Cannabinoids

Subjects: Biochemistry & Molecular Biology

Contributor: Agata Lewandowska

Cannabinoids can be classified as (1) endocannabinoids (AEA, 2-AG), (2) phytocannabinoids (THC, CBD), and (3) synthetic analogs (AJA)—. Phytocannabinoids constitute more than 110 chemical compounds, while synthetic analogs are even more numerous.

cannabis cannabinoids inflammation anti-inflammatory antioxidative immunology

1. Introduction

Cannabis (Cannabis sativa L.) has been known and used since ancient times. It contains cannabinoids— A C21 terpene phenolic group of compounds, amino acids, fatty acids, steroids, along with secondary metabolites such as flavonoids, stilbenoids, terpenoids, alkaloids, lignans, and many others [1][2].

In recent years, significant growth of interest in the natural properties of its compounds has been observed, such as anti-inflammatory and antioxidative effects. They have been proved in numerous animal studies models and confirmed in clinical studies in patients suffering from inflammatory diseases, such as arthritis [3][4]. In terms of chemistry, the anti-inflammatory properties of cannabinoids can be related to an increase in glucocorticosteroid-like hormones production, which is used in anti-inflammatory therapy, and a decrease in prostaglandin synthesis, whose role in inflammatory conditions is commonly known [3]. Cannabinoids including (1) phytocannabinoids like Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD); (2) their synthetic analogs like ajulemic acid (AJA; C 25H 36O 4) and nabilone (C 24H 36O 3); (3) endogenous cannabinoids like anandamide (N-arachidonoylethanolamine; AEA) and 2-arachidonoyl glycerol (2-AG); as well as (4) their derivatives like elmiric acids [5].

Anti-inflammatory effects are also shown in non-cannabinoid compounds of cannabis—such as olivetol, cannflavins, and beta-caryophyllene (BCP)—a fragrant terpenoid known to be a full agonist of the CB2 receptor. CB2 is a G protein-coupled receptor, an important therapeutic target in many diseases [6][7]. Cannflavins A and B, on the other hand, appear to be cannabis specific plant flavonoids, known as flavones, which inhibit the production of prostaglandin E2 and the leukotrienes [8].

2. Endocannabinoid System (ECS) and Cannabinoids

The endocannabinoid system (ECS) consists of cannabinoid receptors CB1 and CB2, their endogenous lipid ligands—anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), and the enzymes responsible for their biosynthesis (DAGLα, DAGLβ for 2-AG; NAPE-PLD for AEA) or degradation (fatty acid amide hydrolase—FAAH for

AEA and monoacylglycerol lipase—MAGL for 2-AG) [9]. There are also alternative paths of endocannabinoid degradation, such as oxidation of AEA and 2-AG by cyclooxygenase, specific lipoxygenases, and P450 cytochrome [10]. AEA binds to central CB1 receptors and—to a lesser extent—peripheral CB2 receptors. 2-AG is a partial CB1 and CB2 agonist to which it binds with a comparable affinity [10]. Phytocannabinoids like Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) demonstrate a similar activity to anandamide and 2-AG.

THC is the main psychoactive cannabinoid due to its lipophilic structure capable of penetrating the blood–brain barrier and activating CB1 receptors widely expressed in the brain tissue [11]. CBD is the second of the two predominant phytocannabinoids of *Cannabis sativa* L. Compared to THC, CBD shows lower affinity to CB1 and CB2 receptors. Moreover, at low concentrations, it even demonstrates a slightly antagonistic effect and acts as a negative allosteric modulator of CB1—therefore indirectly changes the receptor's potential to bind its orthosteric ligands, such as THC [12]. CBD is not psychoactive and shows numerous advantageous pharmacological effects, including anti-inflammatory and antioxidative properties. The chemistry and pharmacology of CBD have been thoroughly tested, together with various molecular targets, such as cannabinoid receptors and other compounds of ECS affected by CBD. Moreover, preclinical and clinical trials led to a better understanding of CBD's therapeutical potential in many diseases, including those associated with oxidative stress [13].

