Chapter 1
What Is The Endocannabinoid System and Why Should You Care About It?

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To keep your mind healthy, your joints strong, your mood calm, and your digestive system comfortable, your body was given an amazing tool. That tool is called the endocannabinoid system. Researchers discovered its existence only as recently as 1988, when they were investigating how cannabinoids found in the marijuana plant (*Cannabis sativa*) affect the body.

The interesting thing about this system is that you don't need marijuana to activate it. It's a perfectly natural pathway that has served humankind and other mammals for millennia. Your body makes its own cannabinoids that work through this same system. These cannabinoids that your body makes are called endocannabinoids. There are also hemp-based cannabinoids (phytocannabinoids)—such as cannabidiol (CBD)—that work through the endocannabinoid system. These phytocannabinoids can even increase levels of your natural cannabinoids. CBD, unlike marijuana, works on the endocannabinoid system without making you high because it does not contain enough tetrahydrocannabinol (THC). That's the component of marijuana responsible for its psychoactive effects.

Even though your body makes endocannabinoids, many aspects of modern life can lead to an endocannabinoid deficiency (more on this later). That's when hemp-based CBD oil can be especially effective.

Your Body's Locks and Keys

Cells throughout your body have receptors. These receptors act like locks. They need certain substances that act like keys to open or close the receptor locks. Depending on the cell's location in the body and receptor involved, this can open or close different doors to health or disease depending upon whether the substance acting like a receptor key is beneficial or harmful and whether it locks or unlocks the receptor. Substances that bind to receptors to act like keys include drugs, hormones, and neurotransmitters (chemicals released from nerve cells).

In 1988, scientists Allyn Howlett and William Devane at the St. Louis University School of Medicine discovered that brains in mammals have receptors that react to cannabis-derived compounds.[1] These receptors are known as cannabinoid receptors. They're the most abundant form of neurotransmitter receptor in the brain. These cannabinoid receptors respond to endocannabinoids. Plant-derived cannabinoids such as CBD from hemp and THC from marijuana also interact with these receptors.

CB1 and CB2 were the first two cannabinoid receptors discovered.[1] CB1 receptors are primarily located in the brain.[1] By contrast, CB2 receptors are located in the gastrointestinal (GI) tract, liver, spleen, endocrine glands, and the reproductive system.[1] The immune system and the

peripheral nervous system also contain CB2 receptors.[1] The peripheral nervous system is the part of the nervous system located outside the brain and spinal cord.

The Endocannabinoid System's Role in Your Health

There is a lot more for us to learn about the endocannabinoid system's role in health. However, thousands of studies have now explored the many ways in which this system benefits us. The table below shows in which health concerns the endocannabinoid system plays a role.

	Table 1: The Many Ways the Endocannabinoid System Regulates Health
Gut Health	• The endocannabinoid system is involved in regulating visceral pain and irritable bowel syndrome.[2,3] • Endocannabinoids also help ensure we don't get constipated or develop diarrhea.[3] • The endocannabinoid system helps regulate intestinal permeability, meaning it can support the health of people with leaky gut.[4] • The phytocannabinoid CBD may have a role to play in supporting the health of people with ulcerative colitis.[5]
Brain Function and Mental Health	• Endocannabinoids play a role in the gut-brain axis, the communication that occurs between the gut and the brain.[6] • The endocannabinoid system is involved in regulating anxiety, posttraumatic stress disorder, depression, bipolar disorder, and schizophrenia.[7]
Pain	• CB2 receptors stimulate opioid receptors to cause pain relief in a non-addictive manner.[8] • CB2 receptors may be involved in blocking the effect of painful stimuli in inflammatory processes of the nervous system.[9] • The endocannabinoid system may be the reason why stress can lead to abdominal pain.[3] • The pain-relieving effects of acetaminophen may be because one of its metabolites indirectly activates CB1 receptors.[10] • The endocannabinoid system also is involved in the regulation of endometriosis-associated pain.[11]
Joint Health	• In rat studies of animals with osteoarthritis, transdermal or oral CBD improved joint health, reduced joint inflammation and swelling, and improved the ability of the animals to bear their own weight. CBD administered in advance of inducing osteoarthritis in animals blocked the development of joint pain and nerve damage.[12,13] • Researchers have found cannabinoid receptors on human articular cartilage from patients with symptomatic osteoarthritis.[14]

Stress	• CBD's role in promoting a calm mood is related to its effects on the serotonin receptor and the ability to control blood flow in regions of the brain involved in anxiety.[15] • A number of clinical studies have shown CBD has a calming effect on people who have to give a public speech.[16-19]
Sleep	• Low-dose CBD can be stimulating and lead to wakefulness. However, higher doses of CBD can encourage restful sleep.[20] • CBD may reduce stress and improve the quality and quantity of sleep.[21] • CBD may be beneficial in REM sleep behavior disorder (a condition where people kick, move, or act out dreams in their sleep) and to feel less sleepy during the day.[22]
Women's Health	• The endocannabinoid system plays an important role in fertility.[23] • The endocannabinoid system is present within ovaries.[24] • CBD may reduce discomfort in women with endometriosis.[25] • Menopausal health and breast health may also be regulated by the endocannabinoid system.[26,27]
Men's Health	• CBD may play a role in prostate health.[28,29]
Urinary Tract Health	• Cannabinoid receptors are present in the lower urinary tract and areas involved in urinary tract control.[30] • Phytocannabinoids may support the health of the bladder, urethra, and prostate.[30]
Epilepsy	• CBD, administered together with anti-seizure medication, can support the health of people with seizures.[31-34]
Immunity	• The endocannabinoid system can be involved in both enhancing and suppressing immunity.[35] • The endocannabinoid system is involved in the body's response to respiratory syncytial virus (RSV), the primary cause of severe bronchiolitis and pneumonia in children.[36-38] • CBD can support a healthy immune response in the liver.[39] • All five major cannabinoids—cannabidiol, cannabichromene, cannabigerol, THC, and cannabinol—help control a variety of methicillin-resistant *Staphylococcus aureus* (MRSA) strains of bacteria.[40]
Inflammation	• Cannabinoids play a role in the recruitment of immune cells to the location of intestinal inflammation.[41] • Cannabidiol also has been shown to block the production of pro-inflammatory proteins known as cytokines.[42] • CBD has reduced markers of inflammation in a number of cell culture and animal studies.[43-46] • Cannabinoids ability to support a healthy inflammatory response are not associated with the adverse effects produced by NSAIDs.[47]

ADHD/Autism	• Researchers have observed low levels of certain endocannabinoids in children with autism spectrum disorder (ASD).[48] • Problems with endocannabinoid function are thought to play a role in the social challenges that occur in kids with ASD.[49] • In adults with ADHD, CBD may help reduce hyperactivity, impulsivity, and ability to control behavior. However, more studies are needed in this group of people.[50]

Getting To Know The Endocannabinoids

There are two main endocannabinoids produced in the body: anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These activate CB1, CB2, and other receptors in the endocannabinoid system, serving as the "keys" that fit into the receptor "locks" (more on this later). Each of these endocannabinoids play an important role in health. AEA is involved in the perception of pain, emotional health, and energy metabolism (the body's generation of energy from nutrients).[51] It is nicknamed "the bliss molecule" since it's involved in mood.

Like AEA, 2-AG is found throughout the body including the brain, cardiovascular system, and intestines.[52,1] 2-AG may even be involved in orgasms during sex, indicating that AEA isn't the only bliss molecule.[53]

Another key player in the endocannabinoid system are enzymes that break down the endocannabinoids. For example, the enzyme fatty acid amide hydrolase—FAAH for short—breaks down AEA.[54] Some substances like CBD can increase levels of AEA by blocking FAAH actions.[55] Blocking FAAH may help support pain management and neurodegenerative health and relieve occasional anxiety.[54]

Endocannabinoid Deficiency

Certain factors can cause what's known as endocannabinoid deficiency. This happens when the body doesn't make enough endocannabinoids to maintain optimal health or there are a reduced number of cannabinoid receptors. For example, early life stress leads to changes in AEA and 2-AG tissue levels within the amygdala and hippocampus regions of the brain.[56] Stress in early childhood can also reduce the number of CB1 receptors in all brain regions later in life.[56] These changes can lead to an inability to cope with stress as time goes on.[56]

Endocannabinoid deficiency can also result due to genetic reasons or because of disease or injury.[1] Researchers have proposed that endocannabinoid deficiency may be the cause of migraines, fibromyalagia, and irritable bowel syndrome.[1] It may also play a role in autism spectrum disorder.[1]

A Balancing Act

The goal is not always to increase endocannabinoid levels. Instead, sometimes lowering endocannabinoid levels is what is needed for optimal health. We must always strive for a balanced endocannabinoid system. For example, lower AEA was associated with the improvement in migraines that occur when patients with these headaches participate in aerobic exercise.[57] In addition, weight loss and improved mood after aerobic exercise training are linked to lower plasma AEA in healthy people.[58] In addition, high 2-AG levels are linked to excessive hunger in sleep-deprived people.[59]

Beyond Cannabinoid Receptors

Earlier, we discussed the cannabinoid receptors CB1 and CB2. However, endocannabinoids, CBD, and other hemp-derived cannabinoids interact with other receptors, too. Here are some of these other receptors:

• **G-protein coupled receptors (GP- CRs: GPR18, GPR55 and GPR119)** – GPR18 is expressed primarily in immune cells while GPR55 is expressed in several brain areas as well as in some neurons with larger diameters.[60] GPR55 may also be expressed in the immune system as well as in immune-regulating cells located in the brain and spinal cord known as microglia.[60] GPR55 can also be activated in the bone.[60]

• **Type 1 vanilloid receptors ($TRPV_1$)** – These receptors may be involved in some of the beneficial effects of cannabinoids. For example, scientists have found $TRPV_1$ receptors in neurons that play a role in pain management.[61]

• **Serotonin receptor (5-HT1A**) – Scientists have shown that endocannabinoids and plant-derived cannabinoids can affect the serotonin receptor subtype 5-HT1A. Serotonin is known as the "feel-good" neurotransmitter. Optimal levels of this neurotransmitter lead to a sense of well-being and happiness. The mood-boosting effects of CBD are due in part to activation of the 5-HT1A receptor.[62]

• **Other cannabinoid receptors** – Cannabinoids may interact with other receptors. These other receptors may be involved in some of the pain-relieving effects linked to cannabinoids.[63,64]

The Pain-Killing Endocannabinoid Lookalike

There is a substance known as palmitoylethanolamide (PEA). It's not an endocannabinoid but it works on the endocannabinoid system by helping the body make better use of the endocannabinoid AEA.[65] PEA is best known for its role in pain management. PEA is a natural painkiller.[65] Your body makes it when it's in pain. PEA is also found in some foods including egg yolks, peanuts, and soybeans. However, it's not found in cannabis.

There's now a lot of evidence to indicate PEA reduces neuroinflammation, a process that's linked to pain.[65] It does this in part by blocking mast cells and regulating glial cells in the central nervous system.[65] If you have hay fever then you're all too familiar with what overactivated mast cells can do. They release inflammatory substances such as histamine. Glial cells play a role in the health of your neurons.

Researchers reviewed the results of 12 clinical trials to find out whether PEA could reduce pain.[65] The researchers concluded that PEA supplementation was better at progressively decreasing pain intensity compared with control. According to these scientists, "These results confirm that PEA might represent an exciting, new therapeutic strategy to manage chronic and neuropathic pain associated with neuroinflammation."

The Remarkable Cannabinoid System

Cannabinoids—both the endocannabinoids made in your body and hemp-based cannabinoids like CBD—play a role in virtually every area of health. Well-being and happiness, pain management, a healthy digestive system, a good night's rest, a strong immune system, reproductive health, and healthy joints are all dependent upon this system. Taking steps to keep your endocannabinoid system healthy is therefore critical to optimal health.

The statements mentioned in this content have not been evaluated by the FDA, and are not intended to prevent, diagnosis, or treat any disease. Always work with your personal healthcare provider.

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Chapter 2
CBD's Mechanisms in the Body: How This Amazing Cannabinoid Keeps You Healthy

Cannabidiol (CBD) from hemp oil has taken center stage recently as a way to address many areas of health including supporting a healthy pain response in the joints and other areas of the body, dealing with occasional sleep problems and everyday stress, and supporting a healthy attention span, focus, and concentration, to name just a few of its benefits. (I summarized its health benefits in Table 1 of Chapter 1, and I'll be talking more about those benefits as this book unfolds.) In June 2018, CBD ended up even more in the spotlight when the US Food and Drug Administration (FDA) approved the first CBD-based drug, Epidiolex®, for treatment of rare, severe epilepsy.

Is CBD the Answer to the Opioid Addiction Crisis?

Overuse of opioid drugs, which are highly addictive and lead to fatal overdoses, has hit epidemic proportions. Every day, 128 people in the United States die from an opioid overdose.[1]

It's estimated that 21% to 29% of people using opioids for chronic pain misuse these drugs.[2] Not only are opioids potentially dangerous, but taking opioids can actually backfire. Sometimes a patient taking opioids for the treatment of pain could instead make the pain worse since they react even more to certain painful stimuli.[3]

This crisis has its origins in 1937, when German scientists at the IG Farben company first synthesized the opioid medication methadone to use for surgery-related pain. They claimed it was less addictive than morphine or heroin. However, this claim was clearly false. Methadone is longer-acting than morphine or heroin.[4] It's more addictive than these substances and causes withdrawal symptoms that last longer.[4]

Pharmaceutical companies began releasing new opioid painkillers including Vicodin® (a combination of Hydrocodone Bitartrate and acetaminophen) in 1984, OxyContin® in 1995, and Percocet® (Oxycodone plus acetaminophen) in 1999.[5] This led to an onslaught of opioid over-prescribing. After all, the pharmaceutical industry assured physicians that these medications were not addictive.[1]

In 2007 came a turnaround point. Purdue Frederick Company Inc., an affiliate of Purdue Pharma, along with three of the company's executives admitted to misbranding OxyContin®. The company had made false statements about the drug, claiming it was less addictive than other opioids and that people taking it were less likely to abuse it. Purdue Frederick pleaded guilty to criminal charges and paid $634 million in fines.[6]

Clearly, we need another alternative to support a healthy pain response. And that alternative may very well be CBD, which does not produce a high and isn't addictive. Later in this book, I'll discuss CBD's ability to support comfortable knee and hip joints, as well as promote a healthy pain response in the neck, back, and more. For now, let's take a look at the way in which CBD can benefit so many areas of health.

How CBD Works

CBD has shown a lot of promise both in doctor's offices and in studies. But how does this hemp-derived cannabinoid work?

As a reminder, in Chapter 1, I covered CBD's effects on CB1 and CB2 receptors and how CBD acts like a key that fits into those receptor locks. These receptors are part of what's known as the endocannabinoid system, which plays a role in keeping us healthy, both physically and mentally. I also discussed the other receptors that CBD acts upon and explained that two main endocannabinoids produced in the body—anandamide (AEA) and 2-arachidonoylglycerol (2-AG)—activate these same receptors. A lot of what we know about CBD comes from what researchers have observed about the effects of AEA and 2-AG on the body.

