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The molecular activity of cannabidiol in the regulation of Nrf2 system interacting with NF-κB pathway under oxidative stress

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ABSTRACT

Cannabidiol (CBD), the major non-psychoactive phytocannabinoid of *Cannabis sativa* L., is one of the most studied compounds in pharmacotherapeutic approaches to treat oxidative stress-related diseases such as cardiovascular, metabolic, neurodegenerative, and neoplastic diseases. The literature data to date indicate the possibility of both antioxidant and pro-oxidative effects of CBD. Thus, the mechanism of action of this natural compound in the regulation of nuclear factor 2 associated with erythroid 2 (Nrf2), which plays the role of the main cytoprotective regulator of redox balance and inflammation under oxidative stress conditions, seems to be particularly important. Moreover, Nrf2 is strongly correlated with the cellular neoplastic profile and malignancy, which in turn is critical in determining the cellular response induced by CBD under pathophysiological conditions. This paper summarizes the CBD-mediated pathways of regulation of the Nrf2 system by altering the expression and modification of both proteins directly involved in Nrf2 transcriptional activity and proteins involved in the relationship between Nrf2 and the nuclear factor kappa B (NF-κB) which is another redox-sensitive transcription factor.

1. Introduction

In the last decade, there has been great interest in the pharmacotherapeutic potential of secondary metabolites of *Cannabis sativa* L. such as phytocannabinoids and their synthetic derivatives, due to their chemical properties and associated biological effects. One of the most studied phytocannabinoid in the context of pharmacotherapy is cannabidiol (CBD). CBD can modulate intracellular redox and inflammation signaling [1] due to both direct regulation of the generation of reactive oxygen species (ROS) and agonistic/antagonistic effect on the activity of membrane receptors and modulating the metabolism of endocannabinoids [2]. CBD shows remarkable antioxidant activity on several cells, such as UV irradiated keratinocytes [3] and skin fibroblasts [4], primary human keratinocytes [5], and murine microglial cells [6]. On the other hand, CBD has also been reported to have pro-oxidative effects related to mitochondrial dysfunction and ROS overproduction in human monocytes [7] and colorectal cancer cells [8], as well as endoplasmic reticulum stress by excessive ROS generation and Ca^{2+} influx in breast cancer cells [9].

One of the key points to understanding the mechanism of action of cannabidiol under oxidative stress, which plays a key role in many diseases such as cardiovascular [9], metabolic [10], neurodegenerative [11] and cancerous [12], may be CBD-mediated regulation of nuclear factor-erythroid 2 factor 2 (Nrf2) pathway. The key role of the Nrf2 system is the modulation of antioxidant defense [13] and influences the regulation of molecular signaling involved in apoptosis, ferroptosis, tumor differentiation, and transformation [14]. These biological processes bring the link between the redox-modulating effect of CBD and Nrf2 pathway along. In coordination with the CBD's contribution to the regulation of redox balance, including both its antioxidant and pro-oxidative effects, the literature indicates the possibility of influencing both the upregulation and downregulation of the Nrf2 pathway in oxidative microcellular environments. It was found, among others, that the use of CBD (1 μM) can enhance the effectiveness of Nrf2 by increasing the level of its activators (such as p21 and p62) and reducing the level of its inhibitors (cytosolic ECH-like protein associated with Kelch1, Keap1; and nuclear Bach1) in irradiated skin keratinocytes [15]. On the other hand, the proteomic data obtained from skin keratinocytes of nude rats treated topically with 4 μM CBD after UVA/B irradiation (*in vivo*) indicate a significant decrease in the UV-induced levels of Nrf2 and

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Cu,Zn-superoxide dismutase (Cu,Zn-SOD) [16]. Moreover, another study shows CBD-induced upregulation of Nrf2 and HMOX1 expression (up to 6 μM CBD), while this phytocannabinoid (10 μM) downregulated Nrf2 and promoted autophagy in human umbilical vein endothelial cells [17].

Together with all the findings showing CBD-mediated regulation of the Nrf2 system, there is still limited information regarding the mechanism of action of this phytocannabinoid and its activity on the Nrf2 pathway. Additionally, the interactions of CBD with pathway dependent on another redox-sensitive transcription factor nuclear factor kappa B (NF-κB), which is known to interact strongly with the Nrf2 system [18], is also critically important for the determination of cellular response to oxidative stress. Therefore, this review summarizes how this phytocannabinoid affects the Nrf2 system, especially by interfering with Nrf2 and NF-κB crosstalk.

2. Cannabidiol, a natural compound interfering with redox balance

Since the day CBD (a terpenophenolic compound, $C_{21}H_{30}O_2$) was firstly identified by Mechoulam [19], it has drawn great interest due to its pharmacotherapeutic potential deriving from its chemical structure. Its modulatory activity in controlling ROS generation helps to maintain redox balance, but also affects oxidative signaling. Therefore, under oxidative conditions, CBD can modulate intracellular pathways such as inflammation, differentiation, and apoptosis, in which oxidative signaling is involved [1]. CBD directly changes the redox status of cells by affecting ROS generation due to interruption of free radical chain reactions, transition metal ions chelation, or activity of anti-/-pro-oxidant enzymes. Also, it can indirectly regulate the redox status through the modulation of the endocannabinoid metabolism (anandamide, AEA, and 2-arachidonoylglycerol, 2-AG) and the activity of membrane receptors, including peroxisome proliferator-activated receptor gamma (PPARγ) which can cooperate with Nrf2 and NF-κB [2,20].

2.1. Multidirectional action of CBD in the redox modulation

In vitro and *in vivo* studies carried out with different cells have pointed out both antioxidant and pro-oxidant capacity of CBD caused by its modulatory action in intracellular ROS level. The antioxidant action of CBD has been shown in several cell types including mouse hippocampal neuronal cells by increasing SOD1 and glutathione peroxidase (GPx) activities and glutathione (GSH) level [21] and skin keratinocytes by decreasing UV-induced ROS generation [3]. A study with keratinocytes showed a CBD-induced enhancement in the activity of Cu,Zn-SOD, thioredoxin reductase (TrxR), and the level of thioredoxin (Trx) [15]. Also, another study in human umbilical vein endothelial cells demonstrated a significant increase in the level of HMOX1 mRNA and protein together with Nrf2 level caused by CBD action [17]. Moreover, CBD intervention to prevent excessive production of ROS protects cell metabolism against oxidative damage of other macromolecules such as lipids [22,23] and proteins leading to the maintenance of protein homeostasis [24] which are the critical targets for oxidative damages-associated pathology [Fig. 1].

