BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20161

Article

Cannabis and cannabinoids as an alternative remedy in metabolic syndrome

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Metabolic syndrome (MetS), an epidemic defined as a group of interconnected physiological, biochemistry, clinical, and metabolic factors, directly increases the risk of cardiovascular disease, atherosclerosis, type 2 diabetes, and death. MetS therapy includes diet, physical exercise, and a poly-pharmacological intervention. *Cannabis* is mainly recognized for its recreational uses and has several medical applications for neurological diseases, due to its hypnotic, anxiolytic, antinociceptive, anti-inflammatory, and anticonvulsant activities. Although several clinical observations in *Cannabis* smokers suggest metabolic effects, its utility in metabolic disorders is unclear. This review aims to determine under what conditions *Cannabis* might be useful in the treatment of MetS. *Cannabis* contains 120 phytocannabinoids, of which Δ^9-THC mediates its psychoactive effects. Cannabinoids exert biological effects through interactions with the endocannabinoid system, which modulates several physiologic and metabolic pathways through cannabinoid receptors (CB1/CB2). Signaling through both receptors inhibits neurotransmitter release. In general, endocannabinoid system stimulation in *Cannabis* smokers and Δ^9-THC signaling through CB1 have been implicated in MetS development, obesity, and type 2 diabetes. In contrast, CB1 antagonists and non-psychotropic phytocannabinoids like cannabidiol reduce these effects through interactions with both cannabinoid and non-cannabinoid receptors. These pharmacological approaches represent a source of new therapeutic agents for MetS. However, more studies are necessary to support the therapeutic potential of *Cannabis* and cannabinoids in metabolic abnormalities.

Keywords: *Cannabis*. Cannabinoids. Metabolic syndrome. CB1 antagonists. Cannabidiol. Diabetes mellitus.

INTRODUCTION

Metabolic syndrome (MetS) is currently considered an epidemic that can be defined as an intimately interconnected group of physiological, biochemistry, clinical, and metabolic factors that directly increase the risk of cardiovascular disease, atherosclerosis, type 2 diabetes, and death. These outcomes are driven by an atherogenic state, dyslipidemia, hypertension, impaired glucose tolerance, a pro-inflammatory/prothrombotic state, and oxidative stress (Crepaldi, Maggi, 2006). The origin of this concept (Table I), usually attributed to Reaven in 1988, introduced the idea of insulin resistance in cardiovascular disease and type 2 diabetes (Crepaldi, Maggi, 2006). Insulin resistance is present in 20 to 45% of the population and is currently considered a fundamental factor in MetS. At present, distinct organizations have proposed different diagnostic criteria for MetS (Table II): the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF). In general, the global prevalence of MetS ranges from 10 to 84% depending on the region (urban or rural environment), population (sex, age, race, and ethnicity), as well as the diagnostic criteria used (Vanita, Jhansi, 2011).

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TABLE I - Metabolic syndrome: Origen of the concept (Crepaldi, Maggi, 2006; Kaur, 2014)

Author (año)	Proposal	Risk factors
Kylin (1920)	Association	Hypertension/hyperglycemia/goat
Vague (1947)	Association	Obesity visceral/ metabolic abnormalities in ECD and DT2
Avogaro and Crepaldi (1965)	Metabolic syndrome	Hypertension/hyperglycemia/obesity
Reaven (1988)	Syndrome "X"	Introduce the concept of IR in ECV and DT2 (obesity was omitted)
Kaplan (1989)	"The quartet of death"	Obesity/IG, hypertriglyceridemia/hypertension
Haffner *et al.* (1992)	Insulin resistance syndrome	Obesity/IG, hypertriglyceridemia/hypertension

TABLE II - Clinical diagnostic criteria for metabolic syndrome (modified from Kaur, 2014)

Organism/Clinical parameter	Insulin resistance	Bodyweight	Lipids	Blood pressure	Glucose	Other
World Health Organization (WHO)	IGT, IFG, T2DM, Sensibility to the insulin + another 2	Waist/hip >0.9 (M), <0.85 (W) or IMC >30 kg/m^2	TG >150 mg/ dl and/or HDL-C <35 mg/ dL (M) and/or <39 mg/dl (W)	≥140/90 mm Hg	IGT, IFG, or DT2	MCA or ALB/ CREA
European Group for the study of Insulin Resistance (EGIR)	Plasmatic insulin >75 percentile + another 2	WC ≥94 cm (M), >80 cm (W)	TG >150 mg/ dl and/or HDL-C <35 mg/dL (M or W)	≥140/90 mm Hg or Rx hypertension	IGT, IFG (without DT2)	-
National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III)	None; with at least 3 of the 5 next parameters	WC ≥102 cm (M); ≥88 cm (W)	TG >150 mg/dl HDL-C <40 mg/dL (M) <50 mg/dl (W)	≥130/85 mm Hg	≥110 mg/ dl (include diabetes)	-
American Association of Clinical Endocrinologist (AACE)	IGT or IFG + or anyone of the next factors with base in clinical trials	BMI ≥ 25 kg/m^2	TG >150 mg/dl HDL-C <40 mg/dL (M) <50 mg/dl (W)	≥130/85 mm Hg	IGT, IFG (without DT2)	Other of IR
International Diabetes Federation (IDF)	None	WC incremented (specific population) + 2 of the next	TG >150 mg/ dl or Rx TG HDL-C <40 mg/ dL (M) <50 mg/dl (W) or Rx HDL-C	≥130 systolic 85 mm Hg diastolic or Rx of hypertension	≥100 mg/ dl (include diabetes)	-

IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; T2DM: Type 2 diabetes mellitus; M: Man; W: Woman; WC: waist circumference; BMI: Body mass index; TG; triglycerides; HDL-C: High-density lipoprotein-cholesterol; MCA: Microalbuminuria >20 mg/min or ALB/CRE: Albumin/Creatinine ratio >30 mg/g; IR: Insulin resistance.

The pathophysiology of MetS is complex; several risk factors participate, such as sedentarism, smoking, increased caloric intake, and stress, all which induce positive energy balance factors that can associate with genetic factors in patients

based on two principal theories (thrifty genotype or thrifty phenotype) (Ong, Dunger, 2000; Chacín *et al.*, 2011). These factors lead to hypertrophy and hyperplasia of adipose tissue, alter the metabolism of free fatty acids (FFA) and the release of adipocytokines (associated with chronic, low-grade inflammation), and affect distinct organic systems resulting in dyslipidemia, diabetes, a hypercoagulable state, and hypertension. All of these aspects interact with each other in a complex network of interactions that culminate in MetS (Figure 1).

