BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 160, 523–529

0007-1188/10
www.brjpharmacol.org

THEMED ISSUE: CANNABINOIDS

REVIEW

Phytocannabinoids beyond the *Cannabis* plant – do they exist?

Jürg Gertsch[1], Roger G Pertwee[2] and Vincenzo Di Marzo[3]

[1]*Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland,* [2]*School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK, and* [3]*Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, NA, Italy*

It is intriguing that during human cultural evolution man has detected plant natural products that appear to target key protein receptors of important physiological systems rather selectively. Plants containing such secondary metabolites usually belong to unique chemotaxa, induce potent pharmacological effects and have typically been used for recreational and medicinal purposes or as poisons. *Cannabis sativa* L. has a long history as a medicinal plant and was fundamental in the discovery of the endocannabinoid system. The major psychoactive *Cannabis* constituent Δ^9-tetrahydrocannabinol (Δ^9-THC) potently activates the G-protein-coupled cannabinoid receptor CB_1 and also modulates the cannabinoid receptor CB_2. In the last few years, several other non-cannabinoid plant constituents have been reported to bind to and functionally interact with CB receptors. Moreover, certain plant natural products, from both *Cannabis* and other plants, also target other proteins of the endocannabinoid system, such as hydrolytic enzymes that control endocannabinoid levels. In this commentary we summarize and critically discuss recent findings.
British Journal of Pharmacology (2010) **160,** 523–529; doi:10.1111/j.1476-5381.2010.00745.x
This article is part of a themed issue on Cannabinoids. To view the editorial for this themed issue visit http://dx.doi.org/10.1111/j.1476-5381.2010.00831.x

Keywords: phytocannabinoid; cannabinoid; plant natural products; *Cannabis*; endocannabinoid system

Abbreviations: CB_1, type-1 cannabinoid receptor; CB_2, type-2 cannabinoid receptor; CP55940, (–)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol; Δ^9-THC, Δ^9-tetrahydrocannabinol; DIM, 3,3′-diindolylmethane; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; FDA, US Food and Drug Administration; $G_{i/o}$, G-protein alpha subunit; GPR55, orphan receptor G-protein-coupled receptor 55; MAGL, monoacylglycerol lipase; NAEs, *N*-acylethanolamines; PPAR, peroxisome proliferator-activated protein; SR144528, (1S-endo)-5-(4-Chloro-3-methylphenyl)-1-((4-methylphenyl)methyl)-N-(1,3,3-trimethylbicyclo(2.2.1)hept-2-yl)-1H-pyrazole-3-carboxamide; SR141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride; Tmax, time to maximal concentration in plasma (pharmacokinetic parameter); TRPV1, transient receptor potential vanilloid-1 receptor; WIN55212-2, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphtaleneylmethanone

Today we perceive the endocannabinoid system (ECS) as a rather complex lipid signalling network in which different proteins play distinct roles in the control or in the modulation of numerous physiological and pathophysiological processes (Pertwee, 2005; Di Marzo, 2008). The ECS comprises classical cannabinoid receptors (CB_1 and CB_2), potentially also the orphan receptor GPR55, and arachidonic acid-derived ligands, which, however, also promiscuously target other receptors like, e.g. TRPV1 and PPAR-gamma (O'Sullivan, 2007; De Petrocellis and Di Marzo, 2010; Ross, 2009; Pertwee, 2010). Importantly, the enzymes degrading the endocannabinoids anandamide and 2-arachidonoyl glycerol, namely fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), have been shown to be promising therapeutic targets (Di Marzo, 2008). Finally, there appears to be an anandamide cellular reuptake mechanism that can be blocked by specific

