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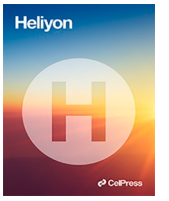

Review article

Effects of astaxanthin on depressive and sleep symptoms: A narrative mini-review

Yi-Fan Peng, Lin-Lin Wang, Juan-Hua Gu, Yue-Qin Zeng *

Academy of Biomedical Engineering, Kunming Medical University, Kunming, 650500, China

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ABSTRACT

Major depressive disorder (MDD) is a prevalent psychiatric condition that results in persistent feelings of sadness and loss of interest, imposing a significant economic burden on health systems and society. Impaired sleep is both a symptom and a risk factor for depression. Natural astaxanthin (AST), a carotenoid primarily derived from algae and aquatic animals, possesses multiple pharmacological properties such as anti-inflammatory, anti-apoptotic, and antioxidant stress effects. Prior research suggests that AST may have antidepressant properties. This mini-review highlights the potential mechanisms by which AST can prevent depression, providing novel insights into drug research for depression treatment. Specifically, this mechanism suggests that astaxanthin may improve sleep and thus potentially aid in the treatment of depression.

1. Introduction

Depression, or major depressive disorder (MDD), is a prevalent mood disorder that manifests as a reduction in an individual's capacity to experience pleasure. It has been identified as one of the leading causes of mortality and morbidity in modern times [1,2]. The World Health Organization's most recent estimates indicate that over 300 million individuals are affected by depression [3]. Depression has climbed from the 15th position to the 10th leading cause of all-cause disability-adjusted life years (DALYs) in China between 1990 and 2017 [4]. Depression's high prevalence imposes a significant social and economic burden around the world. Despite decades of research, the neurobiological underpinnings of depression remain unclear. However, oxidative stress has been identified as a crucial factor in the development of depression [5]. Oxidative stress occurs when peroxisomal oxidases produce elevated levels of reactive oxygen species (ROS) and superoxide anions ($O2^{\bullet-}$) within cells. This process leads to the inactivation of catalase and

Abbreviations: AST, astaxanthin; MDD, major depressive disorder; ROS, reactive oxygen species; TPH2, tryptophan hydroxylase-2; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH associated protein-1; NF-κB, nuclear factor-kappaB; GFAP, Glial fibrillary acidic protein; TrkB, tyrosine receptor kinase B; TrkB-T1, TrkB truncated receptor; NMDAR, glutamate N-methyl-D-aspartate receptor; NR2B, N-methyl-D-aspartate receptor 2B; PI3K, phosphoinositide 3-kinase; Akt: protein kinase B, CREB; cAMP-response element binding protein, mTOR; mammalian target of rapamycin, COX-2; cyclooxygenase-2, BDNF; brain-derived neurotrophic factor, ipRGCs; intrinsically photosensitive retinal ganglion cells, SCN; suprachiasmatic nucleus, NR2C; N-methyl-D-aspartate receptor 2C, GABA; γ-aminobutyric acid, TTFL; transcriptional-translational feedback loops, BMAL1; brain and muscle ARNT-like 1, CLOCK; circadian locomotor output cycles kaput, PER1-3; Period1-3, CYR1/2; cryptochrome1/2, eEF2; elongation factor-2, AMPAR; α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid receptor, $p75^{NTR}$: p75 neurotrophin receptor; 5-HT, 5-hydroxytryptamine; Cx43, connexin 43; REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep; ERK, extracellular regulated protein kinases; SUD, substance use disorder.

* Corresponding author. Academy of Biomedical Engineering, Kunming Medical University, Kunming, China.
E-mail address: z_yueqin@hotmail.com (Y.-Q. Zeng).

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subsequent increases in levels of hydrogen peroxide (H_2O_2) [6]. Elevated levels of H_2O_2 can induce further oxidation of tryptophan hydroxylase-2 (TPH2), leading to dysfunction of the 5-hydroxytryptamine (5-HT) system and ultimately resulting in depression-like behaviors [6]. Brain-derived neurotrophic factor (BDNF) is a risk factor that can contribute to the development of major depressive disorder. Individuals who are prone to depression may have low levels of BDNF, which can interfere with the interaction between Keap1 and Nrf2 proteins and trigger the activation of antioxidant enzymes. This can eventually lead to chronic oxidative stress [7]. In postmortem brain samples taken from patients with MDD, there is a notable decrease in the expression of both Bdnf mRNA and proteins. This reduction is particularly pronounced in the hippocampus and amygdala regions of the brain [8]. When there is excessive generation of reactive oxygen species (ROS) and antioxidant-related enzymes become exhausted, it can activate pro-inflammatory signaling pathways [5]. The occurrence and progression of depression are associated with neuroinflammatory signaling pathways, which include pro-inflammatory cytokines (such as IL-1β, IL-6, and TNF-α) and activated NF-κB [9]. As the inflammation progresses, essential macromolecules are damaged and induce apoptosis [5]. This is the reason why a significant increase in apoptosis was found in postmortem brain samples of depressed patients [10].

Today, an increasing number of patients are seeking alternative therapies - including herbal medicines - to manage chronic conditions. In the United States, the use and expenditure on alternative medicine increased by 45.2% between 1990 and 1997 [11]. Clinical studies have found that St. John's wort and curcumin exhibit good efficacy as antidepressants [12,13]. Astaxanthin ($C_{40}H_{52}O_4$, AST) is a red-orange fat-soluble carotenoid found in the marine world of algae and aquatic animals [14]. *Trans*-isomeric forms are typically the natural presentation of it in nature (Fig. 1) [15]. AST has been approved as a dietary supplement (nutraceutical) since 1999 [16]. Astaxanthin also plays a role in promoting skin health, particularly in the prevention or reduction of skin photoaging [17]. For human consumption, the only form of astaxanthin approved as safe and effective is derived from the microalgae Haematococcus pluvialis [15]. Astaxanthin (AST) has been shown to have several potential benefits for individuals with depression. It can reduce the pro-inflammatory factor cyclooxygenase-2 (COX-2), activate the Nrf2 pathway, increase BDNF levels, and promote neurogenesis by crossing the blood-brain barrier (BBB) [14,18,19]. Additionally, AST possesses various neuroprotective properties such as antioxidant stress, anti-inflammatory effects, and anti-apoptotic properties [20]. Given these beneficial effects, AST may represent a promising alternative therapeutic approach for depression [21].