Endocannabinoids seem to present affinity not only to CB1 and CB2 but also G protein-coupled receptors (GPR3, GPR6, GPR12, GPR18, GPR55, GPR119) [14], transient receptor potential vanilloid channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1), ligand-gated ion channels (5-HT3, glycine, nicotinic acetylcholine), and peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) [15][10][16].

3. Cannabinoids in the Inflammatory Bowel Diseases

The potential use of cannabinoids in inflammatory bowel diseases was a subject of research in recent years, not only on possible benefits associated with the anti-inflammatory effect but also the relief of the extraintestinal symptoms [17]. Although consecutive in vitro and in vivo research appeared promising, clinical trials are scarce [18]. Cannabinoids exert diverse effects on the digestive tract, regulating gastric hydrochloric acid secretion, motor activity, release and transport of ions, and visceral sensation [19].

CB1 and CB2 receptors are located in all layers of the bowel, including the myenteric and submucosal plexus and epithelium [20]. In vitro research confirmed the presence of CB1 and CB2 receptors in healthy human colon tissue, along with their reactivity to inflammation and epithelial injury [21]. Apart from CB1 and CB2 receptors, GPR55 and PPAR-α receptors have also been detected in the canine alimentary tract [22].

Apart from the classical path, cannabinoids, both natural and synthetic, seem to show affinity to G protein-coupled receptor 55 (GPR55) [23]. The involvement of GPR55 in the development of neuropathic and inflammatory pain by modulation of releasing pro-inflammatory cytokines has been proven, and the effects seem to be contradictory to those caused by cannabinoid receptors [14]. A pharmacological blockade achieved by administering a specific inhibitor in mice with experimentally induced colitis led to reducing lymphocyte and macrophage recruitment.

Additionally, it caused a decrease in COX-2 expression, an inflammatory marker, as well as pro-inflammatory cytokines, such as IL-1β and TNF-α [14]. A possible protective capacity of cannabinoids against carcinogenesis in the colon is likely due to the inhibition of a release of pro-inflammatory cytokines, such as IFNγ, TNF-α, IL-17A, and IL-22 [24]. Further research is necessary, however.

The influence of cannabinoids, such as THC or CBD, in treating inflammatory bowel diseases in humans seems promising, although clinical trials evaluating their therapeutic potential are very limited and based only on small research groups, mostly Crohn's disease and ulcerative colitis.

4. Cannabinoids in Inflammatory Skin Diseases

In human skin, cannabinoid receptors CB1 and CB2 are located in keratinocytes, hair follicles, sebaceous glands, sensory neurons, cells of the immune system, and fibroblasts [15][25][26]. FAAH and MAGL were also identified in the skin and its appendages, suggesting that it actively regulates its metabolic processes [15]. The ECS seems to have an impact on various dermal effects. Cannabinoids inhibit the proliferation and differentiation of epidermis keratinocytes and conduce to their apoptosis [27][25][28][29]. Additionally, stimulating CB2 causes the release of opioid peptides, which leads to analgesic effects [30]. Cannabinoids also participate in the modulation of the development and function of hair follicles and sebaceous glands. They significantly affect neuro-immuno-endocrine regulation of skin functioning and preserving its homeostasis [31][32]. It seems crucial that the ECS takes part in the coordination of the inflammatory response in the skin [15][25][28][31][33][34]. Functioning of the complex immunological protective barrier relies on the cooperation of different immune cells—such as macrophages, mast cells, T lymphocytes, dendritic cells, and Langerhans cells—together with keratinocytes, fibroblasts, melanocytes, and other cells present in the skin. The cooperation is complemented by receptors and pro- and anti-inflammatory cytokines and chemokines [28]. Dysfunction of this system can be observed in many diseases, such as atopic dermatitis, psoriasis, scleroderma, acne, dermatomyositis, keratin and hair growth disorders, carcinogenesis, together with symptoms such as pruritus, which shows potential for the future use of cannabinoids in the therapy of these disorders [15][27][28][31][35][36][37][38][39].