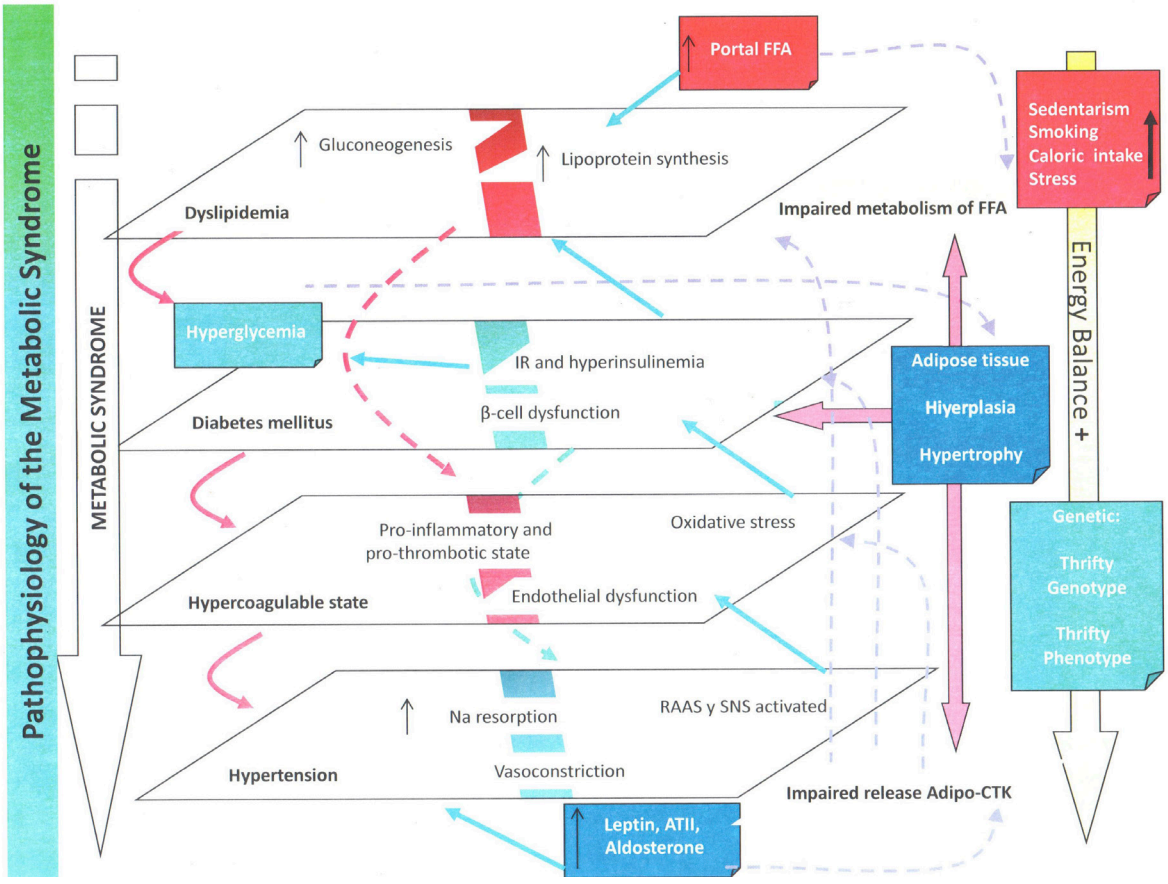

FIGURE 1 - A complex network of interactions that are culminating in the MetS. Several risk factors have been proposed; as sedentarism, smoke increased caloric intake and stress. These induce positive, energetic balance factors associated with con genetic factors (thrifty genotype or thrifty phenotype). All propitious hypertrophy and hyperplasia of the adipose tissue alter the metabolism of free fatty acids (FFA) and the release of adipocytokines (Adipo-CTK), affecting distinct organic systems, with increments in the FFA portal circulation, and in the levels of leptin, ATII and aldosterone. All this results in dyslipidemia, diabetes, hypercoagulable state, and hypertension. All of them affecting each other in a complex network of interactions that were culminating in the MetS. IR: insulin resistance; RAAS: Renin-Angiotensin-Aldosterone System; SNS Sympathetic Nervous System; ATII: Angiotensin II.

Peptide hormones play a role in the pathogenesis of MetS, like ghrelin, a blood-borne orexigenic signal from the gut to the brain, which can interact with leptin in the control of appetite (Ukkola, 2011). In MetS, ghrelin presents with low plasma levels as a physiological counterpart to high leptin levels, probably due to leptin resistance, equally participating in the progression of MetS (Ukkola, 2011). Ghrelin levels

are increased in negative energy balance, such as in fasting, and decrease in positive energy balance, as in obesity and MetS (López-Lopez *et al*., 2018). Given the complexity of MetS, complete treatment requires changes to the diet, physical exercise, and poly-pharmacological intervention, including hypoglycemic agents for diabetes, hypolipidemics for dyslipidemia, antithrombotics (aspirin), antihypertensives, and anti-obesity agents (Mastinu *et al*., 2018). Besides, MetS links well with alterations associated to psychological factors, neuroendocrine functioning, and immunological response. Stressful events and psychological distress appear to correlate with visceral fat levels that may lead to metabolic abnormalities (López-Lopez *et al*., 2018). In particular, psychological distress can be associated with biological alterations in MetS, causing autonomic nervous dysfunction, dysregulation of the hypothalamic-pituitary-adrenal axis, and blunted serotonin function (López-Lopez *et al*., 2018). Accordingly, a multidisciplinary therapy based on a psychoneuroimmunology approach might be useful in the prevention and treatment of MetS.

Cannabis sativa is an Angiosperm, of the Class Magnoliopside (Dicotyledonous), IV Order Rosales, Family Cannabaceae. Although *Cannabis* originates from central Asia, it has three subspecies, i.e. sativa and indica, with a background from the Asiatic south-east, and ruderalis from Russia and Africa, which are now used as mixtures and varieties worldwide (McPartland, 2018). Throughout history, *Cannabis sativa* has had several medical uses. In China, 5000 years ago, it was reported as a treatment for fatigue, malaria, constipation, and rheumatic pain (Bonini *et al*., 2018). *Cannabis* oils have been used for eczema, psoriasis, and other inflammatory diseases (Bonini *et al*., 2018). In India, 3000 years ago, *Cannabis* was used as a hypnotic, tranquilizer, and anxiolytic in the treatment of mania and hysteria (Kuddus, Ginawi, Al-Hazimi, 2013); this was also documented in Assyrian clay tablets and on the Egyptian Ebers Papyrus. At the end of the ancient era (400-60 years BC). *Cannabis* was recommended for pain in India, Egypt, and Greece, among other beneficial effects. In the medieval period, *Cannabis* was associated with lowly social conditions, and its cultivation and commercialization began in Italy in the Mediterranean region (Bonini *et al*., 2018). Later, during the British colonialism of India, in Europe, the uses of *Cannabis* included euphoria, sedation, stimulation of appetite, hallucinations, and aphrodisiac effects (Bonini *et al*., 2018).

In the 19th century, the introduction of *Cannabis* in western medicine was for use as an analgesic, anti-inflammatory, antiemetic, and anticonvulsant. In the 20th century, some extracts were investigated for mental disorders, as a sedative and hypnotic agent (Madras, 2015). From 1930, the medical use of *Cannabis* was restricted, and although it was declared a prohibited plant in the latter part of the 20th century, in the present century, it has come to be accepted culturally and legally in many countries, mainly for recreational and medicinal use (Aguilar *et al*., 2018). The majority of studies on the acute effects of *Cannabis* have been performed in recreational users, with less information from clinical studies conducted in medicinal *Cannabis* consumers (Abramovici, 2018). Despite the popularity of *Cannabis* use for neurological ailments, its potential metabolic effects have only recently been investigated, and its medical utility in metabolic diseases is still controversial. Several clinical observations in smokers of *Cannabis* suggest specific metabolic effects (Farokhnia *et al*., 2020).

The association between the effects of *Cannabis sativa* and MetS occurred with the discovery of the endocannabinoid system, which emerged as a critical pathway in the regulation of energy balance. It is currently one of the major contenders as a therapeutic target for the treatment of obesity and related disorders, where the hyperactivation and upregulation of CB1 in central and peripheral systems play essential roles in metabolic disorders. In particular, CB1 is located at the level of the hypothalamic circuits that regulate food intake and the hunger/satiety balance and has been implicated in hyperphagia and weight gain. This has led to new compounds able to selectively block CB1, which have shown utility in weight control in obesity, improving cardiovascular risk factors at the experimental level (Mastinu *et al*., 2013). On the other hand, non-psychotropic cannabinoids, like cannabidiol (CBD), have been recognized as moderate modulators of CB1

and CB2, and can exert pharmacological effects through other receptors implicated in the regulation of metabolism (Mastinu *et al.*, 2020).

Since MetS is an epidemic that increases the risk of cardiovascular, atherosclerotic, type 2 diabetes, and death (Monnerie *et al.*, 2020), it is essential to analyze the utility of *Cannabis* and its components in MetS in order to elucidate under what conditions it might be useful in MetS.

Chemistry of *Cannabis*: cannabinoids

From the point of view chemistry, *Cannabis* is considered a complex species, with around 565 identified compounds classified as cannabinoids and non-cannabinoids. The latter include terpenes, fatty acids, flavonoids, amino acids, proteins, enzymes, glycoproteins, hydrocarbons, alcohols, aldehydes, ketones, esters, lactones, steroids, vitamins, and pigments (Radwan *et al.*, 2017). Some researchers have suggested that these non-cannabinoid compounds might participate in the action of cannabinoids through an entourage effect; however, the in vitro experimental evidence does not support this hypothesis (Finlay *et al.*, 2020), and it is still necessary to perform in vivo studies. It is clear that there are differences in the presence and the relative abundance of these components among *Cannabis* extracts, vapors, and smoke, and also among *Cannabis* varieties (Abramovici, 2018). Other variables can impact the concentration of the compounds of *Cannabis*, such as genotype, soil quality, pollution, pesticide use, light conditions, temperature, and insects. Thus, the kind of preparation and growth conditions may modify the content of psychoactive components in *Cannabis*, impacting on its biological properties.

Cannabinoids are terpene-phenolic compounds with 21 carbons, with a ring derived from geranyl pyrophosphate, and formed of three unique rings: tetrahydropyran, cyclohexane, and benzene (Figure 2). There are at least 120 cannabinoids described from *Cannabis*, with 11 subclasses (Table III) (Radwan *et al.*, 2017). Of these components, the delta-9-tetrahydrocannabinol (Δ^9-THC) is known for its psychoactive effect. In addition to the stereoisomers of the Δ^9-THC, all with the same molecular formula $C_{21}H_{30}O_2$, other compounds have similar structural characteristics as Δ^9-THC, such as Δ^8-THC, but have no psychoactive properties (Radwan *et al.*, 2017).