Correspondence: Jürg Gertsch, Institute of Biochemistry and Molecular Medicine, Bühlstrasse 28, University of Bern, 3012 Bern, Switzerland. E-mail: gertsch@mci.unibe.ch
The molecular receptor nomenclature used throughout this commentary conforms to the BJP's Guide to Receptors and Channels (Alexander *et al.*, 2009).
Received 12 January 2010; revised 18 February 2010; accepted 23 February 2010

inhibitors (Di Marzo, 2008). Both cannabinoid receptor agonists and antagonists have actual or potential therapeutic applications (Di Marzo, 2008; Oesch and Gertsch, 2009; Pertwee, 2009). Cannabinoids are defined as the terpenophenolic constituents of *Cannabis sativa* L and until recently, the phenylterpenoid Δ^9-THC and some of its naturally occurring derivatives were the only plant natural products known to directly interact with cannabinoid receptors. However, in the last few years, several non-cannabinoid plant natural products have been reported to act as cannabinoid receptor ligands. This prompts us to define 'phytocannabinoids' as any plant-derived natural product capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids or both. Direct cannabinoid receptor ligands are compounds that show high binding affinities (in the lower nM range) for cannabinoid receptors and exert discrete functional effects (i.e. agonism, neutral antagonism or inverse agonism). By contrast, indirect ligands target either key proteins within the ECS that regulate tissue levels of endocannabinoids or allosteric sites on the CB_1 receptor. Certain plant natural products, including some cannabinoids, possess at least some of these properties. Given the often high variability of molecular pharmacological data obtained in different laboratories and the distinct degrees of scrutiny of the experimental setup, molecular pharmacological data on natural products should always be interpreted with care (Gertsch, 2009). For example, the availability of CB receptor KO mice provides a powerful means of investigating the actual cannabimimetic nature of a particular compound *in vivo*. This commentary focuses on natural products from medicinal and dietary plants which have been reported to interact with the ECS.

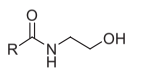
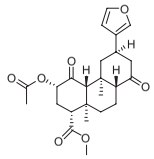
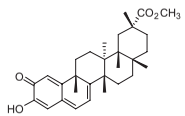
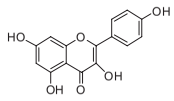
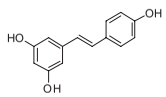
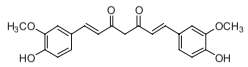
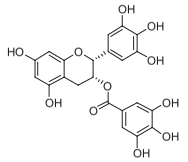
Fatty acid derivatives

Despite the fact that *N*-acylethanolamines (NAEs) (Table 1) from plants do not interact with CB receptors (plants do not generally produce arachidonic acid, which is the acyl scaffold favoured for CB interaction) they have been shown to inhibit FAAH, thus leading to an increase in endocannabinoid tone. *N*-linoleoylethanolamide and *N*-oleoylethanolamide, which are found not only in chocolate (*Theobroma cacao* L.) but also other plants (Di Marzo *et al*., 1998), and the widespread NAE palmitoylethanolamide, inhibit anandamide breakdown (Maurelli *et al*., 1995; Di Tomaso *et al*., 1996). Certain *N*-alkylamides (alkamides) from *Echinacea* spp. (Table 2) have been shown to interact functionally with the human CB_2 receptor with low nM to μM K_i values (Gertsch *et al*., 2006). These *N*-isobutylamides selectively act at the CB_2 receptor over the CB_1 receptor, leading to an increase in intracellular calcium which could be blocked by the selective CB_2 receptor inverse agonist SR144528, but they do not modulate the $G_{\alpha i}$ signalling pathway. Intriguingly, CB_2 receptor-binding *N*-alkylamides show similar anti-inflammatory effects as anandamide (e.g. inhibition of TNF-α) at low nM concentrations (Raduner *et al*., 2006). Certain *Echinacea N*-alkylamides inhibit anandamide reuptake *in vitro* (Chicca *et al*., 2009). Like anandamide, *N*-alkylamides also target PPAR-gamma (Spelman *et al*., 2009). Different *Echinacea N*-isobutylamides are orally bioavailable resulting in nM plasma levels in humans (Woelkart *et al*., 2008). The polyacetylenic polyyne falcarinol, which is found in different plants of the Apiaceae family (e.g. in carrots) shows significant binding interactions with both cannabinoid receptors, but appears to selectively undergo an alkylation reaction with the CB_1 receptor (K_i value <1 μM), leading to relatively potent inverse agonistic and pro-inflammatory effects in human skin (Leonti *et al*., 2010). Finally, it has been proposed that certain dietary fatty acids, which can also be found in plants, can modulate the ECS by influencing the availability of phospholipid biosynthetic precursors of endocannabinoids (Banni and Di Marzo, 2009).

