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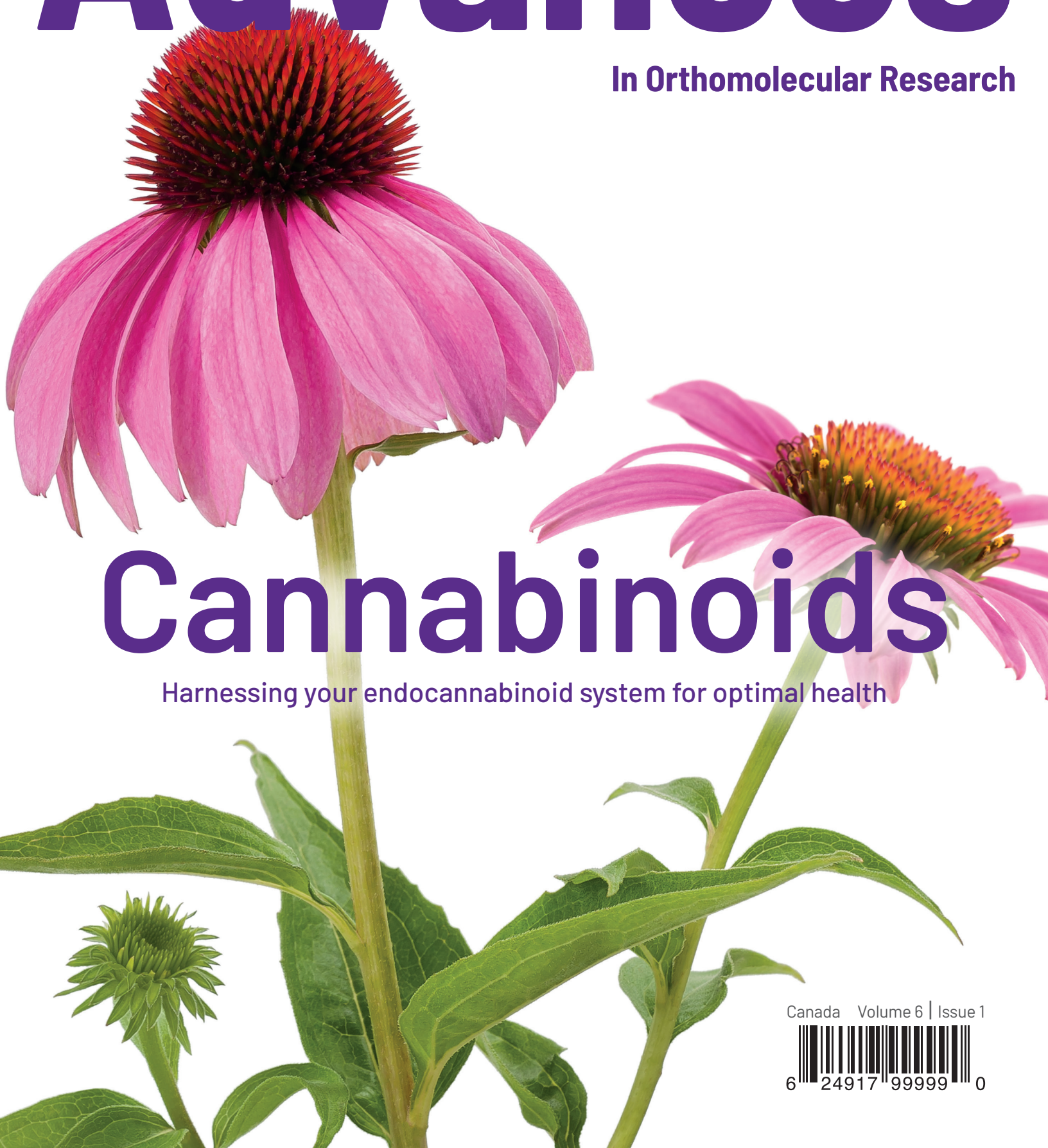

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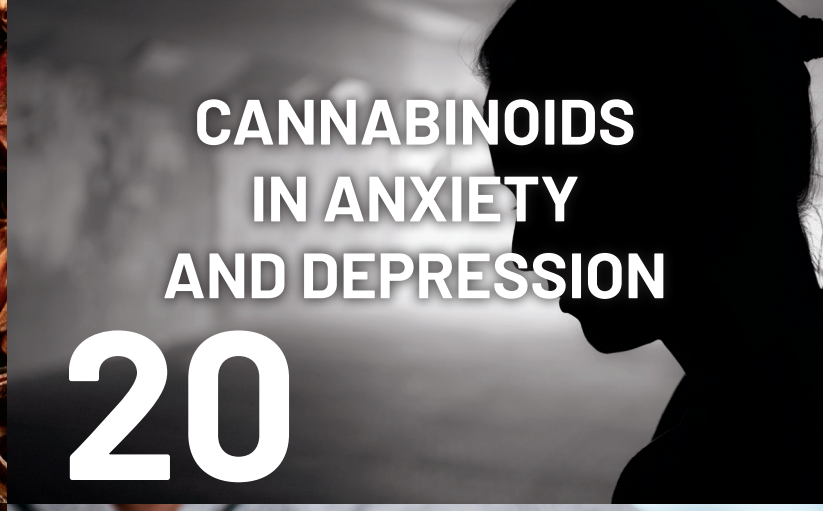

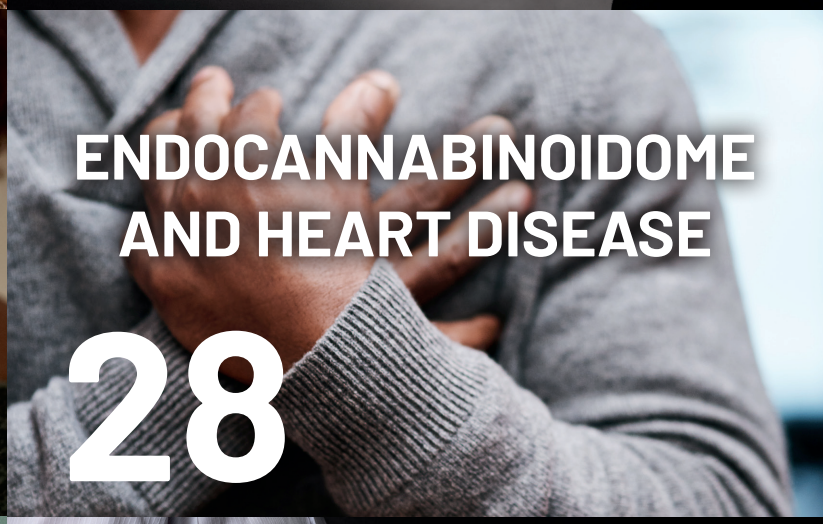

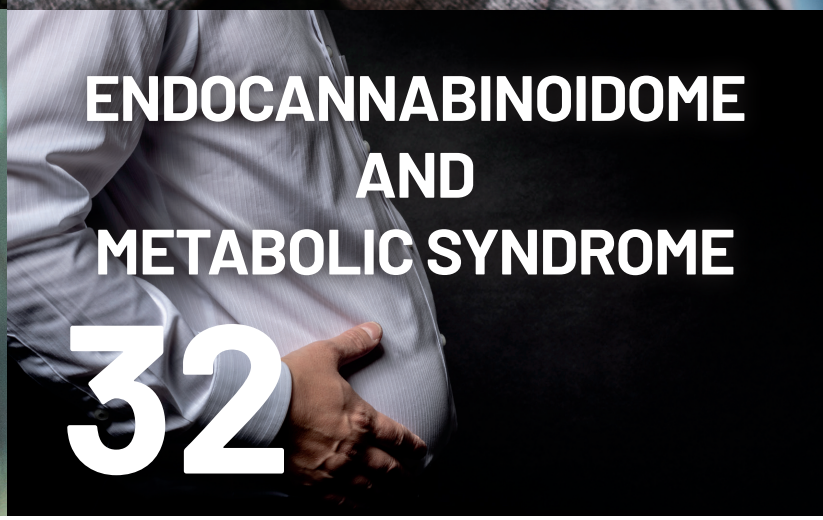

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Dietary Sources of Phytocannabinoids

Plants have been a predominant source of medicine for the majority of history; nature is considered **“the master craftsman of molecules”.**

Vegetation has been an infinite source of molecules for drug development, with more than 50% of currently approved and available drugs derived from natural sources (Rates, 2001; Veeresham, 2012).

It has only been in the last 28 years that science has given us a better understanding of the myriad of benefits of the endocannabinoid system (ECS). Since then, the last few years have brought forth non-cannabis plants that have stimulatory, antagonistic, or modulatory effects on the ECS. These plants have constituents that have been reported to bind to and functionally interact with the endogenous cannabinoid receptors, thereby opening up the definition of “phytocannabinoids” to any plant derived natural product capable of (i) direct interaction with the cannabinoid receptors or; (ii) sharing chemical similarities with cannabinoids (Russo, 2016).

Phytocannabinoids, both from cannabis and non-cannabis plants, also target other aspects of the ECS outside of the cannabinoid receptors. These compounds modulate the hydrolytic enzymes that control endocannabinoid levels or have allosteric binding sites on the cannabinoid receptors, thereby increasing or decreasing the binding affinity for the ligands and modulating downstream signalling of the ECS (Gertsch et al., 2010). It is interesting to note that the identified possible cannabimimetics or phytocannabinoids are lipids or lipid soluble, which would explain the ease at which these components interact and modulate the ECS.

There are four major ways by which the phytocannabinoids interact with the ECS. These include:

i. Phytocannabinoids that bind to and interact with the Cannabinoid Receptor 1 (CB1)

ii. Phytocannabinoids that bind to and interact with the Cannabinoid Receptor 2 (CB2)

iii. Phytocannabinoids that target “orphan” receptors in the ECS

iv. Phytocannabinoids that inhibit the activity of the enzymatic cascade of the endogenous cannabinoid signalling system.

Research is attempting to identify plants that contain the same components as cannabis sativa – CBD, THC, CBG, etc. Although cannabinoid-like compounds have been identified in certain plants, direct identification of the phytocannabinoids – CBD, THC, etc. have not definitively been identified in other plants.

Table 1 summarizes some of the phytocannabinoids/exogenous cannabinoids found in non-cannabis-related plants and their possible mechanisms of action:

Exogenous Cannabinoid	Plant Source	Affinity for ECS?	Function
N-acylethanolamines	Widespread in plants	No affinity for CB1/2 receptors	FAAH inhibitors (Indirect cannabimimetic)
Salvinorin A	Salvia divinorum Epling & Jatvia-M	Insignificant affinity to CB receptors but stronger interaction with CB1/κ-opioid receptor dimers	Indirect cannabimimetic effects at CB1
Pristmimerin	Relatively widespread in the Celastraceae family	No affinity for CB1/2 receptors	Potent reversible MAGL inhibitor
Kaempferol	Widespread in plants	No affinity for CB1/2 receptors	FAAH inhibitor (Thors et al., 2008; Gertsch et al., 2010)
N-Alkylamides	Echinacea spp	Selective CB2 affinity	Partial agonist
B-Caryophyllene	Widespread in plants	Selective CB2 affinity	Full agonist
Tea catechins (gallated catechins)	Green tea (*Camellia sinensis*)	Minor CB2, stronger CB1 affinity	Unknown
Falcarinol	Relatively widespread in Apiaceae family	Non-selective CB1 affinity	Inverse agonist inhibition of AEA
Rutamarin	Ruta graveolens L	Selective CB2 affinity	Unknown
Diindolylmethane (DIM)	Relatively widespread in the Brassica genus	Selective CB2 affinity	Partial agonist at CB2 receptor
Palmitoyethanolamide (PEA)	Widespread in plants – including palm, coconuts, olives and other plant sources	Affinity for TRPV1, GPCR55 and ion channels	FAAH inhibitor

Table 1: phytocannabinoids/exogenous cannabinoids found in non-cannabis-related plants

Phytocannabinoids that interact with the CB1:

Tetrahydrocannabidiol (THC) is known as the primary modulator of the CB1 receptor, also known as the primary psychoactive component of the cannabis plant, with a major homeostatic influence on the central nervous system (CNS). Salvinorin A., from Salvia divinorum (also known as Sage of the diviners, ska maría pastora, Seer's Sage, Yerba de la pastora or simply Salvia) was studied as a potential CB1 agonist. Initial results were conflicting until later studies confirmed the interaction with CB1/κ-opioid receptor dimers, possibly indicating that the two systems might produce converging effects on the same pathway (Russo, 2016). This interesting phenomenon requires further evaluation, especially to fully elucidate the complex relationship between Salvia and the ECS.

Another plant with CB1-binding activity is kava kava (Piper methysticum), also known as the mystic pepper, is a crop of the South Pacific Islands. The active ingredients in this plant are the lipid-soluble kavalactones, which have been most closely associated with the GABA receptor activity and a role in anxiety and muscle tone. Recent research shows a new component – yangonine – that has CB1 interacting activity. Whether it acts as an agonist or antagonist is still under investigation, so any role as an effector of the ECS needs further investigation.

A few plant components have been identified with structural analogy to THC or a binding affinity for CB1. The Japanese Liverwort, Radula perrottetii, has an interesting component, a THC analogue – perrotetinene. The New Zealand version of this plant, Radula marginata has perrottetinenic acid, another THC analogue. Maca, Lepidium meyenii, also known as Peruvian ginseng, contains an N-benzylamide, with a binding affinity for the CB1 receptor, while N-methylbutanamide from Heliopsis helianthoides, commonly known as the oxeye sunflower, has an even stronger binding affinity for the same receptor (Russo, 2016). Additional studies will reveal any functional and potential clinical effects of these components on the ECS.

Certain alkylamides from the Echinacea species (purple coneflower) have been identified. These alkylamides have been observed to bear a similarity to endocannabinoids, AEA and 2-AG. Some of these alkylamides have been found to have inverse agonistic effects at the CB1 (Hohmann et al., 2011). More research on the functional effects of these interactions is still needed. Another proposed inverse agonist with the CB1 receptor is Falcarinol, a natural pesticide and fatty alcohol found in plants of the Apiaceae family, such as carrots, red ginseng and ivy. Falcarinol, when used in high doses, undergoes selective alkylation with CB1 leading to a potent pro-inflammatory response in human skin (Gertsch et al., 2010).

Phytocannabinoids that interact with the CB2:

Cannabidiol (CBD) is the major component of cannabis sativa that interacts with the CB2 receptor; this interaction is associated with the anti-inflammatory effects of CBD. Numerous plants and natural health products have been studied and shown to provide anti-inflammatory benefits and knowing what we know now, it is not outside the realm of possibility to try to determine if these products have an effect on the endocannabinoid system, through an affinity with the CB2 receptor.

In 2010, a publication suggested that tea catechins have an affinity for cannabinoid receptors, which promoted the catechins effects on inflammation, neuroprotection and food intake. Study results showed that gallated tea catechins - (–)-epigallocatechin-3-O-gallate, EGCG, (–) - epigallocatechin, EGC, and (–)-epicatechin-3-O-gallate, ECG – have an affinity for both CB1 and CB2 receptors, with a stronger affinity to CB1 observed. Only EGCG had a strong affinity for the CB2 receptor. The results of this study suggest therefore that the activities of these catechins are mediated by the ECS (Korte et al., 2010). It should be noted that these catechins do not only exist in tea (camellia sinensis) but are also present in many fruits and even some legumes.