In general, the types of cannabinoids isolated from *Cannabis* are recognized as phytocannabinoids or natural cannabinoids, whereas those obtained from chemical synthesis are known as synthetic cannabinoids (Table IV) (FICF, 2007; WHO**,** 2018). The cannabinoids exert their biological effects through interactions with the endocannabinoid system, whose fundamental components are endocannabinoids (Meccariello *et al.*, 2020).

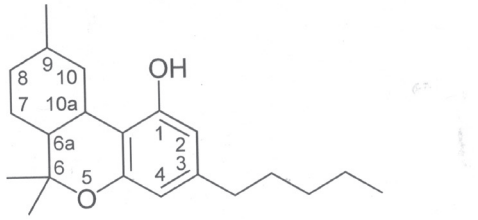

FIGURE 2 - The general structure of cannabinoids. Cannabinoids are terpene-phenolic compounds with 21 carbons, with a ring from the geranyl-pyrophosphate, and formed of three unique rings: tetrahydropyran, cyclohexane, and benzene.

TABLE III - Sub-types of cannabinoids (120 compounds) (Abbreviated from Radwan *et al.*, 2017)

No.	Type	No. de compounds
1	Δ^9-tetrahydrocannabinol (Δ^9-THC)	23
2	Δ^8-tetrahydrocannabinol (Δ^8-THC)	5
3	Cannabigerol (CBG)	16
4	Cannabicromene (CBC)	9
5	Cannabidiol (CBD)	7
6	Cannabinodiol (CBND)	2
7	Cannabielsoine (CBE)	5
8	Cannabicyclol (CBL)	3
9	Cannabinol (CBN)	11
10	Cannabitriol (CBT)	9
11	Miscellaneous	30

TABLE IV - Pharmacological action associated with some synthetic cannabinoids used in clinics and experimentally (Modified from FICF, 2007)

Used in clinic		Experimental	
Dronabinol (Marinol®)	Synthetic THC in sesame oil. Anorexia-cachexia in AIDS patients. Nausea and vomit due to antineoplastic therapy	CP55,940	Bicyclic cannabinoid. Like THC, it was used to demonstrate the existence of specific cannabinoid receptors in rat
Nabilone®	THC analog. Nausea and vomit due to antineoplastic therapy	HU-210	Analog of the THC 100-800 times more potent
Levonantradol	Tetracyclic cannabinoid (intramuscular)	HU-308, AM1241, JWH015	CB2 agonists
HU-211 (Dexanabinol)	No-psychotropic Cannabinoid. TNF inhibitor and NMDA antagonist. Clinical assay: Phase III (neuroprotector)	Win-55,212-2	CB1 cannabimimetic, structurally no associated to cannabinoids
		PRS-211,092	No-selective agonist
		ACEA	CB1 agonist
		AM630	CB2 antagonist

Endocannabinoid system (ECS)

The ECS is considered a complex signaling system that regulates several physiological and metabolic pathways (Abramovici, 2018). This system modulates processes in all stages of life (prenatal, puberty, adolescence, adulthood, and old age). It is amply distributed inside the organism, at the tissue, cellular, and sub-cellular levels (Zou, Kumar, 2018). Table V lists the fundamental physiological processes in which the ECS participates at the central and peripheral levels.

The ECS constitutes cannabinoid receptors, endogenous ligands (endocannabinoids), synthesis and degradation enzymes, signaling pathways, and associated transport systems (McPartland, Guy, Di Marzo, 2014). Among the endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG), vidoramine, noladin ether, and N-arachidonoyl-dopamine (Ramos, Fernández, 2000). The alteration of the ECS is associated with several pathological conditions: behavioral, neurological, metabolic, reproductive, and cancer. Hence, Meccariello *et al.* (2020) suggested that the system's modulation through a pharmacological approach may be relevant in the treatment of these pathologies.

TABLE V - Physiological processes in which the endocannabinoid system is participating (McPartland, Guy, Di Marzo, 2014; Nahtigal *et al.*, 2016; Pazos, Gandes, 2017; Meccariello *et al.*, 2020)

Central	Peripherical
Appetite and ingest	Inflammation
Nociception	Hormonal release
Frame of mind	Insulin sensibilization
Synaptic transmission	Cardiovascular function
Neuroprotection	Respiratory function
Motor function	Reproductive function
Memory	Immunomodulator
Learning	Bone formation
Fear	Energetic metabolism
Neural development Thermogenesis Sleep/wake cycle Synaptic plasticity Stress response	Architecture, proliferation, motility, adhesion and cellular apoptosis

Cannabinoid receptors

The endocannabinoids, phytocannabinoids, and synthetic cannabinoids are promiscuous molecules that can activate several receptors, including cannabinoid receptors 1 and 2 (CB1 and CB2), transient receptor potential vanilloid-1 (TRPV-1), G protein-coupled receptors (GPR18, GPR19, and GPR55), peroxisome proliferator-activated- receptors (PPAR), subunit alpha 1 of the glycine receptor (GlyR), and subunit beta 2 of the GABA-A receptor, among others (Cassano *et al.*, 2020).

The main action of phytocannabinoids and endocannabinoids occurs through their interactions with CB1 and CB2, which are $G_{i/0}$ protein-coupled receptors of the inhibitory type. Interestingly, CB receptors are amply distributed in the organism at the central and peripheral levels (Table VI); in both cases, CB1 is more extensively distributed than CB2. However, CB2 is a highly inducible receptor that increases expression by 100 times in tissue injury; in inflammatory processes, its activation does not produce psychoactive effects and it is responsible for the immunomodulatory properties of *Cannabis* (Katchan, David, Shoenfeld, 2016; Cassano *et al.*, 2020). It is notable that CB1 is the most abundant G-protein coupled receptor in the brain. This receptor is expressed at the subcellular level in mitochondria in the brain and striated muscle. Both receptors present polymorphic variants (Howlett, Abood, 2017; Gutiérrez-Rodríguez *et al.*, 2018), which explain the great versatility of potential functions associated with their activation.

The other cannabinoid receptors, such as GPR55 and TRPV1, are involved in the modulation of bone density, blood pressure, and promoting cancer growth (Iannotti, Marzo, Petrosino, 2016), as well as in the detection of pain and heat, osmoregulation, neurotransmission, neuronal stabilization, and other sensorial modalities (Katchan, David, Shoenfeld, 2016; Iannotti, Marzo, Petrosino, 2016). PPAR is associated with the modulation of energy balance, inflammation, and insulin sensitivity (Cassano *et al.*, 2020; Fellous *et al.*, 2020). In this way, the vast distribution of cannabinoid receptors and their functional versatility, both neurological and metabolic, have allowed researchers to propose using cannabinoids as homeostatic modulators, aimed at improving health and disease treatment, probably through the epigenetic modulation of the ECS, as suggested recently (Meccariello *et al.*, 2020). However, the experimental and clinical evidence is still insufficient, and further investigation is mandatory.

TABLE VI - CB1 and CB2 distribution in the organism (Howlett, Abood, 2017; Cassano *et al.*, 2020)

	Central	Peripherical
CB1	Cortex	Spleen
	Nucleus accumbens	Tonsils
	Basal ganglia	Heart
	Hypothalamus	Prostate
	Cerebellum	Uterus
	Hippocampus	Ovary
	Amygdala	Sympathetic nerve endings
	Spinal cord	Adipose tissue
	Brainstem	Muscle
		Liver

TABLE VI - CB1 and CB2 distribution in the organism (Howlett, Abood, 2017; Cassano *et al*., 2020)

	Central	Peripherical
		Gastrointestinal apparatus
		Pancreas
CB2	Glial cells	Spleen
	Spinal cord	Tonsils
		Heart
		Immune system: B and T cells, and macrophages
		Endothelium
		Bones
		Liver
		Pancreas

Cannabinoid signaling pathways

CB1 and CB2 are functionally similar; nevertheless, there are some differences between the two. The activation of CB receptors leads to four basic cellular processes. The basal pathway of CB1 is associated with the activation of G proteins and inhibiting adenylyl cyclase (Fernandez-Lopez *et al*., 2013). This activation reduces cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), resulting in the opening of inwardly-rectifying K^+ channels, inhibition of voltage-sensitive Ca^{2+} channels, and hyperpolarization of presynaptic terminals, preventing the release of excitatory and inhibitory neurotransmitters (e.g., glutamate, gamma-aminobutyric acid (GABA), glutamate, dopamine, noradrenaline, 5-hydroxytryptamine, and acetylcholine) (Fernandez-Lopez *et al*., 2013; Zou, Kumar, 2018;). CB1 is linked to neutral sphingomyelinase, an enzyme that mediates the generation of ceramide, which participates in the control of cell function by cannabinoids throughout the activation of transcription factors such as ERK1/2 (extracellular signal-regulated kinase, pERK), JNK (c-Jun N-terminal kinase), p38 MAPK (mitogen-activated protein kinases), FAK (focal adhesion kinase), PI3K (phosphoinositide-3 kinase), and PKB/Akt (protein kinase B). This regulates functions like proliferation, apoptosis, vasoconstriction, vasodilatation, cell adhesion, and carbohydrate and lipid metabolism (Fernandez-Lopez *et al*., 2013; Al-Zoubi, Morales, Regio, 2019). In addition to G proteins, the CB1 interacts with β-arrestins, which serve as regulators of cellular signaling or receptor trafficking and compete with cannabinoid receptor-interacting protein 1a (CRIP1a). CRIP1a attenuates the G protein signaling cascade by modulating Gi/o subtypes, which interact with CB1, and also attenuates its internalization via β-arrestins (Booth *et al*., 2019).