In Chapter 1, I also delved briefly into the effects of an enzyme known as FAAH. This enzyme breaks down the endocannabinoid AEA. In doing so, it generally weakens AEA's beneficial

effects. AEA is sometimes called the "bliss molecule" since it plays an important part in maintaining a happy mood and staying optimistic. CBD can increase levels of AEA by blocking FAAH.[7] Blocking FAAH may help support pain management and neurodegenerative health, maintain healthy levels of beta-amyloid proteins, and relieve occasional stress and frustration.[8-12] When people take opioids, they start to become tolerant to the drugs' effects, so they have to take higher and higher doses for these medications to remain effective. Based on results of animal research, blocking FAAH may also stop this tolerance to opioids.[13]

Meet MAGL

In this chapter, I am going to introduce another enzyme involved in the endocannabinoid system. It's called monoacylglycerol lipase—MAGL for short. While FAAH breaks down the endocannabinoid AEA, MAGL breaks down AEA's endocannabinoid sibling 2-AG.[14] In animal studies, blocking MAGL maintains gastric health when taking non-steroidal anti-inflammatory drugs (NSAIDs).[14] These type of drugs—such as aspirin and ibuprofen—are extremely damaging to gastric health and can cause ulcers. Patients with ulcerative colitis also have elevated MAGL levels, suggesting that in these people the endocannabinoid 2-AG is being broken down faster.[15]

Blocking MAGL also can strengthen the intestinal wall, possibly reducing leaky gut.[14] This is a condition where weakened intestinal walls leads to the escape of food particles and inflammatory substances into the circulation. This can cause problems throughout the body. Leaky gut is linked to food intolerances, brain health, and much more. In fact, in my patients, I have noticed that resolving leaky gut leads to dramatic improvements in overall health.

CBD reduces MAGL's ability to break down the endocannabinoid 2-AG.[16] CBD's ability to block MAGL's actions may be part of the reason it can produce feelings of calm during occasional stress, promote a healthy gastrointestinal tract, and reduce cravings in people with addictions.[14,16,17] By blocking the enzymes FAAH and MAGL, CBD may protect the GI tract from the negative effects of NSAIDs since the GI damage caused by these medications is linked to FAAH and MAGL activity.[18,19]

Beyond CBD's Healthful Properties

CBD is the most talked about cannabinoid in hemp because it's found in high levels. But hemp also contains other phytocannabinoids that are beneficial to health. These are found at much lower levels than CBD, but work together with CBD to provide synergistic benefits. And these other phytocannabinoids even have healthful properties on their own. One of these phytocannabinoids is cannabigerol (CBG). CBG is antibacterial and supports a healthy inflammatory response.[20,21] What's more, it can promote well-being and happiness, thanks to its ability to increase the "bliss molecule" anandamide.[22]

CBG also promotes a healthy pain response, supports healthy cells in the colon and other areas of the body, and is neuroprotective.[22-25] In fact, CBG and CBD each have different neuroprotective effects, indicating they can work together to support brain and nervous system health in people with neurodegenerative concerns.[25] In addition, Cannabis with high levels of

CBD and CBG inhibits the activity of the enzyme aldose reductase in human cell culture studies.[26] Blocking aldose reductase is involved in diabetic health.

Cannabinol (CBN) is another phytocannabinoid in hemp. In animal research, CBN teamed up with CBD to support comfortable muscles and temporomandibular health.[27]

The "Hemptourage Effect"

Two decades ago, Doctors Mechoulam and Ben-Shabat proposed a concept known as the entourage effect.[28,29] Originally, it referred to the ability of certain endocannabinoid system components to boost the beneficial effects of the two most important actors in this system: anandamide and 2-arachidonylglycerol.[28]

Today, the entourage effect is commonly used to refer to an interesting phenomenon: the ability of CBD to work together with its other minor components to produce even greater health benefits. The term "hemptourage effect" is now used to describe the potential synergistic interactions that take place between the CBD in hemp oil and hemp's other constituents.

Terrific Terpenes

Substances in hemp that work together with CBD are called terpenes, which contain beneficial compounds known as terpenoids, the largest group of plant chemicals. Some of these terpenes are also found in cannabis and are responsible for its aroma. The table below shows some of the ways these terpenes can promote health.

Some Terpenes Found in Hemp and How They Benefit Health[22,29]	
D-Limonene	• Also found in citrus fruits, d-limonene is relaxing. In rodent studies, it has increased brain levels of two hormones related to mood and happiness: serotonin and dopamine (DA). • Inhaling citrus fragrance improved mood in depressed human subjects. Nine of the 12 subjects were able to stop taking antidepressant medications. • D-limonene also supported healthy immunity.

Myrcene	• Supports a healthy inflammatory response and a healthy liver after exposure to toxins. • In rodent studies, acts like an analgesic and relaxes muscles. • Promotes relaxation and sleep.
D-Linalool	• Also found in lavender, linalool is calming. • Acted as an anti-convulsant in rodents and inhibited seizures. • Compared with a placebo, inhaling lavender decreased the use of morphine opioids in morbidly obese people who underwent gastric banding surgery.
α-Pinene	• α-Pinene is the most common terpenoid in nature. In addition to hemp, it's found in conifer trees and other plant essential oils, where it acts like a natural insect repellant. • It supports a healthy inflammatory response. • A human study found it supported lung health by clearing the airways. • It supports cognitive function. This could mean it acts synergistically with CBD in counteracting the short-term memory problems caused by THC intoxication after marijuana use. • In a mouse study, essential oils that included pinene and limonene enhanced absorption of estrogen through the skin.

Nerolidol	• Also found at low levels in citrus fruit peels, nerolidol is calming. • A rodent study found it supports colon health. • It may also be able to stop fungal growth. • May weaken protozoan parasites such as malaria and leishmania.
Caryophyllene (Humulene)	• Also found in lemon balm (*Melissa officinalis*) and eucalyptus. • Serves as a natural insecticide and antifungal in plants. • May block fungal growth. An 8% concentration eradicated a fungal infection in 15 days. • In cell culture research, it stopped blood platelets from sticking together. • Reduced paw swelling in rodents given an inflammatory substance.
Phytol	• Present in hemp extracts through the breakdown of chlorophyll and tocopherol. • Leads to relaxation thanks to its ability to raise levels of the calming neurotransmitter GABA. It blocks an enzyme responsible for breaking down GABA.
beta-Amyrin	• Supports a healthy inflammatory response and the body's response to unwanted microorganisms and fungus.

Teaming Up with Terpenes

Many terpenes found in hemp may work together with CBD and other phytocannabinoids in hemp. In fact, many terpenes have complimentary actions to CBD. Take a look at the table

below to get an idea how these terpenes work together with other components of hemp oil. Since this is such a large topic, I'll devote a chapter to terpenes later on in the book.

How Terpenes Work Together with Other Hemp Components[22]	
Limonene + Linalool + Pinene + CBD	• CBD reduces the increased sebum production linked to acne. • Limonene was more effective at suppressing *Propionibacterium acnes*, an acne-related pathogen, compared with triclosan. Linalool and limonene are known to reduce markers of *P. acnes*-related inflammation. • Pinene suppresses *P. acnes* and *Staph* spp. • CBD supports cognitive function in people exposed to THC from cannabis, which is known to affect memory. In cell culture, CBD also reduces formation of beta-amyloid proteins. Low levels of beta-amyloid is linked to a healthy memory during aging. Limonene, pinene, and linalool likely work with CBD to support cognitive health through their ability to improve mood. • Pinene also improves mental focus, thus acting synergistically to CBD's ability to support a sharp memory.
Pinene + CBD + CBG	• Pure CBD and CBG blocked methicillin-resistant Staphylococcus aureus (MRSA) in a structure-activity study. This type of study looks at the link between a substance's chemical structure and its actual biological activity against a microorganism. • High-pinene essential oils were also effective against MRSA and other antibiotic-resistant bacteria.
Limonene + linalool + CBD	• CBD is calming and reduces everyday stress. Researchers have proposed that using

	limonene and linalool with CBD could add to CBD's relaxing effects since both of these terpenes are also very calming.

Hemp's Powerful Health Benefits

Now that I've discussed the mechanisms involved in the beneficial effects of CBD and other components of hemp, in the chapters that follow I'll go into detail about the specific ways CBD from hemp oil can make you feel happier and healthier.

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Chapter 3
CBD and Its Role in Calming Stress

The statements mentioned in this content have not been evaluated by the FDA, and are not intended to prevent, diagnosis, or treat any disease. Always work with your personal healthcare provider.

Fear, stress, and anxiety are normal responses triggered when the body perceives threats to survival. However, in modern times, we encounter situations such as deadlines at work, unemployment, financial challenges, caring for our elderly relatives, and many other situations that cause our body to get stuck in stress mode. This leads to excessive and ongoing fear, stress, and anxiety. A number of mental disorders are also associated with excessive fear and anxiety, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). CBD can soothe mild stress and anxiety by virtue of its effects on the central nervous system.[1,2]

CBD interacts with several receptors that regulate fear and anxiety-related behaviors such as the cannabinoid receptor CB_1, the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor.[3] I discussed these receptors in detail in chapter 1. Remember that CBD works through the endocannabinoid system. And the endocannabinoid system plays an important role in reducing stress and anxiety.

Your Body's Own Stress-Reduction Mechanism

The endocannabinoid system regulates emotional behavior. It determines how you respond to unpleasant events and leads to an appropriate response to stress.[4-6] As I talked about in previous chapters, endocannabinoids that are part of the endocannabinoid system activate CB_1 receptors. These endocannabinoids act like locks that fit into the receptor "key." Activation of CB_1 receptors regulates anxiety and fear.[6] In animal research, CB_1 receptor activation led to an improved response to bad memories.[7]

When you're under stress, your body is tasked with sending you back into your non-stress state of peaceful balance. In order to accomplish this, it performs what's called a negative feedback loop. The loop begins when stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This leads to a stress response or stress cascade, as it's sometimes called. This stress cascade helps the body make the necessary changes required to cope with stress. When the body is knocked out of balance by a stressor it triggers the release of corticotropin-releasing hormone (CRH) from the brain region known as the hypothalamus. This in turn leads to the release of adrenocortiotropin hormone (ACTH) into the circulation. This is a signal for the adrenal cortex to release glucocorticoids into the blood. In an effort to restore your body back into the pre-stress state, the glucocorticoids stop the release of CRH, shutting down the stress response.[8]

The activation of CB_1 receptors also play a critical role in this negative feedback loop that occurs as your body deals with stress. CRH release can lead to anxiety. CRH increases the production of the enzyme fatty acid amide hydrolase (FAAH), which reduces the endocannabinoid anandamide (AEA) within the amygdala of the brain. By activating the CB_1 receptor, CRH release is cut off and AEA levels increase, which can have a calming effect.[9] On the other hand, chronic, unpredictable stress can throw off the endocannabinoid system in the hippocampus and amygdala of the brain, leading to anxiety.[10]

CBD works through the endocannabinoid system to soothe stressful feelings.[11] Although CBD doesn't act directly on the CB_1 receptor, it can act indirectly.[11] It also blocks the actions of FAAH and in doing so increases levels of AEA.[11] It may counteract the FAAH-raising effects of CRH.[11] CBD can also work through the serotonin receptor.[12] Serotonin is a "feel-good" hormone that contributes to feelings of calm and relaxation.

CBD can also modify blood flow in brain areas that are involved in anxiety, such as the amygdala, hippocampus, hypothalamus, and cingulate cortex.[13] This is another way in which CBD can produce feelings of calm and relaxation.

CBD and the Stress of Public Speaking

To test whether CBD can relax people who are under stress, scientists undertook several studies of CBD's effect on people giving public speeches. In one of those studies, researchers caused anxiety in a group of 57 healthy male subjects by having them perform a simulated public speaking test.[14] In this double-blind study, the participants were given different doses of CBD (150 mg, 300 mg, 600 mg) or a placebo. CBD (300 mg) significantly reduced anxiety during the speech.

In an earlier study, researchers compared the effects of the anti-anxiety drugs ipsapirone (5 mg) or diazepam (10 mg) with CBD (300 mg) or placebo in 40 healthy volunteers during a simulated public speaking test.[15] Compared to the placebo, CBD or ipsapirone were each effective at reducing the anxiety caused by public speaking.

CBD produced the same effects in people with generalized social anxiety disorder (SAD).[16] Because a pronounced fear of public speaking is one hallmark of this disorder, researchers had 24 patients with SAD and 12 healthy controls perform a public speaking test.[16] In this double-blind, randomized study, 12 of the SAD subjects took 600 mg of CBD 1½ hours before public speaking, while 12 SAD patients received a placebo. The healthy controls didn't receive any treatment.

The study authors used three methods of determining anxiety levels in the participants. The scientists looked at ratings on the Visual Analogue Mood Scale (VAMS), which allows study subjects to rate their level of anxiety, cognitive impairment, and sedation, and the Negative Self-Statement Scale (SSPS-N), which is based upon theories that social anxiety is the result of thinking poorly of yourself and believing others also think poorly of you. The researchers also measured blood pressure, heart rate, skin conductance, and physical reactions to stress at six different points during the public speaking test. Compared with the placebo group, SAD patients taking the CBD experienced significantly less anxiety, cognitive impairment, and

emotional discomfort during their speech. The CBD-group also was more relaxed when they were anticipating giving the speech. The SAD patients taking the placebo experienced increases on the Negative Self-Statement Scale. Patients in the CBD group experienced almost no increase in negative self-statements. The responses of the SAD patients given CBD were similar to healthy controls, meaning the CBD led to a more normal stress response in regards to public speaking.

CBD and Blood Pressure Spikes Caused by Stress

Long-term stress is associated with the development of cardiovascular disease.[17] Social isolation, depression, not having enough money, stressful family life, and problems at work are linked to both an increased risk of cardiovascular disease and worsening of already existing cardiovascular conditions.[18] Evidence from animal studies and some recent interesting human studies suggest that CBD may regulate the body's cardiovascular response to stress. Restraining rats is a way that researchers cause stress in the animals. In one study, CBD injections reduced the cardiovascular response to restraint stress and the typical stressed out behavior of the animals when restrained.[19]

Blood pressure rises when a person is under stress. Two human studies have found that CBD may support healthy blood pressure when we're feeling anxious about a situation or under physical stress. In one of the randomized, placebo-controlled, double-blind studies, researchers gave 26 healthy males 600 mg of oral CBD or a placebo for a week.[20] The men participated in isometric exercise and their blood pressure was measured both during rest and during exercise. In response to stress, participants in the CBD group had lower systolic blood pressure both after the initial dose and after repeated seven days of use. After a week on CBD, the men's carotid artery widened and the arteries became more flexible. According to the researchers, "CBD reduces BP at rest after a single dose but the effect is lost after seven days of treatment (tolerance); however, BP reduction during stress persists."

