Natural Health Research

TRUSTWORTHY SCIENCE

Overview of the Endocannabinoid System and the Variety of Natural Compounds That Modulate It

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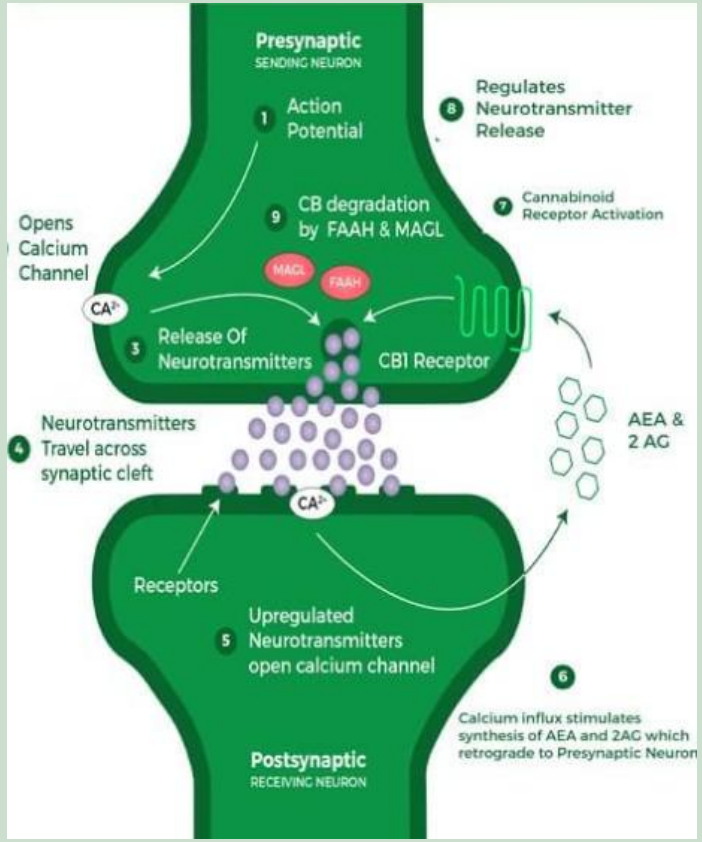
Endocannabinoid System

- A widespread physiological system involved in maintaining homeostasis across various organs.
- Can be called a master regulator: Has various enzymes, receptors with several ligands.
- Clinical Relevance: Targeted in pain management, neurodegenerative diseases, and mental health treatments.
- Physiological Roles:
  - Neurotransmission
  - Pain regulation
  - Inflammation & immunity
  - Metabolism & appetite
  - Stress & mood

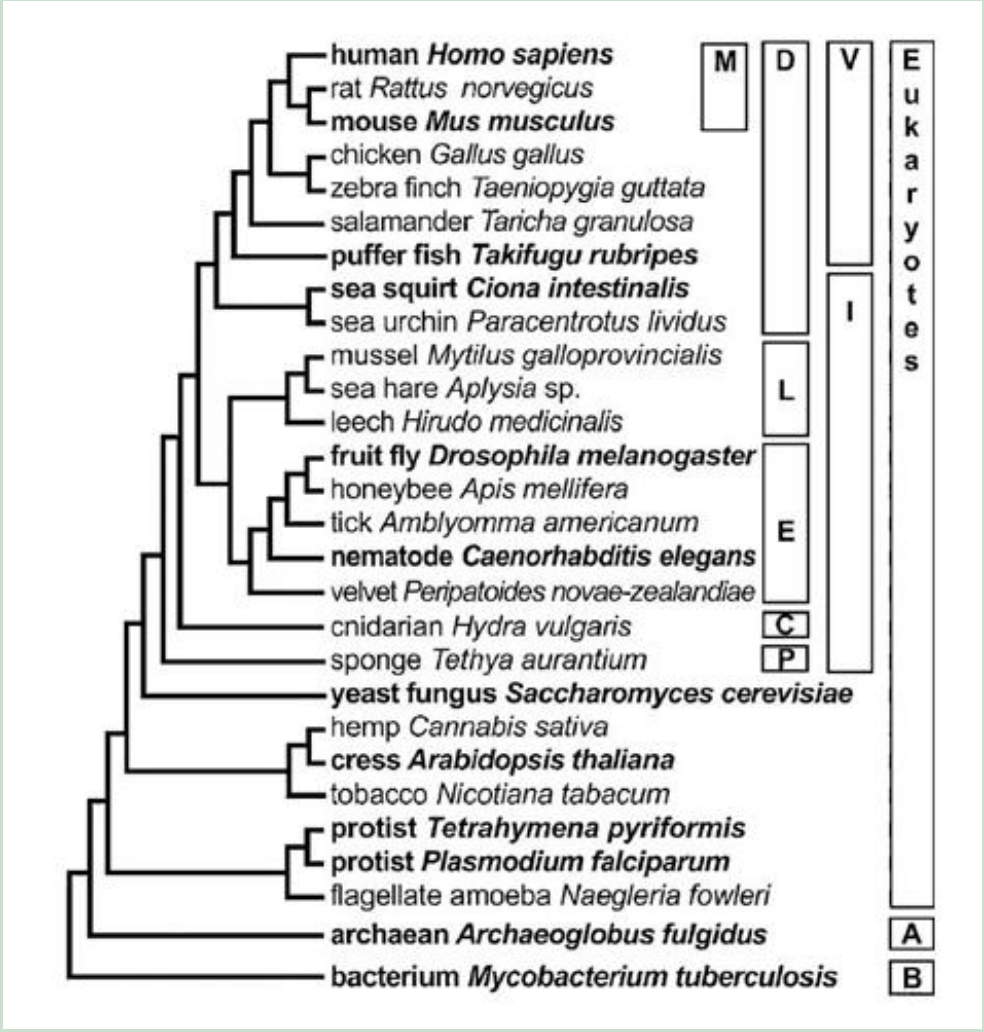
Endocannabinoid System

- This presentation provides a brief overview of ECS physiology and pharmacology and explores the variety of natural compounds that may modulate this system.
- Endogenous ligands are endocannabinoids (ECs) made from arachidonic acid-containing lipid molecules generated from membrane glycerophospholipids, and phospholipids in cell membranes, and can be modulated by the diet.
- Phytocannabinoids are non-cannabis plant compounds that interact with the ECS. Most research is focused on compounds called alkamides, but other plant compounds, including polyphenols, terpenes, and lipids may also influence ECS signaling.



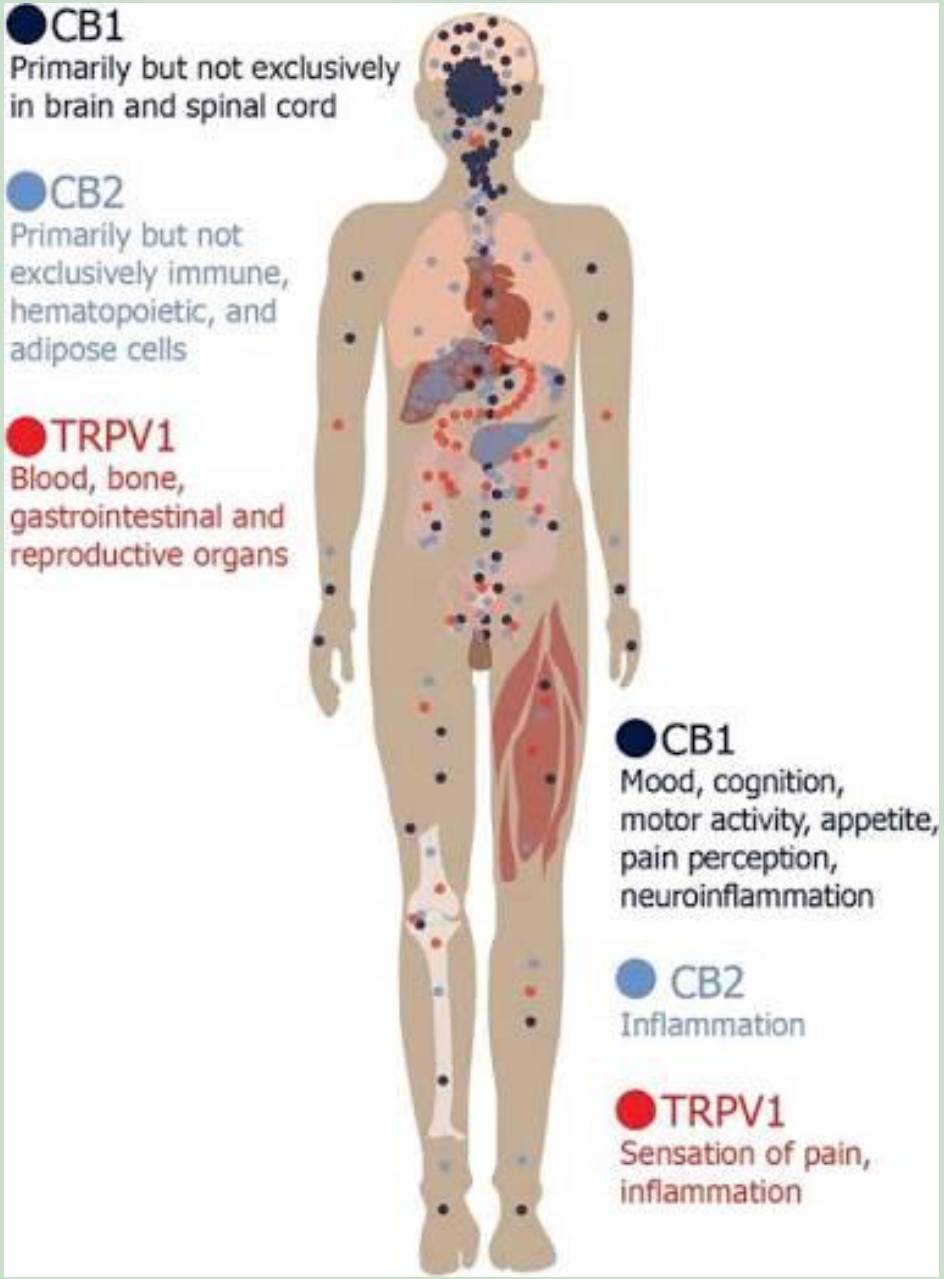
Evolutionary Origins of the ECS

- Organisms have been studied for compounds, receptors, and genes related to the ECS.
- Olivetol and related alkylresorcinols, foundational precursors in Cannabis, are found as a secondary metabolite in some lichens, bacteria including cyanobacteria, Fungi, and grains.
- The biochemical pathways for the endocannabinoid system is older than animal life, and many higher plants.



CB1 Receptor:

- Most abundant GPCR in the brain, predominant in the CNS.
- **Key functions: Neurotransmitter release inhibition, cognition, emotion, reward, pain.**
- Mediates inhibition of neurotransmitter release (dopamine, GABA, glutamate); present in neuronal and astrocyte mitochondria.
- Primary mediator of THC.



