Cannabidiol (CBD) is one of the main constituents of the plant Cannabis sativa. Surveys suggest that medicinal cannabis is popular amongst people diagnosed with cancer. CBD is one of the key constituents of cannabis, and does not have the potentially intoxicating effects that tetrahydrocannabinol (THC), the other key phytocannabinoid has.

Research suggests that CBD may be able to address some of the hallmarks of cancer, as well as treat many of the symptoms and signs associated with cancer and its orthodox treatment. There is also evidence that CBD can work synergistically with some chemotherapeutic agents. CBD shows much promise in the integrative management of cancer.

1. Introduction
Survey data indicates that cancer sufferers are using cannabis medicinally. A cross-sectional survey in 926 patients at the Fred Hutchinson Cancer Research Centre (Seattle) found that 66% had used cannabis previously, with 24% of respondents having used cannabis in the past year and 21% in the past month. Of the 24% (n = 222) of respondents who were active users, around 75% used cannabis for physical symptoms (pain, nausea, appetite), 63% for neuropsychiatric symptoms (stress, coping with illness, depression/improve mood, sleep), and 26% reported they believed cannabis was helping to treat their cancer. Encouragingly, regardless of symptom, approximately 51% judged cannabis to be of ‘major benefit’ and 39% of ‘moderate benefit’. An anonymous online survey of 612 US-based members of the Breastcancer.org and Healthline.com communities with a self-reported diagnosis of breast cancer within 5 years found that 42% used cannabis for relief of symptoms (including pain (78%), insomnia (70%), anxiety (57%), stress (51%) and nausea/vomiting (46%)) with 46% of the belief that cannabis can treat the cancer itself. Of those using cannabis, 79% had used it during treatment (systemic therapies, radiation, surgery).

2. What Is Cannabis and Cannabidiol?
The plant Cannabis sativa has been used medicinally for thousands of years in many cultures including Chinese, Japanese, Indian, and Egyptian, whilst its medicinal use in western countries such as the US, England, and parts of Europe began to occur much later, particularly in the 19th century.

2.1. Constituents of Cannabis
There are over 540 secondary metabolites in the cannabis plant, of which there are over 120 phytocannabinoids, divided into 11 classes. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most well-researched of the phytocannabinoids. In addition, over 200 terpenes have been isolated from cannabis, along with phenols, steroids, polysaccharides, coumarins, glycosides, flavonoids, alcohols, and other plant nutrients, and these have their own therapeutic actions. The so-called ‘entourage effect’ refers to the cooperative effect between the various constituents of the plant, whereby the therapeutic effect of the other constituents may contribute to the overall therapeutic effect of the main phytocannabinoids (i.e., THC, CBD). I like to use the analogy of a rock band, with the rockstars on stage being THC and CBD, the rest of the band members the other phytocannabinoids and terpenes, and the ‘roadies’ being other plant nutrients like polyphenols and so on—there’s no show without the band or the roadies.

2.2. Cultivars of Cannabis
There are several hundred different ‘strains’ or cultivated varieties (‘cultivars’) of cannabis, and their chemical profiles will differ. That is, the relative amounts of key phytocannabinoids, terpenes, and other plant nutrients will be different in different cultivars of cannabis. And so, the therapeutic actions of different cultivars can also differ.

2.3. Cannabis and Cannabidiol Products
Medicinal cannabis products include dried flower (which can be smoked or vaped) and proprietary forms: (1) cannabis-based liquid extracts, e.g., nabiximols (approximately 1:1 ratio of THC and CBD); (2) phytocannabinoid botanicals: dense cannabis extracts manufactured as oils, oils in capsules, pills, sublingual or intranasal sprays, suppositories, transdermal patches, E-Liquids for vaporization, and topical ointments; and (3) single molecule drugs: synthetic or semi-synthetic prescription drugs (e.g., nabilone, dronabinol, which are FDA-approved).