Terpenes

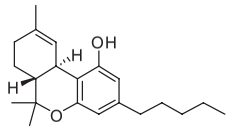
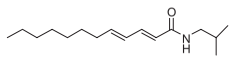
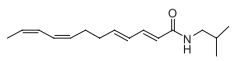
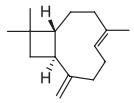
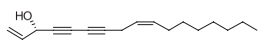
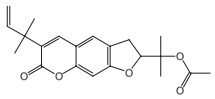
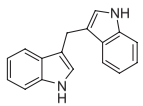
The bicyclic sesquiterpene, β-caryophyllene (trans-isomer) (Table 2), which is a plant volatile very frequently found in plants, has been shown to selectively target the CB_2 receptor at nM concentrations (K_i = 155 nM) and to act as a full agonist (Gertsch *et al*., 2008). Remarkably, β-caryophyllene is also a major compound in *Cannabis sativa* L. essential oil. Thus, *Cannabis* produces two entirely different chemical scaffolds able to differentially target CB receptors. While studies on the pharmacokinetics of β-caryophyllene are still ongoing, it is already clear that this cyclobutane-ring containing terpene is readily bioavailable, and, unlike many polyphenolic natural products, is not metabolized immediately but shows a Tmax >1 h after one single oral administration (J.G., unpublished data). Orally administed β-caryophyllene (<5 $mg \cdot kg^{-1}$) produces strong anti-inflammatory and analgesic effects in wild-type mice but not in CB_2 receptor knockout mice, which is a clear indication that it may be a functional CB_2 ligand. Ongoing studies show that β-caryophyllene is effective at reducing neuropathic pain in a CB_2 receptor-dependent manner (Zimmer *et al*., 2009). Therefore, the FDA approved food additive β-caryophyllene has the potential to become an attractive candidate for clinical trials targeting the CB_2 receptor (Gertsch, 2008). Interestingly, the diterpene salvinorin A from *Salvia divinorum* Epling & Jativa-M (Table 1) has been reported to be a selective high-affinity kappa-opioid receptor (KOP) agonist, but recent data also suggest that it may interact with a putative CB receptor/KOP heterodimer which may be formed during inflammatory conditions (Fichna *et al*., 2009). To date, binding experiments have shown that salvinorin A has very low affinity for homomeric cannabinoid receptors and does not inhibit endocannabinoid degradation (Capasso *et al*., 2008). Consequently, further research is needed to establish whether salvinorin A interacts with a putative cannabinoid/KOP heterodimeric receptor or whether the cannabimimetic effects reported are indirectly mediated via KOP. More recently, two naturally occurring quinonoid triterpenoids, pristimerin (Table 1) and euphol, were found to inhibit MAGL with high potency (IC_{50} = 93 nM and 315 nM respectively) through a reversible mechanism (King *et al*., 2009). As this class of triterpenes is relatively frequent in nature, it may not be unusual to find 'indirect' rather than 'direct' agonists of cannabinoid receptors among plant secondary metabolites. Several distinct triterpenes are known to modulate immune

Table 1 Plant natural products that have been suggested to exert cannabimimetic effects but do not interact directly with cannabinoid (CB) receptors

Structure	*Name*	*Origin*	*CB receptor affinity*	*Function*	In vivo *efficacy*	*Other targets (ECS)*	*References*
 R = linoleoyl; oleoyl; palmitoyl	*N*-acylethanolamines	Widespread in plants	No affinity	FAAH inhibitors Indirect cannabimimetics	Validated in CB_1 and CB_2 KO mice	GPR55	Maurelli *et al.*, 1995; Di Tomaso *et al.*, 1996; Di Marzo, 2008
	Salvinorin A	*Salvia divinorum* Epling & Jativa-M	Insignificant affinity to CB receptors	Indirect cannabimimetic effects at CB_1 (mechanism unknown)	No data	KOP agonist	Capasso *et al.*, 2008; Fichna *et al.*, 2009;
	Pristimerin	Relatively widespread in the Celastraceae	No data	Potent reversible MAGL inhibitor (IC_{50} value <100 nM)	No data	No data	King *et al.*, 2009
	Kaempferol	Widespread in plants	No affinity	FAAH inhibitor (IC_{50} value <1 μM)	No data	No data	Thors *et al.*, 2007; 2008
	Trans-resveratrol	Relatively widespread in plants (e.g. *Vitis vinifera* L.)	Insignificant affinity	Insignificant effects	No data	No data	Prather *et al.*, 2009
	Curcumin	*Curcuma* spp.	Insignificant affinity	Insignificant effects	No data	No data	Prather *et al.*, 2009
	Epigallocatechin-3-*O*-gallate	Relatively widespread in plants (e.g. *Camellia sinensis* L.)	Insignificant affinity	No data	No data	No data	Korte *et al.*, 2010

ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase.

Table 2 Plant natural products that have been shown to interact directly with cannabinoid (CB) receptors

Structure	*Name*	*Origin*	*CB receptor affinity*	*Function*	In vivo *efficacy*	*Other targets (ECS)*	*References*
	Δ^9-THC	*Cannabis sativa* L.	Non-selective CB_1 and CB_2 affinity (K_i values <50 nM) (human)	Parial agonist G_i/o Inhibition by SR141716 and SR144528	Validated in CB_1 and CB_2 KO mice	GPR55 PPARs Different ion channels	Mechoulam, 1986; Pertwee, 2006
	*N*-alkylamide	*Echinacea* spp.	Selective CB_2 affinity (K_i value <100 nM) (human)	Parial agonist $[Ca^{2+}]_i$ Inhibition by SR144528	No data	PPAR-γ Inhibition of AEA transport Partial FAAH inhibtion	Raduner *et al*., 2006; Chicca *et al*., 2009
	*N*-alkylamide	*Echinacea* spp.	Selective CB_2 affinity (K_i value <100 nM) (human)	Parial agonist $[Ca^{2+}]$ i Inhibition by SR144528	No data	PPAR-γ Inhibition of AEA transport Parial FAAH inhibition	Raduner *et al*., 2006; Chicca *et al*., 2009
	β-caryophyllene	Widespread in plants	Selective CB_2 affinity (K_i value <200 nM) (human)	Full agonist G_i/o $[Ca^{2+}]_i$	Validated in CB_2 KO mice	No data	Gertsch *et al*., 2008
	Falcarinol	Relatively widespread in Apiaceae (e.g. *Daucus carota* L.)	Non-selective CB_1 affinity (K_i value <1 μM) (human)	CB_1 receptor-selective inverse (covalent) agonist Inhibition of AEA/ WIN55212-2	No data	No data	Leonti *et al*., 2010
	Rutamarin	*Ruta graveolens* L.	Selective CB_2 affinity (K_i value <10 μM) (human)	No data	No data	No data	Rollinger *et al*., 2009
	DIM 3,3-diindolylmethane metabolite from indole-3-carbinol	Relatively widespread in the *Brassica* genus	Selective CB_2 affinity (K_i value ≅1 μM) (human)	Partial agonist at CB_2 receptor	No data	No data	Yin *et al*., 2009

Δ^9-THC is shown as the major phytocannabinoid from *Cannabis sativa* L. but there are several other structurally related cannabinoids that interact with CB receptors.
Δ^9-THC, Δ^9-tetrahydrocannabinol; DIM, 3,3′-diindolylmethane; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; PPAR, peroxisome proliferator-activated protein.

functions through yet unknown mechanisms (Rios, 2010) and it will thus be interesting to see in a more systematic study whether other similar triterpenoids are also able to inhibit MAGL.