2. Method

To search for relevant literature from 1980 to 2022 on PubMed and Web of Science, we utilized a set of targeted keywords that included "astaxanthin" or "depression" and "depression," "circadian rhythm," "sleep," "insomnia," or "sleep quality." Our aim was to obtain a comprehensive pool of information that would be useful for our research. We conducted a search on PubMed to collect data on animal experiments and clinical trials related to the keywords "astaxanthin" and "depression or sleep." Additionally, we paid attention to papers published in high-impact international journals and references cited within these papers to investigate the underlying mechanisms of antidepressants and circadian rhythms. This approach aimed to provide a thorough understanding of the topic and ensure that our research was based on reliable and significant scientific findings.

2.1. Circadian rhythm system and depression

Circadian rhythms are a set of physiological, behavioral, and metabolic oscillations that conform to a 24-h cycle. This cycle consists of inputs, oscillators, and outputs [22,23]. The central circadian clock in mammals is located in the suprachiasmatic nucleus (SCN), which receives light signals via intrinsic photoreceptor retinal ganglion cells (ipRGCs). These signals are then transmitted to other brain regions and surrounding organs, where they regulate various rhythms [24,25]. The circadian system is primarily controlled at a molecular level through complex interactions involving the core clock genes. These genes include *Clock*, *Bmal1*, *Per1-3*, and *Cry1-2*, which are regulated through a series of positive (CLOCK: BMAL1) and negative (PER: CRY) transcriptional-translational feedback loops. Sleep/wake patterns are closely associated with the circadian rhythm system, and the SCN can directly regulate sleep by controlling the synthesis of melatonin in the pineal gland [26]. During the day, light signals inhibit the production of melatonin, while melatonin is synthesized and released at night [27]. Research studies have demonstrated that melatonin can synchronize circadian rhythms and significantly improve sleep efficiency and quality [28]. Melatonin has two types of G-protein-coupled receptors, known as MT1 and MT2 [29]. The activation of the MT1 receptor is primarily involved in the regulation of rapid eye movement (REM) sleep, while the MT2 receptor is responsible for increasing non-rapid eye movement (NREM) sleep [30].

Circadian rhythm disturbances are frequently observed in individual with depression [31]. Approximately 90% of people with major depressive disorder (MDD) experience difficulty falling asleep, prolonged sleep latency, early awakening, and fragmented sleep [32,33]. In individuals with depression, the REM latency is typically shortened and there may be a delay in the sleep-wake phase [34,

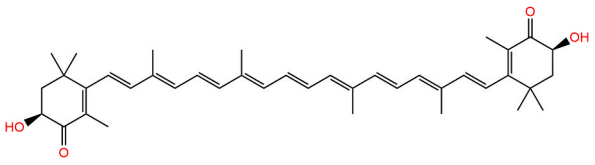

Fig. 1. (3S, 3′S)- Astaxanthin.

35]. Patients with depression release melatonin significantly earlier, causing the circadian rhythm to be earlier than their sleep time. This is consistent with early awakening in depression [36]. These alterations can lead to impaired sleep quality in both NREM and REM stages, decreasing the number of slow-wave sleep (SWS) cycles [33,37]. Iman Hashemzadeh et al. conducted a survey that supports this view. They found that patients with comorbid substance use disorder (SUD) and major depressive disorder (MDD) experienced more early awakening, poorer sleep quality, and worse quality of life compared to patients with SUD alone [38]. A recent study has suggested that REM sleep plays a role in preventing emotional overreaction through somatodendritic decoupling, which can help dissolve negative emotions such as fear and stress [39]. Therefore, improving sleep quality may serve as an early predictor of the effectiveness of antidepressants [40,41]. When sleep function is disrupted, toxic substances produced in the brain cannot be effectively eliminated, leading to potential damage to neurons and glial cells [42]. The lack of sleep can also significantly increase blood-brain barrier permeability, likely due to astrocyte damage [43,44]. Pathological changes in astrocytes are involved in depression, with decreased glial fibrous acid protein (GFAP)-positive astrocyte density [45,46]. They have molecular clocks that can restore clock gene expression of SCN neurons through glutamate, playing a role in controlling rhythms [47,48]. Astrocyte expression of *Per1* is regulated by glutamate, serotonin, and dopamine-activated extracellular regulated protein kinases (ERK) signaling pathways [49]. Persistent damage can further disrupt circadian rhythms and worsen insomnia.

There are significant molecular changes associated with major depressive disorders. Abnormal *Per2* expression in rodents is associated with depressive-like behavior [50,51]. In a rat model of depression, researchers found that the peaks of Per2 were advanced by approximately 4 h in the SCN, while *Bmal1* was delayed by about 4 h [52]. When the light and dark cycle was changed to 22 h in a rat model of depression, the rats showed increased immobility during the dark phase and decreased immobility during the light phase. These changes indicate depressive behavior and disrupted circadian rhythm [53]. Clinical studies have reported variants of *Bmal1*, *Per2,* and *Cry2* genes in patients with depression [54,55]. Analysis of postmortem brain tissue in individuals with major depressive disorder showed a decrease in the expression of rhythm genes such as Bmal1 and Per2 [56]. Overall, depression is associated with disturbances in the circadian rhythm, and the clock genes that are most closely linked to this condition are *Bmal1* and *Per2*.

