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BIOACTIVE COMPOUNDS FROM FOOD AND DIETARY SUPPLEMENTS AS MODULATORS OF THE ENDOCANNABINOID SYSTEM

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Abstract

The endocannabinoid system (ECS) is a complex signaling network involved in the regulation of homeostasis, energy metabolism, immune responses, neuroprotection, and inflammatory processes. Its discovery followed the identification of receptors targeted by phytocannabinoids from *Cannabis sativa*, which stimulated intensive research into endogenous ligands, cannabinoid receptors, and their physiological roles. In recent years, an increasing body of scientific evidence has indicated that numerous bioactive compounds present in food and dietary supplements may modulate ECS activity through various molecular mechanisms.

The aim of this paper is to present current knowledge on the effects of bioactive compounds from food and dietary supplements on the endocannabinoid system and to establish a functional and mechanistic framework for their classification according to molecular targets, signaling pathways, and modes of ECS modulation.

Particular emphasis is placed on compounds that directly or indirectly modulate cannabinoid receptor activity, affect the synthesis and degradation of endocannabinoids, or act through other signaling pathways functionally associated with the ECS. The paper discusses **beta-caryophyllene, omega-3 fatty acids, polyphenols, flavonoids, terpenes, palmitoylethanolamide (PEA),** and other dietary bioactive compounds for which experimental and clinical data suggest potential beneficial effects.

The novelty of this paper lies in integrating the available evidence into a functional model that classifies bioactive compounds according to their mechanisms of action on the ECS rather than solely according to their chemical origin. Such an approach enables a better understanding of the interactions between diet and the endocannabinoid system and may provide a basis for the development of **functional foods, dietary supplements, and personalized nutritional strategies** aimed at maintaining health and preventing chronic non-communicable diseases.

Keywords: endocannabinoid system; bioactive compounds; dietary supplements; functional foods; beta-caryophyllene.

INTRODUCTION

The **endocannabinoid system (ECS)** is a complex signaling network involved in maintaining homeostasis in the body. It participates in the regulation of **energy metabolism, appetite, pain, inflammation, immune response, mood, sleep, neuroprotection, and gastrointestinal function**.

The ECS consists of the cannabinoid receptors **CB1 and CB2**, endogenous ligands, particularly **anandamide (AEA)** and **2-arachidonoylglycerol (2-AG)**, and enzymes involved in their synthesis and degradation, such as **FAAH (**Fatty Acid Amide Hydrolase and **MAGL(**Monoacylglycerol Lipase .

AIM OF THE STUDY

To present the most important **bioactive compounds from food and dietary supplements** that act as modulators of the endocannabinoid system and to classify them according to their **molecular targets, signaling pathways, and modes of ECS modulation**.