In the other randomized, placebo-controlled, crossover study, nine healthy male subjects were given 600 mg of CBD or a placebo.[18] A crossover study is where scientists place the subjects on one protocol (in this case CBD supplementation) for a specific time and then switch the subjects to the placebo for another period of time. The researchers caused stress in the subjects by exposing them to cold and exercise and giving them a test designed to produce mental stress. Diastolic and systolic blood pressure were significantly lower immediately following the stress test in men who had taken CBD. After exposure to cold, men taking the CBD experienced a significant drop in systolic blood pressure and mean arterial pressure. The researchers also found that diastolic blood pressure was significantly less in the men given CBD during cold stress. During exercise stress, CBD lowered systolic blood pressure and mean arterial pressure.

Researchers believe CBD's ability to lower blood pressure during stress may be an added benefit of its calming properties.[18] By relaxing the mind, it may relax the body and the cardiovascular system, too.

More Restful Sleep

Stress can lead to insomnia and a lack of restorative sleep. CBD's calming effect can help promote better sleep even during stressful times. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness.[21] In patients with post-traumatic stress disorder (PTSD), CBD combined with routine psychiatric care has improved the quality of sleep and reduced nightmares.[22]

In a case study, researchers investigated the effects of CBD on a ten-year-old girl with PTSD due to sexual abuse and who had little parental supervision when the girl was under the age of five.[23] The girl had tried pharmaceutical medications, but they only provided partial relief and any benefits were only temporary and accompanied by major side effects. On the other hand, CBD oil led to a prolonged decline in anxiety and steadily improved quality and quantity of sleep. The study authors concluded, "This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder."

Researchers conducted a larger human study of 72 patients whose primary concern was either anxiety or poor sleep.[24] The subjects were given CBD along with their usual treatment at a large psychiatric outpatient clinic. CBD supplementation was associated with a significant decline in anxiety in 57 of the patients (79.2%) during the first month of use and the participants continued to feel this increased calmness throughout the study. Sleep improved in 48 of the patients (66.7%) in the first month of CBD supplementation, but these results fluctuated over time, indicating mild improvement. CBD was well tolerated although three of the participants experienced fatigue. The doses used in this study (25 mg/day to 175 mg/day) were much lower compared with other clinical studies that used 300 mg/day to 600 mg/day, which may explain why even though CBD caused a noteworthy decline in anxiety it only resulted in a modest improvement in sleep.

Evidence from rodent studies mirror CBD's beneficial effects in humans. One group of researchers triggered PTSD-like anxiety in rats by having them navigate a maze.[25] CBD blocked the suppression in rapid eye movement (REM) sleep caused by anxiety. Getting enough rapid eye movement sleep, the stage in which most of our dreams occur, is essential to feeling refreshed and energized. It's also important for learning, memory, and happiness.

Hemp Oil: Teaming Up with Terpenes

Supplementing with hemp oil can provide advantages over CBD alone. As I mentioned in previous chapters, hemp oil contains beneficial compounds known as terpenes, which have their own stress-reducing effects. For example, the terpene d-limonene soothes anxious thoughts by increasing levels of serotonin and dopamine,[26] both hormones linked to mood and happiness. Another terpene found in hemp, d-linalool, also promotes relaxation, likely by influencing glutamate and GABA neurotransmitter pathways involved in stress management.[27] In mice, d-linalool prevented conflict among the animals.[28] Many essential oils known for their

stress-relieving properties, such as lavender, contain d-linalool. It's thought to be the main active component in lavender responsible for the anti-anxiety effects of lavender oil.

A third relaxing terpene in hemp is myrcene. Myrcene calms the mind and promotes sleep.[27] Nerolidol and phytol are terpenes that, like their other hemp-derived cousins, promote relaxation.[27] Phytol is also found in green tea, and its presence there could explain why green tea is so relaxing even though it contains caffeine.[27] Phytol raises levels of the calming neurotransmitter GABA and blocks an enzyme responsible for breaking down GABA.[27] In mice, nerolidol increases the animals' interest in exploring brightly lit open areas, an indication of reduced anxiety.[29]

Side Benefits of Reducing Stress

By reducing stress, CBD can indirectly enhance a couple other areas of health. First, by promoting feelings of calm under pressure, it can support healthy immunity. Psychological stress is known to reduce immune function.[30-33] I will discuss CBD's potential role in immune support later in this book. Second, by lowering stress, CBD may also support a healthy inflammatory response. Stress is well known to increase inflammation.[34] I'll talk about this aspect of CBD more in future chapters.

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Chapter 4
CBD's Role in A Healthy Pain Response

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One of the most common reasons patients seek medical care is due to pain. I know this from personal experience as a large number of patients who visit my clinical practice are in pain. Approximately 40% of adults in the United States are suffering from chronic pain, with an estimated annual cost of up to $635 billion.[1] Being in pain can significantly damage your quality of life and interfere with both physical and mental activities. You often are unable to do the things you love to do and your work productivity may suffer. Conventional medicine's answer to pain is often a prescription to opioid drugs. In chapter 2 of this book, I briefly touched upon the dangers of opioid side effects and addiction.

By contrast, phytocannabinoids like CBD are safer and aren't addictive. The CB_1 receptor is found throughout many areas of the body but its expression is weak in brain stem regions that control respiration. Since cannabinoids work through this receptor, the potentially fatal

respiratory depression that occurs with opioid drugs does not occur with cannabinoids.[2] Cannabinoids like CBD also reduce opioid tolerance and dependence.[3]

New research indicates that CBD actually allows people to eliminate or reduce their use of opioids. In an eight-week study, researchers investigated 97 patients between 30 and 65 years old who suffered from chronic pain who had been on opioids for at least one year.[4] More than half of the chronic pain patients (53%) reduced or eliminated opioid use within eight weeks after beginning supplementation with CBD-rich hemp extract. Quality of life improved in nearly all CBD users (94%). The participants taking the CBD-rich hemp extract experienced significantly improved sleep and reduced pain severity. Unlike opioids, CBD is not addictive and is therefore a safer alternative.[5]

CBD and Joint Pain

Osteoarthritis (OA) is a disease that leads to joint degeneration, intermittent inflammation, and peripheral neuropathy (nerve pain). There's a lot of logical reasons why CBD would be effective for sore, stiff joints. For example, receptors responsive to cannabinoids, including CB_1, CB_2, GPR55, PPAR α, and PPAR γ, are located on human joint cartilage from people who have osteoarthritis symptoms.[6] Cartilage cells from OA-affected joints express a wide range of cannabinoid receptors.[6] This suggests that cartilage cells can respond to cannabinoids like CBD. What's more, osteoarthritis leads to a combination of inflammatory, nociceptive, and neuropathic pain.[7] Most pain is nociceptive pain. It refers to the type of pain that results from injury to body tissues. The endocannabinoid system reduces nociceptive as well as the other two types of OA-related pain.[7]

A number of animal studies have investigated the role of CBD in managing pain from osteoarthritis and rheumatoid arthritis. In one of these studies, researchers investigated whether CBD could relieve osteoarthritis-related pain.[8] They also studied whether CBD could support a healthy inflammatory response and stop the development of OA-related pain and joint neuropathy. The scientists induced OA in male rats and then observed the effects of injecting CBD into the animals' joints. In end-stage OA, CBD dose-dependently improved measures of joint health. CBD also reduced transient joint inflammation. Prophylactic administration of CBD before the disease was at its worst stopped the development of later joint pain and protected nerve health. The researchers concluded, "These findings suggest that CBD may be a safe, useful therapeutic for treating OA joint neuropathic pain."

Additional research strongly suggests CBD has a role to play in supporting joint health during rheumatoid arthritis. In an animal model of rheumatoid arthritis, CBD injected at 5 mg/kg per day or 25 mg/kg per day orally led to clinical improvement and protection against severe joint damage.[9] It also supported healthy levels of inflammatory markers both in cell culture and in mice. According to the scientists, "Taken together, these data show that CBD, through its combined immunosuppressive and anti-inflammatory actions, has a potent anti-arthritic effect" in an animal model of rheumatoid arthritis.

CBD and Nerve Pain

Neuropathic pain is a form of chronic pain that occurs due to damage to the central or peripheral nervous systems. This type of pain is caused by physical trauma such as from accidents, surgery, or stroke, diseases like diabetes, cancer, and immune conditions, and certain medications such as cancer chemotherapy drugs. It is a severe, abnormal pain that often is triggered even when there is no stimulus or in the presence of normally harmless stimuli such as a light touch or stroking (like that which occurs when putting on clothing). Mild temperature changes, such as those that occur when you shower, can also trigger a painful response. Neuropathic pain is also linked to accompanying mental disturbances such as depression, anxiety, sleep problems, and less social interactions with family and friends.

Standard pharmaceuticals used for neuropathic pain are not always effective. At least half of people who suffer from this type of pain don't experience meaningful pain relief after taking these medications.[1] Furthermore, the drugs often produce severe side effects such as dizziness, sedation, depression, and sleep disorders.[1] Consequently, many people find them intolerable.

In many studies of neuropathic pain in rodents, CBD had a beneficial effect. For example, mice were given a chemotherapy agent known to cause neuropathic pain.[10] Cannabidiol injected into the abdomen of the animals before the chemotherapy agent reduced (but didn't prevent) the chemotherapy-induced neuropathy. After CBD, the mice's hind paws were less painful after pressure was administered.

In another study, researchers investigated CBD's effects on neuropathic pain caused by sciatic nerve injury or inflammation in rats.[11] Giving the rats CBD orally from day seven to two weeks after onset of the injury or inflammation decreased the increased sensitivity to pain after exposure to heat and touch.

Additionally, other researchers administered moderately high doses of intranasal cannabidiol in one group of mice and injected cannabidiol into the abdominal area of another group mice (intraperitoneal administration).[12] At the same time, the scientists induced type 1 diabetes in the animals. Both the intranasal cannabidiol and intraperitoneal cannabidiol reduced the development of peripheral neuropathic pain. The pain reduction continued even after cannabidiol was discontinued and without any improvement in diabetes in the animals.

THC, the psychoactive component of cannabis, may be more effective at relieving pain compared with CBD.[1] However, CBD can be used in higher doses compared with THC since it does not produce the high that THC does.[1] This gives CBD an advantage over THC.

Most of the clinical research on CBD and neuropathic pain used a combination of both CBD and THC.[13-15] Despite the lack of human studies focusing on CBD-use alone in neuropathic pain, there's a lot of evidence from preclinical animal studies showing its effectiveness.[5] What's more, as mentioned earlier in the chapter, CBD use can help people wean off of opioids and isn't addictive. This indicates CBD is a preferable option to many pain relievers.

CBD May Soothe Muscle Pain

Approximately 10% of the population suffers from widespread musculoskeletal pain.[16] This group includes the 2% to 4% of the population that has fibromyalgia.[17] People in pain frequently use marijuana or other products containing THC and CBD. The National Pain Report, a survey of 1,300 people, compared three regulatory body-approved pharmaceutical fibromyalgia treatments with cannabis.[18] In regards to effectiveness of the treatments, the survey respondents strongly preferred cannabis over the prescription medicines.

CBD alone without THC may have a role to play in supporting the health of people with muscle and musculoskeletal pain. In a rat study, researchers used intramuscular injections of CBD and the mildly psychoactive cannabinoid cannabinol (CBN), alone and both combined to determine whether they could decrease muscle pain in the animals.[19] CBD or CBN each decreased muscle pain. When used together, there was longer-lasting pain reduction compared to when each was used separately. However, CBN, as a breakdown product of THC, is mildly psychoactive and therefore many people may be reluctant to use it. This study showed that CBD does have a pain-reducing effect on its own and that CBD or CBD combined with CBN "may provide analgesic relief for chronic muscle pain disorders such as temporomandibular disorders and fibromyalgia without central side effects."

In Chapter 1, I discussed a substance known as palmitoylethanolamide (PEA), which isn't an endocannabinoid but works on the endocannabinoid system by helping the body make better use of the endocannabinoid AEA. In my patients suffering from pain, I often use both CBD and PEA for the best effects. PEA is able to reduce temporomandibular joint (TMJ) pain.[20] It also can increase the effectiveness of standard fibromyalgia treatments.[21]

Visceral Pain and Irritable Bowel Syndrome

CBD may also reduce visceral pain, including pain involved in irritable bowel syndrome (IBS). Visceral pain affects the area surrounding the stomach, rectum, bladder, or uterus. An example is the abdominal pain that happens during IBS. Menstrual cramps and pelvic pain caused by bladder infections are other types of visceral pain.

CBD works through the endocannabinoid system, which regulates pain sensitivity caused by chronic stress.[22,23] Changes to this system may be the reason why there's a link between chronic stress and irritable bowel disease(IBD)/IBS.[22,23] Research in rodents indicates stress during early life alters the endocannabinoid system, which increases the chances of developing IBS.[24]

Through its ability to regulate visceral pain, the endocannabinoid system may also be involved in the way in which psychological stress damages GI function. During stress, concentrations of the endocannabinoid anandamide decline while levels of the endocannabinoid 2-AG in the brain increase.[25] By relieving stress, CBD may block stress-induced visceral pain. CBD benefits the hypothalamus-pituitary-adrenal (HPA) axis in mice exposed to psychological stress.[26] The

HPA axis controls the production of the stress hormone cortisol and is involved in the way the body handles stress. In addition, a number of human studies show CBD has a calming effect. I discussed these studies and other evidence of CBD's stress-reducing properties in Chapter 2 of this book.

Headaches and Other Types of Pain

CBD may be able to reduce a variety of different kinds of pain. For example, there's evidence it may reduce headaches and migraines.[27] While there have been no clinical trials on the use of CBD and endometriosis, the endocannabinoid system is involved in regulating the pain that accompanies this condition.[28] This suggests that CBD could play a role in supporting a healthy pain response in this disorder. In addition, cannabinoid-rich hemp oil reduced body pain and other symptoms in girls who reacted adversely to the human papillomavirus (HPV) vaccine.[29] Furthermore, in seven kidney transplant patients, a group of patients who often experience pain, researchers gave the study subjects varying doses of CBD from 50 to 150 mg twice a day for three weeks.[30] Two patients experienced complete improvement in pain, four experienced a partial improvement in the first 15 days, and one patient had no change.

How Cannabinoids Like CBD Reduce Pain - Mechanism of Action

CBD and cannabigerol (CBG) both have analgesic effects and their pain-relieving abilities may also be due to their ability to support a healthy inflammatory response.[31]
Endocannabinoids produced in the body can also block pain-inducing mechanisms in the gastrointestinal tract, the spine, and other areas of the body.[32] This may lead to reducing pain in IBS, as well as from headaches, muscle spasms, and fibromyalgia.[32] Deficiencies in endocannabinoids may lead to pain,[32] and replenishing levels of these endocannabinoids through supplementation with CBD and other cannabinoids may help.

CBD's potential ability to reduce pain may involve a type of receptor known as type 1 vanilloid receptor ($TRPV_1$). Researchers have found the $TRPV_1$ receptor in neurons that help regulate pain.[33] I went into more detail about $TRPV_1$ in Chapter one of this book.
CBD works in a way that's different from substances like non-steroidal anti-inflammatory drugs (NSAIDS). Unlike those drugs, it doesn't inhibit the COX-1 enzymes.[34,35] Blocking this enzyme is linked to gastrointestinal ulcers and bleeding. In addition, CBD doesn't inhibit COX-2.[34,35] Inhibition of this enzyme is associated with heart attacks and strokes.

