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Cannabidiol: State of the art and new challenges for therapeutic applications

Simona Pisanti [a,*,1], Anna Maria Malfitano [a,1], Elena Ciaglia [a], Anna Lamberti [a], Roberta Ranieri [a], Gaia Cuomo [a], Mario Abate [a], Giorgio Faggiana [a], Maria Chiara Proto [b], Donatella Fiore [b], Chiara Laezza [c], Maurizio Bifulco [a,d,*]

[a] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Italy
[b] Department of Pharmacy, University of Salerno, Italy
[c] IEOS CNR Naples, Italy
[d] Corporea, Fondazione Idis-Città della Scienza, Naples, Italy

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ABSTRACT

Over the past years, several lines of evidence support a therapeutic potential of *Cannabis* derivatives and in particular phytocannabinoids. Δ^9-THC and cannabidiol (CBD) are the most abundant phytocannabinoids in *Cannabis* plants and therapeutic application for both compounds have been suggested. However, CBD is recently emerging as a therapeutic agent in numerous pathological conditions since devoid of the psychoactive side effects exhibited instead by Δ^9-THC. In this review, we highlight the pharmacological activities of CBD, its cannabinoid receptor-dependent and -independent action, its biological effects focusing on immunomodulation, angiogenetic properties, and modulation of neuronal and cardiovascular function. Furthermore, the therapeutic potential of cannabidiol is also highlighted, in particular in nuerological diseases and cancer.

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Abbreviations: (5-HT)1A, 5-hydroxytryptamine receptor; Δ^9-THC, delta-9-tetrahydrocannabinol; 2-AG, 2-arachidonoylglycerol; A2A, adenosine receptor; AEA, anandamide; ALI, acute lung injury; Aml-1, acute myeloid leukemia; APP, amyloid precursor protein; AR, androgen receptor; Aβ, beta-amyloid; BDS, botanical drug substance; CBC, cannabichromene; CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CCL, chemokine (C-C motif) ligand; CHO, Chinese hamster ovary; CNS, central nervous system; COX, cyclo-oxygenase; CRC, colorectal cancer; CYP, cytochromes P450; EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FAAH, fatty acid amide hydrolase; FAK, focal adhesion kinase; GPR55, G Protein Coupled Receptor-55; GSCs, glioma stem-like cells; GSH, glutathione; HIF-1α, hypoxia-inducible factor-1-α; HSP, heat shock proteins; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LAK, lymphokine-activated killer; LAK, lymphokine-activated killer; LGS, Lennox-Gastaut syndrome; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDSC, myeloid-derived suppressor cells; MHRA, medications health care products regulation agency; MIP-2, macrophage inflammatory protein-2; MMP, matrix metalloproteinases; MOG, myelin oligodendrocyte glycoprotein; MT1-MMP, membrane type 1-matrix metalloproteinase 1; NF-kB, nuclear factor-k B; NK, natural killer; NKT, natural killer T; NMDA, *N*-methyl-D-aspartate receptor; NO, nitric oxide; NREM, non-REM; PAI-1, plasminogen activator inhibitor; PARP, poly (ADP ribose) polymerase; PI3K, phosphatydilinositol-3-kinase; PPARγ, peroxisome proliferator-activated receptor; RBD, REM behaviour disorder; REM, rapid eye movement; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TAM, tumor-associated macrophages; TH, tyrosine hydroxylase; THCV, tetrahydrocannabivarin; TIMP-1, matrix metalloproteases-1; TNF-α, tumour necrosis factor-alpha; TRPM8, transient receptor potential melastatin type-8; TRPV, transient potential vanilloid receptor; VCAM-1, vascular cell adhesion molecule-1.

* Corresponding authors at: Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Via Salvatore Allende, Baronissi, SA, Italy.
E-mail addresses: spisanti@unisa.it (S. Pisanti), mbifulco@unisa.it (M. Bifulco).

[1] These authors equally contributed to the work.