Consequently, CBD effectively weakens the lipid peroxidation process with a reduction in the level of lipid peroxidation products, including polyunsaturated fatty acids (PUFAs) metabolites formed as a result of oxidative fragmentation with the generation of electrophilic aldehydes such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) and products of oxidative cyclization of the hydrocarbon chains of phospholipid PUFAs such as F_2-isoprostanes [3,21,25]. These products are recognized as markers of oxidative stress [26]. Under pro-oxidative conditions, CBD treatment has been also shown to prevent excessive adduct formation between lipid peroxidation products and proteins [24,27]. These adducts can change protein functions and ultimately intracellular signaling, which also affects biological pathways such as inflammation, differentiation, and cell death, in which these proteins are involved [28]. The protective effect of CBD on cells against oxidative stress was also demonstrated in keratinocytes from UV-irradiated rats by reducing UV-induced levels of protein carbonyls [29] indicating oxidative protein damage [30]. Likewise, it has been known that CBD can normalize total protein expression in skin

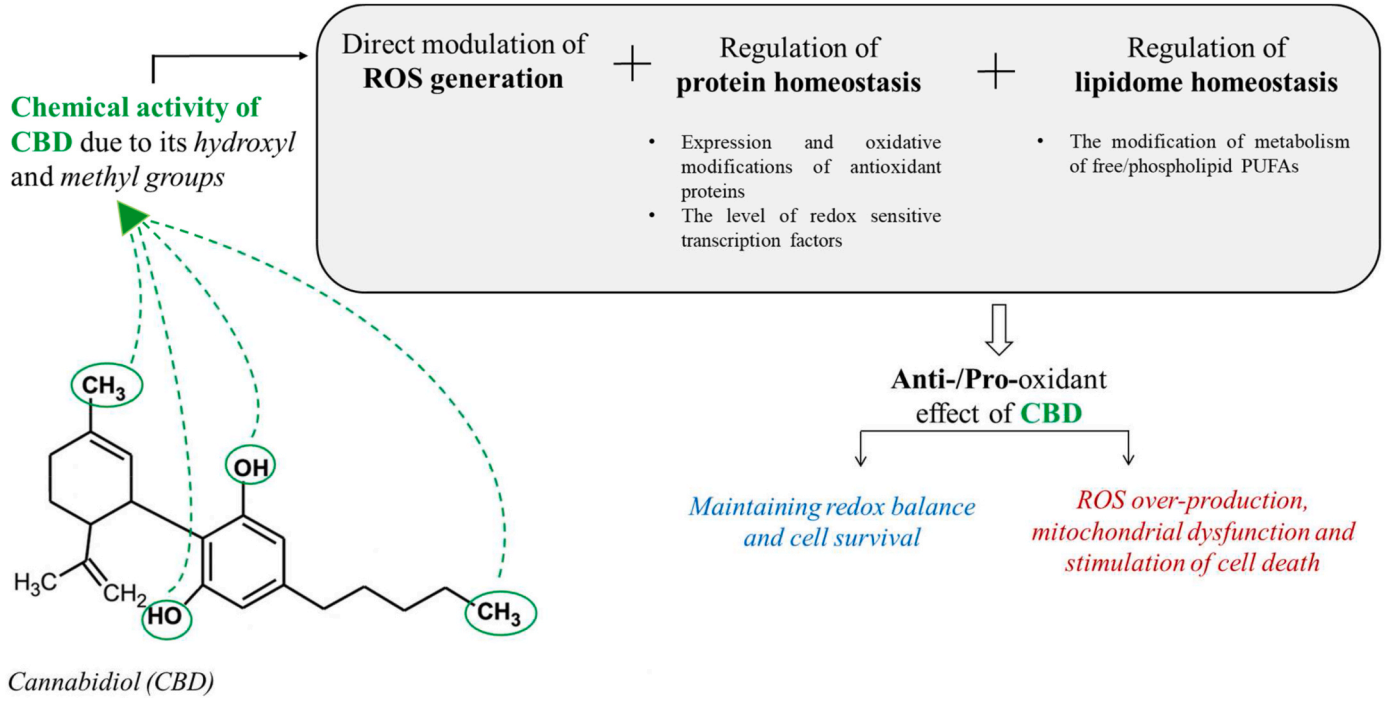

Fig. 1. The antioxidant and pro-oxidant abilities of cannabidiol (CBD) in relation to its chemical structure including hydroxyl groups (OH) in the phenolic ring and methyl groups (CH_3) in the cyclohexene ring and the pentyl chain of the phenolic ring. (ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids).

keratinocytes of nude rats which is dramatically increased by the oxidative effect of UV radiation [16].

Regardless of its antioxidant activity, CBD – as a result of metabolic changes in cells, e.g. caused by the neoplastic process – may also show pro-oxidative effect, in this case having a therapeutic nature due to the cellular response to the pro-oxidative environment associated with the dynamics of cell survival [31]. Several studies indicate the relationship between CBD-mediated ROS production and apoptosis as well as autophagy. It has been shown, inter alia, that CBD (up to 16 μM) promotes high production of ROS in the mitochondria of human monocytes, and consequently induces apoptosis in a dose-dependent manner [7]. Another work in colorectal cancer cells also demonstrates autophagy by increasing ROS overproduction-mediated mitochondrial dysfunction due to CBD application (4 μM) [8]. In addition, in human THP-1 monocytes, a higher concentration of CBD (25 μM) can also promote the expression of cyclooxygenase 2 [32], which generates nitric oxide responsible for oxidative stress and associated pro-inflammation and pathogenic stimulation [33]. Moreover, CBD used before and after irradiation of keratinocytes with UVB showed a significant reduction in the total formation of MDA- and 4-HNE-protein adducts [34]. But at the same time, MDA-protein adducts formation was more effectively reduced than 4-HNE-protein adducts which play an important role in promoting oxidative stress and apoptosis [35]. Together with all, it is also noteworthy that the changes triggered by CBD on lipid metabolism may also cause an autophagic response. Another study suggests that a CBD-induced increase in phosphatidylethanolamines and a decrease in sphingomyelin levels observed in UV-irradiated keratinocytes of nude rats may indicate pro-autophagic action of CBD [22]. Particularly, the CBD-mediated decrease in sphingomyelin level is also important to understand CBD action in regulating intracellular redox status by modifying lipid metabolism. A study using the eye lens cell membrane model indicates that an increase in the level of sphingomyelin in the cell membrane has been pointed out as an antioxidant response to protect the eye from oxidative damage [36].

The multidirectional metabolic effects of CBD, including the intracellular redox state, is the result of both the chemical structure of CBD, and also the changes in the intracellular microenvironment due to its actions, including those resulting from the dose and duration of CBD treatment [1]. Its direct redox-modulating effect is mainly the result of the hydroxyl groups and the pentyl chain in the phenolic ring as well as the methyl group of the cyclohexene ring of CBD [2] (Fig. 1). In addition to the direct modulating effect of CBD on ROS levels and the consequent redox balance, this phytocannabinoid also acts indirectly by altering endocannabinoid levels and modulating the activation of membrane receptors coupled to G protein [2]. This modulation plays a key role in regulating both redox balance and inflammation [2]. Further factors of redox balance modulation are the dose and duration of action of CBD on the cell as well as organism. Both factors can cause completely different cellular responses, from unequivocally antioxidant to pro-oxidative [1]. The increase in the expression of NOX4 and p22phox NAP(P)H pro-oxidative enzymes in human leukemia cells [37], as well as the reduction of GSH levels in primary lymphocytes [38] observed in the literature increase the possibility of CBD pro-oxidative activity. Moreover, the regulatory effect of CBD on the redox system by influencing lipid metabolism and triggering the associated cell response is also important in terms of Nrf2's participation in this activity. The Nrf2 activity reducing ROS generation is also known to promote down-regulation of fatty acid synthesis [39] as well as to reduce lipid peroxidation and ferroptosis [13]. Considering the redox regulatory activity of CBD and the overlap between this activity and the Nrf2 system, it is important to understand the molecular activity of this phytocannabinoid on the Nrf2 pathway.