The bottom line? Clinical experience, preclinical studies in animals, and some human studies show that CBD may support a healthy pain response. It's non-addictive and isn't psychoactive like THC. Therefore, I find it to be extremely clinically useful when dealing with my many patients who are suffering from pain.

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Chapter Five

Hemp-Oil Derived CBD Lifts Mood and Controls Addictions

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Depression is an all-too-common psychiatric disorder. An estimated 20% of people suffer from depression.[1] Regularly feeling sad, empty, or losing interest or no longer taking pleasure in everyday activities (anhedonia) are some symptoms of depression. Not being able to concentrate or make decisions, insomnia, or feeling excessively sleepy during the day are also indications you or a loved one may be depressed.

Depression is also linked to addiction, as many depressed people turn to substance abuse as a way to try to make their bad feelings disappear. As many as 30% to 40% of individuals with a drug addiction also meet the criteria for depression or an anxiety disorder.[2]
The conventional treatment for depression is to prescribe antidepressant medications. However, many people don't respond to these drugs or discontinue use due to side effects.[3]

How the Endocannabinoid System Boosts Mood

The endocannabinoid system is involved in keeping us in a happy state of mind. As a reminder, your body makes endocannabinoids called AEA and 2-AG. These endocannabinoids are part of the endocannabinoid system along with CB1 and CB2 cannabinoid receptors activated by AEA and 2-AG and enzymes responsible for the endocannabinoid's breakdown. In animal research, a deficiency in endocannabinoids is linked to depression.[4] In animal studies of depression and stress, 2-AG brain tissue concentrations and AEA levels are altered.[4]

A common way for researchers to study depression in rodents is to administer a forced swim test. It has been noted that antidepressant-like substances given to the rodents before the test will cause them to swim longer and harder. The animals not given any antidepressant will often stop making movements beyond those necessary to lift their heads above water. In one of these tests, the endocannabinoid AEA reduced the amount of time mice remained immobile.[5]

There's also evidence in humans that when the endocannabinoid system isn't working properly, it may result in depression. In postmortem studies of alcoholic suicide victims, higher than normal levels of endocannabioids were found in the dorsolateral prefrontal cortex area of the brain.[6] The study authors suggested that these increases in endocannabinoid levels may cause emotional discomfort during depression and that alcoholic suicidal patients may have a

hyperactive endocannabinoid system. They concluded that the endocannabinoid system, "may be a novel therapeutic target for the treatment of suicidal behavior."

In addition, clinical trials of untreated depressed patients have observed a rise in serum AEA levels.[7] Plus, there's a link between higher endocannabinoid levels and higher blood pressure levels in depressed women.[8] What's more, female patients with major depression have lower levels of the endocannabinoid 2-AG.[7] The clinical conclusion is that balance, sustaining a healthy promoting homeostasis, is essential to best control the impact of dysregulation of the endocannabinoid system as an exacerbating factor in mental health signs and symptoms.

CBD's Role in Promoting A Happy Mood and Increased Motivation

Studies in animals and limited research in humans—as well as results doctors like myself are seeing in clinical practice—indicate CBD is a natural mood booster. In forced swim tests in mice, CBD caused the mice to swim longer and harder, an indication it was improving their mood and motivation.[9] According to the study authors, "The data support a promising therapeutic profile for CBD as a new fast-acting antidepressant drug."

In other rodent studies, CBD has produced similar results, decreasing immobility in the forced swim test and increasing the animals' likelihood to explore a maze and novel objects.[10,11] This suggests CBD can improve feelings of hopelessness and maintain pleasure felt while participating in daily activities.

Despite reports from many physicians who are giving CBD to depressed patients with good results, human trials using CBD in depression are lacking. However, as I reported in Chapter 3 of this book, there are a number of human studies showing CBD can reduce stress. Ongoing stress is known to trigger depression and CBD's ability to soothe stressful feelings may be the reason why there are many reports of it being a natural mood booster.

There are many other logical ways in which CBD could improve mood, some of them related to the means by which CBD reduces stress. These have all been demonstrated in rat studies. First, CBD triggers hippocampal neurogenesis, the birth of new neurons in the hippocampus.[12] Long-term stress as well as depression can reduce hippocampal neurogenesis, but CBD has a protective effect.[13] This all comes back to the endocannabinoid system, as the means by which CBD triggers this neurogenesis depends on there being present high enough levels of the endocannabinoid AEA.[14] In patients with minor depression, AEA levels were higher compared with controls, suggesting that AEA is neuroprotective in patients with less severe depression.[14]

CBD also acts on the serotonin (5-HT_{1A}) receptor.[14] Serotonin is a neurotransmitter involved in feelings of well-being and happiness. Plus, in animal research, CBD elevates levels of brain-derived neurotrophic factor (BDNF), which is involved in the survival of nerve cells.[9] Low levels of BDNF are associated with major depressive disorder in humans.[15]

Another way in which CBD increases feelings of well-being is by blocking the enzyme FAAH, which, as I mentioned in Chapter 1, breaks down the endocannabinoid AEA. By blocking FAAH, CBD increases levels of AEA, which is also known as the "bliss molecule" since it promotes feelings of happiness.

CBD and Addictions

CBD is one of the most useful tools I've used in my clinical practice in helping patients who suffer from addictions, whether it's to alcohol, drugs, or cigarettes. As I mentioned earlier in this chapter, people who suffer from addictions often also suffer from depression. And chronic stress can be a trigger for addicts to turn to drugs or alcohol. After a period of withdrawal, the willpower to avoid a relapse in drug use is one of the biggest challenges in the treatment of addiction. CBD's ability to boost mood and soothe away stress can be extremely beneficial in helping people with addictions avoid drugs, alcohol, and tobacco.

Preclinical studies in animals and human trials have found that CBD reduces cravings. For example, a randomized, double blind placebo controlled study evaluated the use of cannabidiol (CBD) or a placebo in 24 smokers who wished to stop smoking.[16] Half of the participants used an inhaler of CBD while the other half used a placebo whenever they felt the urge to smoke over the course of a week. There were no differences in the number of cigarettes smoked in smokers using the placebo inhaler. However, subjects using the CBD inhaler smoked approximately 40% fewer cigarettes.

CBD's ability to reduce nicotine cravings is likely accomplished through its interactions with the endocannabinoid system, specifically its ability to block the enzyme FAAH and increase levels of the "bliss molecule" endocannabinoid AEA. Studies have shown that blocking FAAH stops nicotine cravings, as well as nicotine's ability to produce dopamine and therefore its pleasurable effects.[17,18] By blocking FAAH, CBD also reduces anxiety during nicotine withdrawal.[19]

CBD and Opioid Addiction

In Chapter 2, I briefly covered CBD's possible role in solving the opioid addiction crisis. Opioid painkillers are highly addictive and lead to fatal overdoses. As I discussed in Chapter 2, every day, 128 people in the United States die from an opioid overdose. Receptors in the endocannabinoid system interact with opioid receptors.[20] CBD works at least in part through the endocannabinoid system, so it makes sense that it has a role to play in stopping opioid addiction.

Withdrawal symptoms of drug use may include such symptoms as sleep disturbances, anxiety, unease or dissatisfaction (dysphoria), and fatigue. People withdrawing from drugs also are unable to handle stress and have recurrent intense cravings for the drug, which can last for months or years and lead to relapse. Animal studies show CBD can stop opioid-drug seeking behavior and reduce withdrawal symptoms. For example, in one study, rats were able to avoid using heroin, an opioid drug, similar to the way that humans with addictions must exercise self-control to avoid relapsing.[21]

In addicts there are emotional events and triggers that lead to relapses and the researchers exposed the animals to similar triggers.[21] Compared to a placebo control, CBD did not change the rats' self-administration of heroin nor overall drug-seeking behavior. However, it reduced heroin-seeking behavior when the rats were exposed to a specific trigger cue. CBD stopped the animals from seeking out heroin even 24 hours and two weeks after the rats were given CBD. In other rodent research, CBD and another phytocannabinoid cannabinol (CBN) were able to reduce withdrawal symptoms in animals addicted to morphine.[22,23]

Emerging evidence in humans has found similar results. In a double-blind study of heroin-addicted people who had not used the drug for seven days, participants were randomized to receive three consecutive days of CBD or placebo.[24] The study found that a single administration of CBD reduced drug cravings caused by typical triggers immediately after CBD use, 24 hours later, and even a week after the last dose was given. CBD also reduced anxiety while withdrawing from the heroin. The scientists believe their findings suggest that CBD is likely to prevent a relapse.

A case study nicely demonstrates how CBD can be used in people with both depression and addictions.[25] The case study was of a young patient with multiple substance use disorder including cannabis, cocaine, and ecstasy combined with severe depression, social phobia, and narcissistic personality disorder. After antidepressant medications didn't work, the researchers administered CBD capsules in increasing dosages (100 mg to 600 mg over eight weeks). CBD was safe and well tolerated. What's more, after treatment with CBD, the patient's depression improved as well as anxiety symptoms such as phobias, paranoia, and dissociation (feeling disconnected from thoughts, feelings, and memories). The patient stopped using addictive drugs including THC (marijuana) without showing withdrawal symptoms.

CBD's Role in Cocaine Addiction and Alcoholism

In some rodent studies, CBD hasn't been as beneficial in cocaine withdrawal and relapse.[26,27] However, in other rodent studies, it has reduced intake of cocaine and blocked the liver toxicity and seizures caused by cocaine.[28,29] For alcohol withdrawal and long-term reduction of cravings, many doctors report it is effective, especially if combined with a full protocol of supplements that can help with withdrawal. Furthermore, in rodent studies, CBD reduced alcohol-seeking behavior that occurs after common triggers and stress.[30] It also blocked convulsions caused by alcohol withdrawal.[30] In addition, in both rodent and cell culture studies, CBD was neuroprotective after exposure to alcohol and reduced liver toxicity caused by alcohol.[30]

Clinical Considerations

It is essential to address nutritional, metabolic, endocrine, and lifestyle variables when assisting individuals with mood and addiction disorders. One or more epigenetic factors can serve as impediments to successfully addressing the underlying physiological susceptibilities that have yielded the clinical presentation of altered neurochemistry.

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Chapter 6

Keeping Your Brain and Central Nervous System Healthy

The statements mentioned in this content have not been evaluated by the FDA, and are not intended to prevent, diagnosis, or treat any disease. Always work with your personal healthcare provider.

There's a lot of evidence building up in the medical literature to show cannabidiol and other cannabinoids like CBG protect the brain. They can do this in a number of ways, including acting as antioxidants and reducing neuroinflammation.[1] This means they're useful in supporting the health of patients with Alzheimer's disease, Huntington's, Parkinson's, autism, ADHD, epilepsy, schizophrenia, and multiple sclerosis. In this chapter, I'll talk about how CBD and other cannabinoids can promote neurological health and keep your brain healthy and strong now and throughout your golden years. CBD and phytocannabinoids found in hemp oil may be the solution to keep your independence as you age.

Alzheimer's

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common form of dementia, responsible for more than 60% of cases.[2] Worldwide, 33 million people suffer from this debilitating illness.[2] Alzheimer's disease is characterized by cognitive decline caused by the buildup of amyloid beta (A β) proteins. These sticky proteins disrupt communication between brain cells and activate immune cells. The activated immune cells trigger inflammation. In turn, brain cells are destroyed. Cell culture studies have shown CBD can protect against neurotoxicity caused by A β .[2]

Inflammation that occurs in the brain and central nervous system (CNS) is called neuroinflammation. Cells in the CNS known as astrocytes keep this important bodily system balanced by recycling of neurotransmitters and providing nutrients to neurons. Any injury to the CNS can lead to changes in these astrocytes. These changes are what scientists call reactive gliosis. CBD can reduce reactive gliosis and neuroinflammation to encourage neurogenesis, the creation of new brain cells.[2]

In cell culture studies, CBD protects neurons, blocks the degeneration of brain cells, and controls the migration of immune cells known as microglia.[2] Microglial activation is toxic to the brain and CBD protects against this neurotoxicity.[2] In vitro, CBD also reduces tau overexpression.[2] Like amyloid beta, tau is a protein that accumulates in the brain. It has some beneficial effects, but it can form clumps of toxic neurofibrillary tangles, which lead to the neurodegeneration of Alzheimer's.

In rodent models of Alzheimer's, CBD reverses and stops cognitive dysfunction.[2,3] Other rodent models of Alzheimer's disease have found CBD promotes a healthy inflammatory response.[4] It's also neuroprotective.[4] For example, in a mouse model of AD, the scientists injected the animals with human amyloid beta and then treated the animals daily with abdominal injections of CBD for a week.[4] CBD suppressed a marker of activated astrocytes that is one of the main features of reactive gliosis caused by the buildup of amyloid beta. The results suggested CBD reduced damage caused by Aβ . Other animal research shows CBD can block the gliosis and neuroinflammation linked to Alzheimer's.[5]
It also promotes neurogenesis.[5]

Most impressively, researchers induced Alzheimer's in mice by injecting the animals with Aβ . CBD injections for 1 week and then 3 times/week for the following 2 weeks improved cognition.[3] The researchers measured the spatial learning of the mice by having them try to navigate the Morris Water Maze. Spatial learning refers to the ability to find your way in and around your surroundings. CBD treatment reversed the cognitive problems that occurred in the mice injected with Aβ and improved spatial learning in the animals.

In a mouse model of genetic Alzheimer's, animals were treated for three weeks with injections of CBD after they developed cognitive problems and signs of AD pathology in their brains.[6] CBD reversed the cognitive declines in two types of memory: object recognition and social recognition.

Unfortunately, despite a lot of evidence from preclinical animal studies showing CBD may have a role to play in supporting the health of Alzheimer's patients, to my knowledge there haven't been any human studies of CBD in AD. Hopefully, based on all the promising preclinical evidence, scientists will soon study CBD's effects in this group of people.

Parkinson's Disease

Parkinson's disease (PD) is a common neurodegenerative disorder. Its prevalence increases with age, with 1% of the population over 60 years old suffering from the disorder.[7] There are two primary characteristics of the disease. First, there's what scientists call motor impairment which includes hypokinesia (slow movement), tremors, and muscle rigidity. Second, people with PD have non-motor symptoms such as sleep disturbances, cognitive problems, anxiety, depression, and psychotic symptoms. These problems are caused by the destruction of neurons that produce the brain chemical dopamine. This leads to low levels of dopamine, an important neurotransmitter involved in feeling pleasure, thinking, planning, and focusing.

Several human studies show CBD may have some impressive benefits in people with PD. In one of those studies, researchers investigated the effects of CBD in six PD patients who had psychotic symptoms for at least three months.[8] The patients received a flexible oral dose of CBD starting with 150 mg/day for four weeks combined with their standard therapy. After using CBD, the participants experienced a significant improvement in the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire. CBD also lowered the scores of the Unified Parkinson's Disease Rating Scale, showing it could improve other aspects of the condition as

well. CBD didn't lead to any adverse effects. According to the researchers, "These preliminary data suggest that CBD may be effective, safe and well tolerated for the treatment of the psychosis in PD."

