Trends in Pharmacological Sciences

CellPress

Review

Beyond Cannabis: Plants and the Endocannabinoid System

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Plants have been the predominant source of medicines throughout the vast majority of human history, and remain so today outside of industrialized societies. One of the most versatile in terms of its phytochemistry is cannabis, whose investigation has led directly to the discovery of a unique and widespread homeostatic physiological regulator, the endocannabinoid system. While it had been the conventional wisdom until recently that only cannabis harbored active agents affecting the endocannabinoid system, in recent decades the search has widened and identified numerous additional plants whose components stimulate, antagonize, or modulate different aspects of this system. These include common foodstuffs, herbs, spices, and more exotic ingredients: kava, chocolate, black pepper, and many others that are examined in this review.

Trends

The endocannabinoid system (ECS) is a homeostatic regulator of neurotransmitter activity and almost every other physiological system in the body.

Its name derives from cannabis, the plant that produces cannabinoids (tetrahydrocannabinol, cannabidiol, caryophyllene, and others), and whose investigation elucidated the myriad functions of the ECS.

In the past two decades, additional research has discovered that many other plant foods and herbs modulate the ECS directly and indirectly. Advancing this knowledge may have important implications for human health and nutrition.

Overview of the Endocannabinoid System

Cannabis (*Cannabis sativa*) has been an important tool in the herbalist's arsenal and the medical pharmacopoeia for millennia, but it has only been in the past 25 years that science has provided a better understanding of its myriad benefits. This began with the discovery of **cannabinoid receptors** (see Glossary) [CB_1, CB_2, and the ionotropic cannabinoid receptor, **transient receptor potential vanilloid 1** (**TRPV1**)], followed by endogenous **cannabinoids** [or endocannabinoids, **anandamide** (**AEA**), and **2-arachidonoylglycerol** (**2-AG**)] and their regulatory metabolic and catabolic enzymes [**fatty acid amide hydrolase** (**FAAH**), **monoacylglycerol lipase** (**MAGL**), and others], the triad now known collectively as the endocannabinoid system (ECS) [1,2]. The ECS performs major regulatory **homeostatic** functions in the brain, skin, digestive tract, liver, cardiovascular system, genitourinary function, and even bone [1,3]. Various lifestyle factors including diet and aerobic activity affect the overall ECS function or '**endocannabinoid tone**', a function of the density of cannabinoid receptors, their functional status (upregulated or downregulated) and relative abundance or dearth of endocannabinoids (see [4] for an excellent review). Some have been sufficiently bold as to suggest that a clinical endocannabinoid deficiency underlies many human maladies producing pain and psychiatric disturbances [4,5]. Recently, numerous herbal agents and food plants beyond cannabis have been examined for their possible modulatory effects on the ECS. Perhaps it is appropriate to alter slightly the common adage to reflect, 'You are what you ingest', as perhaps there are many more lessons to be learned in the foraged forests and fields that may help to nurture human health.

Plants Affecting CB_1, the Psychoactive Cannabinoid Receptor

CB_1, the neuromodulatory cannabinoid receptor, was discovered in 1988 as a result of decades of research on tetrahydrocannabinol (THC), the primary psychoactive component of cannabis [6], and has proven to have a major homeostatic influence in the central nervous system (CNS), wherein it is the most abundant G-protein-coupled receptor (GPCR) [7], far exceeding those for the neurotransmitters that it modulates. A similar integral role is played in various other physiological systems throughout the body. The ECS functions have been characterized as, 'relax, eat, sleep, forget and protect' [8], but the list of systems it modulates increases each year with additional research discoveries.

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It has been a long-held belief that natural substances that affected CB_1 were limited to THC and a few other phytocannabinoids (cannabinol, Δ^8-THC, tetrahydrocannabivarin), but that situation has changed of late, as other plants that modulate the receptor deserve examination. In this era of **genetically modified organisms** (**GMOs**), experimentation has yielded transgenic *Pichia* spp. yeasts that express tetrahydrocannabinolic acid (THCA) synthase [9,10], the biosynthetic enzyme that catalyzes formation of THCA, the agent in cannabis that becomes THC upon heating and decarboxylation, and this effort may extend in the future to attempts to synthesize novel cannabinoids.

That notwithstanding, efforts have commenced to identify similar psychoactive molecules in other plants. One such effort pertained to *Salvia divinorum*, a psychoactive divinatory plant of Mexico that is smoked or ingested as a dissociative hallucinogen. This agent had previously tested negatively in a NovaScreen™ for neurotransmitter receptors [11]. Interestingly, although salvinorin A, the primary active molecule in the plant was negative for CB_1 activity, extracts of the whole leaves were positive [12] (Figure 1). Shortly after this report, salvinorin A was identified as a specific κ-opioid agonist [13]. Subsequent work demonstrated that this substance had a low CB_1 affinity and no effects on endocannabinoid degradation [14], and the next year salvinorin A was shown to interact with CB_1/κ-opioid receptor dimers [15], possibly indicating that the two systems might produce converging effects on the same pathway, and indicating that a complex relationship of *Salvia* to the ECS deserves to be more fully elucidated.