3. The modulatory activity of cannabidiol with respect to the Nrf2 pathway

Nrf2, a redox-sensitive transcription factor that is involved in the maintenance of cellular homeostasis and antioxidative mechanism [40], stimulates the transcription of genes encoding cytoprotective and detoxifying enzymes, including NAD(P)H dehydrogenase [quinone] 1 (NQO1) [41], heme oxygenase-1 (HO-1, HMOX1) [42], glutathione reductase (GR), TrxR, catalase (CAT) and SOD [43]. Nrf2 presents cytoprotective action resulting from a cellular response to stress conditions such as oxidative stress and inflammation caused by xenobiotics [44]. However, hyperactivity of Nrf2 has been found to be associated with cell differentiation and proliferation as well as malignant transformation and down-regulation of apoptosis [14]. Due to the Nrf2 activation causing ROS detoxification in cancer cells, which are characterized by a high level of ROS generation, as well as Nrf2-associated expression of anti-apoptotic factors such as anti-apoptotic protein Bcl-2 [45], Nrf2 has recently also been identified as an oncogene [14].

3.1. The activation pathways of Nrf2 system

Nrf2 activation is regulated in two pathways defined as the canonical (Keap1-dependent) and non-canonical (Keap1-independent) pathways (Fig. 2). In the canonical pathway, under homeostatic conditions, Keap1 homodimerizes and binds to the Cullin-based (Cul3) E3 ligase (formation of Keap1-Cul3-RBX1 complex). The created complex ultimately promotes the ubiquitination and proteasomal degradation of Nrf2 via binding to its Neh2 domain [46]. Under the stress conditions caused by electrophiles or ROS over-generation, the cysteine residues of Keap1 are oxidatively modified. This modification causes Nrf2 dissociation from the Keap1-Cul3-RBX1 complex and Nrf2 translocates to the nucleus, where heterodimerizes with small Maf protein. Formed complex, after attaching to DNA in a specific sequence antioxidant response element (ARE), initiates transcription of cytoprotective genes [40]. In the non-canonical pathway under homeostatic conditions: following glycogen synthase kinase-3 (GSK3)–mediated phosphorylation of Nrf2, Nrf2 binds to beta-transducin repeats-containing protein (β-TrCP). After that, Nrf2 is ubiquitinated and degraded by 26S proteasome due to interaction between β-TrCP and Skp1-Cul1-Rbx1 ubiquitin ligase complex [46]. In addition to this, a recent study in cortical neurons and astrocytes showing Nrf2 activation Keap1-independent manner suggests that the effect of oxidative stress, as well as classical and electrophilic Nrf2 inducers, could be additive to Nrf2 activation. Moreover, the mechanism responsible for Nrf2 activation may be cell-specific and possibly dependent on the intensity and duration of oxidative stress [47]. This situation should be considered in the development of the Nrf2-associated therapeutic strategies for the diseases accompanied by oxidative stress, from viral infection to cardiovascular diseases and cancer [48–50].

Literature data from recent years indicate the importance of Nrf2 to redox conditions in adaptation to the microcellular environment with increased ROS levels [51], especially in neoplastic cells. In the pathophysiology of cancer, oxidative stress related to the production or reduction of ROS level is one of the key points in modulating the dynamics of cell survival or tumor progression [52]. Intracellular ROS can induce cancer cell cycle arrest, aging and apoptosis, so it is important to evaluate the cellular antioxidant response associated with chemo- and/or radiotherapy, which increases intracellular ROS levels [53]. In this context, the antioxidant response of cells caused by the activation of the Nrf2-ARE signaling pathway constitutes a critical protection against oxidative stress, and thus, promotes the growth of neoplastic cells and their resistance to chemotherapeutic agents [54]. Consequently, the literature data strongly indicates the importance of using natural compounds in anti-cancer therapy to counteract Nrf2 activity in neoplasms [55]. Thus, the ROS level modulating effect of CBD along with its antioxidant effects as mentioned above shows a promising therapeutic