As mentioned above, N-alkylamides identified in the Echinacea species, with similarities to endocannabinoids. Some of these alkylamides are shown to interact functionally with the human CB2 receptor. The CB2 binding alkylamides are suggested to have similar anti-inflammatory and immuno-modulatory activity as the endocannabinoid anandamide, and are therefore officially classified as cannabimimetics. These same alkylamides also target other receptors, like PPAR-γ (Gertsch et al., 2008; Gertsch et al., 2010). Other plants containing similar alkylamides include other plants found in the Brassicaceae, Astaraceae family, including Chrysanthemums, Spilanthes, Piperaceae and the Xanthoxylum species (Gertsch et al., 2006; Gertsch et al., 2010; Hadju et al., 2014).

Generally, the masses are aware of THC, and there is growing awareness of CBD and its benefits. However, there are other minor phytocannabinoids that are not well known. Terpenes are the underdogs of the cannabis sativa plants – these are a large and diverse class of organic aromatic oils, with strong scents. These terpenes are generally produced by many plants to deter herbivores and predators, however, recent evidence points to the role of terpenes in the ECS and the "Entourage Effect" of cannabis plants on the human system. All of the compounds present are able to work together for a health benefit, while preventing serious adverse effects. Some plant sources of terpenes include citrus fruits (oranges, limes and lemons), pine trees, lavender, clove oils, black pepper oils, musk and let's not forget cannabis, to name a few (Russo, 2011).

β-caryophyllene (BCP) is a widely studied terpene found in the cannabis plant, but also widespread in oils of the balsams of copaiba species, black pepper, lemon balm, cloves and hops. Studies suggest that orally administered BCP produces strong anti-inflammatory and analgesic effect in wild type mice but not in CB2 knock out mice, suggesting that this terpene works in a CB2 dependent manner. In comparison to phenylbutazone, a non-steroidal anti-inflammatory drug (NSAID), BCP not only has a strong anti-inflammatory and analgesic effect, but is also protective to the gastric lining (Russo, 2016). The activities of other terpenes on the ECS are under investigation. Rhododendron anthopogonoides, from the Ericaceae family, is traditionally used as an expectorant and for chronic bronchitis. This plant contains several flavonoids, terpenes and others. Recently, two analogues of cannabinoids and related compounds were isolated from this plant. The inference is that the presence of these compounds and their potential roles in the ECS lead to the observed immunomodulatory effects observed traditionally (Iwata and Kitanaka, 2011). More studies are needed to confirm this proposed activity.

Phytocannabinoids that target "orphan" receptors and the enzymatic cascade of the ECS:

Beyond BCP, black pepper, cloves and other oils, contain additional components which have effects on the ECS. For instance, black pepper also contains isobutylamide and guineesnsine. These compounds have inhibitory effects of the reuptake of AEA in a dose-dependent manner, without any significant effect on the cannabinoid receptors, FAAH or MAGL (Russo, 2016).

Fatty acid amides (FAA) like N-linoleoylethanolamide (LEA), N-oleoylethanolamide (OEA) and Palmitoyethanolamide (PEA) are found in a wide variety of plants. These FAAs have a similar chemical structure to endocannabinoid, and as a matter of fact, PEA is endogenously produced in the human body. These amides have multiple roles in the ECS and inhibit AEA breakdown (Di Marzo et al., 1998; Gertsch et al., 2010). The identification of LEA and OEA in chocolate (Theobroma cacao L.) led to the incorrect belief that there are endocannabinoids in chocolate – this is untrue, although chocolate does contain the amides that have an effect on the ECS.

Additionally, these amides are moderate inhibitors of FAAH (the hydrolase that breaks down AEA), comparable to the alkylamides isolated/found in the Echinacea species. In contrast to the Echinacea alkylamides, OEA, LEA and PEA also activate the TRPV1 channels, just like CBD and AEA and many other plant bioactives, including those from ginger, black pepper and the latex of the North African Spurge (Gertsch et al., 2010; Russo, 2016).

Kaempferol, a flavonoid found in Kaempferia galanga (a relative of ginger), apples, blackberries and many other plants, was demonstrated to be a potent inhibitor of FAAH. At the same time, some macamides, which are N-benzylamides from Maca (Peruvian ginseng or *Lepidium meyenii*) have shown reversible FAAH inhibition (Russo, 2016). More research is needed to not only identify and confirm phytocannabinoids, but also to understand the mechanism of action, functionality and health benefits of these plant components that target the ECS.

It is quite clear that the current knowledge of the endocannabinoids and components widespread in plants leaves much to be learned. However, the importance of this information shows that the effects of cellular signalling may have very important implications, not only for plant growth and development but also in human health and wellness.

References:

1. Pert, C. B., & Snyder, S. H. (1973). Opiate Receptor: Demonstration in Nervous Tissue. Science, 179(4,077), 1011–1014. https://doi.org/10.1126/science.179.4077.1011
2. Howlett, A. C., Bidaut-Russell, M., Devane, W., Melvin, L., Johnson, M. R., & Herkenham, M. (1990). The Cannabinoid Receptor: biochemical, anatomical and behavioural characterization. TINS, 13(10), 420–423.
3. Di Marzo, V., Melck, D., Bisogno, T., & De Petrocellis, L. (1998). Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. Trends in Neurosciences, 21(12), 521–528. https://doi.org/10.1016/S0166-2236(98)01283-1
4. Rates S.M.K. (2001). Plants as source of drugs. Toxicon, 39(2001). 603 – 613. https://doi-org.ezproxy.lib.ucalgary.ca/10.1016/S0041-0101(00)00154-9
5. Gertsch, J., Raduner, S., & Altmann, K. H. (2006). New natural noncannabinoid ligands for cannabinoid Type-2 (CB2) receptors. Journal of Receptors and Signal Transduction, 26(5–6), 709–730. https://doi.org/10.1080/10799890600942674
6. Gertsch, J. (2008). Immunomodulatory lipids in plants: Plant fatty acid amides and the human endocannabinoid system. Planta Medica, 74(6), 638–650. https://doi.org/10.1055/s-2008-1034302
7. Bifulco, P. M. (2009). The endocannabinoid system: From biology to therapy. Pharmacological Research, 60(2), 75–76. https://doi.org/10.1016/j.phrs.2009.04.015
8. Gertsch, J., Pertwee, R. G., & Di Marzo, V. (2010). Phytocannabinoids beyond the Cannabis plant - Do they exist? British Journal of Pharmacology, 160(3), 523–529. https://doi.org/10.1111/j.1476-5381.2010.00745.x
9. Korte, G., Dreiseitel, A., Schreier, P., Oehme, A., Locher, S., Geiger, S., Sand, P. G. (2010). Tea catechins' affinity for human cannabinoid receptors. Phytomedicine, 17(1), 19–22. https://doi.org/10.1016/j.phymed.2009.10.001
10. Hohmann, J. et al. (2011) Alkamides and a neolignan from Echi- nacea purpurea roots and the interaction of alkamides with G-protein-coupled cannabinoid receptors. Phytochemistry 72, 1848–1853
11. Iwata, N., & Kitanaka, S. (2011). New cannabinoid-like chromane and chromene derivatives from Rhododendron anthopogonoides. Chemical and Pharmaceutical Bulletin, 59(11), 1409–1412. https://doi.org/10.1248/cpb.59.1409
12. Russo E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British journal of pharmacology, 163(7), 1344–1364. doi:10.1111/j.1476-5381.2011.01238.x
13. Veeresham C. (2012). Natural products derived from plants as a source of drugs. Journal of advanced pharmaceutical technology & research, 3(4), 200–201. doi:10.4103/2231-4040.104709
14. Di Marzo, V., & Wang, J. W. (2014). The Endocannabinoidome: The World of Endocannabinoids and Related Mediators. The Endocannabinoidome: The World of Endocannabinoids and Related Mediators. https://doi.org/10.1016/C2013-0-13461-7
15. Hajdu, Z., Nicolussi, S., Rau, M., Lorántfy, L., Forgo, P., Hohmann, J., Gertsch, J. (2014). Identification of endocannabinoid system-modulating N-alkylamides from Heliopsis helianthoides var. scabra and Lepidium meyenii. Journal of Natural Products, 77(7), 1663–1669. https://doi.org/10.1021/np500292g
16. Lu, H.-C., & Mackie, K. (2016). An introduction to the endogenous cannabinoid system Hui-Chen. Biological Psychiatry, 79(7), 516–525. https://doi.org/10.1159/000443368.Drug
17. Russo, E. B. (2016). Beyond Cannabis: Plants and the Endocannabinoid System. Trends in Pharmacological Sciences, 37(7), 594–606. https://doi.org/10.1016/j.tips.2016.04.005
18. Jarvis, S., Rassmussen, S., & Winters, B. (2017). Role of the Endocannabinoid System and Medical Cannabis. Journal for Nurse Practitioners, 13(8), 525–531. https://doi.org/10.1016/j.nurpra.2017.05.014

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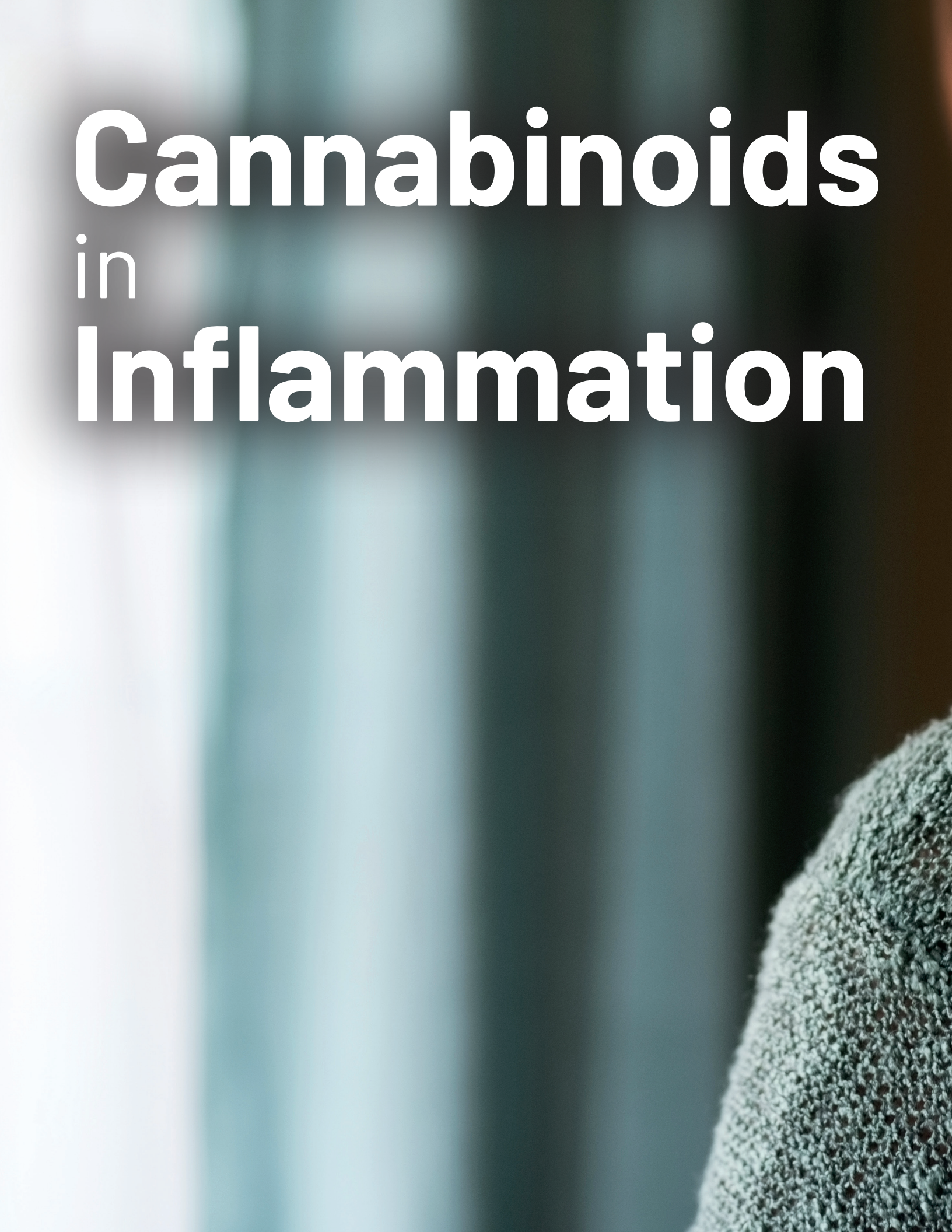
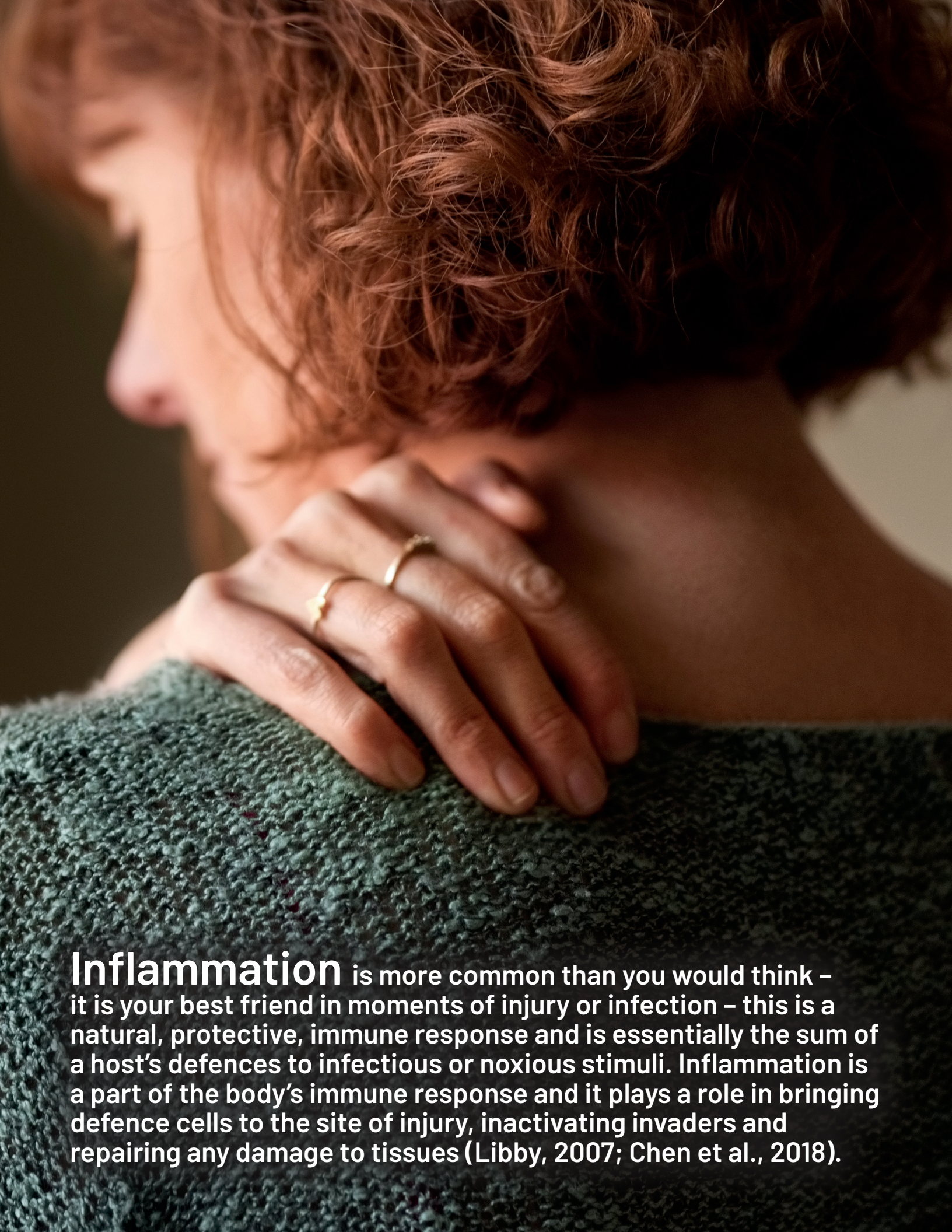
Cannabinoids in Inflammation





Inflammation is more common than you would think – it is your best friend in moments of injury or infection – this is a natural, protective, immune response and is essentially the sum of a host's defences to infectious or noxious stimuli. Inflammation is a part of the body's immune response and it plays a role in bringing defence cells to the site of injury, inactivating invaders and repairing any damage to tissues (Libby, 2007; Chen et al., 2018).