Activation of CB2 receptors by natural or synthetic ligands, in general, affects similar signaling pathways: links to G proteins, inhibition of cAMP via adenylate cyclase and activation of ERK1/2, Akt, and MAPK cascade (stimulating cell survival, migration, and growth), stimulation of ceramide synthesis and potential activation of arrestin-specific signaling, decreased PKA activity and stimulated MAPK pathways. These pathways result in the positive regulation of many genes, by activation of a pathway, inhibition/downregulation of a pathway or through of combination of all of them (Oyagawa *et al*., 2018). Activation of MAP kinase, probably mediated by PKC, has also been reported. CB2 receptor activation increases the release of Ca^{2+} from the endoplasmic reticulum and mitochondrial Ca^{2+} via the PLC-IP3 signaling pathway. Unlike CB1 receptors, it appears that CB2 receptors are not associated with potassium channels, which is probably the most critical difference between the two receptors, causing them to be functionally different (Vecera *et al*., 2020).

Pharmacological effects of *Cannabis*

The most common form of *Cannabis* use is in smoke for recreational use. In this case, the acute pharmacological effects occur as a result of central and peripheral stimulation, shown in Table VII. The chronic consumption of *Cannabis* smoke results in a hyperactive endocannabinoid system at the central and peripheral levels. The chronic effects are mediated by overstimulation of CB1, resulting in a broad spectrum of highly complex effects that can be analyzed separately depending on the system that is being affected

(Abramovici, 2018): CNS cardiovascular (León *et al*., 2018) and cerebrovascular, respiratory (Abrams, 2018), gastrointestinal, skeletal muscle, eye, immune (Katchan, David, Shoenfeld, 2016), and reproductive. Many of the effects are biphasic, i.e. increased with acute or smaller doses, or decreased with larger doses or chronic use (Abramovici, 2018).

Cannabis smoking in recreational users causes physical and mental alterations, i.e. short-term psychoactive effects, like euphoria and relaxation, time distortion, intensification of ordinary sensory experiences (eating, watching films, and listening to music), loss of inhibition and laughter; these are followed by a depressive period (Abramovici, 2018). Some data also indicate that chronic *Cannabis* use decreases obesity and other metabolic diseases, suggesting a role in the modulation of appetite (Farokhnia *et al*., 2020).

TABLE VII - Acute pharmacological effects of recreative smoke use of *Cannabis* (Abuhasira, Shbiro, Landschaft, 2018)

Central	Peripherical
Relaxation	
Euphoria	
Increased sensorial experiences (sounds, taste, color)	
Time distortion	Pulse acceleration
Disinhibition	Increased blood pressure
Impaired concentration capacity	tachycardia
Reverie of the mind	Mydriasis
Tremor	
Vertigo	
Depression	
Motor incoordination	
Memory affectation	

Contribution of the ECS to the development of MetS and associated pathologies

The contribution of the ECS to the development of MetS is linked to obesity and type 2 diabetes (Di Marzo, Piscitelli, Mechoulam, 2011). At the hypothalamic level, several orexigenic and anorexigenic pathways are affected by the ECS, increasing food intake and inhibiting the sensation of satiety, actions linked especially to CB1 (Di Marzo, Piscitelli, Mechoulam, 2011). At the peripheral level, the ECS also influences the endocrine system involved in metabolism by participating in the inhibition of insulin secretion and glucose capture and oxidation in muscle and in adipose tissue. Moreover, the ECS increases blood levels of the hunger hormone ghrelin, induces lipogenesis and the release of FFA from the liver, stimulates lipogenesis in adipose tissue, and reduces adiponectin (Farokhnia *et al*., 2020). Thus, feelings of hunger and satiety result from orchestrated communication between peripheral signals (leptin, insulin, and ghrelin) and sensory neurons in the hypothalamus, among other regions. Ghrelin levels are increased in negative energy balance, such as in fasting and anorexia nervosa, and are decreased in positive energy balance, i.e. in obesity. Therefore, together with leptin and insulin, ghrelin forms part of a set of peripheral signs that informs the brain about the status of energy stores and contributes to long-term weight regulation (López-López *et al*., 2018). In this way, the increase of hypothalamic endocannabinoids has been associated with defective leptin signaling. Leptin represents an essential signaling molecule between fat tissue and central areas involved in weight and feeding regulation, and participates in the mechanism of action of cannabinoids. Hypothalamic leptin receptor stimulation promotes pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) release; this suppresses feeding and inhibits the release of neuropeptide Y(NPY) and agouti-related protein (AGRP), which typically promote feeding to maintain energy homeostasis (Lazzari *et al*., 2011).

The stimulated ECS enhances visceral fat accumulation and obesity, reduces energy expenditure, and promotes lipogenesis (Valenzuela *et al*., 2010). The ECS affects insulin sensitivity independently of weight gain in the liver, adipose tissue, and skeletal muscle. It also indirectly contributes to β-cell failure through activation of the Nlrp3-ASC inflammasome in infiltrating macrophages, resulting in β-cell apoptosis, propitiating insulin resistance in type 2 diabetes in conjunction with MetS. Hence, the ECS is involved in the development of obesity-dependent insulin resistance because of excess

food intake and increased body weight (Valenzuela *et al*., 2010; Gruden *et al*., 2016).

Interestingly, the pathophysiological mechanisms in MetS induce effects in the organism similar to overstimulation of the endocannabinoid system, by modifying several metabolic pathways that increase body weight, insulin resistance, visceral fat, and dyslipidemia to generate obesity, type 2 diabetes, and other abnormalities associated with MetS (Argueta, DiPatrizio, 2017). Paradoxically, hyperphagia and obesity also stimulate endocannabinoid signaling at peripheral CB1 receptors, propitiating a vicious circle that might complete and aggravate MetS (Argueta, DiPatrizio, 2017).

Activated CB1 receptors contribute to diabetes-associated inflammation and reactive oxygen species (ROS) generation, promoting tissue injury and the development of diabetic complications. CB1 activation increases lipogenesis, plasma triglycerides, insulin, and leptin resistance, and decreases adiponectin, fatty acid oxidation, HDL cholesterol, glucose tolerance, and thermogenesis (Van Eenige *et al*., 2018; Cinar, Iyer, Kunos, 2020). Also, it increases appetite and food intake, especially sweet and tasty food, involving different pathways associated with the brain "reward" system and also involving organs like the pancreas, liver, adipose tissue, skeletal muscle, and CNS (Tibiriça, 2010; Tam *et al*., 2018). In this last case, neurotransmitter release in reward-related brain regions linked to the mesolimbic dopaminergic pathway is crucial in the regulation of food intake. By acting on glutamatergic terminals, endocannabinoids reduce the activation of GABAergic NAc neurons projecting into the ventral tegmental area (VTA). Consequently, dopamine producing VTA neurons are relieved from their inhibition and are allowed to release dopamine, likely driving the motivation for food. This same circuit can be rewired by short exposure to palatable food, which can prime feeding behavior. The strengthening of excitatory synaptic transmission mediates this effect onto dopamine neurons that are offset by a short-term increase in endocannabinoid tone. Recent studies further suggest that not just neuronal, but astroglial CB1 might play a role in energy metabolism by modulating the action of leptin onto astrocytes and that mitochondrial CB1 might affect the function of hypothalamic circuits critically involved in the regulation of feeding (Simon, Cota, 2017). Taken together, these effects promote hyperglycemia, obesity, and cardiovascular risk, and contribute to increased ROS generation by mitochondria, as well as angiotensin II receptor type 1 expression. CB1 activation augments the inflammatory response, mediated by increased VCAM and MCP1 expression, and stimulates cell death via MAPK, involving cardiomyocytes, endothelial cells, smooth muscle (increased cell death and increased proliferation/migration, respectively), and fibroblasts, leading to a pro-fibrotic response. All these processes induce endothelial and cardiac dysfunction (Horvát *et al*., 2012).

