The Endocannabinoid System: An Essential Player in the Regulation of Mood

A significant 46% of Australians will experience a mental health disorder during their lifetime.[1] Unfortunately, symptoms of anxiety and depression have doubled in Australia since the start of the Coronavirus disease 2019 (COVID-19) pandemic,[2] and in New Zealand more than 50% of those surveyed during the first 10 weeks of the pandemic reported feeling anxious or depressed.[3] One thing is certain: supporting a healthy stress response is now more important than ever. The endocannabinoid system (ECS), a regulatory network involved in homeostatic roles including modulating sleep, mood, memory, appetite and digestion, pain, cardiovascular, immune and inflammatory functions,[4,5] has recently been implicated in the aetiology of anxiety and depression. Before exploring the role of the ECS in stress and mood, it is important to first understand its components, including its receptors, ligands and synthesising and degrading enzymes.

Welcome to the Endocannabinoidome

Cannabinoid receptor type 1 (CB1) is the most abundant G protein-coupled receptor in the brain,[6,7] with particularly dense populations in limbic brain regions involved in stress and anxiety, including the hippocampus, prefrontal cortex, amygdala and various hypothalamic nuclei (Figure 1).[8,9] CB1 receptors are highly expressed on gamma-aminobutyric acid (GABA) interneurons, with lower levels on glutamatergic, cholinergic, dopaminergic, serotonergic and noradrenergic neurons.[10,11,12] As such, CB1 is involved in the balance between GABAergic and glutamatergic signalling.[13] Unlike traditional neurotransmission, the ECS functions in a retrograde mechanism, whereby endocannabinoids (eCBs) are released by the postsynaptic dendrite and travel back to the axon terminal of the presynaptic neuron.[14] Once eCBs bind to the cannabinoid receptor on the presynaptic neuron, subsequent neurotransmitter release (e.g., glutamate) is inhibited (Figure 2).[15] Research indicates that CB1 activation at low levels generally produces anxiolytic effects, while high level CB1 activation or blockage of the receptor causes anxiety[16] and depression.[17] For this reason, CB1 is the ECS receptor most frequently implicated in mood disorders. Conversely, cannabinoid receptor type 2 (CB2) is mainly located peripherally in the immune system, as well as in several brain regions with dopamine-related function.[18]

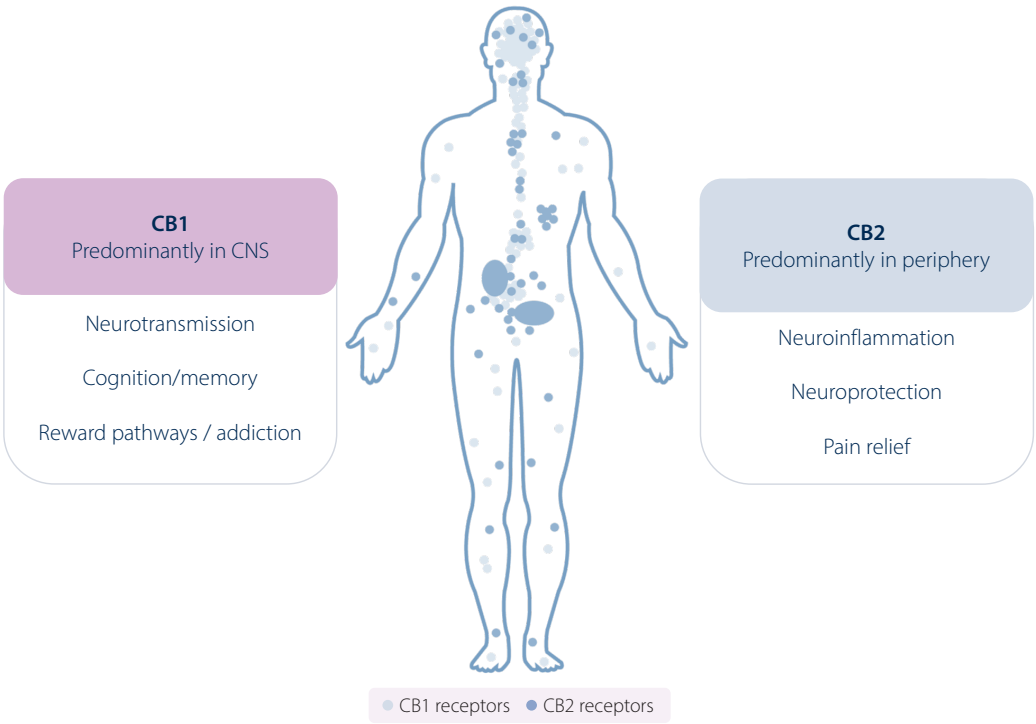

Figure 1. Location and Function of Cannabinoid Receptor Type 1 (CB1) and 2 (CB2) in the Central Nervous System (CNS) and Periphery.[19,20,21]

The primary endogenous eCBs are N-arachidonoylethanolamide (anandamide; AEA) and 2-arachidonoyglycerol (2-AG).[22] Unlike traditional neurotransmitters, eCBs do not accumulate in secretory vesicles but are synthesised 'on-demand' from omega-6 polyunsaturated fatty acid and arachidonic acid (AA),[23] with the concentration at the synapse being dependant on the relative rate of synthesis and degradation.[24,25] AEA is catabolised by fatty acid amide hydrolase (FAAH), while 2-AG is degraded by monoacylglycerol lipase (MAGL).[26]

Some eCBs are also active at receptors beyond CB1 and CB2, such as transient receptor potential vanilloid subtype 1 (TRPV1) and peroxisome proliferator activating receptor-α (PPAR-α).[27] In addition, eCB-like mediators such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) share metabolic pathways with eCBs[28] and activate PPAR-α rather than CB receptors.[29,30] PPAR-α activation tends to have an anti-inflammatory effect[31] and the receptor is emerging as a promising target for mood disorders.[32]

These discoveries have led to an expansion of the ECS to the 'endocannabinoidome', encompassing eCB-like mediators and the diverse receptors they effect.[33]

The Endocannabinoid System Modulates the Stress Response

The ECS regulates the effects of stress and is tightly linked with the hypothalamic-pituitary adrenal (HPA) axis for this purpose. Corticotropin-releasing hormone (CRH) increases FAAH activity, leading to reduced AEA levels via enzymatic breakdown.[34,35] Studies have demonstrated that this decline in AEA appears to contribute to the manifestation of the stress response, including increases in anxiety.[36] Meanwhile, HPA axis activation and the resultant glucocorticoid release increases synaptic 2-AG,[37] which leads to modulation and termination of the stress response (Figure 2).[38]

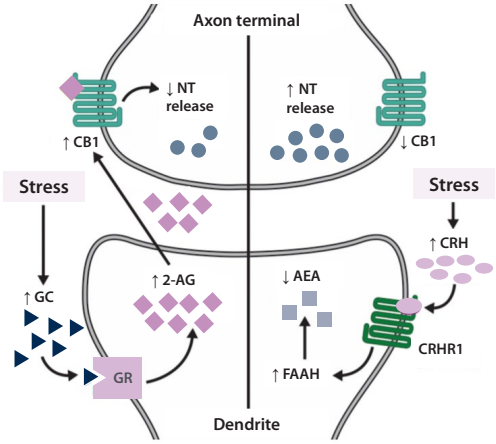

Figure 2. The Interplay Between Stress and the Endocannabinoid System.[39]
GC: Glucocorticoid; GR: Glucocorticoid receptor; 2-AG: 2-arachidonoylglycerol, CB1: Cannabinoid receptor type 1; NT: Neurotransmitter; CRH: Corticotropin-releasing hormone; CRHR1: Corticotropin releasing hormone receptor 1; FAAH: Fatty acid amide hydrolase; AEA: N-arachidonoylethanolamide.