Inflammation, characterized by rubor (redness), calor (heat), tumor (swelling) and dolor (pain), as well as the eventual loss of function, is classified into two main categories – acute and chronic (Ahmed, 2011; Chen et al., 2018). Table 1 outlines the major differences between acute and chronic inflammation.

	Acute	Chronic
Cause	Harmful bacteria / tissue injury / immediate trauma	Harmful bacteria that the body can't get rid of and remains in the system/unresolved tissue injury / trauma or an overactive immune response
Onset	Rapid	Generally slow
Duration	A few days	Months to years
Outcome	Inflammatory response is resolved or can become chronic when the cause is unresolved	Autoimmune disorders, fibrosis, tissue damage and necrosis of the affected tissue

Table 1: phytocannabinoids/exogenous cannabinoids found in non-cannabis-related plants

Inflammation starts as a slow burn inside of your body and acts as an emergency beacon to respond rapidly to acute inflammatory signals; however, lingering inflammatory signals will lead to a chronic response to inflammation. When inflammation becomes chronic, your body's natural defense system starts to turn on you and attack your joints, tissues and blood vessels, wreaking havoc (Rabb et al., 2016).

The idea that inflammation is a major cause of many chronic diseases is not new; however, due to the lack of a defined or continuing inducer, it becomes quite difficult to come up with an appropriate therapeutic intervention. An estimated 15% of human cancer is associated with chronic infection and inflammation. Furthermore, chronic inflammation is linked to other conditions, including rheumatoid arthritis, multiple sclerosis, asthma, heart attacks, diabetes, strokes, Alzheimer's and Parkinson's disease (Rabb et al., 2016; Chen et al., 2018). These stats demonstrate the role of inflammation in health and disease and aid in understanding the mechanism of the inflammatory response is one-step in right direction.

Mechanism of Inflammation/Inflammatory Response:

The mechanism of inflammation is quite an involved process. Several key regulators involved in the selective expression of pro-inflammatory molecules mediate it. Inflammation is initiated by the recognition of specific molecular changes associated with triggers, including infections, necrosis, trauma, physical or chemical injury, foreign bodies, immune reactions (hypersensitivity or autoimmune reactions) (Ahmed, 2011). These invaders or triggers can elicit many responses, particularly surrounding the cells/tissues that have been injured.

Although the inflammatory response is dependent on the precise nature of the offending stimulus and its location in the body, the responses all share a common mechanism, which is summarized as follows:

i. Recognition of the offending stimuli by cell surface pattern receptors
ii. Activation of inflammatory signalling pathways
iii. Release of inflammatory markers
iv. Recruitment of inflammatory cells to the site of offense
v. Players in the inflammatory response pathways include:
vi. Mast cells, which release histamines for vasodilation and increased vascular permeability, allowing more immune cells migrate to the site of inflammation/injury.
vii. Macrophages, which are activated monocytes, secrete inflammatory cytokines such as the tumor necrosis factor alpha (TNF-α) and Interleukin-1 (IL-1). These cytokines cause a local effect, which includes vasodilation and vascular permeability, and a systemic effect that includes tissue repair through increased fibroblast activity and collagen synthesis.
viii. Complement proteins cause lysis of invading pathogens or coat the pathogens with markers that recruit phagocytes for engulfing and destruction of the pathogens. These complement proteins will also stimulate tissue repair.
ix. Mast cells, along with endothelial cells and granulocytes are responsible for the release of prostaglandins and leukotrienes, which are arachidonic acid metabolites that lead to increased vascular permeability and inflammatory response.

As mentioned previously, acute inflammatory response is your best friend in times of injury and infection, to ensure continued wellbeing. When the offending injury/pathogen has been taken care of, the inflammatory response is resolved. In the case of persistent, chronic inflammation, the underlying root cause must be resolved to prevent further damage to tissues and loss of function, as well as chronic disease states.

The Role of the Endocannabinoid System in Inflammation:

With increasing legality of cannabis around the world, it is crucial to understand the role of the endocannabinoid system (ECS) in health and disease, as well as the safety and efficacy of both endogenous and phytocannabinoids. Increasing levels of evidence supports the upregulation of cannabinoid receptors, CB1 and CB2, as well as the release of endocannabinoids from macrophages, dendritic cells, platelets and parenchymal cells in response to inflammatory stimuli. Additionally, cell culture and animal studies suggest that treatment with isolated endocannabinoids – 2-Arachidonylglycerol (2-AG) and anandamide (AEA), decrease the levels of lipopolysaccharide mediated increases in pro-inflammatory cytokines, including TNF-α, IL-6, IL-12 and interferon-γ (Kelly et al., 2017).

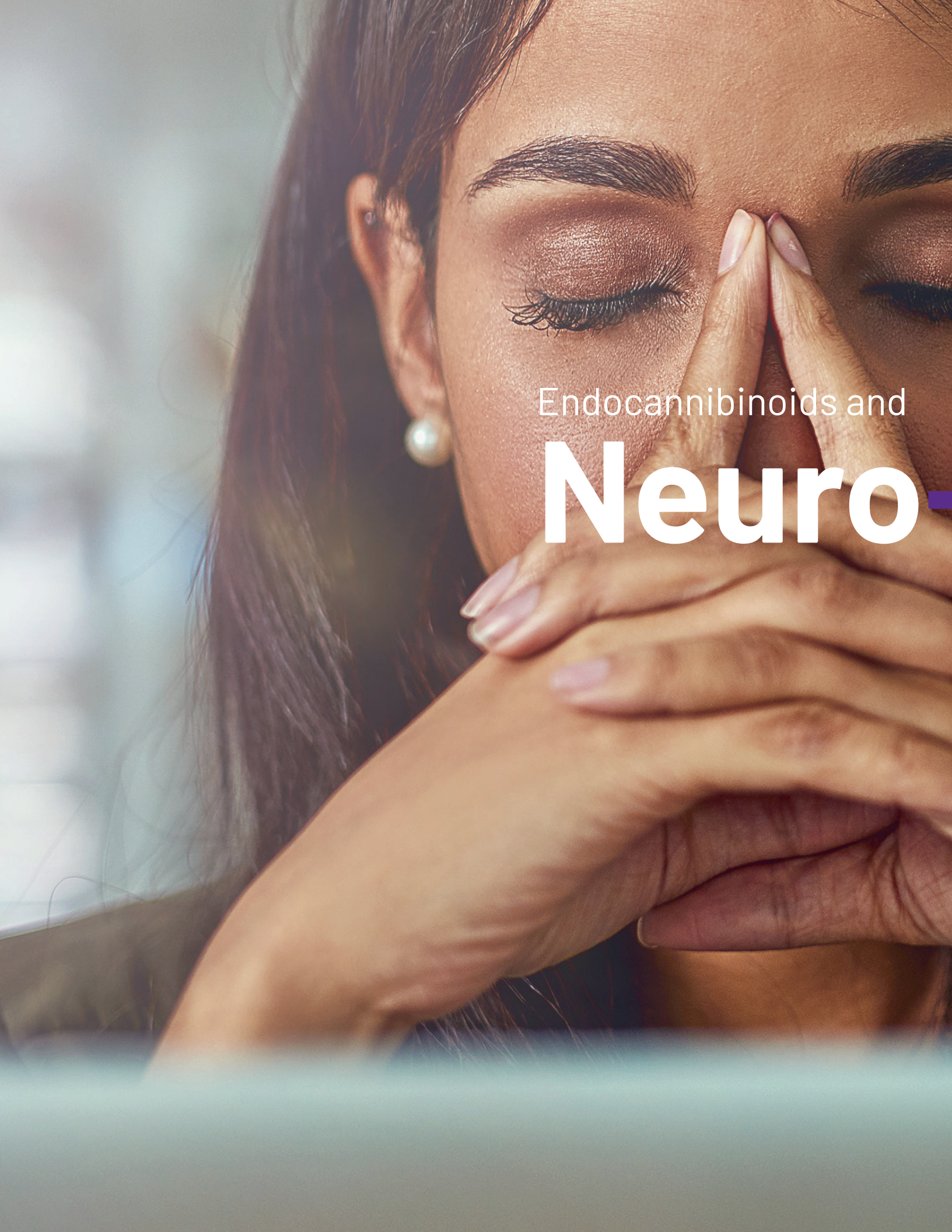
The activation of the CB2 receptor by phytocannabinoids, like cannabidiol (CBD), have reported immunomodulatory activity. The downstream effect of the CB2 receptor offsets the inflammatory response by inhibiting the production of pro-inflammatory mediators. Moreover, levels of CB2 receptor and endocannabinoids have been found to increase under stressful and inflammatory conditions, therefore suggesting an auto-protective role of the ECS in limiting inflammation (Donvito et al., 2017).

AEA and 2-AG have been found to mediate inflammation by acting at different steps through the inflammatory response. The phytocannabinoid tetrahydrocannabidiol (THC) and AEA suppress pro-inflammatory cytokines and enhance anti-inflammatory cytokines in both innate and adaptive immunity. AEA also inhibits microglial nitric oxide (NO) synthesis through the mitogen-activating protein kinase (MAPK) pathway, while inhibiting TNF-α and nuclear factor kappa B (NF-κB). Additional evidence suggests the ECS modulates the inflammatory response by suppressing the activity of pro-inflammatory Th1 and promoting the activity of the anti-inflammatory Th2. Interestingly, AEA and 2-AG are present in the synovial fluid of patients affected by both rheumatoid arthritis and osteoarthritis. This is not the case in healthy controls, suggesting an upregulation in response to inflammation and cartilage degradation and a compensatory role in arthritis (Barrie & Manolios, 2017).

Finally, cell culture and animal studies have shown that the inhibition of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), the enzymes that degrade AEA and 2-AG respectively, promote the anti-inflammatory response and reduces pain and inflammation in animal models (Donvito et al., 2017). Some studies suggest a pro-inflammatory role for the activation of CB1 receptors in acute responses to inflammatory stimuli, however, more research is required to confirm the exact role CB1 receptor activation plays in the inflammatory response and any pro-inflammatory effects are resolved following the removal of the offending stimulus (Barrie & Manolios, 2017).

References:

1. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. What is an inflammation? 2010 Nov 23 [Updated 2018 Feb 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279298/
2. Ahmed, A. U. (2011). An overview of inflammation: Mechanism and consequences. Frontiers of Biology in China, 6(4), 274–281. https://doi.org/10.1007/s11515-011-1123-9
3. Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., … Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204–7218. Retrieved from www.impactjournals.com/oncotarget/
4. Christopher D. Buckley, Derek W. Gilroy, and C. N. S. (2014). Pro-Resolving lipid mediators and Mechanisms in the resolution of acute inflammation. Immunity, 40(3), 315–327. https://doi.org/10.1016/j.immuni.2014.02.009
5. Rabb, H., Griffin, M. D., McKay, Di. B., Swaminathan, S., Pickkers, P., Rosner, M. H., … Ronco, C. (2016). Inflammation in AKI: Current understanding, key questions, and knowledge gaps. Journal of the American Society of Nephrology, 27(2), 371–379. https://doi.org/10.1681/ASN.2015030261
6. Libby, P. (2007). Inflammatory Mechanisms: The Molecular Basis of Inflammation and Disease. Nutrition Reviews, II(December), S140–S146. https://doi.org/10.1301/nr.2007.dec.S140
7. Kelly, M. E. M., Lehmann, C., & Zhou, J. (2017). The Endocannabinoid System in Local and Systemic Inflammation. Colloquium Series on Integrated Systems Physiology: From Molecule to Function (Vol. 9). https://doi.org/10.4199/c00151ed1v01y201702isp074
8. Donvito, G., Nass, S. R., Wilkerson, J. L., Curry, Z. A., Schurman, L. D., Kinsey, S. G. & Lichtman, A. H. (2018). The Endogenous Cannabinoid System: A Budding Source of Targets for Treating Inflammatory and Neuropathic Pain. Neuropsychopharmacology, 43(1), 52–79. https://doi.org/10.1038/npp.2017.204
9. Barrie, N. & Manolios, N. (2017). The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease. European Journal of Rheumatology, 4(3), 210–218. https://doi.org/10.5152/eurjrheum.2017.17025
10. Seol, T. K., Lee, W., Park, S., Kim, K. N., Kim, T. Y., Oh, Y. N. & Jun, J. H. (2017). Effect of palmitoylethanolamide on inflammatory and neuropathic pain in rats. Korean Journal of Anesthesiology, 70(5), 561–566. https://doi.org/10.4097/kjae.2017.70.5.561
11. Keppel Hesselink, J. M., Kopsky, D. J. & Witkamp, R. F. (2014). Palmitoylethanolamide (PEA)-'Promiscuous' anti-inflammatory and analgesic molecule at the interface between nutrition and pharma. PharmaNutrition, 2(1), 19–25. https://doi.org/10.1016/j.phanu.2013.11.127
12. Keppel Hesselink, J. M., De Boer, T. & Witkamp, R. F. (2013). Palmitoylethanolamide: A natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. International Journal of Inflammation, 2013. https://doi.org/10.1155/2013/151028
13. Peritore, A. F., Siracusa, R., Crupi, R. & Cuzzocrea, S. (2019). Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients, 11(9), 1–22. https://doi.org/10.3390/nu11092175
14. Beggiato, S., Tomasini, M. C. & Ferraro, L. (2019). Palmitoylethanolamide (PEA) as a Potential Therapeutic Agent in Alzheimer's Disease. Frontiers in Pharmacology, 10(July), 1–12. https://doi.org/10.3389/fphar.2019.00821
15. Bujak, J. K., Kosmala, D., Szopa, I. M., Majchrzak, K. & Bednarczyk, P. (2019). Inflammation, Cancer and Immunity—Implication of TRPV1 Channel. Frontiers in Oncology, 9(October), 1–16. https://doi.org/10.3389/fonc.2019.01087



Endocannibinoids and

Neuro

-inflammation

Immunological mechanisms including inflammation of the nervous system may well be the central cause of many diseases including; Alzheimer's, Parkinson's, Multiple Sclerosis, ALS, Schizophrenia and even cognitive decline and depression.

While there are many players of the immune system that are likely involved, to simplify things the following are the prime suspects involved; neurones, astrocytes, oligodendrocytes, macrophages and mast cells.

The neurone is the nerve cell that is vital for brain function involved in communicating, responsible for sending messages (nerve signals) to and from the brain to all parts of the body via the intricate nervous system. The neurone is integral, and must be protected at all costs.