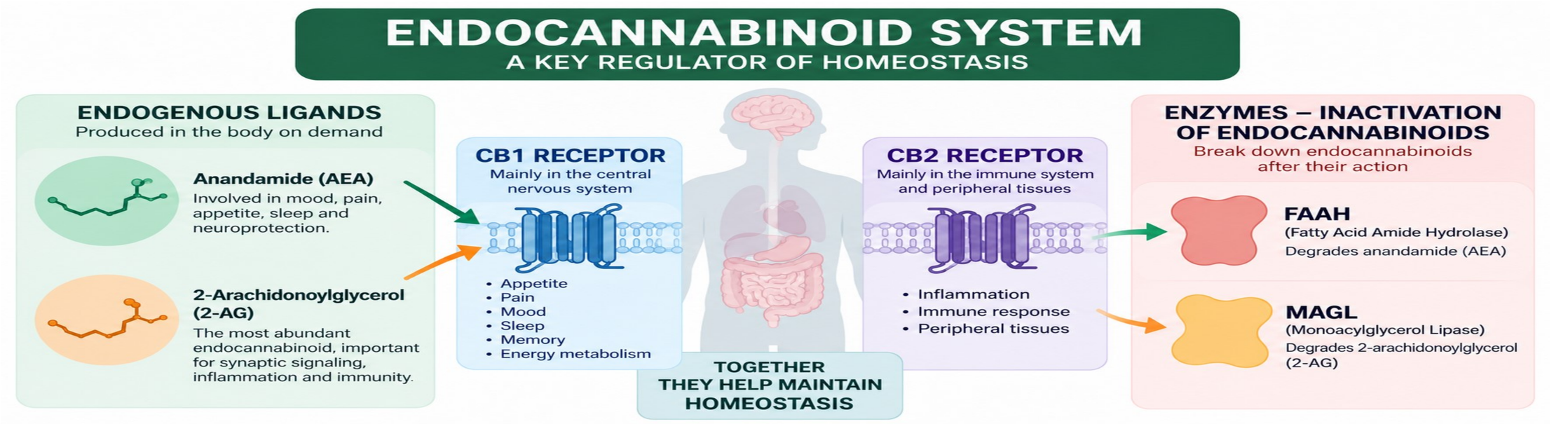
ENDOCANNABINOID SYSTEM – KEY COMPONENTS

- **CB1 receptors** – are predominantly expressed in the central nervous system and are involved in the regulation of **appetite, pain, mood, sleep, memory, and energy metabolism**.
- **CB2 receptors** – are associated with the **immune system, inflammation, and peripheral tissues**; their activation plays an important role in controlling inflammatory and immune responses.
- **Anandamide (AEA)** – an endogenous cannabinoid associated with **mood, pain, appetite, sleep, and neuroprotection**.
- **2-Arachidonoylglycerol (2-AG)** – the most abundant endocannabinoid, important for **synaptic signaling, inflammation, immunity, and nervous system function**.

Table 1. Key bioactive compounds: cannabinoids and cannabinoid-like molecules

Compound	Group	Main Target(s)	Key Role / Significance
Anandamide (AEA)	Endocannabinoid	CB1, CB2, FAAH	Mood, pain, appetite, sleep, neuroprotection
2-AG	Endocannabinoid	CB1, CB2, MAGL	Inflammation, immunity, synaptic signaling
Cannabidiol (CBD)	Phytocannabinoid	TRPV1, PPAR-γ, FAAH; indirect CB1/CB2 modulation	Neuroprotection, pain, inflammation, oxidative stress
Tetrahydrocannabinol (THC)	Phytocannabinoid	CB1, CB2	Direct ECS activation; psychoactive and legally regulated
β-Caryophyllene	Dietary cannabimimetic terpene	Selective CB2 agonist	Anti-inflammatory and immunomodulatory potential; non-psychoactive
Palmitoylethanolamide (PEA)	Endocannabinoid-like lipid	PPAR-α, mast cells, microglia	Pain, inflammation, neuroinflammation
Oleoylethanolamide (OEA)	Endocannabinoid-like lipid	PPAR-α	Satiety, lipid metabolism, energy balance
Cannabigerol (CBG)	Phytocannabinoid	CB1/CB2, TRP channels	Potential anti-inflammatory, neuroprotective and gastrointestinal effects

Bioactive food compounds can modulate the endocannabinoid system through cannabinoid receptors, PPARs, TRP channels and endocannabinoid-metabolizing enzymes.