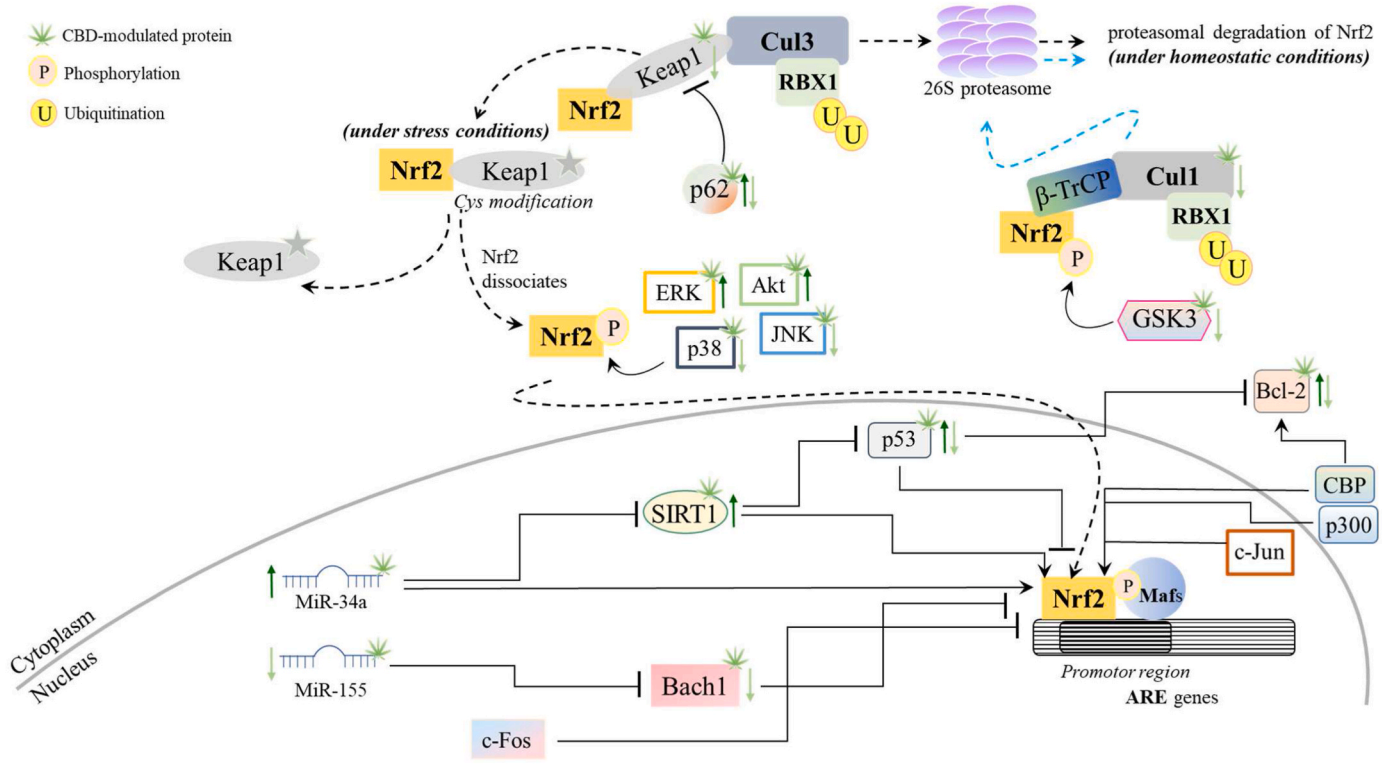

Fig. 2. Under homeostatic conditions regarding *canonical pathway of Nrf2*, Nrf2 is degraded via formation of the Nrf2-Keap1-Cul3-RBX1 complex and ubiquitination. Due to the stress-associated oxidative modification of Keap1, Nrf2 dissociates from the Keap1-Cul3-RBX1 complex and translocates to the nucleus. In the *non-canonical pathway* under homeostatic conditions, Nrf2 binds to β-TrCP via its phosphorylation mediated by GSK3. Following this, Nrf2 is ubiquitinated and degraded due to interaction between β-TrCP and Skp1-Cul1-Rbx1 ubiquitin ligase complex. Cannabidiol (CBD) can modulate the redox status of cells by interfering with canonical and non-canonical pathways of Nrf2 and altering the level of proteins and miRNAs participating in Nrf2 activity. (The **black** and **blue dashed** arrows are used for canonical and non-canonical pathways, respectively; the **dark green** or **soft-green** arrows are used for CBD-mediated increase or decrease in the level of proteins and miRNAs, respectively; the **black** or **end-cut** arrows are used for up-regulation and down-regulation of Nrf2 activity, respectively; Kelch-like ECH-associated protein 1, Keap1; Cullin-based E3 ligase (Cul3); RING-box protein 1 (RBX1); glycogen synthase kinase-3 (GSK3); beta-transducin repeats-containing protein (β-TrCP); Cullin 1 (Cul1); antioxidant response element (ARE); protein kinase B (Akt); mitogen-activated protein kinases (MAPKs); c-Jun N-terminal kinase, JNK; extracellular response kinase, ERK; B-cell lymphoma 2, Bcl-2; CREB-binding protein (CBP); sirtuin1 (SIRT1); micro-RNA, miRNAs/miR). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

potential, disrupting the critical relationship between ROS detoxification and Nrf2 activity. Moreover, a study using canine urothelial carcinoma cells suggests that CBD, as a single agent or in combination with mitoxantrone and vinblastine shows a decrease in cell viability but also an increase in apoptotic response with CBD administration, compared to single-agent treatment [56].

3.2. CBD-mediated regulation of Nrf2 expression

It has been shown that CBD can regulate the expression level and activity of Nrf2. For the transcription of the *NFE2L2* gene encoding Nrf2, a study in pancreatic cancer indicates that *NFE2L2* transcription is associated with K-Ras, B-Raf, Myc oncogenic alleles, and Jun protein [12]. CBD was found to prolong animal survival with daily intraperitoneal administration of this phytocannabinoid (100 mg/kg) to mice with genetic ablation of G protein-coupled receptor 55 (GPR55) with $KRAS^{WT/G12D}/TP53^{WT/R172H}/Pdx1\text{-}Cre^{+/+}$ belonging to relevant model of pancreatic ductal adenocarcinoma [57,58]. Another study demonstrated a decrease in melanoma viability and proliferation has been also observed via an increase in autophagy and apoptosis due to combination treatment (THC + CBD) to mice bearing B-Raf wild-type melanoma [59]. Also, CBD-upregulated expression of N-Myc-downstream regulated gene 1 (NDRG1), encoding NDRG1 protein involved in stress response and whose expression is repressed by the proto-oncogenes MYCN and MYC [60], has been determined in BV-2 cells treated with CBD (10 μM) [61]. However, even with these data, information on the effects of CBD on the activity of mentioned oncogenes and Jun proteins is still very limited.

Turning to Nrf2, the regulatory effect of CBD on the transcriptional activity of Nrf2 has been shown in several studies. A significant increase in the expression of Nrf2-driven antioxidant proteins such as HMOX1 and metallothioneins (Mt1 and Mt2) has been demonstrated in the MOG35-55-specific T cell line (T_{MOG}) treated with CBD (5 μM) [62]. Also, the level and the activity of antioxidant enzymes, including alanine aminotransferase (ALT) and SOD, in the serum of mice with induced liver fibrosis were significantly increased by animal treatment with CBD (4 and 8 mg/kg) which correlated with increased Nrf2 expression [63]. Another study in UVA/B irradiated skin keratinocytes showed CBD-induced (1 μM) levels of TxrR and Cu,Zn-SOD [15]. Moreover, this study also showed a CBD-induced decrease in the levels of Nrf2 inhibitors (Keap 1, Bach1) together with an increase in the levels of Nrf2 activators (KAP1, p21, p62) [15]. A similar effect of CBD (30–120 μM) the mentioned p21 level was also observed in the gastric cancer cells (line SGC-7901), which in turn led to cell cycle arrest at the G0–G1 phase, thereby suggesting that CBD may have therapeutic effects on this cancer [64]. On the other hand, the use of combination techniques involving RNA sequencing and sequential window acquisition of all theoretical mass spectrometry (SWATH-MS) by showing the increase in HMOX1 expression and inhibition of Bach1 in human epidermal keratinocytes treated with CBD (10 μM) indicated that this phytocannabinoid behaved as a Bach1 inhibitor and a weak Nrf2 activator [5].

3.3. CBD involvement in Nrf2 activation via reaction with p62 or Keap1 as well as AKT/MAPK signaling

Regarding both the canonical and non-canonical Nrf2 pathways, it is also known that CBD can affect Nrf2 activity by regulating the proteins involved in these pathways. A study in mesenchymal stem cells derived from gingiva showed that the use of CBD (5 μM) can inhibit the expression of GSK3β [65]. GSK3β is known to promote β-TrCP - mediated Nrf2 degradation via phosphorylation of Nrf2 in the cytosol. Also, it has been known that GSK3β can phosphorylate Fyn protein in the cytosol and causes its nuclear transport resulting in phosphorylation of Nrf2, its nuclear export, and degradation [66]. On the other hand, CBD-induced inhibition of Cullin 1, involved in the Skp1-Cul1/Rbx1 complex leading to the degradation of Nrf2 [67], was reported in MCF7 human breast adenocarcinoma cells [68]. This situation demonstrates the importance of CBD's regulatory effect on the proteasomal degradation of Nrf2 which is a critical part of the regulation of Nrf2 activity. This may confirm that the regulatory effect of CBD on the proteostasis network has been demonstrated by CBD-mediated protection in the expression and oxidative modifications of proteins involved in proteasome activity and protein folding [24]. Moreover, several studies show the CBD-mediated regulation of p62 expression in both an increasing [69] and decreasing trend [70], in Sprague Dawley rats using CBD (100 mg/kg) [69] and in Sprague Dawley rats with hemorrhagic shock-induced brain injury using this phytocannabinoid (5 mg/kg) [70], respectively. This indicates not only CBD effects on the regulation of autophagy but also another way for CBD-mediated regulation of the Nrf2 pathway. Because p62 phosphorylation can activate autophagy due to proteasome inhibition, and p62 participates in the Keap1–Nrf2 pathway [71]. Nrf2 can be also activated by competitively binding p62 to Keap1 and this inhibitor's autophagic degradation due to p62 interaction [72]. Moreover, it has been observed in the case of several neoplastic cell lines (subtypes of lymphoma and osteosarcoma) that CBD by lowering the level of p62, it significantly reduces the survival and proliferation of these cells [73]. Thus, the CBD-regulated Nrf2 activity could be considered from the perspective of p62, which is also suggested as a therapeutic target for tumorigenesis [74].

