Review

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The melatonin contained in beer can provide health benefits, due to its antioxidant, anti-inflammatory and immunomodulatory properties

MDolores Maldonado,[a*] Jerusa Romero-Aibar[b] and JRamón Calvo[a]

Abstract

Beer is a fermented beverage with a low alcohol content originating from cereal fermentation (barley or wheat). It forms part of the diet for many people. It contains melatonin (*N*-acetyl-5-methoxytryptamine). Melatonin is a molecule with a wide range of antioxidant, oncostatic, immunomodulatory, and cytoprotective properties. The aim of this work was to review the data supporting the idea that a moderate consumption of beer, because of its melatonin content, is particularly useful in healthy diets and in other physiological situations (such as pregnancy, menopause, and old age). Data source: a) The MEDLINE /PubMed search was conducted from 1975 to April 2022, and b) Our own experience and published studies on melatonin, the immune system, and beer. We provide a review of research on the mechanisms of melatonin generation in beer, its concentrations, and its possible effects on health. The melatonin contained in beer, as part of a healthy diet and in some special physiological situations, could act as a protective factor and improve the quality of life of those who drink it in moderation.

Keywords: beer; melatonin; Mediterranean diet; antioxidant; immunomodulation

INTRODUCTION

Beer is a fermented beverage with a low alcohol content. It is part of the Mediterranean diet,[1,2] although other non-Mediterranean countries such as Germany, the UK, or the Czech Republic have a large brewing culture and they are among the countries with the highest consumption of beer.[3] Beer contains a small amount of alcohol and is widely accepted throughout the world for its use when socializing.[4] Its consumption must therefore be carried out responsibly and in moderation. Beer has several components such as cereals (barley or wheat), hops, water, yeast, and other ingredients that appear at the time of its preparation (malting, mashing, and boiling, fermentation, and maturation) such as, for example, polyphenols, sugar, alcohol, or melatonin. The beer's melatonin comes from the cereals used in its elaboration, and from the yeast, *Saccharomyces cerevisiae*, specifically from the second fermentation[5,6] (Fig. 1).

The melatonin content in beer is variable and depends on the fermentation conditions, the quality of the cereals used, the alcohol strength of the beer, and the processing system used.[7] For example, craft beers have higher levels of melatonin (333 ± 7 pg / mL) than commercial ones (113 ± 4,13 pg / mL) at equal alcohol levels.[5] There are also differences between different types of commercial beer depending on the alcohol content – that is, total melatonin, from 58 ± 1,44 pg / mL for dealcoholized beers to 169 ± 2,4 pg / mL for beers with higher measured alcohol values.[5]

Melatonin, a molecule derived from tryptophan metabolism, is a multifaceted free radical scavenger, antioxidant, and anti-inflammatory substance.[8,9] It is found throughout evolution from vertebrates to plants.[10-12] In mammals, melatonin is produced by the pineal gland and by a variety of extrapineal tissues; pineal melatonin is secreted into the blood in a circadian manner and with systemic effects,[13] whereas in extrapineal tissues it is produced continuously, with local effects such as those that occur in bone, fatty tissue, brain, and the immune system, among others.[14,15] Extrapineal melatonin plays a pivotal role as an intra, auto and paracrine signal molecule in those tissues where it is synthesized and released.[16] Melatonin is a molecule that is soluble in alcohol and water, with amphiphilicity properties that allow it to

* Correspondence to: MDolores Maldonado, Department Medical Biochemistry, Molecular Biology, and Immunology, University of Seville Medical School, Avda. Sánchez Pizjuán 4, 41009. Seville, Spain, E-mail: aibar@us.es (Maldonado)

a Department of Medical Biochemistry, Molecular Biology, and Immunology, University of Seville Medical School, Sevilla, Spain

b Superior Laboratory Technician, National Institute of Toxicology and Forensic Sciences of Tenerife, Madrid, Spain

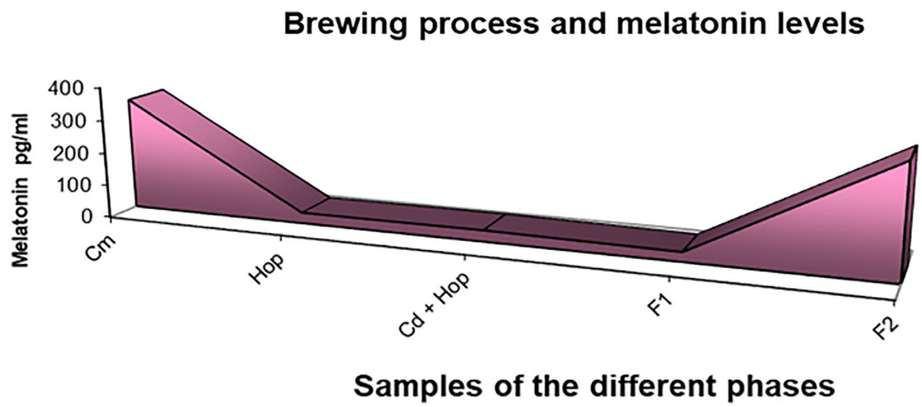

Figure 1. Melatonin generation during the brewing process. Cm: cereal concentrate must; Hop: Hop infusion; Cd: cereal diluted must; F1: first fermentation; F2: second fermentation.

