Biomedicine & Pharmacotherapy 142 (2021) 111963

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

An overview on plants cannabinoids endorsed with cardiovascular effects

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ARTICLE INFO

Keywords:
Cannabinoids
Receptors
Cardiovascular diseases
Plants
Phytochemicals

ABSTRACT

Nowadays cardiovascular diseases (CVDs) are the major causes for the reduction of the quality of life. The endocannabinoid system is an attractive therapeutic target for the treatment of cardiovascular disorders due to its involvement in vasomotor control, cardiac contractility, blood pressure and vascular inflammation. Alteration in cannabinoid signalling can be often related to cardiotoxicity, circulatory shock, hypertension, and atherosclerosis. Plants have been the major sources of medicines until modern eras in which researchers are experiencing a rediscovery of natural compounds as novel therapeutics. One of the most versatile plant is *Cannabis sativa* L., containing phytocannabinoids that may play a role in the treatment of CVDs. The aim of this review is to collect and investigate several less studied plants rich in cannabinoid-like active compounds able to interact with cannabinoid system; these plants may play a pivotal role in the treatment of disorders related to the cardiovascular system.

1. Introduction

Nowadays Cardiovascular diseases (CVDs) including stroke, heart failure, peripheral arterial disease, and other cardiac and vascular conditions, constitute the leading cause of global mortality and the major responsible for the reduction of the life's quality. In 2017, CVDs caused an estimated 17.8 million deaths world-wide corresponding to 330 million years of life lost and 35.6 million years lived with disability [1]. The discovery of novel treatments is mandatory representing a great challenge in medicinal chemistry. Focusing the attention on target-based drug discovery, the investigation of novel drug targets closely involved in the regulation of cardiovascular system represents a well consolidated strategy for the identification of lead molecules against CVDs.

Plants are the major sources of medicines in the modern eras in which we are witnessing to the re-evaluation of natural compounds; in this scenario one of the most versatile plant belongs to the genus *Cannabis* such as *Cannabis sativa* L. Numerous physical, and emotional benefits have been attributed to this plant, but the physiological target remained unknown since the identification of endocannabinoid system (ECS), CB1 and CB2 receptors and their endogenous ligands namely *N*-arachidonoyl-ethanolamine (anandamide, NAE) and 2-Arachidonoyl-glycerol (2-AG) [2,3].

The most famous compound contained in *Cannabis* is Δ^9-THC, but this plant also contains many other non-psychoactive substances, including Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), Δ^9-tetrahydrocannabivarin (THCV), cannabivarin (CBV), cannabidivarin (CBDV) (Fig. 1) [4].

The CB1 receptor has been cloned in 1990 in Tom Bonner's laboratory from rats and lately in 1993 from humans. The cloning of CB2 receptors opened the era of an emerging powerful target for the pharmacotherapy [5–7].

The endocannabinoid system comprises the CB1 and the CB2 receptors belonging to the seven transmembrane domains GPCRs family coupled to $G_{i/o}$ dependent signalling pathways. They are variously distributed in the central nervous system (CNS), specifically in axons and pre-synaptic terminals, hippocampus, cortex, where they are implicated in the control of memory, sedation, hypothermia, hypotension, and pain sensation [8–10] (Fig. 2). The endocannabinoid system is also known to modulate anxiety and feeding behavior interacting with different ligands, as in the case of Hemopressin and RVD-hemopressin [11–13].

The CB1 receptor signalling is mostly due to G_i protein inducing a decrease in cAMP intracellular concentration by inhibiting adenylate-cyclase, however CB1 receptor activation may also led to adenylate

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https://doi.org/10.1016/j.biopha.2021.111963
Received 4 May 2021; Received in revised form 14 July 2021; Accepted 22 July 2021
Available online 28 July 2021

cyclase stimulation mediated by Gs. [14].

The CB2 receptor is highly expressed in immune cells, B-cells, natural killer cells, macrophage, monocytes, polymorphonucleate neutrophils, T8 and T4 cells, and brain and it's involved in inflammatory reactions, immune response and modulation of cytokine expression [10,14–17].

The endocannabinoid system also comprises arachidonic acid derivatives able to bind to TRPV1 and PPAR-γ over cannabinoid receptors, fatty acid amide hydrolases (FAAH) and monoacylglycerol lipase (MAGL) enzymes, which are involved in metabolism and reuptake mechanisms respectively [18–20].

Alteration in cannabinoid signalling can be often related to pathophysiological conditions, including cardiotoxicity, circulatory shock, hypertension and atherosclerosis, making the cannabinoid system an interesting target fot the management of CVDs [21–25].

N-arachidonoylethanolamine (AEA) binds CB1 receptors in low micromolar range, but it is also able to exert a cardiovascular regulation inducing a triphasic response, characterized by activation of TRPV1 ion channel receptors on vagal sensory nerves. This promotes a hypotensive effect in the heart transient drop called phase I, accompanied by bradycardia and decreased cardiac contractility [24,25]. A second phase (phase II) is characterized by the rise in blood pressure followed by prolonged hypotension (phase III) due to the stimulation of CBR1 CB2

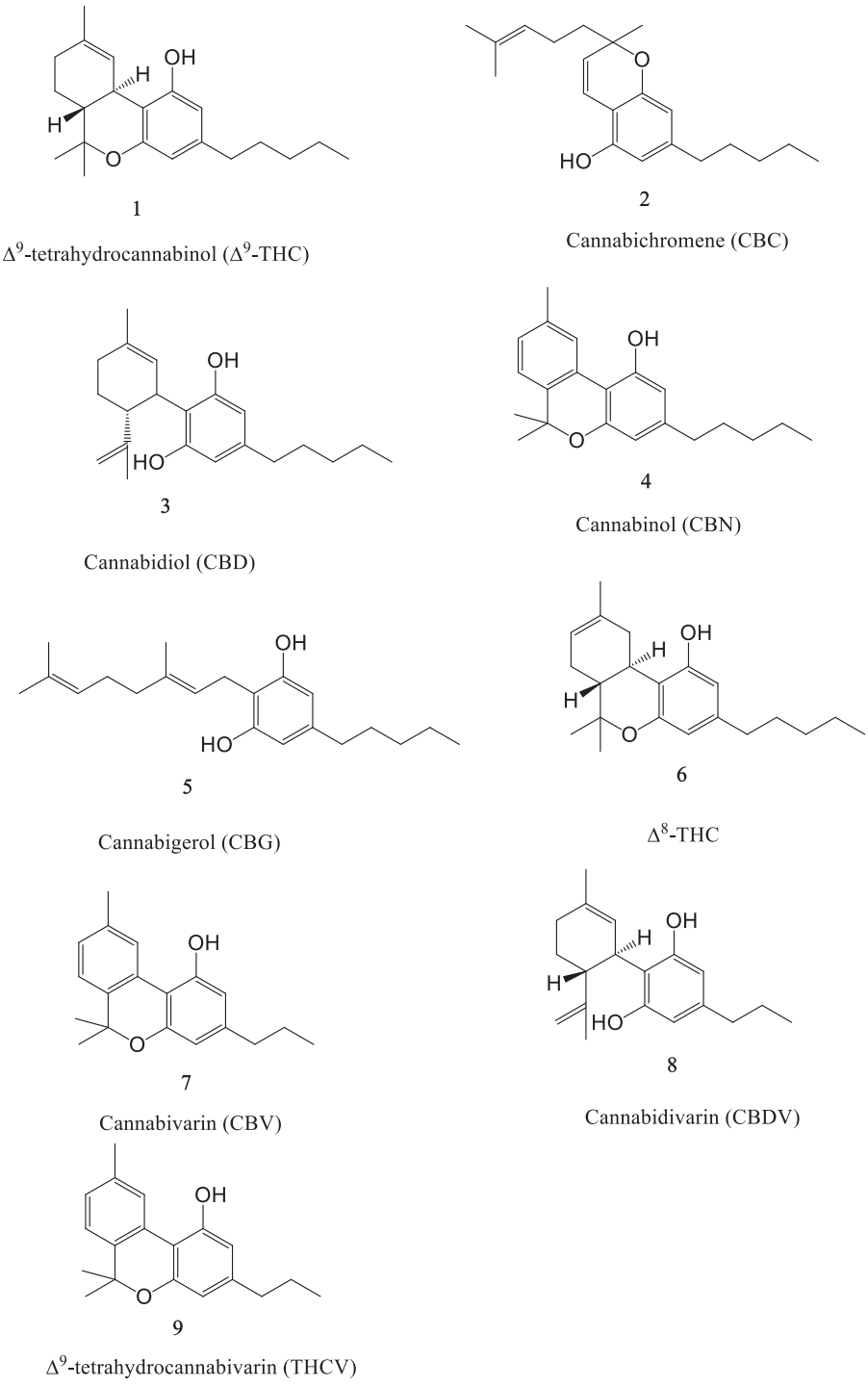


Fig. 1. The most relevant compounds found in *Cannabis sativa* L.

receptors are implicated in the adhesion, migration, proliferation, and function of immune cells during the process of atherosclerotic plaque formation [25–27].

Endogenous lipids with structural similarities to AEA may also produce vascular actions: *N*-arachidonoyl dopamine is a CB1 and TRPV1 receptors agonist able to provoke mesenteric vasorelaxation, while *N*-arachidonoyl serine is a vasorelaxant agent with no activity on CB or TRPV1 receptors [28,29].

The main involvement of endocannabinoid system in regulation of cardiovascular parameters suggests its pivotal role in the treatment of pathological hypertension, metabolic syndrome, heart failure, sepsis, stroke and atherosclerosis. More specifically, CB1 receptors mediate negative inotropy and activate vasodilatation in vascular tissues, while CB2 has implication in cardiovascular diseases, atherosclerosis, restenosis myocardial and cerebral ischaemia/reperfusion injury, justifying the importance of the endocannabinoid system as therapeutic novel target for the development of cardioprotective agents and natural remedies [30,31].

The aim of this review is to highlight several less studied plants beyond *Cannabis*, containing cannabinoid-like active compounds that interact with cannabinoid system, playing a pivotal role in the control of disorders related to the circulatory system.

2. *Otanthus maritimus L.*

Otanthus maritimus L. is an aromatic perennal herb of Mediterranean area and Ireland; it's part of the *Astraceae's* family and according to traditional medicine, it could be used for the treatment of toothache, asthmatic bronchitis, and urinary bladder inflammation [32]. Several scientific publications reported the characterization of umpteen constituents isolated from *O. Maritimus* L. which are responsible of various pharmacological effects as sesamine and sesamine like compounds, polyphenols, sesquiterpenic cyclic esters besides amides, thiophenamides, polyacetylenes sesquiterpene hydrocarbons mostly derived from the roots of the plant [33–35]. The aerial parts of the *O. maritimus* L. contain terpenoids, aliphatic esters, flavonoids sesquiterpene lactones, monoterpene diols, sesamine and sesamine like compounds [36–38], while the roots contain fatty acid amides and sesquiterpenes. Numerous compounds have been identified from *O. maritimus* L. essential oils as chrysanthenone, filifolone and α-pinene as anti-fungal agents [39].