Unfortunately, chronic stress can lead to downregulation of CB1 receptors[40,41] and blunted eCB signalling,[42] contributing to dysregulation of the ECS which in turn promotes poor stress adaptation and an excessive stress response.[43]

The Silent Pandemic

Supporting Patients Through a Mental Health Crisis

Endocannabinoid Dysfunction is Implicated in Poor Mental Health

A growing body of evidence suggests dysregulation of the ECS is involved in several mental health conditions. For example, significantly reduced serum levels of AEA and/or 2-AG have been reported in females with untreated clinical depression[44,45,46] and individuals with post-traumatic stress disorder (PTSD).[47] Moreover, a strong negative correlation between hair analysis PEA and OEA levels, and PTSD symptoms has been uncovered,[48] suggesting these eCB-like mediators have a role to play in mental health.

Chronic stress caused by social isolation appears to derange both the ECS and HPA axis. A small space flight simulation study in six healthy males found significantly reduced serum 2-AG following 520 days of isolation, while adrenaline, noradrenaline and cortisol levels were all elevated.[49] Given the number of COVID-19 related lockdowns and resultant social isolation experienced by many in Australia and New Zealand, this finding points to the need to reduce allostatic load and support recovery in those presenting with symptoms of chronic stress such as low mood or anxiety.

Tonifying the Endocannabinoid System

Endocannabinoid tone reflects the relative levels of eCBs as well as the abundance of CB receptors.[50] Pioneer in cannabis science, Dr Ethan Russo suggests dysfunction in digestion (e.g., irritable bowel syndrome), sleep, mood and pain sensitivity (e.g., migraine, fibromyalgia) can all be indicative of reduced ECS tone.[51] As such, he coined the term 'clinical endocannabinoid deficiency' to describe the contribution of poor endocannabinoid tone to these symptoms. In contrast, increasing eCB levels by enhancing their synthesis or inhibiting their degradation can augment ECS tone and relieve symptoms (Box 1).[52,53]

Is it also possible to have too many eCBs? Indeed, the ECS may be upregulated in obesity and neurodegenerative, inflammatory, metabolic and cardiovascular diseases.[54,55] However, consensus on the interpretation of this finding has not been reached, with some suggesting that this reflects an autoprotective change to the ECS[56] or excess AA consumption, typical of a western diet (as AA is a precursor to eCBs).[57] For an exploration of the impact of poor metabolic health on mood disorders, please refer to accompanying documents *Brain Insulin Resistance: A Forgotten Play in the Silent Pandemic* and *The Interplay of Mitochondria and Insulin in Mood*.

What does this mean in terms of therapeutic intervention? Since the concentration of eCBs, AEA and/or 2-AG, may vary depending on the condition (e.g. cardiovascular disease versus depression),[58] the treatment aim should not be on increasing or decreasing eCB levels, but rather on supporting the *regulation* of the ECS to assist a return to homeostasis.

How FAAH Would you go to Support Mental Health?

Given evidence indicates ECS dysregulation in depression and anxiety, researchers have turned to ECS modulation in a bid to support mental health. FAAH, the enzyme involved in the degradation of AEA, PEA and OEA, has been linked with anxiety,[59] while pharmacologic FAAH inhibitors have been found to provide significant anxiolytic effects to individuals with social anxiety disorder[60] and protect against stress-induced negative affect in healthy adults.[61] As such, natural FAAH inhibitors are being investigated to support anxious and depressed individuals. *Lavandula angustifolia* (lavender) oil[62] and compounds such as genistein and daidzein (from soy),[63] and the flavonoid kaempferol (abundantly found in broccoli, apples and strawberries)[64] have been shown to inhibit FAAH to varying degrees. More compounds that impact this important enzyme are sure to be discovered in the future.

Relieve: Herbal Medicines to Reduce Symptoms and Regulate Endocannabinoid Tone

As chronic stress dysregulates the ECS, holistic care with an emphasis on restoring an appropriate stress response and rebuilding resilience will naturally support the ECS and improve mental wellbeing. Various therapeutics that are used to relieve symptoms of anxiety and low mood, also support ECS regulation (Table 1). For example, honokiol, a constituent of *Magnolia officinalis* (magnolia) is a CB1 agonist.[65] Animal research indicates that magnolia's anxiolytic and neuroprotective effects are at least partly mediated by this CB1 modulation.[66] When combined with GABAergic herbs such as *Passiflora incarnata* (passionflower)[67] and *Ziziphus jujuba var. spinosa* (zizyphus),[68] *Herbal Support for Hyper HPA and Stress* can help to relieve anxiety caused by excess stress.

For those suffering low mood in addition to anxiety, consider *Lavender Oil and Theanine for Anxiety, Panic and Low Mood*. Emerging research indicates constituents of plants with volatile oils, such as the sesquiterpene β-caryophyllene in *Lavandula angustifolia* (lavender) and *Melissa officinalis* (lemon balm) may exert some of their action via the ECS.[69] Specifically, preclinical studies demonstrate that lavender oil is a FAAH inhibitor,[70] suggesting this herb has the potential to reduce anxiety via improving ECS tone. Indeed, numerous human clinical trials confirm the anxiolytic and antidepressant effects of both lavender oil[71,72,73] and lemon balm.[74,75] Meanwhile, L-theanine, an amino acid isolated from green tea, has been associated with increased brain-derived neurotrophic factor (BDNF) and improved anxiety and depressive symptoms in several studies.[76,77,78,79]

Neuroinflammation (often associated with reduced BDNF levels) is implicated in the pathogenesis of both anxiety and depression,[80] as is explored in accompanying document, *When Silent Inflammation Becomes Loud*. In fact, there is a complex bidirectional relationship between the ECS and immune system, likely mediated by microglia which express both CB1 and CB2 receptors.[81,82,83] CB2 activation in microglia appears to have anti-inflammatory effects,[84] and the CB2 agonist β-caryophyllene (a constituent in herbs such as lavender and lemon balm) has been found to reduce anxiety and depressive-like behaviours in an animal study.[85]

Table 1. Therapeutics to Support the ECS and Relieve Symptoms.

Consideration	Therapeutic	ECS Function	Additional Actions
Lavender Oil and Theanine for Anxiety, Panic and Low Mood	*Melissa officinalis* (lemon balm)	Lemon balm contains terpenes that may have ECS regulating action.[86,87]	Lemon balm inhibits GABA-transaminase (which breaks down GABA)[88] and has been found to have anxiolytic and antidepressant effects in clinical trials.[89,90,91]
	Lavandula angustifolia (lavender)	Lavender oil is a FAAH inhibitor,[92] and contains terpenes that may have ECS regulating action.[93,94]	Human trials confirm the anxiolytic effects of lavender oil.[95,96]
	L-theanine	L-theanine may have ECS action (preclinical research, in combination with lemon balm and magnolia).[97]	L-theanine reduces glutamate transmission[98] and has been found to increase BDNF and improve anxiety and depressive symptoms in several studies.[99,100,101,102,103]

Chronic pain is a major risk factor for mood disorders.[104] ECS regulating therapeutics including cannabidiol (CBD; a phytocannabinoid derived from *Cannabis sativa*) and the eCB-like mediator PEA may have benefits for mental health. CBD is a CB1/CB2 and TRPV1 agonist, with preclinical research suggesting anxiolytic, antidepressant, anti-inflammatory, neuroprotective and analgesic action.[105,106] However, despite its growing popularity, two recent systematic reviews conclude that CBD currently has insufficient evidence to support its use in mood disorders.[107,108]

PEA boasts a plethora of preclinical studies indicating anti-inflammatory, neuroprotective and analgesic effects.[109,110] Moreover, a human clinical trial found that 1,200 mg/d PEA was associated with significantly greater improvement in depressive symptoms when added to selective serotonin reuptake inhibitor (SSRI) treatment in 54 patients with major depression.[111] The mechanisms underlying PEA's purported antidepressant effects are still being elucidated, with researchers speculating that they may be modulated by PEA's anti-inflammatory action via TRPV1[112] or PPAR-α binding,[113] or its ability to enhance BDNF production.[114] Despite these promising findings, further clinical trials are needed before recommending either PEA or CBD as a standalone treatment for anxiety or depression.