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1. Introduction

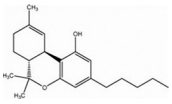
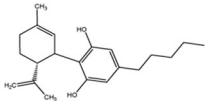
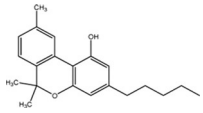
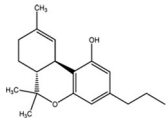
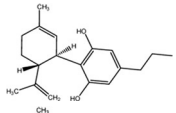
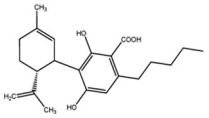
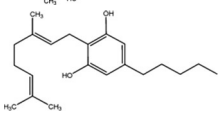
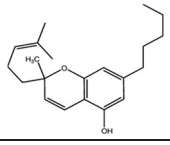
1.1. Phytocannabinoids: focus on CBD

Cannabis sativa contains hundreds of chemical entities produced by secondary metabolism including, beyond cannabinoids, terpenes and phenolic compounds, each one with potential interesting biological properties (Andre, Hausman, & Guerriero, 2016). Known cannabinoids are more than 90, even if some derive from breakdown reactions. Currently, the scientific community indicates with the term 'cannabinoid' these terpenophenols derived from *Cannabis sativa* but also synthetic compounds able to directly or indirectly act on cannabinoid receptors (Appendino, Chianese, & Taglialatela-Scafati, 2011). Delta-9-tetrahydrocannabinol (Δ^9-THC) is the main component of *Cannabis sativa* and the first cannabinoid to be discovered and studied, well known for its psychoactive effects (Russo, 2011). Among the other major phytocannabinoids isolated from the plant there are: CBD (Mechoulam & Shvo, 1963), cannabichromene (CBC) (Gaoni & Mechoulam, 1966), cannabigerol (CBG) (Gaoni & Mechoulam, 1964), cannabidivarin (CBDV) and tetrahydrocannabivarin (THCV) (Gill, Paton, & Pertwee, 1970; Vollner, Bieniek, & Korte, 1969) (Table 1). Although these compounds have similar chemical structures, they can elicit different pharmacological actions. Mainly, their pharmacological properties rely on the interaction with components of the endocannabinoid system machinery like cannabinoid receptors and enzymes of endocannabinoid synthesis and degradation. Focusing on CBD, it is well known that this compound is the second major comonent of the plant, the most prevalent in the fibre-type hemp, it is not associated with psychoactivity and does not affect motor function, memory or body temperature on its own. It displays with respect to Δ^9-THC lower CB_1 and CB_2 receptor affinity (Bisogno et al., 2001; Pertwee, 1999; Showalter, Compton, Martin, & Abood, 1996; Thomas, Gilliam, Burch, Roche, & Seltzman, 1998) and it was found to be an inverse agonist at the human CB_2 receptor, property that may contribute to its anti-inflammatory effects (Thomas et al., 2007). Beyond numerous *per se* pharmacological effects, CBD acts as an entourage molecule, reducing the collateral effects of Δ^9-THC, thus ameliorating its safety profile.

1.2. Overview of the pharmacological action of CBD

Thanks to its good safety profile and the lack of psychoactivity, CBD is undoubtedly the more interesting cannabinoid with a lot of reported pharmacological effects in several models of pathologies, ranging from inflammatory and neurodegenerative diseases, to epilepsy, autoimmune disorders like multiple sclerosis, arthritis, schizophrenia and cancer (Table 2). CBD shows lower CB_1 and CB_2 receptor affinity with respect to Δ9-THC. In the presence of Δ^9-THC, it is able to antagonize CB_1 at low nanomolar concentrations, finding that supports its regulatory properties on Δ^9-THC related adverse effects like tachycardia, anxiety, sedation and hunger in humans and rats (Murillo-Rodríguez, Millán-Aldaco, Palomero-Rivero, Mechoulam, & Drucker-Colín, 2006; Nicholson, Turner, Stone, & Robson, 2004; Russo & Guy, 2006). Indeed, both human and animal studies suggest anxiolytic properties associated with CBD. In generalized social anxiety disorders, CBD significantly decreased anxiety in patients and such effect was associated with its action on paralimbic and limbic areas as revealed by single photon emission

Table 1
Molecular structure and mechanism of action of phytocannabinoids.

Phytocannabinoids		
Δ^9-tetrahydrocannabinol (Δ^9-THC)		Psychoactive. Most abundant in drug-type plants Partial agonist CB1 ≈ CB2
Cannabidiol (CBD)		Non psychoactive. Most abundant in fiber-type plants. Not specific antagonist of CB1 e CB2 Inhibitor of AEA uptake and metabolism
Cannabinol (CBN)		Weak CB1 agonist, partial CB2 agonist
Δ^9-tetrahydrocannabivarin		Δ9-THCV antagonizes Δ9-THC at low doses (<3 mg/kg) CB1 agonist at greater doses (10 mg/kg)
Cannabidivarin (CBDV)		Mechanism of action unknown
Cannabidiolic acid		Selective inhibitor of COX2 TRPA1 and TRPV1 agonist
Cannabigerol		TRPA1 and TRPV1 agonist CB agonist; inhibitor of AEA reuptake
Cannabichromene		TRPA1 agonist Inhibitor of AEA reuptake

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