CB2 Receptor:

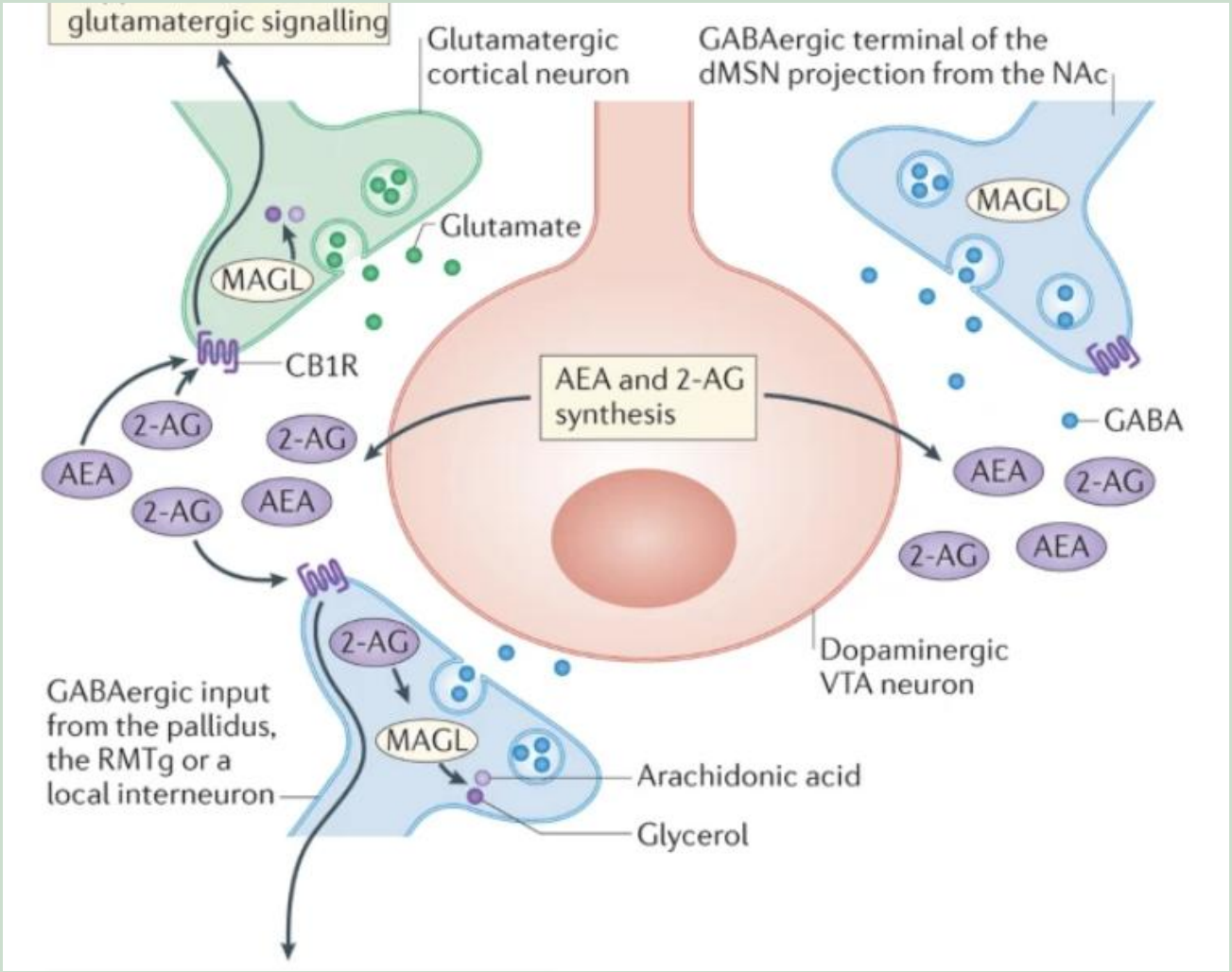
- Functionally distinct, shares only 44% amino acid with CB1.
- **The key immunomodulatory cannabinoid receptor.**
- Primarily expressed on immune cells — B cells, NK cells, monocytes/macrophages, neutrophils, and T cells (in decreasing rank order).
- Has no psychoactive effects.

Both found in on plasma membranes of neurons and glia.

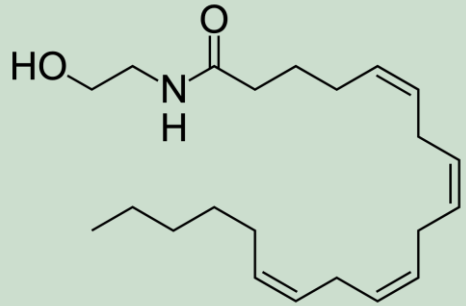
EC Retrograde Signaling

ECs can then cross through the membrane, either via passive diffusion or with the help of endocannabinoid membrane transporters -

Travel across the synapse, where they retrogradely activate presynaptic cannabinoid type 1 receptors (CB1r)



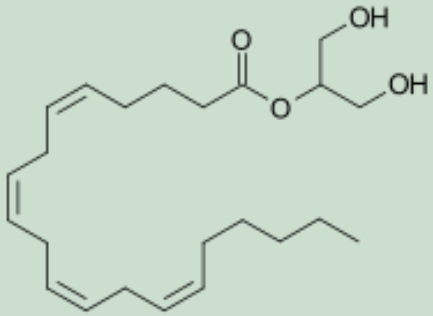
Endocannabinoids (ECs)

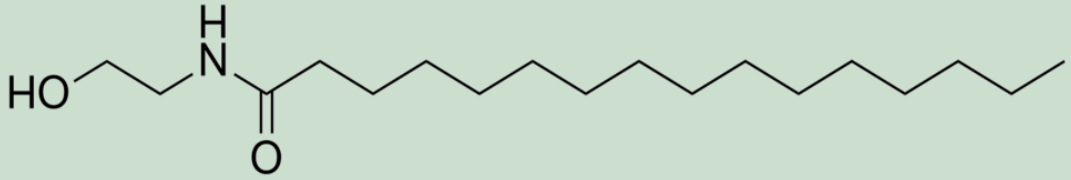


Derived from Omega 3 & 6 fatty acids.

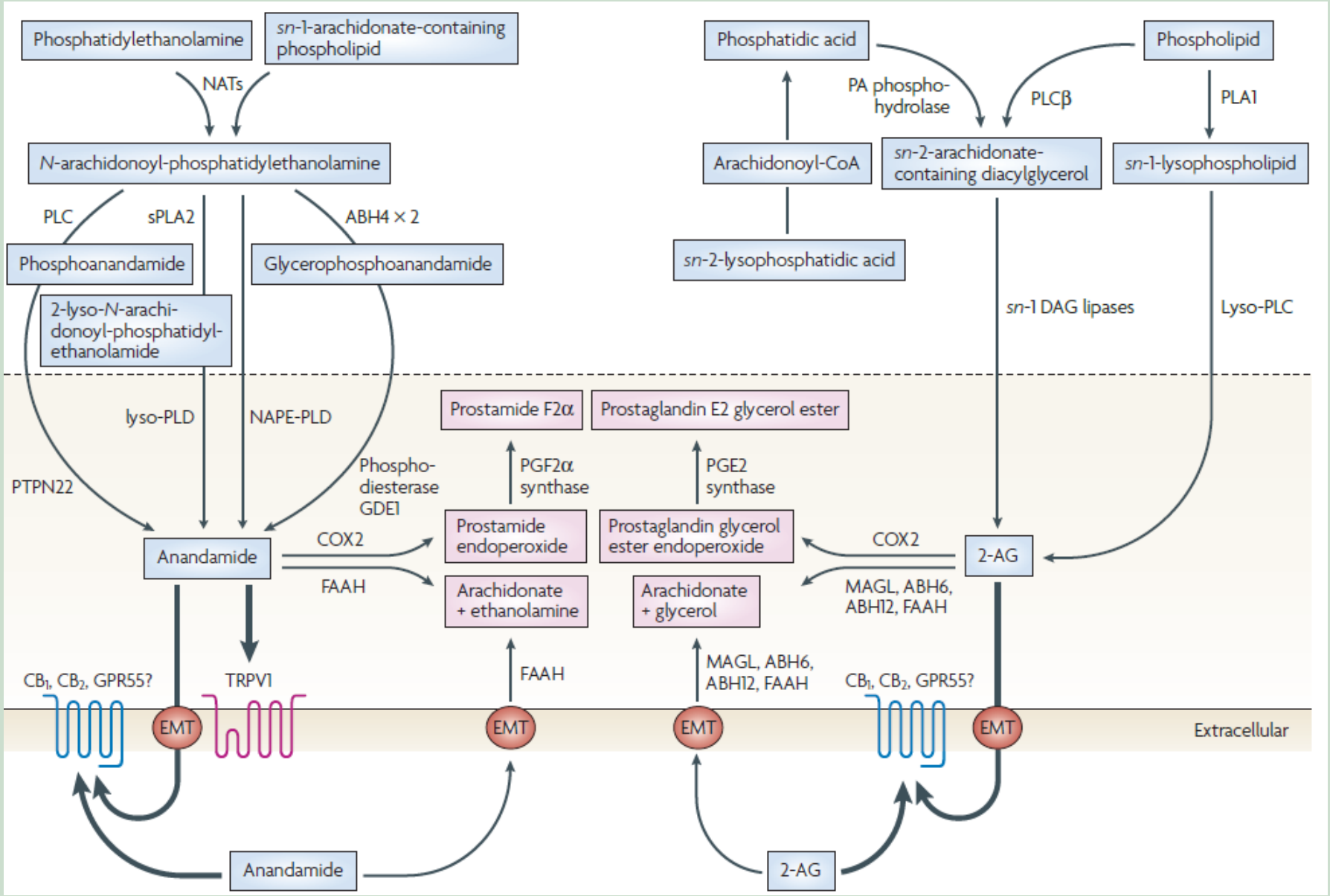
Act on 3 main receptors: CB1, CB2, & GPR55 by direct signaling.

1. Anandamide (AEA) - weaker, TRPV
2. 2-Arachidonoylglycerol (2-AG) - stronger
3. N-Arachidonyl Dopamine (NADA)
4. Other endogenous ligands: Palmitoylethanolamide (PEA)