Note that in the consumer literature, the terms full-spectrum and broad-spectrum are often used in relation to cannabis and CBD products: full-spectrum denotes the presence of all the phytocannabinoids, terpenes, and other plant nutrients naturally
found in the plant in the final product, and broad-spectrum denotes the presence of many of the phytocannabinoids and terpenes naturally found in the plant but not all of them. Typically, a broad-spectrum CBD product will have the THC removed.

Flower and cannabis oil products differ in terms of their relative amounts of the key phytocannabinoids, THC and CBD, as well as the types and relative amounts of terpenes and minor phytocannabinoids (which have their own therapeutic actions).

If researchers consider CBD products available on the market, it is clear that they vary considerably. Whole plant (full-spectrum, broad-spectrum) CBD products will differ in terms of amount (concentration, percentage) of CBD and other phytocannabinoids present, as well as the types and relative amounts of terpenes and other plant nutrients present. CBD-predominant products typically have very low amounts of THC. If the CBD oil has been derived from a hemp plant (hemp is simply a cannabis cultivar bred to have a very low amount of THC), then it will contain less than 0.3% THC if produced in the US (the upper legal limit of THC). An important point to note is that whole plant products are likely to work differently to CBD isolate.

2.4. Differences between THC and CBD

THC is responsible for the potentially intoxicating effects associated with cannabis (the potential for causing intoxication, i.e., the euphoria or ‘high’ associated with cannabis, is dose-dependent), but unlike THC, CBD is not potentially intoxicating and not associated with the typical symptoms associated with cannabis intoxication, making it perhaps more attractive as a treatment option. Both THC and CBD have many therapeutic actions in common, but their mechanisms of action differ.

2.5. Therapeutic Actions of CBD

CBD has many therapeutic actions, set out in Table 1. From this table, researchers see how broad the therapeutic actions of this phytocannabinoid are, and researchers already start to see the potential relevance of CBD to cancer, its pathomechanisms, and signs/symptoms associated with cancer and its orthodox treatment.

### Table 1. Therapeutic Actions of CBD (adapted from[10]).

<table>
<thead>
<tr>
<th>Action</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>analgesic</td>
<td>immune-modulatory</td>
</tr>
<tr>
<td>anti-nausea</td>
<td>antioxidant</td>
</tr>
<tr>
<td>anti-emetic</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td>anxiolytic</td>
<td>antibiotic, anti-bacterial</td>
</tr>
<tr>
<td>antidepressant</td>
<td>neuroprotective</td>
</tr>
<tr>
<td>anti-psychotic</td>
<td>anti-cancer and anti-tumoral</td>
</tr>
<tr>
<td>anti-convulsant/anti-epileptic</td>
<td>anti-cancer and anti-tumoral</td>
</tr>
<tr>
<td>anti-asthmatic</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>antioxidant</td>
</tr>
</tbody>
</table>

Now that researchers understand a little about CBD, let’s look at their endocannabinoid system (ECS). As in many respects, the reason that cannabis may be so broad in its therapeutic applications is due to the presence of this ‘ready-made system’ that the constituents of cannabis interact with.

3. Endocannabinoid System

3.1. Role of the Endocannabinoid System

The ECS is one of the most important neuroregulatory systems researchers have, responsible for the homeostasis of most systems in the body. The ECS modulates the following: the immune system (innate, adaptive); inflammation; pain/analgesia; stress response, emotions/moods, cognitive function, memory and memory extinction; sleep; gastrointestinal (GI) tract homeostasis (including regulation of food intake and satiation, gastroprotection, nausea and emesis, gastric secretion, visceral sensation, GI motility, ion transport, intestinal inflammation and cell proliferation in the gut); energy homeostasis and regulation of lipid and glucose metabolism; embryological development; the cycle of cell life and death, cancer cell control, cyto-protection; neurotransmitters, neuroprotection, neural plasticity, and many others.

3.2. Components of the Endocannabinoid System

Discovered in the 1990’s, at a simplistic level there are three key components of the endocannabinoid system (ECS): (1) lipid-derived endocannabinoids (the two main ones are N-arachidonylethanolamine or anandamide (abbreviated AEA) and 2-arachidonoylglycerol (2-AG)), but there are others, the enzymes that synthesise and degrade them (fatty acid amide hydrolase (FAAH) and mono acyl glycerol lipase (MAGL) being two main ones degrading AEA and 2-AG respectively) plus...
various transporter systems, and (2) cannabinoid receptors (CB1 and CB2 receptors) [42].

