Cannabidiol (CBD) and potential in medicinal use in rheumatoid arthritis

Torsten Lowin

Corresponding author:
Dr. Torsten Lowin
Klinik für Rheumatologie
Hiller Forschungszentrum für Rheumatologie
Merowingerplatz 1a
40225 Düsseldorf.
Telephone: +49 211 81-06150
Fax: +49 211 81-06153
E-Mail: torsten.lowin@med.uni-duesseldorf.de
torsten.lowin@gmail.com

Abstract

Rheumatoid arthritis (RA) is a chronic autoinflammatory disease accompanied by pro-inflammatory cytokine production, hyperalgesia, central sensitization and several co-morbidities related to immune- and nervous system dysfunction such as hypertension and depression. Although systematic studies are lacking, anecdotal reports from patients using cannabidiol (CBD) on top of their standard medication suggests that CBD might decrease inflammation, pain and comorbidities related to RA. In addition, CBD might also curb neuro-immunological changes associated with chronic inflammation. These effects are attributable to multiple receptors and proteins modulated by CBD including transient receptor potential (TRP) ion channels, fatty acid binding proteins, classical cannabinoid receptors (CB_1 and CB_2) but also other G-protein coupled receptors and mitochondrial proteins. Besides the thicket of potential targets, the effectiveness of CBD in RA might also be determined by its concentration since bioavailability can change dramatically dependent on formulation and route of administration.

Keywords: Cannabidiol, rheumatoid arthritis, inflammation, cytokines, depression, cardiovascular disease, hypertension, pain

Abbreviations

ACPA	Anti–Citrullinated Protein Antibody
AIDS	Acquired Immunodeficiency Syndrome
CB_1/CB_2	Cannabinoid Receptor 1/2
CBD	Cannabidiol
CCL	(C-C motif) Ligand
CD	Cluster of Differentiation
CGRP	Calcitonin Gene-Related Peptide
CXCL	C-X-C motif Chemokine Ligand
DMARD	Disease Modifying Anti-Rheumatic Drug
HLA	Human Leucocyte Antigen
IFN	Interferon
IgG/IgM	Immunoglobulin G/M
IL	Interleukin
LPS	Lipopolysaccharide
MCP-1	Monocyte Chemoattractant Protein-1
MMP	Matrix Metalloprotease
mPTP	mitochondrial Permeability Transition Pore
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PBMC	Peripheral Blood Mononuclear Cells
RA	Rheumatoid arthritis
RASF	Rheumatoid arthritis synovial fibroblast
SF	Synovial Fibroblast
TGF- β	transforming growth factor β
Th	T helper
THC	δ^9-Tetrahydrocannabinol
TLR	Toll-like Receptor
TNFα	Tumor necrosis factor
TRP	Transient Receptor Potential
TRPV1	Transient Receptor Potential Vanilloid 1

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disorder with unknown aetiology and a prevalence between 0.25 to 1% in the general population. It has a female to male preponderance of at least 2:1 suggesting a hormonal influence on disease onset (Almoallim et al., 2021). In the joints of RA patients cell composition is altered. While the lining layer in healthy synovial tissue consists of 1-3 cell layers containing resident macrophages and fibroblasts, the sublining also contains few lymphocytes, adipocytes and endothelial cells. In the course of RA, the lining layer increases in size due to the proliferation of resident fibroblasts which is caused by changes in the microenvironment elicited by the influx of lymphocytes and inflammatory monocytes (Scherer et al., 2020). Untreated RA leads to cartilage destruction and bone erosion and may render affected individuals severely disabled (Bluml et al., 2014). The immunopathogenic sequelae of RA is depicted in figure 1.

Local and systemic pro-inflammatory cytokine and autoantibody production are a hallmark of RA and, therefore, glucocorticoids and conventional disease-modifying anti-rheumatic drugs (DMARDS, e. g. methotrexate) are used as first line therapy. However, classical DMARDs are often not effective enough alone or may provide undesirable side effects in some patients and long-term glucocorticoid therapy entails serious toxicity (Kour et al., 2021; Moore & Wallace, 2021). Therefore, advanced biological therapies that target tumor necrosis factor (TNF) or interleukin 6 (IL-6) are often employed (Curtis & Singh, 2011). More recently, janus kinase inhibitors like tofacitinib targeting the signaling pathways of several pro-inflammatory cytokines have been successfully introduced (Garufi et al., 2022). While those treatments can offer symptom relief, 30-40% of patients are unresponsive to the initial biological therapy regardless of drug and its mechanism of action underlining the heterogeneity of the disease (Buch, 2018) .

Besides systemic inflammation, RA is also associated with peripheral and central sensitization towards nociceptive stimuli, and, while inflammation can be contained with adequate therapy, pain often persists even when the disease is well controlled (Mathias et al., 2021). In fact, most patients use medical cannabis to reduce pain as standard therapeutics only offer modest relief and are associated with severe side effects that often lead to discontinuation of treatment (Fine, 2013; Guillouard et al., 2021).

Pain, pro-inflammatory cytokines and subsequent disturbances in the autonomic nervous system and hypothalamus pituitary axis support the development of comorbidities such as depression, fatigue, sleep disturbances or cardiovascular events and many RA patients consider those more burdensome than the disease itself (Aslam & Khan, 2018; Figus et al., 2021). Due to the heterogeneity of these co-morbidities, therapeutic interventions are difficult and seldomly offer appreciable relief.

In light of the multitude of factors that influence disease progression in RA, new therapeutics are urgently needed and since its (medical) legalization more patients use cannabis as an alternative treatment (Sarzi-Puttini et al., 2019). While the use of δ^9-tetrahydrocannabinol (THC) is limited by its psychotropic properties, cannabidiol (CBD) is considered a safe alternative with the potential to provide symptom relief by targeting inflammation, pain and comorbidities at once (Fitzcharles et al., 2020).

CBD is underresearched in the context of inflammatory conditions

CBD is sold and used in many countries and manufacturers of CBD-based products often proclaim beneficial effects of this phytocannabinoid despite the lack of clinical studies (Wagoner et al., 2021). Therefore, systematic human studies regarding the efficacy of CBD in RA and other inflammatory conditions are urgently needed as many patients with rheumatic diseases use medical cannabis (Nowell et al., 2022). However, *in vitro* and *in vivo* studies in human and murine models of RA and inflammation provide some evidence for the beneficial effects of CBD as discussed in this chapter.

Impact of CBD on inflammation in RA

Synovial inflammation in (seropositive) RA originates from autoreactive T cells, since reports have shown that patients with AIDS associated with a low count of CD4 T cells go into remission (Ornstein et al., 1995). The generation of autoreactive T cells is supported by genetic alterations that predispose individuals for RA, e. g. mutations in human leucocyte antigen (HLA) haplotypes (HLA-DR1) (Scherer et al., 2020). In addition, autoreactive B cells appear long before joint problems arise, as antibodies against the Fc portion of immunoglobulin G (rheumatoid factor) and against citrullinated proteins (ACPA) are detected years before disease onset (Scherer et al., 2020). When RA is fully expressed, the influence of monocytes/macrophages and synovial fibroblasts predominate as these cells actively engage in cartilage invasion and joint destruction through production of matrix degrading enzymes and pro-inflammatory cytokines (Knab et al., 2022; Tu et al., 2021).