Then there is a group of hierarchical microglial cells which are separated into different classes:

- Astrocytes are the most abundant (up to ten to twelve times greater number than the neurones!) and look after the health of the nerve cell. They ensure proper energy, pH, electrolytes and nutrient levels are maintained.
- Oligodendrocytes are glial cells that have specific duties like ensuring that the nerve cells are properly insulated with the covering or the myelin sheath so that conduction of signals along the nerve cells occurs with maximum speed and efficiency.
- The macrophages, the lowest in the hierarchy, are responsible for the waste management, cleaning up the waste (dead nerve cells as well as other debris), and disposing of these. In addition, they assist in immune function when there is infiltration by the enemy, like pathogenic bacteria or viruses that want to harm the brain. Typically, macrophages are found at locations where they can quickly encounter the enemy like the blood vessels. They also act as the gate keepers especially in the key areas of the brain called the blood-brain-barrier, which is strictly guarded for entry, and most visitors are turned back except for the most important VIPs like oxygen, glucose and energy molecules. Macrophages perform vital functions but nonetheless, they are at the bottom of the hierarchy because they get all the dirtiest jobs.
- Mast cells are not part of the glial hierarchy, and are considered outsiders. They are usually the first responders at a site of danger. They are armed to the teeth with powerful chemicals like enzymes (tryptases and other proteases), histamine, serotonin, lactoperoxidases used for killing bacteria and viruses, plus a whole host of other chemicals (chemokines, cytokines and complement) available at their disposal should the need arise. Mast cells like to throw their weight around, and to let other cells know who is the boss.

These cells are in constant communication with one another to ensure rapid response to any impending danger. Such communication is all good and healthy for the body.

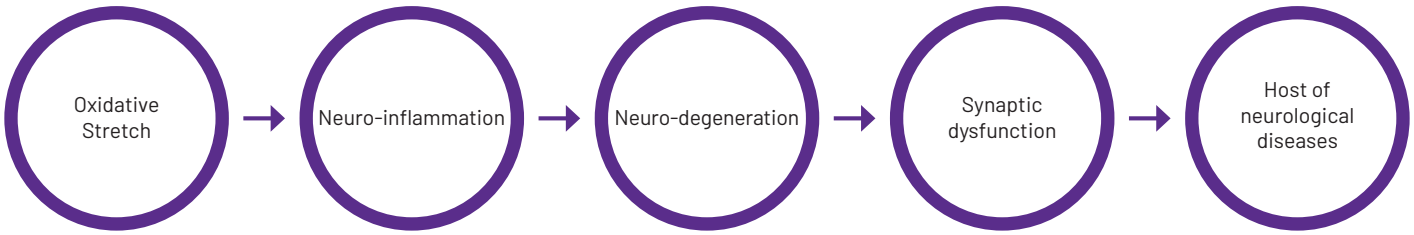
Unfortunately, when microglia and astrocytes come into contact with toxic chemicals like pesticides, solvents, carcinogens, etc. they become excited and overactive, and begin to produce large amounts of free radicals. Free radicals are highly reactive species, and initiate destructive chain reactions, which rapidly spread much like dominos falling one after another. In turn, microglia and astrocytes also start producing chemokines – chemicals that attract other cells, and cytokines- chemicals, which recruit destructive cells, and one in particular, the mast cells.

Mast cells usually deal with situations heavy-handedly. While containing the invaders, which is what mast cells are meant to do, they will at times get carried away with their sense of worth, and start spewing out all these powerful chemicals which they have at their disposal. This causes even more destruction, like throwing petrol on a fire, with the generation of more free radicals and more inflammatory molecules (i.e., NF kappa B). This results in a mess, and unfortunately, for the neurone, because of their delicate and frail nature, they are susceptible to getting hurt. Bottom line is there is an excessive amount of inflammation which triggers a vicious cycle of neurodegenerative cascade which causes even more destruction.

The cascade of neurodegeneration caused by microglia, astrocytes, macrophages and mast cells going rogue, and causing oxidative stress and synaptic dysfunction are at the heart of neurological diseases.

These events cause the "improper" handling or processing of amyloid precursor protein (APP). APP if not processed properly, develops into the highly toxic and destructive beta amyloid peptide which starts depositing in different areas of the brain. These isolated deposits are no different from the cholesterol plaques being deposited in blood vessels causing heart disease and stroke, but in the brain, these plaques form around the neurone instead of the blood vessels. These amyloid plaques are like an octopus with far-reaching tentacles that strangles the nerve cell to death.

Here is a depiction of events, though there is still debate as to what is the initiating event and chronology:



Palmitoylethanolamide (PEA), a long-chain fatty acid amide generally produced by the body in response to various triggers, acts as a local anti-injury molecule by down-regulating the mast cells. Simply put, PEA is produced locally and helps modulate communication between all the key players, sorting through any miscommunication, and telling everyone to "chill out", especially the mast cells. The result is the rogue mast cells quieten down (reduce their excitability) and go away to fight another invader at another time.

References:

1. Zadori D. et al. "Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines" J Alzheimers Dis. 2018; 62:523-547
2. Steardo, L. et al. "Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes, Front. Neurosci. 2015; 9: 259-273
3. Skaper, S. D. et al. "An inflammation-centric view of neurological disease: beyond the neurone" 2018; Front. Cell. Neurosci. 12; 72:
4. Skaper S.D. et al. "Mast cells, glia and neuroinflammation; partners in crime?" Immunology, 2014; 141: 314-327
5. Saito T. and Saido T.C. "Neuroinflammation in mouse models of Alzheimer's disease" Clin. Exp. Neuroimmunology, 2018; 9: 211-218
6. Cai, Q. and Tammineni, P." Mitochondrial aspects of synaptic dysfunction in Alzheimer's disease" J Alzheimer's disease, 2017; 57: 1087-1103

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Background – Anxiety and Depression:

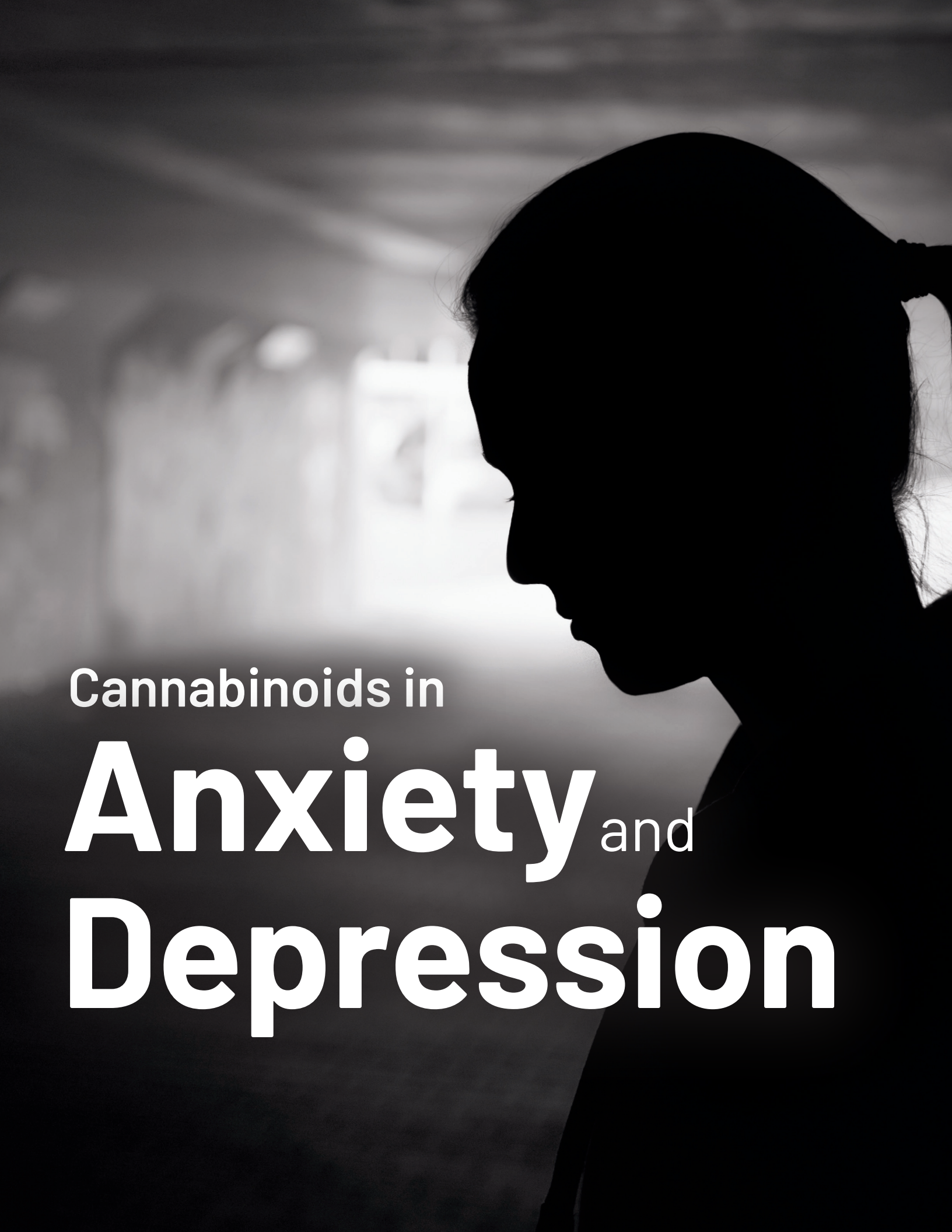
Anxiety and depression are major health problems plaguing the world today, and represent one of the major groups of disorders seen in psychiatry, and in the rest of medicine as well.

In fact, typing the word anxiety into pubmed yields over 200,000 peer-reviewed publications; depression yielding over 500,000 publications.

Between antiquity and the late 19th century, there was an extensive period during which, anxiety (French: anxiété; German: Angst) remained unclassified as a separate illness, even though typical cases of anxiety disorders were reported and classified under different names and conditions. There are indications that Greco-Roman philosophers and physicians identified anxiety as a distinct negative affect. In the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a definition of anxiety has been provided. Anxiety is defined as the anticipation of future threat – easily distinguished from fear.

General anxiety is a normal emotion that humans evolved with to promote survival and everyone feels anxious from time to time, as a normal response to stressful situations. The word anxiety derives from the Latin substantive angor and the corresponding verb ango (to constrict). Joseph Lévy-Valensi (1879 to 1943), a professor of psychiatry in Paris who died at Auschwitz, defined "anxiété" in his textbook of psychiatry as a dark and distressing feeling of expectation. Anxiété was described as including the psychological and cognitive aspects of worrying. However, there is a clinical threshold between everyday anxiety and distressing pathological anxiety requiring treatment. This is subject to clinical judgment, although consensus now separates anxiety from acute stress disorder and post-traumatic stress disorder (PTSD). High levels of anxiety and depression are associated with a higher likelihood of suicide, longer duration of illness and a lack of response to treatment (Crocq, 2015; Kupfer, 2015).

Currently, with an increase in digital media use, the impact on emotional well-being, in regards to fear, anxiety and depression are being evaluated in multiple clinical and research stages. The amount of time spent online replaces in-person interactions, thereby intensifying social impairments, anxiety and depression (Jacobson & Newman, 2014; Hoge et al., 2017).



Cannabinoids in

Anxiety and Depression

Depression, on the other hand, has more links in history and is traditionally considered a self-limiting disorder. Depression is considered one of the most prevalent disorders of mental health, but although depression is very common, it is often ignored and treatment options are limited. This is a common, debilitating disorder affecting over 300 million people in the world today, with the World Health Organization (WHO) ranking depression as the single largest contributor to global disability (WHO 2012, 2014). Multiple questions plague the depression community, including:

- What exactly is depression?
- Do all depressed people suffer from the same etiology?
- Are there different shapes or severity of depression? Should they all be classified as depression?
- Should we be managing depression in similar ways?

Answering the aforementioned questions will be important in dealing with depression. Depression is an eminently treatable condition, although current available evidence and publications are plagued by publication bias (Ledford, 2014; Hollon, 2016; Stingaris, 2017).

Although depression and anxiety are distinctly classified in the DSM-5, in most cases, they occur together, yielding a lifetime prevalence of 16% to 50%. Approximately 70% of people with major depression have comorbid lifetime anxiety disorders. Many people have a diagnosis of both an anxiety disorder and clinical/major depression and symptoms of one usually improves along with the other, confirming the role of one in the development and progression of the other (Mayo clinic). Additionally, studies have shown that anxiety predicts later depression and in comparison to those with pure diagnoses, individuals with comorbid anxiety and depression experience great chronicity and severity of each diagnosis, poorer work and psychosocial functioning, lower perceived quality of life and a heightened risk of suicide (Jacobson & Newman 2014).

Treatments for Anxiety and Depression:

Recent years and research brought scientific understanding of the biochemical activity of plants, after the isolation of the active constituents. Additionally, the research into cannabis and its phytocannabinoids have given much insight into psychoactive plants and how they affect the central nervous system (CNS). It is now widely accepted that the "silver bullet" treatment model is no longer adequate, especially in the treatment/management of chronic diseases. As a result, cocktails of drugs are now considered the norm and plant products are a good source of a cocktail of phytoactive ingredients with health benefits.

Current treatment for anxiety and depression include psychotherapy (psychological counselling)/ cognitive behavioural therapy and medications, such as antidepressants, used alone or in combination. Depression is more likely due to a combination of genetic, biological, environmental and psychological factors and as such, a multi-prong approach to treatment must be implemented. Symptoms of depressive disorders respond to different classes of medications, including the common selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). SSRIs, like citalopram, fluoxetine and sertraline, work by blocking the reabsorption or reuptake of serotonin, which leads to mood improvement. On the other hand, SNRIs, like duloxetine and levomilnacipran, are notable for their dual mechanisms of action – increasing the levels of the neurotransmitters serotonin and norepinephrine by inhibiting their reuptake into brain cells and improving mood (Anthes, 2014; Monteggia et al., 2014; Hollon, 2016). These all seem like great options, until the side effects hit – side effects include insomnia, sexual dysfunction, weight gain, stomach upset, headaches, increases in blood pressure, dependency and in some more severe cases, are associated with an increased risk in suicidal ideation. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOi) are other classes of antidepressants that can be prescribed when SSRIs and SNRIs are ineffective (Lakhan & Vieira, 2010). These alternate antidepressants are riddled with serious adverse effects and can sometimes still remain ineffective (ADAA, 2016) and as such, medicine and patients alike are looking into alternate resources for better management of their mental health.

Alternative Treatments for Anxiety and Depression:

There is an ever-growing body of scientific evidence for the use of complementary and alternative medicines as an approach to managing or supporting the symptoms of anxiety and depression. Furthermore, with the rising cost of prescription medications and the occurrence of unwanted and unexpected side effects, patients and doctors alike are starting to gravitate towards natural and herbal remedies for the treatment and management of psychological conditions. Complementary medicine is often used along with conventional medicine, as long as there is health care professional oversight to ensure the safety of use.

Herbs such as passionflower, kava, St. John's wort and valerian root, as well as the amino acid lysine and the cation magnesium, have been used for centuries in folk and traditional medicine to calm the mind and positively enhance mood. However, the efficacy and safety of utilizing natural health products (NHPs) to treat anxiety, both as a symptom and as a disorder, has only just begun to be rigorously tested in clinical trials. Publications have reviewed some of the available data associated with a number of NHPs including, St. John's Wort, S-adenosyl-methionine (SAM-e), B vitamins, inositol, choline, kava, omega-3 fatty acids/fish extracts, valerian, lavender, melatonin, passionflower, skullcap, hops, lemon balm, black cohosh, ginkgo biloba, extracts of magnolia and phellodendron bark, gamma aminobutyric acid (GABA), theanine, tryptophan and 5-hydroxytryptophan (5-HTP). They have concluded that there is some benefit to the use of NHPs in the management of anxiety and depression (Lakhan & Vieira, 2010).