Another common foodstuff, the carrot, *Daucus carota*, contains falcarinol (carotatoxin), a natural pesticide and fungicide, in concentrations of 2 mg/kg [16], which covalently binds CB_1 (K_i = 594 nM) (Figure 1), acting as an inverse agonist, blocking AEA in keratinocytes, and producing contact dermatitis in the presence of histamine. The particular relevance of these findings remains to be determined and would include consideration of whether carrots pose a particular allergy risk or, whether, despite their high glycemic index, the CB_1 antagonism may suggest their use as an appetite suppressant if carotatoxin is even absorbed via the gastrointestinal tract.

Kava kava, *Piper methysticum*, the 'mystic pepper', is a convivial beverage of the South Pacific Islands derived from the plant's roots [17,18], whose active ingredients are lipid-soluble kavalactones. Dried rhizomes may be chewed or, alternatively, are extracted in water, sometimes with the addition of ethanol or acetone. Clinical studies have usually been performed with a standardized extract, WS1490. The kavalactones have been most closely associated with $GABA_B$ receptor activity affecting anxiety and muscle tone, but one major such component, yangonin, has recently demonstrated significant CB_1-binding activity (K_i = 729 nM, with 65.4% displacement of CP55940 at 10 μM, and 98.4% at 25 μM) [19] (Figure 1). Whether yangonin is a CB_1 agonist or antagonist is under current investigation. It demonstrated no significant binding at CB_2, and other kavalactones were inactive at both receptors. Given that yangonin has few off-target liabilities (COX-2 inhibition, 34% displacement only at a lofty concentration, 387 μM [20]), this component deserves additional study, especially since the fact that traditional preparation of kava may yield 250–1250 mg of yangonin per serving, which was thought to be pharmacologically relevant (Alessia Ligresti, 2014, personal communication). Certainly, additional study of selectively bred chemovars of kava with higher yangonin content is indicated, along with investigation of various extraction methods for greatest yield.

Another plant family yielding possible **cannabimimetic** CB_1 ligands are Japanese liverwort, *Radula perrottetii*, yielding the THC structural analog, perrottetinene [21], and the New Zealand liverwort, *Radula marginata*, yielding perrottetinenic acid [22] (Figure 1). These findings have spurred a spate of Internet 'trip reports' from amateur psychonauts variably documenting

Glossary

Adaptogen: a botanical agent that promotes homeostasis, alleviates fatigue, anxiety and distress, and improves everyday functions without producing prominent associated adverse events.
Allosteric modulator: an agent that binds to a separate site on a receptor than the main (orthosteric) site that alters its binding properties. The effect may increase (positive allosteric modulator, PAM) or decrease (negative allosteric modulator, NAM) binding properties.
Anandamide (arachidonylethanolamide, AEA): is an endogenous ligand for the CB_1 receptor, from *Ananda*, the Sanskrit word for 'bliss'.
2-Arachidonoylglycerol (2-AG): an endocannabinoid that is a full agonist at CB_1 and CB_2 receptors.
Cannabimimetic: a substance that mimics the effects of cannabis or a cannabinoid.
Cannabinoids: are of three types: phytocannabinoids are plant-based chemicals in cannabis and rarely in other plants, endocannabinoids are endogenous chemicals in chordates that bind cannabinoid receptors, while synthetic cannabinoids were developed to interact with these systems.
Cannabinoid receptors: G-protein-coupled receptors where one or another of THC, anandamide, and 2-AG bind. The best known are CB_1, the psychoactive, neuromodulatory, and analgesic receptor, and CB_2, an anti-inflammatory immunomodulatory receptor, but also TRPV1, the ionotropic cannabinoid receptor for capsaicin that regulates temperature and pain responses.
Cannabinoid tetrad: a set of four signs in animal experiments that a substance stimulates CB_1: hypomotility, catalepsy, analgesia, and hypothermia.
Desensitization: when the continued presence of an agonist at the receptor reduces its effects and functionally becomes an antagonist.
Endocannabinoid tone: the state of a person's ECS based on serum or tissue levels of AEA and 2-AG, density of cannabinoid receptors, and availability of FAAH and MAGL catabolic enzymatic activity.
Fatty acid amide hydrolase (FAAH): membrane-attached enzyme that cleaves AEA into ethanolamine

prominent psychoactive versus no effects after smoking these agents. However, recent additional research confirms CB_1 agonistic activity (Jürg Gertsch, 2016, personal communication) that, hopefully, will provide relevant context for the relative potency and possible therapeutic potential of this botanical agent.

An *N*-benzylamide from *Lepidium meyenii* (*vide infra*) bound CB_1 (K_i = 480 nM) (Figure 1) with no mention of functional effects; only additional research will indicate whether this finding holds pharmacological relevance. An *N*-methylbutanamide from *Heliopsis helianthoides* var. *scabra* was even more potent (K_i = 310 nM) with no observed effects on AEA uptake or FAAH inhibition [23], but once more the clinical applicability, if any, remains to be determined.