However, it is much more complex and what researchers have are many more components that make up an ‘extended ECS’ [6]. Firstly, there are other receptors that cannabinoids (endocannabinoids and/or phytocannabinoids) interact with, including G-Protein Receptors (GPR55, GPR18, and GPR119), transient receptor potential vanilloid (TRPV) ion channels (TRPV1 and 2), and peroxisome proliferator activated receptors (PPARα and PPARγ) [13][14]. There are other endocannabinoid-like substances (e.g., N-palmitylolethanolamide [PEA], oleoylethanolamide [OEA] and oleamide). There are also more recently discovered hemopressin-derived peptides (inverse agonists of CB1 receptors), novel lipid compounds (lipoxins and resolvins) that also regulate physiological allostasis, and n-3 endocannabinoid epoxides originating from docosahexanoic acid (DHA) and eicosapentanoic acid (EPA) (de Melo Reis et al., 2021).

Cannabinimimetic compounds including omega (n-3 and n-6) fatty acids can signal through the ECS (Frietas et al., 2017); indeed, both AEA and 2-AG are derived from arachidonic acid (from n-6 PUFAs) and levels of the endocannabinoids and their activity are influenced by the ratio of n-6 to n-3 polyunsaturated fatty acids in diet [33].

The endocannabinoids actually have several biosynthetic and degrading pathways and enzymes which may be shared with endocannabinoid-like mediators; degradation of AEA and 2-AG leads to arachidonic acid plus several other bioactive signalling molecules [34][35][36][37]. The term ‘endocannabinoidome’ was coined to describe the endocannabinoids, endocannabinoid-like mediators, and the many receptors and metabolic enzymes [34]. See de Melo Reis et al. [33] and Di Marzo and Piscitelli [39] for good descriptions of the ECS and regulation of homeostasis.

### 3.3. Where Are the CB1 Receptors and CB2 Receptors Located?

CB1 receptors are abundant in the central nervous system (brain, spinal cord) but are also found peripherally in many tissues and organs (though at a lower level of expression than in the brain) [38]. Several isoforms have been found: CB1, CB1A, and CB1β [39][40].

CB1 receptors are found in high concentrations in areas of the brain associated with mood/emotions and cognitive processes as well as movement [2]. Another interesting fact is that CB1 receptors appear ten times more frequently in the brain than mu-opioid receptors, and can co-localise with them to augment the pain-relieving effects of opioids [41][42]. CB1 receptors maintain the delicate balance between neuronal inhibition and excitation, in particular in GABAergic, glutamatergic, and dopaminergic transmission [43]. CB1 receptors are also abundant on the outer membranes of mitochondria [44].

CB2 receptors are particularly abundant in the cells and tissues and organs of the immune system, are also found in many other parts of the body including the brain (where they are highly inducible under conditions of inflammation) [34][45]. CB2 receptors are key mediators of cannabinoid regulation of the immune and inflammatory systems [12], where in general, CB2 receptor activation usually mediates immunosuppressive effects, attenuating the autoimmune inflammatory response, and thereby limiting tissue injury [46]. In addition, a CB2 isoform has been identified, CB2A, in the liver, spleen, neurons, and brain cortex [47]. See Table 2 for locations of CB1 and CB2 receptors in the body.