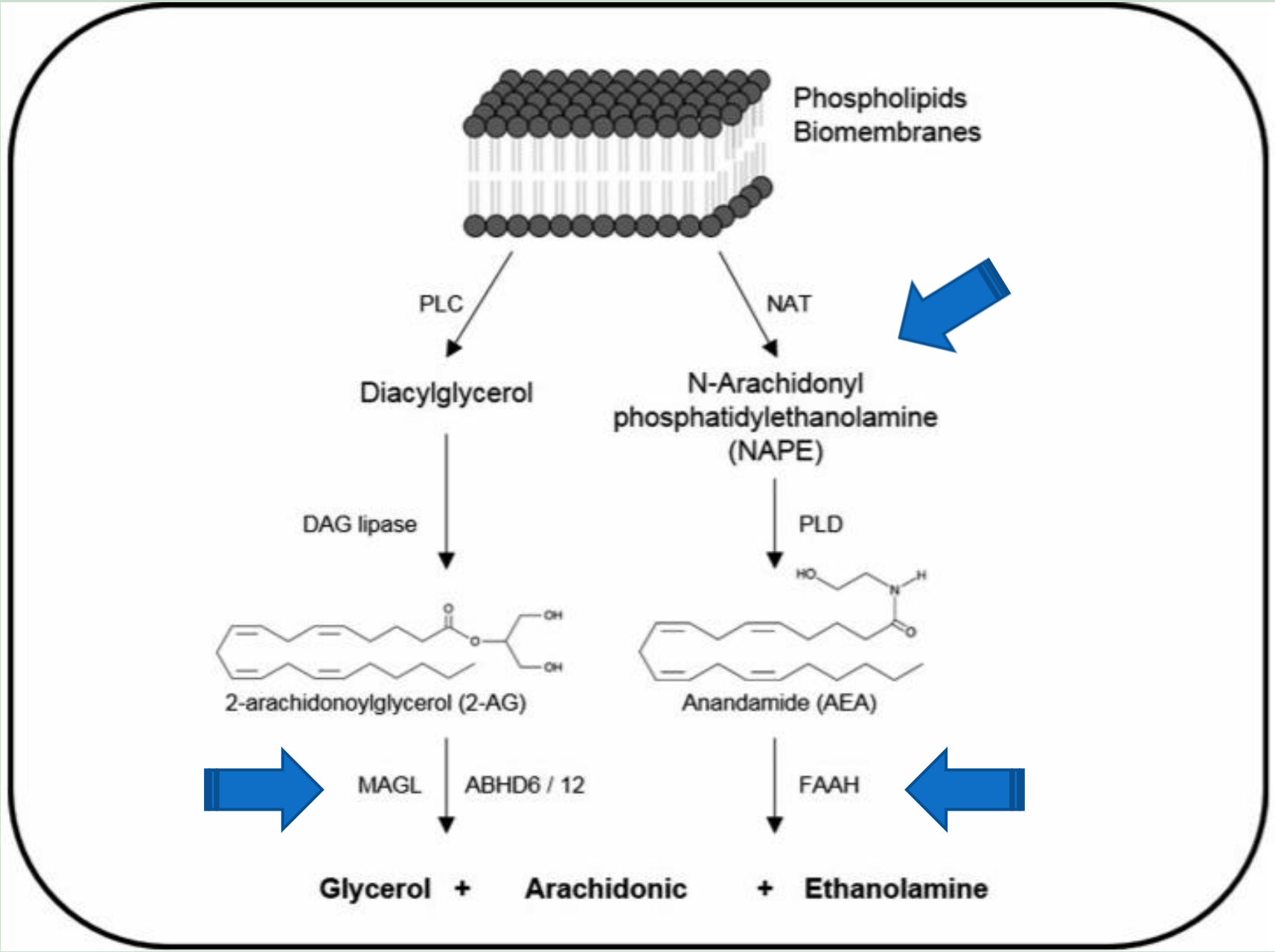


Biosynthesis, action and inactivation of ECs



Key components of the ECS

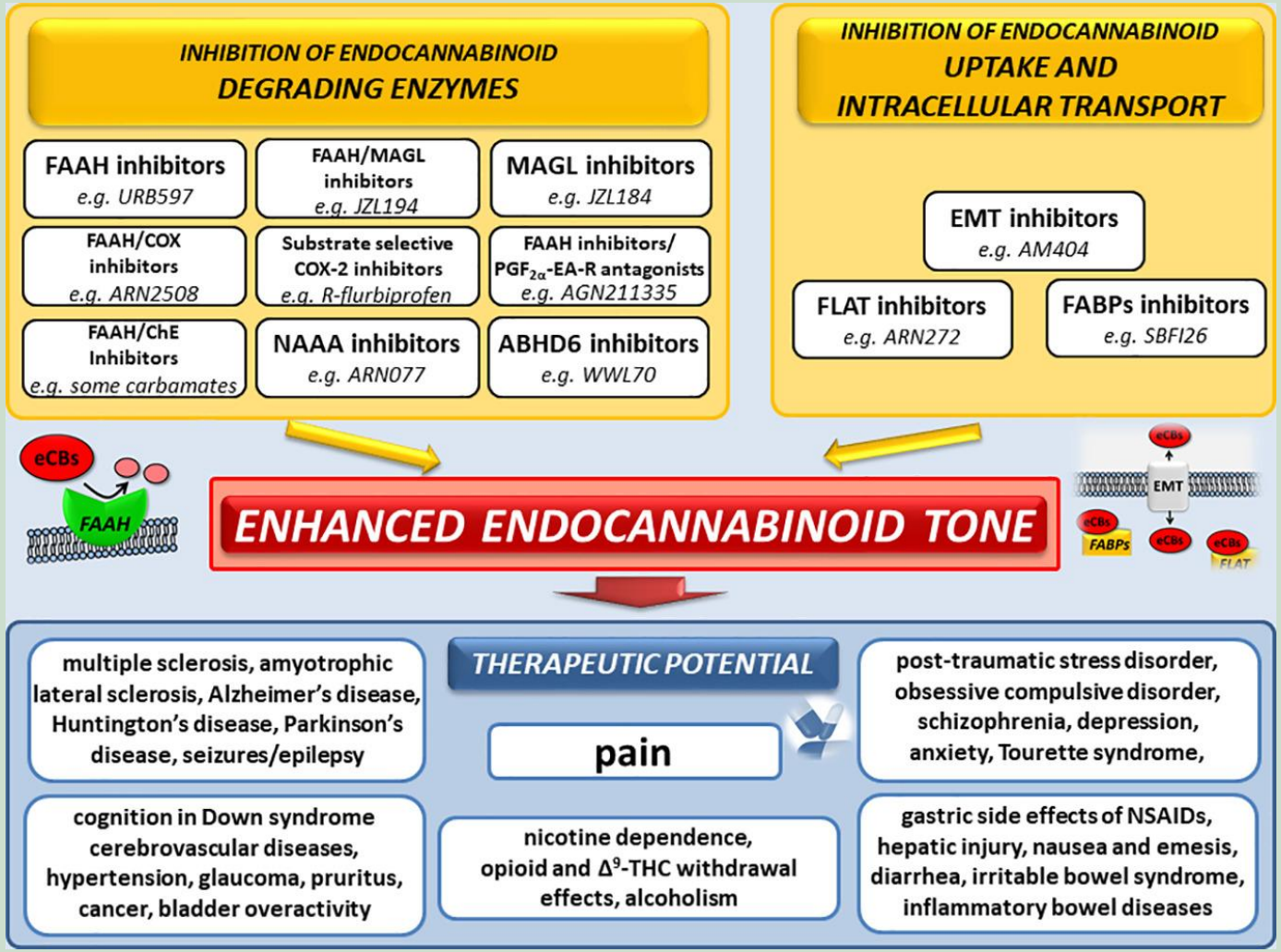
If modulation of the ECS isn't at the receptor, it is acting on FAAH, MGL, or NAPE, usually inhibition.



Endocannabinoid Tone

Refers to concentration and receptor signaling of anandamide (AEA) and 2-AG.

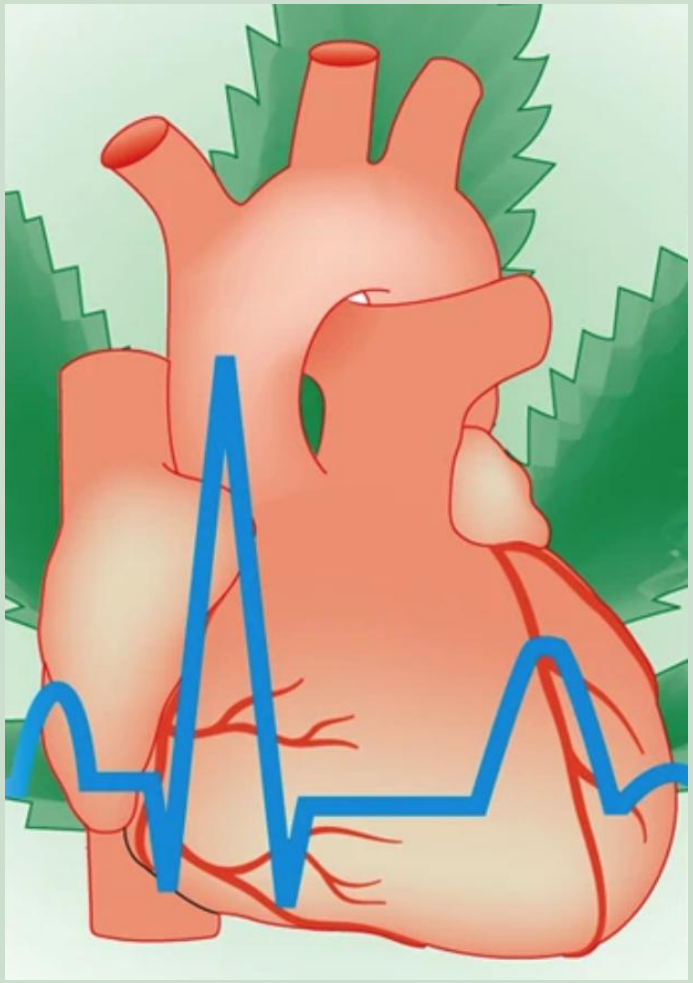
- Depends on synthesis, degradation, and reuptake/transport rate — how quickly AEA and 2-AG are removed from the extracellular space via carrier proteins.
- Endocannabinoid tone upregulated in numerous pathological states including inflammatory, neurodegenerative, cardiovascular, and metabolic diseases.



Clinical Endocannabinoid Deficiency

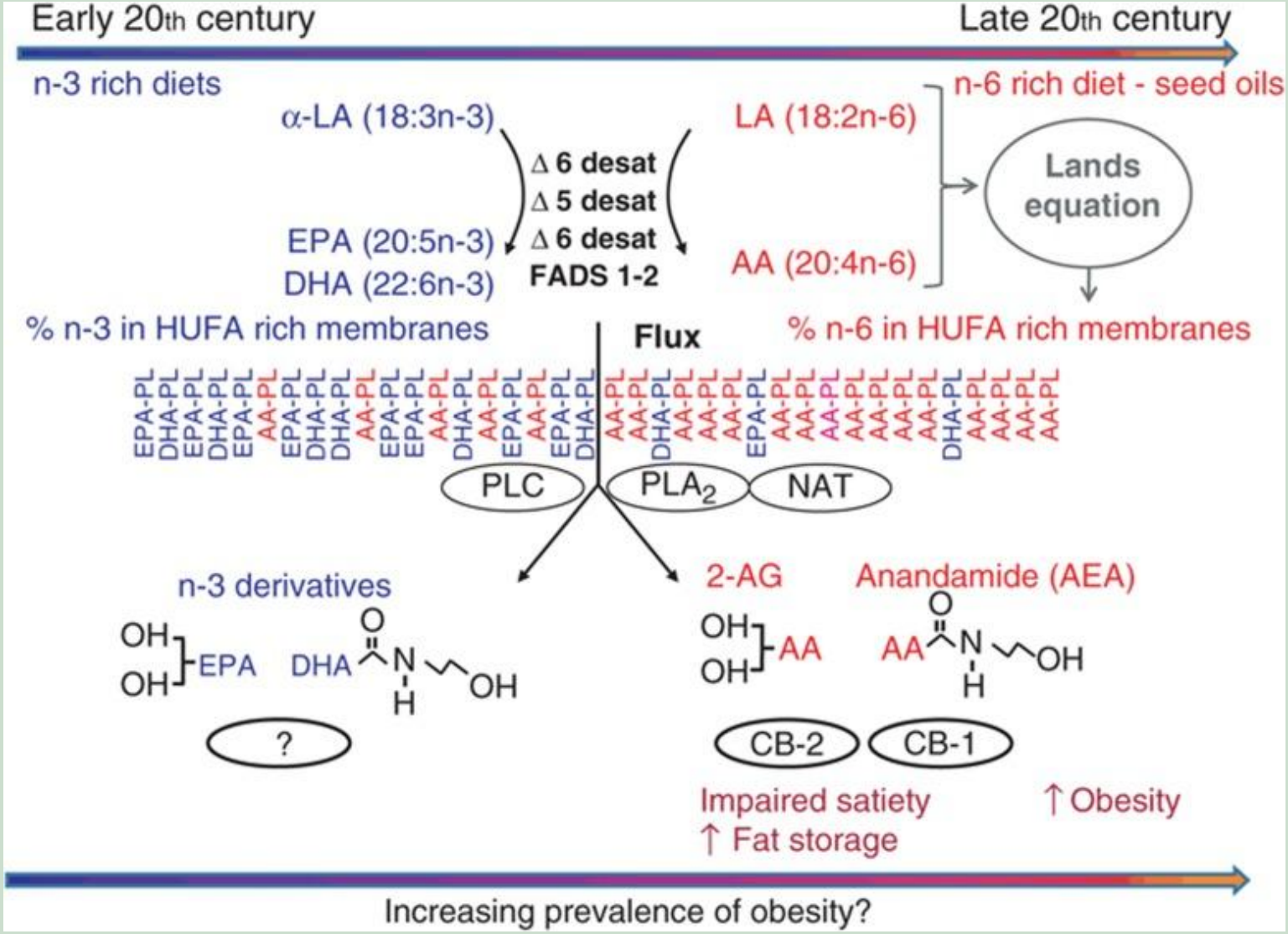
- Named by Ethan Russo, MD in 2004
- Occurs when low or poor ECS signaling or tone contributes to disease states or stress related illnesses associated with a distinct group of conditions that present with central sensitization, hyperalgesia, and treatment resistance.
  - Migraine HA - Deficiency lowers threshold for migraine initiation.
  - FMS - Deficiency permits central sensitization and hyperalgesia.
  - IBS - Deficiency impairs GI homeostasis.
  - Depression / Anxiety - Deficiency disinhibits HPA axis and impairs stress recovery.