It has also been shown that the acetyltransferases p300 and CREB-binding protein (CBP) acetylate Nrf2 and enhance bindings of Nrf2 to the promoter region of ARE genes [75]. CREB and CBP can also bind to the promoter region of the anti-apoptotic Bcl-2 gene and up-regulate gene expression [76]. Moreover, the c-Jun subunit of activator protein 1 (AP1) can dimerize with Nrf2 and activate ARE transcription, while c-Fos protein (a proto-oncogene) can suppress it [77]. However, there is no information directly targeting CBD effects on p300 and CBP activity, it has been shown that CBD (after intraperitoneal injection of 10, 20, 40, 80 mg CBD/kg b.w.) can reduce methamphetamine-induced p-CREB protein expression in Sprague–Dawley rats [78]. But also, another study suggests that CBD (from 1 to 20 μM) stimulated phosphorylation of CREB in cytokine-induced killer cells (CIKs) with a donor-specific variability in phospho-CREB [79]. Moreover, activation of protein kinase B (Akt), mitogen-activated protein kinases (MAPKs) (c-Jun N-terminal kinase, JNK; extracellular response kinase, ERK; p38) were reported in Nrf2-mediated expressions [80]. On the other hand, active JNK-mediated direct phosphorylation of Nrf2 and its degradation through polyubiquitination of Nrf2 has been suggested in a study showing down-regulation of ARE genes in acetaminophen-induced liver injury in mice [81]. In addition, the balance of MAPK and AKT signaling pathways, due to their regulatory roles in cell survival, proliferation, and apoptosis [82], is critical to maintaining intracellular homeostasis as shown in phenotypic changes in vascular smooth muscle cells under physiological and pathological conditions [83]. JNKs, on the other hand, are involved in the regulation of cell proliferation, cancer growth, therapy resistance, and apoptosis [84]. Thus, the activities, structural modifications, or changes in the expression of these proteins are critical in the regulation of the Nrf2 pathway and associated Nrf2-mediated cellular responses. CBD-mediated reduction of JNK activation has been shown in CBD-treated diabetic mice (1, 10, or 20 mg/kg) [85]. However, the study in Wistar rats indicated CBD (5 mg/kg)-induced PI3K/AKT and MAPK/ERK pathways associated with reducing reperfusion myocardial damage [86]. Moreover, CBD (4 μM) has been shown to reduce the p38 level in keratinocytes in the skin of healthy and psoriatic people [87]. It may therefore be suggested that changes in CBD-mediated AKT, as well as MAPK signaling, may play an important role in determining the cellular response to regulate intracellular homeostasis in pathological conditions by modulating Nrf2 transcription.

3.4. CBD effects on the regulatory RNAs concerning the Nrf2 pathway

The effectiveness of regulatory RNAs in the modulation of gene expression is also very important for CBD activity in relation to the Nrf2 pathway. CBD (10 μM) has been shown to reduce lipopolysaccharide (LPS)-stimulated expression of microRNA-155 (miR-155) and to increase the level of miR-34a, which are redox-sensitive microRNAs (miRNAs) involved in the regulation of Nrf2 in microglia (BV-2) cells of mice [88]. In contrast, miR-155, by inhibiting Bach1, increases the expression of HMOX1 [89]. Moreover, miR-34a has been shown to reduce the expression of sirtuin1 (SIRT1) [90], which can regulate the deacetylation of Nrf2, increasing the stability and nuclear transport of Nrf2 and enhancing its transcriptional activity [89]. The use of the THC + CBD combination therapy (10 mg/kg each) in C57BL/6 mice with experimental autoimmune encephalomyelitis showed downregulation of miR-155 [91]. CBD's interference in the activity and/or levels of miR-155 and miR-34a may have a key role in the cellular response related to the regulation of cell survival and proliferation under conditions of oxidative stress by altering Nrf2 activity. Moreover, miRNAs have critical impacts on the regulation of gene expression and associated biological processes such as proliferation, apoptosis, tumorigenesis [92], and even cell-cell communication (as suggested via vesicle-free extracellular miRNAs) [93]. Considering this regulatory role of miRNAs, and other transcription regulatory molecules involved in the Nrf2 pathway (such as miR-365-1, miR-193b, miR-29-b1, miR-93, miR-153, miR-27-a, miR-142–5p [94], miR-21 [95], miR-144 [96], miR-125b [97], miR-181a [98], hsa_circ_0005915 [99], miR-145–5p, miR-104–5p, miR-200a [100]) may be important to evaluate CBD action which may have a great potential to change Nrf2 activity.

3.5. CBD's involvement in neoplastic transformation by regulating cell survival through the modulation of the Nrf2 system

CBD-mediated up-regulation of the Nrf2 system and associated strong antioxidant cellular response also bring along regulation of cell survival. A study in primary glioma stem cells using 2 μM CBD showed a robust CBD-induced ROS level and CBD-inhibited cell survival [101]. Interestingly, the same study showed that following CBD treatment can promote reprogramming of glioma stem cells associated with tumor re-growth via expression of antioxidant response system Xc catalytic subunit xCT and HMOX1. This situation clearly shows the importance of CBD-induced Nrf2 activity associated with tumorigenesis. Literature indicates a strong association between prolonged activation and accumulation of Nrf2 and neoplastic transformation as well as chemo-resistance and radio-resistance of cells [102]. In addition, it has been shown that CBD (2.5/100g of petroleum jelly) on the nude skin of rats significantly reduced the level of Nrf2 which was enhanced strongly by UVA/B radiation as a cellular antioxidant response to the stress factor [16]. It may indicate the role of CBD in protecting skin cells against UV-induced malignancy [103].

The rat study, mentioned above, also indicates a potential regulatory role of CBD in apoptosis via showing modulation of the level of anti-apoptotic Bcl-2 protein. The UVA-induced level of Bcl-2 was decreased by CBD application, and the CBD-induced Bcl-2 level was decreased by UVB [16]. Interestingly, a recent study in cisplatin-resistant

non-small-cell lung cancer cells draws attention to CBD-mediated (15.8 μM) reduction in tumor progression and metastasis through inhibition of cell growth by reducing Nrf2 expression, increasing ROS generation, and targeting transient receptor potential vanilloid-2 (TRPV2) [104]. Moreover, Böckmann's study also suggests CBD-mediated protective autophagy due to CBD (10 μM)-induced level of LC3A/B-II, an autophagy marker, as well as an increase of Nrf2-driven HMOX1 in a concentration-dependent manner [17]. Also, this study shows that the inhibition of autophagy using bafilomycin A1 can evoke apoptosis induction of CBD. These results show the potential of CBD to negatively regulate malignancy and neoplastic transformation in different cell types, through the modulation of Nrf2 at relatively high concentrations. Thus, all data mentioned above also highlight the role of Bcl-2 and the activity of TRPV receptor regulations in CBD-mediated Nrf2 modulation. Literature data also indicate Nrf2-induced Bcl-2 activation [105] and Nrf2-mediated downstream signal of the TRPV1 [106].