O. maritimus. L. oil is able to inhibit the NO production stimulated by LPS in macrophages, without showing cytotoxicity, making it suitable for pharmaceutical purposes [33].

Ruiu and co-workers evaluated the binding affinity of the dichloromethane extract of *O. Maritimus* L. roots for the CB1 and CB2 receptors in order to isolate and identify the bioactive constituents (Fig. 3) [39,40].

According to their findings, the 1-[(2*E*,4*E*,8*Z*)-tetradecatrienoyl] piperidine (**11**) and two alkylamides (**12** and **13**) were the most potent binders of CB1 and CB2 receptors with a K_i value of 0.8 μM and 0.16 μM respectively for 1-[(2*E*,4*E*,8*Z*)-tetradecatrienoyl]piperidine (**11**) and a good binding affinity of 0.9 μM to CB2, 2.6 μM to CB1 and 0.55 μM to CB2 and 102 μM to CB1 for compounds **12** and **13** respectively (Fig. 3). The authors also identified a series of thienylheptatrienamides (**14–18**), among them compound piperidinyl-amide **16** contributed moderately to CB2 binding affinity of the extract, whereas all others were able to bind cannabinoid and opioid receptors with low affinity [39,40].

3. Kava kava (*Piper methysticum F.*)

Kava ("intoxicating pepper"; *Piper methysticum Forster*) is a perennial tropical shrub widely cultivated in the South Pacific Island Countries used as beverage in social ceremonies and in traditional medicine to treat convulsion, pain, headache menstrual problems, skin diseases [41].

In clinical trials, Kava demonstrated ansiolitic and ipotensive effects; it is effecacious in the treatment of stress and mood disorders compatibly to benzodiazepine (BZDs) and tricyclic antidepressants, showing reduced side effects when compared to them [41,42]. The sedative and anti-anxiety properties can be due to CYP3A4 in vitro inhibition [43–46].

The most relevant compounds isolated from Kava are kavalactones (lipid-soluble α-pyrones) including kavain, 7,8-dihydrokavain, methysticin, 7,8-dihydromethysticin, yangonin and desmethoxyyangonin (Fig. 4).

Several mechanisms of action of kava extract and kavalactones have been proposed; the major molecular target types identified and characterized are: α-aminobutyric acid (GABA) and benzodiazepine receptor sites voltage-gated Na^+ and Ca^{2+} ion channels, monoamine uptake and catabolism, and arachidonate cascade [46].

Alessia Ligresti and co-workers examined the ability of these kavalactones derivatives to activate CB1 and CB2 receptors comparing the results with THC and other synthetic analogues [47]; through three different bioassays they showed that yangonin is able to displace the

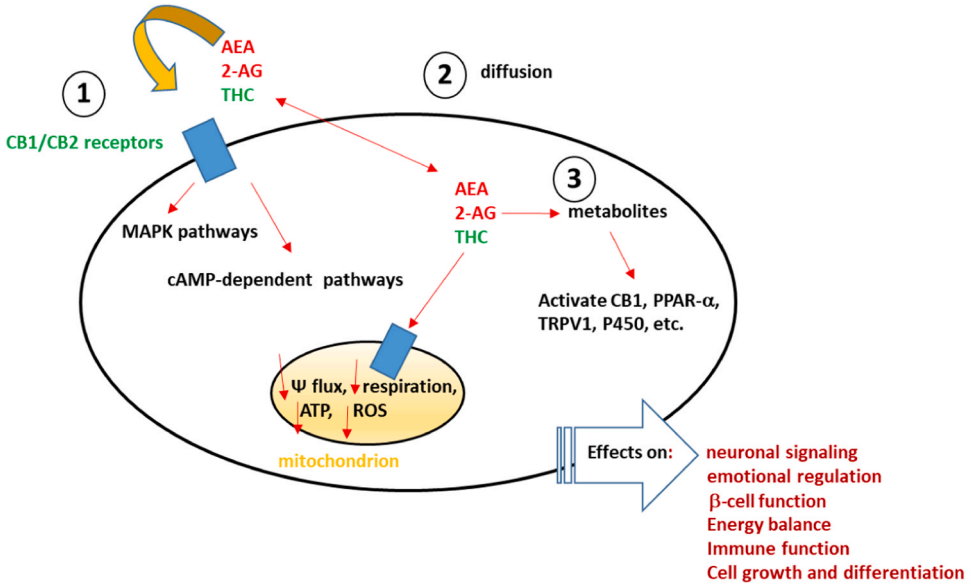
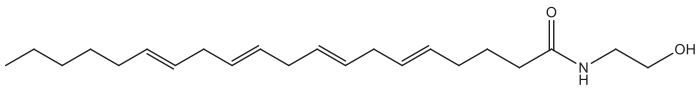


Fig. 2. Possible mechanisms of cannabinoid-like active compounds.



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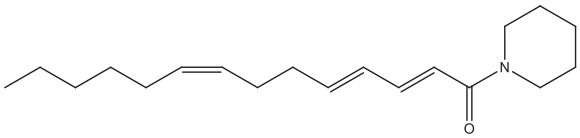
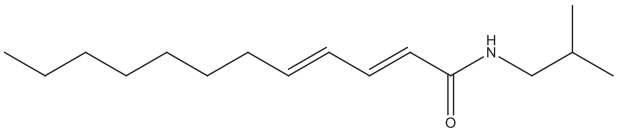


11

1-(2E,4E,8Z)-1-(piperidin-1-yl)tetradeca-2,4,8-trien-1-one(2*E*,4*E*,8Z)-1-(piperidin-1-yl)tetradeca-2,4,8-trien-1-one



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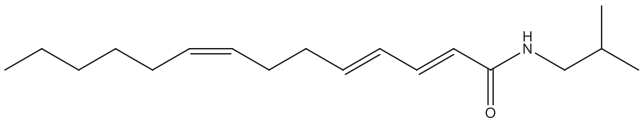
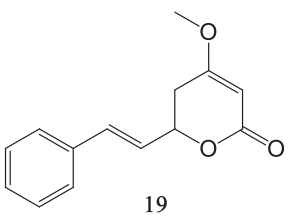
dodeca-2E,4E-dienoic acid isobutylamide(2*E*,4*E*)-N-isobutyldodeca-2,4-dienamide



13

tetradeca-2E,4E,8Z-trienoic acid isobutylamide

Fig. 3. Thienylheptatrienamides and other compounds found in *Otanthus Maritimus* L. dichloromethane extract.



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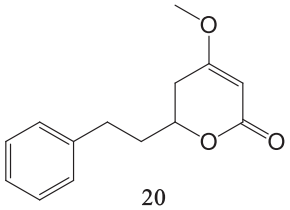
kavain



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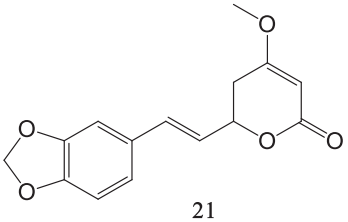
7,8-dihydrokavain



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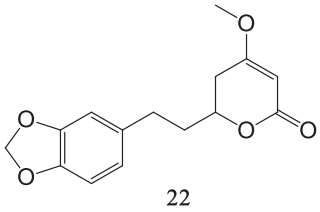
Methysticin



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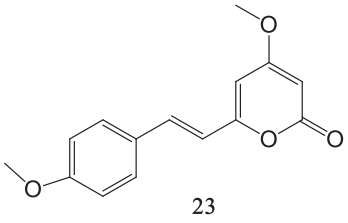
7,8 dihydro-methysticin



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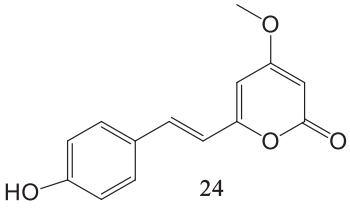
Yagonin



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Desmetoxy yagonin

Fig. 4. Most abundant Kavalactones in Kava.

reference radioligand, with a CB1 receptor affinity of $K_i = 0.72$ μM, 170 fold lower than THC, the main psychoactive constituent of *Cannabis* ($K_i = 0.0041$ μM) despite they didn't establish any interaction type (agonist or antagonist) with these receptors; the other compounds are weaker ligands at both receptors, and they are weak inhibitors of FAAH and MAGL enzymes. These results suggested that yagonin could interact with the endocannabinoid system in an effective way contributing to its physiological effects. Many non-kavalactone components have been also described for *P. methysticum*, among these cinnemaldehyde, cinnamic acid, capasaicin/piperidine and vannilins are secondary metabolites known to regulate the TRP channels [47].

The abundant use of kava may be related to weight loss, liver and renal dysfunctions, pulmonary hypertension, lymphocytopenia and decreasing in platelet volumes [48,49].

4. *Daucus carota L.*

Daucus carota (carrot) is a rich source of α- and β-carotene; a diet rich in carotenoid-containing fruits and vegetables is associated with a reduced risk of cancers.

Carrots also contain high concentration of falcarinol (FaOH), falcarindiol (FaDOH) and falcarindiol 3-acetate ($FaDOH_3Ac$). Falcarinol occurs in Apiaceae vegetables as *Daucus carota*, L. *parsley*, celery fennel and pastinake, it may also act as a moderate skin irritant, aggravating histamin-induced edema skin; its pro-allergenic activity seems to be linked to antagonistic action on CB1 receptors in keratinocytes, which prevents the anti-inflammatory action of anandamide. Falcarinol showed receptor affinity to both CB1 and CB2 with a CB1 antagonist profile [50] (Fig. 5).

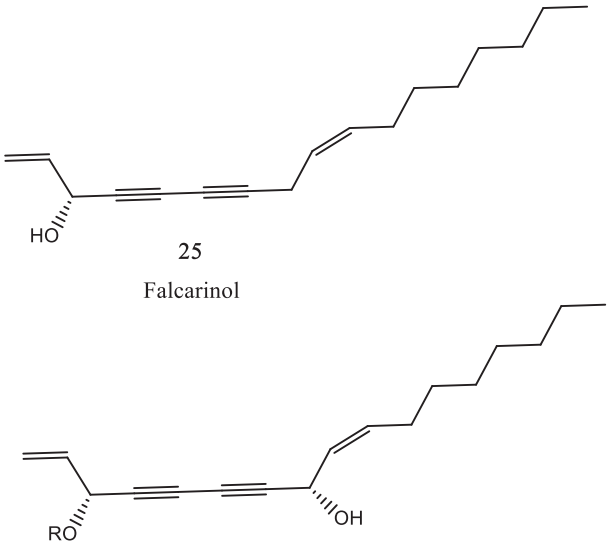
Natural polyacetylenes contain two or more triple bonds or alkynyl functional groups, among these the C17-polyacetylenes result unstable to light and/or high temperature, thus gentle techniques should be applied for successful chromatographic isolation of reference materials to study their bioactivity in cell-based assays or intervention studies [51, 52].