T cells. RA is characterized by an imbalance of T cell subsets promoting pro-inflammatory T helper (Th) 17 and Th1 cells and reducing anti-inflammatory T regulatory cells (T regs). Excess Th17 and Th1 activation are main contributors to IL-17, TNF and interferon-γ (IFN-γ) production and these cytokines are connected to disease severity in RA. CBD (≥5μM) has been shown to suppress mouse T cell function by inhibiting IL-2 and IFN-γ production and this was also associated with a diminished immune response against sheep red blood cells (Kaplan et al., 2008). These inhibitory effects also occurred in cannabinoid receptor 1 and 2 (CB_1/CB_2) knockout mice and it has been shown that CBD induces apoptosis in mouse lymphocytes by increasing oxidative stress with subsequent caspase-8 activation (Wu et al., 2008). In primary human lymphocytes, a *Cannabis sativa* extract containing 14% CBD and 0.2% THC showed a similar reduction of IL-2 and IFN-γ production but with no overt effect on cell viability. In contrast to results obtained in mouse T cells, the effects on human T cells were mediated by TRPV1 and CB_2 (Devi et al., 2022). *In vivo*, CBD is also not associated with cell death as daily ingestion of 50mg did not change the composition and number of T cells in the 8 week observation period (Kisiolek et al., 2022). An important factor determining whether CBD promotes or decreases T cell activation and lineage commitment is the magnitude of cell stimulation. While optimal stimulation of T cells by CD3/CD28 ligation or high concentrations of ionomycin/phorbol myristate acetate results in inhibitory effects by CBD, suboptimally activated T cells are supported by CBD (Chen et al., 2012). In the latter setting, T cells are skewed towards a T regulatory phenotype supporting anti-inflammatory pathways (Dhital et al., 2017).

B cells. One aspect of RA is the generation of ectopic lymphoid structures in synovial tissue that resemble secondary lymphoid organs like lymph nodes or the spleen. Here, B cells interact with follicular dendritic cells and T cells and undergo

class switch recombination, maturation and the production of autoantibodies. Besides autoantibody production, B cells also secrete several pro-inflammatory cytokines upon activation such as TNF, IFN-γ and IL-6 among others (Wu et al., 2021). Therefore, therapeutics targeting B cells can offer symptom relief in RA (Tavakolpour et al., 2019). However, only a few studies investigated the impact of CBD on the function of B cells. In a human B cell line, CBD (8µM - 32µM) dose-dependently decreased the production of chemokines IL-8, (C-C motif) ligand (CCL) 3 and CCL4 (Srivastava et al., 1998). In addition, it was reported that CBD (≥ 5µM) decreases IL-6, IL-10 and TNF production by CpG-activated mouse B cells and enhances the number of early apoptotic cells while concomitantly decreasing the number of living B cells. In addition, CBD enhances intracellular calcium levels in human and mouse B cells and increases the uptake of the fluorescent cationic dye PoPo3-iodide that is considered a surrogate marker for drug uptake (Lowin et al., 2022). Antibody secretion is also increased by CBD (10µM) as human B cells that were co-cultured with rheumatoid arthritis synovial fibroblasts (RASF) demonstrate increased IgM and IgG production when activated with the TLR9 agonist CpG. Although the increase in antibody production by CBD might suggest a pro-inflammatory influence, the specificity of the generated antibodies was not tested. Therefore, these antibodies might also have anti-inflammatory and homeostatic functions comparable to natural immunoglobulin M and G produced by B1 (mouse) or $CD45^+$ $CD27^+$ $CD70^-$ (human) B cells (Gronwall & Silverman, 2014).

Monocytes/Macrophages/Synovial fibroblasts. While lymphocytes play important roles in the induction of arthritis, innate immune cells (e.g. macrophages) and associated mesenchymal sentinel cells (synovial fibroblasts, SF) support and maintain synovial inflammation (Knab et al., 2022). In the healthy joint, resident macrophages (type A synoviocytes) and SF (type B synoviocytes) form the lining layer, an epithelial-like barrier with tight cell-cell contacts that separates synovial fluid from synovial tissue. Lining layer macrophages promote an anti-inflammatory environment by inhibiting the entry of danger signals into synovial tissue and SF not only produce components of the extracellular matrix but also remodel the tissue microenvironment. These homeostatic functions are lost during the course of arthritis and the influx of pro-inflammatory monocytes and activation of resident fibroblasts disrupt the integrity of the synovial lining layer. In fact, activated SF and macrophages are key players in the destruction of cartilage and bone erosions as they produce copious amounts of pro-inflammatory chemokines, cytokines and matrix metalloproteases (Knab et al., 2022).

In vitro and *in vivo* studies show pro-inflammatory but also anti-inflammatory effects of CBD on macrophages. When activated with lipopolysaccharide (LPS), CBD (5-500nM or 30mg/kg, i. p.) reduces anti-inflammatory IL-10 production and concomitantly enhances pro-inflammatory IL-12 production by mouse peritoneal macrophages (Sacerdote et al., 2005). In line with these results, CBD (75mg/kg, oral) increases the expression of IL-6, IL-23 and granulocyte colony stimulating factor in a mouse model of lung inflammation (Karmaus et al., 2013). In human macrophages, CBD inhibits pro-inflammatory cytokine production depending on activation stimulus. Using Tamm-Horsfall protein-1 (THP-1)-derived macrophages, it was demonstrated that CBD (10µM) decreases toll-like receptor 4 (TLR4) mediated production of C-X-C motif chemokine ligand 10 (CXCL10), interferon-β, TNF, IL-6, IL-10 and IL-1β (Fitzpatrick et al., 2020; Yeisley et al., 2021). However, KG-1 macrophages, a cell line isolated from a donor with acute myeloid leukemia, increase the production of IL-6, IL-8 and CCL2 in response to CBD (10µM) (Anil et

al., 2021). Similar dichotomous results were obtained when using primary peripheral monocytes activated with TLR agonists. While CBD (1-10µM) reduced IL-6, transforming growth factor β (TGF-β) and IL-1β production, it increased levels of monocyte chemoattractant protein-1 (MCP-1), IL-10 and TNF. This differential regulation was dependent on the specific TLR that was activated and confirmed stimulus dependent effects of CBD (Sermet et al., 2021). When using peripheral blood mononuclear cells (PBMCs), CBD also exerts pro- and anti-inflammatory effects regarding cytokine production which is dependent on stimulation. Using LPS, CBD (10µM) enhances TNF production by PBMCs but under stimulation with the TLR9 agonist CpG or IFN-γ, CBD reduces TNF levels (Fitzpatrick et al., 2022). Similarly, IL-10 production was augmented by CBD (10µM) when PBMCs were incubated with the B cell receptor activator anti-immunoglobulin M but was reduced when used together with CpG (Lowin et al., 2022).

The mechanism of action is mostly still unclear but studies suggest that CBD induces apoptosis by promoting the assembly of the mitochondrial permeability transition pore (mPTP) (Wu et al., 2018). In line with this, CBD (>10µM) blunts IL-6, IL-8 and matrix metalloprotease-3 (MMP-3) production by RASF and this effect is due to extensive cell death mediated by the assembly of the mPTP which entails intracellular calcium overload and cell disintegration (Lowin et al., 2020).

A summary of effects of CBD on cells involved in RA pathogenesis is depicted in figure 2.

Effects of CBD in *in vivo* arthritis models

One common murine model of arthritis using either different strains of rat or mice employ bovine or chicken collagen type 2 together with complete Freund's adjuvants (incomplete Freund's adjuvants in rats) to induce a specific immune response. The resulting disease resembles human RA in respect of histology, disease manifestation and treatment response (Griffiths et al., 2007; Inglis et al., 2007).