Polyphenols

The dietary polyphenols trans-resveratrol and curcumin (Table 1) were reported to bind selectively to the human CB_1 cannabinoid receptor with low nM K_i values (5.9 nM and 45 nM respectively) and to exert potent pharmacological effects in mice similar to those induced by the CB_1 receptor inverse agonist rimonabant (Seely *et al*., 2009). Intrigued by this unexpected finding, our research groups independently measured the binding affinities of these compounds for CB_1 and CB_2 receptors in our laboratories. In our experiments, trans-resveratrol and curcumin only displaced [^{3}H]CP55 940 from cannabinoid receptors at high μM concentrations, suggesting that they lack significant affinity for these receptors. Also polydatin, a glycosilated form of resveratrol, was inactive in these binding assays. Recently, the senior author of the original report retracted the paper (Prather *et al*., 2009). Hence, neither trans-resveratrol nor curcumin interact functionally with the CB_1 receptor, despite the fact that these compounds appear to share the ability of the CB_1 receptor inverse agonist, rimonabant, to induce weight loss in mice.

More recently, catechin-derivatives were shown to bind to human cannabinoid receptors rather non-selectively at high μM concentrations (Korte *et al*., 2010). Among these, epigallocatechin 3-gallate and (-)-epigallocatechin (Table 1) were reported to bind to the CB_1 receptor with K_i values of 33.6 and 35.7 μM respectively. However, these K_i values may not be correct. For the calculation of the K_i values the Cheng-Prussof equation ($K_i = IC_{50}/1+([S]/K_d)$ was not applied correctly. The EC_{50} values used to calculate the K_i values were approximations as neither compound produced more than 60% radioligand displacement even at the highest concentration used. Catechins are very widespread plant secondary metabolites which may provide nutritional health benefits. The same group has recently reported similar CB_1 and CB_2 receptor K_i values for delphinidin and cyanidin, two hydrophilic anthocyanidins (Korte *et al*., 2009). In both reports, no functional data were shown. In our hands, flavonoid-type compounds (catechins, anthocyanidins, flavones) lead to negligible or very high K_i values, which likely reflect a nonspecific molecular denaturation of the protein surface rather than a functional binding interaction. Similar potentially artefactual effects would most likely be observed with other GPCRs.

Plant polyphenols, such as phenylpropanoids (e.g. epigallocatechin 3-*O*-gallate, curcumin, resveratrol) possess chemical scaffolds which at μM concentrations bind to protein targets *in vitro* with limited specificity. This is clearly reflected by numerous reports on protein binding interactions that such compounds undergo in the μM range (Anand *et al*., 2008; Bisht *et al*., 2009). At the macroscopic level, polyphenols (i.e. tannins) have been used to tan leather by denaturing of proteins, and at the microscopic level μM concentrations of polyphenols interact with multiple protein binding sites (via their hydroxyl groups) non-specifically and therefore such compounds score as frequent hitters *in vitro*. The great majority of established cannabinoid receptor ligands are highly lipophilic, which reflects the nature of the active site within cannabinoid receptors. Thus, hydrophilic polyphenols like catechins and anthocyanidins would clearly be atypical cannabinoid receptor ligands.

More interesting are findings that certain flavonoids inhibit fatty acid amide hydrolase (FAAH), which is the enzyme responsible for the breakdown of the endogenous CB receptor ligand anandamide (Thors *et al*., 2007; 2008). Both the isoflavonoid genistein and the flavonoids kaempferol (Table 1), 7-hydroxyflavone and 3,7-dihydroxyflavone have been shown to concentration-dependently inhibit anandamide hydrolysis in rat brain homogenates, albeit at relatively high concentrations (IC_{50} values between 2 and 10 μM). Nevertheless, the authors of these studies showed a preliminary structure-activity relationship with 7-hydroxyflavone being the most potent inhibitor (IC_{50} value <1 μM).

An abundant literature is devoted to mechanisms underlying the biological activity of plant polyphenols (Landis-Piwowar and Dou, 2008; Bisht *et al*., 2009). However, although most beneficial and potentially therapeutic effects of trans-resveratrol, curcumin, catechins and kaempferol-type flavonoids are typically detected in the low μM range *in vitro*, all such compounds show limited bioavailability and poor pharmacokinetics *in vivo* with reported plasma concentrations in the low nM range (DuPont *et al*., 2004; Garcea *et al*., 2004; Boocock *et al*., 2007).