Cannabidiol and TRPV1 Agonists/Desensitizers and Mimics

Cannabidiol (CBD) is a nonintoxicating phytocannabinoid that, although it barely binds to CB_1 and CB_2 orthosteric sites [24], demonstrates the ability to antagonize those receptors even at low nM concentrations. This ability was recently attributed to its status as a negative **allosteric modulator** at CB_1 [25]. Although 'cannabinoid-like' compounds with anti-inflammatory activity were reported from flax (*Linum usitatissimum*) [26], CBD has not been definitively identified in other plants. CBD demonstrates a stunning number of other pharmacological targets of medical importance (reviewed in [27]), including its ability, shared with AEA, as a TRPV1 agonist [28] with an EC_{50} of 3.2–3.5 μM (Figure 2), very much in line with the archetypal substance, capsaicin from chili peppers (*Capsicum annuum*, *inter alia*) (Figure 2). TRPV1 agonism is a trait shared with other common foodstuffs, ginger (*Zingiber officinale*), black pepper (*Piper nigrum*), and the latex of the North African spurge (*Euphorbia resinifera*) (Figure 2) [29]. Ferruginene B, from the alpine *Rhododendron ferrugineum*, also showed weak TRPV1 activity (>20 μM) [30], likely precluding pharmacological relevance.

TRPV1 agonists fall into two classes, the pungent or caustic substances (capsaicin, piperine), and those that are nonirritating (CBD). While the former substances cause pain upon application, continued exposure to TRPV1 agonists cause conformational change in the receptor and a refractory state due to **desensitization** of the receptor, making them functional antagonists upon chronic application [31]. This tachyphylaxis or diminishing response after repetitive exposure represents a transition from an open to closed receptor state [32]. Ideally, a therapeutic agent of this class would not cause pain acutely, but would desensitize the receptor and display a favorable desensitization/irritancy ratio [33]. CBD seems to fit both criteria, inasmuch as, in addition to its potency, it desensitizes TRPV1 at 10 μM [28], potentially 'turning down the heat and pain' [29]. Possible therapeutic targets for CBD or similar agents would include: neuropathic pain (causalgia, complex regional pain syndrome, migraine), burns, irritable bladder, interstitial cystitis, prostatitis, chronic pelvic pain, fibromyalgia, inflammatory bowel disease, irritable bowel syndrome, pancreatic pain, and various dermatological pruritic conditions.

Cannabigerol, a Neglected Phytocannabinoid

Cannabigerol is a 'minor phytocannabinoid' whose precursor, cannabigerolic acid, is the parent compound to THC, CBD, and cannabichromene, prior to decarboxylation, but is normally present in cannabis in only trace amounts as it normally rapidly throughputs to the downstream substances [27]. It displays fascinating pharmacology in its own right, including GABA inhibition [34], antidepressant effects in rodents [35], prominent chemotherapeutic benefits [36], inhibition of keratinocyte proliferation [37], antibiotic effects including against MRSA [38], α-2 adrenergic agonism [39], AEA reuptake inhibition [40], and TRPM8 antagonism [41]. Whereas, research on and therapeutic application of this substance have been impeded by its forbidden status in some countries such as the USA because of its usual source, a possible alternative has been present for decades in *Helichrysum umbraculigerum*, a flowering plant of Southern Africa that produces

and arachidonic acid. Various compounds may inhibit FAAH and increase AEA levels, thus elevating 'endocannabinoid tone'.

Fructooligosaccharides (FOS): complex plant sugar polymers, the preferred feedstock for beneficial enteric bacteria.

Genetically modified organism (GMO): a plant or animal that has had its genetic code modified or that harbors DNA transferred from another organism.

Homeostasis: a state of natural physiological balance in which there is neither an excess nor deficit of activity.

Monoacylglycerol lipase (MAGL): enzyme that cleaves 2-AG. Inhibitors of its activity may enhance or prolong its effects.

Prebiotic: a plant food, usually rich in inulin and/or fructooligosaccharides, that promotes beneficial enteric bacteria.

Probiotic: a food (sauerkraut, yogurt, kefir) or dietary supplement that supplies beneficial bacteria (*Bifidobacteria*, *Lactobacilli*) to the colon.

Terpenoid: the most common plant chemicals. Monoterpenoids have 10 carbons, sesquiterpenoids 15, diterpenoids 20, triterpenoids, 30, and so on, often responsible for odor, taste, and medicinal effects.

Transient receptor potential vanilloid 1 (TRPV1): transmembrane receptor channel activated by heat, acid, ethanol, and AEA; the site where capsaicin, the piquant component of chili peppers is active.