Dysbiosis Alters Endocannabinoid Signalling

A fascinating animal study recently shed light on the cross talk between the ECS and the gut microbiome (Figure 3).[115] In a mouse model of depression, a faecal microbiota transfer (FMT) to healthy mice transmitted both depressive symptoms and reduced neurogenesis. Depression was associated with dysbiosis (decreased *Lactobacilli* abundance and increased *Ruminococcaceae* and *Porphyromonodaceae* species), which altered fatty acid metabolism culminating in reduced levels of 2-AG. Interestingly, supplementing AA (the precursor to eCB synthesis) or blocking the MAGL enzyme (which degrades 2-AG) successfully alleviated the FMT-induced depressive symptoms and improved neurogenesis. Moreover, simply supplementing a strain of the probiotic *Lactobacillus plantarum* reversed depressive behaviour and significantly increased hippocampal 2-AG and AEA concentrations. *L. plantarum* additionally improved neurogenesis, suggesting that supporting microbiome health and correcting dysbiosis may be an essential component to regulating the ECS and supporting mood.

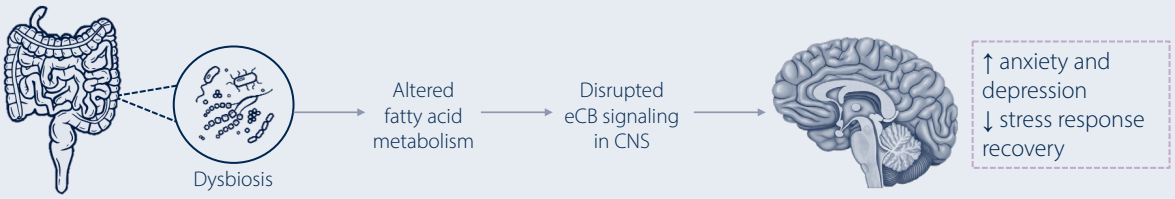

Figure 3. Intestinal Dysbiosis Dysregulates Endocannabinoid (eCB) Signalling in the Central Nervous System (CNS).[116]

To learn more about the influence of the microbiota-gut-brain axis, and which therapies support this axis and promote mental wellbeing, tune into the **Microbiota-Gut-Brain Axis** webinar, available on demand at Metagenics Institute*.

Restore and Rebuild: Holistic Care Supports Stress Resilience and the ECS

As aforementioned, restoring the stress response will naturally support the ECS and improve wellbeing. In addition to therapeutics, lifestyle factors such as a healthy diet and regular exercise can help rebuild resilience and support the ECS (Table 2, Figure 4). For example, yoga has been found to decrease subjective stress, anxiety and depression in several clinical trials.[117,118] A recent study found that a four-day yoga retreat was associated with significant increases in serum AEA and 2-AG, implicating the ECS in the underlying mechanism of yoga's stress-relieving action.[119] Similarly, most Practitioners will include physical activity in their holistic prescription to support patients' mental health but may be unaware that the ECS may be at least partially responsible for exercises' beneficial effects on mood. In fact, Raichlen and colleagues suggest that the well-known 'runner's high' may be related to eCB release during exercise.[120] Moderate intensity exercise increases levels of AEA and improves mood symptoms in both healthy individuals[121] and those with clinical depression[122] and PTSD.[123] Circulating concentrations of BDNF are also elevated following exercise, which may contribute (independently or in conjunction with eCBs) to the neuroplastic and antidepressant effects of movement.[124]

*metagenicsinstitute.com.au or metagenicsinstitute.co.nz

Table 2. Diet and Lifestyle to Restore an Appropriate Stress Response, Rebuild Resilience and Support the ECS.

Holistic recommendation	Rationale
Moderate intensity exercise	Moderate intensity exercise increases circulating eCBs, particularly AEA[125,126] and has a beneficial effect on mood.[127]
Mediterranean diet; sufficient fat intake	AEA and 2-AG are synthesized from omega-6 polyunsaturated fatty acid and AA.a[128] Studies indicate some eCBs derived from dietary omega-3 have anti-inflammatory effects.[129,130] The Mediterranean diet is well established in supporting optimal mood[131] and recent research suggests part of its mechanism may be modulated by the ECS.[132]
Lavender, lemon balm and other herbs and spices containing β-caryophyllene (e.g., oregano, cinnamon, basil, coriander, sage, hemp, cloves, rosemary, black pepper)	β-caryophyllene binds to CB2 receptors[133] and preclinical research suggests β-caryophyllene reduces neuroinflammation,[134] and anxiety and depressive-like behaviours rodents.[135]
Prebiotics and probiotics	Dysbiosis (specifically a reduction in *Lactobacilli*) alters fatty acid metabolism and eCB synthesis and signalling, while probiotics have been found to increase eCB production and reduce depressive symptoms in animal studies.[136] *Lactobacillus plantarum 299v* has been shown to enhance *Lactobacilli* concentration and reduce salivary cortisol in response to stress,[137] indicating *Lpc-37™ and 299v for Gut-Brain Axis Support, Emotional Wellbeing and Stress Response.*
Dark chocolate and cacao	Cacao contains molecular elements which are similar to eCBs.[138] Cross-sectional research indicates dark chocolate consumption may be associated with lower risk of depression.[139]
Avoid excess alcohol	While CB1 is involved in the reinforcing properties of alcohol, preclinical studies indicate heavy/chronic alcohol consumption dysregulates the ECS, altering eCB levels and CB1 expression.[140]
Stress management	As chronic stress dysregulates the ECS[141,142] stress management techniques are essential. A four-day yoga retreat was associated with significant reduction in depression and anxiety and increased AEA, 2- AG and BDNF, implicating the ECS in the underlying mechanism of yoga for mental wellbeing.[143]

The Mediterranean diet (MD) is well established in supporting optimal mental wellbeing[144] and recent research suggests part of its benefit may also be modulated by the ECS.[145] The high polyunsaturated fat content of the MD may support balanced eCB production, as AEA and 2-AG are synthesized from omega-6 polyunsaturated fatty acid and AA,[146] while eCBs derived from dietary omega-3 have anti-inflammatory effects.[147,148] Moreover, PEA is naturally found in several foods that may be part of the MD, including soy bean, peanut, black eyed bean and corn.[149] The MD additionally modulates the gut microbiome towards a less inflammatory composition.[150] Dysbiosis (specifically a reduction in *Lactobacilli*) alters fatty acid metabolism and eCB synthesis and signalling, while probiotics have been found to both enhance eCB production and reduce depressive symptoms (Box 2).[151] *Lactobacillus plantarum 299v* has been shown to enhance *Lactobacilli* concentration and reduce salivary cortisol in response to stress.[152] Therefore, Practitioners can consider *Lpc-37™ and 299v for Gut-Brain Axis Support, Emotional Wellbeing and Stress Response.*