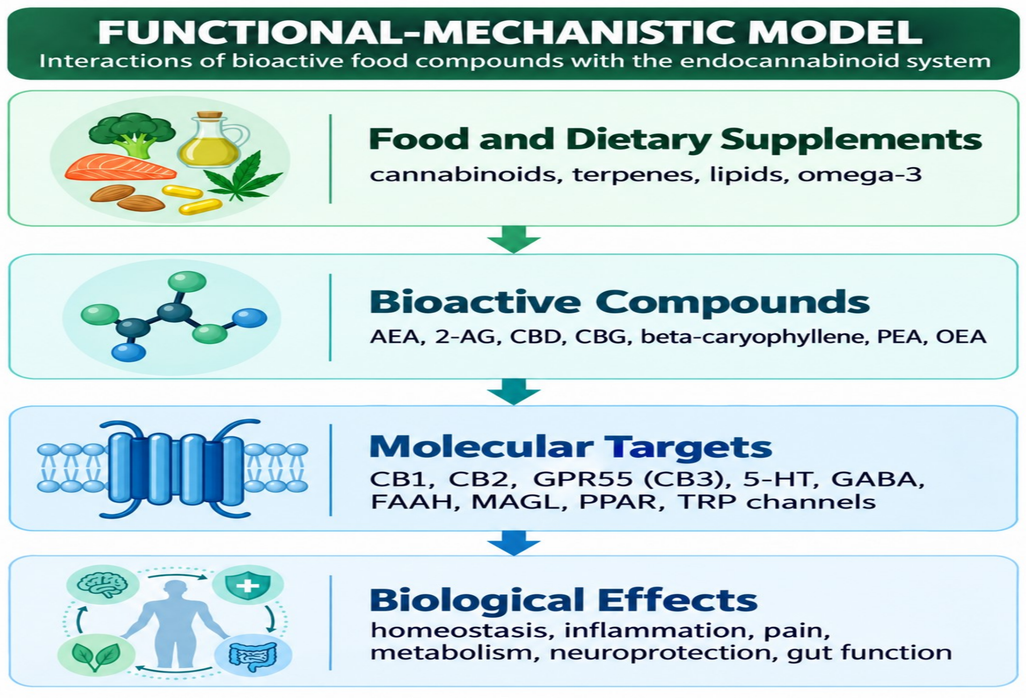
MECHANISMS OF ECS MODULATION

- **Direct action on CB1 and CB2 receptors:** Phytocannabinoids and certain dietary compounds can activate or modulate cannabinoid receptors; **β-caryophyllene** is particularly notable as a selective **CB2 receptor agonist**.
- **Effects on endocannabinoid degradation:** Modulation of the enzymes **FAAH** and **MAGL** can alter the levels and duration of action of endocannabinoids.
- **Interaction with more than 30 receptors:** ECS-related compounds may interact with a broad range of receptors and signaling pathways beyond CB1 and CB2.
- **Activation of PPAR receptors: PEA** and **OEA** act through **PPAR-α receptors**, which are involved in the regulation of inflammation, lipid metabolism, pain, and neuroinflammation.
- **Modulation of inflammation and immune response:** Activation of **CB2- and PPAR-related signaling pathways** may contribute to reducing pro-inflammatory mediators.

Interaction with the gut microbiota: Diet, probiotics, prebiotics, and bioactive lipids may influence the gut–brain axis, intestinal barrier function, and functional ECS tone.

DIETARY SOURCES AND SUPPLEMENTS OF PARTICULAR INTEREST

- **β-Caryophyllene:** Found in **black pepper, cloves, oregano, basil, and hops**; a dietary compound with cannabinoid-like activity mediated through the **CB2 receptor**.
- **PEA – Palmitoylethanolamide:** An endogenous lipid mediator and dietary supplement investigated in relation to **pain, chronic inflammation, neuroinflammation, and recovery**.
- **OEA – Oleoylethanolamide:** A lipid mediator associated with **satiety, fat metabolism, and energy balance**.
- **CBD and CBG:** Phytocannabinoids from *Cannabis sativa*, investigated for their potential **anti-inflammatory, neuroprotective, and analgesic effects**, with particular attention to **legal regulation and safety of use**.
- **Omega-3 fatty acids: EPA and DHA** may influence the synthesis of lipid mediators associated with the ECS and contribute to the regulation of **inflammation and nervous system function**



CONCLUSION

The **endocannabinoid system** is an important regulator of homeostasis, and bioactive compounds from food and dietary supplements may influence its activity through **direct or indirect mechanisms**.
The most important compounds include the endocannabinoids **AEA and 2-AG**, the phytocannabinoids **CBD and CBG**, the dietary cannabimimetic compound **β-caryophyllene**, and the endocannabinoid-like lipids **PEA and OEA**.
Compounds without psychoactive effects are of particular nutritional and functional interest, especially **β-caryophyllene, PEA, OEA, omega-3 fatty acids, and non-psychoactive phytocannabinoids**. Their further study may contribute to the development of **functional foods, dietary supplements, and personalized nutritional strategies** aimed at maintaining health and preventing chronic non-communicable diseases.

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