Other plant natural products with binding affinity to the CB_2 receptor

Other plant natural products have been shown to bind weakly to the CB_2 receptor. These include the coumarin derivative rutamarin from the medicinal plant *Ruta graveolens* L. (Rollinger *et al*., 2009) and 3,3′-diindolylmethane (DIM) (Table 2), which is an anticarcinogenic metabolite generated by ingestion of indole-3-carbinol. Indole-3-carbinol is commonly found in *Brassica* vegetables. DIM has been shown to be a weak CB_2 receptor partial agonist (Yin *et al*., 2009).

Conclusions

There is no doubt that phytocannabinoids from *Cannabis* have greatly influenced research on the ECS and without the milestone discovery that Δ^9-THC is the main psychoactive principle (reviewed in Mechoulam, 1986) many of the subsequent discoveries in the field of cannabinoid research would probably not have been made. Furthermore, with the development of therapeutic *Cannabis* extracts, as with Sativex™, this plant is also likely to provide new pharmaceutical applications in the future. The question remains as to why *Cannabis sativa* L. appears to be the only plant that produces a metabolite (Δ^9-THC acid) that readily leads to its decarboxylation product Δ^9-THC, which is the most potent phytocannabinoid activator of the CB_1 receptor. Interestingly enough, while nature may have been rather parsimonious in its provision of botanical secondary metabolites that activate the

CB_1 receptor, there is an increasing number of plant-derived natural products reported to target the CB_2 receptor to varying degrees. Flavonoids, which belong to natural polyphenols that readily interact with proteins, may target some of the proteins within the ECS, such as FAAH. However, no convincing evidence has been provided that polyphenols modulate cannabinoid receptors with significant potency. The finding that certain triterpenes potently inhibit MAGL further adds to the repertoire of plant-produced 'indirect' cannabinoid receptor agonists. Although higher plants do not contain endocannabinoids and lack the classical G-protein-coupled cannabinoid receptors, they do express enzyme isoforms that resemble some of the enzymes known to be important in the processing of endocannabinoids (Shrestha *et al*., 2006). Plants produce fatty acid amides, some of which are able to inhibit the degradation of anandamide but do not generally bind with significant affinity to CB receptors (Gertsch *et al*., 2006; Di Marzo *et al*., 2007). At present, the only phytocannabinoid that has been discovered to also exist in plants other than *Cannabis* is β-caryophyllene, which is among the most abundant plant essential oil components. Although Δ^9-THC is a partial agonist at both CB_1 and CB_2 receptors, it has significant lower efficacy at the CB_2 receptor. Another phytocannabinoid, Δ^9-tetrahydrocannabivarin, has also recently been shown to be a CB_2 receptor partial agonist, but is also a CB_1 receptor antagonist (Bolognini *et al*., 2010). Therefore, β-caryophyllene, which is also one of the most abundant secondary metabolites in *Cannabis* essential oil, could be considered as a true CB_2 receptor-selective *Cannabis* constituent. During mammalian evolution contacts with 'direct' CB_2 receptor active plant metabolites like β-caryophyllene or 'indirect' cannabinoid receptor agonists (FAAH and MAGL inhibitors) in diet may have led to hitherto unrecognized physiological effects. Although it is tempting to believe that these compounds exert beneficial effects in humans, clinical evidence is lacking. Future studies will have to determine whether there are additional apparently nontoxic CB_2 receptor-selective ligands in plants other than *Cannabis* and whether they could in fact be exploited therapeutically.

Conflict of interest

The authors state no conflicts of interest.

References

Alexander SPH, Mathie A, Peters JA (2009). Guide to Receptors and Channels (GRAC), 4th edition. *Br J Pharmacol* **158** (Suppl. 1): S1–S254.

Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B *et al*. (2008). Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochem Pharmacol* **76**: S1590–S1611.

Banni S, Di Marzo V (2009). Effect of dietary fat on endocannabinoids and related mediators: Consequences on energy homeostasis, inflammation and mood. *Mol Nutr Food Res* **54**: S82–S92.

Bisht K, Wagner KH, Bulmer AC (2009). Curcumin, resveratrol and flavonoids as anti-inflammatory, cyto- and DNA-protective dietary compounds. *Toxicology* (doi:10.1016/j.tox.2009.11.008). (ahead of print).