CB2 receptor agonists were studied for their potential in reducing inflammation and wound healing in mouse skin [40]. CB2 receptor activation led to reduced infiltration of neutrophils and macrophages, increased keratinocyte proliferation, and faster wound healing. Moreover, the expression of monocyte chemoattractant protein-1 (MCP-1), stromal cell-derived factor 1 (SDF-1), IL-6, IL-1β, TNF-α, transforming growth factor-beta 1 (TGF-β1), and vascular endothelial growth factor (VEGF) were also decreased. CB2 agonists lead to a significant decrease in pro-inflammatory M1 macrophages and a slight increase in anti-inflammatory M2 macrophages. Analogously, there was observed a decrease in gene expression, levels of proteins associated with M1 macrophages, and a release of cytokines (IL-6, IL-12, CD86, inducible nitric oxide synthase—iNOS), along with an increase in levels of cytokines associated with M2 macrophages (IL-4, IL-10, CD206, and arginase-1) [40]. In another study, authors demonstrated a decrease in pro-inflammatory factors, such as IL-6 and MCP-1, an increase in an anti-inflammatory factor—TGF-β, and faster wound healing after using a CB2 agonist [41]. Similarly, beta-caryophyllene, a CB2

receptor agonist, caused skin wound epithelialization by increasing the proliferation and migration of keratinocytes in mice [42].

It has been detected that levels of anandamide and 2-AG increase in mouse skin after experimentally inducing allergic contact dermatitis [43]. Moreover, mice deprived of both cannabinoid receptors show a more severe inflammatory reaction. Using CB1 and CB2 receptor agonists resulted in the attenuation of the inflammatory response, while the antagonists-exacerbation [43]. The influence of CB2 receptor agonists on artificially induced dermatitis in mice improved edema and skin lesions [44]. Presented research unambiguously points out that CB2 receptors, as a part of the ECS, impact the inflammatory reaction in the skin. Furthermore, the local application of CB1 agonists shows positive effects in mitigating inflammatory symptoms in the skin in an animal model [38].

5. Cannabinoids in the other Disorders

Immunological effects of cannabinoids imply the possibility of their therapeutic usage in respiratory tract disorders associated with inflammation [45]. The ability to dilate bronchi and the anti-inflammatory effect suggest the potential of cannabinoids in treating inflammatory and obstructive airway diseases. Preclinical research revealed the beneficial effects of the administration of CB1 agonists to alleviate experimentally induced contractions in the airways [46][47][48]. There are also reports of CB2 receptor involvement in counteracting bronchi contractions [49]. Apart from the anti-inflammatory and spasmolytic effects, in guinea pigs, the activation of CB2 receptors also inhibited cough reflex [50]. However, the significance of the mentioned properties is still unknown [51]. In another study, CB1 receptors appeared involved in the airway dilatation [52] and CB2 receptors in inhibition of activation of mast cells and eosinophils [48]. The potentially beneficial effects of CB1 and CB2 receptor activation in the airways were observed in guinea pigs with the induced asthma-like reaction after administration of a non-specific agonist [52]. In the experimental group, cough, suffocation, and airway obturation improved, along with decreased eosinophil infiltration, mast cell activation, free radicals release, and levels of TNF-α and prostaglandin D2 levels (PGD-2) compared to the control group [52].

The expression of CB1 receptors is remarkably high in the central nervous system (CNS), especially in the olfactory bulb, hippocampus, basal ganglia, and cerebellum [53]. Although CB2 receptors are mainly located in immune cells, their presence has also been detected in the CNS, making them an attractive potential target in counteracting inflammation in the nervous system [53]. A significant increase in expression of CB2 receptors in inflamed microglial cells associated with changes in levels of pro- and anti-inflammatory cytokines suggests the neuroprotective effects of the ECS [54]. Moreover, activation of CB2 receptors reduces recruitment and adhesion of neutrophils to the brain's epithelium [55]. Changes in the expression of CB1 receptors also seem to be of importance [53]. CB1 receptors are involved in protecting against cell apoptosis by reducing excessive calcium release, and as a result—excitotoxicity [56]. CB1 receptors protected GABAergic neurons by reducing excitatory currents in experimentally induced autoimmune encephalomyelitis in mice [57].