The Silent Pandemic

Supporting Patients Through a Mental Health Crisis

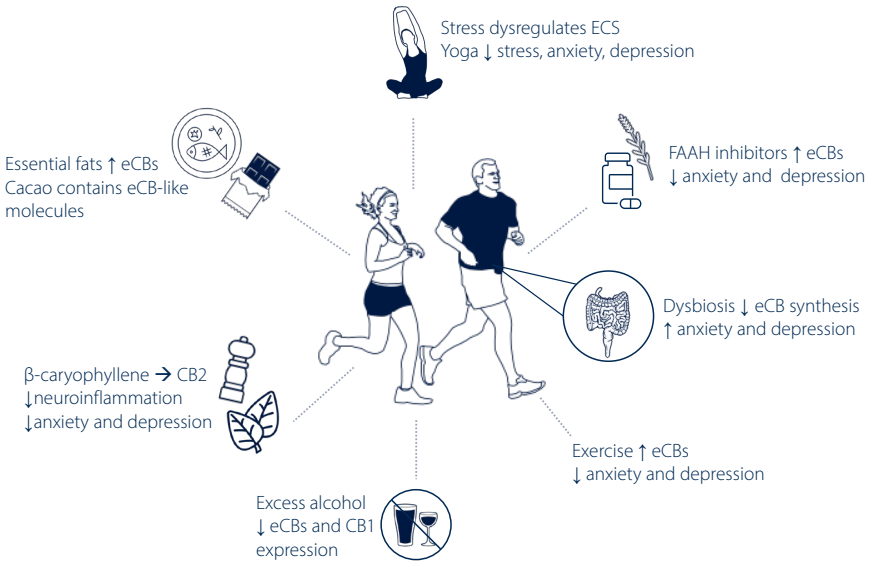

Figure 4. Holistic Care Regulates Endocannabinoid Tone and Function.[153,154,155,156,157,158,159,160]

ECS: Endocannabinoid system; eCB: Endocannabinoid; CB1: Cannabinoid receptor type 1; CB2: Cannabinoid receptor type 2; FAAH: Fatty acid amide hydrolase.

Nurturing the Endocannabinoid System Supports Mood

The endocannabinoid system is essential for regulating stress and mood. A growing body of research implicates the ECS in symptoms associated with chronic stress, depression and anxiety. Although the evidence is not yet equivocal, it is certain that holistic care to relieve, restore and rebuild a healthy stress response (Table 3) assists with ECS regulation and will support patients living with poor mental health and the ongoing stress of the COVID-19 pandemic. Future studies will continue to refine our understanding of the part played by the ECS – an essential player in the regulation of mood.

Table 3: Considerations to Support Patients with Stress, Anxiety and ECS Dysregulation.

	Considerations
RELIEVE	If anxious and tense: *Herbal Support for Hyper HPA and Stress* If low mood and panicky: *Lavender Oil and Theanine for Anxiety, Panic and Low Mood*
RESTORE	*Lpc-37™ and 299v for Gut-Brain Axis Support, Emotional Wellbeing and Stress Response*
REBUILD	**Emotional Support** • Social support • Meaning and purpose • Therapy **Lifestyle Changes** • Movement • Mindfulness • Sleep hygiene • Nutrition

References

1 Australian Insittute of Health and Wellness (AIHW). Mental health [Internet]. AIHW; 2020 [updated 2020 Jul 23, cited 2021 Dec 7]. Available from https://www.aihw.gov.au/reports/australias-health/mental-health

2 Hunt D. We asked 9,000 Australians about their mental health needs post-COVID — this is what they want [Internet]. The Conversation; 2021 [updated 2021 Sep 1, cited 2021 Dec 2]. Available from https://theconversation.com/we-asked-9-000-australians-about-their-mental-health-needs-post-covid-this-is-what-they-want-165885

3 Gasteiger N, Vedhara K, Massey A, Jia R, Ayling K, Chalder T, et al. Depression, anxiety and stress during the COVID-19 pandemic: Results from a New Zealand cohort study on mental well-being. BMJ Open. 2021 May 3;11(5):e045325. doi: 10.1136/bmjopen-2020-045325

4 Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. Int J Mol Sci. 2018 Mar 13;19(3):833. doi: 10.3390/ijms19030833

5 de Melo Reis RA, Isaac AR, Freitas HR, de Almeida MM, Schuck PF, Ferreira GC, et al. Quality of life and a surveillant endocannabinoid system. Front Neurosci. 2021 Oct 28;15:747229. doi: 10.3389/fnins.2021.747229

6 McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS One. 2014 Mar 12;9(3):e89566. doi: 10.1371/journal.pone.0089566

7 Navarrete F, García-Gutiérrez MS, Jurado-Barba R, Rubio G, Gasparyan A, Austrich-Olivares A, et al. Endocannabinoid system components as potential biomarkers in psychiatry. Front Psychiatry. 2020 Apr 27;11:315. doi: 10.3389/fpsyt.2020.00315

8 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-

9 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

10 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

11 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-5

12 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

13 Borgonetti V, Governa P, Biagi M, Galeotti N. Novel therapeutic approach for the management of mood disorders: In vivo and in vitro effect of a combination of l-theanine, melissa officinalis l. and magnolia officinalis. Nutrients. 2020 Jun 17;12(6):1803. doi: 10.3390/nu12061803

14 Augustin SM, Lovinger DM. Functional relevance of endocannabinoid-dependent synaptic plasticity in the central nervous system. ACS Chem Neurosci. 2018 Sep 19;9(9):2146-61. doi: 10.1021/acschemneuro.7b00508

15 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

16 Navarrete F, García-Gutiérrez MS, Jurado-Barba R, Rubio G, Gasparyan A, Austrich-Olivares A, et al. Endocannabinoid system components as potential biomarkers in psychiatry. Front Psychiatry. 2020 Apr 27;11:315. doi: 10.3389/fpsyt.2020.00315

17 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

18 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-5

19 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-5

20 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

21 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-5

22 Toczek M, Malinowska B. Enhanced endocannabinoid tone as a potential target of pharmacotherapy. Life Sci. 2018 Jul 1;204:20-45. doi: 10.1016/j.lfs.2018.04.054

23 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids and their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

24 Navarrete F, García-Gutiérrez MS, Jurado-Barba R, Rubio G, Gasparyan A, Austrich-Olivares A, et al. Endocannabinoid system components as potential biomarkers in psychiatry. Front Psychiatry. 2020 Apr 27;11:315. doi: 10.3389/fpsyt.2020.00315.

25 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-341. doi: 10.1038/s41401-018-0051-5.

26 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

27 Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016 Jan;41(1):80-102. doi: 10.1038/npp.2015.166

28 Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Psychobiological responses to aerobic exercise in individuals with posttraumatic stress disorder. J Trauma Stress. 2018 Feb;31(1):134-45. doi: 10.1002/jts.22253

29 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

30 Stensson N, Gerdle B, Ernberg M, Mannerkorpi K, Kosek E, Ghafouri B. Increased anandamide and decreased pain and depression after exercise in fibromyalgia. Med Sci Sports Exerc. 2020 Jul;52(7):1617-28. doi: 10.1249/MSS.0000000000002293

31 Li S, Yang B, Du Y, Lin Y, Liu J, Huang S, et al. Targeting PPARα for the treatment and understanding of cardiovascular diseases. Cell Physiol Biochem. 2018;51(6):2760-75. doi: 10.1159/000495969

32 Tufano M, Pinna G. Is there a future for PPARs in the treatment of neuropsychiatric disorders? Molecules. 2020 Feb 27;25(5):1062. doi: 10.3390/molecules25051062

33 Forteza F, Giorgini G, Raymond F. Neurobiological processes induced by aerobic exercise through the endocannabinoidome. Cells. 2021 Apr 17;10(4):938. doi: 10.3390/cells10040938.