On the other hand, patients with depression show reduced levels of glutamate metabolites in the medial frontal cortex region [57]. The decrease in glutamate may be influenced by various factors, such as abnormal changes in glutamate synthesis, metabolism, and reuptake into neurons and glial cells [58,59]. Moreover, reduced levels of γ-aminobutyric acid (GABA) have been detected in the cerebrospinal fluid of individuals with depression [60]. Postmortem studies have also shown decreased levels of GABA synthesis [61]. Structural and functional abnormalities have also been observed in both glutamate and GABA receptors in patients with depression, providing further evidence of dysregulation in the delivery of these neurotransmitters [60,62]. GABA is a crucial neurotransmitter that affects circadian rhythms, typically being released at night and binding to GABAA receptors in the postsynaptic membrane. This binding causes changes in Ca^{2+} concentrations, which in turn inhibit Per2 synthesis [49].

2.2. The antidepressant effect of astaxanthin and its impact on circadian rhythm

There have been several reports on the effects of AST treatment on rodent behavior. We have summarized the role of AST in rodent antidepressant-like behavior in Table 1. In terms of sleep, a clinical trial has shown that intake of zinc and AST can improve sleep-onset latency [63]. However, due to the relatively low absorption efficiency of AST, which is an astaxanthin fatty acid diester, the aforementioned study did not specifically examine the effect of AST on sleep alone. As a result, it is challenging to determine whether AST directly influences sleep. A recent study of people who are severely depressed showed improvements in sleep after AST oral

Table 1
Summary of anti-depressive-like behavior effect of rodent models with astaxanthin.

Tested Parameters	Animal models	AST dosage	Effect	Reference
FST, TST, LA, NO, iNOS, nNOS, eNOS, COX-2, NF-κB p65, IL-1β, IL-6, TNF-α, and related mRNA.	Male ICR mice (4–6weeks, 20–22 g) were injected with LPS (0.83 mg/kg).	*Trans*-AST (20,40,80 mg/kg).	*Trans*-AST has counteracted the depressive-like behavior of LPS-induced depression mice.	[65]
OFT, TST, Hole-board test, and oxidative stress estimation.	Adult (6 months) female swiss albino mice were injected intraperitoneally LPS(300 μg/kg).	2 mg/kg.	AST has counteracted the LPS-exposure induced behavioral deficits.	[66]
OFT, EMP, FST, LA, OGTT, pERK, pCREB, pAKT, and BDNF in the PFC.	Male Sprague-Dawley rats (300–350 g) were injected STZ (25 mg/kg).	7.5, 15, 25 mg/kg/d.	AST has counteracted comorbid diabetes and depression disorders.	[67]
OFT, FST, TST, neuronal morphology, p-Pi3K, *p*-Akt, *p*-GSK3β, and *p*-CREB.	Adult male Kunming mice (35–40 g) were injected omethoate (5 mg/kg) every day for 4 weeks.	50 mg/kg/d.	LiCl + AST treatment could counteract depression-like symptom.	[21]
The modified TST, the modified FST, GFAP, cleaved caspase-3, IL-6, IL-1β, and COX-2.	Adult male ICR mice (18–20 g) were injected intraperitoneally STZ (150 mg/kg).	25 mg/kg/d.	AST has an anti-depressant effect on diabetic mice.	[68]
CLET, UALST, FST, *Bdnf* mRNA, *Arc* mRNA.	Audlt male (175–200 g) and femal (125–150 g) Wistar-Unilever rats.	Krill oil 0.2 g/rat/d.	Krill oil improved learning processes and provided antidepressant-like effects.	[69]

Note: FST: forced swimming test, TST: tail suspension test, LA: locomotor activity, NO: nitric oxide, iNOS: inducible nitric oxide synthase, nNOS: neuronal NOS, eNOS: endothelial NOS, OFT: open field test, EMP: elevated plus maze, OGTT: oral glucose tolerance test, CLET: conditioned light extinction test, UALST: unavoidable aversive light stimulus.

administration [64]. The above research is summarized in Table 2.

Molecular docking shows that AST inactivates glutamate N-methyl-D-aspartate (NMDA) receptors because AST is suitable for binding to the NMDA receptor subunit NR2B pocket. Compared to ketamine, it has a close docking score [70]. According to the new mechanistic hypothesis of antidepressants, overstimulation of NMDA receptors triggers the activation of eukaryotic elongation factor-2 (eEF2), which in turn leads to decreased levels of BDNF. By blocking NMDA receptors on postsynaptic neurons and GABA interneurons, antidepressants can produce a direct or indirect beneficial effect on depression [71]. AST has the ability to enhance BDNF levels, potentially by impeding and obstructing NMDA receptors on the postsynaptic membrane, thus preventing eEF2 activation [71,72]. Furthermore, AST stimulates the incorporation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors into the postsynaptic membrane and increases glutamate, finally triggering activation of AMPA receptors to enhance BDNF expression [72,73]. Subsequently, BDNF binds to TrKB receptors on neurons, initiating downstream signaling pathways such as PI3K/AKT/mTORC1 and MAPK/ERK, which ultimately lead to the manifestation of antidepressant effects [71,67]. Interestingly, mTOR involves the expression of *Per1-2*, and the expression of TrkB is regulated by circadian rhythms [74]. BDNF also protects astrocytes from death. Because astrocytes express TrkB-T1 (TrkB truncated receptor) and p75 neurotrophin receptor ($p75^{NTR}$) [75,76]. BDNF combines TrkB-T1 to activate the ERK and Akt signaling pathways. It also activates the PKCζ-CK2-Nrf2 pathway of dimers consisting of TrkB-T1 and $p75^{NTR}$ [75,76]. Additionally, AST raises levels of 5-HT, which could affect the rhythm of astrocytes [49,77]. Based on previous research, we have put forward hypotheses regarding the antidepressant effects of AST and its potential role in regulating circadian rhythms (Fig. 2). These intricate regulatory mechanisms could impact melatonin expression and play a role in regulating sleep patterns.