CB1 stimulation also promotes systemic inflammation via NFκB activation, increasing TNF-α and IL-6 expression and augmenting inflammatory cells (polymorphonuclear cells, lymphocytes, monocytes, and macrophages), with increased ROS generation, resulting in significant additional production of endocannabinoids; this causes tissue injury and diabetic complications such as retinopathy, cardiomyopathy, neuropathy, and nephropathy (Frisher *et al*., 2010). CB1 activation is involved in cell growth and the differentiation of adipocytes, and in the modulation of adipokine secretion and lipogenesis (Muniyappa *et al*., 2013). In contrast, decreasing CB1 receptor signaling improves insulin sensitivity, metabolic disorders, and atherosclerosis, including cytoprotection through a reduction in ROS (Martín *et al*., 2018; Guillamat-Prats *et al*., 2019).

Metabolic actions associated with smoked *Cannabis*: clinical evidence

Penner, Buettner and Mittleman (2013) studied in 4657 American adults the impact of smoked *Cannabis* on glucose, insulin, and insulin resistance. They found that users had higher values of HDL-C, with lower fasted insulin levels (16%) and insulin resistance (17%) than non-users. Paradoxically, users exhibited increased appetite and caloric intake, although the prevalence of diabetes and high body mass index was lower. In the same year, Muniyappa *et al.* (2013) studied 60 patients to determine whether the chronic use of smoked *Cannabis* might be associated with liver steatosis, insulin resistance, β-cell functionality, or dyslipidemia (Muniyappa *et al*., 2013). In adipose tissue, an association was observed between

visceral adiposity and insulin resistance, with differential effects related to insulin resistance, although there was little impact on glucose and lipid metabolism. Other studies also reported an association between *Cannabis* use and a lower prevalence of diabetes (Rajavashisth *et al*., 2012). However, in contrast to these results, in 2015, Thompson and Hay questioned the robustness of these clinical studies, arguing for the need to include other variables such as behavior and environment, use of other drugs, psychological factors, and personality. Since all these variables may potentially have an influence on metabolism, these considerations are relevant for further studies.

In 2016, Vidot *et al*. explored the relationship between *Cannabis* consumption and MetS in several stages of adulthood in the US with data from National Health and Nutrition Examination Surveys 2005-2010 (NHANES). The results showed a specific association with a low probability of suffering from MetS in *Cannabis* users 20-30 and 45-59 years old (Table VIII). However, there are newly evident limitations of this study. In this case, the same authors showed that the design of a cross-sectional study does not allow for determining a causal relationship, indicating the necessity to include other variables like diet, physical activity, and diabetes, among other factors that may influence MetS in *Cannabis* users (Vidot *et al*., 2016). In 2015, Alshaarawy and Anthony analyzed the association between *Cannabis* use and type 2 diabetes, considering the NHANES (2005-2012) data in conjunction with National Drug Use and Health Surveys (NSDUH-2005-2012) data. The authors also discussed the limitations of data from cross-sectional surveys and the self-reporting of type 2 diabetes, suggesting the necessity to perform controlled studies including research on the potential mechanisms that explain the association between *Cannabis* use and metabolic diseases (Alshaarawy, Anthony, 2015).

Recently, Farokhnia *et al*. (2020), in a well-designed study, investigated the effects of oral, smoked, and vaporized *Cannabis* on peripheral concentrations of orexigenic and metabolic hormones in 20 *Cannabis* users through a randomized crossover, double-blind, placebo-controlled study (Table VIII). Each sample contained around 50.6 mg of THC. The results showed diminished GLP-1 and an increase in insulin, whereas ghrelin increased only with oral *Cannabis* (Farokhnia *et al*., 2020). Despite the small sample size, the limited number of measured parameters, lack of behavioral and environmental factors, the use of just one dose, and a majority of male subjects, this study may be considered as one of the first clinical controlled studies with the acute administration of *Cannabis*. This study supports the association with orexigenic and metabolic hormones in *Cannabis* users, opening up the possibility to study the underlying mechanisms responsible for the observed effects.

In 2017, Chia *et al*. (2017) performed a study in humans with Nabilone®, an analog of THC, to study the role of cannabinoids on incretins and metabolic parameters after a 75-g oral glucose tolerance test. The results showed deregulated incretin secretion due to CB1 and CB2 agonism, which affected insulin secretion in response to the ingested nutrients (Table VIII). Another clinical trial performed in 30 patients with painful diabetic neuropathy randomized to either Sativex, containing both THC and cannabidiol, or placebo, failed to show any benefit, although depression was a major confounding factor during the study (Gruden *et al*., 2016).

Recently, several other studies on the association between *Cannabis* use and metabolic diseases have shown contradictory results (Table VIII). Since, in most cases, these studies performed a prospective analysis from population surveys, obtaining additional information about whether *Cannabis* consumption in users and non-users can be useful in MetS or associated pathologies requires further well-designed, longitudinal double-blind, placebo-controlled studies, pre- and post-controlled. These studies should take into account variables like levels of physical activity, diet, caloric intake, BMI, loss of appetite, other licit and illicit drug exposures, the age and clinical status of the subjects, and other genetic and environmental influences. Moreover, it is necessary to measure the dose-response, latency, and duration of *Cannabis* effects, its distinct varieties and associated molecules, as well as the concentrations of its different preparations and mode of use (Roberts *et al*., 2019; Alshaarawy *et al*., 2019; Ngueta, Ndjaboue, 2020; Ngueta, 2020; Okafor *et al*., 2020; Ross *et al*., 2020).

TABLE VIII - Recent clinical studies with *Cannabis* use in MetS and associated diseases

Trial identifier	Type of study	Trial objective	Kind of patients	Sample size	Results	Reference
National Institute on Drug Abuse (NIDA) Intramural Research Program and the Johns Hopkins Bayview Clinical Research Unit	Randomized, crossover, double-blind, placebo-controlled study	Investigate the effects of *Cannabis* by different routes on appetitive and metabolic hormones	Healthy adult *Cannabis* in several presentations	20	*Cannabis* use modulated blood concentrations of some appetitive and metabolic hormones, chiefly insulin	Farokhnia *et al.*, 2020
National Health and Nutrition Examination Survey (NHANES) 2009-2016	Prospective analysis (population survey)	Examine the association of marijuana use with insulin resistance	Adults with different body mass index (BMI) status.	129 509	Marijuana use reduces fasting insulin and HOMA-IR in obese but not non-obese adults, independent of the time of use.	Ngueta, Ndjaboue, 2020
National Health and Nutrition Examination Survey (NHANES) 2009-2016	Prospective analysis (population survey)	Explore the association of marijuana use with mean plasma fasting insulin levels and HOMA-IR	Obese adults with different HOMA-IR.	65 209	Marijuana use reduced fasting insulin levels and HOMA-IR score in US obese adults with HOMA-IR ≥ 2.13, but not in those with HOMA-IR < 2.13 or ≥ 5.72. The impact of *Cannabis* use is more significant after long-term exposure and is independent of BMI.	Ngueta, 2020
Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS),	Prospective analysis (population survey)	Determine whether the self-reported frequency of marijuana use is associated with incident T2D	Women and men with and at risk for HIV	6260	Reduced risk of type 2 diabetes in marijuana users compared to none users, although all associations were not statistically significant. The results were similar for HIV-positive and HIV-negative participants.	Okafor *et al.*, 2020
Longitudinal study (R01 DA031176, PI: Gonzalez)	Prospective analysis from a longitudinal study	Examine the associations between *Cannabis* use and BMI	Adolescents ages 14–17 at risk for escalation in *Cannabis* use	401	Negative association between *Cannabis* use and BMI.	Ross *et al.*, 2020.
Cannabis Eating Experience Questionnaire (CEEQ)	Online survey	Analyze appetite- and eating-related aspects of *Cannabis* self-administration	Adults from UK, Netherlands, and USA	798	Cannabis influences both the motivational factors that lead to the initiation of eating and the hedonic factors implicated in encouraging and maintaining eating.	Roberts *et al.*, 2019
US-based Coronary Artery Risk Development in Young Adults (CARDIA) study	Prospective analysis (population survey)	Examine *Cannabis*-attributable immunomodulation	Young adults	5115	*Cannabis* use was not associated with any of the biomarkers studied. Former *Cannabis* use was inversely associated with fibrinogen levels, whereas the associations were weaker for serum CRP and IL-6.	Alshaarawy *et al.*, 2019

TABLE VIII - Recent clinical studies with *Cannabis* use in MetS and associated diseases