34 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

35 Yin AQ, Wang F, Zhang X. Integrating endocannabinoid signaling in the regulation of anxiety and depression. Acta Pharmacol Sin. 2019 Mar;40(3):336-41. doi: 10.1038/s41401-018-0051-5

36 Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016 Jan;41(1):80-102. doi: 10.1038/npp.2015.166

37 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

38 Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016 Jan;41(1):80-102. doi: 10.1038/npp.2015.166

39 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

40 Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016 Jan;41(1):80-102. doi: 10.1038/npp.2015.166

41 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

42 Desai S, Borg B, Cuttler C, Crombie KM, Rabinak CA, Hill MN, et al. A systematic review and meta-analysis on the effects of exercise on the endocannabinoid system. Cannabis Cannabinoid Res. 2021 Dec 3 [online ahead of print] doi: 10.1089/can.2021.0113

43 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

44 Hill MN, Miller GE, Ho WS, Gorzalka BB, Hillard CJ. Serum endocannabinoid content is altered in females with depressive disorders: A preliminary report. Pharmacopsychiatry. 2008;41:48–53. doi: 10.1055/s2007-993211

45 Hill MN, Miller GE, Ho WS, Gorzalka BB, Hillard CJ. Serum endocannabinoid content is altered in females with depressive disorders: A preliminary report. Pharmacopsychiatry. 2008;41:48–53. doi: 10.1055/s2007-993211

46 Hill MN, Miller GE, Carrier EJ, Gorzalka BB, Hillard CJ. Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology. 2009;34:1257–62. doi: 10.1016/j.psyneuen.2009.03.013

47 Hill MN, Bierer LM, Makotkine I, Golier JA, Galea S, McEwen BS, et al. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Centre attacks. Psychoneuroendocrinology. 2013 Dec;38(12):2952-61. doi: 10.1016/j.psyneuen.2013.08.004

48 Wilker S, Pfeiffer A, Elbert T, Ovuga E, Karabatsiakis A, Krumbholz A, et al. Endocannabinoid concentrations in hair are associated with PTSD symptom severity. Psychoneuroendocrinology. 2016 May;67:198-206. doi: 10.1016/j.psyneuen.2016.02.010

49 Yi B, Nichiporuk I, Nicolas M, Schneider S, Feuerecker M, Vassilieva G, et al. Reductions in circulating endocannabinoid 2-arachidonoylglycerol levels in healthy human subjects exposed to chronic stressors. Prog Neuropsychopharmacol Biol Psychiatry. 2016 Jun 3;67:92-7. doi: 10.1016/j.pnpbp.2016.01.004

50 Russo EB. Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other yreatment-resistant syndromes. Cannabis Cannabinoid Res. 2016 Jul 1;1(1):154-65. doi: 10.1089/can.2016.0009

51 Russo EB. Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis Cannabinoid Res. 2016 Jul 1;1(1):154-65. doi: 10.1089/can.2016.0009

52 Toczek M, Malinowska B. Enhanced endocannabinoid tone as a potential target of pharmacotherapy. Life Sci. 2018 Jul 1;204:20-45. doi: 10.1016/j.lfs.2018.04.054

53 McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS One. 2014 Mar 12;9(3):e89566. doi: 10.1371/journal.pone.0089566

54 Toczek M, Malinowska B. Enhanced endocannabinoid tone as a potential target of pharmacotherapy. Life Sci. 2018 Jul 1;204:20-45. doi: 10.1016/j.lfs.2018.04.054

55 McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS One. 2014 Mar 12;9(3):e89566. doi: 10.1371/journal.pone.0089566

56 Toczek M, Malinowska B. Enhanced endocannabinoid tone as a potential target of pharmacotherapy. Life Sci. 2018 Jul 1;204:20-45. doi: 10.1016/j.lfs.2018.04.054

57 McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS One. 2014 Mar 12;9(3):e89566. doi: 10.1371/journal.pone.0089566

58 Toczek M, Malinowska B. Enhanced endocannabinoid tone as a potential target of pharmacotherapy. Life Sci. 2018 Jul 1;204:20-45. doi: 10.1016/j.lfs.2018.04.054

59 Schmidt ME, Liebowitz MR, Stein MB, Grunfeld J, Van Hove I, Simmons WK, et al. The effects of inhibition of fatty acid amide hydrolase (FAAH) by JNJ-42165279 in social anxiety disorder: A double-blind, randomized, placebo-controlled proof-of-concept study. Neuropsychopharmacology. 2021 Apr;46(5):1004-10. doi: 10.1038/s41386-020-00888-1

60 Schmidt ME, Liebowitz MR, Stein MB, Grunfeld J, Van Hove I, Simmons WK, et al. The effects of inhibition of fatty acid amide hydrolase (FAAH) by JNJ-42165279 in social anxiety disorder: A double-blind, randomized, placebo-controlled proof-of-concept study. Neuropsychopharmacology. 2021 Apr;46(5):1004-10. doi: 10.1038/s41386-020-00888-1

61 Mayo LM, Asratian A, Lindé J, Morena M, Haataja R, Hammar V, et al. Elevated anandamide, enhanced recall of fear extinction, and attenuated stress responses following inhibition of fatty acid amide hydrolase: A randomized, controlled experimental medicine trial. Biol Psychiatry. 2020 Mar 15;87(6):538-47. doi: 10.1016/j.biopsych.2019.07.034

62 Sanna MD, Les F, Lopez V, Galeotti N. Lavender (Lavandula angustifolia) essential oil alleviates neuropathic pain in mice with spared nerve injury. Front Pharmacol. 2019 May 9;10:472. doi: 10.3389/fphar.2019.00472

63 Thors L, Eriksson J, Fowler CJ. Inhibition of the cellular uptake of anandamide by genistein and its analogue daidzein in cells with different levels of fatty acid amide hydrolase-driven uptake. Br J Pharmacol. 2007 Nov;152(5):744-50. doi: 10.1038/sj.bjp.0707401

64 Thors L, Belghiti M, Fowler CJ. Inhibition of fatty acid amide hydrolase by kaempferol and related naturally occurring flavonoids. Br J Pharmacol. 2008 Sep;155(2):244-52. doi: 10.1038/bjp.2008.237

65 Rempel V, Fuchs A, Hinz S, Karcz T, Lehr M, Koetter U, et al. Magnolia extract, magnolol, and metabolites: Activation of cannabinoid CB2 receptors and blockade of the related GPR55. ACS Med Chem Lett. 2012 Nov 14;4(1):41-5. doi: 10.1021/ml300235q

66 Borgonetti V, Governa P, Manetti F, Miraldi E, Biagi M, Galeotti N. A honokiol-enriched Magnolia officinalis bark extract possesses anxiolytic-like activity with neuroprotective effect through the modulation of CB1 receptor. J Pharm Pharmacol. 2021 Aug 12;73(9):1161-68. doi: 10.1093/jpp/rgab067