The mechanisms of actions of herbal formulations primarily involve the modulation of neuronal communication, through specific plant metabolites that bind to neurotransmitter/neuromodulatory receptors and through alterations of neurotransmitter synthesis and functions. Other possible actions including stimulating or sedating the CNS activity and regulating healthy functioning of the endocrine system (Sarris et al., 2011).

It is hard to narrow down the mechanism of action of herbal formulation/NHPs, seeing as one plant could contain upwards of thousands of phytochemicals and plant metabolites, each with a different biological activity on receptors and signalling pathways. This makes it difficult to clearly define the mechanism of action, unlike conventional pharmaceuticals.

Table 1 summarizes some of the evidence available for the most commonly studied NHPs in anxiety and depression.

NHP	Type of Studies (experimental models)	Experimental evidence of activity
Passionflower	Animal & Human studies	Significant reduction in Hamilton Anxiety Scale (HAMA) scores, as a measure of anxiety. Dry mouth, headache and constipation are some of the adverse effects that have been noted in human clinical studies, with the use of passionflower. Thought to have anti-anxiety effects due to its content of GABA, a neurotransmitter that helps regulate mood (Elsas et al., 2010; Kim et al., 2017).
Kava	Animal & Human studies	Human evidence shows anti-anxiety benefits. It should be noted that the preparations for the kava used for the studies widely vary in the method of preparation and standardization and as such, the results from these studies need to be reviewed for preparation to come to a necessary conclusion on the benefits of kava in anxiety and depression models.
St. John's Wort	Animal & Human studies	Insufficient evidence for the use of St. John's wort in anxiety and depressive models. The contraindications and adverse effects experienced using St. John's wort makes this form of therapy inefficient for anxiety and depression.
Magnesium	Animal & Human studies	When used with other vitamins and minerals, there is some evidence for the use of magnesium in anxiety reduction, compared with placebo.
Vitamin B12	Animal & Human studies	When used with other vitamins and minerals, especially vitamin B6, there is some evidence for the use of vitamin B12 in anxiety reduction, compared with placebo.
Borage	Animal & Human studies	There is insufficient evidence for the benefits of borage in anxiety and depression. More research is needed to prove or disprove the cognitive effects of borage in humans.
Lavender	Animal & Human studies	Multiple sources of evidence showing the GABA modulating effects of lavender and downstream effects on anxiety and depression are quickly filling up peer-reviewed journals. The available evidence shows significant decrease in anxiety and depressive scales when lavender is used, alone and in combination with other herbal products.
Panax ginseng	Animal & Human studies	A decrease in stress levels is observed with Panax ginseng in individuals exposed to high stress levels. Some evidence also shows benefits against anxiety relating to sexual performance – this evidence is promising but more research is needed for correlation of use. Effects on anxiety and depression show little to no evidence.

NHP	Type of Studies (experimental models)	Experimental evidence of activity
Rhodiola rosea	Animal & Human studies	Animal studies show some benefits of rhodiola rosea in animal models of anxiety. R. rosea may have beneficial effects on physical performance, mental performance, and certain mental health conditions. This may be due to modulation of neurological pathways with both antidepressant and anxiolytic effects or its effects on monoamine oxidase inhibition (Sarris et al., 2011). There is, however, a lack of independent replications of the single different studies. Further investigation is needed, especially if this herb is to be used to prescribed medication.
Saffron	Animal & Human studies	There is ample evidence for the benefits of saffron in anxiety and various stages of depression. Additionally, the evidence does show that saffron is comparable in efficacy, to certain medications used in anxiety and depression (e.g., fluoxetine). Some studies have also started to explore the added benefits with conventional antidepressants. The results are promising. Patents for saffron's use in mood disorders and depression have been granted.
Bacopa	Animal & Human studies	There are few human studies. The general outcomes for bacopa in humans are for enhancing cognitive performance. The evidence for anxiety and depression in humans are sparse and more evidence is needed to make a conclusion on the benefits of bacopa for anxiety and depression.
California poppy	Animal (no human clinical studies for use in anxiety/ depression)	Animal studies show some benefits of California poppy in animal models of anxiety.
Chamomile	Animal & Human studies	Clinically significant differences between placebo and chamomile groups show a reduction in anxiety and depressive scales. Chamomile may have modest benefits for people with anxiety, with comorbid depression.
Ginkgo	Animal & Human studies	Various preclinical and clinical studies have shown a positive effect of Ginkgo biloba to improve cognitive abilities in impaired individuals and reducing anxiety under pathological conditions. Although Ginkgo is generally considered safe, more attention is needed to monitor adverse events, especially when it relates to cognitive health.
Lemon balm	Animal & Human studies	High doses of lemon balm are associated with significant reduction in scores of depression, anxiety and stress.
Withania somnifera	Animal & Human studies	Mild effects have been observed and some of the results are based on self-assessment. More research and evidence is needed.

Table 1: Most commonly studied NHPs in anxiety and depression

The Endocannabinoid System in Anxiety and Depression:

The discovery of the endocannabinoid system (ECS) has opened up a host of avenues for health and wellness. The ECS is a complex physiological network that has an important role in major pathological conditions (Bifulco, 2009). Studies have looked at the theory of clinical endocannabinoid deficiency, especially, as it pertains to brain disorders, including anxiety and depression. Preclinical evidence suggests that a reduction in the ECS activity is a contributing factor to depressive symptoms. Knock out models of CB1 receptor on GABAergic neurons in mice led to increase in anxiety and depressive symptoms (Bassi et al., 2018). Evidence for the function of the ECS in major depression has been observed in multiple studies and certain genetic polymorphisms in both the CB1 and CB2 receptors are associated with major depression and bipolar disorder. Additionally, resistance to treatment was observed in patients with depression, having polymorphisms in the CB1 receptor. Accumulating evidence points to the fact that endocannabinoid signalling may be compromised in patients with major depression (McLaughlin et al., 2011; Huang et al., 2016; Russo, 2016; Lutz et al., 2018).

Anecdotal accounts from apparently healthy cannabis users infer many psychoactive benefits to cannabis, which has bioactive components, called cannabinoids, that confer effects such as relaxation, reduced anxiety, increased well-being and euphoria, to name a few. This suggests that cannabinoid signalling has a central role in the control of stress, fear and anxiety. In recent years, researchers have focused on the therapeutic potential of cannabis-related compounds for various mood disorders. Both anecdotal and clinical evidence suggest that low-dose cannabinoid administration might have some of the aforementioned health benefits; however, high dose cannabinoid administration can elicit anxiety, panic attacks and psychotomimetic effects (McLaughlin et al., 2011). A randomized, double-blind, placebo-controlled trial in 15 humans demonstrated that up to 600 mg of CBD (cannabidiol) reduced measured anxiety compared to increased levels with a 10 mg dose of Δ9-THC. CBD appears to activate other receptors outside CB2, including 5-HT1A and TRPV1, both of which are involved in the anxiolytic and mitigating panic/fear responses to stress (Fusar-Poli et al., 2009). Ongoing studies on the use of cannabis will ensure that proper dosage is administered for specific health indications but while that is going on, we should not forget that the discovery of the benefits of this plant, are related to the discovery of the ECS as well as the endogenous cannabinoids that humans produce. Additionally, it is well established that phytocannabinoids exist in other plants outside cannabis and some of these plants are well characterized for phytochemicals, safety and efficacy in various health conditions.

The clinical effect of different antidepressants is shown to be mediated by a modulation of ECS activity in specific brain regions. Studies have shown that treatments with tricyclic antidepressants are associated with an increase in CB1 receptor density in the hippocampus and hypothalamus, as well as a reduction in the activation of hypothalamic-pituitary-adrenal (HPA) axis in response to stressful stimulus (Bassi et al., 2018).

The activity of the ECS includes the modulation of activity in the limbic areas involved in reward processing and the regulation of other neurotransmitters, as well as a reduction in HPA activation. Research findings suggest that blocking fatty acid amide hydrolase (FAAH), the enzyme that breaks down anadamide (AEA), decreases anxiety in animal models. Monoacylglycerol lipase (MAGL, MGL) is the enzyme responsible for the metabolism of the endocannabinoid, 2-arachidonylglycerol (2-AG). The inhibition of this enzyme in animal models has been shown to reduce anxiety and depressive symptoms (Hill & Patel, 2013).

The serotonin receptor, 5-HT1A, has a large body of evidence that shows its intimate involvement in anxiety and depression. This is a common target of SSRIs. Recent research now suggests that cannabidiol (CBD), a well-known cannabinoid from cannabis sativa, also exerts agonistic effects on this receptor, and could be one of the mechanisms of anti-anxiety and antidepressive activities of cannabis (Ruehle et al., 2012). All of this evidence points to the role and importance of the endocannabinoid system in psychological disorders, specifically in anxiety and depression.

Palmitoyethanolamide in Modulating Anxiety and Depressive Symptoms:

N-Palmitoylethanolamide (PEA) is an endogenously produced endocannabinoid-like molecule, with research dating back over 50 years and more than 1500 publications on pubmed. This fatty acid amide with structural similarity to endocannabinoids, AEA and 2-AG, has been implicated in many health conditions, due to the many signalling pathways by which it exerts its effects. PEA has been well established as a naturally occurring anti-inflammatory, analgesic and neuroprotective agent, produced by the cells but also found in dietary sources, including egg yolks, soy and peanuts (Petrosino & Di Marzo, 2017).

The antidepressant activity of PEA has been evaluated extensively in animal models, alone and in combination with conventional antidepressants, like fluoxetine and results suggest comparable antidepressant activity of PEA to fluoxetine (Coppola & Mondola, 2014). Research evidence indicates that some antidepressants, like imipramine and escitalopram could increase levels of PEA in the brain (Ghazizadeh-Hashemi et al., 2018). Further research is needed to confirm this activity of conventional antidepressants. Animal studies show that administration of PEA normalizes nuclear levels of the peroxisome proliferator-activated receptor alpha (PPARα) and decreased the concentrations of serum adrenocorticotropic hormone and corticosterone, peripheral biomarkers of the HPA axis, in animals subjected to chronic unpredictable mild stress (CUMS). Using an antagonist against PPARα abolished the effects of PEA in the CUMS rats (Li et al., 2019).

With sufficient preclinical evidence, human clinical studies have commenced. In 2018, a clinical study as published to assess the use of PEA, as an add-on to Citalopram – a common SSRI used in the treatment of major depressive disorders (MDD). In this study, PEA demonstrated rapid onset adjunct effect in MDD clinical patients, making it a potential adjuvant therapy for MDD (Ghazizadeh-Hashemi et al., 2018).

PEA has a pleitropic mechanism of action, suggesting a potential role as a standalone therapeutic option in depressive disorders. A clinical trial with 15 women diagnosed with MDD, on no previous medication showed a significant decrease in the serum levels of PEA, following exposure to social stress, in comparison to 15 age-matched healthy controls (Hill et al., 2009).

Additionally, new research has identified a role for inflammation in depression's pathogenesis. It has been observed that depression and inflammation tend to acts as fodder for each other, with the presence of inflammation increasing the risk of depressive symptoms (Kiecolt-Glaser et al., 2015). This is important to note, seeing as a major biological activity of PEA is as an anti-inflammatory agent. It is therefore not out of the realm of possibilities that PEA can affect multiple signalling pathways involved in the pathogenesis of anxiety and depression.

These findings suggest that chronic physiological and psychological conditions, like anxiety, depression, stress, chronic pain and inflammation, can decrease the levels of this very important endocannabinoid-like lipid-signalling molecule and therefore supplementation with an adequate source of PEA may support and help manage chronic conditions, like anxiety and depression.

References:

1. Amsterdam, J. D., Li, Y., Soeller, I., Rockwell, K., Mao, J. J., & Shults, J. (2009). A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. Journal of clinical psychopharmacology, 29(4), 378–382. doi:10.1097/JCP.0b013e3181ac935c
2. Amsterdam, J. D., Shults, J., Soeller, I., Mao, J. J., Rockwell, K., & Newberg, A. B. (2012). Chamomile (Matricaria recutita) may provide antidepressant activity in anxious, depressed humans: an exploratory study. Alternative therapies in health and medicine, 18(5), 44–49.
3. Anthes, E. (2014). Depression: A change of mind. Science, 515(7526), 185–187. https://doi.org/10.1126/science.358.6365.856
4. Anxiety Disorders Association of America. (2016). Depression. https://adaa.org/sites/default/files/Depression-ADAA_Brochure-2016.pdf
5. Anxiety Disorders Association of America. Treating Anxiety Disorders. https://adaa.org/sites/default/files/Treating%20Anxiety%20Disorders.pdf
6. Alsmadi, A. M., Tawalbeh, L. I., Gammoh, O. S., Shawagfeh, M. Q., Zalloum, W., Ashour, A., & Attarian, H. (2018). The effect of Ginkgo biloba and psycho-education on stress, anxiety and fatigue among refugees. Proceedings of Singapore Healthcare, 27(1), 26–32. https://doi.org/10.1177/2010105817716184
7. Calabrese, C., Gregory, W. L., Leo, M., Kraemer, D., Bone, K., & Oken, B. (2008). Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. Journal of alternative and complementary medicine (New York, N.Y.), 14(6), 707–713. doi:10.1089/acm.2008.0018
8. Chandrasekhar, K., Kapoor, J., & Anishetty, S. (2012). A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian journal of psychological medicine, 34(3), 255–262. doi:10.4103/0253-7176.106022
9. Coppola, M., & Mondola, R. (2014). Is there a role for palmitoylethanolamide in the treatment of depression? Medical Hypotheses, 82(5), 507–511. https://doi.org/10.1016/j.mehy.2013.12.016
10. Crocq, M. A. (2015). A history of anxiety: From Hippocrates to DSM. Dialogues in Clinical Neuroscience, 17(3), 319–325.
11. Cropley M, Banks AP, Boyle J. The effects of Rhodiola rosea L. extract on anxiety, stress, cognition and other mood symptoms. Phytother Res PTR. 2015; 29:1934–9.
12. De Gregorio, D., Manchia, M., Carpiniello, B., Valtorta, F., Nobile, M., Gobbi, G., & Comai, S. (2019). Role of palmitoylethanolamide (PEA) in depression: Translational evidence: Special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. Journal of Affective Disorders, 255(July 2018), 195–200. https://doi.org/10.1016/j.jad.2018.10.117
13. Elsas, S. M., Rossi, D. J., Raber, J., White, G., Seeley, C. A., Gregory, W. L., … Soumyanath, A. (2010). Passiflora incarnata L. (Passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. Phytomedicine: international journal of phytotherapy and phytopharmacology, 17(12), 940–949. doi:10.1016/j.phymed.2010.03.002
14. Fathinezhad Z, Sewell RDE, Lorigooini Z, Rafieian-Kopaei M. Depression and Treatment with Effective Herbs. Curr Pharm Des. 2019;25(6):738–745. doi:10.2174/1381612825666190402105803
15. Ghazizadeh-Hashemi, M., Ghajar, A., Shalbafan, M. R., Ghazizadeh-Hashemi, F., Afarideh, M., Malekpour, F., … Akhondzadeh, S. (2018). Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. Journal of Affective Disorders, 232(November 2017), 127–133. https://doi.org/10.1016/j.jad.2018.02.057
16. Jacobson, N. C., & Newman, M. G. (2014). Depression over a decade later. Journal of Anxiety Disorders, 28(5), 437–445. https://doi.org/10.1016/j.janxdis.2014.03.007
17. https://adaa.org/sites/default/files/Depression-ADAA_Brochure-2016.pdf
18. https://adaa.org/sites/default/files/Treating%20Anxiety%20Disorders.pdf
19. https://www.mayoclinic.org/diseases-conditions/depression/expert-answers/depression-and-anxiety/faq-20057989
20. https://patents.google.com/patent/US20190099464A1/en
21. Hill, M.N., Miller, G.E., Carrier, E.J., Gorzalka, B.B., Hillard, C.J., (2009). Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology 34, 1257–1262. https://doi.org/10.1016/j.psyneuen.2009.03.013.
22. Hill, M. N., & Patel, S. (2013). Translational evidence for the involvement of the endocannabinoid system in stress-related psychiatric illnesses. Biology of Mood & Anxiety Disorders, 3(1), 19. https://doi.org/10.1186/2045-5380-3-19
23. Hyman S. E. (2014). Revitalizing psychiatric therapeutics. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 39(1), 220–229. doi:10.1038/npp.2013.181
24. Hoge, E., Bickham, D., & Cantor, J. (2017). Digital media, anxiety, and depression in children. Pediatrics, 140(November), S76–S80. https://doi.org/10.1542/peds.2016-1758G
25. Hollon, S. D. (2016). The efficacy and acceptability of psychological interventions for depression: Where we are now and where we are going. Epidemiology and Psychiatric Sciences, 25(4), 295–300. https://doi.org/10.1017/S2045796015000748
26. Huang, W., Chen, W., & Zhang, X. (2016). Endocannabinoid system: Role in depression, reward and pain control (Review). Molecular Medicine Reports, 14, 2899–2903. https://doi.org/10.3892/mmr.2016.5585
27. Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: Depression fans the flames and feasts on the heat. American Journal of Psychiatry, 172(11), 1075–1091. https://doi.org/10.1176/appi.ajp.2015.15020152
28. Kupfer, D. J. (2015). Anxiety and DSM-5. Dialogues in Clinical Neuroscience, 17(3), 245–246.
29. Keefe, J. R., Amsterdam, J., Li, Q. S., Soeller, I., DeRubeis, R., & Mao, J. J. (2017). Specific expectancies are associated with symptomatic outcomes and side effect burden in a trial of chamomile extract for generalized anxiety disorder. Journal of psychiatric research, 84, 90–97. doi:10.1016/j.jpsychires.2016.09.029
30. Kim, M., Lim, H. S., Lee, H. H., & Kim, T. H. (2017). Role Identification of Passiflora Incarnata Linnaeus: A Mini Review. Journal of menopausal medicine, 23(3), 156–159. doi:10.6118/jmm.2017.23.3.156
31. Khaksarian, M., Behzadifar, M., Behzadifar, M., Alipour, M., Jahanpanah, F., Re, T. S., … Bragazzi, N. L. (2019). The efficacy of Crocus sativus (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis. Psychology research and behavior management, 12, 297–305. doi:10.2147/PRBM.S199343
32. Lakhan, S. E., & Vieira, K. F. (2010). Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review. Nutrition journal, 9, 42. doi:10.1186/1475-2891-9-42
33. Li, M., Wang, D., Bi, W., Jiang, Z. er, Piao, R., & Yu, H. (2019). N-palmitoylethanolamide exerts antidepressant-like effects in rats: Involvement of PPARa pathway in the hippocampus. Journal of Pharmacology and Experimental Therapeutics, 369(1), 163–172. https://doi.org/10.1124/jpet.118.254524
34. McLaughlin, R. J., Bambico, F. R., & Gobbi, G. (2011). Role of the endocannabinoid system in etiopathology of major depression. Neurobiology of Depression, (September), 203–222. https://doi.org/10.1201/b11232-11
35. Monteggia, L. M., Malenka, R., & K, D. (2014). Depression: The best way forward. Nature, 515(7526), 200–201.
36. Maniscalco I, Toffol E, Giupponi G, Conca A. (2015). The interaction of Rhodiola rosea and antidepressants. A case report. Neuropsychiatr Klin Diagn Ther Rehabil Organ Ges Osterreichischer Nervenarzte Psychiater. 2015; 29:36–8.
37. Petrosino, S., & Di Marzo, V. (2017). The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. British Journal of Pharmacology, 174(11), 1349–1365. https://doi.org/10.1111/bph.13580
38. Ruehle, S., Rey, A. A., Remmers, F., & Lutz, B. (2012). The endocannabinoid system in anxiety, fear memory and habituation. Journal of Psychopharmacology, 26(1), 23–39. https://doi.org/10.1177/0269881111408958
39. Rho, S. S., Woo, Y. S., & Bahk, W. M. (2018). Ginkgo biloba induced mood dysregulation: a case report. BMC complementary and alternative medicine, 18(1), 14. doi:10.1186/s12906-018-2081-4
40. Sarris, J., et al., Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence, Eur. Neuropsychopharmacol. (2011), doi:10.1016/j.euroneuro.2011.04.002
41. Scholey, A., Gibbs, A., Neale, C., Perry, N., Ossoukhova, A., Bilog, V., … Buchwald-Werner, S. (2014). Anti-stress effects of lemon balm-containing foods. Nutrients, 6(11), 4805–4821. doi:10.3390/nu6114805
42. Smith, K. (2014). Mental Health: A world of depression. Nature, 515(7526), 181–182.
43. Sandeep Kumar Singh, George E. Barreto, Gjumrakch Aliev and Valentina Echeverria, "Ginkgo biloba as an Alternative Medicine in the Treatment of Anxiety in Dementia and other Psychiatric Disorders", Current Drug Metabolism (2017) 18:112. https://doi.org/10.2174/1389200217666161201112206
44. Stringaris, A. (2017). Editorial: What is depression? Journal of Child Psychology and Psychiatry and Allied Disciplines, 58(12), 1287–1289. https://doi.org/10.1111/jcpp.12844

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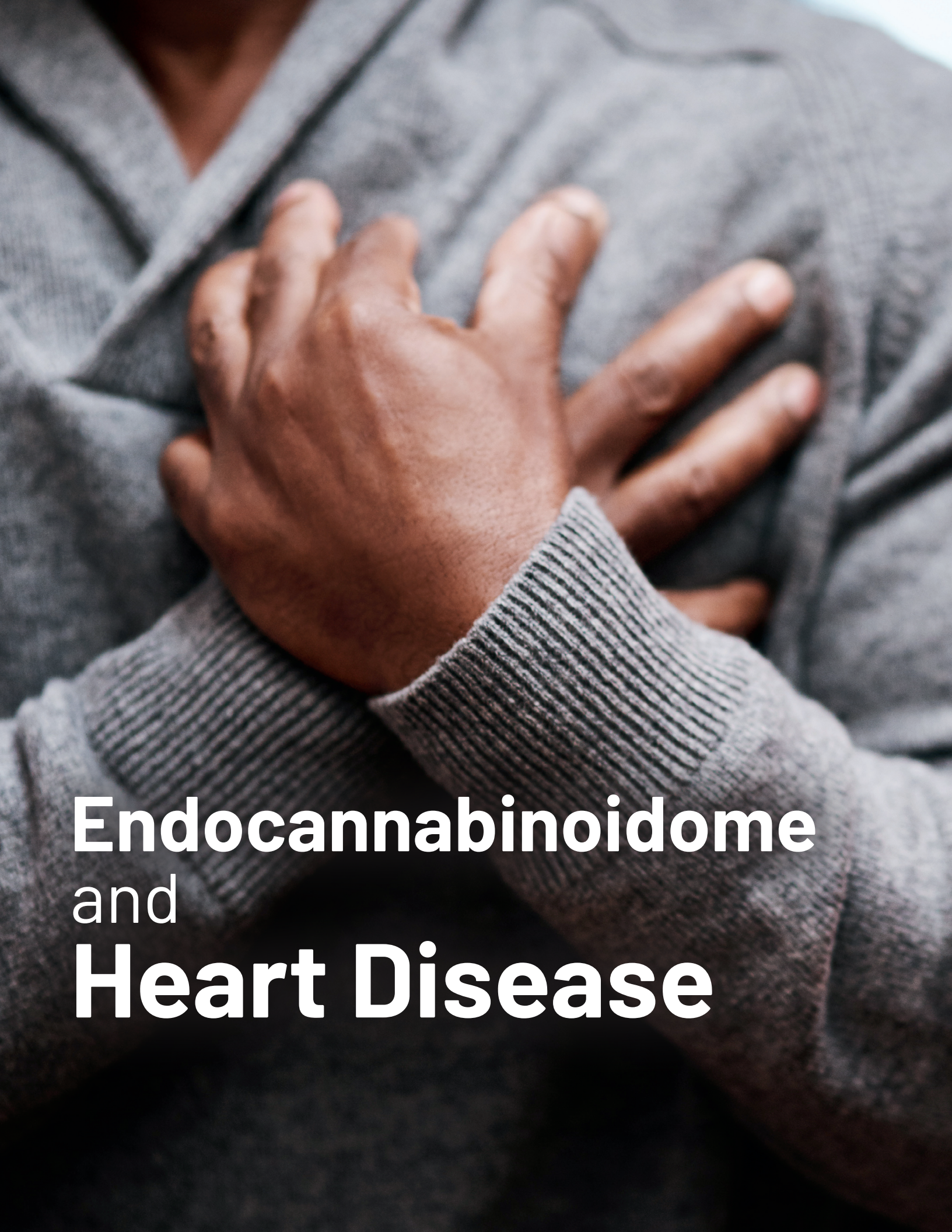
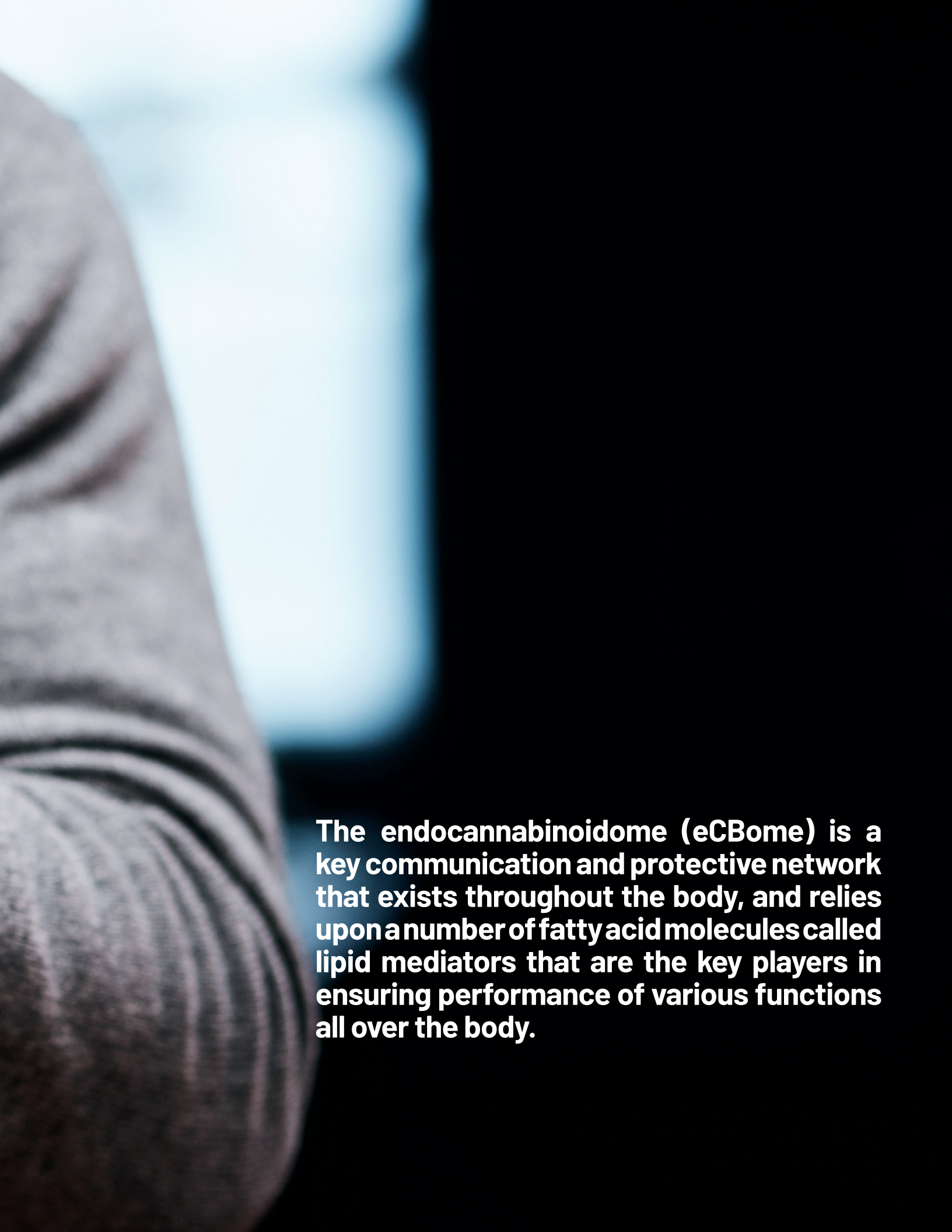


Endocannabinoidome and Heart Disease



The endocannabinoidome (eCBome) is a key communication and protective network that exists throughout the body, and relies upon a number of fatty acid molecules called lipid mediators that are the key players in ensuring performance of various functions all over the body.

eCBome plays an important, and active role in the control of energy generation (calories in) and expenditure (calories out), as well as metabolism of other key molecules like glucose, fats (or lipids). It also influences the hormone insulin. Therefore, it is likely that eCBome plays a key role in a number of disease conditions including diabetes, obesity, cholesterol, heart disease and stroke (See figure 1).

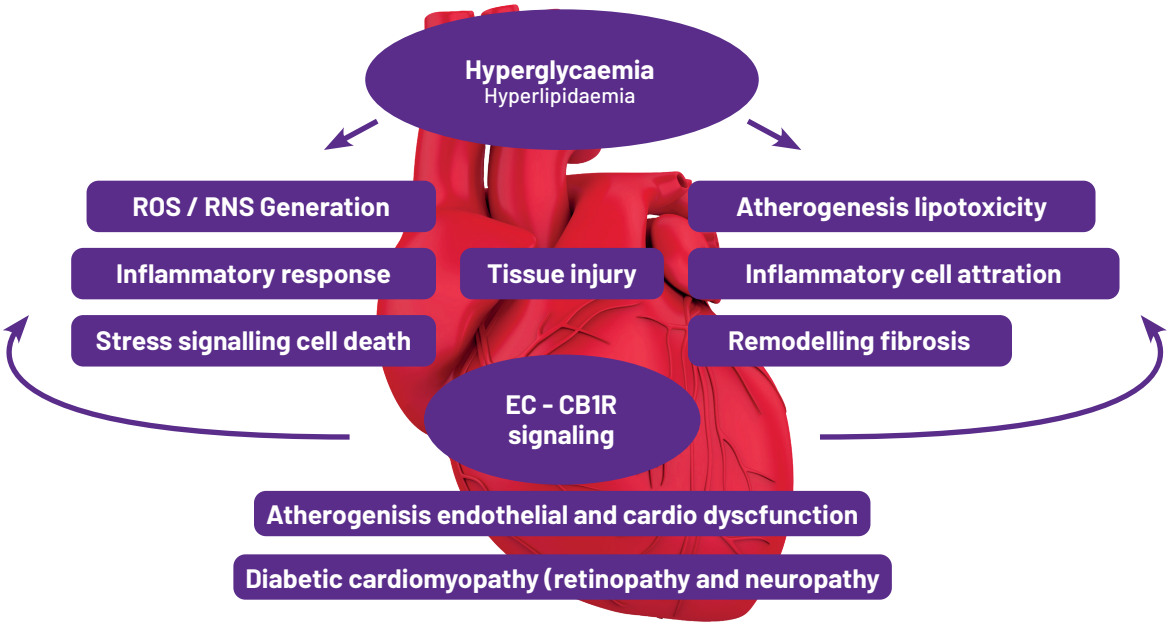


Figure 1: Role of the EC-CB1 receptor signalling in diabetic cardiovascular complications.

