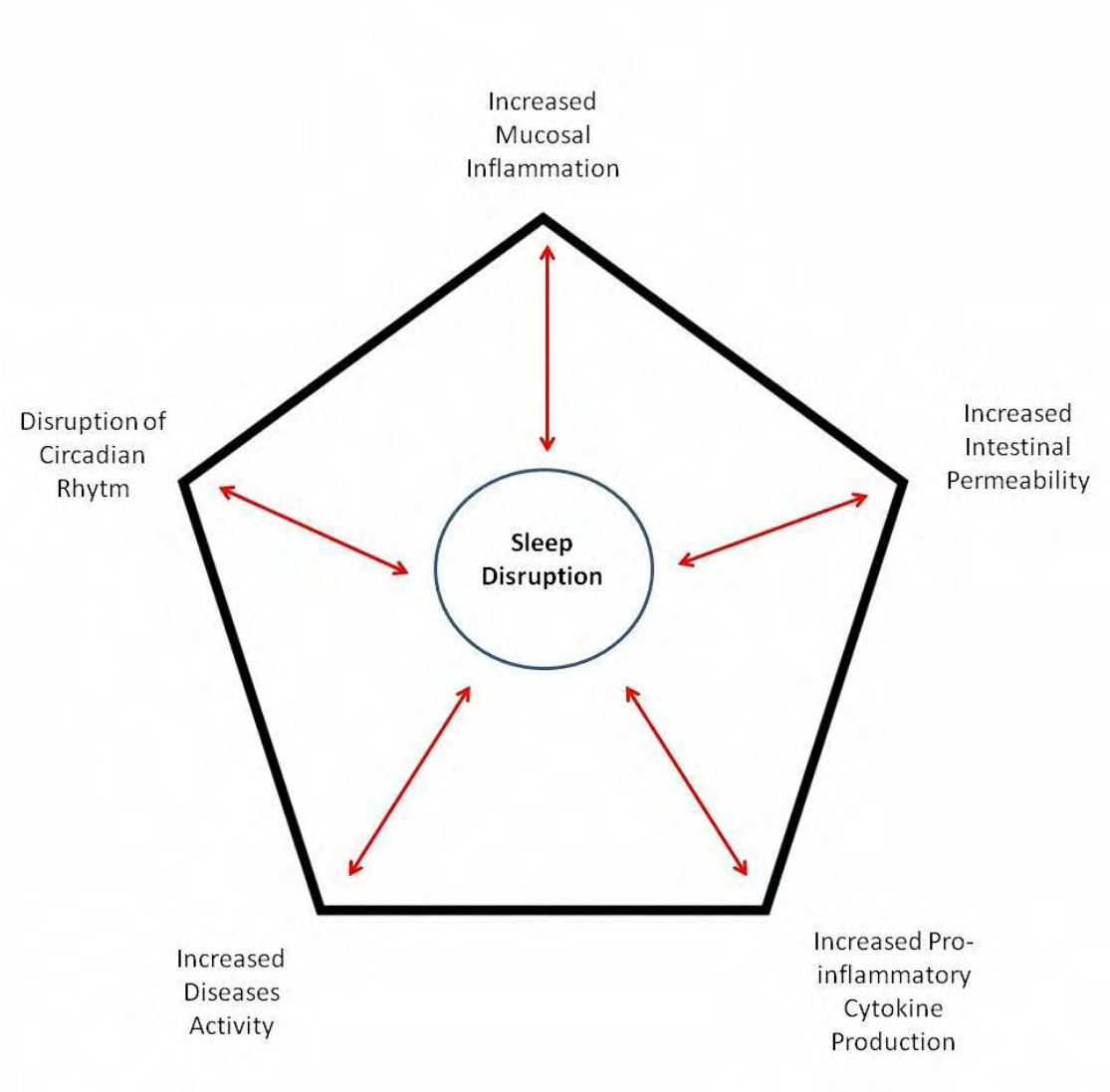