On the other hand, anti-apoptotic Bcl-2 and its inhibitors have a critical impact on the regulation of p53-dependent apoptosis [107]. During stress conditions, the interaction between p53 and Bcl-2 family members, which can determine an apoptotic threshold, is one of the important factors controlling the survival of the cell. The positive regulation of p53 signaling promotes apoptotic response through the induction of apoptotic Bax and inhibition of anti-apoptotic Bcl-2 [108]. SIRT1, which can induce Nrf2 transcriptional activity as mentioned above, negatively regulates the p53 transcription-dependent apoptosis [109]. Also, p53 can attenuate the expression and function of Nrf2 [110]. Moreover, it has been shown that an increase in the nuclear import of Nrf2 and its phosphorylation using tert-butylhydroquinone in mesenchymal stem cells enhances nuclear SIRT1 at both mRNA and protein levels while decreasing the p53 level [111]. In addition to the CBD-mediated expression of Bcl-2 mentioned above, a CBD-induced increase in p53 and Bax levels and a decrease in Bcl-2 levels were also demonstrated in three cervical cancer cell lines (SiHa, HeLa, and ME-180) [112]. Also, it was found that p53 was decreased by CBD (100 ng/rat) in a model of ischemic stroke in rats [113]. In addition, recent years' research indicates a significant increase in SIRT1 expression and autophagy by protecting mitochondrial dysfunction in neural SH-SY5Y cells treated with CBD at 25 μM [114]. Therefore, CBD-mediated modulation of p53, SIRT1, and Bcl-2 expression as well as associated modulation of cell survival status should be considered in accordance with Nrf2-associated cell survival, especially for the development of treatment strategies in malignancy.

3.6. The effect of CBD metabolism on redox balance including Nrf2 action

In order to consciously use the above-mentioned effects of CBD, from antioxidant to pro-oxidative, depending on the dose and/or duration used, both the pharmacokinetics and the safety/toxicity of preparations containing this compound should be taken into account. It is known that the metabolism of CBD involves the primary oxidation of C_9 (from methyl group) to alcohol and carboxylic acid and oxidation of this phytocannabinoid side chain [115]. As a result of the action of enzymes from the cytochrome P450 family, the first phase metabolism of CBD takes place with the formation of a large group of metabolites, including primarily derivatives of 7-carboxy-cannabidiol (7-COOH-CBD) [116]. However, the mode of administration, dose, and exposure time all influence the pharmacokinetics of CBD, resulting in high intra- and inter-individual variability of the metabolites [116]. Despite the lack of data on the effect of CBD metabolites on redox metabolism, it can be assumed that the particularly long-term effects of CBD may influence cellular metabolism depending on the dose. CBD in a relatively low doses has an antioxidant effect on cell survival. On the other hand, this compound in a relatively high dose, acting pro-oxidatively, affects the dynamics of cell survival. In both cases, however, the safety of using CBD as a therapeutic agent must also be considered. In this context, recent studies have shown that CBD is not harmful to metabolism and liver functions when used at low doses [117]. Together with this, the need to use CBD in long-term therapy, such as e.g. anti-cancer therapy, requires further detailed studies to assess the individual biological variability of the body's response in terms of pharmacokinetics and efficacy of this compound, as well as metabolic disorders related to redox balance, in which the Nrf2 system plays a key role.

4. The role of cannabidiol in the Nrf2 - NF-κB crosstalk

4.1. NF-kB activation pathways

Due to pathologies related in particular to redox imbalance, the molecular mechanisms of the interaction between two redox-sensitive transcription factors, Nrf2 and NF-κB, and their metabolic pathways have been analyzed for several years [100]. Thus, it may be suggested that CBD-mediated alterations of Nrf2 - NF-κB are one of the key points in modulating intracellular redox homeostasis and determination of the cellular response under the conditions of oxidative stress and associated chronic inflammation. NF-κB family elements, consisting of p50, p52, p65 (RelA), Rel B, and c-Rel, participate in the regulation of inflammation and cell differentiation through the activation of a large number of genes encoding pro-inflammatory cytokines and chemokines such as interleukin-1 (IL-1), IL-6, IL-23, tumor necrosis factor-alpha (TNF-α), interferon (IFN-γ) [118]. Similar to Nrf2 activation, NF-κB also has two major activation pathways, the canonical and non-canonical pathways (Fig. 3), stimulated by immune or stress responses caused by microbial components, cytokines, and growth factors, and redox imbalance [119]. The canonical pathway is activated by the stimulation of cytokine receptors, pattern-recognition receptors (PRRs), TNF receptor (TNFR) superfamily members, T-cell receptor (TCR), and B-cell receptors. IκB kinase (IKK) complex (consisting of catalytic subunits IκBα and IκBβ and regulatory subunit NF-κB - essential modulator NEMO)/IκBγ) phosphorylates inhibitor of nuclear factor kappa B (IκBα). After that, IκBα is degraded by ubiquitin-dependent proteasomal degradation. Then, mainly p50/RelA and p50/c-Rel dimers translocate to the nucleus to express pro-inflammatory mediators [120]. However, the noncanonical pathway is actuated by stimulation of specific receptors from the TNFR superfamily which are LTβR, BAFFR, CD40, and RANK receptors. IκBα is phosphorylated by NF-κB-inducing kinase (NIK), and phosphorylated IκBα promotes p100 phosphorylation and its ubiquitination. Following this, the C-terminal IκB-like structure of p100 is degraded by 26S proteasome and mature p52 protein is formed. The p52 protein translocates to the nucleus with RelB for the transcription of pro-inflammatory genes [121].

4.2. CBD effects on the NF-kB pathways activation

Literature indicates that CBD can modulate the NF-κB pathway. CBD (1–10 μM) was shown to decrease the level of pro-inflammatory cytokines TNF-α and IL-1β by inhibiting the NF-κB pathway in LPS-treated mouse microglial cells [6]. It was also shown that UV-irradiated keratinocytes treated with CBD (1 μM) have stimulated the Nrf2 pathway and at the same time downregulation of the NF-κB pathway along with increased expression of phosphorylated IκBβ [15]. Moreover, a similar effect of CBD (30 μM) on the Nrf2 pathway (including Keap1 downregulation and Nrf2 activation) correlated with blanking the NF-κB pathway by lowering the TNF-α was also observed in animals with oral mucositis [122]. On the other hand, CBD (2.5 μM) did not affect the level of NF-κB family member p50 in response to TNF-α in C2C12 muscle cells [123]. Consequently, CBD-mediated modulation of the NF-κB signaling pathway is suggested to be strongly dependent on cell specificity and CBD concentration [124], as is the effect of CBD on the Nrf2 pathway. However, information on the effects of CBD regarding the expression and function of the NF-κB subunits as well as the IKK and NIK complex is still lacking.