3. Discussion

While depression is a significant issue, there are medications available that can alleviate its symptoms. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is a prescription drug used to treat major depressive disorder. However, common side effects of fluoxetine include nausea, anxiety, and sleep disturbances, among others [78]. In comparison to fluoxetine, natural AST offers many advantages and has been extensively utilized in nutraceuticals, cosmetics, food, and beverage products, due to its high safety profile [79]. As astaxanthin is edible and safe for human consumption, there is no need to be concerned about toxicity or side effects in future clinical studies. Research has shown that AST or AST-containing foods may have a positive effect on sleep, suggesting a potential anti-depressive effect, although the underlying molecular mechanisms remain unclear. As insomnia has been linked to *Per* and *Bmal1* genes, AST may modulate related pathways. Therefore, several key questions need to be addressed, such as whether AST has an antidepressant mechanism akin to ketamine, if it can affect the rhythm of astrocytes and neurons in the SCN and regulate the phase of melatonin expression, and whether it improves sleep in depressed patients. Our research group has found that AST can impact the expression of *Per2* (although these findings are unpublished) and require further confirmation. It's worth noting that circadian rhythms regulate the expression of $p75^{NTR}$ and TrkB genes [74,76]. Additionally, proper timing of medication or supplement intake is crucial, as it can influence your body's circadian rhythms and result in varying outcomes at different times. Certain medications may work best when taken at specific times during the day, while others may cause more pronounced side effects if taken at particular periods, such as those impacting sleep or digestion [80].

AST has limited clinical applications due to its low aqueous solubility and bioavailability [81]. Its effectiveness in improving sleep may be impacted as a result. To address this issue, scientists have explored multiple methods to enhance AST's bioavailability, such as using polymeric, lipid-based, inorganic, and hybrid nanocarriers [81,82]. This trend is likely to continue in future research involving AST. With further investigation into AST, we anticipate it will demonstrate additional valuable applications in the pharmaceutical and biomedical fields.

4. Conclusion

Although astaxanthin has demonstrated promising antidepressant effects in animal studies, clinical research has yielded limited data on its efficacy. Given the high degree of bias associated with individual clinical trials, it remains unclear whether these findings translate to human treatment. However, based on the mechanisms discussed earlier, astaxanthin may play a significant role in enhancing antidepressant and sleep-improving effects. To provide more conclusive evidence, additional clinical trials should be conducted to determine its effectiveness in humans.

Table 2
Existing clinical studies of astaxanthin in antidepressant or sleep improvement.

Study design	Sample	AST dosage	Diagnosis criteria	Outcome	Reference
Randomised, double-blind, placebo-controlled, parallel-group comparisons.	There were 25 participants in the astaxanthin group. There were 29 participants in the placebo group.	12 mg/d.	Profile of Mood States 2nd Edition (POMS2).Oguri–Shirakawa–Azumi Sleep Inventory (OSA-MA).	Participants with a score >65 (depression) had significantly improved sleep	[64]