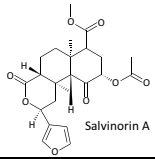
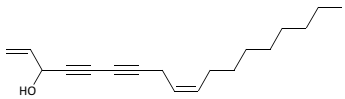
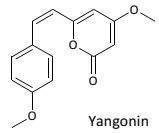
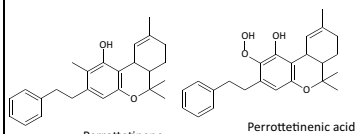
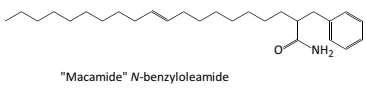
Salvia divinorum	 *Salvia divinorum*	Salvinorin A	 Salvinorin A
Daucus carota	 Carrot	Falcarinol (carotatoxin)	 Falcarinol
Piper methysticum	 Kava kava	Yangonin	 Yangonin
Radula marginata	 New Zealand liverwort	Perrottetinene Perrottetinenic Acid	 Perrottetinene Perrottetinenic acid
Lepidium meyenii	 Maca tuber  Powder	"Macamide" *N*-benzyloleamide	 "Macamide" *N*-benzyloleamide

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Figure 1. Plant-Based CB_1 Agonists. (All images: EBR, except maca tuber, courtesy Wikipedia: https://en.wikipedia.org/wiki/Lepidium_meyenii#/media/File:Maca.gif, public domain).

cannabigerol and cannabigerolic acid in its aerial parts [42]. This species was thus the first beyond cannabis demonstrated to harbor phytocannabinoids but, unfortunately, the original publication made no mention of relative concentrations. This issue is under current investigation. The entire genus merits additional research, as it harbors numerous unique phytochemicals [43], some of which are smoked by indigenous South African peoples [44], suggestive of psychopharmacological effects.

β-Caryophyllene, at once a Sesquiterpenoid and Phytocannabinoid

β-Caryophyllene is a sesquiterpenoid that is frequently the most abundant **terpenoid** in cannabis extracts [27] (Figure 3). It has been long known for its prominent anti-inflammatory properties on experimentally induced fibrosis comparable in potency to phenylbutazone [45], the nonsteroidal anti-inflammatory drug (NSAID) of equine medicine. Caryophyllene, in contrast to NSAIDs, is protective of the gastric lining [46]. Around a decade ago, it was observed that caryophyllene is a selective full agonist (100 nM) at CB_2 [47], whose dietary intake at as little as 4 mg/kg/day might render it an effective anti-inflammatory [48]. Other possible applications are legion, from pruritus in dermatitis [49], to fibrosis in the liver, heart, and other organs [50]. This potential is more likely considering the fact that this particular phytocannabinoid is widespread in plant kingdom essential oils (Figure 3), with balsams of *Copaiba* spp. (up to 53.3%) the richest source, but also including black pepper (*P. nigrum*) (up to 35%), lemon balm (*Melissa officinalis*) (up to 19.1%), cloves (*Syzygium aromaticum*) (up to 12.4%), and hops, the closest botanical relative of cannabis (*Humulus lupulus*) (up to 9.8%) [51].

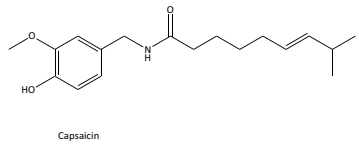
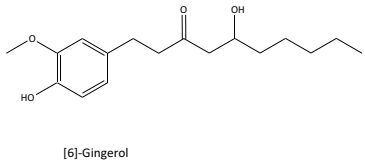
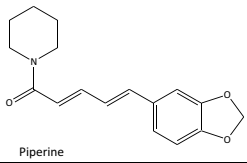
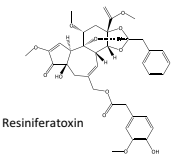
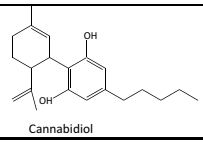
Capsicum annuum	 Chili peppers	Capsaicin	 Capsaicin
Zingiber officinale	 Ginger	Gingerol, zingerone	 [6]-Gingerol
Piper nigrum	 Black pepper	Piperine	 Piperine
Euphorbia resinifera	 Resin spurge	Resiniferatoxin	 Resiniferatoxin
Cannabis sativa	 CBD trichomes	Cannabidiol	 Cannabidiol

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Figure 2. Plant Sources of Transient Receptor Potential Vanilloid 1 (TRPV1) Agonists. (All images: EBR.).

Additional CB_2 Agents: *Echinacea* Alkamides and Others

Certain alkylamides ('alkamides') of *Echinacea* spp., used to treat the common cold and as overall immunity boosters, were observed to resemble the structures of AEA and 2-AG [52]. This prompted investigation of additional activities of these compounds, including an 11-fold induction of tumor necrosis factor-alpha (TNF-α), in human monocytes and macrophages while upregulating its mRNA expression at nM concentrations, mediated via CB_2, but yet inhibiting lipopolysaccharide (LPS)-stimulated TNF-α protein. The *Echinacea* alkamides also demonstrated CB_2 agonistic activity (that was blocked by SR144528), and the ability to modulate cyclic AMP. Overall, these dual immunomodulatory actions of the alkamides highlight their assignation as the 'active ingredients' of *Echinacea*.