cross the plasma membrane freely, and so it can rapidly accumulate within cells and react with the cytosolic target.[5]

Numerous pathologies are generated by risk factors such as sedentary lifestyle, stress, tobacco, obesity, or a diet rich in fats. All these factors can be modified and improved with healthy behavioral habits such as a suitable diet, physical exercise, or by ceasing smoking.[17] An adequate diet to cover the body's energy demands includes the consumption of proteins preferably from fish, fibers of fruit and vegetables, natural largely unrefined sugars, and low fat foods.[18] Melatonin is a normal food component found in yeast and plant material, including edible plant products and medical herbs,[7,12] which can influence the level of melatonin in the circulation and promote healthy benefits by virtue of its cytoprotective,[14] anti-inflammatory,[19] antioxidant[9,20] or anti-apoptotic properties.[14] The effects of melatonin are dose dependent and are related to the time and manner of administration. It can work at physiological and pharmacological doses but pharmacological doses are usually more effective than physiological ones.[19,21]

This review summarizes current evidence regarding the issue of whether the moderate consumption of beer, as part of the Mediterranean diet, could have beneficial health effects due to the various chemicals in the plants that constitute its ingredients, melatonin being one such substance with high antioxidant power.

The report focuses on the actions of melatonin in the brain, tumor tissues, adipose tissues, bone marrow, and bone structures, which have implications for humans. It is hoped that this review will trigger studies on the function of beer in reducing oxidative stress and providing general antioxidative protection. The paper also asks several relevant questions and suggests that moderate consumption of beer could have a therapeutic potential, protecting the body's structures and systems.

NATURAL SOURCES OF MELATONIN AND HEALTH BENEFITS

Common foods and beverages such as olive oil, coffee, wine, and even beer are rich sources of melatonin.[1,7,22-26] It is also found in many common fruits and vegetables, including tomatoes, grape skins, tart cherries, walnuts, and other fermented food products, with concentrations markedly higher than those found in vertebrate tissues.[27-29] Most foods and drinks consumed by humans contain melatonin, and their intake probably increases circulating melatonin levels and the total antioxidant status of human serum. This molecule is absorbed in the gastrointestinal tract and it easily crosses all morphophysiological barriers and tissue and cell membranes.[30,31] Increasing circulating levels of melatonin through dietary supplements thus intensifies its health benefits and generates no undesirable effects.[32]

Plants do not have a specific immune system. However, they have developed a sophisticated innate or natural immune system that allows them to avoid infections and defend themselves from external challenges such as excessive sun or water or lack thereof.[33] Melatonin has been found in plants as one of the defense hormones, regulating the activation of the immune response, controlling apoptosis and oxidative stress. All this protects the plant cell by modifying its architecture. Furthermore, melatonin plays a key role in circadian rhythms and in seasonal photoperiodic regulation in both animal and plant systems.[34,35] Almost all stages of plant development are controlled by the circadian clock – for example, germination, growth, and the onset of flowering. Other processes, such as stomatal opening, hormone regulation, signaling, and responses to biotic and abiotic attacks, are also modulated by the circadian clock.[36] Melatonin synthesis is inducible in plants when they are exposed to abiotic stresses (extremes of temperature, toxins, increased soil salinity, drought, etc.) as well as to biotic stresses (fungal or parasite infections), which explains why plants contain melatonin.[37,38]

The health effects of diets rich in melatonin-containing foods should be considered[39,40]. For example, drinking a beer or a coffee would allow us to increase circulating levels of melatonin from the outside; without forgetting that as we age, melatonin levels decrease, and the number of pathologies increases. Coinciding with our findings, other authors, such as Arnao *et al*. 2009,[41] found relatively high levels of melatonin in barley, which is an important cereal used in brewing. The sources of melatonin in beer are cereals (barley, wheat, rye, etc.) and as a result of the action of yeast in the second fermentation,[1] as we can see in Fig. 1.