Falcarinol and Falcarindiol exhibit also anti-inflammatory and anti-platelet-aggregatory properties, falcarinol inhibits lipoxygenases and modulates prostaglandin catabolism by inhibiting 15-hydroxy-prostaglandin dehydrogenase. Moreover, these polyacetylenes possess anti-fungal, anti-inflammatory and anticancer activity, resulting cytotoxic against numerous cancer cell lines with cytotoxic activity towards human gastric adenocarcinoma (MK-1) cancer cells [53].

The antiproliferative effect of FaOH (Falcarinol), FaDOH (Falcarindiol) and FaDOH3Ac (Falcarindiol-3 acetate) on cancer cells is probably related to their ability to arrest the cell cycle progression at G2/M inducting apoptosis [53].

Leonti and co-workers analysed the binding affinities of pure falcarinol on CB1 and CB2 receptors, comparing the results with [^{3}H] CP55′940 (CB1 $K_i = 3.78 \pm 0.23$ mM; CB2 $K_i = 2.36 \pm 0.04$ mM); when tested using [^{3}H] anandamide as radioligand, the Ki values obtained were significantly and selectively lower for the CB1 receptor then CB2 receptor (CB1 $K_i = 594 \pm 37$ nM; CB2 $K_i = 2.1 \pm 0.16$ mM); the authors hypothesized a covalent interaction with CB1 receptor. Furthermore, they incubated falcarinol and rimonabant with CB1 receptor membrane preparations revealing a selective blocking of the anandamide binding site in the CB1 receptor. Falcarinol gave a response comparable to that of rimonabant to CB1, with approximately 100-fold weaker binding affinity, with an almost identical response curve shifted to the dextralateral side by two log units. Falcarinol also inhibited the effect of WIN55′212–2 at 5–20 mM concentration, thus providing further evidence of its antagonist activity on CB1 receptor [50].

Falcarinol may also act as a very weak partial agonist at the CB2 receptor via G_o or other signals not yet known, similarly to those of *N*-alkylamides from *Echinacea*.



25 Falcarinol

26 Falcarindiol, R= H

27 Falcarindiol 3-acetate, R= $COCH_3$

Fig. 5. Falcarinol and Falcarindiol derivatives chemical structures.

5. *Radula Perrottetii T.*

Liverworts belong to the bryophyte division, the first group to colonize the earth during the Cambrian period 543–490 million years ago and have been identified as a rich source of secondary metabolites, including indole alkaloids, terpenoids and flavonoids [54].

Radula genus contains bibenzyls type of secondary metabolite perrottetinene (PET), an analogue of Δ^9-THC. *Cis*-perrottetinene (*cis*-PET) has been isolated for the first time from *Radula Perrottetii*, *R. marginata* and later from *R. laxiramea* by Cullman and Becker, its structure was fully characterized and resulted to be quite similar to that of Δ^9-*trans*-THC [55–57].

Despite the similarity between *trans*-THC and *cis*-perrottetinene, only recently Chicca et al. reported a study on the in vitro and in vivo pharmacology of the natural *cis*-perrottetinene and the non-natural *trans*-perrottetinene [58], also comparing (−)-*cis*-perrottetinene and typical cannabinoids on CBR1 and CBR2 cannabinoid-like biochemical effects in animals (Fig. 6).

Cis-PET is a mild psychoactive cannabinoid, able to activate CB1 in high nanomolar range, while *trans*-PET is four time more potent than the *cis* analogue; both compounds activate CB2 with K_i values of 220 nM and 120 nM respectively resulting partial CB1 receptor agonists reaching 60–80% of the effect of full agonist CP55′940 in [^{35}S] GTPγS binding assays.

Cis-PET (EC_{50} 406 ± 175 nM) is less potent than Δ^9-*trans*-THC on CB1 receptor and less potent than *trans*-PET (EC_{50} 171 ± 116 nM), but showed similar EC_{50} value at CB2 compared with *cis*-PET. At CB2, *trans*-PET resulted less potent than *cis*-PET, revealing a stereochemical preference toward CB2 over CB1 binding when compared to the Δ^9-THC isomers. These compounds are inactive on FAAH and MAGL enzymes. *Cis*-PET and *trans*-PET showed cannabimimetic effect by producing hypothermic, catalepsic, hypo locomotor and analgesic effects at the doses of 50 mg/kg (*cis*-PET) and 40 mg/kg (*trans*-PET), after intraperitoneal injection *in vivo*; These effects are abolished by pre-treatment with rimonabant (CB1 antagonist) suggesting the stimulation of CB1 receptors located in the brain [59,60].

6. *Echinacea sp. M.*

Echinacea has a long history of medicinal use for a wide variety of conditions such as infections (viral and bacterial), syphilis, as an ‘‘antitoxin’’ for snakebites, pathological skin conditions (boils and abscesses). Traditionally Echinacea was used for nasopharyngeal catarrh, pyorrhoea, tonsillitis, influenza-like infections, recurrent infections of the respiratory tract and lower urinary tract [61].

Echinacea preparations are the most common herbal immunomodulators, mostly used for upper respiratory tract infections (URTIs) also due to the low toxicity of this herbal medicine, [62]; the most abundantly species are *Echinacea angustifolia*, *Echinacea purpurea* and *Echinacea pallida*.

Several class of compounds (alkamides, caffeic acid derivatives, polysaccharides and polyenes) are considered responsible for the activity of *Echinacea*. In particular alkamides are bioavailable after oral administration in humans, whereas caffeic acid derivatives don’t contribute to its activity [63].

Alkylamides as dodeca-2E,4E-dienoic acid isobutylamide and dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide were found to be the principal bioactive compounds of *E. purpurea* and *E. angustifolia* extracts [63].

These lipide-like compounds bind the human CB2 receptors, acting

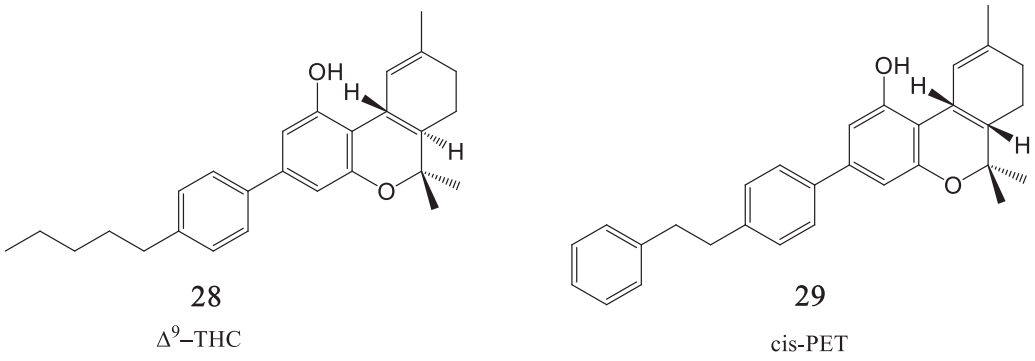


Fig. 6. Structural analogies between Δ^9-THC and *cis*-PET.

as full agonists with more selectivity for CB2 (57 and 60 nM respectively for compounds **30** and **31**) compared to CB1 receptors. The alkylamides **30** and **31** also show lower affinity to the CB1 receptor at 30–100 times higher concentrations (K_i >1500 nM), while compound **32** completely lost the CB2 affinity (Fig. 7). Alkylamides also inhibited FAAH thus enhancing the activity of CB1 and CB2 ligands [60].

Alkamides possess antioxidant effect on Cu^{II} containing oxidases of human low-density lipoprotein (LDL), with synergistic antioxidant effect in combination with other alkylamides [64].

These compounds possess antithrombotic activities due to the anti-coagulant effect by monitoring activated partial thromboplastin time (aPTT), prothrombin time (PT) and cell-based thrombin and activated factor X (FXa) [62].

Alkamides could modulate TNF-α^2 expression in human monocytes and macrophages, probably due to the interaction of alkylamides with the CB2 on monocytes, resulting in the activation of *c*-Jun *N*-terminal kinase, mitogen-activated protein kinase, and nuclear factor B (NF-B), which leads to the expression of TNF-α^2 mRNA (Fig. 8). Anandamide is more able to bind these receptors, probably due to its ability to assume a curved/U-shaped conformation which allows to interact efficaciously with CB1 receptor. Moreover, alkylamides binding CB2 elevated total Ca^{2+} concentration in promyelocytic HL60 cells and in receptor-transfected Chinese hamster ovary cells [65].

Woelkart et al. identified and isolated twelve alkamides and tested their affinity towards CB1 and CB2 receptors (Fig. 8) [66].

They showed that compounds **45** and **46** were the most active on CB1 receptor (K_i 2.0 μM and 4.1 μM) and compound **34** resulted the most active on CB2 (K_i 1.9 μM). The authors also asserted that alkylamides are sensible to hydrolysis by serine-proteases, taking in consideration that the binding efficacy toward CBRs is superior if co-administered with a protease inhibitor. For alkylamides was noticed only a weak inhibitory activity on FAAH, which could prolong the endocannabinoid activity and could enhance endogenous cannabinergic signalling by preventing the anandamide metabolism. [63].

7. *Protium heptaphyllum B.*

Protium heptaphyllum B. is a tree belonging to the *Burseraceae* family producing an aromatic resin with pharmacological activities in nervous, immunological systems and gastrointestinal tract. It was used in folk medicine as an analgesic and anti-inflammatory agent, its expectorant activity mostly due to the *Protium heptaphyllum B*. oil composition, that has received special attention because of its chemical composition and possible pharmacological activities [67].

This species, as well as other members of the family of *Burseraceae*, exudes an oily resin called breu-branco from the trunk. The resin is chemically composed of a mixture of triterpenes from the α-amyrin (ursane) and β-amyrin (oleane) series and an essential oil rich in mono- and sesquiterpenes. These triterpenes were also found in *Cassia obtusifolia*, *Byrsonima crassifolia*, *Amphipterygium adstringens* and *Eucalyptus globus* [68,69].