Trial identifier	Type of study	Trial objective	Kind of patients	Sample size	Results	Reference
National Inpatient Sample 2009–2010 database using the Ninth Revision of International Classification of Disease code 304.3.	Prospective analysis (population survey)	Examine the prevalence of cardiovascular risk factors and events amongst patients with *Cannabis* use	Patients aged 18–55 years	316 397	*Cannabis* users increased the prevalence of most risk factors, including hypertension, obesity, tobacco use, and alcohol use, although diabetes mellitus was more frequently observed in non-cannabis users. Hyperlipidemia rates were similar between both groups.	Kalla *et al*., 2018
US-based Coronary Artery Risk Development in Young Adults (CARDIA) study	Prospective analysis (population survey)	Determine the association between lifetime exposure to *Cannabis* and subclinical atherosclerosis in mid-life.	Young adults	3498	Cumulative marijuana use was not associated with measures of atherosclerosis among middle-aged adults never exposed to tobacco. Still, a trend to increase the risk of atherosclerosis with very high exposure to *Cannabis* was observed.	Auer *et al*., 2017
Baltimore Longitudinal Study of Aging (BLSA)	Randomized, double-blind, crossover study	Determine that the stimulation of the endocannabinoid system due to Nabilone regulates incretin secretion.	Healthy men of 21- to 55-year-olds Nabilone (THC analog)	20 lean, 20 obese	Nabilone induced a highly significant elevation (80%) in post-dose fasting GIP levels. Post-dose fasting insulin levels were elevated. Elevated GIP levels in obesity were observed as a consequence of increased endocannabinoid levels by Nabilone.	Chia *et al*., 2017
National Health and Nutrition Examination Survey (NHANES) 2005-2010	Prospective analysis (population survey)	Explore the relationship of *Cannabis* use with MetS	Users of 20- to 59-year-olds	8478	A specific association with the minor probability of suffer MetS in Cannabis users of 20-30 and 45-59 years old was observed.	Vidot *et al*., 2016

Metabolic actions associated with cannabinoids: experimental evidence

The pharmacological actions of cannabinoids in diabetes and metabolic diseases have been explored in several experimental studies in which distinct CB1 and CB2 agonists and antagonists were used (Cinar, Iyer, Kunos, 2020). Alterations to glucose metabolism via overactivation of the ECS were initially contradictory regarding insulin secretion (increased or decreased) and the role of insulin resistance in β-cell dysfunction (Li *et al*., 2010; Vilches-Flores *et al*., 2013). However, the current consensus has established that CB1 activation contributes to the development of diabetes with proapoptotic effects in β-cells, inflammation in the islets of Langerhans, and suppression of the insulin receptor (IR) signaling pathway via IRS2-AKT-FoxO1 and decreased IR kinase activity (Shin *et al*., 2018). Generally, CB1 agonists promote energy intake and storage, altering lipid and protein metabolism, and promoting inflammation, oxidative stress, fibrosis, and the development of micro- and macrovascular complications (Cinar, Iyer, Kunos, 2020). CB1 is a negative regulator of β-cell function and a mediator of islet inflammation under conditions of metabolic stress

(González-Mariscal *et al*., 2018). Therefore, these data point to β-cell CB1 as a valuable therapeutic target with anti-inflammatory effects in diabetes.

As all these deleterious effects occur by the activation of CB1, it clear that blockade of CB1 might be beneficial in MetS (Cinar, Iyer, Kunos, 2020). González-Mariscal *et al.* (2016a) and Shin et al. (2018), among others, they used different research approaches, both genetic and pharmacological and in vivo and in vitro models to study the influence of blocking CB1 receptors on β cell lines, human islets and null mice of CB1 receptors. Their findings made it clear that the blockage of CB1 improves insulin responsiveness through the regulation of insulin, glucokinase, and glucose transporter 2 gene expression and increases insulin secretion mediated by incretins in humans (Chia *et al*., 2017). González-Mariscal *et al.* (2016b) demonstrated the existence of CB1 receptor isoforms that operate differentially depending on the tissue involved, particularly in the liver, β-cells, and brain. They later postulated that the ablation of CB1 in mouse β-cells increases cell proliferation and insulin secretion, inhibiting the high fat/high sugar diet-induced inflammation of murine islets (González-Mariscal *et al*., 2018).

Concerning the metabolic functions mediated by CB2, its stimulation had an inhibiting effect on insulin secretion and weight gain in rats subjected to a high fat diet (HFD) for 14 days, which was confirmed using the selective CB2 antagonist AM630 (Ignatowska-Jankowska, Jankowski, Swiergiel, 2011). Zhang *et al.* in 2016 explored the role of the CB2 receptor in glucose tolerance and insulin sensitivity in high-fat/streptozotocin-induced diabetic mice by assessing the function of β-cells and fat deposition. The results showed that CB2 activation ameliorated insulin resistance and increased β-cell insulin secretion, suggesting some lipolytic role (Zhang *et al*., 2016). In mice, CB2 activation also reduced food intake, fat mass, and adipocyte cell size (Tarragon, Moreno, 2018). Therefore, although the roles of CB2 in insulin secretion are contradictory, in general, selective CB2 agonists hold therapeutic promise in diabetes and diabetic complications by attenuating the inflammatory response and oxidative stress (Gruden *et al*., 2016).

CB2 agonists have also shown anti-inflammatory effects in cell culture models involving human astrocytes pre-stimulated with IL-1β, human endothelial cells pre-stimulated with TNF-α, human T-lymphocytes, and neutrophils (Scharf, 2017). CB2 agonists regulate the pathogenesis and progression of various inflammation- and immune-related diseases by increasing the recruitment, migration, and adhesion of leukocytes, and by modulating the release of chemokines and cytokines (increased production of anti-inflammatory IL-10 and reduced TNF-α, IL-2, IL-12, and IFN-γ expression) in in vivo and in vitro models of chronic diseases, including atherosclerosis, multiple sclerosis, and metabolic disorders (Hu, Tao, Hu, 2019; Mastinu *et al*., 2018; Vecera *et al*., 2020). In contrast, antagonism with selective CB2 ligands such as SR144528 blocks the anti-inflammatory effects elicited by the activation of this receptor. CB2 agonism also blocks ROS production in response to lipopolysaccharides, attenuating oxidative stress damage in various tissue types, including the brain, kidney, heart, and liver. There is evidence to suggest that stimulation of CB2 may also convey beneficial free radical scavenging effects, as CB2 stimulation in RAW264.7 macrophages suppressed CB1-stimulated ROS production through a pathway involving the small G protein Rap1 (Guillamat-Prats *et al*., 2019).

Interestingly, CB2 agonists do not have unwanted central side effects and appear to be protective in most diabetic complications. The antioxidant and anti-inflammatory effects mediated by CB2 receptors have shown a beneficial impact in several diabetes complications using various in vivo and in vitro approaches. Studies using CB2 agonists and antagonists, as well as the deletion of CB2 receptors, in models of myocardial infarction and diabetic cardiomyopathy have demonstrated the involvement of AMPK-mTOR-p70S6K signaling-mediated autophagy (Hu, Tao, Hu, 2019; Guillamat-Prats *et al*., 2019). The action on CB2 is implicated in the adhesion, migration, proliferation, and function of immune cells during atherosclerotic plaque formation. Also, activation of renal CB2 decreases the injurious effects of metabolic chronic pathologies, while antagonism with selective CB2 ligands produces the opposite results. JWH133 (a CB2 agonist) in ischemia-reperfusion injury of the mouse kidney prevents ischemia-reperfusion damage (Martín *et al*., 2018), whereas

AM1241 (another CB2 agonist) improves nephropathy due to STZ-induced diabetes and cisplatin-induced nephrotoxicity. These beneficial effects also involve the attenuation of NF-κB activation and the promotion of survival mechanisms via AKT/protein kinase B activation (Horvát *et al*., 2012; Gruden *et al*., 2016).

Although the potential utility of CB1 antagonists or CB2 agonists in the treatment obesity, diabetes, and MetS, including diabetic complications among other diseases, has been shown in clinical and experimental studies, further studies yet are required. These should assess various aspects such as the simultaneous evaluation of CB1 antagonists and CB2 agonists, determination of the clinical implications of polymorphisms in CB1 and CB2, the assessment of new CB1 antagonists that do not cross the brain-blood barrier or more selective CB2 agonists, and studying the therapeutic potential of other natural cannabinoids (Horvát *et al*., 2012; Gruden *et al*., 2016; Mastinu *et al*., 2018). One of the fundamental aspects that should be investigated is associated with the assessment of CB1 antagonists, in particular rimonabant, with potential for the treatment of disorders related to glucose homeostasis (Borowska *et al*., 2018). Also, the use of cannabinoids other than THC should not be overlooked because they have also demonstrated beneficial metabolic effects, especially cannabidiol (CBD), a potent antioxidant and anti-inflammatory agent with therapeutic potential in diabetes and its complications. CBD does not only exert its beneficial effects through conventional CB receptors and has been approved for human use (Horvát *et al*., 2012; Gruden *et al*., 2016).