What causes heart disease has been an ongoing topic of research. If the initiating event can be identified, then it is possible to prevent or treat heart disease more effectively. Currently, we know the initiating event likely starts with the damage to the cellular lining called endothelium of the blood vessels. This damage may be due to a number of factors; like high blood pressure and erratic flow of the blood, smoking, lack of exercise, or a poor diet. High blood pressure creates eddy currents that may damage the endothelium via the mechanical shearing action. The damage generates oxygen and nitrogen free radicals. These cellular terrorists are highly toxic, causing further damage via a domino effect.

Hyperglycaemia and hyperlipidaemia, associated with diabetes, promote increased reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation in the endothelium, vascular smooth muscle, and induces cell death and recruitment of inflammatory cells. Hyperglycaemia also directly or indirectly leads to enhanced EC-CB1 receptor signalling, which in turn amplifies these pathological processes facilitating tissue injury, cardiovascular dysfunction and eventually development of diabetic cardiovascular complications such as cardiomyopathy, nephropathy, retinopathy and enhanced atherosclerosis.

The endothelium has a single-layered lining and therefore, is extremely prone to damage. The body has a number of protective mechanisms to prevent, and minimize such damage, via generation of nitric oxide (NO) molecules. The molecules are a vasodilator; inhibit platelet aggregation, leukocyte adhesion, endothelial permeability, low-density lipoprotein (LDL) oxidation and smooth muscle cell proliferation. NO also quenches and neutralizes these free radicals, however, may be inadequate or over run by the overwhelming damaging effects of free radicals to mitigate all damage.

Atherosclerosis is an inflammatory disease of arterial walls, precipitated by high levels of low-density lipoproteins (LDL). After there is damage to the vessel wall, the LDL particle burrows its way through the endothelial lining, and then waits, plans and plots further damage. If the offending damage isn't removed or alleviated through lifestyle factors such as normalization of blood pressure or addressing poor diet and lack of physical activity, the LDL particle begins to oxidize and forms oxLDL molecules (see figure 2), which is even more aggressive and damaging to the blood vessel.

The oxLDL further triggers an inflammatory process, which results in the clustering of a wide variety of immune cells, including monocytes and neutrophils. Activated neutrophils and T-cells release cytokines that promote macrophages and vascular smooth muscle cells (VSMCs) migration into the lesion. Both macrophages and VSMCs take up oxLDL. To make matters worse, the endothelial lining is now breached or "leaky" which allows entry of certain cells and molecules where they shouldn't be. Some of the key inflammatory cells present in these clusters are the mast cells, a heavily armed powerhouse of potent chemicals, which are inadvertently released and further inflame the situation.

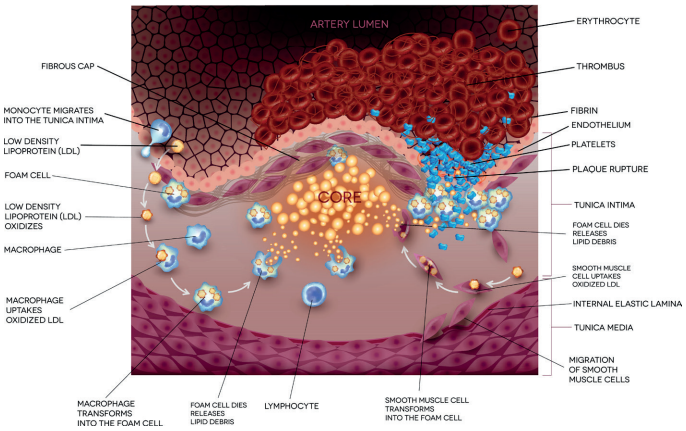
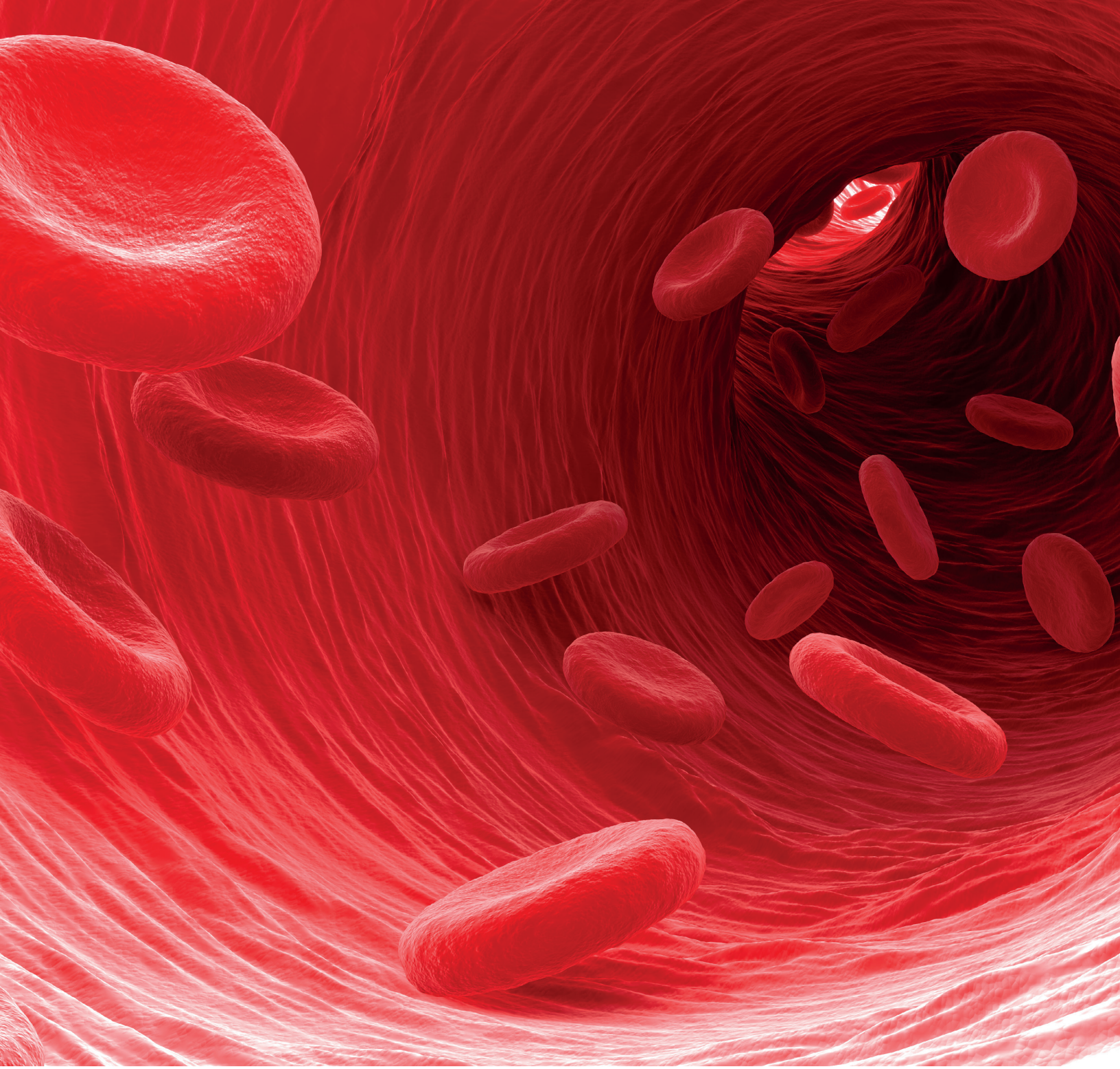


Figure 2: Unstable plaque formation.



The oxLDL particle starts to change and begins to grow and look different. Under the microscope, it looks fatter, has foam like characteristics and is now called a "foam cell". Soon additional players start interacting and help develop a sticky plaque, which grows further and eventually blocks the blood vessel, depriving the organ (heart, brain, kidneys, muscle, etc.) of oxygen and nutrients causing an ischemic situation.

The eCBome system consists of a number of fatty acid signalling molecules called endocannabinoids (eCB's), such as AEA or 2-AG, as well as a group of closely related endocannabinoid-like molecules like PEA and OEA. Since there are CB1 and CB2 receptors present in the endothelium, monocytes, T-cells, VSMCs, and neutrophils it is believed there may be potential to reduce the inflammation associated with this biochemical process, stabilize the plaque build-up and prevent the disease progression with eCB interventions.

References:

1. Fulmer, L. M. and Thewke D. P. "The endocannabinoid system and heart disease: The role of cannabinoid receptor 2", Cardiovasc. Hematol. Disord. Drug Targets. 2018; 18 : 34-51
2. Guillamat-Prats, R. et al. "Endocannabinoid signalling in atherosclerosis and related metabolic complications", Thromb Haemost, 2019; 119: 567-575
3. Pacher, P. et al. "The emerging role of the endocannabinoid system in cardiovascular disease" Semin Immunopathol, 2009; 31: 63-77
4. Sierra, S. et al. "The endocannabinoid system in cardiovascular function: novel insights and clinical implications" Clinical Autonomic Research, 2018;28: 35-52

Endocannabinoidome and Metabolic Syndrome

Metabolic Syndrome (MetS) is a cluster of closely related diseases including diabetes, hyperglycemia, obesity and hypertension.

There is increasing clinical evidence that enhanced endocannabinoidome (eCBome) activation is associated with metabolic disorders. High levels of circulating endocannabinoids (eCB) are usually seen in patients with heart disease, as well as in obese - compared to lean - patients, which in turn determines body fat, triglyceride and cholesterol levels. This observation may be somewhat alarming, given the fact that we are considering manipulating the eCBome via the use of phytocannabinoids to reduce MetS. It is important to note, however, that while eCB levels are being increased, the key determining factor is which receptors are being activated, as different receptors play different roles in health and disease.

Whilst the plasma levels of various eCBs are high in certain disease states, and there is a strong correlation with heart disease, diabetes, and high cholesterol levels, it is natural to think of eCBs as a causative factor. However, it is an alteration in the balance between the CB1 receptor and CB2 receptor signalling that seems to be more closely linked with causation in MetS. In people with these conditions, we often see increased CB1 receptor expression, while the CB2 receptor is downregulated. Lack of exercise and a Western type diet also influence the eCBome system negatively due to over activation of CB1 receptors in the affected tissues in diabetes, heart disease, high blood pressure and obesity.

THC, present in cannabis sativa, strongly activates CB1 receptors in the brain, hence the pronounced psychotropic effect that is experienced. At the same time, THC also activates CB1 receptors in other tissues outside the brain, like the heart tissue, pancreas, liver, and muscle cells, which unfortunately, promotes heart disease, and metabolic syndrome.

Blocking of the CB1 receptor from activation will have a positive health benefit. This has been confirmed by a synthetic CB1 antagonist, which blocked the CB1 receptor. Similarly, activation of CB1 receptors in animals shows corresponding increased disease effects on the tissues. With the legalization of cannabis in many countries, it is concerning that use of THC rich actives (e.g., oils), may have a likelihood in causing an increase of heart disease, and metabolic syndrome due to the CB1 activation.

On the other hand, CB2 activation has been shown to have a protective effect. CBD found in cannabis sativa, as well as from hemp, has the opposite action to THC, and promotes heart health, and reduces the incidence of metabolic syndrome as well as having kidney protective effects. In fact, kidney disease is promoted by CB1 activation while CB2 activation promotes a protective effect (See figure 1). Similarly, activation of the receptor GPR55, will likely have similar health benefits to CB2 activation as shown by animal studies (See figures 2, 3 and 4).

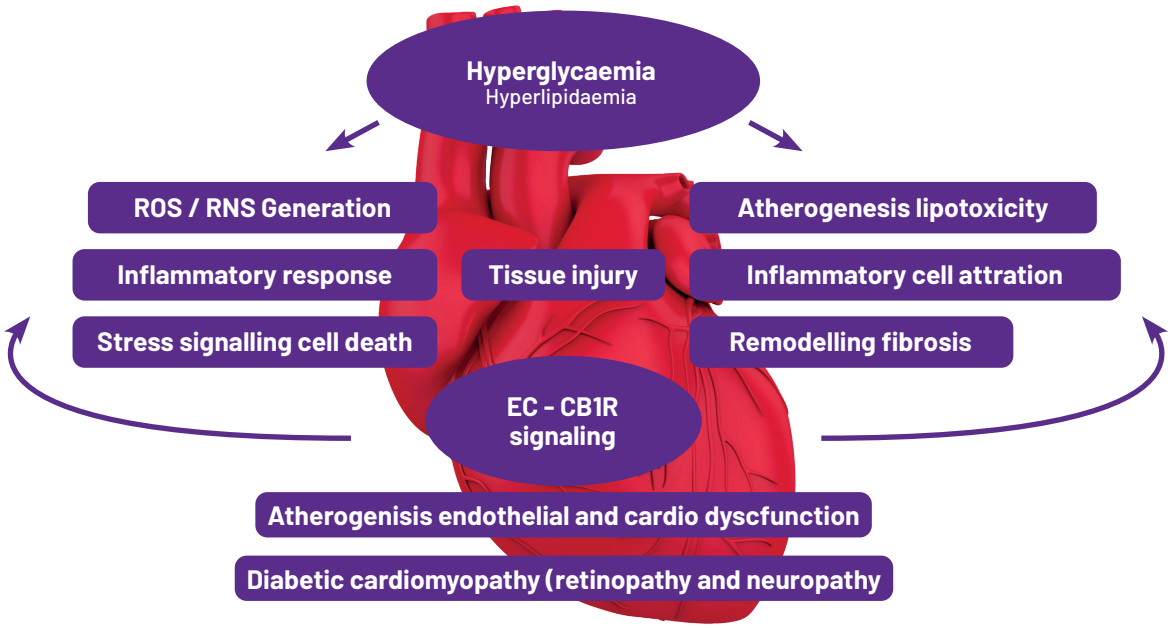


Figure 1: Role of the EC-CB1 receptor signalling in diabetic cardiovascular complications.

So, what is critical is which receptor is being activated, and which is being turned off that determines influence of circulating eCB's on health and disease. In general, activation of CB1 receptor causes heart disease and metabolic syndrome whilst activation of CB2 or GPR55 seems to have a protective effect.

Endocannabinoidome and Type 2 Diabetes:

Briefly, in the brain CB1 receptors are activated in the hypothalamus which causes release of orexigenic peptides like ghrelin which enhance food intake. In addition, CB1 receptors affect the limbic system by increasing the craving for more food. Together, there is increased consumption of calories. In the peripheral organs, CB1 receptors increase energy storage at the expense of energy expenditure, which leads to excess fat storage in the adipose tissues and fat accumulation in the liver, which results in obesity.