In a double-blind study of 21 Parkinson's patients without dementia or coexisting psychiatric conditions, the patients received either 75 mg or 300 mg/day CBD or a placebo.[9] Although CBD did not lead to improvements in PD symptoms or neuroprotective effects, patients receiving 300 mg/day CBD were found to have a significantly better quality of life. The study authors believe this may have been due to CBD's ability to calm the mind and boost mood along with its beneficial effects in psychosis.

Parkinson's patients often experience a condition known as REM sleep behavior disorder (RBD).[10] This condition is associated with vivid nightmares, and patients often act out their nightmares in their sleep, such as trying to run away from someone chasing them in their dreams. In a study of four PD patients, CBD quickly and significantly reduced the frequency of RBD-related problems without causing any side effects.[10]

The human studies conducted on CBD in PD showed that this phytocannabinoid may reduce non-movement-related symptoms of PD. However, in rodent models of PD, CBD has improved movement-related symptoms. For example, CBD stopped abnormal movements from occurring when rodents were given antipsychotic drugs known to cause rigidity of the body.[11,12]

One way in which CBD may benefit PD is through its ability to protect the mitochondria, the powerhouses of the cells.[13] Research shows that when the mitochondria are not working properly it can lead to the development of PD.[14]

CBD increases mitochondrial activity.[13] Furthermore, in rats exposed to iron overload, which resembles neurodegenerative disorders, CBD reverses the damage that excess iron does to mitochondrial DNA.[15]

Huntington's Disease

Huntington's disease is an inherited neurological disorder caused by a mutation in the gene encoding the protein huntingtin. It's characterized by involuntary movements (chorea) and cognitive problems. There's a lot of reasons why CBD and other phytocannabinoids could play a role in supporting health in Huntington's disease. Research in animals shows that endocannabinoid system activity is significantly reduced in HD, often at the early stages of the disease.[16,17]

Studies in rodents also show CBD may keep brain cells healthy. In one study, researchers exposed striatal neurons—a type of brain cell affected in HD—to a mitochondrial toxin.[18] This toxin causes changes similar to those that occur in HD. However, CBD protected the neurons from the toxin's damaging effects. Many of the animal studies combined CBD with THC, the psychoactive component of marijuana. In these studies, the scientists gave the animals either the drug Sativex® which is a combination of CBD and THC or a similar combination of phytocannabinoids. In these studies, the CBD/THC combination protected the animals' neurons.[19,20]

There aren't a lot of studies in humans investigating whether CBD alone has a role to play in supporting the health of people with HD. In humans, researchers have studied CBD combined with THC in the drug Sativex® or synthetic cannabinoids. In HD, patients suffer from dystonia, involuntary muscle contractions leading to twitching or repetitive movements. One trial, which investigated several different types of pharmaceutical cannabinoids including Sativex® in seven HD patients, observed a lot of beneficial effects including improved motor skills and less dystonia.[21] The CBD/THC combinations also improved the patients' behavior. They were less irritable and apathetic. Plus, in some cases, they experienced less hypersalivation. Researchers are currently conducting a clinical trial of CBD combined with THC to see whether it can benefit people with HD. Results aren't ready yet, but it will be interesting to see what the outcome will be.[22]

To my knowledge, there was only one small trial of 15 patients with HD who were given CBD alone rather than administering this phytocannabinoid together with THC.[23] In this double-blind, randomized study the participants were given an average daily dose of about 700 mg/day for 6 weeks and then crossed over to a sesame oil placebo for six weeks. CBD was found to be safe, but it did not benefit the patients. A lot more studies need to be done before we can truly say whether CBD is effective.

It's even entirely likely that when CBD is combined with other cannabinoids, such as in hemp oil, the hemptourage effect kicks in to produce better results. One review found that CBG, CBC, and CBDV were effective in rodent and cell culture models of HD.[24] CBG blocked the loss of neurons caused by a toxin and reduced the activity of genes linked to HD. CBG also reduced inflammatory markers. Plus, HD-related problems with movement improved in rodents given CBG

Autism

Autism Spectrum Disorder (ASD) is characterized by poor social communication, restricted and repetitive patterns of behavior, interests, or activities, and intellectual disabilities. People with ASD also often suffer from coexisting conditions such as sleep problems, epilepsy, and attention deficit/hyperactivity disorder.

There's good reason why CBD should support the health of people with ASD. The endocannabinoid system of ASD patients with seizures, anxiety, cognitive problems, and impaired sleep often isn't working the way it's supposed to.[25]
Additionally, compared with healthy controls, children with ASD have lower plasma levels of the body's naturally produced endocannabinoid anandamide.[26] These low anandamide levels are thought to play a role in problems that ASD patients have in social interactions with other people.[27]

There are many anecdotal reports that CBD works well in people with autism. Plus, as mentioned above, there's strong justification why it would work in ASD. However, surprisingly,

there aren't a lot of studies backing up CBD's use in ASD. Many of the studies that investigate CBD in autism used both CBD and THC. One study used cannabis with a high CBD content in 60 children with ASD who had severe behavioral problems.[28] In 61% of the children given the CBD-rich cannabis, parents rated behavioral problems much improved or very much improved.

The justification behind using CBD alone in autism comes from studies that show this phytocannabinoid improves many symptoms that occur autism. These studies did not investigate CBD in autism directly but rather explored its use in problems common to ASD and other disorders. For example, as we've covered in previous chapters, CBD reduces stress and calms anxiety in people giving speeches. It also improves sleep. In animal studies of schizophrenia, CBD stopped social withdrawal and improved social interaction and cognition.[29,30] In addition, in a mouse study of Dravet Syndrome (a severe type of epilepsy), both seizures and autism-like behaviors declined in the animals given CBD.[31]

Attention Deficit Hyperactivity Disorder

As the name of the disorder implies, people who have attention deficit/hyperactivity disorder (ADHD) have a hard time paying attention and are hyperactive. The disorder is also characterized by impulsiveness that interferes with a person's ability to socialize or perform well at school or work. The Centers for Disease Control and Prevention estimates 6.1 million children and adolescents suffer from the disorder.[32] An estimated 29.3% of children with ADHD will still have the condition when they become adults.[33]

The neurotransmitter dopamine doesn't send the messages it's supposed to in people with ADHD. Normally, dopamine acts on CB_1 receptors in the endocannabinoid system. When dopamine doesn't regulate the endocannabinoid system the way it should, it can lead to hyperactivity.[34]

Much of the basis for using CBD in ADHD comes from studies where the phytocannabinoid improved symptoms similar to those suffered by ADHD patients, although the studies weren't done in people suffering from ADHD. In previous chapters I discussed CBD's ability to calm anxious feelings in people giving a speech, and earlier in this chapter I talked about CBD's ability to improve sleep in PD patients. Researchers have studied CBD in combination with THC (Sativex®) in 30 adults with ADHD.[35] In this randomized, controlled study, cognitive performance didn't improve, but hyperactivity, impulsivity, and measures of inhibition were significantly better. A rodent study using CBD without THC also showed promise. In this study, CBD stopped hyperactivity and social withdrawal.[36]

Epilepsy

Past animal studies and clinical trials have found that CBD can reduce seizures in a number of different types of epilepsy. For example, in a randomized, double-blind, placebo-controlled 14-week study of Dravet syndrome patients, CBD combined with anti-epileptic drugs led to

more pronounced reductions in the frequency of convulsive seizures compared with a placebo.[37]

In another study, researchers investigated the effects of either a placebo or cannabidiol together with standard antiepileptic medication in 225 patients with a severe type of epilepsy (Lennox-Gastaut syndrome).[38] In the double-blind, placebo-controlled trial, the subjects were divided into three groups that received either 20 mg per kilogram of body weight of a cannabidiol oral solution or 10 mg per kilogram or a matching placebo, given in two equally divided doses daily for 14 weeks. For 28 days before enrolling in the trial, all of the patients in the study had two or more drop seizures per week. Drop seizures—also called atonic seizures—are those that cause a loss of muscle strength and usually cause the patient to fall.

During the treatment period, median drop seizure frequency was reduced by 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and only 17.2% in the placebo group. There were mild adverse events in some of the patients, primarily those taking the highest dose, including sleepiness, decreased appetite, and diarrhea. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial due to these effects. Liver enzymes were elevated in 14 patients who received CBD.

According to the study authors, "Among children and adults with the Lennox-Gastaut syndrome, the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo."

Many of the more recent studies have used a highly purified form of CBD known as Epidiolex®. In one of these studies, children and adults with treatment-resistant Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) who were also taking anti-epileptic drugs were given Epidiolex® in oral solution.[39] At the study's start, parents and caregivers kept a record of the types and number of seizures experienced. The patients were started out at a dose of 2-10 mg/kg/day. Their dose was then gradually increased up to a maximum dose of 25-50 mg/kg/day. At 12 weeks, CBD use was associated with a 50% reduction in median monthly major motor seizures and a 44% reduction in total seizures. Consistent reductions in both seizure types occurred through 96 weeks. A complete resolution of seizures occurred in 5% of the participants. CBD was safe, although minor adverse events like sleepiness occurred in 30% of the study subjects and 24% suffered from diarrhea. When the researchers followed up with the patients in two years, the Improvements remained.

The researchers concluded, "Overall, these results support previous observational and clinical trial data showing that add-on CBD may be an effective long-term treatment option for patients with LGS or DS."

Schizophrenia

Schizophrenia is a disorder characterized by hallucinations, social withdrawal, and lack of motivation. It occurs in 1% of the population, but is more common in people with close relatives who had the disorder. While not traditionally considered a neurological disorder, recent evidence from scientific journals suggests that this disease may belong under that classification. For example, scientists have found that gene mutations in schizophrenia interfere with excitatory and inhibitory neurotransmission.[40] In other words, signals broadcast by brain chemicals are disrupted in this disease, leading to problems with brain function.

Studies have shown that an imbalanced endocannabinoid system is involved in schizophrenia. Levels of anandamide—an endocannabinoid naturally produced in the human body—are too low in people with psychotic symptoms.[41] A double-blind, randomized, clinical trial showed what happens when CBD is given to schizophrenic patients with low anandamide.[41] In 42 patients with schizophrenia, CBD was used at a dose of 200 mg per day to start and then increased by 200 mg per day until a daily dose of 200 mg four times daily (total 800 mg per day) was reached within the first week.[41] CBD significantly increased serum anandamide levels. This increase in anandamide was linked to clinical improvement.

Although CBD hasn't been found effective in all studies on its use in schizophrenia,[42] there is still a lot of reason to believe CBD may have a role to play in the disorder. For example, in an exploratory double-blind trial, researchers randomized 88 patients with schizophrenia to receive either 1,000 mg/day of CBD or a placebo along with the antipsychotic medications the patients were already taking.[43] After six weeks, patients taking CBD had less psychotic symptoms such as hallucinations compared to the placebo. In addition, the treating physicians of participants in the CBD group were more likely to rate the patients as improved and as "not severely unwell." Patients given the CBD also experienced improvements in cognitive performance and overall functioning, although these improvements didn't reach statistical significance. The patients tolerated the CBD well and adverse events occurred at a similar rate in both the CBD and placebo groups.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease associated with muscle stiffness, spasms, pain, and tremor. Nearly 1 million people in the United States suffer from this disorder, according to a study by the National Multiple Sclerosis Society.[44] The endocannabinoid system regulates the muscle spasms that occur in MS.[45] In an experimental study of MS and of MS tissue, local changes occurred in the endocannabinoid system in areas of MS lesions.[45] In addition, the endocannabinoid system controls the amount of neurodegeneration that occurs due to inflammation.[45]

This is the reason why scientists started studying CBD together with THC in multiple sclerosis. The study results have been so promising that CBD plus THC in Sativex® is an approved anti-inflammatory drug treatment against spasms in multiple sclerosis.[2,46,47] Some studies also suggest a CBD/THC combination may improve neuropathic pain in people with MS.[48]

Other phytocannabinoids like CBG may also help people with MS. A review of the medical literature found that CBG reduced activity of the proinflammatory oxidative enzyme myeloperoxidase (MPO) in a rodent study.[49] Even though this study was done in animals with colitis, MPO is involved in other diseases such as multiple sclerosis.[49]
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Chapter Seven
Cannabidiol's Interesting New Role in Cardiovascular Health

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Worldwide, cardiovascular disease is the number one cause of death with 17.9 million people dying annually from disorders that fall into this category.[1] Lifestyle choices such as the amount you exercise or the number of processed and sugary foods you eat play a huge role in whether or not your heart is healthy. However, there's a lot of evidence—particularly in cell culture and animal studies—that suggests CBD may support cardiovascular health together with making other lifestyle choices that keep your heart healthy.

The Endocannabinoid System and Strokes

After strokes, changes occur in the endocannabinoid system. In the brains of rats, there's an increase in the expression of cannabinoid $(CB)_1$ and CB_2 receptors, suggesting that the endocannabinoid system is involved in the body's response to stroke.[2]
In addition, evidence from humans and animals found elevated levels of the endocannabinoids anandamide (AEA), oleoylethanolamide (OEA), and palmitoylethanolamide (PEA) in neurons.[2] As you may recall from previous chapters, endocannabinoids are cannabinoids your body makes naturally.

To cause strokes in rodents, researchers block blood flow to the cerebral artery. Doing this leads to dead tissue in areas deprived of blood. This dead tissue is known as an infarct. By measuring how big the infarct is before and after giving the animals a particular substance, researchers can tell if that substance is able to reduce the infarct size and heal damaged tissue. In animal studies, CBD reduced the infarct size, suggesting it may stop damage from strokes.[2,3]

In animal studies, CBD also reduces the neural damage caused by strokes.[3,4] It's a powerful antioxidant that protects brain cells from death. In fact, researchers found that it's a stronger antioxidant than vitamin C or alpha-tocopherol (vitamin E).[5] Another way in which CBD protects

neurons is by acting on serotonin receptors. These receptors are involved in both the widening of blood vessels (vasodilation) and protecting neurons in the brain.[6,7] CBD also boosts blood flow to the brain.[6] And it supports a healthy inflammatory response in neurons.[4]

Cannabidiol and Artery Health

CBD may support the health of the arteries by blocking the breakdown of beneficial endocannabinoids the body produces naturally.[8] CBD boosts levels of the anti-inflammatory endocannabinoid anandamide while stopping a rise in the proinflammatory endocannabinoid 2-AG.[8] This allows these endocannabinoids to beneficially react with CB receptors on immune cells known as neutrophils and macrophages, which stops them from contributing to atherosclerotic plaques.[8]

In addition, CBD may assist in the relaxation human arteries.[9] It does this in part by activating the CB_1 receptors and stimulating the release of nitric oxide.[9,10] Balanced levels of nitric oxide are important for arterial health.