Subsequent investigation has elucidated alkamide interaction at CB_2 [53], the ability to inhibit AEA reuptake *in vitro* [54], activity on peroxisome proliferator-activated receptor (PPAR)-γ, a nuclear receptor [55], as an anxiolytic effect in animal models [56], and partial and inverse agonist effects at CB_1 [57]. The latter activity could suggest possible benefits on metabolic syndrome, but also possible adverse event liabilities due to anxiety, depression, and other sequelae [58]. It is very possible that this Native American herbal agent will see much wider clinical application in the future as these remaining issues are sorted and addressed.

Initial reports claimed that epigallocatechin 4-gallate and (–)-epigallocatechin in green tea (*Camellia sinensis*) bound CB_2 at high concentrations [59], but this finding was subsequently challenged [60]. Ferruginene C, a mixture of isomers from *R. ferrugineum*, showed weak

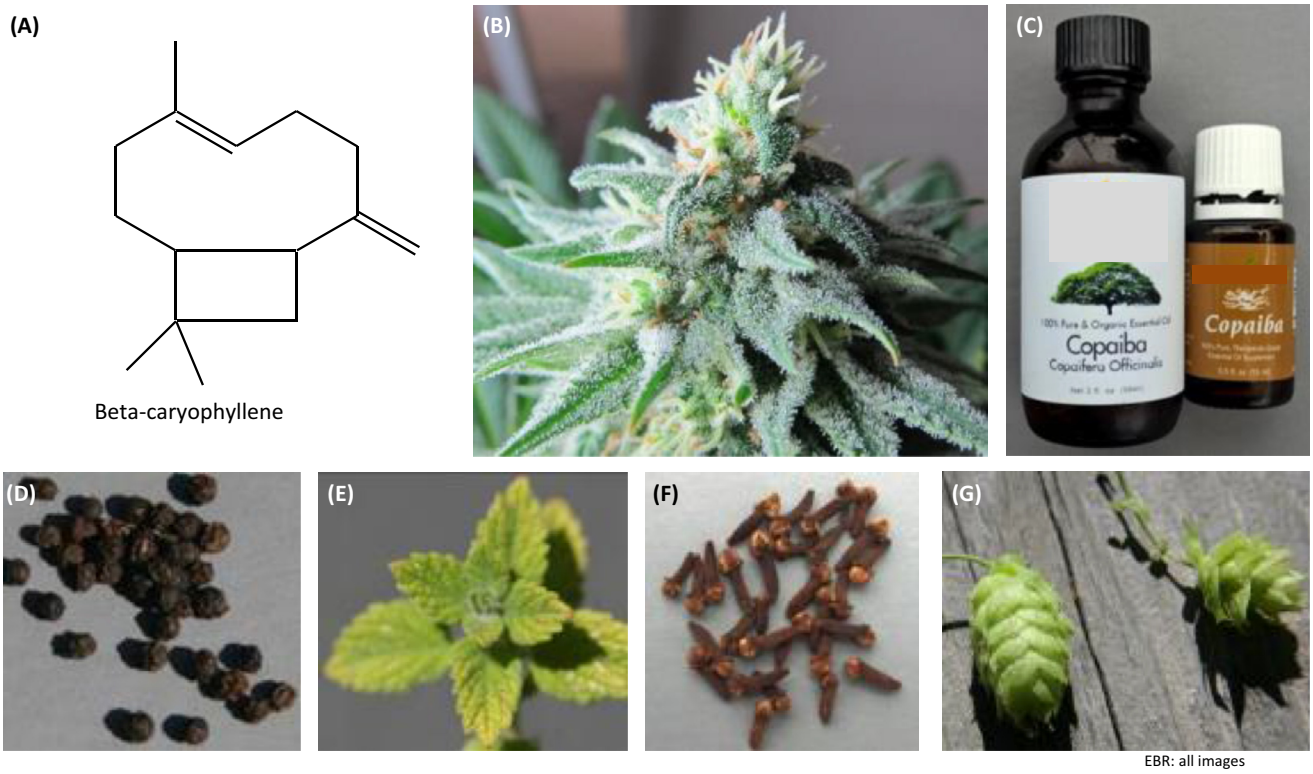


Figure 3. β-Caryophyllene, a CB_2 Agonist, and its Essential Oil Sources. (A) β-Caryophyllene molecule; (B) unfertilized female flower, *Cannabis sativa*; (C) copaiba balsam from *Copaifera officinalis*; (D) peppercorns, *Piper nigrum*; (E) lemon balm, *Melissa officinalis*; (F) cloves, *Syzygium aromaticum*; (G) hops, *Humulus lupulus*. (All images: EBR.).

CB_2 activity, and an IC_{50} of 13.7 μM for cytotoxic effects on HL-60 human promyelocytic leukemia cells [30].