References

1. Flores-Sanchez, I.J.; Verpoorte, R. Secondary metabolism in cannabis. Phytochem. Rev. 2008, 7, 615–639.
2. Schofs, L.; Sparo, M.D.; Bruni, S.F.S. The antimicrobial effect behind Cannabis sativa. Pharmacol. Res. Perspect. 2021, 9, e00761.
3. Gieringer, D.H.; Rosenthal, E.; Carter, G.T. Marijuana Medical Handbook: Practical Guide to the Therapeutic Uses of Marijuana. 2008. Available online: https://www.worldcat.org/title/marijuana-medical-handbook-practical-guide-to-the-therapeutic-uses-of-marijuana/oclc/717176198#.YMxk0rhJ48w.mendeley (accessed on 18 June 2021).
4. Blake, D.R.; Robson, P.; Ho, M.; Jubb, R.W.; McCabe, C. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology 2005, 45, 50–52.
5. Burstein, S.H.; Zurier, R.B. Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation. AAPS J. 2009, 11, 109–119.
6. Gertsch, J.; Leonti, M.; Raduner, S.; Racz, I.; Chen, J.-Z.; Xie, X.-Q.; Altmann, K.-H.; Karsak, M.; Zimmer, A. Beta-caryophyllene is a dietary cannabinoid. Proc. Natl. Acad. Sci. USA 2008, 105, 9099–9104.
7. Sharma, C.; Al Kaabi, J.M.; Nurulain, S.M.; Goyal, S.N.; Kamal, M.A.; Ojha, S. Polypharmacological Properties and Therapeutic Potential of β-Caryophyllene: A Dietary Phytocannabinoid of Pharmaceutical Promise. Curr. Pharm. Des. 2016, 22, 3237–3264.
8. Rea, K.A.; Casaretto, J.A.; Al-Abdul-Wahid, M.S.; Sukumaran, A.; Geddes-McAlister, J.; Rothstein, S.J.; Akhtar, T.A. Biosynthesis of cannflavins A and B from Cannabis sativa L. Phytochemistry 2019, 164, 162–171.
9. Márquez, L.; Suárez, J.; Iglesias, M.; Bermudez-Silva, F.J.; De Fonseca, F.R.; Andreu, M. Ulcerative Colitis Induces Changes on the Expression of the Endocannabinoid System in the Human Colonic Tissue. PLoS ONE 2009, 4, e6893.
10. Lee, Y.; Jo, J.; Chung, H.Y.; Pothoulakis, C.; Im, E. Endocannabinoids in the gastrointestinal tract. Am. J. Physiol. Liver Physiol. 2016, 311, G655–G666.
11. Lima, M.G.; Tardelli, V.S.; Brietzke, E.; Fidalgo, T.M. Cannabis and Inflammatory Mediators. Eur. Addict. Res. 2021, 27, 16–24.
12. Larsen, C.; Shahinas, J. Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials. J. Clin. Med. Res. 2020, 12, 129–141.
13. Atalay, S.; Jarocka-Karpowicz, I.; Skrzydlewska, E. Antioxidative and Anti-Inflammatory Properties of Cannabidiol. Antioxidants 2019, 9, 21.