The *Protium heptaphyllum* resin is rich in triterpenes, such as α-amyrin and β-amyrin (Fig. 9) that posses anxiolytic, antidepressant and anti-inflammatory effect in acute models of inflammation and

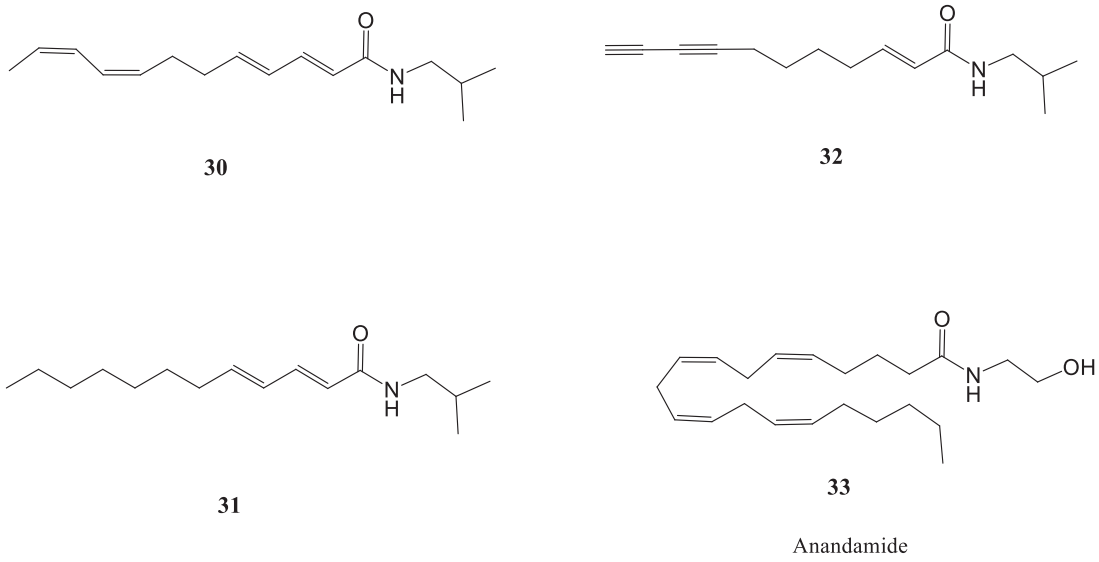
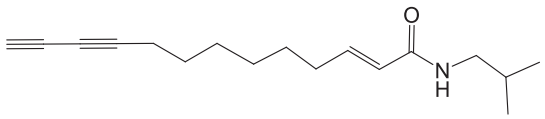
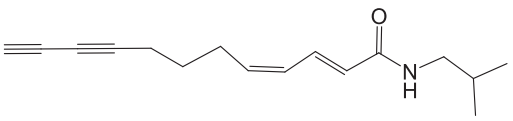


Fig. 7. Alkamides from Echinacea.



34

Tetradeca-2*E*-ene-10,12-diynoic isobutylamide



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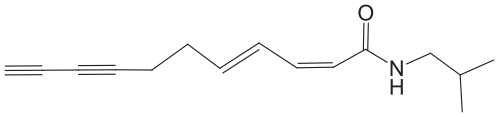

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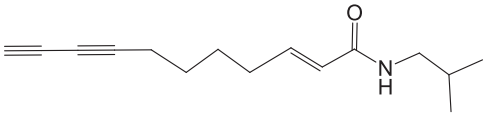
Undeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamides



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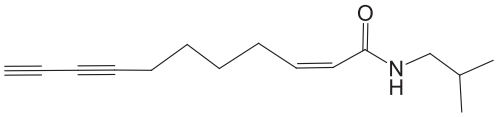

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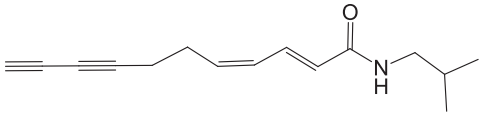
Undeca-2E/Z-ene-8,10-diynoic acid isobutylamides



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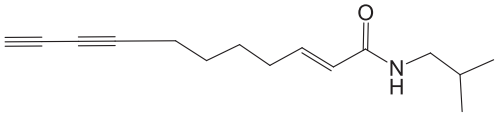
Dodeca-2E,4Z-diene-8,10-diynoic acid isobutylamides



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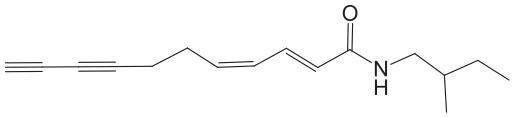
Undeca-2E/Z-ene-8,10-diynoic acid isobutylamides



41

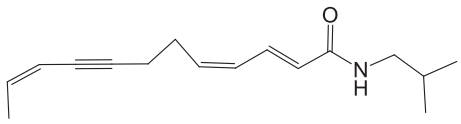
Undeca-2E/Z-ene-8,10-diynoic acid isobutylamides

Fig. 8. Other alkamides from Echinacea.

analgesic activity when administered at peripheral spinal and supraspinal site in acute nociception models [67,68].

Moreover, Aragaó and coworkers demonstrated the antiplatelet activity of α- and β-amyrin isolated from *P. Heptaphyllum* in a concentration dependent manner in comparison to ADP, collagen and arachidonic acid [70–72].

Chicca et al. analysed the cannabinomimetic activity of α/β-amyrin (**47–48**) on cannabinoid receptors, also considering possible indirect effect on cannabinoid system showing that compound **48** slightly induced the displacement of cannabinoid agonist from the CB1 receptors, while **47** inhibited radioligand binding only at high concentration, assessing that both α/β-amyrin were only weak cannabinoid



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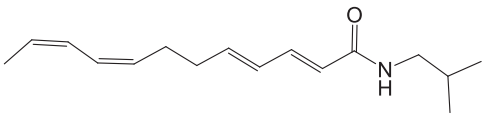
Dodeca-2E,4Z,10Z-triene-8-ynoic acid isobutylamide



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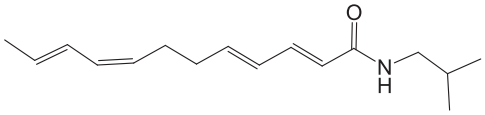

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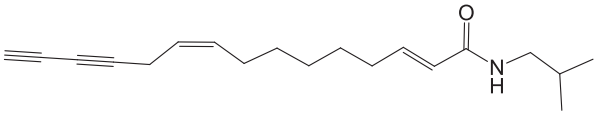
Dodeca-2E,4Z,8Z,10E/Z-tetraenoic acid isobutylamides



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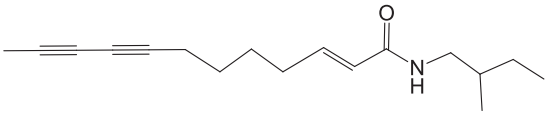
Pentadeca-2E,9Z-diene-12,14-diynoic acid isobutylamides



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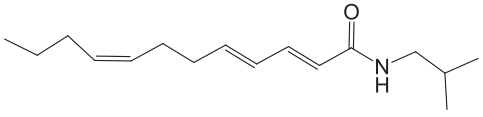
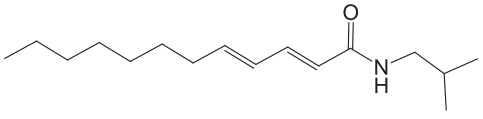
Dodeca-2E-ene-8,10-diynoic acid isobutylamide



47

Dodeca-2E,4Z-8Z-trienoic acid isobutylamide



48

Undeca-2E,4E-dienoic acid isobutylamide

Fig. 8. (*continued*).

ligands; they also evaluated the effects of both isomers on MAGL finding out that both compounds are inhibitors in nanomolar range, with 35–40% inhibitory activity [73].

This interaction has been also demonstrated by Simão da Silva et al. showing that α/β-amyrin bind both CB receptors with very high affinity (Ki= 0.133 nM on CB1 and Ki= 1989 nM on CB2 receptors) without provoking behavioral changes [74].

8. *Magnolia officinalis R. W.*

The bark of *Magnolia officinalis* is widely used in traditional Chinese and Japanese herbal medicine for the treatment of anxiety, sleep-related

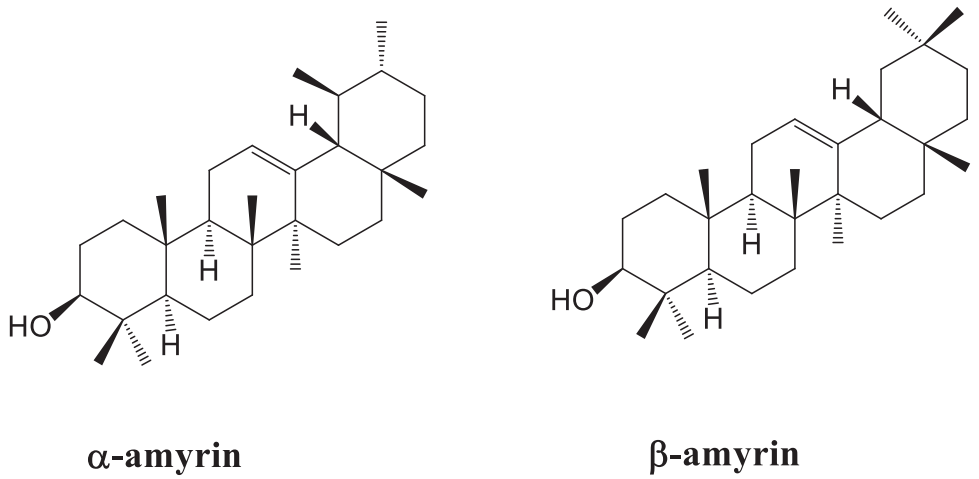


Fig. 9. Structure of α-amyrin and β-amyrin .

problems and allergic diseases. Among the compounds found in Magnolia extract, neo-lignans are the most interesting possessing a striking analogy to the effects described for cannabinoid ligands. Lignans and neolignans are a large group of natural phenols, spread within the plant kingdom.

They are characterized by a dimeric structure formed by a β,β′-linkage between two phenyl propane units with a different degree of oxidation in the side-chains and a different substitution pattern in the aromatic moieties [75] (Fig. 10).

Honokiol possesses anti-atherogenic potential, anti-platelet, and blood pressure reducing power. Honokiol inhibited collagen stimulated platelet aggregation in rats, acting as a potent antagonist of collagen GP VI in human platelets, showing a potential therapeutic power for the prevention of thrombosis [76,77]. Magnolol demonstrated antiplatelet and antithrombotic activities modulated by enhancing the activity and intracellular level of PPAR-β/γ in platelets [78,79].