THE ANTIOXIDANT POWER OF BEER

Melatonin is a powerful antioxidant, alongside classic antioxidants such as vitamins C and E. The compound is produced endogenously (especially at night by the pineal gland) and acquired exogenously (in the diet).[42] Melatonin synthesis begins from the amino acid tryptophan, both in plants and in mammals, although in plants the pathway for melatonin synthesis differs slightly from that of mammals, affecting the mode of action of melatonin in plants.[43] In this biosynthetic procedure, four enzymatic steps are produced: hydroxylation, decarboxylation, acetylation, and methylation. Thus, as indicated in Fig. 2, we arrive at the chemical structure of *N*-acetyl-5-methoxytryptamine (melatonin), a structure that, together with that of its metabolites such as 3-OHMT (3-hydroxymelatonin), 6-OHMT (6-hydroxymelatonin), AMK (N1-acetyl-5-metoxyknuramine), and AFMK (N1-acetyl-N2-formyl-5-metoksknuramine), neutralizes the free radicals generated, scavenging reactive oxygen species/reactive nitrogen species (ROS and RNS) and stimulating the activity of several antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase CAT).[44]

Oxidative stress is a situation produced by an imbalance between pro-oxidant and neutralizing molecules in the human body. The immune system cells are among the largest producers of free radicals, ROS, or RNS, caused by their normal defensive physiology. Radicals and their intermediates are all differentially reactive and often toxic; ROS and RNS are free radicals that come from the metabolism of oxygen and nitrogen, respectively. Phagocytes play a critical role in warding off bacterial infections by engulfing these agents and destroying them through mechanisms where respiratory stress is activated by the enzyme NADPH oxidase, and these free radicals are generated.[45,46] This process is part of what is known as an inflammatory reaction and, in extreme cases, it leads to extensive tissue injury mediated by the generated reactive species. Immune cells, which generate these oxidizing agents, include a variety of phagocytes and leukocytes, such as neutrophils, eosinophils, basophils, monocytes, and macrophages. Phagocytes are normally activated by pro-inflammatory mediators of bacterial products that have receptors on the plasma membrane of leukocytes.[47] The respiratory stress generated in these inflammatory cells produces an excess of free radicals – so many that they can become the source of numerous pathologies. However, if a balance is maintained between the oxidative defense elements (ROS and RNS) and the antioxidants, they will not cause any pathology and the subject will regain homeostasis, a phenomenon called the cellular redox balance.[48]

Several studies have shown associations between the consumption of melatonin-rich foods and beverages and the prevention of several disorders associated with oxidative stress.[7,49,50,51] The mechanisms by which melatonin and its metabolites would improve oxidative stress are (a) directly scavenging free radicals, ROS and RNS – agents that promote inflammation aging and can cause conditions including cancer, cardiovascular, and neurological problems; (b) the generation of antioxidant enzymes such as SOD, CAT, GPx and GR; (c) indirectly by inhibiting pro-oxidant enzymes such as nitric oxide synthase (NOS), inducible nitric oxide synthase (iNOS) and lipoxygenase (LOX); (d) maintenance of mitochondrial homeostasis; (e) transition metal ion chelation (e.g., Fe2+, Cu+). These antioxidant functions of melatonin do not need specific membrane receptors (MT1, MT2, and MT3) to be produced and, although these mechanisms are not mutually exclusive, they are considered receptor-independent functions of melatonin, which are acquired primarily on the evolutionary ladder, long before the melatonin-dependent receptor mechanism.[49]

Under normal conditions, a healthy immunocompetent subject has mean melatonin levels in the blood of 5 pg /mL during the day and 75 pg/mL at night. The synthesis and release of melatonin are modified by epigenetic factors such as age, gonadal hormones, type of diet, exposure to light, chronic diseases, taking medications, etc. These factors can potentially act as enhancers or inhibitors of melatonin secretion.[52,53] We cannot modify factors such as genetics, age, or sex, but we can change our dietary habits. Diet is one of the epigenetic factors most closely linked