Selective antagonists/inverse agonists of CB1: rimonabant

Rimonabant is a selective antagonist/inverse agonist of CB1 with relevant metabolic effects at the central and peripheral level. The blockade of CB1 by daily intraperitoneal administration of rimonabant for 14 days reduced body weight and food intake in non-obese chow-fed rats in a dose-dependent manner; additionally, rimonabant reduced spontaneous or neuropeptide Y (NPY)-elicited sucrose intake in rats, whereas its chronic administration had anti-obesity effects in diet-induced obese mice. It also ameliorated obesity-induced insulin and leptin resistance, improving glucose homeostasis and dyslipidemia, as well as decreasing hepatic steatosis in obese/overweight individuals with metabolic syndrome (Simon, Cota, 2017; Hirsch, Tam, 2019). These studies support the idea that CB1 antagonists might be useful therapeutic tools against obesity and metabolic disorders (Simon, Cota, 2017).

The mechanisms implicated in these actions in the brain may associate with enhancement of the satiety center in the melanocortin system and the inhibition of ghrelin, thereby attenuating the mesolimbic dopamine system, which is a critical pathway involved in reward processing, influencing on AMPK activation (Simon, Cota, 2017; Farokhnia *et al*., 2020). At the peripheral level, rimonabant reduces motility and the nutrient absorption in the gastrointestinal tract and decreases circulating ghrelin levels; ghrelin then modulates food intake by activating the ECS within hypothalamic circuits (Simon, Cota, 2017). Additional reports in vitro showed that rimonabant increases thermogenesis and glucose recapture in skeletal muscle, thereby reducing liver lipogenesis, preventing adipocyte differentiation and lipid storage, and increasing adiponectin. Also, direct administration of rimonabant to islets in vitro inhibited basal insulin hypersecretion due to obesity, and also inhibited glucose-stimulated insulin secretion from islets isolated from lean rats (Li, Bowe, Jones, 2010). Chang *et al.* (2018) studied the effects of CB1 blockade with rimonabant in obese rats (OLETF) for six weeks. Rimonabant did not affect body weight or glycemia, although it ameliorated hepatic fat accumulation and reduced lipid peroxidation and cell death in this organ; rimonabant also reduced TG levels, and inflammatory and fibrosis parameters, implicating a mechanism mediated by the activation of Nrf2, a redox-sensitive transcription factor, and AMPK, a central regulator of cellular energy homeostasis and inflammation (Chang *et al*., 2018).

Although the use of rimonabant and other selective antagonists of CB looked promising, in 2009, its commercialization was prohibited due to the occurrence of severe psychiatric disorders, depression, and an increase in suicidal thoughts (Simon, Cota, 2017). As a result, rimonabant currently represents a pharmacological

tool for the study of the ECS, phytocannabinoids, and metabolic diseases. Since then, compounds with low brain presence were proposed through computational or in vitro chemical tools to design and synthesize compounds that do not penetrate the blood-brain barrier, such as AM251, AM6545, LH-21, NESS06SM, URB447, TM 38857, and JD5037, among others (Chorvat, 2013). This class of compounds can decrease food intake and body weight in a manner comparable to rimonabant while lacking anxiety/depression-like side effects (Simon, Cota, 2017). These properties have been demonstrated throughout diverse in vivo (mice and rats) and in in vitro molecular and cellular assays, i.e. using isolated pancreatic β-cell or pancreatic islets, adipocytes, hepatocytes, macrophages, renal proximal tubular cells, liver perfusion, and models of CNS-mediated neuro-behavioral effects (anxiety), as well as various obesity and diabetes models using hypercaloric diets (high fat or sucrose), olanzapine, streptozotocin (STZ), KKAy mice, CB1 receptor-deficient mice, and leptin-deficient obese mice. Some of these studies included histological analysis in organs implicated in the metabolism of carbohydrates and lipids, and inclusive obese/overweight individuals with metabolic syndrome have been studied (Hirsch, Tam, 2019; González-Mariscal *et al*., 2016a and b)

For instance, AM6545 improved the metabolic profile of mice with diet-induced obesity, increased palatable food and food-reinforced behavior, and improved leptin sensitivity. However, it had limited oral bioavailability. LH-21 exhibited antihypertensive and anti-inflammatory effects (Hirsch, Tam, 2019); NESS06SM ameliorated metabolic abnormalities; URB447 reduced-fat ingestion, probably through the gut (Hirsch, Tam, 2019). TM38837 significantly lowered the potential to promote fear responses in mice. JD5037 did not alter responses in the behavioral assay known as the elevated plus maze (EPM), which is associated with anxiety and diminished diet-induced obesity, by causing the hypersecretion of leptin and driving its anorexigenic downstream response at the central level (i.e. STAT3 phosphorylation). This compound reduced islet inflammation, restored glycemic plasma levels, reduced hepatic steatosis, and reversed hyperleptinemia and insulin resistance (González-Mariscal *et al*., 2016b). Rimonabant and JD-5037 have been proposed as inverse modulators of insulin secretion mediated by incretins (González-Mariscal *et al*., 2016a, and 2018). AM251 and rimonabant have also been proposed as stimulators of pancreatic β-cell proliferation in vitro and in vivo (González-Mariscal *et al*., 2016b).

Another synthetic analog of rimonabant, BAR-1, was evaluated in isolated pancreatic islets from rats and STZ-induced diabetic mice. BAR-1 modified the mRNA abundance of CB1, glucagon, PDX-1, and glucokinase in response to changes in the glucose concentration. Glucose-stimulated insulin secretion was enhanced, and changes in insulin expression also were observed. BAR-1 slowed down weight gain in prediabetic mice, and a partial recovery of islet integrity was observed (Nava-Molina *et al*., 2020). Other inverse agonists of CB1, i.e. MJ08, SR141716, TXX-522, and AJ5012, in general, have shown potent anti-obesity effects and ameliorated insulin resistance in experimental models (Cinar, Iyer, Kunos, 2020), leading to reduced weight and improved hormonal/metabolic abnormalities in rodent models of obesity without eliciting CNS-mediated neuro-behavioral effects, nor anxiety-like behaviors in the elevated plus-maze assay.

The allosteric modulation of CB1 antagonism has also been suggested, which can allosterically modulate the activity of CB1 through a site topographically distinct from the endogenous ligand-binding site. One example is PSNCBAM1, which interacts with the CB1 receptor at a receptor site that is different from the active site where traditional CB1 inverse agonists bind. This compound induced acute hypophagy and weight loss in rats. Therefore, all these strategies might be useful in obesity, type 2 diabetes, and dyslipidemia (Sidibeh *et al*., 2017). However, first, it is necessary to evaluate the utility of these and other associated compounds for their capacity to influence CB1 concerning differences in affinity and intrinsic activity, principally at the central level, that might have some beneficial effect in MetS. Other fundamental factors that require further attention include the peripheral circadian rhythm of CB1 expression in the liver and the consequences of CB1 blockade on reducing systemic obesity-associated inflammation via transformation of the gut microbiome (Pepper *et al*.,

2019), since CB1inhibition with rimonabant altered the microbiome composition of diet-induced obese mice, impacting on the improvement of metabolic parameters (Di Marzo, Silvestri, 2019).

Another therapeutic strategy against obesity and MetS consists in the use of non-psychotropic phytocannabinoids, like CBD and THCV, that may also combine the beneficial effects of simultaneous CB1 inhibition and CB2 stimulation, in conjunction with interactions with other non-cannabinoid receptors (Horvát *et al.*, 2012), resulting in beneficial effects in experimental models of obesity and type 2 diabetes, with additional anti-inflammatory and antioxidants effects.

Non-psychotropic phytocannabinoids: CBD mechanisms of action

Several studies on the metabolic effects of non-psychotropic phytocannabinoids support their potential as therapeutic agents for obesity and MetS (Bielawiec, Harasim-Symbor, Chabowski, 2020). Until now, CBD is the phytocannabinoid no psychoactive more studied. CBD reduced the incidence of diabetes in diabetic non-obese mice, showing immunomodulatory and anti-inflammatory actions (Katchan, David, Shoenfeld, 2016; Cassano *et al.*, 2020). CBD also improved vascular function in type 2 diabetes, by promoting endothelium-dependent vasorelaxation (Stanley *et al.*, 2013). CBD reduced resistin and increased incretins (Jadoon *et al.*, 2016), thereby inhibiting the chemotaxis of murine macrophages through CB2 activation. Rajes *et al.* (2010) reported that CBD reduced cardiac dysfunction, oxidative stress, fibrosis, and inflammation, as well as cell death signaling pathways in diabetic cardiomyopathy (Rajesh *et al.*, 2010; Sidibeh *et al.*, 2017). However, in spontaneously (SHR) and deoxycorticosterone (DOCA-salt) hypertensive rats, CBD failed to modify blood pressure and heart rate (Remiszewski *et al.*, 2020). In an in vitro study using CHO cells transiently co-transfected with cDNA of the $NA^{+}1.5$ α-subunit cultured under high glucose conditions, CBD protected against high glucose-elicited oxidative stress, arrhythmia, and cytotoxicity (Fouda, Ghovanloo, Ruben, 2020). In mice, CBD reduced diabetes and inflammatory markers such as IL-1β, IL-12, IL-6, TNF-α, and IFN-γ, and also increased IL-4 (Laun *et al.*, 2018; Nichols, Kaplan, 2020), possibly as a result of increased levels of the anti-inflammatory endocannabinoid anandamide due to CBD administration, as suggested at the experimental level (Scharf, 2017).