Rempel and co-workers analysed the ability of the major Magnolia's lignans honokiol and magnolol (Fig. 10) and their metabolites to bind to CB receptors; honokiol acted as CB1 agonist and CB2 antagonist and magnolol as a partial agonist at both receptors with a preference for CB2. They also analysed magnolol main metabolites *trans*-isomagnolol and tetrahydromagnolol, which are selective CB2 partial agonists. The main metabolite of magnolol, tetrahydromagnolol resulted a more potent CB2 partial agonist than the parent compound with CB2 selectivity [80].

Moreover magnolia extract related neolignan compounds and magnolol metabolites, were investigated for the first time at the CB-like GPR55 using β-arrestin translocation; tetrahydromagnolol exerted moderately potent GPR55 antagonism (K_b = 13.3 μM) [80].

Toxicological studies revealed that chronic treatment with the methanol extract of *M. Officinalis* reduced the clinical parameters related to kidney functions as serum creatinine, urea nitrogen and serum albumin, in the trated mice [81].

9. *Tuber Melanosporum V.* (Black Truffles)

Truffles were prized by ancient Greeks and Romans as an.

The fame of black truffle is due to its leading role in legendary banquet in 20 A.D.; this subterranean fungal belongs to the genus Ascomycota and it is in great demand by the food market in many countries because of its unique taste and smell, resulting from a blend of hundreds of volatile compounds responsible of their major gastronomic and commercial value. The black truffle contain calcium, iron, rhamnose and high levels of melanin as well as eumelanin and phaeomelanins [82].

Pucci *et al.*, demonstrated that anandamide dose-dependently stimulated melanin synthesis and enhanced tyrosinase gene expression and activity in normal human epidermal [83].

Other studies revealed the presence of ECS components for both AEA and 2-AG metabolism in truffles; moreover they have a high NAPE-PLD to FAAH *ratio* and a low DAGL to MAGL *ratio*, notifiable by a well-detectable content of AEA but not of 2-AG indicating that truffles produce AEA without expressing the major eCBs-binding receptors [84]. AEA pathways is linked to vasorelaxation through activation of CB1 and CB2 receptors, TRPV1, rapresenting a valid approach for CVDs [26], furthermore AEA turned out to overcome the vasocontriction and the vessel damage provoked by ET-1 by mediating vasodilatation [85].

10. *Lepidium meyenii W.* (Peruvian Maca)

Lepidium meyenii (maca) is a Peruvian plant belonging to the brassica family and *Lepidium* genus, used for its nutritional properties, as Maca chichi, a sweet-fermented beverage that enhances fertility in animals and humans. Maca is traditionally consumed after boiling and no toxic effect has been related to ingestion of this plant; the boiling process seems to increase active metabolites and the availability of secondary metabolites. Several works reported that aqueous extract of maca is only effective after boiling pulverized maca hypocotyls while the ethyl acetate fraction of the hydroalcoholic extract of black maca influenced spermatogenesis [86]. Maca reduced the IL-6 level, a phenomenon associated with low systolic blood pressure and healthy [87].

Maca is reported to be helpful for reproductive function as nutraceutical supplement, it improves sexual behaviour in mice and rats, also increasing sperm count and sperm motility.

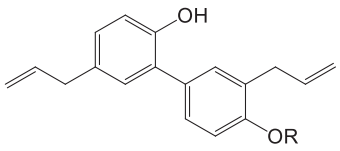
Recently was described an effect on prostate size and an improvement in sexual behaviour in experimental animals. Maca has been used as laxative for the treatment of rheumatism, respiratory problems, premenstrual discomfort, and menopausal symptoms [88]; it stimulates metabolism, improves memory and combats depression, anaemia, leukaemia, AIDS, cancer and alcoholism.

Chemical evaluation regarding the roots of this plant revealed that Maca is mostly constituted by several classes of secondary metabolites including alkaloids, amino acids, glucosinolates, fatty acids and macaenes, macamides (alkamides) [89,90].

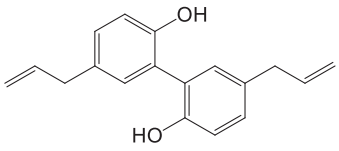
Zhao and co-workers elucidated the chemical composition of the hexane extract of L. *Meyenii* leading to the identification and isolation of novel alkamides, macamides and novel fatty acid, macaene, as well as the *N*-hydroxypyridine derivative, macaridine [91].

Hajdu and co-workers isolated different macamides from L. *Meyenii* and *Heliopsis helianthoides var scabra* as reported in the Fig. 11 [92].

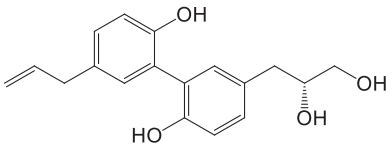
They identified the macamides octadeca-2E,4E,8E,10Z,14Z-pentaene-12-ynoic acid isobutylamide (**57**), octadeca-2E,4E,8E,10Z,14Z-pentaene-12-ynoic acid 2′-methyl-butylamide (**58**),



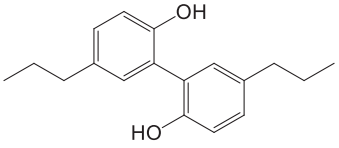
49 Honokiol (R=H)
50 4-methoxyhonokiol (R= CH_3)



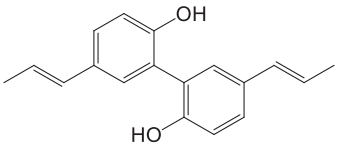
51 Magnolol



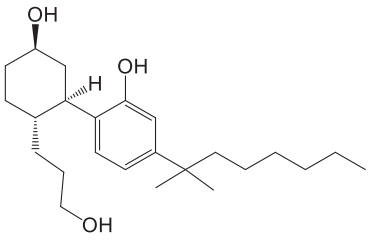
52 4 8,9-dihydroxydihydromagnolol



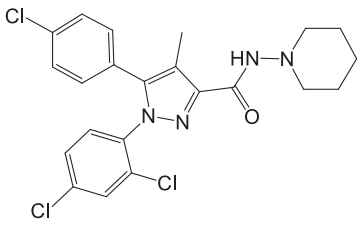
53 Tetrahydromagnolol



54 Trans-isomagnolol



55 CP55,940

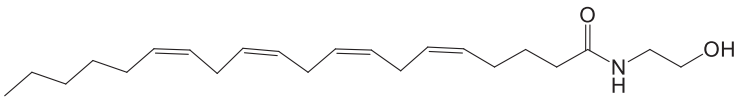


56 Rimonabant

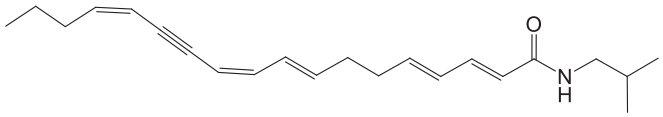
Fig. 10. Magnolol and related compounds.

hexadeca-2E,4E,9Z-triene-12,14-diynoic acid isobutylamide (**59**), and hexadeca-2E,4E,9,12-tetraenoic acid 2′- methylbutylamide (**60**), from *Heliopsis helianthoides* var. *Scabra*, while N-(3-methoxybenzyl)-(9Z,12Z,15Z)-octadecatrienamide (**61**), N-benzyl-(9Z,12Z,15Z)-octadecatrienamide (**62**), and N-benzyl-(9Z,12Z)-octadecadienamide (**63**), were isolated from *Lepidium meyenii*. *N*-alkylamides (NAAs) have been reported to interact with the endocannabinoid system due to their similarity to endocannabinoids, displaying analgesic, anti-inflogosys and modulatory effects on immune system. NAAs have been recognized in several Asteraceae species such as *Achillea, Acmella, Echinacea, Heliopsis* and in *Piperaceae, Rutaceae and Solanaceae*. The isolated NAAs have been tested on several target of ECS, including cannabinoids receptors, FAAH, AEA and MAGL. Macamides are crucial components in Maca plant for CB1 binding and FAAH and AEA transport inhibition, particularly macamide **63** acts as cannabinomimetic targeting ECS.

Moreover, the authors analysed the extracted compounds for their ability to bind the CB1 receptors; compounds **60** and **63** showed submicromolar affinities for the cannabinoid CB1 receptor (K_i values of 0.31 and 0.48 μM, respectively). The compound **63** also exhibited weak FAAH inhibition (IC_{50} = 4 μM) and a potent inhibition of anandamide cellular uptake (IC_{50} = 0.67 μM). The authors speculated that the 9Z,12Z-octadecadiene alkyl chain in macamide is a mimetic of the final portion of the arachidonoyl chain in endocannabinoids. They also found that this compound is more potent than OMDM-2, a specific inhibitor of AEA cellular uptake [92]. Maca is reported to be very safe, without adverse effect except for vaginal bleeding described in a young woman and a maniac episode related to its consumption by a 27 years old man [93].



Anandamide (AEA)



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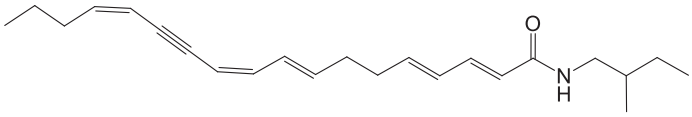

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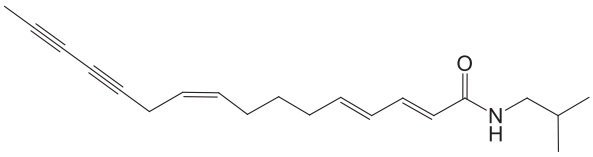

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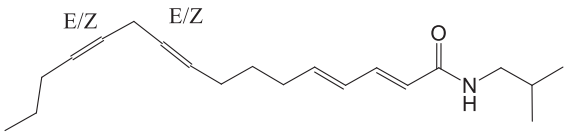

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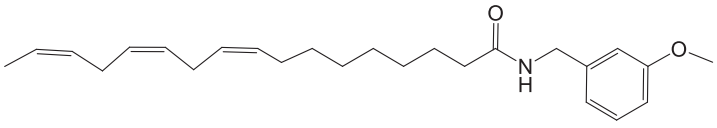

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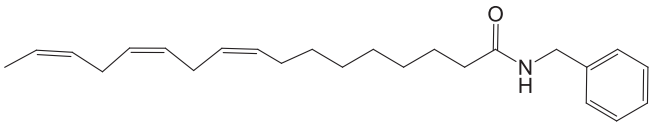

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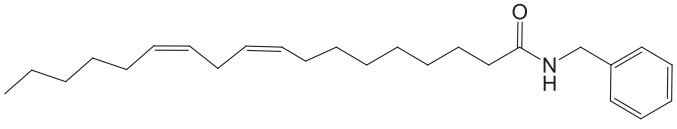


63

Fig. 11. Macamides identified by Hajdu and co-workers [92].