14. Stančić, A.; Jandl, K.; Hasenöhrl, C.; Reichmann, F.; Marsche, G.; Schuligoi, R.; Heinemann, A.; Storr, M.; Schicho, R. The GPR55 antagonist CID16020046 protects against intestinal inflammation. Neurogastroenterol. Motil. 2015, 27, 1432–1445.
15. Scheau, C.; Badarau, I.A.; Mihai, L.-G.; Scheau, A.-E.; Costache, D.O.; Constantin, C.; Calina, D.; Caruntu, C.; Costache, R.S.; Caruntu, A. Cannabinoids in the Pathophysiology of Skin Inflammation. Molecules 2020, 25, 652.
16. Batalla, A.; Bos, J.; Postma, A.; Bossong, M.G. The Impact of Cannabidiol on Human Brain Function: A Systematic Review. Front. Pharmacol. 2021, 11, 618184.
17. Swaminath, A.; Berlin, E.P.; Cheifetz, A.; Hoffenberg, E.; Kinnucan, J.; Wingate, L.; Buchanan, S.; Zmeter, N.; Rubin, D.T. The Role of Cannabis in the Management of Inflammatory Bowel Disease: A Review of Clinical, Scientific, and Regulatory Information. Inflamm. Bowel Dis. 2019, 25, 427–435.
18. Desmarais, A. Evidence supporting the benefits of marijuana for Crohn’s disease and ulcerative colitis is extremely limited: A meta-analysis of the literature. Ann. Gastroenterol. 2020, 33, 495.
19. Izzo, A.A.; Sharkey, K. Cannabinoids and the gut: New developments and emerging concepts. Pharmacol. Ther. 2010, 126, 21–38.
20. Ahmed, W.; Katz, S. Therapeutic Use of Cannabis in Inflammatory Bowel Disease. Gastroenterol. Hepatol. 2016, 12, 668–679.
21. Wright, K.; Rooney, N.; Feeney, M.; Tate, J.; Robertson, D.; Welham, M.; Ward, S. Differential Expression of Cannabinoid Receptors in the Human Colon: Cannabinoids Promote Epithelial Wound Healing. Gastroenterology 2005, 129, 437–453.
22. Galiazzo, G.; Giancola, F.; Stanzani, A.; Fracassi, F.; Bernardini, C.; Forni, M.; Pietra, M.; Chiocchetti, R. Localization of cannabinoid receptors CB1, CB2, GPR55, and PPARα in the canine gastrointestinal tract. Histochem. Cell Biol. 2018, 150, 187–205.
23. Ryberg, E.; Larsson, N.; Sjögren, S.; Hjorth, S.; Hermansson, N.-O.; Leonova, J.; Elebring, T.; Nilsson, K.; Drmota, T.; Greasley, P.J. The orphan receptor GPR55 is a novel cannabinoid receptor. Br. J. Pharmacol. 2007, 152, 1092–1101.
24. Becker, W.; Alrafas, H.R.; Wilson, K.; Miranda, K.; Culpepper, C.; Chatzistamou, I.; Cai, G.; Nagarkatti, M.; Nagarkatti, P.S. Activation of Cannabinoid Receptor 2 Prevents Colitis-Associated Colon Cancer through Myeloid Cell De-activation Upstream of IL-22 Production. iScience 2020, 23, 101504.
25. Caterina, M.J. TRP Channel Cannabinoid Receptors in Skin Sensation, Homeostasis, and Inflammation. ACS Chem. Neurosci. 2014, 5, 1107–1116.