67 Fiebich BL, Weiss G, Hoffmann C. Modulation of the y-aminobutric acid (GABA) system by Passiflora incarnate L. Phytotherapy Research. 2011; 25(6):838-43

68 You Z, Xia Q, Liang F, Tang Y, Xu C, Huang J, et al. Effects on the expression of GABAA receptor subunits by jujuboside A treatment in rat hippocampal neurons. J Ethnopharmacol. 2010;128:419-23

69 Johnson SA, Rodriguez D, Allred K. A systematic review of essential oils and the endocannabinoid system: A connection worthy of further exploration. Evid Based Complement Alternat Med. 2020 May 15;2020:8035301. doi: 10.1155/2020/8035301

70 Sanna MD, Les F, Lopez V, Galeotti N. Lavender (Lavandula angustifolia) essential oil alleviates neuropathic pain in mice with spared nerve injury. Front Pharmacol. 2019 May 9;10:472. doi: 10.3389/fphar.2019.00472

71 Kasper S, Anghelescu I, Dienel A. Efficacy or orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep- a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2015 July 28;25:1960-67. doi: http://dx.doi.org/10.1016/j.euroneuro.2015.07.024

72 Woelk H, Schlafke S. A multi-centre, double-blind, randomised study of the lavender oil preparation Silexan in comparison to lorazepam for generalised anxiety disorder. Phytomed. 2010;17:94-9. doi:10.1016/j.phymed.2009.10.006

73 Firoozeei TS, Feizi A, Rezaeizadeh H, Zargaran A, Roohafza HR, Karimi M. The antidepressant effects of lavender (Lavandula angustifolia): A systematic review and meta-analysis of randomized controlled clinical trials. Complement Ther Med. 2021 Jun;59:102679. doi: 10.1016/j.ctim.2021.102679

74 Motahareh B, Shahin H, Masoud M, Tabandeh S. The effects of Melissa officinalis leaf extract on anxiety among patients undergoing orthopedic surgeries. J Herb Med. 2022;31:100532. doi: 10.1016/j.hermed.2021.100532

75 Haybar H, Javid AZ, Haghighizadeh MH, Valizadeh E, Mohaghegh SM, Mohammadzadeh A. The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. Clin Nutr ESPEN. 2018 Aug;26:47-52. doi: 10.1016/j.clnesp.2018.04.015

76 Miodownik C, Maayan R, Ratner Y, Lerner V, Pintov L, Mar M, et al. Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Clin Neuropharmacol. 2011 Jul-Aug;34(4):155-60. doi: 10.1097/WNF.0b013e318220d8c6

77 Hidese S, Ogawa S, Ota M, Ishida I, Yasukawa Z, Ozeki M, et al. Effects of L-theanine administration on stress-related symptoms and cognitive functions in healthy adults: a randomized controlled trial. Nutrients. 2019 Oct 3;11(10):2362. doi: 10.3390/nu11102362

78 Rothenberg DO, Zhang L. Mechanisms underlying the anti-depressive effects of regular tea consumption. Nutrients. 2019 Jun 17;11(6):1361. doi: 10.3390/nu11061361

79 Yoneda Y, Kawada K, Kuramoto N. Selective upregulation by theanine of Slc38a1 expression in neural stem cell for brain wellness. Molecules. 2020 Jan 15;25(2):347. doi: 10.3390/molecules25020347

80 Rhie SJ, Jung EY, Shim I. The role of neuroinflammation on pathogenesis of affective disorders. J Exerc Rehabil. 2020 Feb 26;16(1):2-9. doi: 10.12965/jer.2040016.008

81 Stampanoni Bassi M, Gilio L, Maffei P, Dolcetti E, Bruno A, Buttari F, et al. Exploiting the multifaceted effects of cannabinoids on mood to boost their therapeutic use against anxiety and depression. Front Mol Neurosci. 2018 Nov 20;11:424. doi: 10.3389/fnmol.2018.00424

82 deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet your stress management professionals: The endocannabinoids. Trends Mol Med. 2020 Oct;26(10):953-68. doi: 10.1016/j.molmed.2020.07.002

83 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

84 Stampanoni Bassi M, Gilio L, Maffei P, Dolcetti E, Bruno A, Buttari F, et al. Exploiting the multifaceted effects of cannabinoids on mood to boost their therapeutic use against anxiety and depression. Front Mol Neurosci. 2018 Nov 20;11:424. doi: 10.3389/fnmol.2018.00424

85 Bahi A, Al Mansouri S, Al Memari E, Al Ameri M, Nurulain SM, Ojha S. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. Physiol Behav. 2014 Aug;135:119-24. doi: 10.1016/j.physbeh.2014.06.003

86 Johnson SA, Rodriguez D, Allred K. A systematic review of essential oils and the endocannabinoid system: A connection worthy of further exploration. Evid Based Complement Alternat Med. 2020 May 15;2020:8035301. doi: 10.1155/2020/8035301

87 Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, Altmann KH, Karsak M, Zimmer A. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci U S A. 2008 Jul 1;105(26):9099-104. doi: 10.1073/pnas.0803601105

88 Borgonetti V, Governa P, Biagi M, Galeotti N. Novel therapeutic approach for the management of mood disorders: In vivo and in vitro effect of a combination of l-theanine, melissa officinalis l. and magnolia officinalis Rehder & E.H. Wilson. Nutrients. 2020 Jun 17;12(6):1803. doi: 10.3390/nu12061803

89 Motahareh B, Shahin H, Masoud M, Tabandeh S. The effects of Melissa officinalis leaf extract on anxiety among patients undergoing orthopedic surgeries. J Herb Med. 2022;31:100532. doi: 10.1016/j.hermed.2021.100532

90 Motahareh B, Shahin H, Masoud M, Tabandeh S. The effects of Melissa officinalis leaf extract on anxiety among patients undergoing orthopedic surgeries. J Herb Med. 2022;31:100532. doi: 10.1016/j.hermed.2021.100532

91 Haybar H, Javid AZ, Haghighizadeh MH, Valizadeh E, Mohaghegh SM, Mohammadzadeh A. The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. Clin Nutr ESPEN. 2018 Aug;26:47-52. doi: 10.1016/j.clnesp.2018.04.015

92 Sanna MD, Les F, Lopez V, Galeotti N. Lavender (lavandula angustifolia mill.) essential oil alleviates neuropathic pain in mice with spared nerve injury. Front Pharmacol. 2019 May 9;10:472. doi: 10.3389/fphar.2019.00472

93 Johnson SA, Rodriguez D, Allred K. A systematic review of essential oils and the endocannabinoid system: A connection worthy of further exploration. Evid Based Complement Alternat Med. 2020 May 15;2020:8035301. doi: 10.1155/2020/8035301

94 Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, et al. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci U S A. 2008 Jul 1;105(26):9099-104. doi: 10.1073/pnas.0803601105

95 Kasper S, Anghelescu I, Dienel A. Efficacy or orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep- a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2015 July 28;25:1960-67. doi: http://dx.doi.org/10.1016/j.euroneuro.2015.07.024

96 Woelk H, Schlafke S. A multi-centre, double-blind, randomised study of the lavender oil preparation Silexan in comparison to lorazepam for generalised anxiety disorder. Phytomed. 2010;17:94-99. doi:10.1016/j.phymed.2009.10.006

97 Borgonetti V, Governa P, Biagi M, Galeotti N. Novel therapeutic approach for the management of mood disorders: In vivo and in vitro effect of a combination of l-theanine, melissa officinalis l. and magnolia officinalis Rehder & E.H. Wilson. Nutrients. 2020 Jun 17;12(6):1803. doi: 10.3390/nu12061803