11. *Curcuma longa L.*

Curcuma longa also known as turmeric or "Indian saffron" for the yellow colour, belongs to *Zingiberaceae* family widely cultivated in India, China and many regions of south Asia. The plant needs temperatures between 20 °C and 30 °C and a considerable amount of annual rainfall. In traditional medicine, turmeric has been used in the treatment of many inflammatory conditions and diseases against arthrosys, muscolar and chest pain, and hepatitis [94]. Curcumin the main biologically active component of *Curcuma longa* is a natural compound which may regulate multiple pathways as intracellular components and key enzymes (Fig. 12). Curcumin possesses safety profile, antioxidant, anti-inflammatory, immunomodulatory and neuroprotective activities.

Curcumin inhibited platelet aggregation induced by adrenaline and collagene [95]. Hassanzadeh and co-workers studied the influence of curcumin or amitriptyline on endocannabinoid release by measuring the brain contents of AEA and 2-AG at various time points; they reported that 4-week/once-daily exposure to the highest dose of curcumin increased the AEA and 2-AG contents in distinct brain regions implicated in the regulation of emotional behaviour and synaptic plasticity [96].

Curcumin modulated the CBRs system in the fibrotic liver, due to a dose-dependently downregulation of CBR1, with pro-fibrogenic activity, and restoring the expression of CBR2, which is anti-fibrogenic in the fibrotic liver [95].

A further demonstration of this interaction has been provided by Hassanzadeh and co-worker, after 4-week treatment with curcumin reporting an enhancement in the concentration of NGF and endocannabinoids, similarly to amitriptyline. This action was reverted by the cannabinoid CB1 neutral antagonist AM4113, but not by CB2 antagonist SR144528 [96].

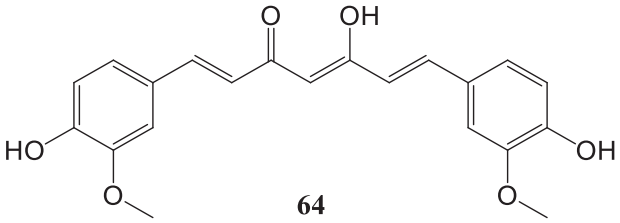
12. *Zingiber officinalis R.*

Ginger (*Zingiber officinale*) has been used extensively for more than 2500 years in China, in Ayurvedic and Western herbal medicine, to fight different pathological conditions as headaches, nausea, and cold's treatment of arthritis, rheumatological conditions and muscular discomfort [97].

The moderate pungency of ginger has been attributed to the mixture of gingerol derivatives in the oleoresin fraction of processed ginger as 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 6-hydroshogaol, and oleoresin which are responsible for the therapeutic effects of ginger. Their consumption may reduce or delay the progression of related diseases, such as cancer, diabetes, and obesity, via modulation of genetic and metabolic activities [98–101].

Z. officinale extract has been reported to alleviate the cyclophosphamide induced cardiotoxicity, showing also anti-platelet aggregation activity [102,103].

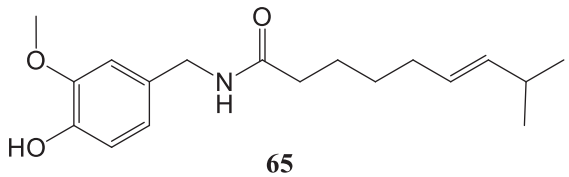
Dedov and co-workers, documented that the constituents of gingerol are relatively potent and efficacious agonists of the VR1 receptor, which activity depends on the size of the side chain determining the hydrophobicity (Fig. 13) [104]. They also reported SAR studied, eliciting that the absence of the side chain in zingerone (the gingerol degradation product) reduced its activity towards the VR1 receptor involved in cardiovascular system regulation [105].



64

Curcumin

Fig. 12. Chemical structure of Curcumin.



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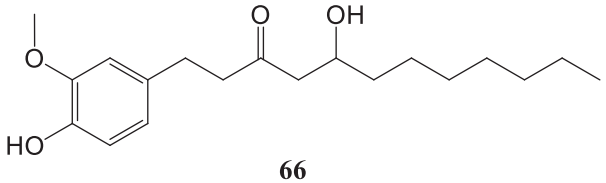
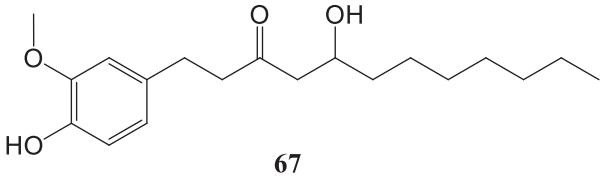
Capsaicin



66

8-Gingerol



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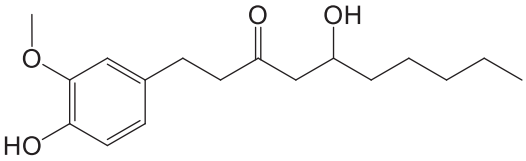
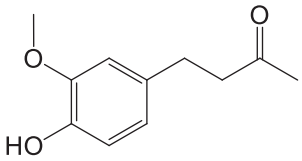
8-Gingerol



68

6-Gingerol



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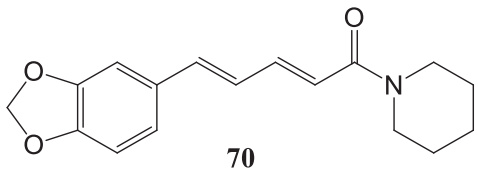
Zingerone

Fig. 13. Compounds contained in Ginger and their analogies with Capsaicin.

13. *Piper nigrum L.*

Black pepper (*Piper nigrum*, *Piperaceae* family) is used worldwide as food additive due to its unique flavour and its essential oil with strong antioxidant and antimicrobial activity. Piperine is the major bioactive



70

Piperine

Fig. 14. Structure of Piperine.

constituent found in black pepper and other Piper spices. It has various pharmacological properties such as anti-oxidative, anti-carcinogenic, anti-inflammatory [106]. Piperine also inhibited platelet aggregation by blocking $cPLA_2$ and reducing the TXA_2 synthase activity [107,108] (Figure 14).

Cherniakov et al. reported that piperine enhanced the adsorption of THC and CBD on single dose administration [109].

Single oral administration of CBD in the SNEDDS formulation PNL with piperine resulted in a statistically significant 2-fold increase in AUC and a 1.4 in C_{max} compared to CBD-PNL [110].

Over piperine, another compound called guineensine (Fig. 15), belonging to *N*-isobutylamide has been reported as a novel potent inhibitor of EC uptake exerting cannabimimetic effects *in vivo*, showing high specificity to AEA uptake inhibition and related effects on ECS modulation.

N-isobutylamide guineensine was identified as novel inhibitor of cellular EC uptake exerting cannabimimetic effects in BALB/c mice through both CB1 receptor-dependent and independent mechanisms. Guineensine shows potent inhibition of AEA uptake *in vitro*, which is comparable or even more potent than the reference inhibitors UCM707 and OMDM-2. Guineensine mechanism is not due to FAAH inhibition, the AEA uptake inhibition can also be observed in FAAH-deficient HMC-1 cells, suggesting that guineensine inhibits a specific target involved in EC uptake with an $EC_{50} = 290$ nM distinct from FAAH. Guineensine may act as indirect CB1 receptor agonist modulating EC levels through specific uptake inhibition [110].

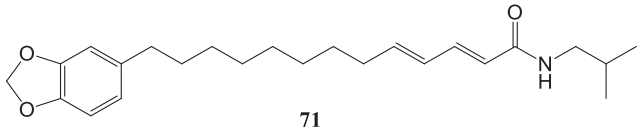
Piperine provokes hemorrhagic stomach ulceration and enteritis located in the small intestine in mice, while a toxic effect in human is far to be observed due to the high amount of piperine to be consumed [111].

14. *Linum usitatissimum L.*

Flax (*Linum usitatissimum*) is an annual plant widely distributed and cultivated in the Mediterranean area, largely used in medicine and industry, mainly produced for the fibers, the linseeds and the oil. Linseed products are highly recommended due to their content of secoisolariciresinol diglucoside (SDG), with antioxidant properties that slow the progression of atherosclerosis, possessing also anticancer properties [112].

Flax oil is the richest source of α-linoleic acid able to reduce cardiovascular diseases, cancer and inflammatory mediators and other polyunsaturated fatty acids. Stirkzewska and co-workers reported that flask seedcakes, leaves, stems, fibers analysed by UPLC-MS qualitative and quantitative methods based on retention time, UV spectra and mass spectrometry analysis, contain terpenophenols (cannabinoid-like compounds) [113].

Toxicological studies reported the absence of toxicity in flaxseeds as dietary supplement, while some compounds as cyanogenic glycosides and linatine have been identified as potentially toxic [114].



71

Guineensine

Fig. 15. Structure of Guineensine.

15. *Helichrysum Umbraculigerum Less*

Helichrysum Umbraculigerum belongs to the Asteraceae family, this large genus consists of approximately 500–600 species original from south Europe, south-west Asia, south India, Sri Lanka and Australia, Africa and Madagascar. The traditional uses of Helichrysum species are extensively described and seem to be quite stackable to those of cannabis, against nausea and vomiting, respiratory diseases and dysentery [115].

African Helichrysum species are used for ritual inebriating fumigations, this folk use presumably underlies the trade of some South-African Helichrysum species for recreational narcotic purposes; phytocannabinoids from both the alkyl- and aralkyl series have been reported from the South-African plant *Helichrysum umbraculigerum Less* [116].

Pollastro et al. investigated the phytochemical profile of the acetone extract from H. Umbraculigerum as a natural source of cannabigerol, the precursor of the alkylcannabinoid family [117].

The HPLC analysis revealed a high content in terms of resorcinoids derived from bibenzyl type of aralkyl phytocannabinoids and phloroglucinoids. Among the compounds contained in Helichrysum, Heli-CBG modulates CB receptors and thermo-TRPs (Fig. 16) [117].

The Cannabigerol binds CB1 and CB2 ($K_i = 0.439 \pm 0.082$ μM for **74** and 0.337 ± 0.034 μM for **75**) [98,99]; its phenethyl analogues Heli-Cannabigerol derivatives show an even lower affinity with value of $K_i = 3.72 \pm 1.19$ μM for **74** and 0.828 ± 0.094 μM for **75** with an improved activity on TRPM8 ($K_i = 1.38 \pm 0.12$ μM and 3.07 ± 0.38 μM, respectively).