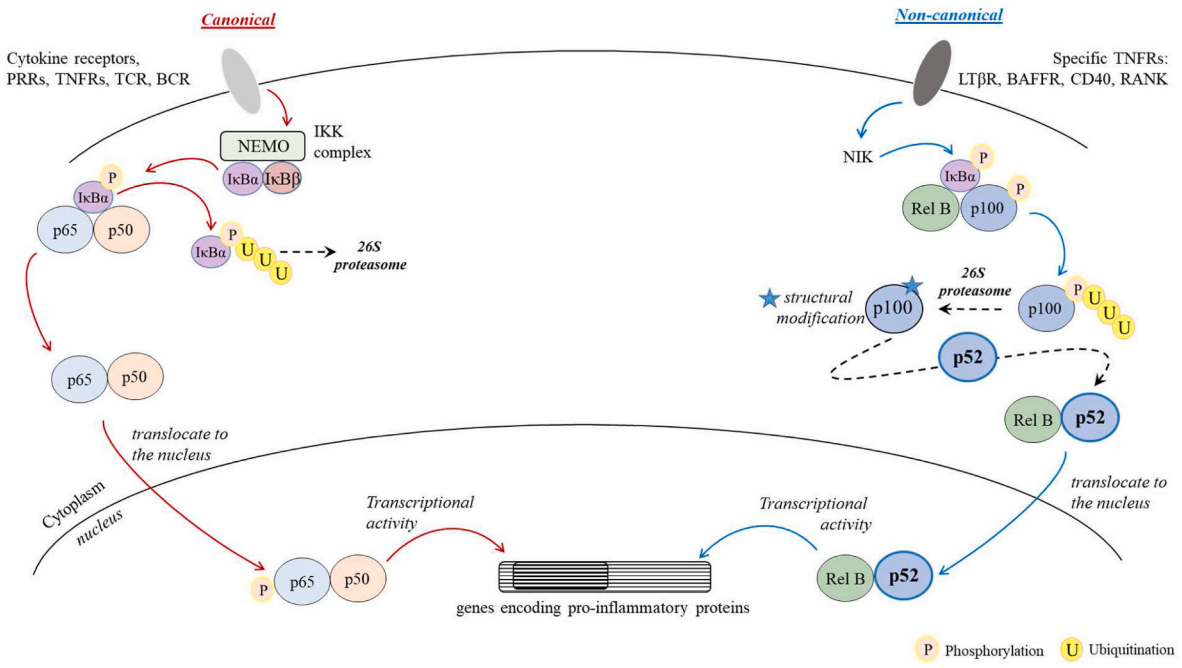

Fig. 3. Due to the stimulation of immune or stress responses, the NF-κB pathway is activated which promotes the transcription of genes encoding pro-inflammatory proteins including IL-1, IL-6, IL-23, TNF-α, IFN-γ. In the **canonical** activation of the NF-κB pathway, IKK complex phosphorylates NF-κB inhibitor IκBα. Then, following IκBα ubiquitination, IκBα is degraded in the 26S proteasome and p65-p50 translocates to the nucleus. In the **non-canonical** activation of the NF-κB pathway, NIK phosphorylates IκBα and phosphorylated IκBα promotes p100 phosphorylation and its ubiquitination. After that, p100 is degraded in the 26S proteasome and mature p52 protein is formed. Mature p52 protein translocates to the nucleus with RelB. (TNF receptor, TNFR; T-cell receptor, TCR; B-cell receptors, BCR; The lymphotoxin-β receptor, LTβR; BAFF receptor, B-cell activating factor receptor, BAFFR; 40- to 45-kD type I membrane protein, cluster of differentiation-40, CD40; receptor activator of nuclear factor κB, RANK; IκB kinase complex, IKK; inhibitor of nuclear factor kappa B -α and –β, IκBα and IκBβ; NF-κB-inducing kinase, NIK).

4.3. CBD activity in the Nrf2-NF-κB interaction network

The role of CBD's influence on p65, due to the Nrf2 - NF-κB crosstalk, appears to play an important role in modulating Nrf2 activity (Fig. 4). The NF-κB subunit p65 can modulate Nrf2 activity due to direct physical interaction with Keap1 in a dose-dependent manner [125]. Moreover, p65 interaction with Keap1 can cause nuclear translocation of Keap1 and associated negative regulation of the Nrf2-ARE pathway due to an increase in Keap1-mediated ubiquitination of Nrf2 [125]. P65 is also a substrate for the kinase GSK3β, which binds β-TrCP and phosphorylates Nrf2. GSK3β-mediated phosphorylation of p65 is known to modulate NF-κB activity by regulating p65 DNA binding affinity [18]. Moreover, Nrf2 and p65 can competitively interact with acetyltransferases CBP/p300 which are transcription co-factors that positively regulate Nrf2 activation via acetylation of Nrf2. Thus, Nrf2 can reduce p65 transcriptional activity by decreasing p65 - CBP/p300 interaction, or

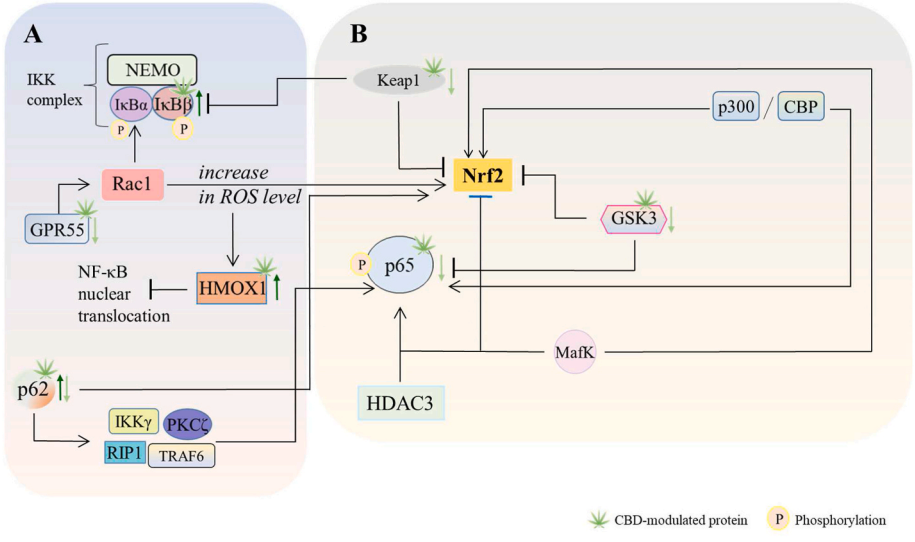

Fig. 4. Cannabidiol (CBD)-modulated proteins in the Nrf2 - NF-κB (p65 and p62) crosstalk. Nrf2 and p65 can negatively affect each other's transcriptional activities by decreasing their interactions with CBP/p300. On the other hand, Keap1 can interact with IκBβ and promote its proteasomal degradation. Moreover, p62, can promote Nrf2 activation and also NF-κB activity by stimulation of TRAF6, PKCζ, RIP1 and IKKγ. (the **dark green** or **soft-green** arrows are used for CBD-mediated increase or decrease in the level of proteins, respectively; the **black** or **end-cut** arrows are used for *up-regulation* and *down-regulation* of activity; glycogen synthase kinase-3, GSK3; CREB-binding protein (CBP); histone deacetylase-3, HDAC3; inhibitor of nuclear factor kappa B -α and –β, IκBα and IκBβ; G protein-coupled receptor 55, GPR55; IκB kinase complex, IKK; NF-κB - essential modulator, NEMO; small GTP-binding protein, Rac1; heme oxygenase-1, HMOX1; TNF-α receptor-associated factor 6, TRAF6; protein kinase C-zeta, PKCζ; receptor-interacting protein, RIP1; reactive oxygen species, ROS)
A. Regulatory feedback loop between p62 and Nrf2 B. The antagonistic effect between Nrf2 and p65.. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

vice versa [126]. It is also known that the acetylation of p65 at Lys-310 and Lys-221 by histone deacetylases (HDACs) is critical for its transcriptional activity, whereby activation of p65 may result in down-regulation of the Nrf2-driven ARE genes by recruiting HDAC3 via promoting the interaction between HDAC3 and CBP/MafK [127,128]. Moreover, it has been indicated that MafK can also promote the interaction of p65 and CBP, as well as an increase in the Nrf2 activity which can reduce excessive p65 acetylation [18]. However, there is no information about the direct effect of CBD on HDACs expression and activity, and only limited literature data indicate THC-induced HDAC3 expression in a dose-dependent manner [129]. The direct or indirect effect of CBD on HDAC may have an indirectly significant effect on the modulation of the Nrf2 pathway. In the context of the antagonistic effect of Nrf2 and p65 on mutual activity, a study using CBD (15 mg/kg b.w.) on transgenic mouse brain tumor cells showed CBD-induced lack of p65 phosphorylation in Ser-311, attenuation of NF-κB signaling and ultimately promoting cancer cell death due to CBD cytotoxicity. This study suggested antagonistic activity between Nrf2 and p65 mediated by CBD [130]. It has also been shown that an attempt to apply CBD (2.5 μM) to TNFα-treated C2C12 myoblasts did not change the level of phosphorylated p65 in Ser-536 [123]. Table 1.