Increased Endocannabinoid Tone



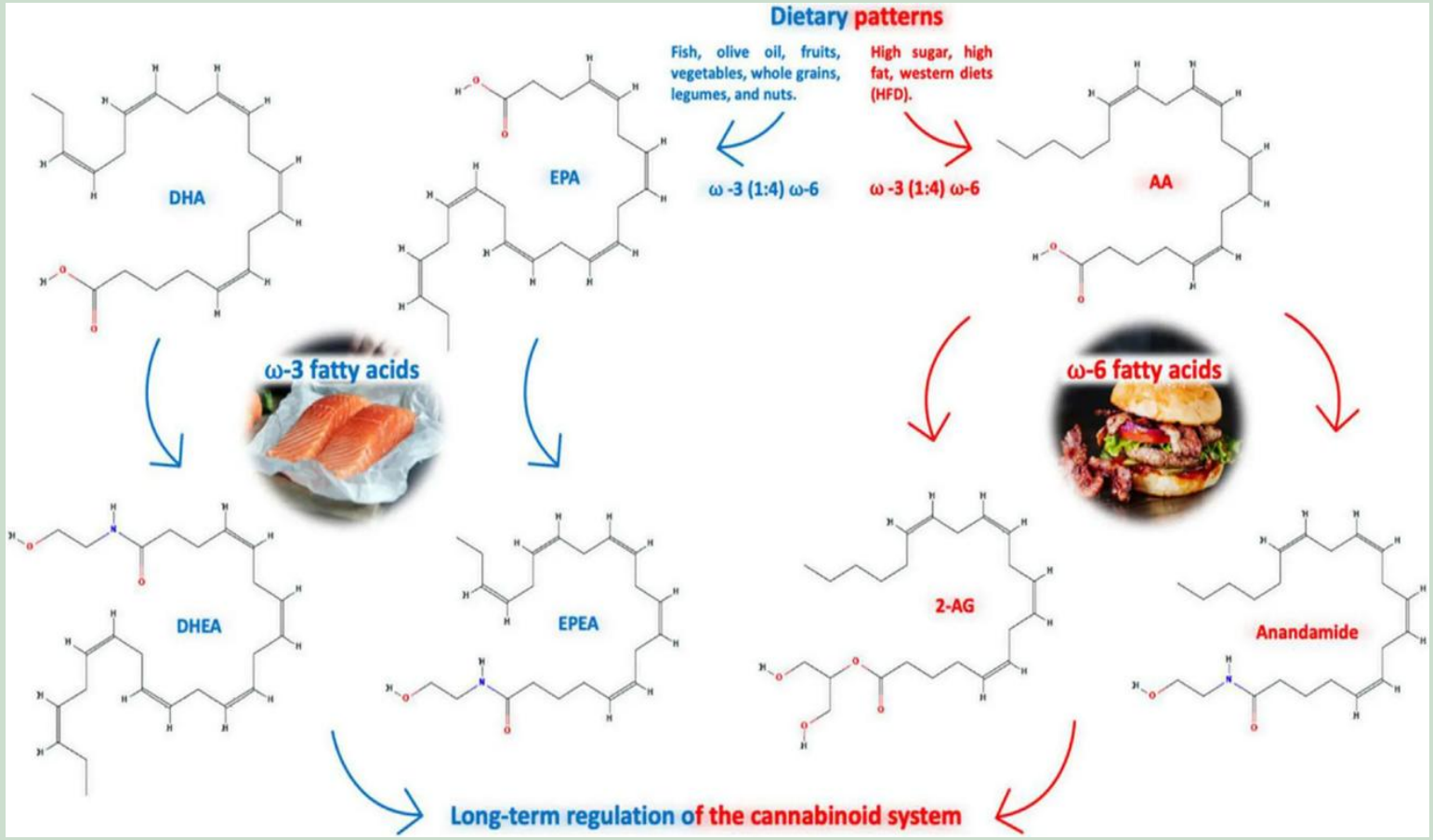
- High Omega-6 linoleic acid (LA) intake can excessively increase AEA and 2-AG, leading to diabetogenic and obesogenic effects.
- Associated conditions: Obesity, metabolic syndrome, NAFLD / NASH, hypertension, atherosclerosis, IBD, Chronic pain (in early phase), cancer, and several SUDs.
- A comprehensive review published in 2020 found that omega-6 fatty acids increased endocannabinoid levels, reinforcing the concept that the omega-6/omega-3 ratio is a key determinant of ECS tone.

Dietary Linoleic Acid Elevates Endogenous 2-AG and Anandamide and Induces Obesity



The ω-6/ ω-3 ratio & its effects on the Endocannabinoid System

High AEA from AA found in many conditions: Depression, PCOS, CAD, HF, ACS, obesity, insulin resistance, multiple sclerosis, ALS, Huntington's, Parkinson’s, Alzheimer's.

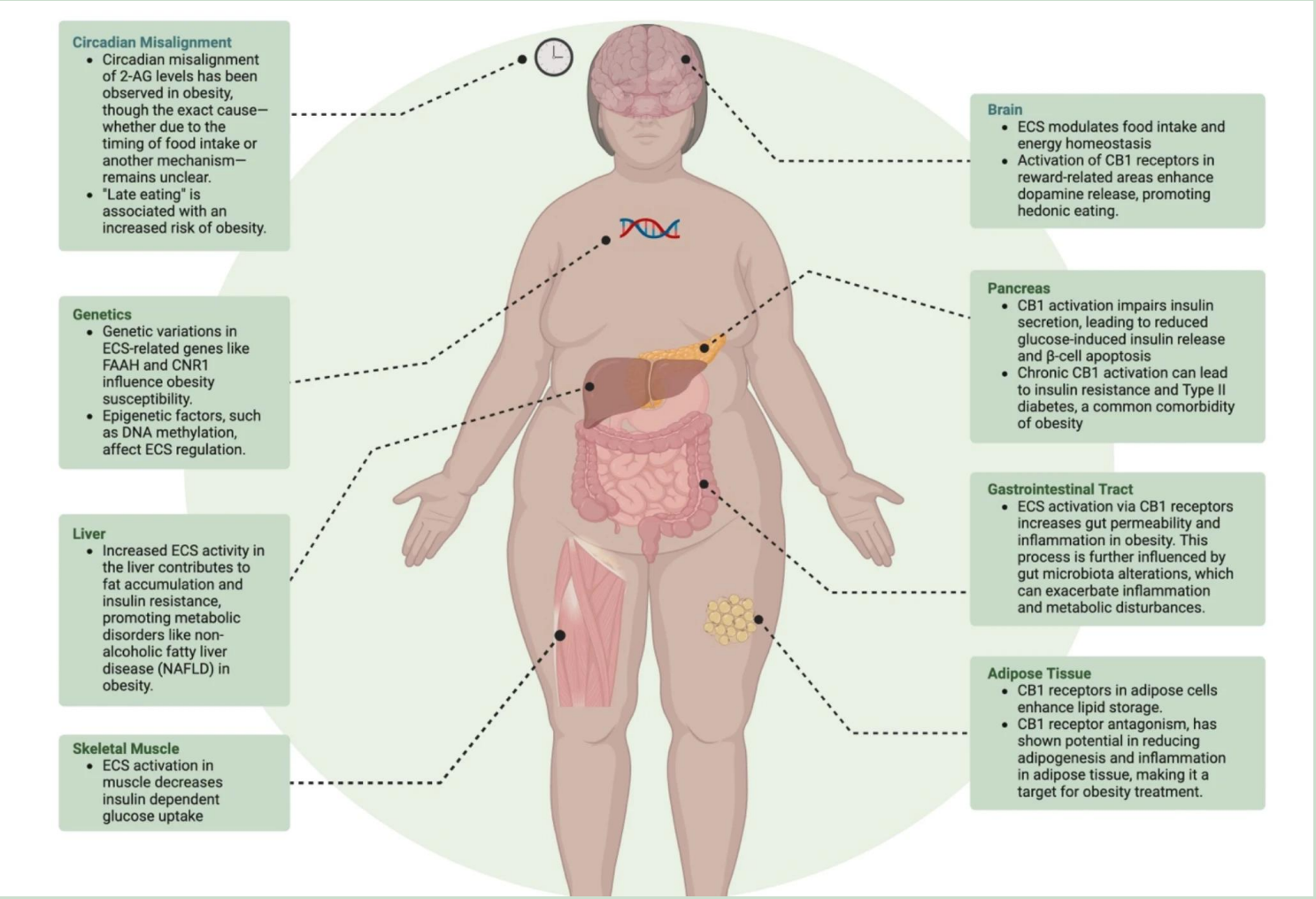


The ω-6/ ω-3 ratio & its effects on the Endocannabinoid System

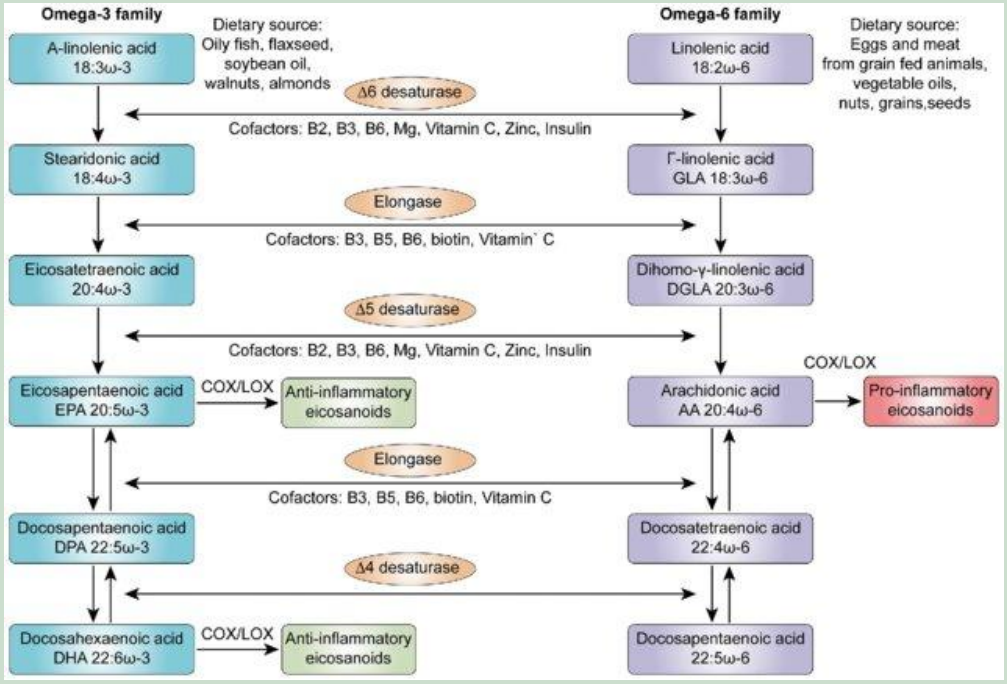
- ECs are metabolites products of dietary essential polyunsaturated fatty acids LA but after it is converted to arachidonic acid (ARA), is the main precursor for the two endocannabinoids.
- Endocannabinoids produced from ARA regulate energy homeostasis and adiposity through modulation of energy intake and thermogenic capacity.
- Endocannabinoids derived from ALA, α-*linolenic* 18:3(n-3) are Synaptamide (docosahexaenoylethanolamide, DHEA),and eicosapentanoyl ethanolamide (EPEA or EPA-EA).

The Omega-6/Omega-3 ratio & its effects on the Endocannabinoid System

- Obesity is associated with a dysregulated endocannabinoid system which may reflect enhanced inflammation.
- Endocannabinoids as an ARA reservoir.