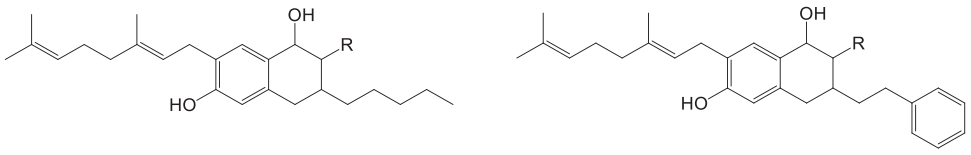
16. *Humulus lupulus L.*

Humulus lupulus L. is well-known all over the world for beer production which peculiar flavour is mostly due to the hops, the female inflorescences of Humulus lupus rich in polyphenolic compounds, terpenes and acyl phloroglucide. Hop cones have long been used in traditional medicine for the treatment of sleeping disorders as a mild sedative, and for the activation of gastric function as bitter stomachic, depression, exitability, apprehensiveness, delirium, anxiety and gastrointestinal disorders. Several works have been published aimed to elucidate the phytochemical composition of this useful plant, leading to the identification of pharmacologically relevant compounds such as flavanones, chalcones, phloroglucinol derivatives [118].

Cannabaceae families (of which are part *Cannabis sativa* and *Humulus lupulus)* contain different terpenes (mainly mono- and sesquiterpenes: up to 99%). Both plants produce a resin rich in terpenes, accumulating on the female flowers abundant in trichomes with annex glandulaes. Pharmaceutical properties of monoterpenes have been reviewed by Nuutinen, and find to be generally antibacterial, antioxidative, antiarhythmic, also they may modulate plates aggregation, pain and inflammation, histamine release, with antcancer and anti-diabetogenic properties [119].

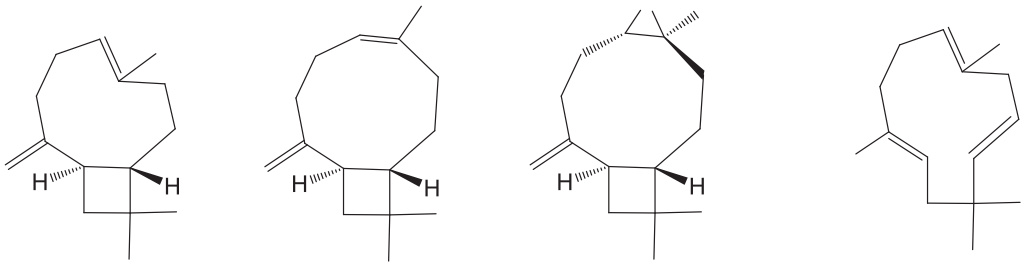
As reported by Santos et al. β-caryophyllene is a phytocannabinoid with neuroprotective potential associated with antioxidant mechanisms and modulation of the inflammatory response, both events mediated by the selective activation of CB2 receptors (Fig. 17). β-caryophyllene is unable to activate CB1 receptors, bue it has a very good affinity (K_i of 150 nM and EC_{50} is 1.9 mM) for CB2 receptor, resulting in a selective full agonist toward this receptor. Due to its high selectivity, β-caryophyllene is useful for the modulation of various pathological conditions [120].

Both CB2 and PPAR-γ are involved in the anti-inflammatory,



72 Cannabigerol R= H
73 Cannabigerolic Acid R= COOH
74 Heli-Cannabigerol R=H
75 Heli-Cannabigerolic ester R= COOMe

Fig. 16. Structure Cannabigerol (**72**), Cannabigerolic acid (**73**), Heli-cannabigerol (**74**) and Heli-cannabigerolic methyl ester (**75**).



76 (E)-BCP
77 (Z)-BCP
78 BCP oxide
79 α–humulene

Fig. 17. Chemical structures of the bicyclic sesquiterpenes (*E*)-β-caryophyllene, (*Z*)-β-caryophyllene, caryophyllene oxide, and the isomer α-humulene.

anxiolytic and anti-oxidant effects of BCP [121].

Various bio-activities of β-caryophyllene such as cardioprotection, hepatoprotection, gastroprotection, neuroprotection, nephroprotection, anti-inflammation and immunomodulation have been reported [122], furthermore, the hop extract showed antiplatelet activity both *in vitro* and *in vivo* underlining its possible involvement in the menagment of CVDs, also reducing atherogenic factors [123].

β-caryophillene (BCP) possesses potent therapeutic promises for neuropathic pain, neurodegenerative and metabolic diseases, without showing any significant adverse effects after *in vivo* evaluations, [124] its mechanisms of action its due to both CB2 and peroxisome proliferated activator receptors (PPARs) the toll like receptor complex CD14/TLR4/MD2, synergy with μ-opioid receptor-dependent pathways. BCP has been also tested with promising retuls on multiple sclerosis, was also able to suppress neuroinflammation modulating the up-regulation of interleukin-10 to reduce interferon-γ [125].

The effect was equal to the cannabimimetic CB2 selective JWH-015. Also, it has been found an inhibitory effect of BCP upon microglia and lymphocyted CD4/CD8. Gertsch and co-workers, measured CB2-mediated intracellular calcium transients ($[Ca^{2+}]i$) in promyelotic HL60 cells; (*E*)-BCP concentration-dependently triggered the release of $[Ca^{2+}]i$ like that of 2-arachidonoylglycerol, which is a potent activator of the G_o pathway [126,127].

β-caryophyllene (BCP) generated enormous therapeutic interest due its activity as agonist of CBR2 a medium nanomolar K_i value (≈150 nmol/L) with no affinity for CBR1, evoking the selective activation of G_i/G_o G-proteins [128].

BCP belongs to the cyclic sesquiterpene family, present in thousands of vegetables and essential oils (e.g. cinnamon, oregano, black pepper, basil, and cloves). Because of its abundance in edible plants and vegetables including *Cannabis sativa*, it is considered a dietary CBR2 selective cannabinoid [127].

The results obtained by Meeran et al. showed the inhibitory activity of BCP against DOX-induced chronic cardiotoxicity in rats by ROS scavenging properties and to reduce inflammation and apoptosis; this effect is also due to CB2 receptors activation [128].

Indeed BCP, can modulate the expressions of CBR2 in DOX-induced chronic cardiotoxicity in rats, and it has been also demonstrated that BCP is able to stimulate the activation of PPARγ by CBR2 up-regulation [128].

Furthermore, BCP is safe and well tolerated after oral administration in mice, without producing treatments-related modification in helat conditions, underlining its possible medical purpose [129].

17. *Syzygium aromaticum L.* (cloves)

Syzygium (S.) aromaticum is the dried flower bud flavouring spice, belonging to the Myrtaceae family widely used by Maluku's indigenous for medicinal and commercial purposes as perfume, in soaps industry and as food preservation due to antioxidant and antimicrobial properties [130].

Numerous studies have been reported in literature on antibacterial, antiviral, anticarcinogenic and antifungal activities of some aromatic herbs including clove. Clove is traditionally used for the treatment of tooth infections and toothache mostly due to eugenol and its ability to penetrate dental pulp tissues; it has been also used for the treatment of vomiting, nausea, liver, bowel and stomach disorders. Moreover, sesquiterpenes isolated from clove possess anti-carcinogenic activity. Clove oil is also documented to possess anticoagulant and anti-platelet aggregation activity, inhibiting platelet activating factor and arachidonic acid induced aggregation [131].

Syzygium (S.) aromaticum extracts contain β-caryophyllene [132]. Kamikubol et al. speculated that clove extracts may stimulate AMPK phosphorylation and potently suppresses the palmitate-inducible lipid accumulation in human liver cells (HepG2). [132].

S. aromaticum exerted toxic effect on spermatogenesis, reducing sperm count, sperm motility and density. Clove's oil has been also reported to be toxic at 0.03 concentration mostly to the presence of eugenol which was shown to be cytotoxic to the skin cells, while β-caryophyllene did not contribute to cytotoxicity [133].

18. *Camellia sinensis L.*

Camellia sinensis is a plant of *Theaceae*'s family, largely consumed as fermented herbal tea obtained by different oxydation levels. Tea is an infusion of the dried leaves of *Camellia sinesis* and is the most consumed

drink in the world after water.

Green tea variety is also considered as medicine throughout India, China, Japan and Thailand.

Tea contains around 4000 bioactive compounds represented by polyphenols (mostly flavonoids) 1,3-alkaloids (caffeine, theophylline, and theobromine). One of the most important class of compounds found in green tea are catechins, among them (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), epigallocatechin (EGC) and (-)-epigallocatechin gallate (EGCG) reported in Fig. 18 [134].

Catechins are the most abundant polyphenols in the leaves of tea but are also found in many fruits and in some legumes, in cocoa beans and at cellular level with anti-inflammatory and antioxidant activities. GABAergic, glutamatergic, monoamine and NO systems have been previously proposed as catechin effectors. Only recently, lipid rafts and plasma membrane binding sites have been implicated as molecular targets. Korte and co-workers performed competition binding assays on membrane preparations of recombinant receptors, using [^{3}H]-CP55940 as radiolabelled ligand; the K_i values ranging from 33.6 mM for EGCG to over 2.5 mM for (+)-catechin and (-)-epicatechin to CB1, while the receptor CB2 affinity were generally lower than that of CB1. The cannabimimetic activities can contribute in mitigation of pain, complementing a COX-2 inhibitory role and opioid receptor functionalities of catechins, also modulating food intake [135].

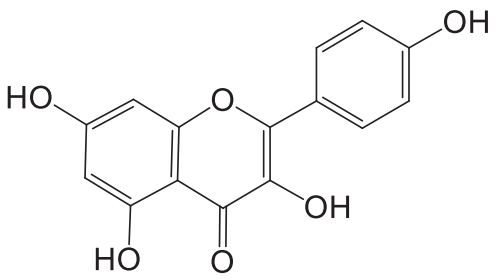
The toxicological effects reported for *Camellia sinensis* are vomiting, diarrhea, weight loss, anorexia, hemolytic anemia liver necrosis, myocardial necrosis in rat models [136].

In a different study reported by Hsu et al. *Camellia sinensis* did not show subacute toxicity related to blood parameters, urinalysis, hematology and serum biochemistry [137].

19. *Kaempferia galanga L.*

Kaempferia galanga has several traditional uses. The rizhoma extract contains several bioactive compounds such as ethyl p-methoxycinnamate, kaempferol (Fig. 19), kaempferide, kaemgalangol A, kaempsulfonic acids, cystargamide B, 3-caren-5-one and xylose [138].