When administered after the first signs of arthritis, CBD (5mg/kg i. p. or 25mg/kg oral) reduces clinical signs of arthritis and joint damage. Moreover, isolated synovial cells from CBD treated animals demonstrate reduced TNF production when compared with control cells. Similarly, when challenging immune cells from draining lymph nodes with collagen type 2, IFN-γ production and in vitro thymocyte proliferation is decreased by CBD (Malfait et al., 2000). These anti-arthritic effects were also recapitulated in a complete Freund's adjuvant-induced monoarthritic knee joint model in rats. Here, CBD was administered via transdermal patches (0.62 – 62.3 mg/day), which resulted in high plasma CBD levels. Knee joint inflammation was reduced by CBD and swelling was attenuated. This was not only associated with increased pain thresholds but also with decreased TNF and calcitonin gene-related peptide (CGRP) levels in dorsal root ganglia (Hammell et al., 2016).

CBD and arthritic pain

Most patients suffering from RA consider pain as the most burdensome symptom which often persists despite adequate treatment of inflammation. This includes inflammatory but also neuropathic pain which is notoriously difficult to treat. During the course of the disease central and peripheral pain processing is altered which establishes lower thresholds in thermal and mechanical sensitivity. In addition, the pain neurotransmitters substance P and CGRP further fuel inflammation by promoting the production of pro-inflammatory cytokines. Currently, pharmacological

interventions counteracting pain involve the use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, both of which are associated with severe adverse events that prevent their long-term use (Walsh & McWilliams, 2014). Therefore, patients use medical cannabis primarily as an alternative to conventional pain medications but data regarding their efficacy is still rare (Nowell et al., 2022). One study assessed the effects of nabiximols (Sativex), a cannabis preparation with an equal ratio of THC and CBD, on arthritic pain in a cohort of 58 patients. Nabiximols shows some effects on morning pain at rest and movement but improvements are only moderate and it is unclear whether THC, CBD or their combination mediates this effect (Blake et al., 2006). However, a recent study compared the efficacy of nabiximols with pure, semisynthetic THC (marinol/dronabinol) in the treatment of severe neuropathic pain and results show that CBD/THC is superior to THC alone (Ueberall et al., 2022). In line with this, topical CBD improves pain in thumb basal joint arthritis but patient sample size in the respective study was small (Heineman et al., 2022). In contrast, pain caused by osteoarthritis or psoriatic arthritis is not modulated by oral CBD (20 or 30mg daily) and topical CBD is ineffective in post operative pain after total knee arthroplasty (Haffar et al., 2022; Vela et al., 2021). In healthy volunteers, CBD (0-800 mg orally) even increases pain thresholds in the cold pressor test which has good predictive validity for the efficacy of pain medications (Arout et al., 2022). A potential mechanism of CBD on pain perception is shown in figure 3.

CBD and RA comorbidities

Synovitis is not the only feature of RA as many extra-articular manifestations and comorbidities manifest during the course of the disease. These include cardiovascular complications, respiratory disease, depression, anxiety and fatigue (Figus et al., 2021). Comorbidities not only arise due to systemic low-level inflammation but also involve the autonomic nervous system which is discussed as a target for future RA therapy (Adlan et al., 2014; Koopman et al., 2011). CBD might curb at least some of the most common comorbidities. Hypertension is counteracted by the vasodilatory action of CBD in human and rat *in vitro* models (Baranowska-Kuczko et al., 2021; Baranowska-Kuczko et al., 2020) although one study shows no influence of chronic CBD in a rat model of primary and secondary hypertension (Remiszewski et al., 2020). A study conducted with human healthy volunteers demonstrates a decrease in blood pressure by a single high dose of CBD (600mg) (Jadoon et al., 2017). In a large online survey including more than 45000 participants in the U.S. and Canada, anxiety and depression are two main reasons for taking CBD-based products (Goodman et al., 2022). Although these effects of CBD need to be confirmed in human studies, preclinical evidence in animal models suggest that CBD has antidepressant and anxiolytic properties (Chaves et al., 2021; Tito et al., 2021).

CBD in RA therapy – Take it or leave it?

Although clinical evidence is merely non-existent for the use of CBD in RA, it might be nonetheless useful for patients. First off, as stated in the previous sections, preclinical data but also anecdotal patient reports suggest an anti-inflammatory and analgesic effect of CBD which might depend on disease severity. CBD seems to work better in patients whose disease is inadequately controlled. This is confirmed by results from a Canadian cannabis clinic where only patients with moderate and severe symptoms benefited from CBD (Rapin et al., 2021). Secondly, CBD might

increase the efficacy of an existing RA medication. It has been shown that CBD increases the uptake of compounds partly by triggering the ion channel TRPV2 which increases chemosensitivity in target cells (Nabissi et al., 2013). In line with this, CBD also enhances drug uptake via TRP -independent pathways, possibly by triggering organic cation transporters through the mobilization of intracellular calcium (Lowin et al., 2020). This effect of CBD might be relevant to all patients that use small molecule-based treatments and CBD might either enhance the efficacy of a given treatment or might help to reduce dosage, thereby limiting side-effects. Lastly, CBD is relatively safe to use. Taking CBD even in high concentrations (up to 50mg/kg) is not associated with severe side effects and it is usually well tolerated (Marchese et al., 2022). However, some people taking pharmacological doses of CBD demonstrate an increase in transaminase levels indicating some form of liver injury. Therefore, caution should be taken especially when combining CBD with other RA medications that are known for liver toxicity e. g. methotrexate (Avouac et al., 2022). For this reason, patients are required to consult their physician before they plan to use CBD. Patients should not be discouraged by a lack of effect. Titration of CBD is recommended, as its action is dose-dependent and most human studies show that high levels (>100mg/day) of CBD are necessary to elicit appreciable effects (Naftali et al., 2019; Urbi et al., 2019). If taken in low concentrations (~10mg/day), CBD does not influence disease activity (Naftali et al., 2017). Therefore, patients should not rely on over-the-counter CBD medications, since their labelled concentrations are often faulty which makes titration impossible (Johnson et al., 2022; Wakshlag et al., 2020). In addition, bioavailability of CBD is highly variable dependent on gastrointestinal absorption and formulation with inhalation reaching the highest reproducible plasma levels despite using low initial CBD concentrations (Devinsky et al., 2021).

Applications to Other Areas

Potential beneficial effects of CBD on the outcome of RA can also be applied to other inflammatory conditions. Many autoimmune diseases share common immunological features namely excessive pro-inflammatory cytokine and autoantibody production, tissue destruction and imbalances in immune cell composition. In addition, pain and comorbidities accompany inflammation and, like in RA, are often refractory to treatment. Therefore, CBD is being investigated as treatment for multiple sclerosis, lupus erythematosus or Crohn’s disease (Rodriguez Mesa et al., 2021). Furthermore, CBD is also discussed as an acute anti-inflammatory agent that might not only curb the cytokine storm associated with bacterial and viral infections but might also limit replication of COVID-19 (Aswad et al., 2022; Nguyen et al., 2022). In addition, CBD holds promise as a topical agent that is being investigated in clinical trials for the treatment of psoriasis and atopic dermatitis (Maghfour et al., 2021; Puaratanaarunkon et al., 2022). Another field where CBD can play its strengths is cancer. It has been shown that CBD influences the viability of many different types of malignant cells *in vitro* and *in vivo* (Valenti et al., 2022). Case reports already confirmed the anti-tumor action of CBD but, like in inflammatory conditions, these results need to be confirmed in clinical studies (Guggisberg et al., 2022).