Why Quality Lipids are Important in the Diet



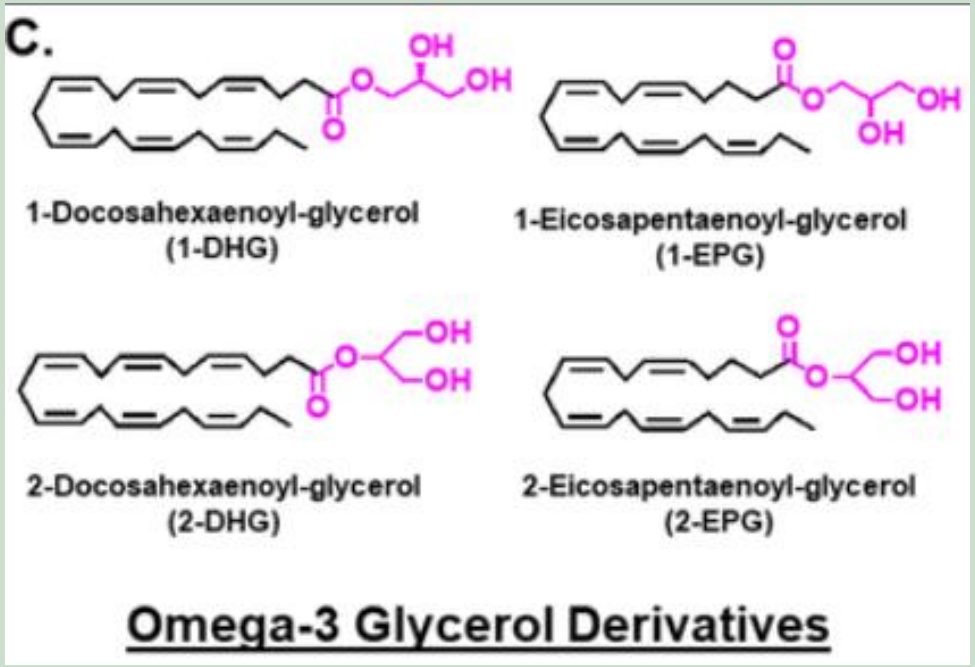
- High Omega-6 fatty acid linoleic acid intake can excessively increase AEA and 2-AG, leading to diabetogenic and obesogenic effects.
- The Omaga 3 fatty α-linolenic acid itself does not directly generate endocannabinoids but modulates the endocannabinoid system indirectly.
- Plus, ALA conversion is inefficient.
- Alters brain levels of anandamide (AEA) and 2-AG.
- ALA has shown reduced AEA, shifted NAPE-PLD and increased FAAH expression in preclinical data.

Why Quality Lipids are Important in the Diet

- Supplementation with marine oils EPA and DHA have shown to reduce the pro-inflammatory omega-6-derived endocannabinoids AEA and 2-AG in a human clinical trial N=84.
- Increased eicosapentaenoyl ethanolamide (EPEA) and docosahexaenoyl ethanolamide (DHEA) in adipose tissue in normal weight, less in metabolically healthy obese patients.

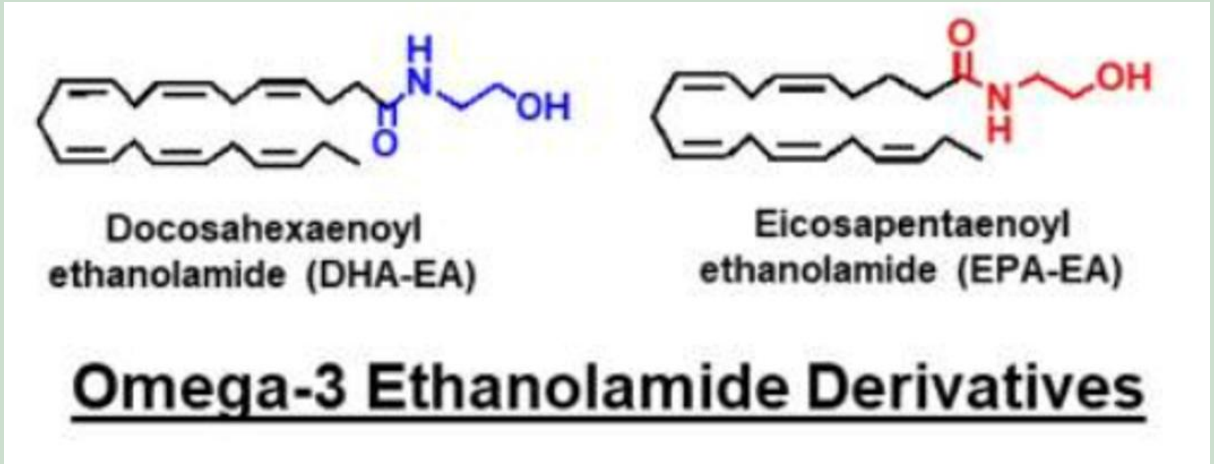
ω-3 eCBs glycerol derivatives

- Eicosapentanoylglycerol (EPG): CB1/CB2 interactions; anti-inflammatory.
- Docosahexanoyl-glycerol (DHG): CB1/CB2 partial agonist; less studied.



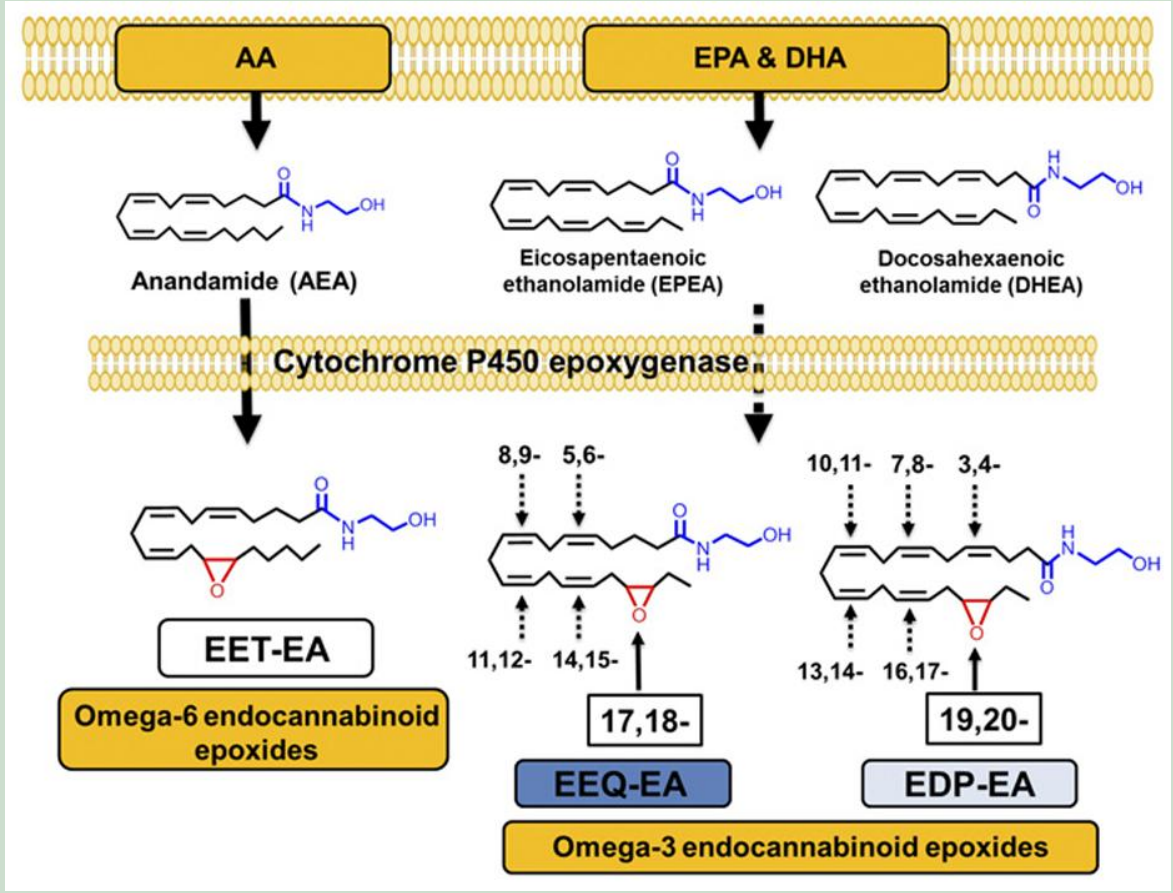
ω-3 eECs Ethanolamide derivatives

- Made from marine fatty acids, EPA and DHA.
- Docosahexaenoyl ethanolamide (DHEA/ DHA-EA, or Synaptamide)
  - Supports neurogenesis, neurite outgrowth, synaptogenesis via GPR110 (ADGRF1); anti-neuroinflammatory.
- Eicosapentaenoyl ethanolamide (or EPEA/ EPA-EA)
  - Anti-inflammatory in adipocytes; anti-proliferative in cancer models.

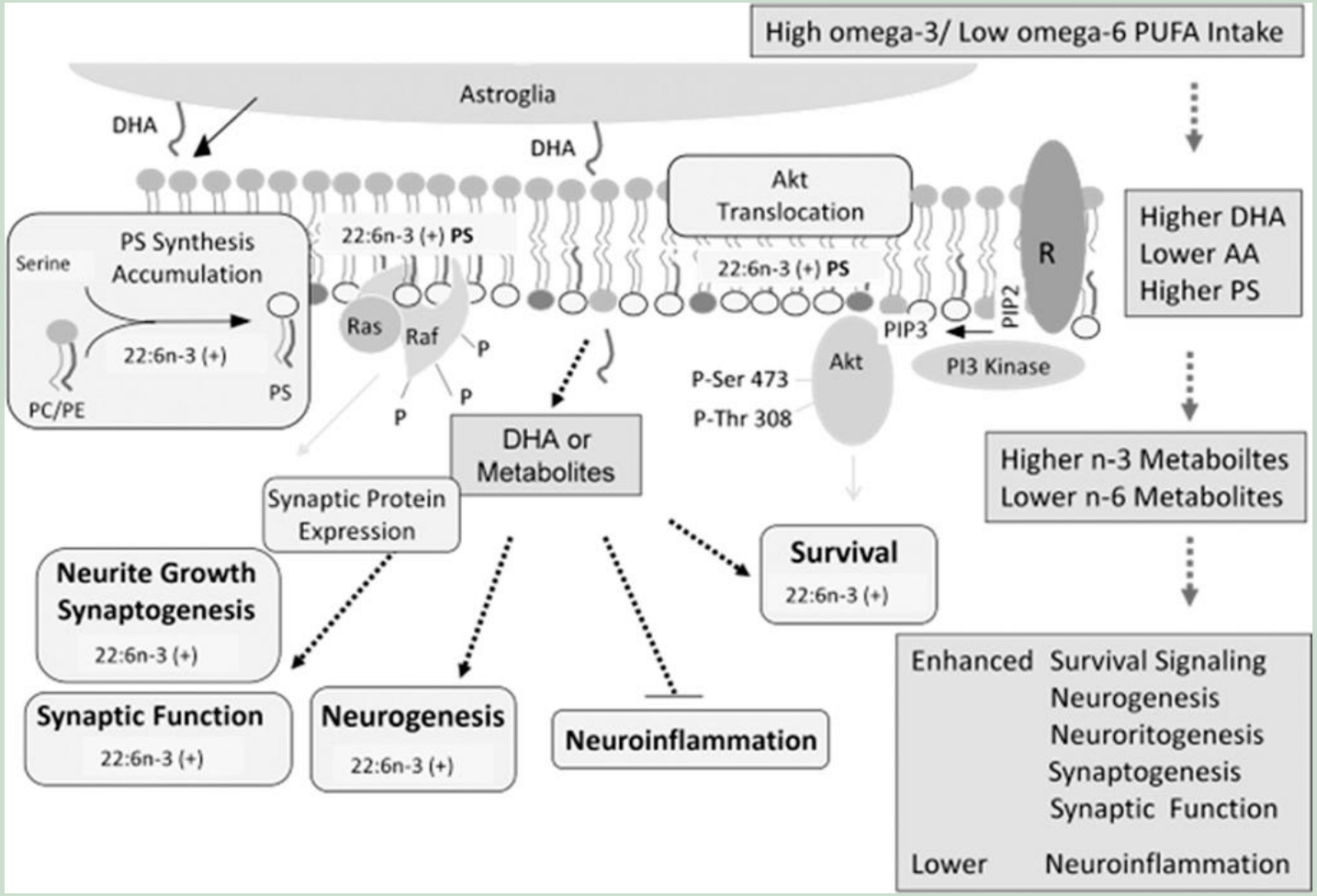


ω-3 Endocannabinoid Epoxides

- Metabolized by CYP from Omega-3 eCBs ethanolamide derivatives
  - Reduces IL-6
  - Increases IL-10
  - Antiangiogenic effects
  - Vasodilatory effects
  - Regulate platelet aggregation
- May be mediated by Synaptamide.