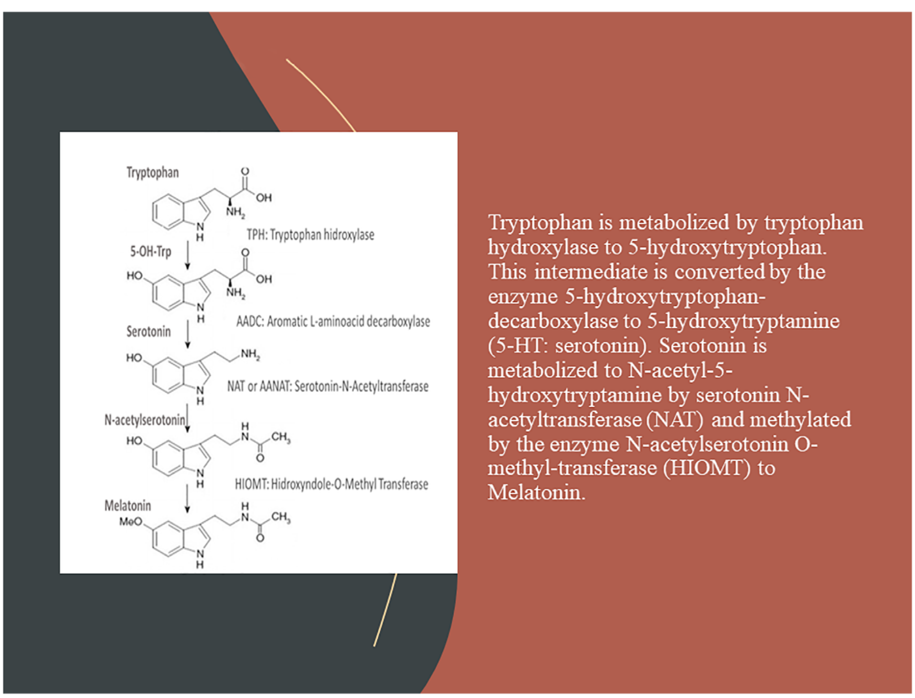

Figure 2. Tryptophan is metabolized by tryptophan hydroxylase to 5-hydroxytryptophan. This intermediate is converted by the enzyme 5-hydroxytryptophan-decarboxylase to 5-hydroxytryptamine (5- HT: serotonin). Serotonin is metabolized to *N*-acetyl-5-hydroxytryptamine by serotonin *N*-acetyltransferase (NAT) and methylated by the enzyme *N*-acetylserotonin *O*-methyl-transferase (HIOMT) to melatonin.

to diseases of metabolic, inflammatory, autoimmune, or infectious nature. With a diet rich in antioxidants, we could therefore modulate the expression or repression of genes that condition the immune response to infections, toxic substances, or traumas, and prevent them.[54]

In addition to melatonin, beer has other compounds that effectively reduce biomolecular destruction caused by oxygen metabolites, such as ascorbic acid, α-tocopherol, polyphenols, citric acid, silicic acid, and glutathione, among others. Those foods and drinks that, like beer, contain melatonin or substances that facilitate its synthesis, such as cofactors (vitamins, minerals, tryptophan, etc.), can modulate melatonin levels by increasing them.[1]

EFFECTS OF BEER ON THE IMMUNE SYSTEM

In the past, the purpose of fermenting foods was to preserve and enhance their flavor, giving them stability and avoiding microbe contamination. The antiseptic properties of beer make it a drink with a long half-life because in its production process it undergoes cooking, a heat treatment that destroys any microorganisms present. The presence of hop tannins, alcohol, and the acidity generated by carbon dioxide reduces the risk of subsequent bacterial contamination.[55,56] In this sense, it is a drink that can be taken safely, without the ability to generate diseases due to food poisoning. But beer also contains melatonin,[1] an immunomodulating molecule capable of counterbalancing the immune system, activating, and breaking its cells or molecules according to the needs of each moment.[57]

Inflammation is one of the most important defense mechanisms that the immune system has to protect us from external and even internal injuries. Infections, wounds, burns, foreign bodies, and chemical products, among others, can initiate and maintain a chronic inflammatory process.[47,58] The immune system facing a defensive action as important as inflammation ensures that this occurs by setting up redundant and synergistic strategies in which it involves numerous cells and mediators to achieve the desired goal. The inflammatory response must be maintained for a limited period – just enough to resolve the infectious process, recover, and return to homeostasis.[47] Chronic inflammation maintained over time underlies numerous pathologies, such as cardiovascular or degenerative diseases. It is therefore important to control inflammation so that it does not become chronic.

Melatonin is synthesized centrally by the pineal gland located in the diencephalon, belonging to the central nervous system (SNC), and released into the bloodstream to perform its functions at the systemic or endocrine level.[59] Melatonin is also generated locally or extrapineally by numerous cells and tissues such as the retina,[60] the gut,[61] the reproductive system[62] and even the immune system, with intracrine, autocrine, and paracrine effects.[19] Both systems are related under the term 'immuno-pineal axis,' allowing the change in melatonin synthesis from pinealocytes to competent cells of the immune system.[59] Melatonin has an immunomodulatory effect on the immune system. In situations of infection or injury to the host (presence of PAMP and DAMP) where an immune defense mechanism is needed; therefore, mast cells and macrophages release melatonin as if it were a more pro-inflammatory cytokine. When defense is sufficient and the infectious process is controlled, melatonin acts on cells that have released it, slowing activation, through specific MT1 and MT2 dependent receptors and independent receptor mechanisms, recovering homeostasis.[19] Many neurodegenerative diseases have chronic subclinical inflammation maintained over time as an etiopathogenic basis.[63] Consumption of beer, moderately, as part of the diet, would provide a constant contribution of melatonin maintained over time that would mitigate chronic inflammation and play a fundamental role in the completion of the process.