### Table 2: Location of CB1 and CB2 Receptors (adapted from [6]).

<table>
<thead>
<tr>
<th>CB1 Receptors</th>
<th>CB2 Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abundant in the Central Nervous System:</strong> Brain nerves/neurons in particular; also present in cerebral blood vessels; also to some extent in microglia, astrocytes; spinal cord</td>
<td><strong>Highly Concentrated in Cells/Tissues/Organs of the Immune System:</strong> Monocytes, macrophages, CD4+ and CD8+ T Cells, B-cells, NK cells, neutrophils, mast cells; spleen, tonsils, thymus</td>
</tr>
<tr>
<td>Also present in: Peripheral Nervous System: sympathetic nerve terminals, trigeminal ganglion, dorsal root ganglion, dermic endings of primary sensory neurons; neurons of parasympathetic nervous system</td>
<td>Also present in: CNS (present in lower levels in CNS): cell bodies and dendrites of central neurons; cortex, brainstem, cerebellum, striatum, hippocampus, amygdala, retina, neuronal, glial (astrocytes, microglia) and endothelial cells of brain;</td>
</tr>
<tr>
<td>Blood, Tissues, Immune Cells: adipose tissue (white, brown), connective tissue, fascia, fibroblasts, skeletal muscle, bone (osteoclasts, osteoblasts); smooth muscle (vascular and visceral); blood vessels, vascular endothelial cells, blood (leukocytes), vascular smooth muscle cells; immune cells including macrophages, mast cells</td>
<td>Spinal Cord and Dorsal Root Ganglia</td>
</tr>
<tr>
<td>Organs &amp; Glands: skin, GI tract, eye, liver, heart, kidney, bladder, adrenal gland, spleen, tonsils. lung, endocrine glands (e.g., thyroid, adrenals, pituitary gland), exocrine glands, reproductive organs: male (testes) and female (uterus, ovaries), placenta</td>
<td>Blood, Tissues, Cells: various human tumours, adipocytes, leucocytes, bone marrow; bone (osteoclasts, osteoblasts, osteocytes), muscle cells, human vascular smooth muscle, endothelial cells</td>
</tr>
<tr>
<td>Highly Concentrated in Cells/Tissues/Organs of the Immune System: Monocytes, macrophages, CD4+ and CD8+ T Cells, B-cells, NK cells, neutrophils, mast cells; spleen, tonsils, thymus</td>
<td>Organs: skin, GI tract, liver, heart, pancreas, spleen, lung, kidneys, bladder, reproductive organs &amp; cells (e.g., ovary); placenta</td>
</tr>
</tbody>
</table>
3.4. How Does the Endocannabinoid System Work?

AEA is a partial agonist at CB1 and CB2 receptors, whilst 2-AG is a full agonist. CB1 and CB2 receptors are G-protein-coupled receptors, and when activated signal through fast pathways (i.e., Ca²⁺ and K⁺ currents) and/or slow pathways (e.g., cyclic AMP-protein kinase A and others). At a simplistic level, in the nervous system the ECS functions as a retrograde signalling system, decreasing the release and transmission of neurotransmitters.

In the nervous system, endocannabinoids are synthesised on demand from plasma membrane phospholipids in the postsynaptic neuron in response to increased intracellular calcium concentration and/or activated G-coupled receptors. When synthesis is triggered, the endocannabinoids move in a retrograde fashion across the synaptic space, from postsynaptic to the presynaptic region, binding with cannabinoid receptors on the presynaptic neuron, and leading to suppression of neuronal excitation and inhibition of depolarisation-induced neurotransmitter release. What happens downstream depends on whether the neurotransmitter is excitatory (e.g., glutamate) or inhibitory (e.g., γ-aminobutyric acid, GABA) and K⁺ currents.

CB1 and CB2 receptors can activate many different intracellular signal transduction pathways, including (depending on cell type): protein kinase A, protein kinase C, Raf-1, JNK, mitogen-activated protein kinases (MAPK), p38 MAPKs, extracellular signal-regulated kinase (ERK 1, 2), c-fos, c-jun, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways, mammalian target of rapamycin (mTOR) and more. Depending on the ligand and subcellular environment, the eventual outcome could be promotion of cell survival or cell death.

That is the simple explanation, but of course it is much more complex than that given the existence of other receptors that the endocannabinoids can bind with and the existence of endocannabinoid-like substances. In addition, degradation of 2-AG also produces bioactive signalling molecules, some of which have opposing effects. For an in-depth exploration of the ECS, see de Melo Reis and colleagues.

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