Plant Inhibitors of Fatty Acid Amide Hydrolase

Kaempferia galanga, or galanga, is a relative of ginger, whose rhizomes produce a flavonoid, kaempferol, also found in apples, blackberries, and many other plants. Kaempferol was demonstrated to be an inhibitor of FAAH, the serine hydrolase that breaks down AEA (K_i = 5 μM) [61] (Figure 4). It is possible that a high dietary intake of this substance could boost serum AEA levels.

Maca (*L. meyenii*) is a radish relative and foodstuff of the high Andes, sometimes called 'Peruvian ginseng' for its use as an **adaptogen**, contains long-chain fatty acid *N*-benzylamides dubbed 'macamides' [62], two of which showed reversible FAAH inhibition at ~10 μM (Figure 4). It was conjectured that the structure of these natural compounds would allow passage through the blood–brain barrier and that despite their low potency, regular consumption could produce alterations in amide signaling in the CNS, but this remains to be determined. Similarly, an *N*-benzylamide of the same species was an FAAH inhibitor (IC_{50} = 4 μM) and inhibitor of AEA uptake (IC_{50} = 670 nM), characterized 'endocannabinoid substrate mimicking' [23]. A related *N*-methylbutanamide showed weak FAAH inhibition.

Contrary to popular belief, there are no endocannabinoids in chocolate, derived from *Theobroma cacao*, but it does contain *N*-linoleoylethanolamide and *N*-oleoylethanolamide [63], which do produce FAAH inhibition [64] (Figure 4).

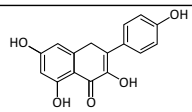
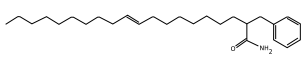
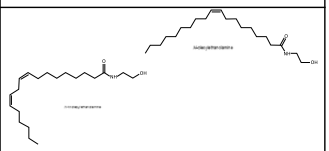
Kaemperia galanga	 Galangal	Kaempferol	 Kaempferol
Lepidium meyenii	 Maca root powder	Macamide	 "Macamide" *N*-Benzyloleamide
Theobroma cacao	  Chocolate	*N*-oleoyl-ethanolamine *N*-linoleyl-ethanolamine	

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Figure 4. Plant Sources of Fatty Acid Amide Hydrolase (FAAH) Inhibition. (All images: EBR.).

Prebiotics and Probiotics

Whereas bacteria are now considered to merit a taxonomic domain of their own, and are properly termed microbiota, rather than microflora, those that inhabit the human gut have an innate relationship to the ECS and, for this reason, the author would like to draw attention to the issue and how dietary plants may modulate their growth and effects.

Beneficial bacteria in the gut may be administered as oral supplements termed **probiotics**. One such strain, *Lactobacillus acidophilus* NCFM induced *CNR2* mRNA expression in human HT-29 epithelial cells ($P < 0.01$), along with pain relief in rats ($P < 0.001$) that was reduced by the CB_2 antagonist, AM-630 ($P < 0.001$) [65]. An analysis in humans of probiotics to treat irritable bowel syndrome showed benefit on symptoms in 34 out of 42 clinical trials [66]. Additional evidence of the relationship of the 'microbiome–gut–brain axis' is supported by the ability of THC to affect the Firmicutes:Bacteroidetes bacterial ratio ($P = 0.021$) and weight gain in rodents despite a high-fat diet [67]. Optimal maintenance of the enteric microbiome is enhanced by dietary intake or supplementation with **prebiotics**, species of vegetation rich in inulin and **fructooligosaccharides** (**FOS**), that resist gastric acid and stimulate health and growth of beneficial bacteria that utilize them as fermentation substrates [68]. Such vegetables, notably acacia fiber (gum Arabic), chicory root, burdock, sunchokes, dandelion greens, onions, garlic, and leeks (Figure 5), are reported to help prevent infectious diarrhea, reduce inflammatory bowel disease symptoms and cancer risk, increase mineral absorption, and decrease obesity [68]. A formal study of *Acacia senegal* fiber in 54 healthy volunteers over 4 weeks showed that 10 g/day intake was optimal to increasing Bifidobacteria counts 40-fold versus water ($P < 0.01$) and 10-fold over inulin ($P < 0.05$) [69]. Additionally, *Lactobacilli* were increased 6-fold versus water ($P < 0.05$) and 7-fold over inulin treatments ($P < 0.03$). The colonic pathogen, *Clostridium difficile*, was also significantly reduced ($P < 0.01$).

It is increasingly apparent that proper dietary choices encompassing prebiotic vegetables and fermented foods may play important roles in future therapeutics targeting the ECS.