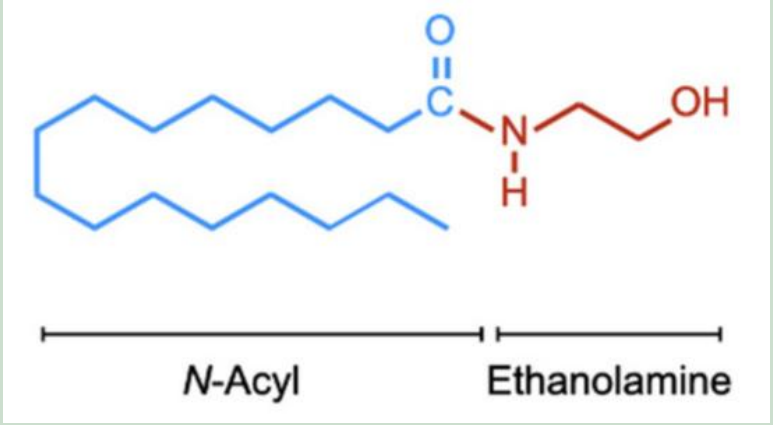
Synaptamide



- Levels directly linked with DHA.
- Has anti-inflammatory, neuroprotective, and neurotrophic actions.
- Preclinical data support shows:
  - Improved cognition & neural plasticity.
  - A neuropathic pain modulation effect.
  - Lower biomarkers and neuroregeneration in traumatic brain injury.
  - PS: phosphatidylserine

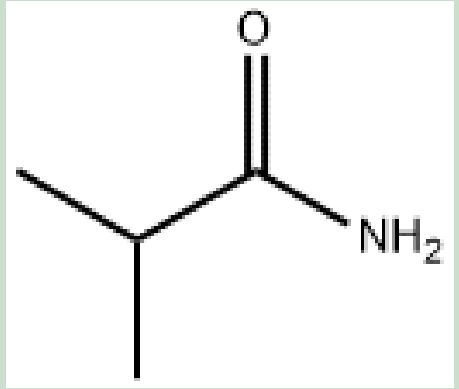
Palmitoylethanolamide (PEA)

- PEA is structurally similar to both endogenous cannabinoids anandamide and 2-arachidonoylglycerol, made in humans from membrane lipids from N-arachidonoyl phosphatidylethanolamine (NAPE).
- PEA allows for the TRPV1 channels to be less responsive to painful stimuli (capsaicin, bradykinin), contributing to its analgesic properties.
- Downmodulates mast cell degranulation and controls microglial activation, reducing neuroinflammation.
- Acts through many receptor targets: PPAR α, γ, β/δ
- Anti-inflammatory.



Cannabimimetic

- Scientific term proposed to cover all ligands of the cannabinoid receptor that are not Cannabis, regardless of their chemical structures or where in nature they are found. Legal term includes synthetic compounds.
- Many are *N*-alkylamides (NAAs), also called alkamides, compounds with a broad functional spectrum.
- Classic structure is a fatty acid chain linked to an amine group via an amide bond attached to a N-isobutylamide moiety.
- Many bind to a CB receptor, predominately CB1.
- Some are indirect, enhance “endocannabinoid tone.”



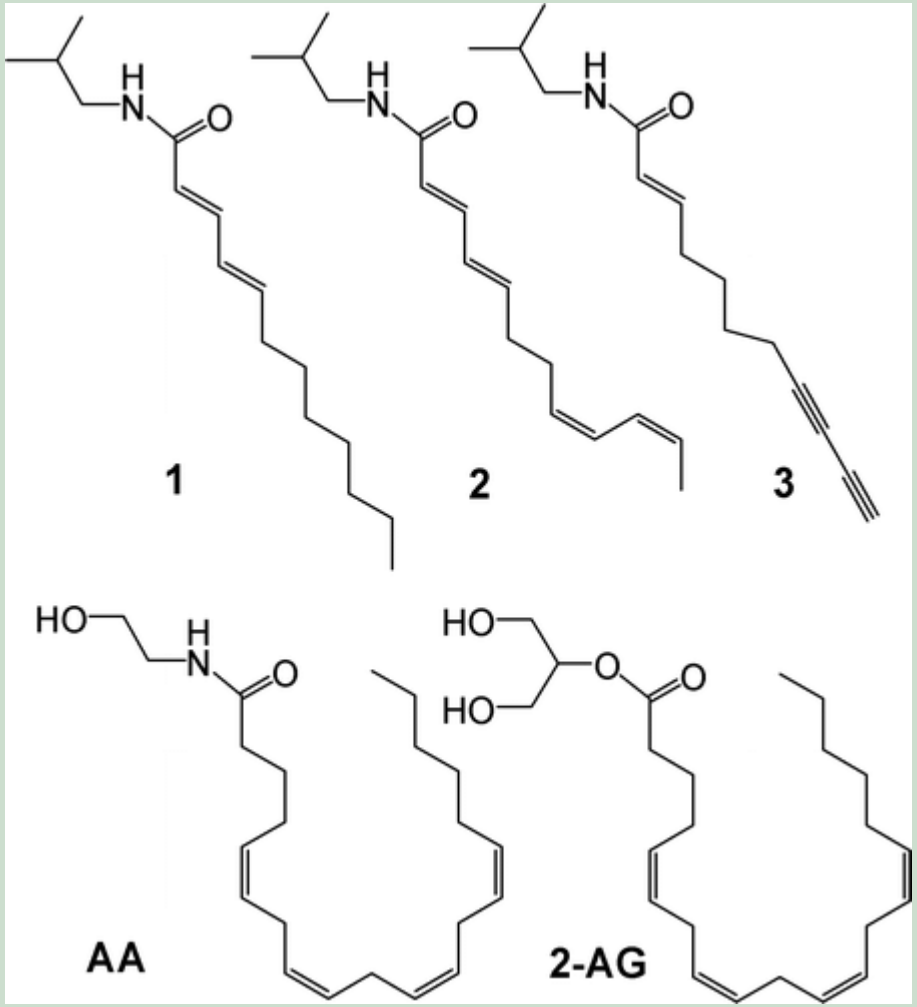
N-Alkylamides from Natural Origin

- Described as biologic alkaloids thought to be produced in plants responsive to environmental stress and promote plant growth.
- Several found in the Asteraceae family.
- *Echinacea* spp contain fatty acid N-alkylamides that activate CB2 receptors.
- *Heliopsis helianthoides* aka oxeye, early or false sunflower, and *Heliopsis longipes* from Mexico.
- *Acmella oleracea*: contains spilanthol
- *Anacyclus pyrethrum:* Spanish chamomile, similar to *Acmella.*
- Maybe present in several spices.

N-alkylamides found in *Echinacea*

Isobutylamide alkylamides bind CB2 with greater affinity than anandamide, as a partial agonist.

- N-isobutylamides aka Alkamides.



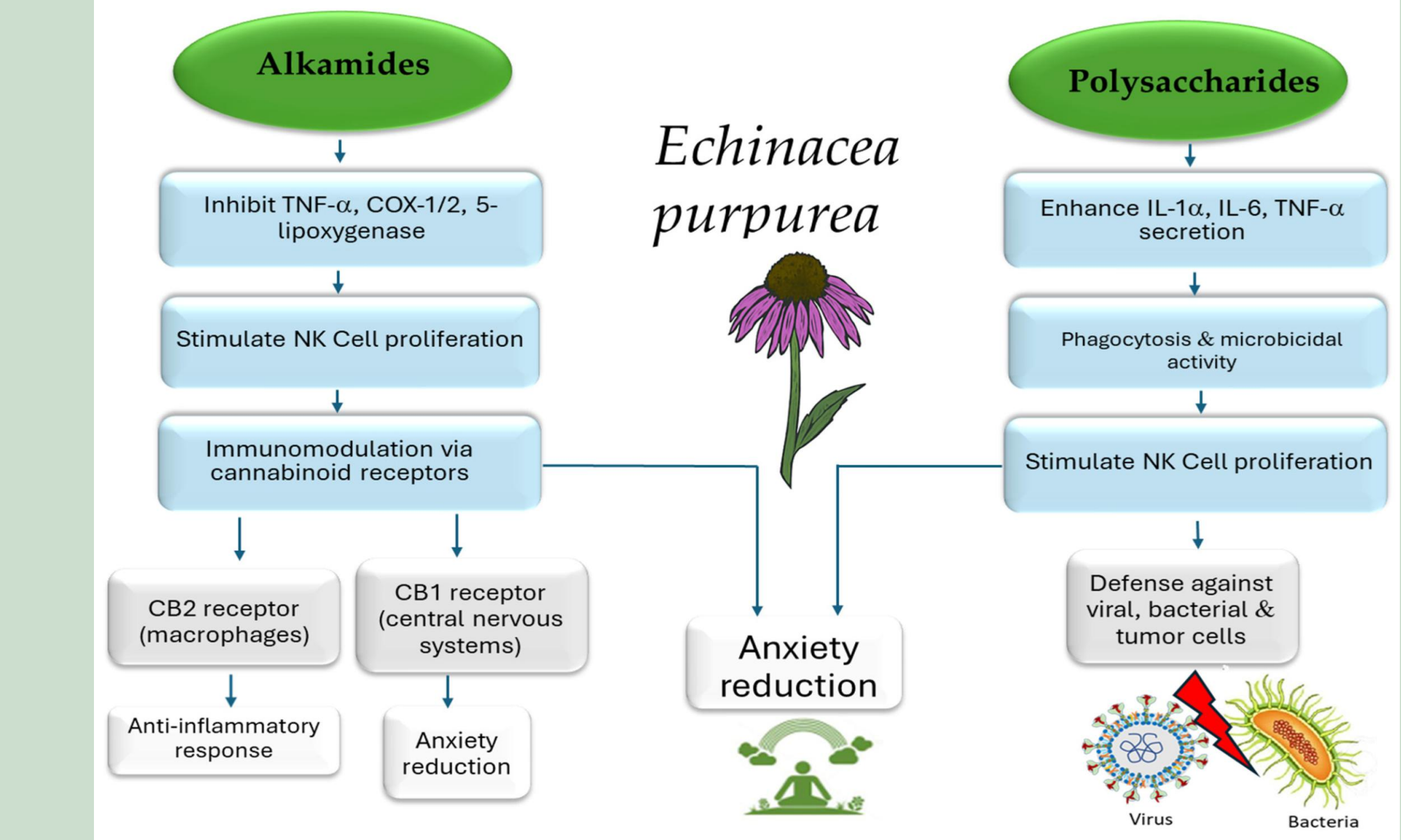
Alkylamides found in *Echinacea* 'Alkamide 8'

- In a preclinical model 2 ECH extracts were evaluated for analgesic and anti-neuropathic effects with Oxaliplatin inducing neuropathy.
  - n-hexane extract (EP4–RE; rich in alkylamides), in a non-polar extract
  - butanolic extract (EP4–RBU; rich in polyphenols), in a polar extract
- Both extracts reduced pain, but the alkylamide extract was more effective than the main constituent, while the polyphenolic extract was not, with chicoric acid as the primary active polyphenol.
- 'Alkamide 8' had better pain relief at 30 m, and same at 45 m.
- Same compound was shown to be detected in plasma after 10 minutes of ingestions a lozenge, sampling point at 10 min, showing improved bioavailability and possible absorption through the oral mucosa.