At times, we experience sleep disturbances or absence of sleep due to multiple causes, including physical and psychological stress derived from work, travel across time meridians, shift work, old age, psychiatric disorders, and social responsibilities, among other causes. This sleep deprivation causes an increase in the inflammatory response in healthy people and aggravates underlying pathologies in sick people.[64,65] Studies have shown that insomnia activates the innate immune system and maintains chronic inflammation through an elevation of nuclear factor- kβ (NF-KB). Melatonin has been shown to inhibit NF-KB and lead immune system cells to a resting state.[19,59] Beer containing melatonin is a good sleep inducer; this makes it useful not only to improve the quality of rest but also to mitigate the underlying inflammation generated by the absence of sleep.[64]

Furthermore, numerous authors are commenting on the important role that diet plays in protecting us from viral infections, including coronavirus disease 2019 (COVID-19). In particular, vitamin D, melatonin, probiotics, lactoferrin, and zinc are essential for the proper functioning of the immune system.[66] Melatonin has been shown, at pharmacological doses, to reduce viral entry into cells, and to reduce the replication, and transmission of coronaviruses.[67] Melatonin is being used as an adjunctive treatment in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, improving host defenses, controlling the cytokine storm, mitigating the clinical course in infected patients, and contributing to the prevention of immune-mediated organ damage.[68,69]

MECHANISMS OF CANCER AMELIORATION BY BEER

The work of yeasts in the beer fermentation process generates inducible or new production compounds derived from the metabolism of tryptophan, melatonin, and serotonin.[56] Beer contains bioactive components with chemoprotective properties that can protect against DNA damage, cellular apoptosis, and cancer.[70] Among the chemoprotective elements of beer, we highlight polyphenols (xanthohumol, catechol, pirogalol, or kanpherol among others),[71] melatonin,[14] or silicon.[2]

Many lifestyle-related factors have been associated with cancers of the digestive system and beyond. In fact, the links between diet, weight, and exercise with the risk of colorectal cancer are some of the closest of all cancers. Thus, for example, being overweight or obese increases the risk of colon and rectal cancer in both men and women, although this association appears to be greater among men. Routinely having a physically active life in moderate to intense forms reduces the risk of colon cancer. A diet with high doses of refined sugars, processed red meat, high levels of alcohol consumption, and low levels of vitamin D can increase the risk of colon-rectal cancer and other cancers such as ovarian, endometrial, or breast cancer.[72-74]

Melatonin has demonstrated its anti-cancer power *in vitro* and *in vivo* through numerous mechanisms of action and in different types of tumors, especially hormone-dependent tumors such as ovarian, prostate, bladder, prolactinoma, and breast cancer, among others.[72,75] Authors like Lozano-Lorca[76] have shown that patients with prostate cancer, with a mean age of 67 years, had lower melatonin levels, in their saliva, than healthy men used as controls, independent of urinary symptomatology or extension and aggressiveness of the tumor. If melatonin levels decrease with age and facilitate tumor appearance, exogenous administration of melatonin in the form of drugs (pharmacological doses) or a diet rich in melatonin (physiological doses) would allow us to combat the presence of these tumors.

Regarding colon cancer, the mechanism of action of melatonin is independent of membrane receptors for melatonin MT1 and MT2. Furthermore, the antioxidant and anti-inflammatory properties of melatonin in tumor cells appear to be involved in counteracting the oxidative state and reducing the production of nitric oxide.[77] In general, the mechanisms of action of melatonin and its effects vary from one context to another.[78] In the presence of cancer cells, therefore, melatonin will exert pro-oxidant and immunostimulant actions, activating caspases 3, 8 and 9; while in the environment of normal cells, indolamine is a powerful antioxidant.[79]

In addition, pretreatment with melatonin can increase the sensitivity of tumor cells to the action of chemotherapy and radiotherapy, prevent tumor metastases by limiting the entry of tumor cells into the vascular stream and their distribution in other organs and systems, block the growth of metastases in places far from the original tumor, and finally reduce the toxicity generated by drugs and therapies used in cancer treatment.[80,81] That is why, drinking a beer along with a proper diet could act as an adjuvant or pretreatment agent for cancer, while improving the wellbeing of the patient.

EFFECTS OF BEER ON BONE MASS

Bone tissue is a structure that is continuously remodeling, with a fine balance between bone formation by osteoblasts and its destruction by osteoclasts or bone macrophages. This balance is maintained and controlled due to the action of a series of hormones, including parathyroid hormone, calcitonin, estradiol, growth hormone, cytokines, and growth factors produced within the bone marrow.[82] Osteoporosis is a systemic disease that affects bone tissue, usually associated with age, and has a high prevalence in women with an increase in bone destruction on the synthesis of bone. This imbalance between bone formation and destruction may be favored by a reduction in the calcitonin hormone in elderly people. This means that people with the disease, especially premenopausal and postmenopausal women, have an increase in the frequency of fractures. Considering that the average life of the population is increasing, and osteoporosis is an age-related disease, there will always be more elderly people with fractures,[83] with the consequent costs that this has for families and health services. Further studies are therefore needed to indicate which preventive factors could mitigate this disease.