Bolognini D, Costa B, Maione S, Comelli F, Marini P, Di Marzo V *et al*. (2010). The plant cannabinoid Δ9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *Br J Pharmacol* **160**: 677–687.

Boocock DJ, Patel KR, Faust GE, Normolle DP, Marczylo TH, Crowell JA *et al*. (2007). Quantitation of trans-resveratrol and detection of its metabolites in human plasma and urine by high performance liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci* **848**: S182–S187.

Capasso R, Borrelli F, Cascio MG, Aviello G, Huben K, Zjawiony JK *et al*. (2008). Inhibitory effect of salvinorin A, from Salvia divinorum, on ileitis-induced hypermotility: cross-talk between kappa-opioid and cannabinoid CB(1) receptors. *Br J Pharmacol* **155**: S681–S689.

Chicca A, Raduner S, Pellati F, Strompen T, Altmann KH, Schoop R *et al*. (2009). Synergistic immunomopharmacological effects of N-alkylamides in Echinacea purpurea herbal extracts. *Int Immunopharmacol* **9**: S850–S858.

De Petrocellis L, Di Marzo V (2010). Non-CB(1), Non-CB(2) receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol* **5**: 103–121.

Di Marzo V (2008). Targeting the endocannabinoid system: to enhance or reduce? *Nat Rev Drug Discov* **7**: S438–S455.

Di Marzo V, Sepe N, De Petrocellis L, Berger A, Crozier G, Fride E *et al*. (1998). Trick or treat from food endocannabinoids. *Nature* **396**: S636–S637.

Di Marzo V, Bisogno T, Petrocellis L (2007). Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol* **14**: S741–S756.

Di Tomaso E, Beltramo M, Piomelli D (1996). Brain cannabinoids in chocolate. *Nature* **382**: S677–S678.

DuPont MS, Day AJ, Bennett RN, Mellon FA, Kroon PA (2004). Absorption of kaempferol from endive, a source of kaempferol-3-glucuronide, in humans. *Eur J Clin Nutr* **58**: S947–S954.

Fichna J, Schicho R, Andrews CN, Bashashati M, Klompus M, McKay DM *et al*. (2009). Salvinorin A inhibits colonic transit and neurogenic ion transport in mice by activating kappa-opioid and cannabinoid receptors. *Neurogastroenterol Motil* **21**: S1326–Se128.

Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA *et al*. (2004). Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. *Br J Cancer* **90**: S1011–S1015.

Gertsch J (2008). Anti-inflammatory cannabinoids in diet: towards a better understanding of CB(2) receptor action? *Commun Integr Biol* **1**: S26–S28.

Gertsch J (2009). How scientific is the science in ethnopharmacology: historical perspectives and epistemiological problems. *J Ethnopharmacol* **122**: S177–S183.

Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ *et al*. (2008). Beta-caryophyllene is a dietary cannabinoid. *Proc Natl Acad Sci USA* **105**: S9099–S9104.

Gertsch J, Raduner S, Altmann KH (2006). New natural noncannabinoid ligands for cannabinoid type-2 (CB2) receptors. *J Recept Signal Transduct Res* **26**: S709–S730.

King AR, Dotsey EY, Lodola A, Jung KM, Ghomian A, Qiu Y *et al*. (2009). Discovery of potent and reversible monoacylglycerol lipase inhibitors. *Chem Biol* **16**: 1045–1052.

Korte G, Dreiseitel A, Schreier P, Oehme A, Locher A, Goeran H *et al*. (2009). An examination of anthocyanins' and anthocyanidins' affinity for cannabinoid receptors. *J Med Food* **12**: S1407–S1410.

Korte G, Dreiseitel A, Schreier P, Oehme A, Locher S, Geiger S *et al*. (2010). Tea catechins' affinity for human cannabinoid receptors. *Phytomedicine* **17**: S19–S22.

Landis-Piwowar KR, Dou QP (2008). Polyphenols: biological activities,

molecular targets, and the effect of methylation. *Curr Mol Pharmacol* **1**: S233–S243.

Leonti M, Casu L, Raduner S, Cottiglia F, Floris C, Altmann K-H *et al*. (2010). Falcarinol is a covalent cannabinoid CB1 receptor antagonist and induces pro-allergic effects in skin. *Biochem Pharmacol* (doi: 10.1016/j.bcp.2010.02.015). (accepted).