CBD also relaxes arteries by interacting with peroxisome proliferator-activated receptors (PPAR γ).[10] Activating these receptors is known to boost cardiovascular health by increasing nitric oxide and reducing blood pressure and atherosclerosis ("hardening of the arteries").[10] Activating PPAR γ can support a healthy inflammatory response by blocking pro-inflammatory proteins known as cytokines and triggering the production of anti-inflammatory cytokines.[10]

However, one of the main ways in which CBD relaxes the arteries may be by acting as a natural calcium channel inhibitor.[11] Calcium channel blockers support healthy blood pressure levels by stopping calcium from entering heart and artery cells. Because calcium triggers strong contractions in the heart and arteries, the presence of calcium can lead to constricted blood vessels. Calcium channel blockers relax and widen blood vessels.

CBD and Heart Health

CBD may be able to support the health of coronary artery tissue deprived of oxygen.[12] When coronary arteries are starved of oxygen (ischemia) and then exposed to oxygen once again (reperfusion), they undergo damage. The damage causes an infarct (dead tissue). This is what happens during and after a heart attack. Heart rhythm also becomes irregular when coronary arteries don't get enough oxygen.

In a rodent study, rats received either a control substance or intravenous CBD 10 minutes before their coronary arteries were blocked and 10 minutes before reperfusion.[12] When administered prior to oxygen deprivation, CBD dose dependently reduced the total number of arrhythmias caused by ischemia and the infarct size. In addition, CBD reduced the infarct size when it was given before reperfusion. When researchers gave CBD to the rodents before they blocked the animal's arteries, it also reduced the number of blood platelets that stuck together (platelet aggregation) compared with animals given the control. Platelet aggregation is involved in the development of coronary artery disease. However, in this study, CBD had no effect on another factor involved in coronary artery disease, mast cell degeneration.

Another rodent study came to a similar conclusion. In this study, CBD also reduced the infarct size in rats after the animals' coronary arteries were deprived of oxygen and then reperfused with oxygen once again.[13] In this study, the beneficial actions of CBD were due to its ability to support a healthy inflammatory response in not only the heart, but also the body.

CBD Maintains Healthy Blood Pressure When Under Stress

As I discussed in Chapter Three, CBD calms people down when exposed to stress. High stress levels can lead to hypertension. Several human studies found that CBD can support healthy blood pressure levels during stressful situations. In a randomized, placebo-controlled, double-blind, crossover study, nine healthy men used 600 mg of CBD or a placebo.[14] A crossover study is where scientists place the subjects on one protocol (in this case CBD supplementation) for a specific time and then switch the subjects to the placebo for another period of time. To cause stress in the subjects, the researchers exposed them to cold and exercise and gave them a test designed to produce mental stress.

Diastolic and systolic blood pressure fell significantly immediately following the stress test in men who had taken CBD. After exposure to cold, men in the CBD group experienced a pronounced drop in systolic blood pressure and mean arterial pressure. The researchers also found that diastolic blood pressure was significantly less in the men given CBD during cold stress. During exercise stress, CBD lowered systolic blood pressure and mean arterial pressure.

For a longer discussion of the way CBD may support healthy blood pressure in people under stress, please review Chapter Three of this book.

Diabetic Heart Health

Diabetes is an important risk factor for atherosclerosis, stroke, and coronary heart disease. In fact, cardiovascular problems are the main cause of morbidity and mortality in people with diabetes.[15] High blood sugar is highly damaging to the cardiovascular system. It triggers a number of harmful processes such as the production of too many reactive oxygen species and reactive nitrogen species and advanced glycation end products (AGEs).[16]

Diabetes is associated with damage to small (microvascular) and large (macrovascular) blood vessels and arteries. The most common macrovascular complication of diabetes is atherosclerosis, which ramps up the risk for strokes, heart attacks, and peripheral artery disease.[16] Atherosclerosis begins when immune cells known as monocytes stick to the artery lining known as the endothelium. High blood sugar encourages these monocytes to adhere to the endothelium, in part by increasing the expression of adhesion molecules ICAM-1 and VCAM-1.[16]

In human coronary artery endothelial cells, CBD blocked the increased activity of adhesion molecules ICAM-1 and VCAM-1 caused by high blood sugar.[16] It also stopped high blood sugar from causing monocytes to stick to the artery lining.[16] In addition, high blood sugar weakened the endothelial lining of the arteries, while CBD kept the arterial lining strong and healthy.[16]

CBD may also support heart health in people with diabetic cardiomyopathy.[17] The high blood sugar and insulin levels that occur in diabetic patients lead to damaging changes in the heart's structure. This is known as cardiomyopathy.

Researchers used a mouse model of type I diabetic cardiomyopathy and then another study using human heart cells exposed to high glucose to find out whether CBD had any beneficial effects.[15] The studies found CBD supported healthy heart function and a healthy inflammatory response, as well as reduced cardiac fibrosis, oxidative/nitrative stress, and cell death. In addition, in human heart cells, CBD reduced the increased reactive oxygen species and cell death caused by high glucose. It would be nice to see human trials conducted in this area, as CBD appears to show a lot of promise.

CBD and Metabolic Syndrome

Metabolic syndrome is a collection of risk factors for heart disease, stroke, and diabetes including high blood pressure, weight gain around the abdomen, high blood sugar, and high cholesterol and triglycerides. In addition to keeping the heart healthy and blood pressure under control during stress, another way in which CBD may defend against the metabolic syndrome is by helping people manage their weight.[18] CBD can reduce hunger and promote weight loss. When the hypothalamus is injured in rodents, it causes increased hunger. This is known as hyperphagia. CBD reduces hyperphagia in rats, suggesting it may reduce food intake.[8] This in turn may help shed pounds from the abdominal area. Further supporting this idea is a human study investigating CBD in epilepsy. This study found that 28% of the subjects receiving CBD experienced a loss of appetite compared to only 5% of the controls.[8]

The bottom line? CBD may support a healthy heart and arteries and blood pressure levels already in the normal range. In my clinical practice, I find that these properties along with its ability to reduce appetite and weight make it an ideal supplement to promote the health of my patients concerned about heart health and metabolic challenges.

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Chapter Eight

Phytocannabinoids and Keeping Your Immune System Healthy

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Scientists have called the endocannabinoid system one of the "gatekeepers" of the immune system.[1] The endocannabinoid system is activated in response to immune challenges like viral or bacterial infections, increasing or decreasing many aspects of immunity.[2] Certain endocannabinoids act on most immune cells and endocannabinoid receptors are also present on these cells.[2] This gives you an idea how important the endocannabinoid system is for proper immune function.

As I mentioned in chapter one of this book, endocannabinoids can bind to and activate other receptors besides cannabinoid receptors. These other receptors include the transient receptor potential vanilloid 1 (TRPV1) channel, peroxisome proliferator-activated receptor (PPAR) α and γ, and the orphan G protein-coupled receptor GPR55. All of these receptors are widely expressed in immune cells.[3] In addition, the ability of endocannabinoids to regulate immunity in several types of immune cells is due to their actions on PPAR α and PPAR γ.[3] The GPR55 receptor also is specifically expressed on immune cells known as monocytes and natural killer (NK) cells.[3]

Because the endocannabinoid system can both enhance and suppress immunity, some researchers have questioned whether using phytocannabinoids like CBD can make a person vulnerable to infectious diseases.[1] However, as I'll discuss in this chapter, even those researchers admit it's really not that simple.[1] CBD may both support and suppress the immune system, depending upon the situation.

CBD in Autoimmune Health

The body maintains immunity when various immune cells work together to protect against foreign invaders. At the same time, the immune system must avoid reactions against self-proteins. In autoimmune conditions, the immune system mistakenly targets a person's own tissues or organs. The body's own immune system attacks "self" because it believes it is going after a harmful pathogen. In this case, it can be advantageous to calm down the immune system.

In an animal study of autoimmune health, CBD oil given to rodents intravenously weakened the activity of immune cells including T cells, B cells, and both T helper and T cytotoxic lymphocyte subsets.[4] These immune cells are involved in the process leading to autoimmune conditions. However, CBD didn't reduce the activity of natural killer cells, a type of white blood cell, nor the activity of natural killer T NKT cells, which share properties of both NK cells and T cells. These type of cells are responsible for the primary, nonspecific response the immune system wages against viruses or tumors. In fact, CBD at a dose of 2.5 mg/kg increased the total and percentage NKT cell numbers, and the percentage number of NK cells. The researchers concluded, "The results suggest that repeated treatment with cannabidiol inhibits specific

immunity by reduction of T, B, T cytotoxic, and T helper cell numbers, and may enhance nonspecific antiviral and antitumor immune response related to NK and NKT cells."

Indeed, other animal studies have shown CBD can calm the immune response in autoimmune conditions. In research using mice, CBD reduced autoimmune hepatitis.[5] It also stopped the development of type-1, autoimmune diabetes in mice.[6] Researchers gave CBD to 11 - 14 week old female mice that were either in a latent diabetes stage or had the initial symptoms of the disease. CBD blocked the manifestations of the disease. Only 32% of the mice in the CBD group developed diabetes compared with 86% and 100% of the untreated animals.

In another study, researchers gave CBD to mice with autoimmune myocarditis (inflammation of the heart).[7] The animals given CBD experienced significant improvement. Myocarditis is an important cause of heart failure and sudden cardiac death in young adults and adolescents. Often, myocarditis has an autoimmune cause, where the immune system attacks a cardiac protein known as myosin. Conventional immunosuppressive therapies for autoimmune myocarditis often don't work well and are linked to toxic side effects.

CBD boosts the action of myeloid-derived suppressor cells (MDSCs), one of the main regulatory cells of the immune system.[5] These cells spring into action at sites of inflammation. They have the ability to interfere with T cell functions. CBD, by activating TRPV1 vanilloid receptors, can trigger MDSCs.[5] This, in turn, can block inflammation and autoimmune hepatitis.[5]

Another way in which CBD may support autoimmune health is by boosting the activity of regulatory T cells (Treg).[8] These types of cells often don't work as well as they should in people with autoimmune conditions.

CBD Supports a Healthy Inflammatory Response in the Lungs

The lungs can get hit hard during viral infections. There's some evidence from animal research that CBD may support the health of the lungs. In one study, researchers caused lung injury in mice then gave the animals CBD 6 hours later.[9] A day later the study authors measured the results. CBD improved markers of healthy lungs such as decreased total lung resistance and elastance, leukocyte migration into the lungs, myeloperoxidase activity in the lung tissue, and protein concentration. It also reduced levels of inflammatory cytokines (TNF and IL-6) and chemokines (MCP-1 and MIP-2) in the lungs.

In another study, this one a mouse model of asthma, CBD reduced inflammation and lung fibrosis.[10] In a similar animal study, scientists triggered the development of asthma in rats.[11] They later injected CBD into the animals abdominal areas. CBD reduced levels of the inflammatory cytokines IL-4, IL-5, IL-13, IL-6, and TNF-α. It did not reduce levels of the anti-inflammatory cytokine IL-10.

By supporting a healthy inflammatory response in the lungs, CBD may reduce coughing and help people breathe easier, if animal studies are confirmed in humans.

CBD, SARS-CoV-2, and COVID-19

Given CBD's effects on the lungs and cytokine production, it's not surprising that some researchers have started to theorize about its potential use in COVID-19. In COVID-19, the body often releases an excessive number of cytokines and other molecules linked to inflammation. This flood of cytokines—known as a cytokine storm—combined with a decrease in natural killer cells is linked to the lung damage, multi-organ failure, and poor outcome that occurs in many patients with COVID-19.

One group of scientists pointed out that there are a number of reasons CBD may support the health of people with COVID-19.[12] First, in studies using human tissue, *Cannabis sativa* (marijuana) that had a high CBD content was able to decrease the expression of two key receptors for SARS-CoV2, the virus that causes COVID-19.[12] Second, cannabidiol supports the immune system and works through the PPAR γ receptor to produce direct antiviral activity.[12] As I mentioned earlier, it may support healthy inflammatory response by reducing the uncontrolled cytokine production that leads to acute lung injury.

Two animal studies strongly suggest CBD may support the health of COVID-19 patients. Acute respiratory distress syndrome (ARDS) is the main cause of death in severe cases of some respiratory viral infections, such as COVID-19. In one study, researchers investigated the effects of CBD on ARDS.[13] The scientists caused ARDS and a cytokine storm in mice. Giving the animals CBD led to a drop in cytokine production. What's more, CBD reduced the symptoms of ARDS.

According to the researchers, "Our results suggest a potential protective role for CBD during ARDS that may extend CBD as part of the treatment of COVID-19 by reducing the cytokine storm, protecting pulmonary tissues, and re-establishing inflammatory homeostasis."

CBD's ability to block cytokines and reduce inflammation in the lungs caught the attention of another group of researchers. In a journal article titled, "Acute inflammation and pathogenesis of SARS-CoV-2 infection: Cannabidiol as a potential anti-inflammatory treatment?" these scientists proposed CBD may be useful in COVID-19.[14] In this article, the researchers wrote, "Therefore, as SARS-CoV2 induces significant damage through pro-inflammatory cytokine storm mediated by macrophages and other immune cells and based on the fact that CBD has broad anti-inflammatory properties, CBD might represent as a potential anti-inflammatory therapeutic approach against SARS-CoV2-induced inflammation." These scientists called for more studies in animals and humans to find out for certain if CBD can benefit COVID patients.

Antibacterial Actions of Phytocannabinoids

It's not just people with viral infections that may benefit from the actions of phytocannabinoids like CBD. Plant-based cannabinoids may go up to bat against bacteria, too. For example, all five of the major cannabinoids in *Cannabis sativa*—cannabidiol, cannabichromene, cannabigerol, THC, and cannabinol—significantly blocked the activity of methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[15]

In addition, some of the terpenes found in CBD-rich hemp oil may have antibacterial actions. For example, α-Pinene significantly weakens MRSA and other bacteria.[16] β-amyrin is another

example of a terpene in hemp oil that has antimicrobial actions.[17] The entourage effect kicks in to support immunity in a synergistic way, with CBD and the terpenes working together.

Soothing Stress to Improve Immunity

Long-lasting stress can weaken your immunity. Feeling overwhelmed in your work and/or home life can make you more vulnerable to colds, flus and other viral infections. Stress can interfere with the endocannabinoid system. Scientists showed this in 12 cosmonauts participating in a greater than 140-day spaceflight mission.[18] The usual markers for stress such as cortisol in saliva weren't changed. However, blood levels of endocannabinoid system components were elevated while the cosmonauts were in-flight, suggesting the endocannabinoid system undergoes changes when the body is under stress. At the same time, the cosmonaut's immune systems were also affected. White blood cell counts were higher whereas natural killer cell levels fell by almost 60% shortly after landing.

In chapter three of this book, I went into great detail about CBD and stress. However, I want to briefly mention CBD's stress-soothing actions in this chapter on immunity. Its ability to calm stress may be another way in which it can support immune health.