26. Wohlman, I.M.; Composto, G.M.; Heck, D.E.; Heindel, N.D.; Lacey, C.J.; Guillon, C.D.; Casillas, R.P.; Croutch, C.R.; Gerecke, N.R.; Laskin, D.L.; et al. Mustard vesicants alter expression of the endocannabinoid system in mouse skin. Toxicol. Appl. Pharmacol. 2016, 303, 30–44.
27. Nam, G.; Jeong, S.K.; Park, B.M.; Lee, S.H.; Kim, H.J.; Hong, S.-P.; Kim, B.; Kim, B.-W. Selective Cannabinoid Receptor-1 Agonists Regulate Mast Cell Activation in an Oxazolone-Induced Atopic Dermatitis Model. Ann. Dermatol. 2016, 28, 22–29.
28. Tóth, K.F.; Ádám, D.; Bíró, T.; Oláh, A. Cannabinoid Signaling in the Skin: Therapeutic Potential of the “C(ut)annabinoid” System. Molecules 2019, 24, 918.
29. Proksch, E.; Soeberdt, M.; Neumann, C.; Kilic, A.; Abels, C. Modulators of the endocannabinoid system influence skin barrier repair, epidermal proliferation, differentiation and inflammation in a mouse model. Exp. Dermatol. 2019, 28, 1058–1065.
30. Ibrahim, M.M.; Porreca, F.; Lai, J.; Albrecht, P.J.; Rice, F.L.; Khodorova, A.; Davar, G.; Makriyannis, A.; Vanderah, T.W.; Mata, H.P.; et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc. Natl. Acad. Sci. USA 2005, 102, 3093–3098.
31. Cintosun, A.; Lara-Corrales, I.; Pope, E. Mechanisms of Cannabinoids and Potential Applicability to Skin Diseases. Clin. Drug Investig. 2020, 40, 293–304.
32. Oláh, A.; Szekanecz, Z.; Bíró, T. Targeting Cannabinoid Signaling in the Immune System: “High”-ly Exciting Questions, Possibilities, and Challenges. Front. Immunol. 2017, 8, 1487.
33. Jeong, S.; Kim, M.S.; Lee, S.H.; Park, B.D. Epidermal Endocannabinoid System (EES) and its Cosmetic Application. Cosmetics 2019, 6, 33.
34. Norooznezhad, A.H.; Norooznezhad, F. Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation. Med. Hypotheses 2017, 99, 15–18.
35. Avila, C.; Massick, S.; Kaffenberger, B.H.; Kwatra, S.G.; Bechtel, M. Cannabinoids for the treatment of chronic pruritus: A review. J. Am. Acad. Dermatol. 2020, 82, 1205–1212.
36. Oláh, A.; Tóth, B.I.; Borbíró, I.; Sugawara, K.; Szöllõsi, A.G.; Czifra, G.; Pál, B.; Ambrus, L.; Kloepper, J.; Camera, E.; et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J. Clin. Investig. 2014, 124, 3713–3724.
37. Spleman, L.; Sinclair, R.; Freeman, M.; Davis, M.; Gebauer, K. 1061 The safety of topical cannabidiol (CBD) for the treatment of acne. J. Investig. Dermatol. 2018, 138, S180.
38. Kim, H.J.; Kim, B.; Park, B.M.; Jeon, J.E.; Lee, S.H.; Mann, S.; Ahn, S.K.; Hong, S.-P.; Jeong, S.K. Topical cannabinoid receptor 1 agonist attenuates the cutaneous inflammatory responses in oxazolone-induced atopic dermatitis model. Int. J. Dermatol. 2015, 54, e401–e408.

39. Wei, J.; Bhattacharyya, S.; Varga, J. Peroxisome proliferator-activated receptor γ: Innate protection from excessive fibrogenesis and potential therapeutic target in systemic sclerosis. Curr. Opin. Rheumatol. 2010, 22, 671–676.

40. Du, Y.; Ren, P.; Wang, Q.; Jiang, S.-K.; Zhang, M.; Li, J.-Y.; Wang, L.-L.; Guan, D.-W. Cannabinoid 2 receptor attenuates inflammation during skin wound healing by inhibiting M1 macrophages rather than activating M2 macrophages. J. Inflamm. 2018, 15, 25.

41. Bort, A.; Alvarado-Vazquez, P.A.; Moracho-Vilrriales, C.; Virga, K.G.; Gumina, G.; Romero-Sandoval, A.; Asbill, S. Effects of JWH015 in cytokine secretion in primary human keratinocytes and fibroblasts and its suitability for topical/transdermal delivery. Mol. Pain 2017, 13, 1744806916688220.

42. Koyama, S.; Purk, A.; Kaur, M.; Soini, H.A.; Novotny, M.V.; Davis, K.; Kao, C.C.; Matsunami, H.; Mescher, A. Beta-caryophyllene enhances wound healing through multiple routes. PLoS ONE 2019, 14, e0216104.

43. Karsak, M.; Gaffal, E.; Date, R.; Wang-Eckhardt, L.; Rehnelt, J.; Petrosino, S.; Starowicz, K.; Steuder, R.; Schlicker, E.; Cravatt, B.; et al. Attenuation of Allergic Contact Dermatitis Through the Endocannabinoid System. Science 2007, 316, 1494–1497.

44. Haruna, T.; Soga, M.; Morioka, Y.; Imura, K.; Furue, Y.; Yamamoto, M.; Hayakawa, J.; Deguchi, M.; Arimura, A.; Yasui, K. The Inhibitory Effect of S-777469, a Cannabinoid Type 2 Receptor Agonist, on Skin Inflammation in Mice. Pharmacology 2017, 99, 259–267.