The role of eCBome in the development of type 2 diabetes (T2D) is shown in figure 2.

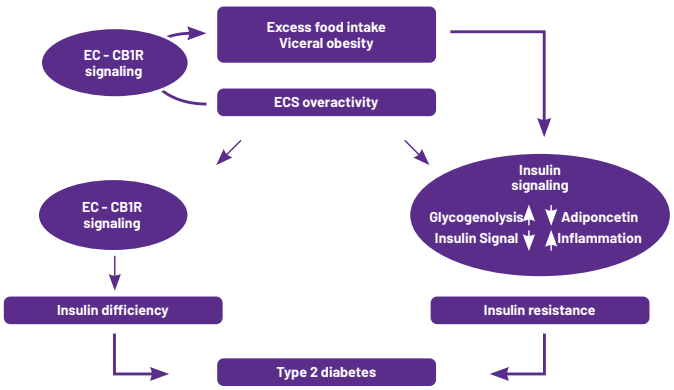


Figure 2

In summary, excess food intake, and obesity enhance the eCBome tone. A hyperactive eCBome causes additional visceral fat accumulation and obesity. This further activates CB1 receptors which cause reduction of energy expenditure, and by enhancing both food intake and fat storage. This is a vicious circle and only exacerbates the problem further with fat deposition and obesity. Furthermore, the eCBome is involved in the development of insulin resistance caused by obesity. Moreover, an overactive eCBome causes damage in a different way by making insulin less effective, affecting its sensitivity and putting up resistance to its action in the tissues like the liver, adipose (fat) tissue and skeletal muscle. Finally, the eCBome causes beta cell failure in the pancreas, which produces insulin, leading to insulin deficiency and eventual development of type 2 diabetes. T2D plays a key role in diabetic complications including diabetes-induced nephropathy (see below), neuropathy, and retinopathy.

eCBome and Kidney Disease:

The fine balance between CB1 and CB2 receptor activation also plays a role in kidney function. Figure 3 shows the effect of how high blood pressure and blood glucose levels, altering the balance of the CB1 in favour of CB2 receptor activation. As in heart disease, and metabolic syndrome, these receptors have opposing effects. The CB2 has a protective effect, countering the damaging effect of CB1 receptor activation. When CB1 is overactive due to uncontrolled diabetes, high blood pressure and obesity, oxidation, and inflammation occurs in the kidney tissue with the loss of nephrons, the functional kidney units that are responsible for filtration of water, protein and ions. As damages progresses and glomerular filtration rate (GFR) goes down, fibrosis sets in which causes even more damage with resulting loss of renal function. T2D is the leading cause of end-stage kidney failure. Figure 4 summarizes the CB1/CB2 alteration effects.

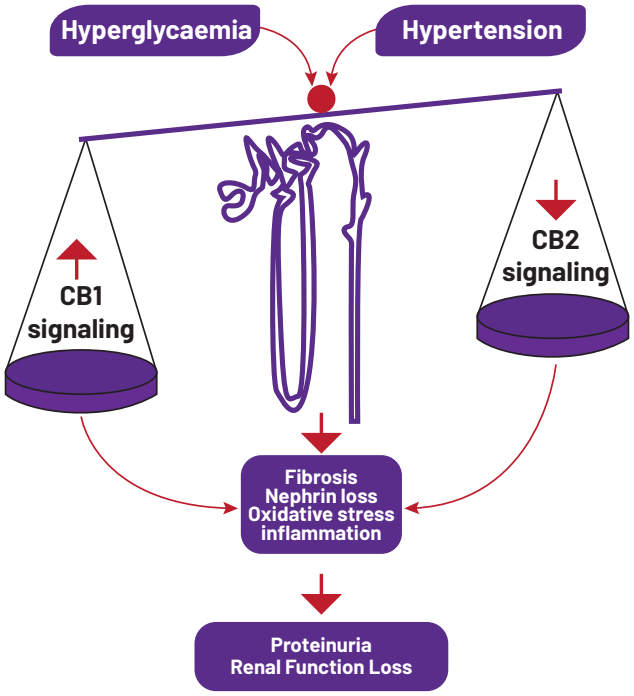


Figure 3: Opposing effects of CB1 receptor and CB2 receptor in the kidneys leading to diabetic nephropathy. The CB1 receptor has damaging pro-oxidative, and pro-inflammatory effects, while opposing protective effects are caused by CB2 receptor activation.

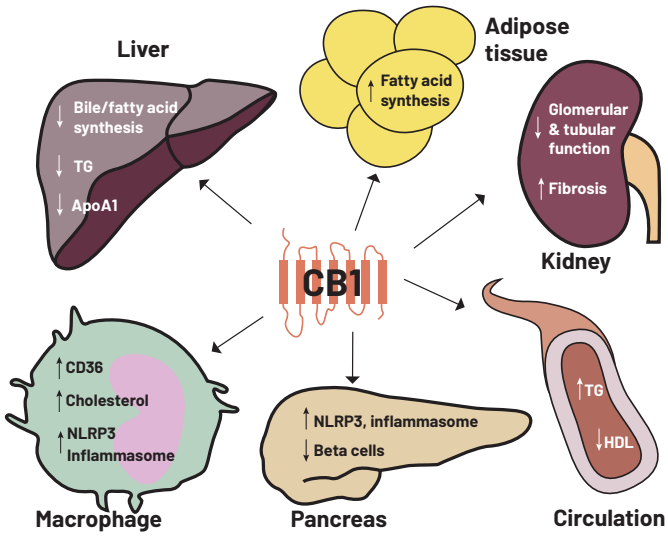


Figure 4: Peripheral and metabolic effects of CB1 signalling. CB1 signalling affects several peripheral organs. In the liver, CB1 activation leads to stimulation of bile/fatty acid synthesis, the accumulation of TG. In macrophages, CB1 stimulation causes intracellular cholesterol accumulation, as a consequence of increased uptake (CD36) and decreased efflux (ABCA1). In pancreas, CB1 activation in infiltrating macrophages directly activates the NLRP3 inflammasome leading to β cell loss. In the kidney, CB1 signalling in podocytes has been linked to glomerular and tubular dysfunction and fibrosis. ABC, ATP-binding cassette transporter; ApoA1, apolipoprotein A1; CB1, cannabinoid receptor 1; HDL, high-density lipoprotein; NLRP3, NLR family pyrin domain-containing 3; TG, triglycerides.

eCBome and High Cholesterol:

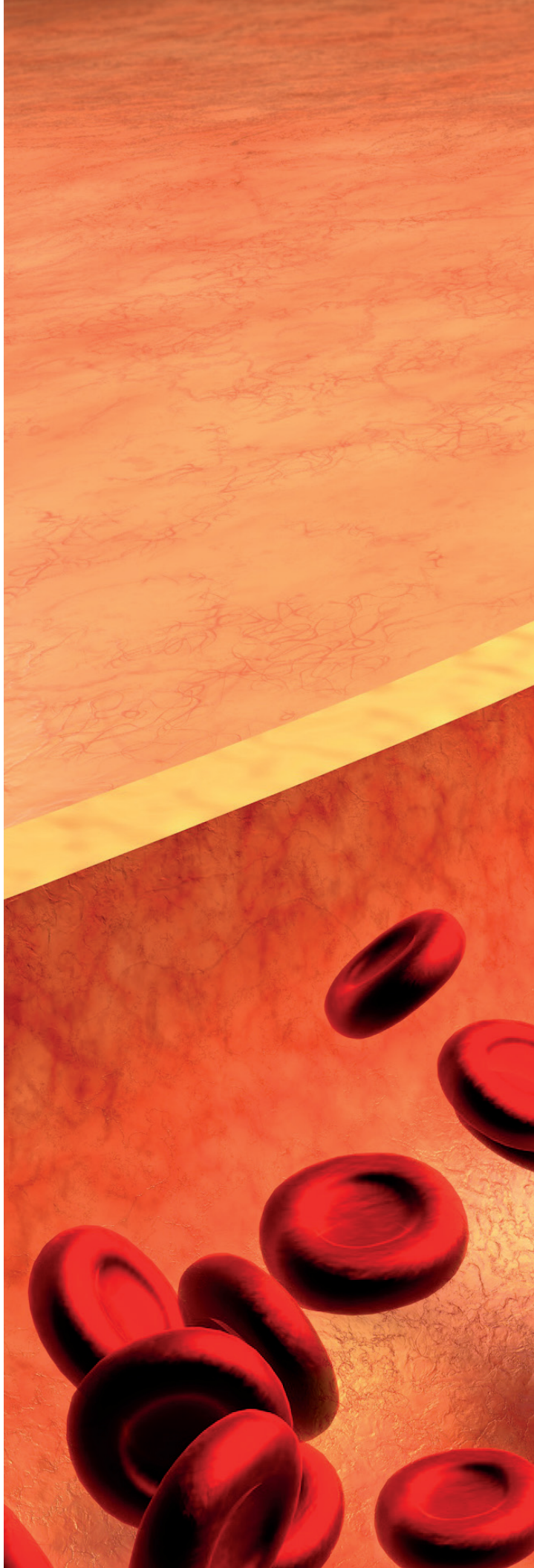
Animal studies have shown a strong association between higher levels of 2-AG, and reduced cholesterol, very low-density lipoprotein (VLDL) which is an even more damaging form of LDL and triglyceride levels. The overall reduced lipid levels were due to the increased cholesterol secretion in the intestines, which was due to increased bile acid production by the liver. In the liver, CB1 activation leads to stimulation of bile/fatty acid synthesis, the accumulation of TG, and the reduction of ApoA1 secretion. The latter is involved in formation of the "good" HDL cholesterol. So reduced formation of ApoA1 results in decreased HDL, and increased TG levels in circulation. Finally, CB1 activation stimulates fatty acid synthesis also in the adipose tissue leading to obesity.

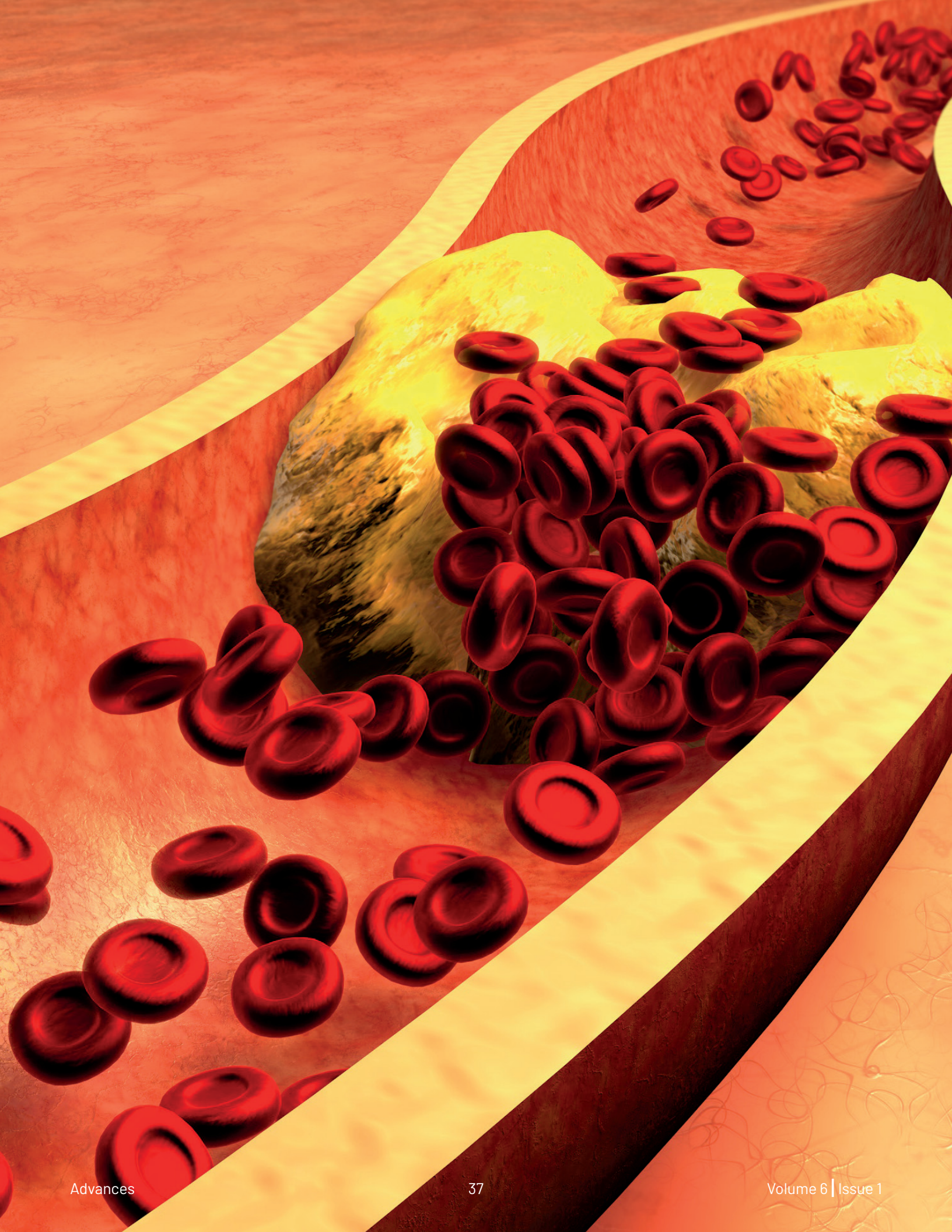
Summary:

In summary, eCBs are raised in a number of disease conditions, however, interpreting the significance of this increase is difficult since eCBs have been described as being "promiscuous" in nature due to the fact they act on a many different receptors, and in different ways of the eCBome. For example, eCBs may act as a direct blocker (antagonist), and at other times it may act as an activator (agonist). But as well, eCBs may act as partial blockers or as inverse blockers and activators depending upon the concentration. Nonetheless, it is becoming clear that receptor activation can be damaging or protective depending on which receptors are being activated. For example, CB1 receptor activation is definitely associated with full gamut of metabolic syndrome, while CB2 receptor, PPAR-alpha, and possible GPR55 activation may lead to protective effects. Thus, blocking CB1 signalling in the vessels, adipose tissue, liver, macrophages and the kidney may have offered a promising therapeutic opportunity. Likewise, additional receptors like GPR55 and PPAR-alpha may offer similar effects as CB2 activation.

References:

1. Vincenzo Di Marzo and Cristoforo Silvestri. "Lifestyle and Metabolic Syndrome: Contribution of the Endocannabinoidome"
2. G. Gruden, F. Barutta, G. Kunos and P. Pacher. "Role of the endocannabinoid system in diabetes and diabetic complications", British Journal of Pharmacology, 2016; 173: 1116-1127
3. Maccarrone, M. et al. Ėndocannabinoid sgnaling at the periphery: 50 years after THC'. Trends in Pharmacological Sci. 2015; 36: 277-296
4. Di Marzo V and Silverstri C, `Lifestyle and metabolic syndrome: Contribution of endocannabinoidome`Nutrients, 2019; 11: 1956-1980
5. Mastinu, A. et al. Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuro-inflammation"
6. Van Eenige, R. et al. "Regulation of adipose tissue metabolism by the endocannabinoid system" Trends Endocrinol Metabolism, 2018; 29: 326-337
7. Endocannabinoid signalling at the periphery: 50 years after THC Mauro Maccarrone Trends in Pharmacological Sciences, May 2015, Vol. 36, No. 5 277





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