We highlight (a) nonmodifiable risk factors, which we cannot do anything to avoid, such as advanced age, previous fractures, female gender, and family history of hip fractures; (b) modifiable risk factors, which we can act to prevent, for example by avoiding smoking, avoiding being overweight, avoiding a sedentary lifestyle, an unhealthy diet, or sun exposure. We have analyzed how beer is a common component of the Mediterranean diet and has beneficial effects on bone health by its content of the melatonin, exerting a hormonal modulation on osteoblasts and osteoclasts, and other compounds that also exist in beer, such as, for example, phytoestrogens and silicon with the ability to improve bone mass.[1,83,84] Melatonin can act by entering our cells and exerting its actions in a receptor-dependent and receptor-independent manner. The specific mechanisms that melatonin exerts on bone are (a) through the differentiation of fat cells from the bone marrow to osteoblasts, and by stimulating these osteoblasts to promote bone growth and increasing the bone mass;[85] (b) by increasing the expression of osteoprotegerin by osteoblasts, thus avoiding the differentiation of osteoclasts; (c) by neutralizing free radicals generated by osteoclasts in bone resorption.[82,86]

As melatonin levels may be lower in some older individuals, such as premenopausal and postmenopausal women, current studies are investigating whether decreased melatonin levels contribute to the development of osteoporosis, and whether treatment with exogenous melatonin can help prevent this condition. The authors concluded that low melatonin levels affect bone metabolism, facilitating fractures and osteoporosis, especially in older women, and that exogenously administered melatonin could be an effective cotreatment in antiosteoporosis therapies.[86,87]

EFFECTS OF THE CONSUMPTION OF BEER ON NEUROPROTECTION

Beer contains melatonin and alcohol, although the percentage of alcohol is low, between 4.5% and 5% in the most commonly consumed beers in Spain.[5] Its moderate consumption provides beneficial antioxidant and neuroprotective effects that could be considered healthy as part of the diet.[88,89] As we age, circulating melatonin levels decline, probably due to the aging of the pineal gland itself. For this reason, more diseases appear, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease.[13,90]

The increase in life expectancy worldwide has generated an increase in the elderly population in whom a series of risk factors accumulate due to organ and system senescence,[91,92] among which we highlight oxidative stress, trauma, infections recurrent, and metabolic alterations.[93] These conditions generate an increase in low-grade chronic inflammation, with activation of the innate immune system and an increase in the release of inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and IL-12. Chronic inflammation is established in our central nervous system (CNS), fed by activated mast cells and microglial cells, two resident cells of the brain with both neuroinflammatory and neuroprotective properties,[63,94,95] which, when altered, cause a series of neuronal injuries and deaths that facilitate the accumulation of proteins such as amyloid, tau aggregates, and α-synuclein.[96,97] This poses a problem for public health and generates a challenge for medical science. Prevention measures are necessary to improve the quality of life of the elderly and to minimize the effects of neuroinflammation. These measures could include a Mediterranean diet, in which beer is consumed.[98,99]

As we have shown in previous work and in those of other colleagues, beer contains melatonin, and its intake contributes to increasing levels of melatonin and antioxidant capacity in human serum.[1,2,5,20] Furthermore, melatonin, because it is an amphiphilic molecule, has the ability to cross the blood–brain barrier and from there it can: (a) Exert its stabilizing role on mast cells at the molecular level, slowing the mast cells by inhibiting the transcription factor NF-Kβ.[19] (b) Melatonin reduces levels of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6.[14,21] Therefore, it reduces the activation climate in microglia and facilitates their transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. The M2 phenotype (releasing anti-inflammatory cytokines IL-10, IL-4, IL-13 and TGF-β) promotes remodelling of the cellular matrix, repairing damage, and suppresses the immune response, preventing brain neuroinflammation and neurodegenerative diseases. (c) Melatonin and its metabolites protect against free radicals generated during activation of respiratory stress by reducing their concentration and protecting neurons.[100-102]

Authors such as Yilmaz *et al.*[103] explain how food and drink made with plants and processed through fermentation generate neuroactive compounds such as gamma-aminobutyric acid, serotonin, melatonin, kynurenic acid, and catecholamines, which have a beneficial effect on mental health and mood. This is because plants and microorganisms share some enzymatic routes used by humans in the synthesis of neuroactive compounds, which is very useful in patients suffering from psychiatric diseases. Further to this beneficial effect, there is also the power of melatonin to induce sleep, which is essential for the proper evolution of treatment for mental illnesses.

In an *in vivo* model using male C57BL/6 mice, in which neuroinflammation was generated using the toxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Yildirim *et al.*[97] demonstrated that 20 milligrams of melatonin per kilogram of mouse weight, administered intraperitoneally decreased neuronal death by decreasing microglial inflammation, and prevented accumulation of the α-synuclein aggregation. On the other hand, Anstey[104] analyzed the results of several studies involving 10 000 people worldwide and found that mild to moderate drinkers were 28% less likely to develop Alzheimer's disease than non-drinkers. Considering the high efficacy of melatonin as a neuroprotective agent and its exceptionally high safety profile, its intake in situations such as neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, or Huntington's disease) would seem not only wise but essential.[105]

EFFECTS OF NONALCOHOLIC BEER ON PREGNANCY

Adherence to a Mediterranean diet, including the consumption of nonalcoholic beer in pregnant women, has been linked to numerous health benefits. This healthy diet pattern has been associated with lower obesity and cardiometabolic risk in adults but it is also important for child development.[106]