Mini-Dictionary of Terms

- ***DMARDs (disease modifying anti rheumatic drugs)***. First line therapy against RA that is maintained over the course of the disease. Includes common drugs like methotrexate but also targeted synthetic drugs like janus kinase inhibitors or anti-cytokine antibodies.
- ***Interleukin 6 (IL-6).*** Pro-inflammatory cytokine that plays a central role in joint destruction by enhancing osteoclast, B cell and macrophage activity; also promotes extra-articular manifestations and comorbidities. Important target of biological DMARDs.
- ***Interleukin 10 (IL-10).*** Anti-inflammatory cytokine that counteracts the action of TNF and IL-6***.*** Elevation of IL-10 levels is favourable in RA.
- ***Mitochondrial Permeability Transition Pore (mPTP)***. Protein complex that is assembled in the mitochondrial membrane in response to cell stress. Mediates cell death by CBD in synovial fibroblasts and monocytes.
- ***TNF.*** Pro-inflammatory cytokine that is a key player in RA development. Important target of biological DMARDs.
- ***Transient Receptor Potential (TRP) channels.*** Large group of ion channels which mediate physiological sensations like pain, osmotic pressure or taste. Many effects of CBD are attributed to the activation of TRP channels.

Key Facts of Rheumatoid Arthritis (RA)

RA is a chronic autoimmune disease associated with joint destruction, systemic low-level inflammation, pain, disability and autoantibody production.

RA affects 0.25 -1% of the general population and has a female to male preponderance of at least 2:1

RA is associated with disturbances in the sensory and autonomic nervous system.

HPA axis response is inadequate in relation to inflammation.

RA is accompanied by several comorbidities such as anxiety, depression, fatigue and cardiovascular disease

Available treatments target inflammation which not only decreases disease activity but also comorbidities

Therapeutics in RA can have severe side-effects like increased incidence of infections, risk of cancer, allergic reactions or liver- and nephrotoxicity

Pain in RA often persists albeit inflammation is adequately controlled

Cannabidiol has not been adequately investigated as potential treatment in RA.

Summary Points

- *CBD inhibits optimally activated T cells and reduces IL-2 and IFN-γ production while promoting T reg development in suboptimally activated T cells*
- *CBD reduces CCL-3, CCL-4, IL-6, IL-8, TNF and IL-10 production by B cells*
- *CBD enhances drug uptake by B cells and synovial fibroblasts*
- *CBD enhances or reduces pro-inflammatory cytokine production by macrophages depended on activation stimulus*
- *CBD induces cell death in monocytes and synovial fibroblasts*
- *CBD ameliorates experimental arthritis in mice*
- *Effects of CBD on arthritic pain are unclear*
- *CBD might curb RA-associated comorbidities such as hypertension and depression*
- *If liver toxicity can be excluded, CBD might be added to a given RA treatment regimen*
- *Besides limiting inflammation, CBD might enhance the efficacy of small molecule RA therapeutics*

Figure 1: Immunopathology of rheumatoid arthritis (RA)

Legend to Figure 1. *Comparison of a healthy and an arthritic joint at the interface between cartilage and synovial tissue. In the healthy joint, synovial lining tissue resident macrophages separate cartilage from synovial tissue (A). These anti-inflammatory macrophages form a tight barrier via desmosomes and tight junctions that does not allow danger signals to enter synovial tissue. The synovial lining consists of 1-3 cell layers and is populated by synovial fibroblasts and macrophages (B).*

In the arthritic joint, this barrier function is lost, danger signals can enter synovial tissue and resident cells are transformed to a pro-inflammatory phenotype that actively degrade cartilage. The sequelae that lead to RA are shown. 1) Genetic contribution that predispose individuals to the development of RA. This includes gene single nucleotide polymorphisms (SNPs) in genes like shared epitope alleles and others. 2) Neo-epitopes e. g. citrullinated peptides elicit an immune response and antibodies with high autoreactivity are generated and enter synovial tissue. Here, autoantibody binding to Fc receptors on macrophages entail activation and cytokine production. Moreover, these autoantibodies activate the complement cascade leading to recruitment of more immune cells and their activation. 3) Influx of monocytes, T cells and B cells that further fuel synovial inflammation. Monocytes are preferentially differentiated into pro-inflammatory M1 macrophages. Macrophages, T and B cells secrete pro-inflammatory cytokines, like TNF, IL-1β and IL-6 that activate synovial fibroblasts (SF). 4) SF in turn start producing large amounts of IL-6 and chemotactic factors that recruit more immune cells from blood. In addition, high IL-6 levels can skew T cell development to the pro-inflammatory Th17 phenotype. 5) The pro-inflammatory environment disrupts the synovial lining which now allows the passage of cytokines, danger signals and resident cells. Matrix metalloproteases are produced by SF and macrophages and these cells start invading and degrading cartilage.

Figure 2: Impact of cannabidiol (CBD) on leucocytes and synovial fibroblasts

Legend to Figure 2. *CBD influences function, chemokine and cytokine production of T cells, B cells, monocytes, macrophages and synovial fibroblasts. Green: Anti-inflammatory effects of CBD; Red: Pro-inflammatory effects, Yellow: Pro- or anti-inflammatory, depending on context. ms = mouse; hu = human; IL = interleukin; IFN = interferon; ROS = reactive oxygen species; CCL = (C-C motif) ligand; TNF = tumor necrosis factor; G-CSF = granulocyte-colony stimulating factor; CXCL = C-X-C motif chemokine ligand; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinase*

Figure 3: Potential mechanism of cannabidiol (CBD) on pain in rheumatoid arthritis (RA)

Legend to Figure 3. *CBD ligates transient receptor potential (TRP) ion channels TRPV1 (vanilloid) and TRPA1 (ankyrin) that are essential for pain perception. 1) During the course of RA, sensory nerve fibres sprout in inflamed synovial tissue. These fibres release the pain transmitters calcitonin gene-related peptide (CGRP) and substance P (SP) upon activation of TRPA1 and/or TRPV1. 2) CGRP and SP do not only act as neurotransmitters that signal to the brain but are also released into tissue. 3) Here, both act as potent vasodilators which leads to the extravasation of leucocytes. In addition, SP also acts in synergy with other pro-inflammatory factors to increase cytokine production by e. g. macrophages. 4) Influx of immune cells is accompanied by an increase of pro-inflammatory cytokine production. TNF, produced by cells of the innate and adaptive immune system sensitizes TRPA1 and TRPV1 and thereby decreases pain thresholds. 5) CBD is an agonist of TRPA1 and TRPV1. Although brief activation (green arrows) of these ion channels might increase pain perception, continuous activation with CBD desensitizes TRP channels promoting analgesia. 6) In addition, CBD decreases TNF production which limits sensitization of TRPA1 and TRPV1.*
Of note, CBD might also influence central pain processing by modulating TRP signaling, since these ion channels are expressed throughout the nervous system.

References

Adlan, A. M., Lip, G. Y., Paton, J. F., Kitas, G. D., & Fisher, J. P. (2014). Autonomic function and rheumatoid arthritis: a systematic review. *Semin Arthritis Rheum*, *44*(3), 283-304.

Almoallim, H., Al Saleh, J., Badsha, H., Ahmed, H. M., Habjoka, S., Menassa, J. A., et al. (2021). A Review of the Prevalence and Unmet Needs in the Management of Rheumatoid Arthritis in Africa and the Middle East. *Rheumatol Ther*, *8*(1), 1-16.