The anti-inflammatory and antioxidant effects of CBD might be associated with weak agonist action on CB1/CB2, which increases CB2 expression. To explain this action, CBD may act as an inverse agonist or allosteric modulator of these and other non-cannabinoid receptors, such as μ- and ∂-opioid receptors (Martínez-Pinilla *et al.*, 2017). At the central level, CBD acts like a negative allosteric modulator of CB1, exerting a homeostatic effect and reducing the strong hunger drive and improving weight loss. CBD has been shown to attenuate CB1 agonist-driven food intake in a rat model of hyperphagia, although there was no difference in food intake seen with CBD in fed or fasting state rats. In a recently published clinical trial investigating CBD for epilepsy, loss of appetite was reported in 28% of the treatment group compared with 5% of the control group. It is currently being investigated in clinical trials as a treatment for hyperphagia in Prader-Willi syndrome. However, CBD anti-inflammatory activity may be antagonized by CB2 antagonists and CB2 agonists. In this way, CBD activates MAPK through PI3K/AKT/mTOR (mammalian target of rapamycin signaling pathway), the activation of which plays an essential role in regulating cell survival, proliferation, and apoptosis (Atalay, Jarocka-Karpowicz, Skrzydlewska, 2020).

Despite of these CBD actions on CB1 and CB2, it is currently well-recognized that CBD shows a reduced ability to bind to CB1 and CB2, exhibiting a non-specific receptor profile (Mastinu *et al.*, 2020). Therefore, to explain the metabolic effects of CBD and its effects on obesity, insulin resistance, type 2 diabetes, and MetS, mechanisms have been suggested associated with non-cannabinoid receptors, acting at multiple pharmacological targets (Scharf, 2017). Thus, in addition to CB1 and CB2, several other receptors have been reported that can explain these effects, such as stimulation of TRPV1, TRPV2, and TRPA1 for inflammation; 5HT1A for depression, anxiolysis, sleep, appetite, and nausea; and inhibition of GPR55 and stimulation of PPARγ for bone density,

arterial pressure, cell proliferation and insulin sensitivity (Smeriglio *et al*., 2018). CBD also has been associated with vasorelaxation mediated by PPARγ stimulation, a sensitizer of insulin receptors, which may be relevant for the prevention of MetS, whereas it delays the development of atherosclerosis (Scharf, 2017).

Of all these receptors, G protein-coupled receptors (GPCRs) stand out, as they have previously been reported to play essential roles in many normal physiological functions and are involved in a variety of pathological conditions. CBD is an inverse agonist for GPR3, GPR12, and GPR55. GPR3 is associated with obesity because experiments with mice lacking GPR3 exhibited a normal weight for 5 months, before subsequently gaining excess weight. Heterozygous and homozygous knockout mice gained significantly more weight than their age-matched wild-type GPR3 littermates. Furthermore, GPR3 knockout mice displayed increased fat droplet accumulation, increased triglyceride content in the liver, and increased leptin concentrations, all of which correlate with increased adiposity. These mice also had decreased energy expenditure and reduced core body temperature, as well as a decrease in several markers for thermogenesis, exhibiting thermogenic dysfunction and subsequent late-onset obesity. For its part, GPR12 also participates in obesity and metabolic disorders. Food intake was not significantly affected in GPR12 knockout mice compared to wild-type mice. However, these mice exhibited increased body weight and body fat mass, decreased respiratory exchange ratio, hepatic steatosis, and dyslipidemia. Therefore, GPR12 plays a significant role in energy balance (Laun et al., 2018). GPR55 regulates glucose, insulin sensitivity, and energy homeostasis and has been suggested as a possible target for CBD in studies performed in silico (Bian *et al*., 2019). Therefore, GPR55 might be a therapeutic target for type 2 diabetes, explaining some of the metabolic actions of CBD. In this context, abnormal-CBD, a synthetic cannabidiol agonist of GPR55 conjunctly with the GPR55 agonist O-1602 reduced endoplasmic reticulum (ER) stress-induced apoptosis in mouse pancreatic β-cell lines (MIN6 and beta-TC-6) through the activation of 3′-5′-cyclic adenosine monophosphate response element-binding protein (CREB), thus up-regulating anti-apoptotic genes such as Bcl-2 and Bcl-xL. Additionally, O-1602 and abnormal-CBD directly activated three kinases, i.e. CaMKIV, Erk1/2, and PKA, to induce CREB activation (Vong *et al*., 2019).

On the other hand, a growing body of experimental evidence strongly suggests that other phytocannabinoids and their derivatives, like CBC, CBDV, Δ^9-THCV, and CBDA, may combine the beneficial effects of simultaneous CB1 inhibition and CB2 stimulation (Horvát *et al*., 2012; Bielawiec, Harasim-Symbor, Chabowski, 2020), thereby improving glycemic control, pancreatic function, adiponectin, and apolipoprotein-A in type 2 diabetes patients. Some of them have putative anti-inflammatory activity (Rock *et al*., 2013; Pollastro *et al*., 2018) and bone-stimulant properties. Δ^9-THCA and CBG showed antiproliferative effects, with potential protective effects in the pancreas, which may prevent the development of type 2 diabetes. Since many of these actions have also been studied in CBD, it is highly recommended to examine more extensively the pharmacological potential of phytocannabinoids distinct from THC, especially those associated with metabolic diseases. Thus, it is essential to study the potential of other phytocannabinoids, such as THCV, to regulate these actions (Jadoon *et al*., 2016). CBDA abrogated cyclooxygenase-2 (COX-2) expression and its enzymatic activity mediated by PPAR β/δ in MDA-MB-231 cancer cells. CBDA inhibited PPARβ/δ-mediated transcriptional activation stimulated by the PPARβ/δ-specific agonist GW501516. Furthermore, the disappearance of cellular actin stress fibers, a hallmark of PPARβ/δ and COX-2 pathway activation, as evoked by GW501516, was effectively reversed by CBDA. Activator protein-1 (AP-1)-driven transcriptional activity, which is directly involved in the regulation of COX-2, was abrogated by the PPARβ/δ-specific inverse agonist GSK0660/ST-247 (Hirao-Suzuki *et al*., 2020).

CBD is not teratogenic or mutagenic, with only low toxicity in humans and other species. Despite the medical uses and beneficial metabolic effects associated with CBD, some adverse effects have been reported, such as an increase in lipid peroxidation, free fatty acid levels, and FAAH activity in normotensive rats (Remiszewski *et al*., 2020). Also, ALT and AST levels were found

to be increased, which may interfere with the hepatic metabolism of some drugs by inactivating cytochromes P450 3A and P450 2C. Caution should be used if CBD is used therapeutically (Remiszewski *et al.*, 2020). The search for new compounds with a better therapeutic profile and activity than CBD, without any adverse effects, is mandatory (Atalay, Jarocka-Karpowicz, Skrzydlewska, 2020). Synthetic cannabinoid agents, although possibly more potent, would not necessarily have the pleiotropic effects ascribed to CBD. In any case, clinical trials investigating CBD and associated compounds in MetS are still necessary (Scharf, 2017).

CONCLUSION

Cannabis preparations have significant therapeutic potential for neurologic and metabolic diseases. However, the use of this plant continues to be controversial, and studies that support its medical use in MetS are required, mainly through controlled clinical studies in MetS patients, rather than only in *Cannabis* users, as well as chemical studies to ameliorate the deleterious effects of *Cannabis* and its components. For this, it is essential to evaluate standardized *Cannabis* products in terms of rational and controlled use. Both CB1 antagonists with restrained passage into the brain and non-psychoactive phytocannabinoids represent a source of new therapeutic agents for the treatment of metabolic abnormalities.

ACKNOWLEDGMENTS

This study was supported by the National Council for Science and Technology (CONACYT) under Grant 17057 (CAMA) and PRODEP-SEP.

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Received for publication on 15th March 2020
Accepted for publication on 27th June 2020