Having an adequate diet is important in general but it is more important for women who want to become pregnant or are already pregnant. In the case of women who wish to achieve a pregnancy and carry it to term, drinking a nonalcoholic beer a day can raise circulating melatonin levels, which is beneficial because (a) melatonin increases the maturation and conservation of the quality of oocytes, protects them from toxic species from oxygen metabolism, and improves *in vitro* fertilization and the subsequent evolution in embryo transfer procedures;[62,106-108] (b) women who are already pregnant must have a diet rich in vitamins and minerals. In this sense, nonalcoholic beer could be a hydration drink, providing a source of vitamins such as folic acid and vitamin B complex (riboflavin, pyridoxine, and niacin), minerals and antioxidants (melatonin, coenzyme Q10 and polyphenols), which are necessary for the optimal development of the fetal central nervous system.[2] Beer contains 90% water, which makes it very useful, due to its organoleptic properties, for hydration (Fig. 3). It also has soluble fiber, which facilitates intestinal transit, often altered by the mechanics of pregnancy itself.[55] Melatonin levels in the blood gradually increase during pregnancy and labor, in synergy with oxytocin for uterine contractility, and return to normal values postpartum. Melatonin from the mother, together with that generated by the placenta, establishes circadian rhythms in the fetus, protects syncytiotrophoblast cells from toxic substances, and improves the exchange of nutrients between the fetus and the mother. Melatonin also has a protective role during pregnancy due to its antioxidant and free radical scavenging activities, compensating for the oxidative challenge associated with the metabolic demands of pregnancy and delivery.[109]

Pregnancy is a great challenge for the mother's immune system, which must respond, in a balanced way, between fetal semiallogenic tolerance and the simultaneous maternal-fetal defense of external infections or toxins. This requires a tightly regulated balance between immune activation and tolerance.[47] A diet rich in melatonin, such as beer without alcohol, can help the woman's body to increase its antioxidant capacity and protect the immune modulation of the mother's defense system and that of the developing fetus.

On the other hand, it has been demonstrated in experimental work with nursing mothers that supplementation of the mother's diet with nonalcoholic beer increases the activity and antioxidant content of breast milk during the first month after delivery and contributes to improving damage caused by oxidative stress in the newborn.[110]

Recommendations on healthy beer intake by gender

Beer is one of the most widely consumed low-alcohol beverages in the world, with the Czech Republic being the country with the highest consumption of beer per capita, at 143.3 L per capita each year. Austria follows with 106 L, and Germany with 104.2 L.[2] There are other non-European countries that are significant consumers of beer – e.g., China is the world's largest consumer, although its per capita consumption is less than 30 L per year; the USA consumes 74.8 L, Brazil 60.4 L, and Russia 58.60 L.[2] The World Health Organization and the Ministry of Health, Consumption, and Social Welfare of the government of Spain recommended that daily alcohol levels of 10–15 g for women and 20–30 g for men should not be exceeded. They also report that consumption should not be daily, but rather days without alcohol should be interspersed and the intake should be together with food, because food slows the absorption of alcohol. Considering that the average degree of alcohol of the beers most commonly drunk in Spain is around a range of 4–5°,[1] and applying the formula in Fig. 4, a beer with 250 mL of volume, with an alcoholic graduation of 4,5 would have 9 g of alcohol. Therefore, in popular terms, the recommendation would be a beer can or 200 mL for women and two cans for men at most per day. Furthermore, it is important to take into consideration the fact that beer consumption adds calories. Considering a standard 2000 kcal diet for a healthy adult, drinking a 250–330 mL glass of beer would provide 7% of the daily energy needs of that adult; the calories provided come from the carbohydrate content (12 g per glass) in the beer from cereals, and alcohol from yeast fermentation. Excessive beer consumption can therefore generate surfeit energy that may lead to weight gain.[111] However, in situations in which people drink too much beer, melatonin in beer could counteract those negative or harmful effects of alcohol. The mechanisms of action by which melatonin could mitigate the detrimental effects of alcohol would be (a) cellular protection of hepatocytes, neurons,[2] mast cells, and other cells through attenuation of oxidative stress;[2,9,14]