Maurelli S, Bisogno T, De Petrocellis L, Di Luccia A, Marino G, Di Marzo V (1995). Two novel classes of neuroactive fatty acid amides are substrates for mouse neuroblastoma 'anandamide amidohydrolase. *FEBS Lett* **377**: S82–S86.

Mechoulam R (1986). Interview with Prof. Raphael Mechoulam, codiscoverer of THC. Interview by Stanley Einstein. *Int J Addict* **21**: S579–S587.

O'Sullivan SE (2007). Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* **152**: 576–582.

Oesch S, Gertsch J (2009). Cannabis receptor ligands as potential anticancer agents – high hopes for new therapies? *J Pharm Pharmacol* **61**: S839–S853.

Pertwee RG (2005). The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids. *AAPS J* **7**: E625–E654.

Pertwee RG (2006). Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol* **147**: S163–S171.

Pertwee RG (2009). Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *Br J Pharmacol* **156**: S397–S411.

Pertwee RG (2010). Receptors targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr Med Chem* **17**: 1360–1381.

Prather PL, Seely KA, Levi MS (2009). Notice of retraction. *J Pharmacol Exp Ther* **331**: 1147.

Raduner S, Majewska A, Chen JZ, Xie XQ, Hamon J, Faller B *et al*. (2006). Alkylamides from Echinacea are a new class of cannabinomimetics. Cannabinoid type-2 receptor-dependent and –independent immunomodulatory effects. *J Biol Chem* **281**: S14192–S1S206.

Rios JL (2010). Effects of triterpenes on the immune system. *J Ethnopharmacol* **128**: 1–14.

Rollinger JM, Schuster D, Danzl B, Schwaiger S, Markt P, Schmidtke M *et al*. (2009). In silico fishing for rationalized ligand discovery exemplified on constituents of Ruta graveolens. *Planta Med* **75**: S195–S204.

Ross RA (2009). The enigmatic pharmacology of GPR55. *Trends Pharmacol Sci* **30**: S156–S163.

Seely KA, Levi MS, Prather PL (2009). The dietary polyphenols trans-resveratrol and curcumin selectively bind human CB1 cannabinoid receptors with nanomolar affinities and function as antagonists/inverse agonists. *J Pharmacol Exp Ther* **330**: S31–S39.

Shrestha R, Kim SC, Dyer JM, Dixon RA, Chapman KD (2006). Plant fatty acid (ethanol) amide hydrolases. *Biochim Biophys Acta* **1761**: S324–S334.

Spelman K, Iiams-Hauser K, Cech NB, Taylor EW, Smirnoff N, Wenner CA (2009). Role for PPARgamma in IL-2 inhibition in T cells by Echinacea-derived undeca-2E-ene-8,10-diynoic acid isobutylamide. *Int Immunopharmacol* **9**: S1260–S1264.

Thors L, Alajakku K, Fowler CJ (2007). The 'specific' tyrosine kinase inhibitor genistein inhibits the enzymic hydrolysis of anandamide: implications for anandamide uptake. *Br J Pharmacol* **150**: S951–S960.

Thors L, Belghiti M, Fowler CJ (2008). Inhibition of fatty acid amide hydrolase by kaempferol and related naturally occurring flavonoids. *Br J Pharmacol* **155**: S244–S252.

Woelkart K, Dittrich P, Beubler E, Pinl F, Schoop R, Suter A *et al*. (2008). Pharmacokinetics of the main alkamides after administration of three different Echinacea purpurea preparations in humans. *Planta Med* **74**: S651–S656.

Yin H, Chu A, Li W, Wang B, Shelton F, Otero F *et al*. (2009). Lipid G protein-coupled receptor ligand identification using beta-arrestin PathHunter assay. *J Biol Chem* **284**: S12328–S12338.

Zimmer A, Racz I, Klauke AL, Markert A, Gertsch J (2009). *Beta-caryophyllene, a phytocannabinoid acting on CB2 receptors*. IACM 5th Conference on cannabinoids in medicine, 2-3. October, Cologne, Germany.