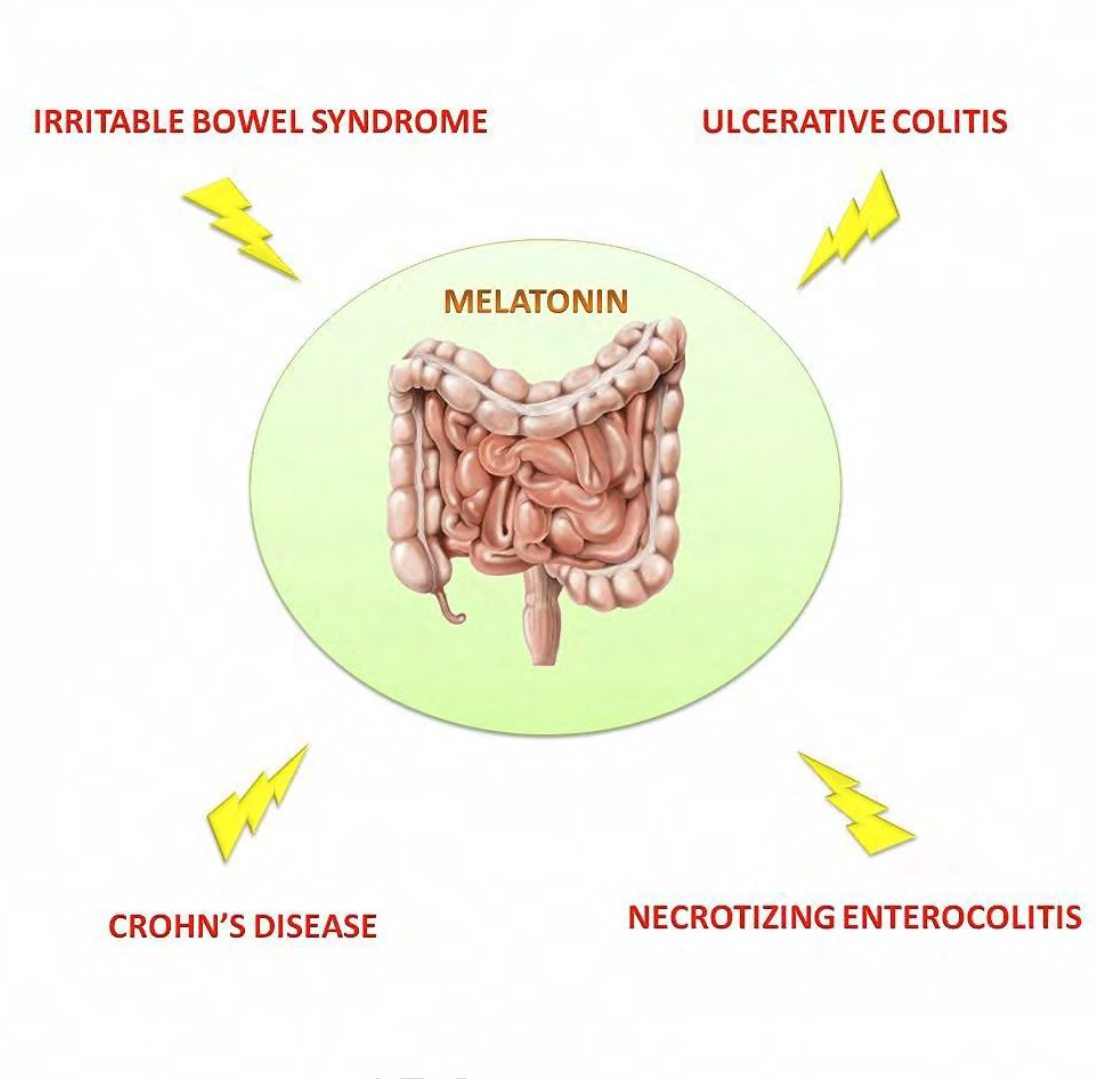


Figure 2



Graphical abstract