Gut-Based Immunity

In chapter nine, I'm going to discuss in great detail how CBD can keep your GI tract comfortable and healthy. But it's worth a mention in this chapter that CBD can support gut-based immunity. A lot of the immune system is located in the GI tract. That's where large numbers of organized lymphoid tissue and immune cells are located.[19] The gut microbiota, the collection of organisms—good and bad—found in the intestines play an important role in a balanced immune response.[20] Excessive inflammation in the gut can lead to intestinal permeability (leaky gut), gut microbiota imbalances, and a weak intestinal immune response.[21,22] The endocannabinoid system shores up the immune response in the gut. And like cannabinoids produced by the body, CBD supports a healthy intestinal inflammatory response in human trials.[23] By keeping your gut healthy, your overall immune system will stay healthy, too.

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Chapter Nine
Are Cannabinoids the Key to a Comfortable, Healthy GI Tract?

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Gastrointestinal problems like inflammatory bowel disease, gastroesophageal reflux disease (GERD), abdominal pain caused by stress, constipation, and diarrhea are all too common and plague many people. Colorectal cancer is also a concern. Worldwide, it's the fourth most deadly cancer leading to nearly 900,000 deaths per year.[1]

Although talking about GI health isn't the most glamorous of topics, it's one of the most necessary aspects of your health. Suppose your GI tract isn't working right. In that case, you can develop problems that seriously interfere with your day-to-day well-being such as diarrhea, constipation, and abdominal pain, to name a few GI-related problems. Surprisingly, there's also a relationship between intestinal problems and obesity. Intestinal health is even linked to mood and happiness, thanks to inhabitants of the intestines known collectively as the microbiota. This is what's referred to as the gut-brain axis. The link between the gut and the brain can impact mental health and brain function. I'll be discussing more about all of these issues—and how the endocannabinoid system is involved—throughout this chapter.

The Endocannabinoid System and The GI Tract

The endocannabinoid system may have an impressive part to play in supporting the health of the GI tract and keeping the gut-brain axis healthy. Endocannabinoids are involved in protecting against increased intestinal permeability (leaky gut).[2,3] Anandamide is considered a "gate opener," which means it can promote leaky gut.[2] However, palmitoylethanolamine and 2-oleoylglycerol are "gatekeepers," in other words preventing substances like undigested food or harmful substances such as lipopolysaccharide (LPS) from escaping the intestines into the systemic circulation.[2,3] From chapter 1, you might remember that PEA is not technically an endocannabinoid, but it works on the endocannabinoid system by helping the body make better use of the endocannabinoid anandamide (AEA).

Researchers have found other links between the gut and the endocannabinoid system. Modifying the gut microbiota by administering prebiotics or antibiotics altered the expression of the CB1 receptor.[3] The CB1—cannabinoid 1—receptor, as you likely recall from earlier in this book, is like a lock that fits certain "keys," including *Cannabis sativa*. The gut microbiota can also boost the actions of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).[3] As I discussed earlier in the book, FAAH and MAGL are enzymes that break down the endocannabinoids AEA and 2-arachidonoylglycerol (2-AG).

Is An Impaired Endocannabinoid System Making People Fat?

The answer to this question is likely yes. A microbiota that's associated with obesity is linked to a higher level of intestinal anandamide.[3] Higher amounts of this endocannabinoid are associated with increased gut permeability—in other words, leaky gut.[3]

To further prove the link between obesity, gut microbiota, and the endocannabinoid system, researchers administered to mice a bacterium called *Akkermansia muciniphila*.[4] Giving the mice this bacterium reversed obesity by increasing intestinal levels of endocannabinoids that reduce inflammation, support the gut barrier, and improve gut peptide secretion.

It works the opposite way as well. By this, I mean that not only can the microbiota influence endocannabinoids, but endocannabinoids from fat tissue can also control the composition of the gut microbiota.[5] For example, blocking an enzyme that synthesizes endocannabinoids in fat tissue leads to obesity, glucose intolerance, altered fat metabolism, and inflammation in fat tissue.[6] These changes were associated with a corresponding alteration in gut microbiota composition.

CBD and the Gut-Brain Axis

Cannabidiol influences both the microbiota and the endocannabinoid system through its effects on digestive, immune, and central nervous system function.[7] Consequently, it may work through the microbiota-gut-brain axis. In fact, researchers believe that it is CBD's effects on this gut-brain axis that are responsible for its beneficial effects in alcoholics.[7] Alcohol causes immune problems including chronic systemic inflammation in the brain and surrounding areas in addition to disturbances in the gut microbiota and leaky gut. These damaging effects of alcohol abuse are linked to alcoholic symptoms such as alcohol craving and problems with

cognitive control.[7] CBD, on the other hand, boosts gastrointestinal and immune system health by reducing intestinal permeability, influencing gut bacteria, and soothing inflammation.[7]

Cannabinoids Soothe Inflammation in the Colon

The endocannbinoid system and what's known as the endocannabinoidome regulate inflammation in the intestines. The endocannabinoidome is a term coined by Vincenzo Di Marzo, a scientist who has extensively studied endocannabinoids.[8] The endocannabinoidome is basically an expanded endocannabinoid system.[8] It includes not only the endocannabinoids and enzymes responsible for their breakdown, but also mediators belonging to the same chemical class as the endocannabinoids such as amides or esters of long-chain fatty acids.[8] These mediators included in the endocannabinoidome are not necessarily related to the endocannabinoids anandamide and 2-AG. Unlike anandamide and 2-AG, these mediators do not act on the receptors CB1 and CB2. The endocannabinoidome is a very complicated system. It includes more than a hundred fatty-acid-derived mediators and more than 50 receptors and enzymes involved in the production or breakdown of lipids.

Due to their role in regulating inflammation in the intestines, the endocannabinoid system and the endocannabinoidome are involved in reducing inflammatory bowel disease (IBD). Endocannabinoids help direct immune cells to the sites of intestinal inflammation.[9,10] CBD's role in reducing inflammation provides more evidence the endocannabinoid system and the endocannabinoidome are involved in suppressing IBD. Cannabidiol blocks the production of proinflammatory cytokines such as TNF-α and IFN-γ and soothes intestinal inflammation.[11,12]

Research confirms this anti-inflammatory effect in humans. In a 10-week study, researchers gave patients with ulcerative colitis a CBD-rich botanical extract.[13] The percentage of patients in remission after treatment was similar between the placebo and CBD group. However, when the study authors looked at illness severity, global impression of change, and patient-reported quality-of-life, all of these outcomes improved in the CBD group. What's more, the patients taking the placebo suffered more gastrointestinal-related adverse effects. In another study using human colon cells taken from ulcerative colitis patients, CBD lowered inflammation and suppressed intestinal damage.[12] According to the researchers, "Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases."

Other evidence points to the endocannabinoid system, CBD, and the endocannabinoidome as reducing intestinal inflammation. This evidence includes:

• CB2-receptor expression is increased in tissue from humans with IBD.[14] This impacts immunity of the mucosal lining in the inflamed colon. The CB2 receptors act together with the CB1 receptors in the lining of the colon. This leads to healing of the intestinal walls.

• CB1 receptors are involved in gut health. We know this to be true because diarrhea occurs more often in people given substances that block these receptors.[15]

• Rodent studies show that blocking FAAH, the enzyme involved in breaking down anandamide, leads to a rise in anandamide levels and stops colitis development.[16,17] In addition, blocking FAAH and the inflammatory enzyme cyclooxygenase (COX) in mice with colitis makes the disease less severe.[18] These improvements were accompanied by a rise in anandamide levels and changes in the CB1 receptor.

• Blocking FAAH and COX is also linked to higher levels of PEA and oleoylethanolamide.[18] PEA levels are 1.8-fold higher in intestinal tissue from ulcerative colitis patients compared with healthy controls.[19] This is likely because PEA is healing the inflammation. PEA is highly anti-inflammatory, blocks the production of inflammatory cytokines, and reduces colitis in mice.[20]

• The phytocannabinoids CBD, THC, and cannabigerol (CBG) reduced intestinal inflammation in animal studies.[21,22] Although THC was the most effective in rats with colitis, CBD made an ineffective THC dose more effective to the point where combining CBD and a lower dose of THC was just as effective as a higher THC-only dose.[21] CBG has also suppressed colitis in mice and blocked the synthesis of reactive oxygen species in intestinal epithelial cells.[22]

• Genetics also play a role in the endocannabinoid-gut link. There's a relationship between variants in the gene encoding CB1 receptors and irritable bowel syndrome.[23]
In addition, variants of the CB1 receptor gene (*CNR1)* and *FAAH* genes occur in people with diarrhea-predominant and alternating forms of IBS.[24] [25] There's also a strong link between a polymorphism in the *CNR1* gene and IBS symptoms, colonic transit in IBS with diarrhea, and intestinal gas.[24] However, pain was not associated with this polymorphism. Other scientists found that *CNR1* mutations are linked to developing IBS symptoms.[25,26]

Impaired Gut Motility: When Things Move Too Slow or Too Fast

Research shows that endocannabinoids and CBD influence gut motility. This refers to the time it takes for food to move through the intestines. Slow gut motility is known as constipation. On

the other hand, when gut motility speeds up too much, it can lead to diarrhea. There are a number of studies that show the endocannabinoid system oversees gut motility. For example, when scientists fed obese mice high-fat diets, the endocannabinoid system in the animals' guts changed.[27] This led to an increase in gut motility. In another study, this one a mouse model of constipation, researchers reduced the activity of diacylglycerol lipase (DGL), the enzyme which makes the endocannabinoid 2-AG.[28] Blocking DGL improved gut motility.

Other studies show that by activating the CB1 receptor, peristalsis and gastrointestinal contraction—processes that move food through the intestines—are suppressed. THC, the component of marijuana that makes you high, activates the CB1 receptor.[29,30] However, CBD doesn't activate this receptor. This means it's less likely to produce constipation and may even normalize bowel movements.[31] In fact, a mouse study of sepsis showed that CBD reduced gut motility in the animals with sepsis but had no effect on the motility of normal mice.[31]

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CBD also governs the activity of the FAAH enzyme, which impacts gut motility by interacting with the endocannabinoid anandamide.[31]

Stress-Related Stomach Pain

The endocannabinoid system may come to the rescue of people who have abdominal pain caused by chronic stress. In fact, changes to the endocannabinoid system may explain why chronic stress is linked to IBD/IBS.[15,32] In studying rodents, scientists have found that stress during early life changes the endocannabinoid system.[33] This, in turn, makes the animals more likely to develop IBS. In addition, chronic stress lowers levels of anandamide while raising 2-AG in the brain and reducing the activity of CB1 receptors in enlargements along peripheral nerves known as sensory ganglia. This in turn regulates visceral pain.[34]

Epigenetics are also involved in this endocannabinoid-abdominal pain connection. Epigenetics involves changes to gene expression that occur in ways other than the genetic code. Epigenetic changes happen because of lifestyle or environmental factors. When a person is chronically stressed, their CB1 receptor activity is altered through epigenetic pathways.[35] This may be the reason why stress can cause abdominal pain.[35] In a way that involves epigenetics, chronic stress impacts the *CB1* gene promoter.[3] This causes a fall in CB1 levels in sensory neurons in the colon and other pelvic organs.

Does CBD Have a Role to Play in GERD?

Swallowed food passes into the stomach thanks to the lower esophageal sphincter, known as the LES for short. The LES also stops the regurgitation of gastric contents back into the esophagus. The encannabinoid system is involved in the mechanisms regulating LES relaxation.[36] Working through the CB1 receptor, cannabinoids stop LES relaxation.[36] Too much relaxation of the LES causes gastroesophageal reflux disease (GERD). There are other ways besides preventing LES relaxation in which cannabinoids may reduce GERD. These include reducing gastric acid secretion and microvascular leakage and bronchoconstriction, which are associated with reflux.[36] Cannabinoids can also reduce pain linked to esophageal hypersensitivity.[36]

Studies on cannabinoids and GERD have focused on THC or synthetic cannabinoids.[37] Unfortunately, there isn't any research on CBD and GERD. However, based on the promising results using THC or synthetic cannabinoids, it would be interesting to explore CBD's effects in clinical studies.

Anti-Nausea Actions

In research using rodents, scientists have found CBD can reduce an upset stomach. In one of those studies, researchers injected CBD into rats and found it reduced nausea and vomiting.[38] It accomplished this by working through serotonin receptors.

Colon Cancer and Cannabinoids

In cancer, including colorectal cancer, the regulation of endocannabinoid production is altered.[39] Expression of endocannabinoid receptors is also changed.[39] In primary tumor tissue from people whose colorectal cancer metastasized, the expression of CB1 receptors is weakened.[39] This weakened activity of the CB1 receptor speeds up the growth of intestinal tumors.[40] In addition, mice without a CB1 receptor suffer from more severe inflammation in the colon.[40] This suggests this cannabinoid receptor protects against tissue inflammation in the colon.[16] Tissue inflammation can lead to cancerous changes in colon tissue and blocking the inflammation can stop the malignant changes.[40] [16] On the other hand, increasing CB1 receptor expression stops the proliferation of colon cancer cell lines.[39,41,42]

This link between CB1 receptor activity and colon health provides evidence that the endocannabinoid system is involved in suppressing colorectal cancer. What's more, both endocannabinoids and phytocannabinoids reduced colon cancer development in rodents. Studies using CBD or a *Cannabis sativa* extract with high CBD content blocked the development

of aberrant crypt foci, polyps, and tumors in the colon of mice.[43] [44] In colorectal cancer cell lines, CBD also stopped cell proliferation.[43] Furthermore, CBD suppresses the activity of the G-protein coupled receptor 55 (GPR55).[45] GPR55 promotes metastasis of colon cancer and CBD's ability to weaken its actions may keep the colon healthy.[45]

To sum up, the endocannbinoid system, the broader endocannabinoidome, and phytocannabinoids like CBD can keep the GI tract healthy. I've found in my clinical practice that CBD supports colon health in my patients that need this kind of support the most.

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Chapter Ten
Beyond CBD: Tapping into the Health Benefits of Terpenes

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As I mentioned in chapter two, hemp oil is an ideal way to consume CBD. That's because it contains not only CBD but also a whole host of beneficial compounds known as terpenes. This combination of CBD working together with terpenes is known either as the entourage effect or the hemptourage effect. The extraction process used to make CBD oil sometimes eliminates or reduces terpene content. However, many manufacturers add terpenes back into the CBD oil.

CBD-rich hemp oil naturally contains terpenes, so that when you ingest it, you get the benefit of the whole plant.

Terpenes are aromatic oils found in plants. They each give off characteristic smells—such as pine or citrus. (In the bullet points below, you can read about specific aromas of each terpene in hemp). Plants develop terpenes to ward off predators or attract pollinators. Concentrations vary within plants depending on factors like fertilizers, climate, age of the plant, and type of soil.

Terpenes vs. Terpenoids

Sometimes these two words are used interchangeably. However, there is a difference between the two: their molecular structures. Terpenes are secreted by the living plant and are responsible for its aroma. Terpenoids are formed when the cannabis flower is dried, cured, or chemically modified.