Peak	Compound
1	Undeca-2 *E*,4*Z*-diene-8,10-diynoic acid isobutylamide and/or undeca-2*Z*,4 *E*-diene-8,10-diynoic acid isobutylamide
2	Dodeca-2 *E*,4 *E*,8*Z*,10*Z*/*E*-tetraenoic acid 2-hydroxy-isobutylamide**
3	Dodeca-2 *E*,4 *E*,8*Z*-trienoic acid 2-hydroxy-isobutylamide **
4	Dodeca-2 *E*,4*Z*-diene-8,10-diynoic acid isobutylamide and/or dodeca-2*Z*,4 *E*-diene-8,10-diynoic acid isobutylamide
5	Dodeca-2 *E*,4*Z*,10 *E*-triene-8-ynoic acid isobutylamide
6	Trideca-2 *E*,7*Z*-diene-8,10-diynoic acid isobutylamide
7	Pentadeca-2 *E*,9*Z*-diene-12,14-diynoic acid 2-hydroxy-isobutylamide**
8	Dodeca-2 *E*,4 *E*,8*Z*,10*Z*-tetraenoic acid isobutylamide and/or dodeca-2 *E*,4 *E*,8*Z*,10 *E*-tetraenoic acid isobutylamide and/or dodeca-2 *E*,4 *E*,8 *E*,10*Z*-tetraenoic acid isobutylamide
9	Dodeca-2 *E*,4 *E*,8*Z*-trienoic acid isobutylamide
10	Dodeca-2 *E*,4 *E*,8*Z*,10*Z*-tetraenoic acid methylbutylamide and/or dodeca-2 *E*,4 *E*,8*Z*,10 *E*-tetraenoic acid methylbutylamide
11	Dodeca-2 *E*,4 *E*-dienoic acid isobutylamide
12	Pentadeca-2 *E*,9*Z*-diene-12,14-diynoic acid isobutylamide

Tentatively identified based on MS/MS data; not reported in *Echinacea* genus up to now.

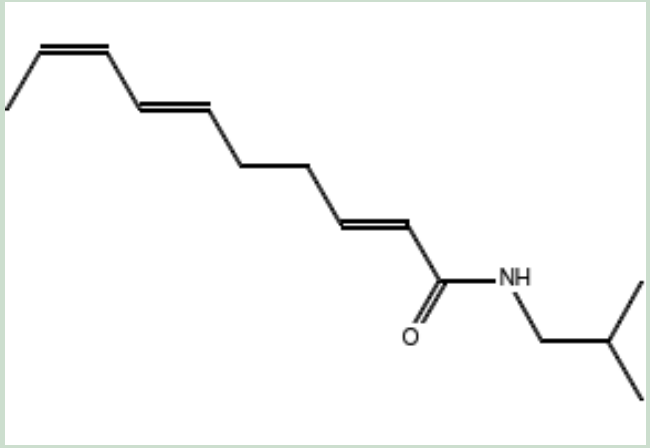
Echinacea ’Alkamide 8’


Alkamides
Inhibit TNF-α, COX-1/2, 5-lipoxygenase
Stimulate NK Cell proliferation
Immunomodulation via cannabinoid receptors
CB2 receptor (macrophages)
Anti-inflammatory response
CB1 receptor (central nervous systems)
Anxiety reduction
Echinacea purpurea
Anxiety reduction
Polysaccharides
Enhance IL-1α, IL-6, TNF-α secretion
Phagocytosis & microbicidal activity
Stimulate NK Cell proliferation
Defense against viral, bacterial & tumor cells
Virus
Bacteria

Acmella oleracea

- Commonly called Spilanthes, paracress, toothache plant, jambu, buzz button
- Medicinal actions: anti-inflammatory, antioxidant, analgesic, anesthetic, antiplasmodial, antibacterial, wound healing, and antipyretic effects.
- Contains many alkamides

Spilanthol from *Acmella oleraca*



- Interacts with the ECS by binding CB1 & CB2 receptors, and modulation of the TRVP receptors.
- Has analgesic and antinociceptive actions, leading to one of its names, toothache plant.
- Causes strong numbing, tingling and salivation, has diuretic actions, and could act as a vasorelaxant.
- Activation of opioidergic, serotonergic, and GABAergic systems (naloxone only partially reverses the analgesic effect, indicating non-opioid mechanisms contribute substantially).

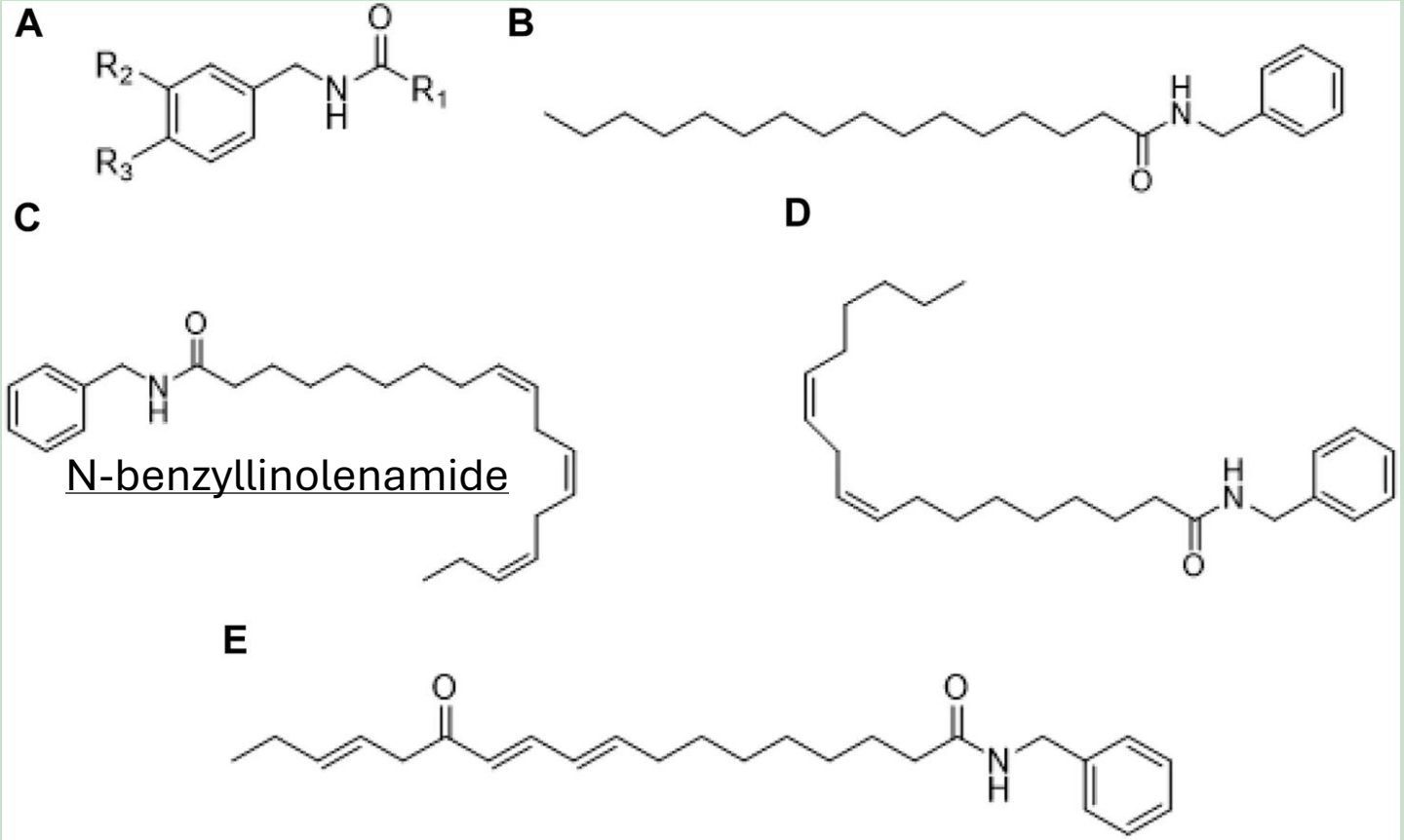
Maca (*Lepidium meyenii*)

- Maca ‘tubers’ can be dried to be used as flour.
- Macamides are secondary metabolites, benzylamides, derived from glucosinolates.
- are secondary metabolites and inhibitors of FAAH.

Macamides from Maca

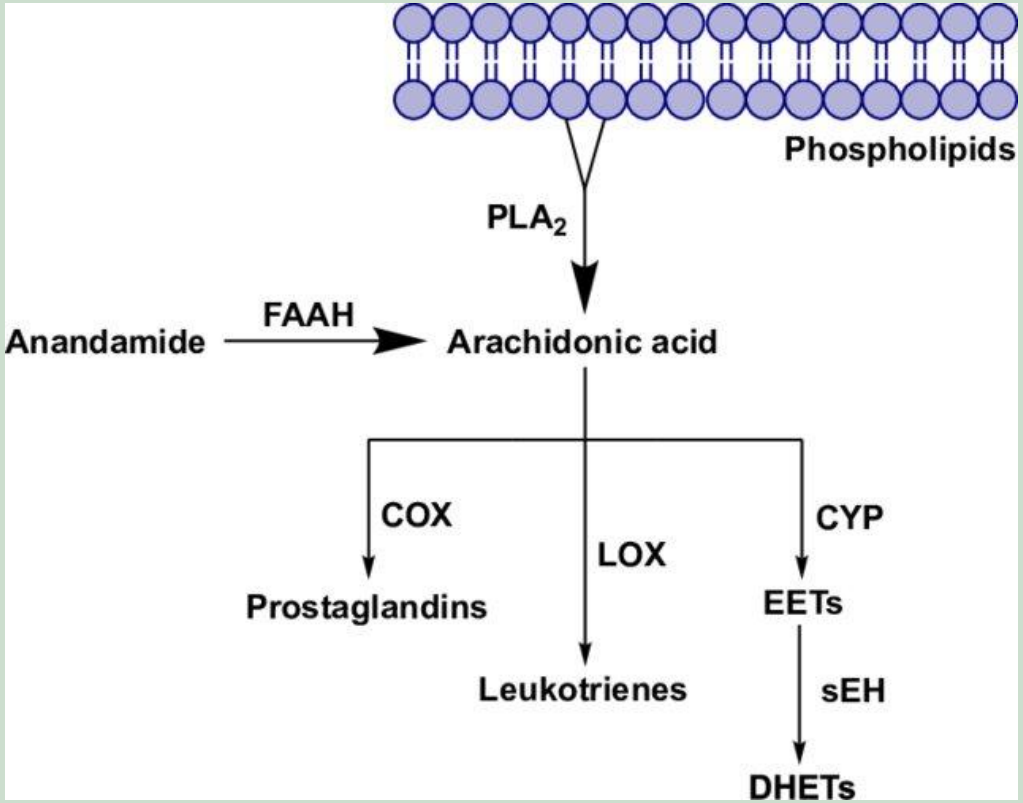
Macamides are secondary metabolites, benzylamides, derived from glucosinolates.

Bind to CB1, show FAAH inhibition.