98 Borgonetti V, Governa P, Biagi M, Galeotti N. Novel therapeutic approach for the management of mood disorders: In vivo and in vitro effect of a combination of l-theanine, melissa officinalis l. and magnolia officinalis Rehder & E.H. Wilson. Nutrients. 2020 Jun 17;12(6):1803. doi: 10.3390/nu12061803

99 Miodownik C, Maayan R, Ratner Y, Lerner V, Pintov L, Mar M, et al. Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Clin Neuropharmacol. 2011 Jul-Aug;34(4):155-60. doi: 10.1097/WNF.0b013e318220d8c6

100 Hidese S, Ogawa S, Ota M, Ishida I, Yasukawa Z, Ozeki M, et al. Effects of L-theanine administration on stress-related symptoms and cognitive functions in healthy adults: a randomized controlled trial. Nutrients. 2019 Oct 3;11(10):2362. doi: 10.3390/nu11102362

101 Rothenberg DO, Zhang L. Mechanisms underlying the anti-depressive effects of regular tea consumption. Nutrients. 2019 Jun 17;11(6):1361. doi: 10.3390/nu11061361

102 Yoneda Y, Kawada K, Kuramoto N. Selective upregulation by theanine of Slc38a1 expression in neural stem cell for brain wellness. Molecules. 2020 Jan 15;25(2):347. doi: 10.3390/molecules25020347

103 Hidese S, Ogawa S, Ota M, Ishida I, Yasukawa Z, Ozeki M, et al. Effects of L-theanine administration on stress-related symptoms and cognitive functions in healthy adults: A randomized controlled trial. Nutrients. 2019 Oct 3;11(10):2362. doi: 10.3390/nu11102362

104 Sheng J, Liu S, Wang Y, Cui R, Zhang X. The link between depression and chronic pain: Neural mechanisms in the brain. Neural Plast. 2017;2017:9724371. doi: 10.1155/2017/9724371

105 Khan R, Naveed S, Mian N, Fida A, Raafey MA, Aedma KK. The therapeutic role of Cannabidiol in mental health: A systematic review. J Cannabis Res. 2020 Jan 2;2(1):2. doi: 10.1186/s42238-019-0012-y

106 García-Gutiérrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J. Cannabidiol: A potential new alternative for the treatment of anxiety, depression, and psychotic Disorders. Biomolecules. 2020 Nov 19;10(11):1575. doi: 10.3390/biom10111575

107 Pinto JV, Saraf G, Frysch C, Vigo D, Keramatian K, Chakrabarty T, et al. Cannabidiol as a treatment for mood disorders: A systematic review. Can J Psychiatry. 2020 Apr;65(4):213-27. doi: 10.1177/0706743719895195

108 Stanciu CN, Brunette MF, Teja N, Budney AJ. Evidence for use of cannabinoids in mood disorders, anxiety disorders, and PTSD: A systematic review. Psychiatr Serv. 2021 Apr 1;72(4):429-436. doi: 10.1176/appi.ps.202000189

109 Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A natural compound for health management. Int J Mol Sci. 2021 May 18;22(10):5305. doi: 10.3390/ijms22105305

110 De Gregorio D, Manchia M, Carpiniello B, Valtorta F, Nobile M, Gobbi G, et al. Role of palmitoylethanolamide (PEA) in depression: Translational evidence: Special section on "translational and neuroscience studies in affective disorders". J Affect Disord. 2019 Aug 1;255:S0165-0327(18)31599-4. doi: 10.1016/j.jad.2018.10.117

111 Ghazizadeh-Hashemi M, Ghajar A, Shalbafan MR, Ghazizadeh-Hashemi F, Afarideh M, Malekpour F, et al. Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. J Affect Disord. 2018 May;232:127-33. doi: 10.1016/j.jad.2018.02.057

112 Ambrosino P, Soldovieri MV, Russo C, Taglialatela M. Activation and desensitization of TRPV1 channels in sensory neurons by the PPARα agonist palmitoylethanolamide. Br J Pharmacol. 2013 Mar;168(6):1430-44. doi: 10.1111/bph.12029

113 Melis M, Scheggi S, Carta G, Madeddu C, Lecca S, Luchicchi A, et al. PPARα regulates cholinergic-driven activity of midbrain dopamine neurons via a novel mechanism involving α7 nicotinic acetylcholine receptors. J Neurosci. 2013 Apr 3;33(14):6203-11. doi: 10.1523/JNEUROSCI.4647-12.2013

114 Cuzzocrea S, Crupi R, Paterniti I, Impellizzeri D, Campolo M, Esposito E. Palmitoylethanolamide enhances brain-derived neurotrophic factor production and neurogenesis in the hippocampus following ischemic brain injury. FASEB J. 2013 Apr 27;1177.13. doi: 10.1096/fasebj.27.1_supplement.1177.13

115 Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, et al. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2

116 Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, et al. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2

117 Sadhasivam S, Alankar S, Maturi R, Vishnubhotla RV, Mudigonda M, Pawale D, et al. Inner engineering practices and advanced 4-day isha yoga retreat are associated with cannabimimetic effects with increased endocannabinoids and short-term and sustained improvement in mental health: A prospective observational study of meditators. Evid Based Complement Alternat Med. 2020 Jun 5;2020:8438272. doi: 10.1155/2020/8438272

118 Shohani M, Badfar G, Nasirkandy MP, Kaikhavani S, Rahmati S, Modmeli Y, et al. The effect of yoga on stress, anxiety, and depression in women. Int J Prev Med. 2018 Feb 21;9:21. doi: 10.4103/ijpvm.IJPVM_242_16

119 Sadhasivam S, Alankar S, Maturi R, Vishnubhotla RV, Mudigonda M, Pawale D, et al. Inner engineering practices and advanced 4-day isha yoga retreat are associated with cannabimimetic effects with increased endocannabinoids and short-term and sustained improvement in mental health: A prospective observational study of meditators. Evid Based Complement Alternat Med. 2020 Jun 5;2020:8438272. doi: 10.1155/2020/8438272

120 Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A. Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high. J Exp Biol. 2012;215(8):1331–6

121 Raichlen DA, Foster AD, Seillier A, Giuffrida A, Gerdeman GL. Exercise-induced endocannabinoid signaling is modulated by intensity. Eur J Appl Physiol. 2013 Apr;113(4):869-75. doi: 10.1007/s00421-012-2495-5

122 Meyer JD, Crombie KM, Cook DB, Hillard CJ, Koltyn KF. Serum endocannabinoid and mood changes after exercise in major depressive disorder. Med Sci Sports Exerc. 2019 Sep;51(9):1909-17. doi: 10.1249/MSS.0000000000002006

123 Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Psychobiological responses to aerobic exercise in individuals with posttraumatic stress disorder. J Trauma Stress. 2018 Feb;31(1):134-145. doi: 10.1002/jts.22253

124 Desai S, Borg B, Cuttler C, Crombie KM, Rabinak CA, Hill MN, et al. A systematic review and meta-analysis on the effects of exercise on the endocannabinoid system. Cannabis Cannabinoid Res. 2021 Dec 3 [online ahead of print] doi: 10.1089/can.2021.0113

125 Meyer JD, Crombie KM, Cook DB, Hillard CJ, Koltyn KF. Serum endocannabinoid and mood changes after exercise in major depressive disorder. Med Sci Sports Exerc. 2019 Sep;51(9):1909-17. doi: 10.1249/MSS.0000000000002006