Anil, S. M., Shalev, N., Vinayaka, A. C., Nadarajan, S., Namdar, D., Belausov, E., et al. (2021). Cannabis compounds exhibit anti-inflammatory activity in vitro in COVID-19-related inflammation in lung epithelial cells and pro-inflammatory activity in macrophages. *Sci Rep*, *11*(1), 1462.

Arout, C. A., Haney, M., Herrmann, E. S., Bedi, G., & Cooper, Z. D. (2022). A placebo-controlled investigation of the analgesic effects, abuse liability, safety and tolerability of a range of oral cannabidiol doses in healthy humans. *Br J Clin Pharmacol*, *88*(1), 347-355.

Aslam, F., & Khan, N. A. (2018). Tools for the Assessment of Comorbidity Burden in Rheumatoid Arthritis. *Front Med (Lausanne)*, *5*, 39.

Aswad, M., Hamza, H., Pechkovsky, A., Zikrach, A., Popov, T., Zohar, Y., et al. (2022). High-CBD Extract (CBD-X) Downregulates Cytokine Storm Systemically and Locally in Inflamed Lungs. *Front Immunol*, *13*, 875546.

Avouac, J., Degrave, R., Vergneault, H., Combier, A., Wanono, S., Boisson, M., et al. (2022). Risk of liver fibrosis induced by methotrexate and other rheumatoid arthritis medications according to the Fibrosis-4 Index. *Clin Exp Rheumatol*, *40*(1), 150-157.

Baranowska-Kuczko, M., Kozlowska, H., Kloza, M., Kusaczuk, M., Harasim-Symbor, E., Biernacki, M., et al. (2021). Vasoprotective Endothelial Effects of Chronic Cannabidiol Treatment and Its Influence on the Endocannabinoid System in Rats with Primary and Secondary Hypertension. *Pharmaceuticals (Basel)*, *14*(11).

Baranowska-Kuczko, M., Kozlowska, H., Kloza, M., Sadowska, O., Kozlowski, M., Kusaczuk, M., et al. (2020). Vasodilatory effects of cannabidiol in human pulmonary and rat small mesenteric arteries: modification by hypertension and the potential pharmacological opportunities. *J Hypertens*, *38*(5), 896-911.

Blake, D. R., Robson, P., Ho, M., Jubb, R. W., & McCabe, C. S. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*, *45*(1), 50-52.

Bluml, S., Redlich, K., & Smolen, J. S. (2014). Mechanisms of tissue damage in arthritis. *Semin Immunopathol*, *36*(5), 531-540.

Buch, M. H. (2018). Defining refractory rheumatoid arthritis. *Ann Rheum Dis*, *77*(7), 966-969.

Chaves, Y. C., Genaro, K., Crippa, J. A., da Cunha, J. M., & Zanoveli, J. M. (2021). Cannabidiol induces antidepressant and anxiolytic-like effects in experimental type-1 diabetic animals by multiple sites of action. *Metab Brain Dis*, *36*(4), 639-652.

Chen, W., Kaplan, B. L., Pike, S. T., Topper, L. A., Lichorobiec, N. R., Simmons, S. O., et al. (2012). Magnitude of stimulation dictates the cannabinoid-mediated differential T cell response to HIVgp120. *J Leukoc Biol*, *92*(5), 1093-1102.

Curtis, J. R., & Singh, J. A. (2011). Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. *Clin Ther*, *33*(6), 679-707.

Devi, S., Zimmermann-Klemd, A. M., Fiebich, B. L., Heinrich, M., Grundemann, C., Steinberger, P., et al. (2022). Immunosuppressive activity of non-psychoactive Cannabis sativa L. extract on the function of human T lymphocytes. *Int Immunopharmacol*, *103*, 108448.

Devinsky, O., Kraft, K., Rusch, L., Fein, M., & Leone-Bay, A. (2021). Improved Bioavailability with Dry Powder Cannabidiol Inhalation: A Phase 1 Clinical Study. *J Pharm Sci*, *110*(12), 3946-3952.

Dhital, S., Stokes, J. V., Park, N., Seo, K. S., & Kaplan, B. L. (2017). Cannabidiol (CBD) induces functional Tregs in response to low-level T cell activation. *Cell Immunol, 312*, 25-34.

Figus, F. A., Piga, M., Azzolin, I., McConnell, R., & Iagnocco, A. (2021). Rheumatoid arthritis: Extra-articular manifestations and comorbidities. *Autoimmun Rev, 20*(4), 102776.

Fine, M. (2013). Quantifying the impact of NSAID-associated adverse events. *Am J Manag Care, 19*(14 Suppl), s267-272.

Fitzcharles, M. A., Clauw, D. J., & Hauser, W. (2020). A cautious hope for cannabidiol (CBD) in rheumatology care. *Arthritis Care Res (Hoboken)*.

Fitzpatrick, J. M., Hackett, B., Costelloe, L., Hind, W., & Downer, E. J. (2022). Botanically-Derived Delta(9)-Tetrahydrocannabinol and Cannabidiol, and Their 1:1 Combination, Modulate Toll-like Receptor 3 and 4 Signalling in Immune Cells from People with Multiple Sclerosis. *Molecules, 27*(6).

Fitzpatrick, J. M., Minogue, E., Curham, L., Tyrrell, H., Gavigan, P., Hind, W., et al. (2020). MyD88-dependent and -independent signalling via TLR3 and TLR4 are differentially modulated by Delta(9)-tetrahydrocannabinol and cannabidiol in human macrophages. *J Neuroimmunol, 343*, 577217.

Garufi, C., Maclean, M., Gadina, M., & Spinelli, F. R. (2022). Affecting the effectors: JAK inhibitors modulation of immune cell numbers and functions in patients with rheumatoid arthritis. *Expert Rev Clin Immunol, 18*(3), 309-319.

Goodman, S., Wadsworth, E., Schauer, G., & Hammond, D. (2022). Use and Perceptions of Cannabidiol Products in Canada and in the United States. *Cannabis Cannabinoid Res, 7*(3), 355-364.

Griffiths, M. M., Cannon, G. W., Corsi, T., Reese, V., & Kunzler, K. (2007). Collagen-induced arthritis in rats. *Methods Mol Med, 136*, 201-214.

Gronwall, C., & Silverman, G. J. (2014). Natural IgM: beneficial autoantibodies for the control of inflammatory and autoimmune disease. *J Clin Immunol, 34 Suppl 1*, S12-21.

Guggisberg, J., Schumacher, M., Gilmore, G., & Zylla, D. M. (2022). Cannabis as an Anticancer Agent: A Review of Clinical Data and Assessment of Case Reports. *Cannabis Cannabinoid Res, 7*(1), 24-33.

Guillouard, M., Authier, N., Pereira, B., Soubrier, M., & Mathieu, S. (2021). Cannabis use assessment and its impact on pain in rheumatologic diseases: a systematic review and meta-analysis. *Rheumatology (Oxford), 60*(2), 549-556.

Haffar, A., Khan, I. A., Abdelaal, M. S., Banerjee, S., Sharkey, P. F., & Lonner, J. H. (2022). Topical Cannabidiol (CBD) After Total Knee Arthroplasty Does Not Decrease Pain or Opioid Use: A Prospective Randomized Double-Blinded Placebo-Controlled Trial. *J Arthroplasty*.

Hammell, D. C., Zhang, L. P., Ma, F., Abshire, S. M., McIlwrath, S. L., Stinchcomb, A. L., et al. (2016). Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. *Eur J Pain, 20*(6), 936-948.