45. Bozkurt, T.E. Endocannabinoid System in the Airways. Molecules 2019, 24, 4626.

46. Bozkurt, T.E.; Larsson, O.; Adner, M. Stimulation of cannabinoid CB1 receptors prevents nerve-mediated airway hyperreactivity in NGF-induced inflammation in mouse airways. Eur. J. Pharmacol. 2016, 776, 132–138.

47. Bozkurt, T.E.; Kaya, Y.; Durlu-Kandilci, N.T.; Onder, S.; Sahin-Erdemli, I. The effect of cannabinoids on dinitrofluorobenzene-induced experimental asthma in mice. Respir. Physiol. Neurobiol. 2016, 231, 7–13.

48. Pini, A.; Mannaioni, G.; Pellegrini-Giampietro, D.; Passani, M.B.; Mastroianni, R.; Bani, D.; Masini, E. The role of cannabinoids in inflammatory modulation of allergic respiratory disorders, inflammatory pain and ischemic stroke. Curr. Drug Targets 2012, 13, 984–993.

49. Cui, Y.-Y.; D'Agostino, B.; Risse, P.-A.; Marrocco, G.; Naline, E.; Zhang, Y.; Chen, H.-Z.; Finance, O.; Rinaldi-Carmona, M.; Rossi, F.; et al. Cannabinoid CB2 receptor activation prevents bronchoconstriction and airway oedema in a model of gastro-oesophageal reflux. Eur. J. Pharmacol. 2007, 573, 206–213.

50. Patel, H.J.; Birrell, M.A.; Crispino, N.; Hele, D.J.; Venkatesan, P.; Barnes, P.J.; Yacoub, M.H.; Belvisi, M.G. Inhibition of guinea-pig and human sensory nerve activity and the cough reflex in

guinea-pigs by cannabinoid (CB2) receptor activation. Br. J. Pharmacol. 2003, 140, 261–268.

51. Tashkin, D.P.; Roth, M.D. Pulmonary effects of inhaled cannabis smoke. Am. J. Drug Alcohol Abus. 2019, 45, 596–609.
52. Giannini, L.; Nistri, S.; Mastroianni, R.; Cinci, L.; Vannacci, A.; Mariottini, C.; Passani, M.B.; Mannaioni, P.F.; Bani, D.; Masini, E. Activation of cannabinoid receptors prevents antigen-induced asthma-like reaction in guinea pigs. J. Cell. Mol. Med. 2008, 12, 2381–2394.
53. Zou, S.; Kumar, U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int. J. Mol. Sci. 2018, 19, 833.
54. Polini, B.; Cervetto, C.; Carpi, S.; Pelassa, S.; Gado, F.; Ferrisi, R.; Bertini, S.; Nieri, P.; Marcoli, M.; Manera, C. Positive Allosteric Modulation of CB1 and CB2 Cannabinoid Receptors Enhances the Neuroprotective Activity of a Dual CB1R/CB2R Orthosteric Agonist. Life 2020, 10, 333.
55. Murikinati, S.; Jüttler, E.; Keinert, T.; Ridder, D.A.; Muhammad, S.; Waibler, Z.; Ledent, C.; Zimmer, A.; Kalinke, U.; Schwaninger, M. Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment. FASEB J. 2010, 24, 788–798.
56. Cassano, T.; Calcagnini, S.; Pace, L.; De Marco, F.; Romano, A.; Gaetani, S. Cannabinoid Receptor 2 Signaling in Neurodegenerative Disorders: From Pathogenesis to a Promising Therapeutic Target. Front. Neurosci. 2017, 11, 30.
57. Musella, A.; Sepman, H.; Mandolesi, G.; Gentile, A.; Fresegna, D.; Haji, N.; Conrad, A.; Lutz, B.; Maccarrone, M.; Centonze, D. Pre- and postsynaptic type-1 cannabinoid receptors control the alterations of glutamate transmission in experimental autoimmune encephalomyelitis. Neuropharmacology 2014, 79, 567–572.