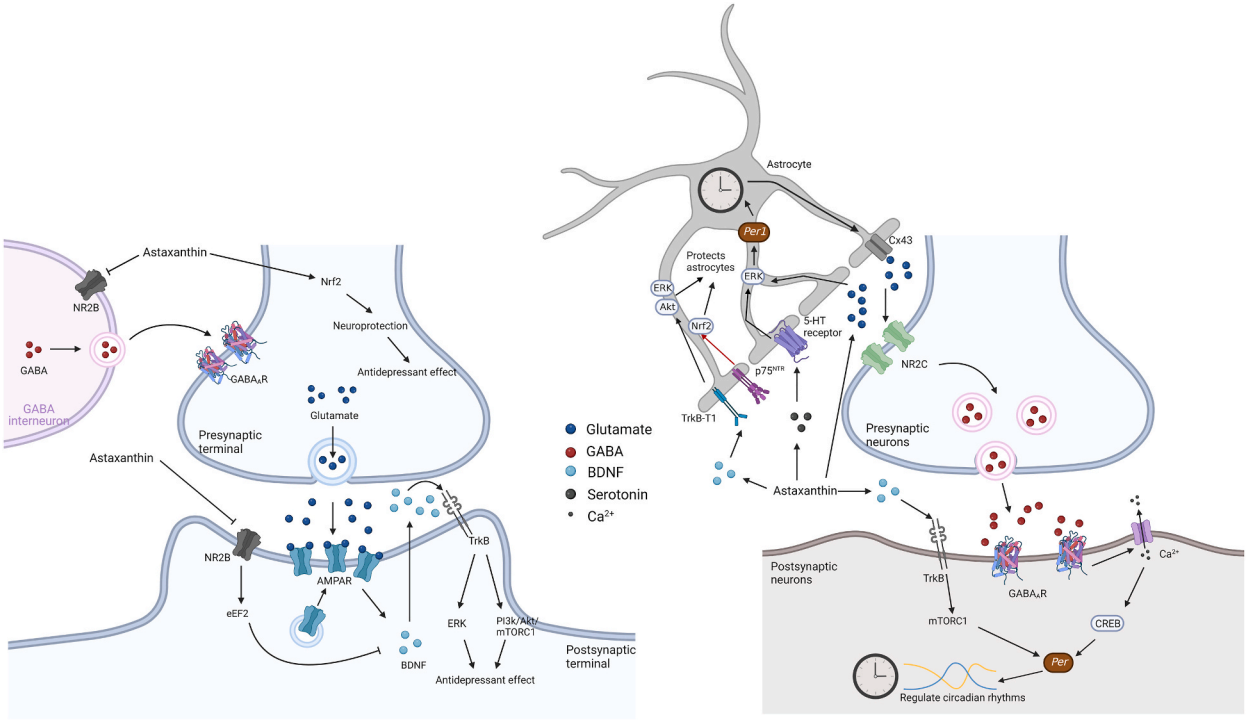

Fig. 2. The polypharmacology of astaxanthin in antidepressants and regulation of circadian rhythms. **A.** Astaxanthin has activated the Nrf2 pathway to show antioxidant activity, thereby playing an antidepressant effect [19]. Another potential mechanism is theoretically similar to ketamine. AST increases GABA release by blocking NR2B receptors on GABAergic interneurons, stimulating glutamate release [70]. Subsequently, glutamate binds to AMPA receptors to increase BDNF synthesis and release [71]. It is worth noting that AST causes AMPA receptors to be inserted more into the postsynaptic membrane, which amplifies glutamate signaling [72]. Blocking NR2B on postsynaptic neurons and increase can also increase BDNF levels. BDNF binds to the TrkB receptor of neurons and activates downstream signaling pathways to improve synaptic plasticity and exert antidepressant effects [71]. **B.** The density of astrocytes and their markers showed significant pathological changes in MDD [46]. These changes may lead to circadian rhythm disorders in patients with depression, and spikes in clock gene expression may occur earlier or later. AST significantly increases BDNF levels and subsequently binds to the TrkB-T1 receptor on astrocytes, triggering anti-apoptotic pathways and protecting astrocytes [75,76]. There are currently no direct reports of the effect of AST on astrocyte rhythms. But AST increases serotonin and glutamate levels, suggesting that it may affect the rhythm of astrocytes [49,73,77]. These effects may normalize the astrocyte rhythm, restores the out-of-balance rhythm, and improves sleep in depressed patients. These effects may normalize astrocyte rhythms, restore the out-of-balance rhythm, regulate Ca^{2+} concentrations in postsynaptic neurons, and regulate the expression of the Per gene [49]. In addition, the BDNF-TrkB-mTOR pathway is also involved in regulating circadian rhythms [74].

Data availability statement

No data was used for the research described in the article.