Macamides from Maca

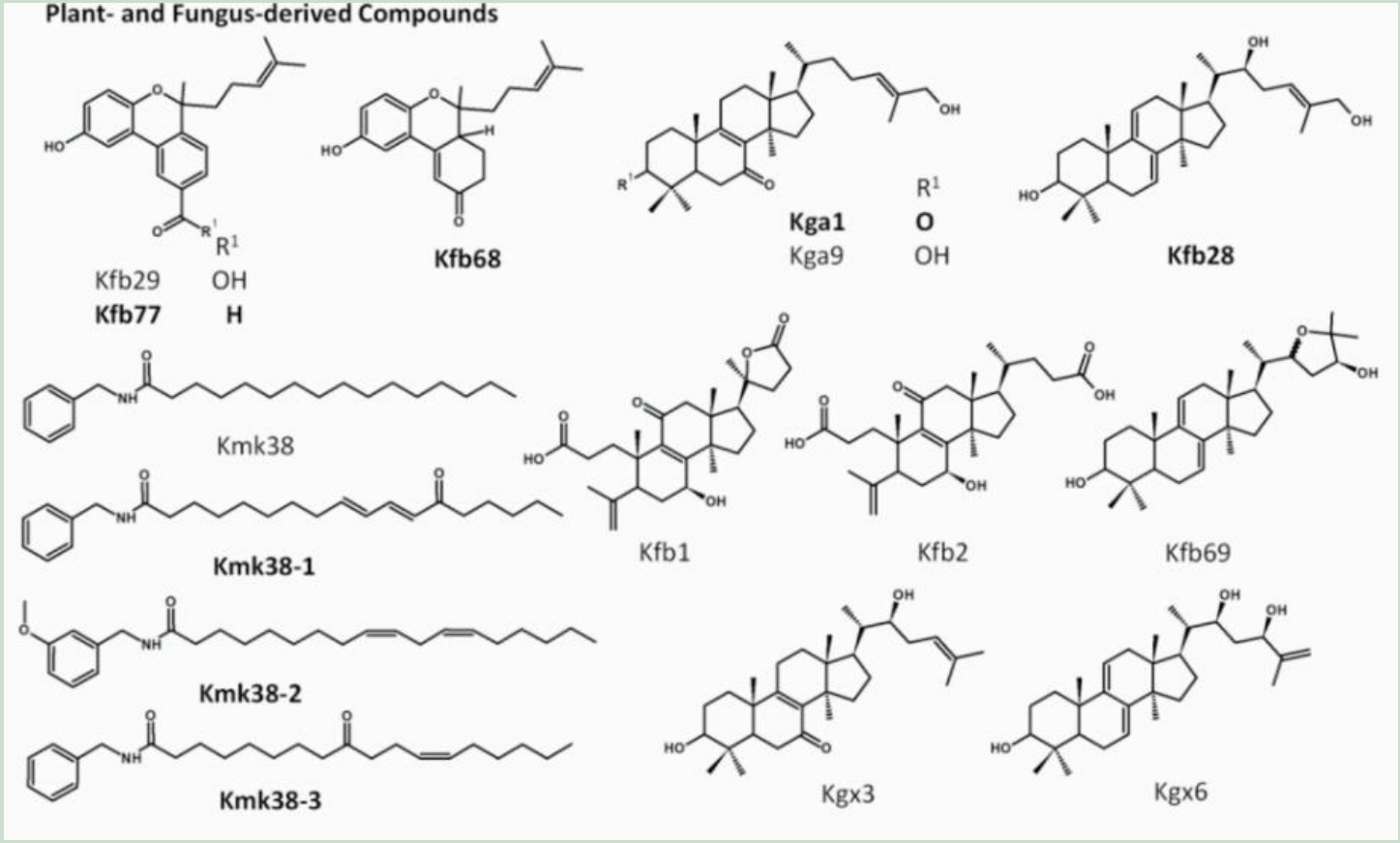
- Macamides are benzylamides secondary metabolites derived from N-benzyllinolenamide.
- Potent inhibitors of soluble epoxide hydrolase (sEH).
- Macamides have potent inhibition of anandamide cellular uptake via sEH to inhibit breakdown, stabilize metabolic products of anandamide that are still active, ethanolamide derivatives, prolonging the effect at the receptor - *Increasing ECS tone.*



Ganoderma species Mycocannabinoids

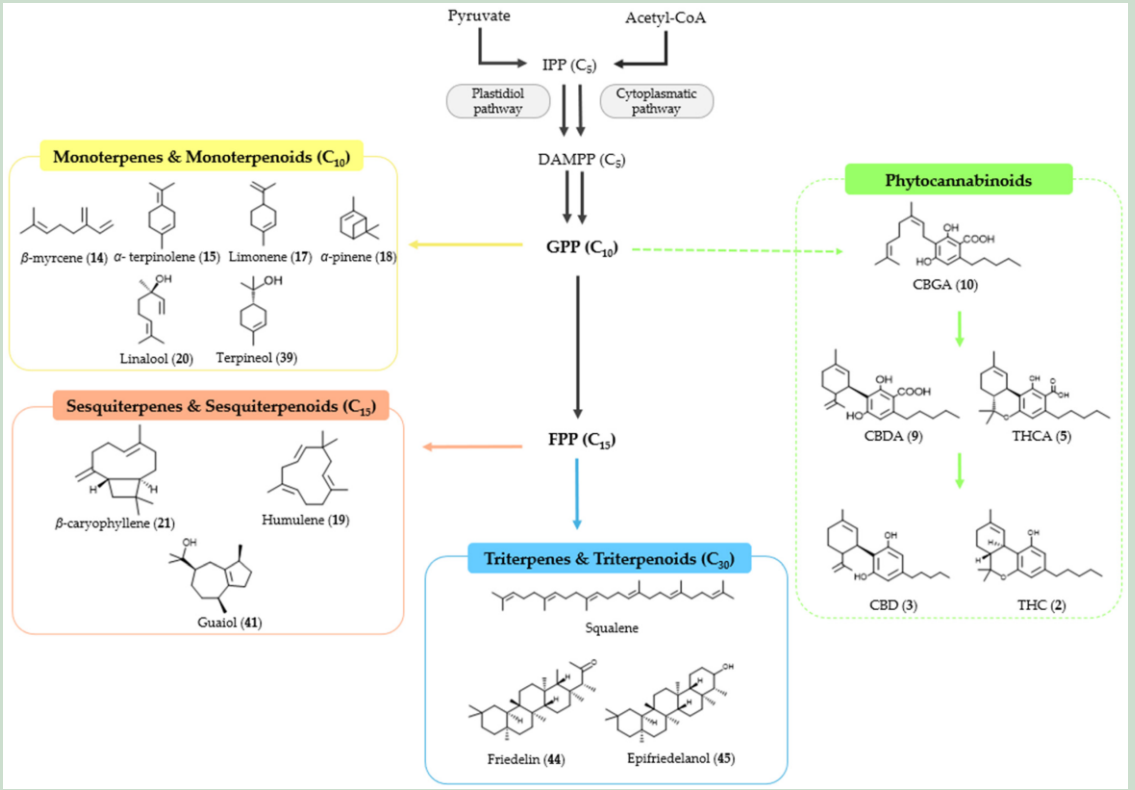
- Four compounds from *Ganoderma hainanense* and *Ganoderma capense* were identified as active on cannabinoid receptors.

FIG. 2: A topotype collection of *Ganoderma sichuanense* (HMAS 244431)

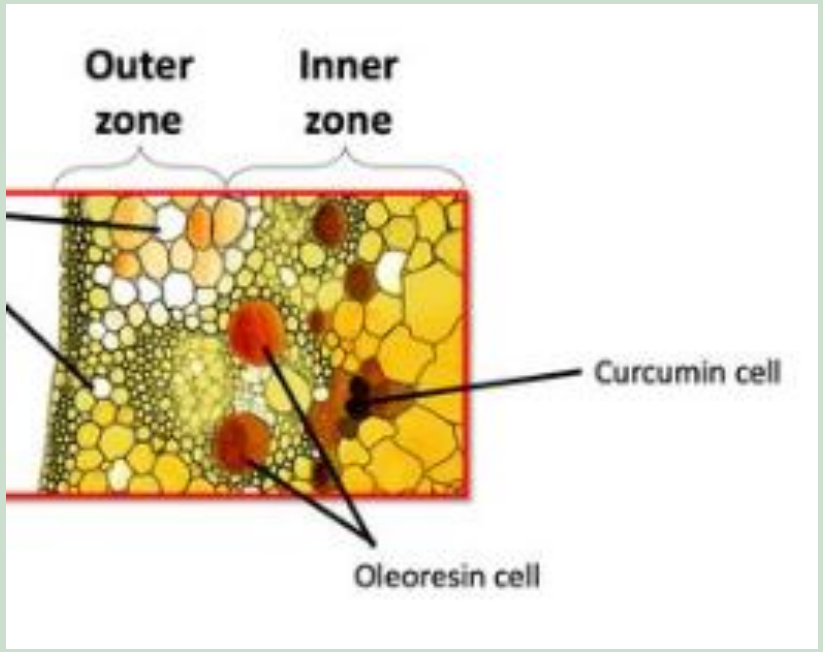


Synergy of compounds: Entourage Effect

- Plants contain hundreds of different compounds that work together to achieve a result that no single compound can achieve.
- Synergy arises from the interactions between a plant's multiple compounds and components and may enhance the plant's overall benefits.
- Compounds thought to enhance the entourage effect include aromatic terpenes β-caryophyllene, α-humulene, geraniol, linalool, β-pinene, myrcene, limonene, and p-cymene; plus, polyphenolic compounds.



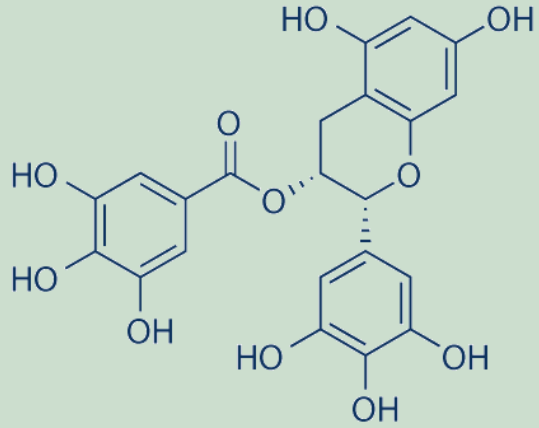
Curcuma and Curcumin



- Preclinical evidence shows Curcumin interacts with the ECS in several ways (but is considered a weak binder).
- Long term administration produced hippocampal nerve growth factor (NGF), increase in AEA and 2-AG, reversed with a CB1 antagonist.
- May act indirectly, possibly by promoting endocannabinoid release or modulating upstream pathways that converge on CB1 signaling.
- Turmeric oleoresin activates CBR2: reduced ROS, downregulated pro-inflammatory cytokines (IL-6, COX-2, metalloproteases), and suppressed NF-κB and ERK1/2 signaling — effects that were reversed by CB2 antagonism.

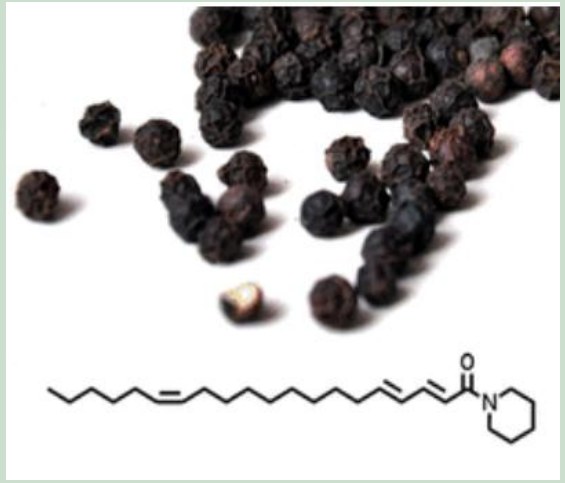
Green Tea (*Camellia sinensis*)

- 2010 study using EGCG, EGC and ECG to assess binding, only EGCG had binding affinity to CB2.
- Showed weak binding, more polyphenols bind to CB1, theoretical role for analgesic, and modulation of food intake.
- Binding to CB2, which has more immune modulation, was weaker.



Black pepper (*Piper nigrum*)

- Contains β-caryophyllene.
- A preclinical trial used a black pepper seed standardized extract evaluating antinociceptive effect via CB2, PPARa and TRVi channels, compared with diclofenac and a reference compound BCP, with 30% β-caryophyllene.
- Doses used were 10mg, 25mg and 50mg/kg doses.
- Animals showed decreased pain by several different evaluations, and pain was reversed with a CB2 antagonist.



β-caryophyllene

- Considered a selective CB2 full agonist, produced by *Cannabis.*
- Reduces PGE2 synthesis.
- Physiological Mechanism: Direct peripheral immunomodulation; shifts macrophages from M1 (pro-inflammatory) to M2 (reparative); inhibits NF-kb.
- β-caryophyllene found in many plants, documented to be high in clove (*Syzygium aromaticum*), *Angelica archangelica, Apium graveolens, Bidens pilosa, Piper nigrum, Origanum vulgare, Coleus barbatus, Salvia rosmarinus,* and *Coriandrum sativum* seeds.

Thank you!

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