Heineman, J. T., Forster, G. L., Stephens, K. L., Cottler, P. S., Timko, M. P., & DeGeorge, B. R., Jr. (2022). A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis. *J Hand Surg Am.*

Inglis, J. J., Criado, G., Medghalchi, M., Andrews, M., Sandison, A., Feldmann, M., et al. (2007). Collagen-induced arthritis in C57BL/6 mice is associated with a robust and sustained T-cell response to type II collagen. *Arthritis Res Ther, 9*(5), R113.

Jadoon, K. A., Tan, G. D., & O'Sullivan, S. E. (2017). A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study. *JCI Insight, 2*(12).

Johnson, E., Kilgore, M., & Babalonis, S. (2022). Label accuracy of unregulated cannabidiol (CBD) products: measured concentration vs. label claim. *J Cannabis Res, 4*(1), 28.

Kaplan, B. L., Springs, A. E., & Kaminski, N. E. (2008). The profile of immune modulation by cannabidiol (CBD) involves deregulation of nuclear factor of activated T cells (NFAT). *Biochem Pharmacol*, *76*(6), 726-737.

Karmaus, P. W., Wagner, J. G., Harkema, J. R., Kaminski, N. E., & Kaplan, B. L. (2013). Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. *J Immunotoxicol*, *10*(3), 321-328.

Kisiolek, J. N., Haughian, J. M., Flores, V. A., Ramani, A. H., & Stewart, L. K. (2022). Eight Weeks of Daily Cannabidiol Ingestion Does Not Alter Peripheral Blood Mononuclear Cell Profile or Natural Killer Cell Cytotoxicity. *FASEB J*, *36 Suppl 1*.

Knab, K., Chambers, D., & Kronke, G. (2022). Synovial Macrophage and Fibroblast Heterogeneity in Joint Homeostasis and Inflammation. *Front Med (Lausanne)*, *9*, 862161.

Koopman, F. A., Stoof, S. P., Straub, R. H., Van Maanen, M. A., Vervoordeldonk, M. J., & Tak, P. P. (2011). Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. *Mol Med*, *17*(9-10), 937-948.

Kour, G., Haq, S. A., Bajaj, B. K., Gupta, P. N., & Ahmed, Z. (2021). Phytochemical add-on therapy to DMARDs therapy in rheumatoid arthritis: In vitro and in vivo bases, clinical evidence and future trends. *Pharmacol Res*, *169*, 105618.

Lowin, T., Laaser, S. A., Kok, C., Bruneau, E., & Pongratz, G. (2022). Cannabidiol: Influence on B Cells, Peripheral Blood Mononuclear Cells, and Peripheral Blood Mononuclear Cell/Rheumatoid Arthritis Synovial Fibroblast Cocultures. *Cannabis Cannabinoid Res*.

Lowin, T., Tingting, R., Zurmahr, J., Classen, T., Schneider, M., & Pongratz, G. (2020). Cannabidiol (CBD): a killer for inflammatory rheumatoid arthritis synovial fibroblasts. *Cell Death Dis*, *11*(8), 714.

Maghfour, J., Rundle, C. W., Rietcheck, H. R., Dercon, S., Lio, P., Mamo, A., et al. (2021). Assessing the effects of topical cannabidiol in patients with atopic dermatitis. *Dermatol Online J*, *27*(2).

Malfait, A. M., Gallily, R., Sumariwalla, P. F., Malik, A. S., Andreakos, E., Mechoulam, R., et al. (2000). The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci U S A*, *97*(17), 9561-9566.

Marchese, F., Vari, M. S., Balagura, G., Riva, A., Salpietro, V., Verrotti, A., et al. (2022). An Open Retrospective Study of a Standardized Cannabidiol Based-Oil in Treatment-Resistant Epilepsy. *Cannabis Cannabinoid Res*, *7*(2), 199-206.

Mathias, K., Amarnani, A., Pal, N., Karri, J., Arkfeld, D., Hagedorn, J. M., et al. (2021). Chronic Pain in Patients with Rheumatoid Arthritis. *Curr Pain Headache Rep*, *25*(9), 59.

Moore, M. N., & Wallace, B. I. (2021). Glucocorticoid and opioid use in rheumatoid arthritis management. *Curr Opin Rheumatol*, *33*(3), 277-283.

Nabissi, M., Morelli, M. B., Santoni, M., & Santoni, G. (2013). Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis*, *34*(1), 48-57.

Naftali, T., Bar-Lev Schleider, L., Sklerovsky Benjaminov, F., Lish, I., Konikoff, F. M., & Ringel, Y. (2019). Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects. *Eur J Gastroenterol Hepatol*, *31*(11), 1376-1381.

Naftali, T., Mechulam, R., Marii, A., Gabay, G., Stein, A., Bronshtain, M., et al. (2017). Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. *Dig Dis Sci*, *62*(6), 1615-1620.

Nguyen, L. C., Yang, D., Nicolaescu, V., Best, T. J., Gula, H., Saxena, D., et al. (2022). Cannabidiol inhibits SARS-CoV-2 replication through induction of the host ER stress and innate immune responses. *Sci Adv*, *8*(8), eabi6110.

Nowell, W. B., Gavigan, K., & S, L. S. (2022). Cannabis for Rheumatic Disease Pain: a Review of Current Literature. *Curr Rheumatol Rep*, *24*(5), 119-131.

Ornstein, M. H., Kerr, L. D., & Spiera, H. (1995). A reexamination of the relationship between active rheumatoid arthritis and the acquired immunodeficiency syndrome. *Arthritis Rheum*, *38*(11), 1701-1706.

Puaratanaarunkon, T., Sittisaksomjai, S., Sivapornpan, N., Pongcharoen, P., Chakkavittumrong, P., Ingkaninan, K., et al. (2022). Topical cannabidiol-based treatment for psoriasis: A dual-centre randomized placebo-controlled study. *J Eur Acad Dermatol Venereol*.

Rapin, L., Gamaoun, R., El Hage, C., Arboleda, M. F., & Prosk, E. (2021). Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. *J Cannabis Res*, *3*(1), 19.

Remiszewski, P., Jarocka-Karpowicz, I., Biernacki, M., Jastrzab, A., Schlicker, E., Toczek, M., et al. (2020). Chronic Cannabidiol Administration Fails to Diminish Blood Pressure in Rats with Primary and Secondary Hypertension Despite Its Effects on Cardiac and Plasma Endocannabinoid System, Oxidative Stress and Lipid Metabolism. *Int J Mol Sci*, *21*(4).

Rodriguez Mesa, X. M., Moreno Vergara, A. F., Contreras Bolanos, L. A., Guevara Moriones, N., Mejia Pineros, A. L., & Santander Gonzalez, S. P. (2021). Therapeutic Prospects of Cannabinoids in the Immunomodulation of Prevalent Autoimmune Diseases. *Cannabis Cannabinoid Res*, *6*(3), 196-210.

Sacerdote, P., Martucci, C., Vaccani, A., Bariselli, F., Panerai, A. E., Colombo, A., et al. (2005). The nonpsychoactive component of marijuana cannabidiol modulates chemotaxis and IL-10 and IL-12 production of murine macrophages both in vivo and in vitro. *J Neuroimmunol*, *159*(1-2), 97-105.

Sarzi-Puttini, P., Ablin, J., Trabelsi, A., Fitzcharles, M. A., Marotto, D., & Hauser, W. (2019). Cannabinoids in the treatment of rheumatic diseases: Pros and cons. *Autoimmun Rev*, *18*(12), 102409.

Scherer, H. U., Haupl, T., & Burmester, G. R. (2020). The etiology of rheumatoid arthritis. *J Autoimmun*, *110*, 102400.