Author contributions

Yi-Fan Peng wrote the manuscript; Lin-Lin Wang and Juan-Hua performed the research. Yue-Qin Zeng: did the critical revision of the manuscript for important intellectual content. Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.S. Gaffrey, J.L. Luby, D.M. Barch, Towards the study of functional brain development in depression: an Interactive Specialization approach, Neurobiol. Dis. 52 (2013) 38–48, https://doi.org/10.1016/j.nbd.2012.06.012.
[2] M.P. Kaster, M. Moretti, M.P. Cunha, et al., Novel approaches for the management of depressive disorders, Eur. J. Pharmacol. 771 (2016) 236–240, https://doi.org/10.1016/j.ejphar.2015.12.029.
[3] WHO, Depression and Other Common Mental Disorders Global Health Estimates.
[4] X. Ren, S. Yu, W. Dong, et al., Burden of depression in China, 1990-2017: findings from the global burden of disease study 2017, J. Affect. Disord. 268 (2020) 95–101, https://doi.org/10.1016/j.jad.2020.03.011.
[5] S. Bhatt, A. Nagappa, C. Patil, Role of oxidative stress in depression, Drug Discov. Today 25 (2020) 1270–1276, https://doi.org/10.1016/j.drudis.2020.05.001.
[6] Q. Ding, Y. Tian, X. Wang, et al., Oxidative damage of tryptophan hydroxylase-2 mediated by peroxisomal superoxide anion radical in brains of mouse with depression, J. Am. Chem. Soc. 142 (2020) 20735–20743, https://doi.org/10.1021/jacs.0c09576.
[7] E. Bouvier, F. Brouillard, J. Molet, et al., Nrf2-dependent persistent oxidative stress results in stress-induced vulnerability to depression, Mol. Psychiatr. 22 (2017) 1701–1713, https://doi.org/10.1038/mp.2016.144.
[8] E. Castren, L.M. Monteggia, Brain-derived neurotrophic factor signaling in depression and antidepressant action, Biol. Psychiatr. 90 (2021) 128–136, https://doi.org/10.1016/j.biopsych.2021.05.008.
[9] F.J. Monje, M. Cabatic, I. Divisch, et al., Constant darkness induces IL-6-dependent depression-like behavior through the NF-kappaB signaling pathway, J. Neurosci. 31 (2011) 9075–9083, https://doi.org/10.1523/JNEUROSCI.1537-11.2011.
[10] R.C. Shelton, J. Claiborne, M. Sidoryk-Wegrzynowicz, et al., Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression, Mol. Psychiatr. 16 (2011) 751–762, https://doi.org/10.1038/mp.2010.52.
[11] D.M. Eisenberg, R.B. Davis, S.L. Ettner, et al., Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey, JAMA 280 (1998) 1569–1575, https://doi.org/10.1001/jama.280.18.1569.
[12] Q.X. Ng, N. Venkatanarayanan, C.Y. Ho, Clinical use of Hypericum perforatum (St John's wort) in depression: a meta-analysis, J. Affect. Disord. 210 (2017) 211–221, https://doi.org/10.1016/j.jad.2016.12.048.
[13] Q.X. Ng, S.S.H. Koh, H.W. Chan, et al., Clinical use of curcumin in depression: a meta-analysis, J. Am. Med. Dir. Assoc. 18 (2017) 503–508, https://doi.org/10.1016/j.jamda.2016.12.071.
[14] C. Galasso, I. Orefice, P. Pellone, et al., On the neuroprotective role of astaxanthin: new perspectives? Mar. Drugs 16 (2018) 247, https://doi.org/10.3390/md16080247.
[15] A. Donoso, J. Gonzalez-Duran, A.A. Munoz, et al., Therapeutic uses of natural astaxanthin: an evidence-based review focused on human clinical trials, Pharmacol. Res. 166 (2021), 105479, https://doi.org/10.1016/j.phrs.2021.105479.
[16] M. Guerin, M.E. Huntley, M. Olaizola, Haematococcus astaxanthin: applications for human health and nutrition, Trends Biotechnol. 21 (2003) 210–216, https://doi.org/10.1016/s0167-7799(03)00078-7.
[17] Q.X. Ng, M. De Deyn, W. Loke, et al., Effects of astaxanthin supplementation on skin health: a systematic review of clinical studies, J. Diet. Suppl. 18 (2021) 169–182, https://doi.org/10.1080/19390211.2020.1739187.
[18] W. Wu, X. Wang, Q. Xiang, et al., Astaxanthin alleviates brain aging in rats by attenuating oxidative stress and increasing BDNF levels, Food Funct. 5 (2014) 158–166, https://doi.org/10.1039/c3fo60400d.
[19] Z. Kohandel, T. Farkhondeh, M. Aschner, et al., Nrf2 a molecular therapeutic target for Astaxanthin, Biomed. Pharmacother. 137 (2021), 111374, https://doi.org/10.1016/j.biopha.2021.111374.
[20] H. Wu, H. Niu, A. Shao, et al., Astaxanthin as a potential neuroprotective agent for neurological diseases, Mar. Drugs 13 (2015) 5750–5766, https://doi.org/10.3390/md13095750.
[21] J. Qiao, L. Rong, Z. Wang, et al., Involvement of Akt/GSK3beta/CREB signaling pathway on chronic omethoate induced depressive-like behavior and improvement effects of combined lithium chloride and astaxanthin treatment, Neurosci. Lett. 649 (2017) 55–61, https://doi.org/10.1016/j.neulet.2017.03.048.
[22] M. Nassan, A. Videnovic, Circadian rhythms in neurodegenerative disorders, Nat. Rev. Neurol. 18 (2022) 7–24, https://doi.org/10.1038/s41582-021-00577-7.
[23] J.S. Takahashi, Transcriptional architecture of the mammalian circadian clock, Nat. Rev. Genet. 18 (2017) 164–179, https://doi.org/10.1038/nrg.2016.150.
[24] H. Dardente, N. Cermakian, Molecular circadian rhythms in central and peripheral clocks in mammals, Chronobiol. Int. 24 (2007) 195–213, https://doi.org/10.1080/07420520701283693.
[25] R. Orozco-Solis, P. Sassone-Corsi, Epigenetic control and the circadian clock: linking metabolism to neuronal responses, Neuroscience 264 (2014) 76–87, https://doi.org/10.1016/j.neuroscience.2014.01.043.
[26] J. Vriend, R.J. Reiter, Melatonin feedback on clock genes: a theory involving the proteasome, J. Pineal Res. 58 (2015) 1–11, https://doi.org/10.1111/jpi.12189.
[27] F. Auld, E.L. Maschauer, I. Morrison, et al., Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders, Sleep Med. Rev. 34 (2017) 10–22, https://doi.org/10.1016/j.smrv.2016.06.005.
[28] Z. Xie, F. Chen, W.A. Li, et al., A review of sleep disorders and melatonin, Neurol. Res. 39 (2017) 559–565, https://doi.org/10.1080/01616412.2017.1315864.
[29] M.L. Dubocovich, P. Delagrange, D.N. Krause, et al., International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors, Pharmacol. Rev. 62 (2010) 343–380, https://doi.org/10.1124/pr.110.002832.
[30] G. Gobbi, S. Comai, Differential function of melatonin MT1 and MT2 receptors in REM and NREM sleep, Front. Endocrinol. 10 (2019) 87, https://doi.org/10.3389/fendo.2019.00087.
[31] F. Fagiani, D. Di Marino, A. Romagnoli, et al., Molecular regulations of circadian rhythm and implications for physiology and diseases, Signal Transduct. Targeted Ther. 7 (2022) 41, https://doi.org/10.1038/s41392-022-00899-y.
[32] D. Riemann, M. Berger, U. Voderholzer, Sleep and depression–results from psychobiological studies: an overview, Biol. Psychol. 57 (2001) 67–103, https://doi.org/10.1016/s0301-0511(01)00090-4.
[33] N. Tsuno, A. Besset, K. Ritchie, Sleep and depression, J. Clin. Psychiatry 66 (2005) 1254–1269, https://doi.org/10.4088/jcp.v66n1008.
[34] E. William, Bunney, B.G.B., molecular clock genes in man and lower animals, Possible Implications for Circadian Abnormalities in Depression 22 (2000) 335–345, https://doi.org/10.1016/S0893-133X(99)00145-1.
[35] J.J. Crouse, J.S. Carpenter, Y.J.C. Song, et al., Circadian rhythm sleep–wake disturbances and depression in young people: implications for prevention and early intervention, Lancet Psychiatr. 8 (2021) 813–823, https://doi.org/10.1016/s2215-0366(21)00034-1.
[36] M.Y. Coleman, E.M. McGlashan, P. Vidafar, et al., Advanced melatonin onset relative to sleep in women with unmedicated major depressive disorder, Chronobiol. Int. 36 (2019) 1373–1383, https://doi.org/10.1080/07420528.2019.1644652.
[37] A.A. Borbély, A. Wirz-Justice, Sleep, sleep deprivation and depression. A hypothesis derived from a model of sleep regulation, Hum. Neurobiol. 1 (1982) 205–210.
[38] I. Hashemzadeh, J.E. Marquez-Arrico, K. Hashemzadeh, et al., Circadian functioning and quality of life in substance use disorder patients with and without comorbid major depressive disorder, Front. Psychiatr. 12 (2021), 750500, https://doi.org/10.3389/fpsyt.2021.750500.