Miscellaneous and Sundry Plants Affecting the ECS

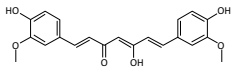
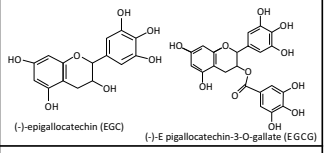
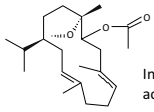
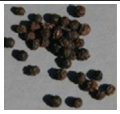
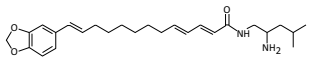
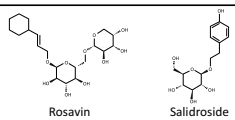
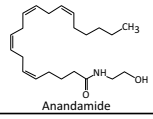
Another plant examined for possible cannabinoid activity was *Columnea ericae* (*Dalbergia picta*), a gesneriad epiphyte of the Amazon that the Siona–Secoya indigenous peoples smoke like tobacco [70] (Figure 6). The plant did display some serotonin 2A receptor activity, whereas none was seen at CB_1 [12].

Figure 5. Array of Prebiotic Plants. (A) Gum Arabic, *Acacia Senegal*, (B) Chicory root, *Cichorium intybus*, (C) Sunchokes (Jerusalem artichokes), *Helianthus tuberosus*, (D) Dandelion greens, *Taraxacum officinale*, (E) Burdock, *Arctium lappa*, (F) Leek, *Allium ampeloprasum*, Garlic, *Allium sativum*, and Onion, *Allium cepa.* (All images: EBR.).

Curcumin, a component of the common spice, turmeric, from *Curcuma longa*, was previously reported to be a high potency inverse agonist at CB_1 similar to the synthetic rimonabant (SR141716A) [71], but this paper was subsequently retracted [72]. This agent was re-examined [60], and found to bind only at very high μM concentrations (Figure 6), calling into question whether dietary intake would be sufficient to produce such an effect.

Some controversy surrounds the possible ECS activity of amyrins, pentacyclic triterpenes from *Protium heptaphyllum*. Initial reporting [73] indicated that 30 mg/kg doses reduced inflammation and hyperalgesia after mouse sciatic nerve ligation. Effects were said to be reversed by both CB_1 and CB_2 antagonists, although dissociation constants were discrepant, $K_i = 1989$ nM for CB_2 and $K_i = 0.133$ nM for CB_1, and no behavioral effects were apparent in the **cannabinoid tetrad**. Subsequent investigation by another very experienced group [74], in contrast, showed no binding at either receptor but, rather, a potent inhibition of 2-AG hydrolysis.

Frankincense, *Boswellia carterii*, displays properties in humans resembling those of cannabis (the cannabinoid tetrad of analgesia, hypothermia, catalepsy, hypomotility), as well as anti-inflammatory, antioxidant, and antiseptic effects [75]. Subsequent research demonstrated potent agonism of its component, incensole acetate, at TRPV3, producing feelings or warmth in skin and mind, anxiolytic and antidepressant effects, as well as c-Fos proto-oncogene activation [76], and nuclear factor kappa B (NF-κB) inhibition with neuroprotective effects after brain trauma in mice [77] (Figure 6).

Columnea ericae		Unknown	Unknown
Curcuma longa	 Turmeric	Curcumin	 Curcumin
Camellia sinensis	  Tea	Epigallocatechin (EGC) Epigallocatechin-3-O-gallate (EGCG)	 (-)-epigallocatechin (EGC) (-)-E pigallocatechin-3-O-gallate (EGCG)
Boswellia carterii	  Frank-incense	Incensole acetate	 Incensole acetate
Piper nigrum	 Black pepper	Guineensine	 Guineensine
Rhodiola rosea	 "Arctic root"	Rosavin salidroside	 Rosavin Salidroside
Tuber melanosporum	 Black truffle	Anandamide (AEA)	 Anandamide

Trends in Pharmacological Sciences

Figure 6. Miscellaneous Hits and Misses of Plants Affecting the Endocannabinoid System. (All images: EBR.).

Beyond caryophyllene and its CB_2 agonism, black pepper also modulates the ECS via the *n*-isobutylamide, guineensine [78] (Figure 6), which inhibited AEA uptake dose-dependently (EC_{50} = 290 nM) without significant effect on FAAH, MAGL, cannabinoid receptors, or fatty acid binding protein 5. It did display cannabimimetic effects in BALB/c mice at 2.5–10 mg/kg greater than placebo ($P < 0.001$), and with associated tetrad effects.

I have noted a great deal of overlap in the reported benefits of the popular adaptogen, *Rhodiola rosea*, in comparison to CBD, including increased alertness, decreased depression, anxiety, among others, suggesting it as a putative ECS modulator. Subsequent analysis [79], performed by Alessia Ligresti in 2014, failed to demonstrate significant CB_1 or CB_2 binding or displacement, nor FAAH inhibition of two alleged key components, rosavin and salidroside (Figure 6).

Finally, a recent investigation reported the presence of endocannabinoid biosynthetic and catabolic enzymes and AEA, but no 2-AG nor cannabinoid receptors, in black truffles, *Tuber melanosporum* [80] (Figure 6). The AEA concentration increased *pari passu* with development of melanin pigmentation in truffles, reaching a concentration of 300–400 nM that was thought to be sufficient to activate CB_1 and CB_2. Two implications, among many of this work, would be an explanation why truffles are so expensive and proof that fungi are more animal than plant. Vegans beware!