Taking Advantage of Terpenes

When it comes to keeping us healthy, terpenes work together with CBD. They boast anti-inflammatory, antioxidant actions that can benefit a number of health concerns. I'll talk about the possible health benefits of terpenes in a little while. First, let's get acquainted with the most important terpenes in CBD-rich hemp oil.

Hemp Oil's Top Terpenes

• **Myrcene** – This terpene has a musky and earthy aroma with an undertone of cloves. It's known for its relaxing properties. In addition to hemp oil, it's also found in hops, lemongrass, parsley, mangoes, and wild thyme.

• **Caryophyllene** – Another terpene found in hemp, caryophyllene acts through the CB2 receptor. It smells like pepper with undertones of cloves. In addition to hemp, it's also found in, of course, black pepper, as well as oregano, cloves, basil, and rosemary.

• **Humulene** – Highly concentrated in the hops used to make beer, humulene is also found in hemp oil. In addition, it's present in coriander, cloves, and basil. Its aroma is woody and earthy. Humulene is a caryophyllene isomer and is also known as alpha-caryophyllene.

• **Linalool** – Found in both hemp oil and lavender, linalool may be the reason for lavender's well-known stress-soothing properties. Linalool may also support a healthy immune system. It has a floral aroma with a hint of spice.

• **Ocimene** – Another terpene found in hemp oil, ocimene is known to act as a natural insecticide. It has a sweet, woody aroma with a hint of citrus. Ocimene is also found in pepper, basil, parsley, mangoes, kumquats, and mint.

• **Terpinolene** – This hemp-derived terpene calms the mood and sympathetic nervous system activity. It's also been found to repel insects. Terpinolene smells like pine and flowers with a herbal aroma lingering in the background. It's also found in pine trees, apples, cumin, and nutmeg.

• **Limonene** – This citrus-smelling terpene is found in hemp oil as well as oranges, lemons, peppermint, juniper, and rosemary. It boosts mood and relieves stress, to name just a couple of its benefits. It's often used in natural cleaning products.

• **Pinene** – Named pinene because it smells like pine and is found in pine trees, this terpene is thought to be the reason why spending time in a forest boosts immunity.[1] Exposing humans to the aroma of α- and β-pinene increased activity of natural killer (NK) cells and intracellular anti-cancer proteins in lymphocytes.[1] This increased NK activity lasted for more than a week after traveling to forests. Pinene is also found in rosemary, dill, basil, parsley, and orange peels.

• **Phytol** – Present in hemp extracts through the breakdown of chlorophyll and tocopherol. Known for its relaxing properties thanks to its ability to raise levels of the calming neurotransmitter GABA.

• **Beta-Amyrin** – This terpene present in hemp has anti-inflammatory actions. It's also antibacterial and antifungal.

Can Terpenes Make You Healthier?

Terpenes play a lot of different roles in health. Below, I'll describe the major health benefits of terpenes in more detail. That way you'll understand why CBD isn't the only reason why you might want to supplement with hemp oil. You may also want to take a look at the table below. It offers an at-a-glance snapshot of which terpenes have which benefits. You can also refer to chapter 2, which has another table listing the benefits of terpenes.

Terpenes found in Hemp Oil	Health Benefits[2-7]
Myrcene	Joint and respiratory health, antibacterial, mosquito repellant, enhances alertness and improves work performance.
Caryophyllene	Antibacterial, anti-cancer, enhances oxygen levels, neuroprotective, protects the liver, anti-convulsant, anti-fungal, anti-diabetic, possible benefits in Alzheimer's disease, anti-aging, reduces pain, protects kidney health, possible cardiovascular benefits
Humulene	Insecticidal, anti-cancer, anti-inflammatory, anti-diabetic
Linalool	Reduces anxiety, neuroprotective, anti-parasitical, anti-convulsant, protects the liver, antibacterial, antioxidant, anti-inflammatory, supports healthy brain function during aging.
Ocimene	Mosquito repellant

Terpinolene	Mood enhancer, antibacterial
Limonene	Anti-cancer, joint health, ulcerative colitis, anti-stress, supports healthy immunity
Pinene	Insecticide, anti-inflammatory, maintains lung health, enhances cognitive function
Phytol	Calming and relaxing
Beta-Amyrin	Anti-inflammatory, anti-fungal, anti-bacterial

Ulcerative Colitis

Many of the terpenes found in hemp oil suppress inflammation. D-limonene is no exception. Its anti-inflammatory abilities may benefit people with conditions characterized by intestinal inflammation. In one study, researchers compared the effects of d-limonene with ibuprofen in a rat model of colitis.[8] D-limonene significantly reduced intestinal inflammatory scores similar to the reduction caused by ibuprofen. The rats given d-limonene also had lower serum levels of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) compared with untreated rats with colitis.

The same researchers gave healthy elderly human subjects a supplement of D-limonene-containing orange peel extract for 56 days.[8] In the participants given the D-limonene-containing supplement, there was a pronounced decline in levels of inflammatory markers, especially peripheral IL-6, compared to subjects not receiving the d-limonene.

In another study, scientists randomly divided rats into three groups: control, untreated rats with ulcerative colitis, and rats with ulcerative colitis receiving 50 or 100 mg/kg D-limonene.[9] D-limonene significantly inhibited disease activity and colonic mucosal damage. It accomplished this by blocking matrix metalloproteinase (MMP)-2 and -9 gene expression, two processes that cause inflammation. D-limonene treatment also resulted in a decline in other markers of inflammation, including prostaglandin E2 (PGE2) production and transforming growth factor-β (TGF-β) gene expression. Plus, treatment with D-limonene had other benefits including significantly increasing antioxidant activity, as well as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) protein expression levels in rats with ulcerative colitis.

Arthritis and Carpal Tunnel Syndrome

Anyone with joint problems or nerve-pain issues should take note of the anti-inflammatory actions of terpenes. Terpenes like limonene block pro-inflammatory compounds such as when the body makes too much nitric oxide.[10] For this reason, researchers believe plants containing limonene can soothe arthritic pain and stiffness.[10]

Osteoarthritis is a degenerative disease. In people who suffer from this disease, synovial tissue of joints becomes inflamed and there is a loss of cartilage. In a model of osteoarthritis, scientists investigated the activity of myrcene and limonene in human cartilage cells

(chondrocytes) stimulated with IL-1β, a type of protein known as a cytokine.[11] IL-1β is a pro-inflammatory cytokine, which means it plays a role in the body's response to inflammation. Limonene and especially myrcene suppressed inflammation in human chondrocytes by reducing the production of nitric oxide, decreasing the expression of the inflammatory marker iNOS, and blocking pathways linked to the inflammatory response.[11] These results suggest myrcene and limonene may reduce the inflammation that occurs during arthritis.

Terpenes are also powerful antioxidants. Their ability to quench free radicals can be useful in nerve-related disorders. In a double-blind, placebo-controlled study of 37 patients with carpal tunnel syndrome, inhaling linalool significantly reduced oxidative stress compared with controls who inhaled a carrier oil.[12] Inhaling linalool also reduced systolic and diastolic blood pressure and pulse rate.

In a study of rats with nerve injury and neuropathic pain, 15 days of limonene treatment reduced hyperalgesia (increased sensitivity to pain).[13] Nerve injury can also lead to depression, and limonene reduced depressive-like behavior in the rats.[13]

Breathing Easier with Terpenes

Studies show terpenes may support lung health in a number of conditions. One of those conditions is asthma, which is characterized by airway inflammation, constricted airways after exposure to allergens, secretion of excess mucus, and other respiratory problems. Myrcene suppressed inflammatory cytokines, controlled asthma, and improved lung tissue in rats.[14]

People with asthma are more sensitive to inhaled irritants. Consequently, researchers studied whether limonene could improve airway health after exposure to an allergen and reduce asthma symptoms in mice.[15] They exposed mice to an allergen and then the animals inhaled limonene. After exposure to limonene, the animals produced less of an important marker of allergic inflammation (immunoglobulin E, IgE). Inhaling limonene also lowered representative Th-2 cell type, which is responsible for making cytokines linked to inflammation. In addition, limonene caused the body to make less of factors important for the migration of inflammatory cells into lung tissue. Levels of TGF-β 1 also declined after inhaling limonene. TGF-β 1 is linked to damaging changes in the respiratory tract—what scientists call airway remodeling. What's more, limonene reduced the number eosinophils that migrated into the lungs, airway fibrosis, and bronchoconstriction.

Terpenes may also soothe the inflammation associated with acute lung injury. This condition has a high mortality rate and there's no specific drug available to treat it. In one study, scientists caused acute lung injury in mice then injected limonene into the animals.[16] Limonene protected the lungs and improved pulmonary function thanks to its anti-inflammatory effects. Even more impressive is evidence from a study in humans. In this study, α-pinene and limonene given orally to patients with chronic obstructive pulmonary disease (COPD) cleared mucus from the respiratory tract.[17]

Linalool also may support the health of people with bronchitis. In patients with uncomplicated acute bronchitis, researchers compared a phytomedicine derived from the steam distillation of the flowering tops of lavender with a placebo.[18] The lavender distillation product reduced the bronchitis severity score at days 7 and 10 of treatment and improved signs and symptoms of acute bronchitis as well as the patients' quality of life compared to placebo. This may have been due to the linalool in the lavender.

Antibacterial, Anti-Viral, Anti-Parasitical Actions

Bacteria tend to live in groups where they are better able to defend themselves against antibiotics and other antibacterial substances. These colonies of bacteria are known as a biofilm. Essential oils containing β-Myrcene and limonene prevented the bacteria in the wounds of mice from forming a biofilm.[19]

β-caryophyllene is another antibacterial terpene. In a randomized, placebo-controlled, double-blind study, 66 subjects with a *Helicobacter pylori* infection were given either 126 mg/day of β-caryophyllene or a placebo.[20] Although the β-caryophyllene didn't eradicate the *H. pylori*, it significantly reduced nausea and epigastric pain. It also decreased levels of the pro-inflammatory cytokine IL-1β, indicating it reduced inflammation.

Terpenes also go up against viruses. Plants that contain β-pinene and limonene significantly reduced the viral infectivity of norovirus in a cell culture study and on food and metal surfaces.[21]

In addition, terpenes may get rid of parasites. In one study, giving a mixture of limonene, β-pinene, and α-pinene to chickens infected with a helminth parasite (*Ascaridia galli*) led to a significant reduction of parasite eggs in the stool.[22]

Terpenes Useful Against Mosquitoes and Ticks

Plants often make terpenes to protect themselves against insects and other predators. So it's not surprising that many terpenes are insecticidal. For example, limonene and β-myrcene act as mosquito repellants and limonene kills mosquito larva.[23,24] What's more, terpinolene was more effective than DEET at killing ticks.[25]

Diabetes

Several terpenes may be able to support healthy blood sugar metabolism. Linalool and humulene significantly increased glucose uptake in fat cells.[2] This suggests these two terpenes help the body use glucose more efficiently. Like most diseases, diabetes and metabolic problems are linked to high levels of inflammation. Scientists measure chronic inflammation and the progression of metabolic diseases like diabetes by looking at levels of circulating inflammatory mediators such as proteins known as cytokines. One group of scientists found

that the terpene humulene lowered the secretion of pro-inflammatory cytokines interleukin 6 (IL-6) and interleukin 8 (IL-8).[2]

The terpene limonene can protect against a damaging process called glycation that occurs at a higher level in diabetics.[26] High blood sugar leads to this ramped up glycation along with the production of high levels of advanced glycation end products (AGEs). These AGEs are to blame for many of the diseases that occur alongside diabetes such as arteriosclerosis, retinopathy, neuropathy, and nephropathy.[26] AGEs cause damaging changes to proteins in the body, leading to inflammation. Research using rats with diabetes found that a plant extract that had limonene as the main compound improved the animals' ability to use glucose and lowered AGE formation.[26] In that same study, the researchers found that purified limonene stopped the formation of cataracts.[26] This was likely because of its ability to act as an antioxidant. The scientists also observed that the purified limonene's anti-glycating actions happened at a much lower dosage compared to the anti-glycating agent, aminoguanidine.[26]

Metabolic Syndrome

Metabolic syndrome is a cluster of risk factors for cardiovascular disease and diabetes including abdominal fat, hypertension, low high-density lipoprotein (HDL) cholesterol, and high triglycerides and fasting blood sugar. Limonene may counteract many of these risk factors for metabolic syndrome. According to a study of mice fed a high-fat diet, limonene lowered triglycerides and LDL cholesterol, while raising HDL cholesterol.[27] Limonene also lowered high blood sugar in the animals.[27] In addition, obese mice given limonene were better at using glucose.[27] This suggests it may be a good option for people with metabolic syndrome.

Limonene's beneficial effects on metabolic health are likely due to its ability to work through two receptors: peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs).[28] In high-fat-diet fed rats with metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), limonene intake reduced fat buildup in the animals.[28] It also caused a drop in blood glucose levels.[28]

Cancer

Terpenes have activity against a number of cancers. Linalool stopped the spread of prostate cancer in cell culture research.[29] It's also stopped colon cancer, leukemia, and cervical cancer cells.[30,31] Linalool triggers apoptosis (programmed cell death) and oxidative stress in the cancer cells.[31] It also causes a process called cell cycle arrest, which stops the cells from proliferating.[31] Plus, its anti-cancer actions may involve supporting immunity.[29]

β-caryophyllene and humulene also have anti-cancer actions, according to cell culture research.[32] These terpenes may block and suppress cancer, make the cancer cells more sensitive to substances that kill them, and protect healthy cells.

One of the few human studies investigating terpene's effects on cancer showed it may be able to support breast health.[33] In this study, an open-label pilot clinical trial, 43 women with newly diagnosed operable breast cancer chose to have a surgical excision of their tumor. They were given 2 grams of limonene daily for two to six weeks leading up to surgery. The researchers collected blood and breast tissue to find out whether the limonene caused any beneficial changes. Limonene had a preference for concentrating in the breast tissue. Taking limonene led to a 22% reduction in expression of cyclin D1. This suggested limonene caused cell-cycle arrest and reduced cell proliferation of the cancer, possibly stopping or reducing its spread.

The same researchers conducted a more recent study using samples collected in the previous trial.[34] In this study, they found limonene had several anti-cancer effects including a reduction in adrenal steroid hormones, an increase in bile acids, and a rise in markers of collagen remodeling or breakdown. Limonene-treatment was also linked to beneficial changes in glucose metabolism. Many of the changes that occurred after taking limonene were associated with a decline in cyclin D1, just like in the previous study.

Improving Work Performance and Alertness

Essential oils containing linalool and myrcene, when inhaled as aromatherapy, improve performance in the workplace.[35] In a study of 42 administrative university workers aromatherapy that contained linalool and myrcene improved both mental and emotional health by reducing stress and boosting the attentiveness and alertness of the participants.[35]

The Bottom Line on Terpenes

In hemp oil, terpenes work together with CBD to promote vibrant good health. Some human studies as well as preclinical animal studies and cell culture experiments conducted on terpenes show that this group of plant-based compounds hold great promise. I've also seen their benefits in clinical practice with my patients. If CBD plays the starring role in hemp oil, look on terpenes as its costars.

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