126 Raichlen DA, Foster AD, Seillier A, Giuffrida A, Gerdeman GL. Exercise-induced endocannabinoid signaling is modulated by intensity. Eur J Appl Physiol. 2013 Apr;113(4):869-75. doi: 10.1007/s00421-012-2495-5

127 Meyer JD, Crombie KM, Cook DB, Hillard CJ, Koltyn KF. Serum endocannabinoid and mood changes after exercise in major depressive disorder. Med Sci Sports Exerc. 2019 Sep;51(9):1909-17. doi: 10.1249/MSS.0000000000002006

128 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

129 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

130 Das A, Watson J, Carnevale L, Arnold W. Omega-3 endocannabinoid-epoxides are novel anti-inflammatory and anti-pain lipid metabolites (FS15-01-19). Curr Dev Nutr. 2019 Jun 13;3(Suppl 1):nzz031.FS15-01-19. doi: 10.1093/cdn/nzz031.FS15-01-19

131 Ventriglio A, Sancassiani F, Contu MP, Latorre M, Di Slavatore M, Fornaro M, et al. Mediterranean diet and its benefits on health and mental health: A literature review. Clin Pract Epidemiol Ment Health. 2020 Jul 30;16(Suppl-1):156-64. doi: 10.2174/1745017902016010156

132 Tagliamonte S, Laiola M, Ferracane R, Vitale M, Gallo MA, Meslier V, et al. Mediterranean diet consumption affects the endocannabinoid system in overweight and obese subjects: possible links with gut microbiome, insulin resistance and inflammation. Eur J Nutr. 2021;60, 3703–16. doi: 10.1007/s00394- 021-02538-8

133 Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, et al. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci U S A. 2008 Jul 1;105(26):9099-104. doi: 10.1073/pnas.0803601105

134 Johnson SA, Rodriguez D, Allred K. A systematic review of essential oils and the endocannabinoid system: A connection worthy of further exploration. Evid Based Complement Alternat Med. 2020 May 15;2020:8035301. doi: 10.1155/2020/8035301

135 Bahi A, Al Mansouri S, Al Memari E, Al Ameri M, Nurulain SM, Ojha S. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. Physiol Behav. 2014 Aug;135:119-24. doi: 10.1016/j.physbeh.2014.06.003

136 Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, et al. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2

137 Andersson H, Tullberg C, Ahrné S, Hamberg K, Lazou Ahrén I, Molin G, et al. Oral administration of Lactobacillus plantarum 299v reduces cortisol levels in human saliva during examination induced stress: a randomized, double-blind controlled trial. Int J Microbiol. 2016;2016:8469018. doi: 10.1155/2016/8469018

138 Nehlig A. The neuroprotective effects of cocoa flavanol and its influence on cognitive performance. Br J Clin Pharmacol. 2013 Mar;75(3):716-27. doi: 10.1111/j.1365-2125.2012.04378.x

139 Jackson SE, Smith L, Firth J, Grabovac I, Soysal P, Koyanagi A, et al. Is there a relationship between chocolate consumption and symptoms of depression? A cross-sectional survey of 13,626 US adults. Depress Anxiety. 2019 Oct;36(10):987-95. doi: 10.1002/da.22950

140 Pava MJ, Woodward JJ. A review of the interactions between alcohol and the endocannabinoid system: implications for alcohol dependence and future directions for research. Alcohol. 2012 May;46(3):185-204. doi: 10.1016/j.alcohol.2012.01.002

141 Morena M, Patel S, Bains JS, Hill MN. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016 Jan;41(1):80-102. doi: 10.1038/npp.2015.166

142 Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol. 2018 Sep 5;834:230-39. doi: 10.1016/j.ejphar.2018.07.039

143 Sadhasivam S, Alankar S, Maturi R, Vishnubhotla RV, Mudigonda M, Pawale D, et al. Inner engineering practices and advanced 4-day isha yoga retreat are associated with cannabimimetic effects with increased endocannabinoids and short-term and sustained improvement in mental health: A prospective observational study of meditators. Evid Based Complement Alternat Med. 2020 Jun 5;2020:8438272. doi: 10.1155/2020/8438272

144 Ventriglio A, Sancassiani F, Contu MP, Latorre M, Di Slavatore M, Fornaro M, et al. Mediterranean diet and its benefits on health and mental health: A literature review. Clin Pract Epidemiol Ment Health. 2020 Jul 30;16(Suppl-1):156-64. doi: 10.2174/1745017902016010156

145 Tagliamonte S, Laiola M, Ferracane R, Vitale M, Gallo MA, Meslier V, et al. Mediterranean diet consumption affects the endocannabinoid system in overweight and obese subjects: possible links with gut microbiome, insulin resistance and inflammation. Eur J Nutr. 2021;60:3703–16. doi: 10.1007/s00394- 021-02538-8

146 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

147 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

148 Das A, Watson J, Carnevale L, Arnold W. Omega-3 endocannabinoid-epoxides are novel anti-inflammatory and anti-pain lipid metabolites (FS15-01-19). Curr Dev Nutr. 2019 Jun 13;3(Suppl 1):nzz031.FS15-01-19. doi: 10.1093/cdn/nzz031.FS15-01-19

149 Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. Br J Pharmacol. 2017 Jun;174(11):1349-65. doi: 10.1111/bph.13580

150 Ghosh TS, Rampelli S, Jeffery IB, Santoro A, Neto M, Capri M, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut. 2020 Jul;69(7):1218-28. doi: 10.1136/gutjnl-2019-319654

151 Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, et al. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2

152 Andersson H, Tullberg C, Ahrné S, Hamberg K, Lazou Ahrén I, Molin G, et al. Oral administration of Lactobacillus plantarum 299v reduces cortisol levels in human saliva during examination induced stress: a randomized, double-blind controlled trial. Int J Microbiol. 2016;2016:8469018. doi: 10.1155/2016/8469018

153 Meyer JD, Crombie KM, Cook DB, Hillard CJ, Koltyn KF. Serum endocannabinoid and mood changes after exercise in major depressive disorder. Med Sci Sports Exerc. 2019 Sep;51(9):1909-17. doi: 10.1249/MSS.0000000000002006

154 Watson JE, Kim JS, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins Other Lipid Mediat. 2019 Aug;143:106337. doi: 10.1016/j.prostaglandins.2019.106337

155 Johnson SA, Rodriguez D, Allred K. A systematic review of essential oils and the endocannabinoid system: A connection worthy of further exploration. Evid Based Complement Alternat Med. 2020 May 15;2020:8035301. doi: 10.1155/2020/8035301

156 Bahi A, Al Mansouri S, Al Memari E, Al Ameri M, Nurulain SM, Ojha S. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. Physiol Behav. 2014 Aug;135:119-24. doi: 10.1016/j.physbeh.2014.06.003

157 Nehlig A. The neuroprotective effects of cocoa flavanol and its influence on cognitive performance. Br J Clin Pharmacol. 2013 Mar;75(3):716-27. doi: 10.1111/j.1365-2125.2012.04378.x

158 Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, et al. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2

159 Shohani M, Badfar G, Nasirkandy MP, Kaikhavani S, Rahmati S, Modmeli Y, et al. The effect of yoga on stress, anxiety, and depression in women. Int J Prev Med. 2018 Feb 21;9:21. doi: 10.4103/ijpvm.IJPVM_242_16

160 Pava MJ, Woodward JJ. A review of the interactions between alcohol and the endocannabinoid system: implications for alcohol dependence and future directions for research. Alcohol. 2012 May;46(3):185-204. doi: 10.1016/j.alcohol.2012.01.002