Levity aside, it is clear the endocannabinoids form but a subset of the *N*-acylethanolamines [81], widespread in plants, and that much remains to be learned concerning their possible pharmacological effects on cell signaling that may have important implications not only for plant growth and development but also for human health. The search continues.

Concluding Remarks

This review has briefly surveyed various components of the ECS and how they may be influenced by common foodstuffs and medicinal plants. Along with other lifestyle factors, such as aerobic exercise, dietary adaptations and supplementation may form important strategies to what has been aptly called 'the care and feeding of the endocannabinoid system' [4]. The investigation of other ECS-active plants should proceed (see Outstanding Questions), with research on especially promising candidates among the terpenoid-producing herbs and other plants bearing glandular trichomes, lipids, or latex. Candidate genera and families might include: *Salvia*, *Piper*, *Rutaceae* (citrus), *Radula* and other liverworts, *Helichrysum*, and *Zingiberaceae* (the greater Ginger family). Beyond surveys of direct activity on CB_1, CB_2, and TRPV1, focus should also extend to allosteric modulation of the receptors, FAAH and MAGL inhibition, and even possible modulatory effects on the putative endocannabinoid transporter molecules.

Since cannabis is such a reservoir of potentially therapeutic components it its own right [27], one might question the need to extend the search to other plants, but this would be short-sighted. Certainly, if common foodstuffs modulate the ECS, the how's and why's of these mechanisms deserve investigation so that their contributions and pitfalls may be clarified. Perhaps such research may reveal molecules that indicate additional cannabinoid receptor subtypes or that offer pharmacological advantage with fewer side effects, such as treating neuropathic pain without attendant psychoactivity, as could be realized by plants producing caryophyllene (*vide supra*).

Many important questions remain. Firstly, what took so long to discover the ECS and plants that affect it, and why are they so relatively rare to date? The factors are multiple, and the historical context is illuminating. Whereas morphine, an alkaloid, was first identified in 1806, despite the best efforts of many scientists, the true structures of THC and CBD were not discovered for another 150 years. Analogously, the endogenous opioid system, endorphins, and enkephalins (simple peptides) were discovered in the 1970s, while almost another two decades were required to identify the components and physiology of the endocannabinoids and other components of the ECS. In short, these 'sticky' lipophilic cannabinoids have been much more difficult to research, and it is only now, in the succeeding single generation, that attention has been turned towards plants beyond cannabis that may also modulate the system. For better or worse, pharmacological research is expensive, funding is elusive, and intellectual property issues dictate that companies would most often prefer to engineer a molecule *de novo* with a specific receptor target in mind rather than investigate natural compounds from a botanical that may be freely available in nature, and lack the possibility of patent protection. When the substances involved may also include potentially forbidden substances resembling THC, which are subject to regulatory scheduling, the barriers to research become greater still. One may wonder, however, how much additional time might have been required to discover the ECS were not cannabis there to lead the way. Despite its seeming ubiquity, and obvious importance as a homeostatic regulator of human physiology, the ECS topic receives short shrift in contemporary medical education, if mentioned at all. This educational deficit, born perhaps of lingering prejudice towards a plant called cannabis, must surely end soon, as it is contrary and detrimental to potential significant contributions to public health.

Barriers aside, this research on plants affecting the ECS portends to lead to important advances in endocannabinoid tone, as well as a better understanding of the complex stance of the

Outstanding Questions

Should plants that express CB_1 agonistic activity suffer legal scrutiny as potential drugs of abuse?

Can plant-based TRPV1 agonists and other dietary components desensitize the receptor and modulate pain syndromes and other disorders?

Should people with chronic pain or arthritis attempt to increase their dietary intake of beta-caryophyllene in an effort to treat their condition?

Can *Echinacea* be utilized to treat conditions beyond the common cold, such as autoimmune diseases or obesity/metabolic syndrome?

Can terpenoids in cannabis or from other sources act as positive or negative allosteric modulators at cannabinoid or other receptors? Can our diets significantly affect AEA and 2-AG levels, thereby increasing endocannabinoid tone?

Can dietary guidelines be developed to optimize ECS function? What is the role of probiotics in that effort? Of prebiotics?

Can prebiotics and probiotics be demonstrated to modulate serum and brain endocannabinoid levels?

Can adaptogens (e.g., *R. rosea*, *Panax ginseng*, *Eleuthero senticosus*, among others) be demonstrated to modulate the ECS with regular usage?

Can pigs or dogs identify AEA in the scent of truffles, and might this affect their enthusiasm for the hunt as they selectively seek it?

Do other darkly pigmented fungi (e.g., morels, *Morchella* spp.) also express anandamide during their growth?

Will other plant species yield valuable ECS modulators?

Can phytochemicals affect function of the putative anandamide transporter?

Will knowledge of the effects on the ECS of plants other than cannabis help temper polarized views on cannabis-based medicine?

ecological roles of phytochemicals and their interactions with our own biochemistry and pathophysiological mechanisms.

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