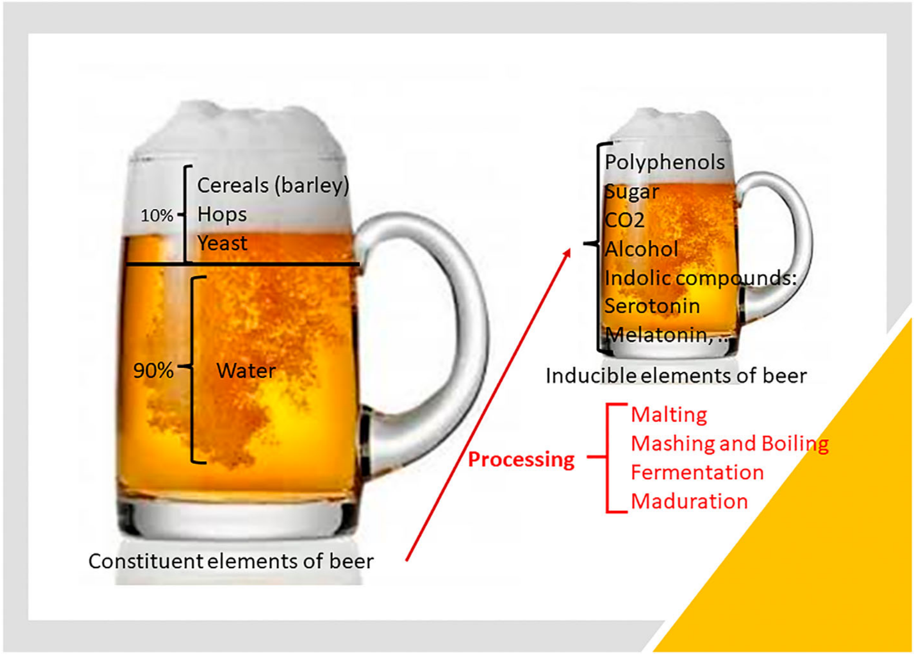

Figure 3. Constitutive and inducible elements of beer in its production process.

$$\text{grams of alcohol} = \frac{V_o\ cm^3 \text{ x alcoholic graduation x } 0{,}8}{100}$$

Figure 4. Mathematical formula to calculate the grams of alcohol in a beer: the amount of alcohol in grams is determined by the volume of the beverage and the percentage of alcohol present.

(b) diminution of the expression of activation and adhesion molecules, preventing leukocytes from sticking to the endothelium;[112] (c) curtailment of the inflammatory response and autophagy.[21,113]

Although the levels of melatonin found in beer and other food beverages may vary between tests, processing conditions, and the method of determination used, part of the melatonin found in beer comes from: (a) The plants used in its preparation such as cereals (barley, wheat, rice, etc.). Melatonin is present in more than 300 species of plants, which represent almost all families of angiosperms.[38] The quantity and quality of malted barley, the cereal most used in brewing, will define part of the melatonin concentration found in beer. Thus, after analyzing 18 different brands of beers consumed in Spain, we observed that all had melatonin and that the one with double malt was one of the most enriched with melatonin, also coinciding with a higher alcohol content.[1] (b) Beer yeasts used in the fermentation process. For this reason, the selection of the yeast strains to be used in beer fermentation is important because they affect the generation of melatonin and other indole compounds in different ways.[114] Although the melatonin levels found in beer are low, in a range of pg/mL to ng/mL, we highlight here that melatonin exerts its functions at physiological and pharmacological doses. This is because melatonin can exert its functions directly by crossing the lipid bilayer of cells and through the saturation of the MT1 and MT2 receptors, which implies that low doses of the melatonin can be sufficient, due to receptor affinities that are half saturated in the physiological range of circulating melatonin. Melatonin is therefore recommended in situations of high oxidative stress, such as infections, cancer, or neurodegenerative diseases.[1,115]

Melatonin plays an important role as prophylactic and as adjunctive therapy in the treatment of SARS-CoV-2 infections,[116,117] and in the treatment of other viral infections, such as those of the *Herpesviridae* family, which are associated with COVID-19.[118] In these cases, pharmacological doses of melatonin in the range of 100–400 mg/d would be needed.[119] However, those people with a Mediterranean diet who already consume physiological doses of melatonin with their diet regularly, would start with a background of this indole that would help the better evolution of the infection.

Drinking a lot of beers to reduce the risk of cancer or other diseases is not a course of action that we would recommend. Perhaps the secret is the adoption of a Mediterranean-style diet, in which an abundance of bioactive compounds provided by fruits, vegetables, beer, wine, and olive oil provides greater protection against ROS and RNS-induced diseases.

CONCLUDING REMARKS

Beer taken in moderation, as part of the diet, can be considered a useful vehicle to provide the body with antioxidant, defensive, and regulating properties of inflammatory homeostasis, thus avoiding some pathologies. There are numerous works that support the important role of nutritional therapy in providing these properties without undesirable effects. Beer contributes to cell protection and health-promoting effects not only because of its melatonin content but also because of the presence of other minerals and antioxidants consisting of polyphenols (xanthohumol), the vitamin B complex, citric acid, ascorbic acid, silicic acid, etc. We cannot recommend beer as a therapeutic agent in certain diseases, but moderate consumption of beer could be considered in the dietary habits of the population as a possible protective factor against various disorders such as osteoporosis, cardiovascular diseases, control of hypertension and constipation, among others.

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AUTHOR CONTRIBUTIONS

MDolores Maldonado conducted the literature review, interpreted the data, and was the major contributor to the manuscript. Jerusa Romero-Aibar participated in the literature review as a senior laboratory technician and helped in revising the manuscript. JRamón Calvo reviewed and validated the review.

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