On the other hand, it has been indicated that Keap1, an adaptor protein for the E3 ligase complex, can interact with IκBβ and ubiquitinate IκBβ resulting in its proteasomal degradation [131]. Thus, the changes in the Keap1 interaction with IκBβ or Nrf2 have a critical impact on the modulation of intracellular redox and inflammatory status under oxidative stress. A study, using Keap1 knocked-down normal human epidermal keratinocytes clearly shows that CBD (10 μM) can induce the expression of HMOX via inducing Bach1 inhibition, Keap1 - independent manner [5]. However, Jastrząb's study has shown that CBD (1uM) treatment causes a decrease in the level of Keap1 which increased in keratinocytes after UV radiation [15]. Moreover, the same study also noted that CBD affects the activity of Keap1 by adduct formation on Cys-288 as well as Cys-151, which are important for interaction with Nrf2 and Cul3 binding [15]. Although CBD is majorly defined as a Bach inhibitor within the Nrf2 pathway [5,132], CBD-mediated Keap1 modulation may also play an auxiliary role. Considering both the antioxidant and pro-oxidant role of CBD mentioned above, in addition to the Bach1-inhibition-related major activity of CBD on the Nrf2 pathway, such auxiliary signals mediated by CBD may also have a great impact on redox-associated cellular response depending on the severity of oxidative stress.

Another protein participating in Nrf2 - NF-κB crosstalk is the small GTP-binding protein Rac1, known to be involved in NADPH oxidase activity [133]. Rac1 can upregulate Nrf2 expression by increasing intracellular ROS level but also, interestingly, through IκBα phosphorylation and inducing the NF-κB pathway [134]. On the other hand, the same study also indicates that a decrease in Nrf2 level causes an increase in ROS and p65 levels due to IκBα phosphorylation [134]. This situation is defined as a regulatory feedback loop. Moreover, up-regulation of HMOX1 gene expression by Rac1-mediated Nrf2 activity may inhibit nuclear translocation of the NF-κB [100]. Despite the lack of data directly indicating the effect of CBD on the expression/structural modification/activity of Rac1, it has been shown that CBD when co-administered with anandamide can lower the level of Rac1, which is involved in downstream signaling of the G protein-coupled receptor - GPR55 [135], of which CBD is antagonist [136]. On the other hand, p62, besides its activity in the Nrf2 pathway, can promote NF-κB activity by increasing TNF-α and IL-1 through the stimulation of TNF-α receptor-associated factor 6 (TRAF6) and protein kinase C-zeta (PKCζ), receptor-interacting protein (RIP1) and IKKγ [137]. As it was mentioned above, it is known that CBD can also positively or negatively modulate p62 expression. It can therefore be said that CBD-mediated modulation of p62 and RAC1 expression/activity (potentially) involves the Nrf2 - NF-κB crosstalk and may play a key regulatory role in redox signaling under pathological conditions.

Moreover, NF-κB activity is also regulated by miRNAs such as miR-342–3p, miR-3664–5p, miR-7, miR-204–5p, miR-146b-5p, miR-18a, miR-650, miR-30a-5p, miR-429 and long non-coding RNAs (lncRNAs) such as LIFR-AS1, SLCO4A1-AS, H19 [100,138]. It has been demonstrated that miR-181a targeting SIRT1, Nrf2, p65, Bcl-2, and Bax can modulate the inflammatory response during sepsis [98]. In addition to the effects of CBD on miRNA mentioned above in relation to Nrf2 activity, treatment with two phytocannabinoids at once (CBD + THC (10 mg/kg each) has also been shown to be able to lower miR-146a-5p rather than miR-146b-5p levels in C57BL/6 mice [91]. However, our knowledge regarding CBD's effects on regulatory RNAs is still very limited. The role of regulatory RNAs in Nrf2 - NF-κB crosstalk dynamics should be evaluated in detail associated with cell differentiation, proliferation, cell migration, and apoptosis, especially in terms of cancer biology, which is important for the potential therapeutic use of this compound.

Table 1
CBD antioxidative and pro-oxidative effects on molecular pathways and macromolecular metabolism modulated by ROS signaling.

	The molecular pathways and macromolecular metabolisms particularly affected by antioxidant and pro-action of CBD
ROS-mediated signaling	Nrf2 pathway [5,15,62,63,119] NF-κB pathway [6,15,119] MAPK and AKT signaling pathways [85,86] Intrinsic apoptotic pathway and autophagy [7,8,59] Oxytosis/ferroptosis pathway [139] Lipid metabolism [3,21,22,25,36] Protein metabolism [16,24,29] *(Oxidatively altered structure and associated functionality by ROS interaction)*

5. Conclusion

Cannabidiol is an effective compound that regulates intracellular redox balance. Its efficacy has been demonstrated in the literature both at the transcriptional level with regard to the redox-sensitive activity of Nrf2 and NF-κB, and at the level of lipid and protein metabolism (Table 1). This phytocannabinoid, with multidirectional antioxidant and pro-oxidant action, by altering redox-sensitive molecular pathways has a significant modulating effect on the cellular response to oxidative stress as summarized in Table 1. In addition to the main regulatory act of CBD as a Bach1 inhibitor [5], CBD affects both the other proteins involved in the Nrf2 pathway (Keap1, MAPKs, GSK3β, SIRT1) and the proteins involved in Nrf2 - NF- κB crosstalk. In this way, CBD, by modulating the activity of Nrf2, depending on the intensity of oxidative stress, can regulate the cellular response in different ways and directions. Moreover, relatively high concentrations of CBD can enhance pro-apoptotic and autophagic cellular responses due to the regulation of Nrf2 transcriptional activity by altering the p53 and Bcl-2 threshold and ultimately mitochondrial functionality. Thus, CBD, which has both antioxidant and pro-oxidative effects depending on the used concentration and the cell specificity, shows great potential for the development of new approaches in the pharmacotherapy of oxidative stress diseases. This is especially true of its potential pharmacological applications in the development and progression of cancer. However, this requires further research to evaluate the effects of CBD on the Nrf2 pathway, especially with regard to regulatory RNAs, in different cell types and the same cell types but from different individuals, taking into account epigenetic factors. Therefore, recent studies have highlighted the anti-cancer potential of CBD in combination with chemotherapy, but also immunotherapy [140].

Authorship

SAE: Acquisition of data, analysis, and interpretation of data,

drafting the article. **AG**: revising the article critically for important intellectual content. **ES**: The conception and design of the study, revising the article critically for important intellectual content, and final approval of the version to be submitted.

Declaration of competing interest

None. The authors have no conflict of interest to declare.

Data availability

No data was used for the research described in the article.

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