[39] M. Aime, N. Calcini, M. Borsa, et al., Paradoxical somatodendritic decoupling supports cortical plasticity during REM sleep, Science 376 (2022) 724–730, https://doi.org/10.1126/science.abk2734.
[40] B.G. Bunney, J.Z. Li, D.M. Walsh, et al., Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder, Mol. Psychiatr. 20 (2015) 48–55, https://doi.org/10.1038/mp.2014.138.
[41] P.A. Geoffroy, L. Palagini, Biological rhythms and chronotherapeutics in depression, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 106 (2021), 110158, https://doi.org/10.1016/j.pnpbp.2020.110158.
[42] A.L. Komaroff, Does sleep flush wastes from the brain? JAMA 325 (2021) 2153–2155, https://doi.org/10.1001/jama.2021.5631.
[43] J. He, H. Hsuchou, Y. He, et al., Sleep restriction impairs blood-brain barrier function, J. Neurosci. 34 (2014) 14697–14706, https://doi.org/10.1523/JNEUROSCI.2111-14.2014.
[44] B.P. Heithoff, K.K. George, A.N. Phares, et al., Astrocytes are necessary for blood-brain barrier maintenance in the adult mouse brain, Glia 69 (2021) 436–472, https://doi.org/10.1002/glia.23908.
[45] J.A. Cobb, K. O'Neill, J. Milner, et al., Density of GFAP-immunoreactive astrocytes is decreased in left hippocampi in major depressive disorder, Neuroscience 316 (2016) 209–220, https://doi.org/10.1016/j.neuroscience.2015.12.044.
[46] G. Rajkowska, C.A. Stockmeier, Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue, Curr. Drug Targets 14 (2013) 1225–1236, https://doi.org/10.2174/13894501113149990156.
[47] M. Brancaccio, A.P. Patton, J.E. Chesham, et al., Astrocytes control circadian timekeeping in the suprachiasmatic nucleus via glutamatergic signaling, Neuron 93 (2017) 1420–1435.e5, https://doi.org/10.1016/j.neuron.2017.02.030.
[48] M. Brancaccio, M.D. Edwards, A.P. Patton, et al., Cell-autonomous clock of astrocytes drives circadian behavior in mammals, Science 363 (2019) 187–192, https://doi.org/10.1126/science.aat4104.
[49] K.B. Koronowski, P. Sassone-Corsi, Communicating clocks shape circadian homeostasis, Science 371 (2021), https://doi.org/10.1126/science.abd0951 eabd0951.
[50] Y. Li, G. Li, J. Li, et al., Depression-like behavior is associated with lower Per2 mRNA expression in the lateral habenula of rats, Gene Brain Behav. 20 (2021), e12702, https://doi.org/10.1111/gbb.12702.
[51] A.L. Russell, L. Miller, H. Yi, et al., Knockout of the circadian gene, Per2, disrupts corticosterone secretion and results in depressive-like behaviors and deficits in startle responses, BMC Neurosci. 22 (2021) 5, https://doi.org/10.1186/s12868-020-00607-y.
[52] S.L. Christiansen, E.V. Bouzinova, J. Fahrenkrug, et al., Altered expression pattern of clock genes in a rat model of depression, Int. J. Neuropsychopharmacol. 19 (2016) pyw061, https://doi.org/10.1093/ijnp/pyw061.
[53] M. Ben-Hamo, T.A. Larson, L.S. Duge, et al., Circadian forced desynchrony of the master clock leads to phenotypic manifestation of depression in rats, eNeuro 3 (2016), https://doi.org/10.1523/ENEURO.0237-16.2016. ENEURO.0237-16.2016.
[54] J.J. Liu, D. Sudic Hukic, Y. Forsell, et al., Depression-associated ARNTL and PER2 genetic variants in psychotic disorders, Chronobiol. Int. 32 (2015) 579–584, https://doi.org/10.3109/07420528.2015.1012588.
[55] L. Kovanen, K. Donner, M. Kaunisto, et al., PRKCDBP (CAVIN3) and CRY2 associate with major depressive disorder, J. Affect. Disord. 207 (2017) 136–140, https://doi.org/10.1016/j.jad.2016.09.034.
[56] J.Z. Li, B.G. Bunney, F. Meng, et al., Circadian patterns of gene expression in the human brain and disruption in major depressive disorder, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 9950–9955, https://doi.org/10.1073/pnas.1305814110.
[57] S. Moriguchi, A. Takamiya, Y. Noda, et al., Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies, Mol. Psychiatr. 24 (2019) 952–964, https://doi.org/10.1038/s41380-018-0252-9.
[58] C.G. Abdallah, L. Jiang, H.M. De Feyter, et al., Glutamate metabolism in major depressive disorder, Am. J. Psychiatr. 171 (2014) 1320–1327, https://doi.org/10.1176/appi.ajp.2014.14010067.
[59] M.S. Lener, M.J. Niciu, E.D. Ballard, et al., Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine, Biol. Psychiatr. 81 (2017) 886–897, https://doi.org/10.1016/j.biopsych.2016.05.005.
[60] C. Fee, M. Banasr, E. Sibille, Somatostatin-positive gamma-aminobutyric acid interneuron deficits in depression: cortical microcircuit and therapeutic perspectives, Biol. Psychiatr. 82 (2017) 549–559, https://doi.org/10.1016/j.biopsych.2017.05.024.
[61] J.P. Guilloux, G. Douillard-Guilloux, R. Kota, et al., Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression, Mol. Psychiatr. 17 (2012) 1130–1142, https://doi.org/10.1038/mp.2011.113.