Kaempferol a natural flavone, is found in many plants (beans, broccoli, cabbage, gooseberries, grapes, kale, strawberries, tomatoes, citrus fruits, Brussels sprouts, apples, and grapefruit) and has a wide range of therapeutic actions, being effective against ailments involving inflammation, cancer, and oxidative stress through modulation of



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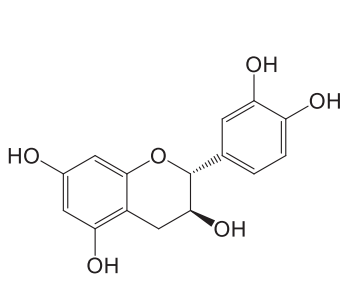
Kaempferol

Fig. 19. Kaempferol chemical structure.



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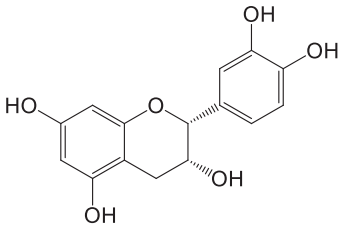
(+)-catechin



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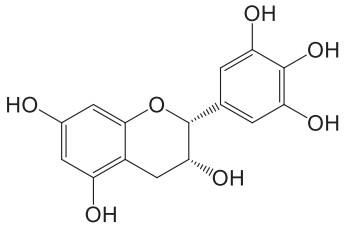
(-)-epicatechin



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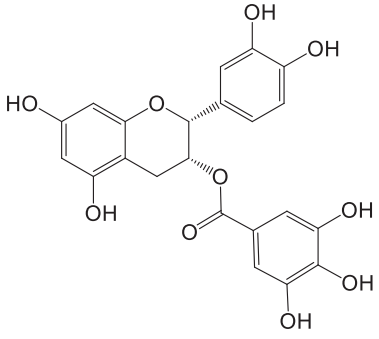
(-)-epigallocatechin (EGC)



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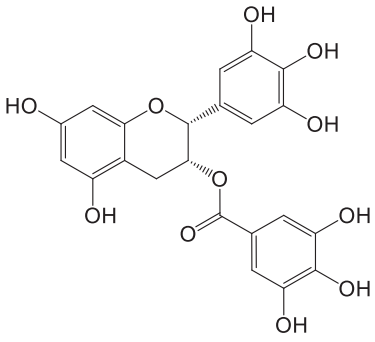
(-)-epicatechin-3-O-gallate (ECG)



84

(-)-epigallocatechin-3-O-gallate (EGCG)

Fig. 18. Most abundant compounds found in *Camelia Sinensis*.

molecular pathways such as NF-kB, PI3k/AKT, MAPK, Bcl2, Caspase 3, and VEGF; moreover kaempferol is capable of exerting beneficial effects against central nervous system disorders as well, depression, anxiety, and cognitive disorders [139–142].

Ahmad and co-worker examined the involvement of kaempferol in modulation of endocannabinoid system; Kaempferol inhibited FAAH in a dose-dependent manner with an IC_{50} value of 1.064 μM. At 200 μM dose, kaempferol (90.79 ± 1.11%) produced an equivalent response to the standard FAAH inhibitor JZL195 at 10 μM (88.02 ± 1.26%) [143].

It is reported that Kaempherol inhibited platelet activation, preventing thrombosis through inhibition of fibrinogen and thrombin interaction [144].

20. *Boswellia carterii R.*

Boswellia oil "Olibanum" is one of the major components of Jerusalem Balsam, which also contains "Myrrh", "Mastic" and "Aloe". *Boswellia sp*. original from Eastern Africa, are used from the aborigine as for its scent and for the medicinal properties, specifically as a diuretic, for schistosomiasis, for gastrointestinal pain, and anti-syphilis. The resin was also known in India as anti-reumatic and anti-inflammatory agent, where boswellic acid and its derivatives were the bioactive substances [145].

Menon and Kar have reported that an ether extract of *Boswellia serrata* resin produced analgesic and sedative effects in rats [146].

Boswellia extract contains novel bioactive components and incensole acetate (IA) which showed an antiinflammatory action (Fig. 20) [147].

IA is a macrocyclic diterpenoid considered as a biomarker of *Boswellia* species; IA showed significant TRPV3-dependent activity in both the elevated plus maze and the Porsolt forced swimming test, also modulating the expression of c-Fos [147]. No noticeable adverse effects have been observed in treated rat, except for a case of dermatitis [148].

21. *Theobroma cacao L.*

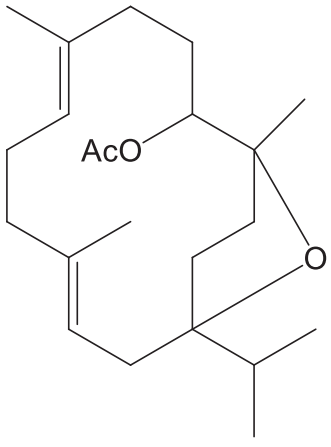
The tropical *Theobroma cacao* belonging to *Sterculiaceae*'s family, is a small evergreen tropical and subtropical tree native of Central America where the Mayans and Aztecs cultivated it for collecting seeds used to make a beverage drink called chocolatl. Cocoa was used by ancient peoples as a medicinal plant for treating various disorders as anaemia, mental fatigue, tuberculosis, fever, gout, kidney stones, and even poor sexual appetite [149].

Cocoa seeds contain a large number of bioactive chemicals, procyanidins present in cocoa inhibited tumorigenesis, tumour growth, and angiogenesis. Procyanidin-enriched cocoa seed extracts caused G2/M arrest and 70% growth inhibition in Caco-2 colon cancer cells [150].

Chocolate contains lipids structurally related to anandamide that binds to and activates cannabinoid receptors mimicking the psychoactive effects of cannabinoid drugs such as heightened sensitivity and euphoria [150].

As reported by diTomaso et al., analysing a cocoa power or chocolate extract, they isolated three compounds e.g. anandamide, *N*-oleoylethanolamine and *N*-linoleoylethanolamine; they displayed electron-impact mass spectra characteristic of these *N*-acylethanolamines (Fig. 21).

N-oleoylethanolamine and *N*-linoleoylethanolamine do not bind or activate CB receptors located in the brain but they act as inhibitors of anandamide hydrolysis in the rat brain acting on anandamide amino hydrolase enzyme [151].



Incensole acetate (IA)

Fig. 20. Incensole acetate structure.

22. *Ruta graveolens L.*

Ruta graveolens L. is a shrubby perennial plant that belongs to the family of Rutacee, it grows in the Mediterranean area also widely cultivated all over the world including Europe, Africa, Asia and South America, China and Japan. Ruta has a strong-smell due to the unpleasant odour emanating from the leaves. The flavour is very bitter, nevertheless it is used in ethnic cuisine such as in Ethiopia where it is also a coffee flavourant and in Italy where it is used to flavor grappa, an Italian type of brandy. *Ruta graveolens* has been used in traditional medicine for its healing properties, as fresh herb, infusion, decoctions, powder or oils [152,153].

Among the most common illnesses cured by *Ruta graveolens*, there are rheumatic diseases, aching pain, eye problems, dermatitis and multiple sclerosis. Finally, abortion and contraception are among the widely and ancient prescriptions of *Ruta graveolens*, thus, according to Wood it was used as a remedy in Latin American folk medicine for abortion [153].

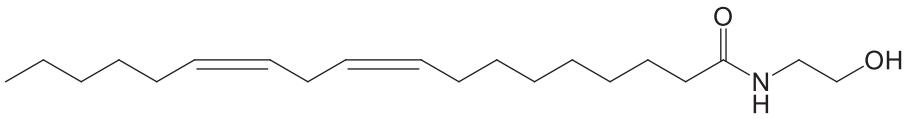
Rollinger et al. purposed a 3D pharmacophore-based parallel screening approach on *Ruta graveolens*, to focus specifically on those secondary metabolites which are characteristic for the natural material under investigation including potentially novel constituents (target fishing) [154].

After *in silico* evaluation, the authors performed biological assays on different compounds, among these rutamarin revealed a selective affinity to the CB2 receptor with a K_i of 2.64 ± 0.2 μg/mL or 7.4 ± 0.6 μM (Figure 22). Displacement data obtained with the Rutae herba dichloromethane extract yielded a K_i value of 16.8 ± 0.9 μg/mL. Given the approximate percentage of rutamarin (15–20%) in the dichloromethane crude extract, rutamarin is the constituent responsible of its biological effect. Methanol extract of the roots of *R. Graveolens* inhibited platelet aggregation induced by arachidonic acid and collagene, while the methanol extract of aerial parts showed antiplatelet aggregation induced by collagene [155].

23. Conclusion

This review has briefly explored various plants in which have been found some bioactive compounds possessing a potential role in the direct or indirect modulation of the endocannabinoid system, acting as CB1/CB2 receptors agonist or antagonist, as FAAH and MAGL inhibitors, or by other ECS modulated systems spread in the human organs.

The abundance of plants containing cannabinoid-like compounds allows to overcome the legal limitation related to the Cannabis use and represents a weapon in our hands in drug discovery and drug design fields, especially considering the close correlation between endocannabinoid and cardiovascular systems. However, the direct interaction of endocannabinoid-containing plants with this target must be surely better investigated considering their safety profile and the risk-benefit *ratio* related to their use and potential toxicologic concerns.



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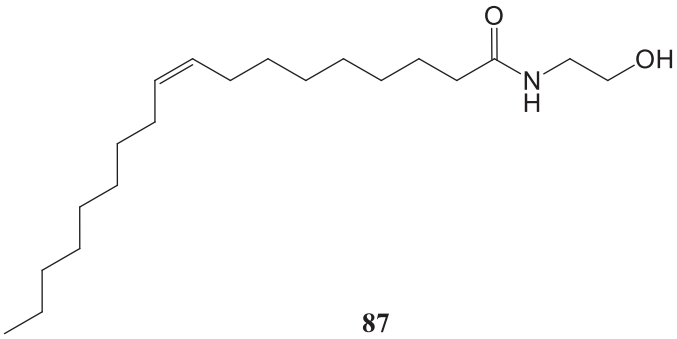
N-linoleoylethanolamine



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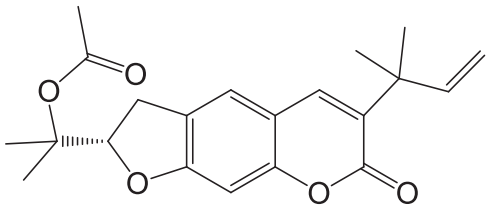
N-linoleoylethanolamine

Fig. 21. *N*-acylethanolamines found in *Theobroma cacao*.



Rutamarin

Fig. 22. Rutamarin chemical structure.

CRediT authorship contribution statement

Marilisa Pia Dimmito: Conceptualization, Software. **Azzurra Stefanucci**: Data curation, Writing – original draft. **Alice Della Valle** and **Giuseppe Scioli**: Software, Validation. **Angelo Cichelli** and **Adriano Mollica:** Writing – review & editing.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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