[62] H. Akil, J. Gordon, R. Hen, et al., Treatment resistant depression: a multi-scale, systems biology approach, Neurosci. Biobehav. Rev. 84 (2018) 272–288, https://doi.org/10.1016/j.neubiorev.2017.08.019.
[63] H. Saito, Y. Cherasse, R. Suzuki, et al., Zinc-rich oysters as well as zinc-yeast- and astaxanthin-enriched food improved sleep efficiency and sleep onset in a randomized controlled trial of healthy individuals, Mol. Nutr. Food Res. 61 (0) (2017), https://doi.org/10.1002/mnfr.201600882.
[64] M. Hayashi, M. Kawamura, Y. Kawashima, et al., Effect of astaxanthin-rich extract derived from Paracoccus carotinifaciens on the status of stress and sleep in adults, J. Clin. Biochem. Nutr. 66 (2020) 92–102, https://doi.org/10.3164/jcbn.19-113.
[65] X. Jiang, L. Chen, L. Shen, et al., Trans-astaxanthin attenuates lipopolysaccharide-induced neuroinflammation and depressive-like behavior in mice, Brain Res. 1649 (2016) 30–37, https://doi.org/10.1016/j.brainres.2016.08.029.
[66] M.M. Al-Amin, R. Sultana, S. Sultana, et al., Astaxanthin ameliorates prenatal LPS-exposed behavioral deficits and oxidative stress in adult offspring, BMC Neurosci. 17 (2016) 11, https://doi.org/10.1186/s12868-016-0245-z.
[67] Y. Ke, S. Bu, H. Ma, et al., Preventive and therapeutic effects of astaxanthin on depressive-like behaviors in high-fat diet and streptozotocin-treated rats, Front. Pharmacol. 10 (2019) 1621, https://doi.org/10.3389/fphar.2019.01621.
[68] X.Y. Zhou, F. Zhang, X.T. Hu, et al., Depression can be prevented by astaxanthin through inhibition of hippocampal inflammation in diabetic mice, Brain Res. 1657 (2017) 262–268, https://doi.org/10.1016/j.brainres.2016.12.018.
[69] K. Wibrand, K. Berge, M. Messaoudi, et al., Enhanced cognitive function and antidepressant-like effects after krill oil supplementation in rats, Lipids Health Dis. 12 (2013) 6, https://doi.org/10.1186/1476-511X-12-6.
[70] K. Sharma, D. Sharma, M. Sharma, et al., Astaxanthin ameliorates behavioral and biochemical alterations in in-vitro and in-vivo model of neuropathic pain, Neurosci. Lett. 674 (2018) 162–170, https://doi.org/10.1016/j.neulet.2018.03.030.
[71] J.H. Krystal, C.G. Abdallah, G. Sanacora, et al., Ketamine: a paradigm shift for depression research and treatment, Neuron 101 (2019) 774–778, https://doi.org/10.1016/j.neuron.2019.02.005.
[72] B. Grimmig, C. Hudson, L. Moss, et al., Astaxanthin supplementation modulates cognitive function and synaptic plasticity in young and aged mice, Geroscience 41 (2019) 77–87, https://doi.org/10.1007/s11357-019-00051-9.
[73] F. Mirsaeed-Ghazi, M. Sharifzadeh, M.R. Ashrafi-Kooshk, et al., Astaxanthin decreases spatial memory and glutamate transport impairment induced by fluoride, Iran. J. Pharm. Res. (IJPR) 20 (2021) 238–254, https://doi.org/10.22037/ijpr.2021.114919.15107.
[74] S. Sato, B. Bunney, L. Mendoza-Viveros, et al., Rapid-acting antidepressants and the circadian clock, Neuropsychopharmacology (2021), https://doi.org/10.1038/s41386-021-01241-w.
[75] J. Saba, J. Turati, D. Ramírez, et al., Astrocyte truncated tropomyosin receptor kinase B mediates brain-derived neurotrophic factor anti-apoptotic effect leading to neuroprotection, J. Neurochem. 146 (2018) 686–702, https://doi.org/10.1111/jnc.14476.
[76] T. Ishii, E. Warabi, G.E. Mann, Circadian control of BDNF-mediated Nrf2 activation in astrocytes protects dopaminergic neurons from ferroptosis, Free Radic. Biol. Med. 133 (2019) 169–178, https://doi.org/10.1016/j.freeradbiomed.2018.09.002.
[77] X. Jiang, K. Zhu, Q. Xu, et al., The antidepressant-like effect of trans-astaxanthin involves the serotonergic system, Oncotarget 8 (2017) 25552–25563, https://doi.org/10.18632/oncotarget.16069.
[78] J.F. Wernicke, Safety and side effect profile of fluoxetine, Expet Opin. Drug Saf. 3 (2004) 495–504, https://doi.org/10.1517/14740338.3.5.495.
[79] B. Stachowiak, P. Szulc, Astaxanthin for the food industry, Molecules 26 (2021) 2666, https://doi.org/10.3390/molecules26092666.

[80] M.D. Ruben, D.F. Smith, G.A. FitzGerald, et al., Dosing time matters, Science 365 (2019) 547–549, https://doi.org/10.1126/science.aax7621.
[81] C. Liu, S. Zhang, D.J. McClements, et al., Design of astaxanthin-loaded core-shell nanoparticles consisting of chitosan oligosaccharides and poly(lactic- co-glycolic acid): enhancement of water solubility, stability, and bioavailability, J. Agric. Food Chem. 67 (2019) 5113–5121, https://doi.org/10.1021/acs.jafc.8b06963.
[82] M. Zare, Z. Norouzi Roshan, E. Assadpour, et al., Improving the cancer prevention/treatment role of carotenoids through various nano-delivery systems, Crit. Rev. Food Sci. Nutr. 61 (2021) 522–534, https://doi.org/10.1080/10408398.2020.1738999.