Sermet, S., Li, J., Bach, A., Crawford, R. B., & Kaminski, N. E. (2021). Cannabidiol selectively modulates interleukin (IL)-1beta and IL-6 production in toll-like receptor activated human peripheral blood monocytes. *Toxicology*, *464*, 153016.

Srivastava, M. D., Srivastava, B. I., & Brouhard, B. (1998). Delta9 tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmacology*, *40*(3), 179-185.

Tavakolpour, S., Alesaeidi, S., Darvishi, M., GhasemiAdl, M., Darabi-Monadi, S., Akhlaghdoust, M., et al. (2019). A comprehensive review of rituximab therapy in rheumatoid arthritis patients. *Clin Rheumatol*, *38*(11), 2977-2994.

Tito, P. A. L., Bernardino, T. C. S., Bellozi, P. M. Q., da Silva, M. C. M., de Miranda, A. S., Vieira, E. L. M., et al. (2021). Cannabidiol prevents lipopolysaccharide-induced sickness behavior and alters cytokine and neurotrophic factor levels in the brain. *Pharmacol Rep*, *73*(6), 1680-1693.

Tu, J., Huang, W., Zhang, W., Mei, J., & Zhu, C. (2021). A Tale of Two Immune Cells in Rheumatoid Arthritis: The Crosstalk Between Macrophages and T Cells in the Synovium. *Front Immunol*, *12*, 655477.

Ueberall, M. A., Essner, U., Vila Silvan, C., & Mueller-Schwefe, G. H. H. (2022). Comparison of the Effectiveness and Tolerability of Nabiximols (THC:CBD) Oromucosal Spray versus Oral Dronabinol (THC) as Add-on Treatment for Severe Neuropathic Pain in Real-World Clinical Practice: Retrospective Analysis of the German Pain e-Registry. *J Pain Res*, *15*, 267-286.

Urbi, B., Broadley, S., Bedlack, R., Russo, E., & Sabet, A. (2019). Study protocol for a randomised, double-blind, placebo-controlled study evaluating the Efficacy of cannabis-based Medicine Extract in slowing the disease pRogression of Amyotrophic Lateral sclerosis or motor neurone Disease: the EMERALD trial. *BMJ Open*, *9*(11), e029449.

Valenti, C., Billi, M., Pancrazi, G. L., Calabria, E., Armogida, N. G., Tortora, G., et al. (2022). Biological effects of cannabidiol on human cancer cells: Systematic review of the literature. *Pharmacol Res*, *181*, 106267.

Vela, J., Dreyer, L., Petersen, K. K., Lars, A. N., Duch, K. S., & Kristensen, S. (2021). Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. *Pain*.

Wagoner, K. G., Lazard, A. J., Romero-Sandoval, E. A., & Reboussin, B. A. (2021). Health Claims About Cannabidiol Products: A Retrospective Analysis of U.S. Food and Drug Administration Warning Letters from 2015 to 2019. *Cannabis Cannabinoid Res*, *6*(6), 559-563.

Wakshlag, J. J., Cital, S., Eaton, S. J., Prussin, R., & Hudalla, C. (2020). Cannabinoid, Terpene, and Heavy Metal Analysis of 29 Over-the-Counter Commercial Veterinary Hemp Supplements. *Vet Med (Auckl)*, *11*, 45-55.

Walsh, D. A., & McWilliams, D. F. (2014). Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol*, *10*(10), 581-592.

Wu, F., Gao, J., Kang, J., Wang, X., Niu, Q., Liu, J., et al. (2021). B Cells in Rheumatoid ArthritisPathogenic Mechanisms and Treatment Prospects. *Front Immunol*, *12*, 750753.

Wu, H. Y., Chu, R. M., Wang, C. C., Lee, C. Y., Lin, S. H., & Jan, T. R. (2008). Cannabidiol-induced apoptosis in primary lymphocytes is associated with oxidative stress-dependent activation of caspase-8. *Toxicol Appl Pharmacol*, *226*(3), 260-270.

Wu, H. Y., Huang, C. H., Lin, Y. H., Wang, C. C., & Jan, T. R. (2018). Cannabidiol induced apoptosis in human monocytes through mitochondrial permeability transition pore-mediated ROS production. *Free Radic Biol Med*, *124*, 311-318.

Yeisley, D. J., Arabiyat, A. S., & Hahn, M. S. (2021). Cannabidiol-Driven Alterations to Inflammatory Protein Landscape of Lipopolysaccharide-Activated Macrophages In Vitro May Be Mediated by Autophagy and Oxidative Stress. *Cannabis Cannabinoid Res*, *6*(3), 253-263.

Fig. 1:

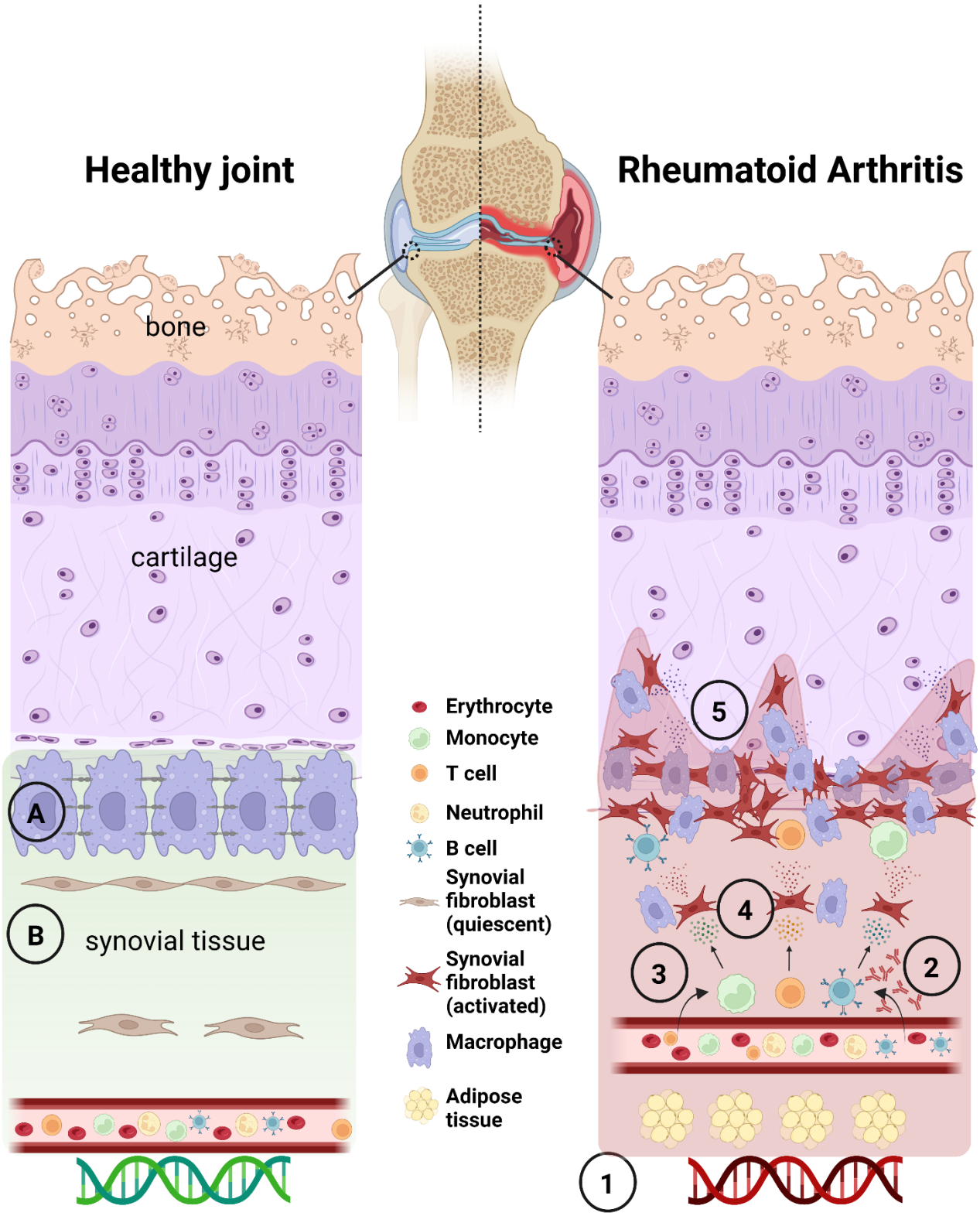

Healthy joint
Rheumatoid Arthritis
bone
cartilage
A
B
synovial tissue
Erythrocyte
Monocyte
T cell
Neutrophil
B cell
Synovial fibroblast (quiescent)
Synovial fibroblast (activated)
Macrophage
Adipose tissue
1
2
3
4
5

Fig. 2:

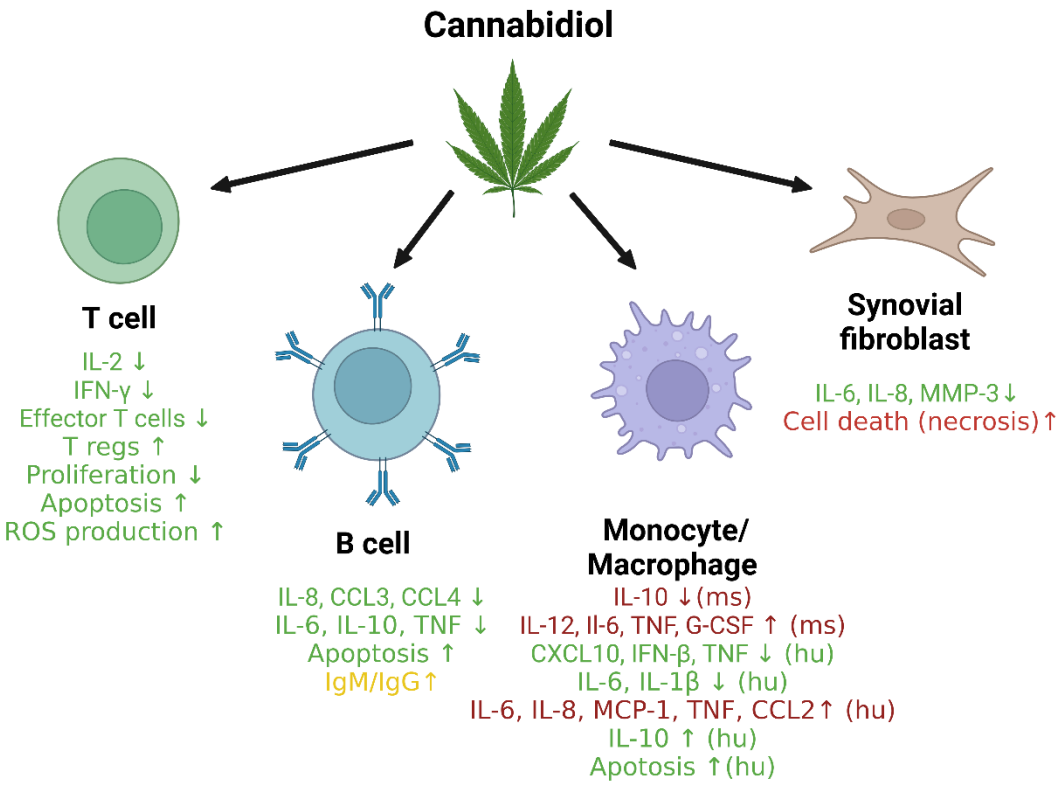
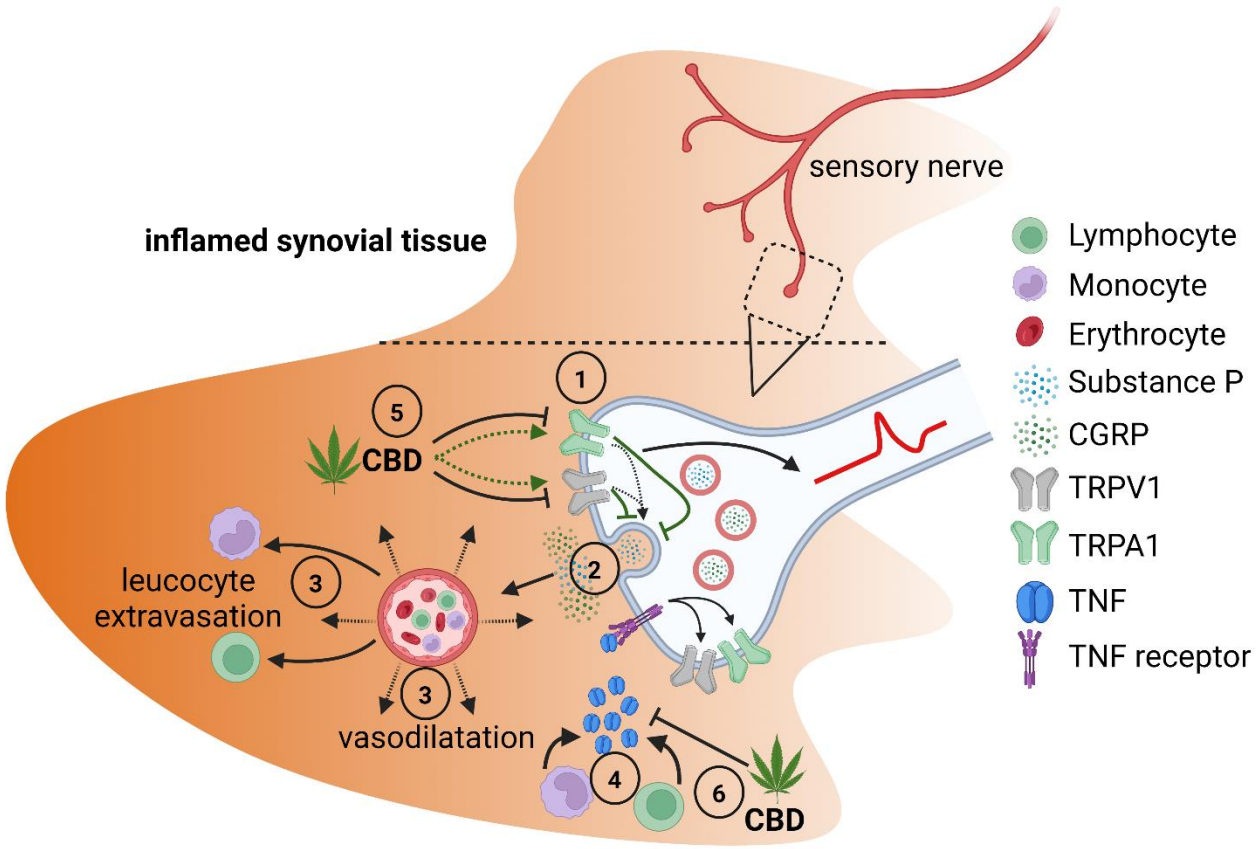

Cannabidiol
T cell
IL-2 ↓
IFN-γ ↓
Effector T cells ↓
T regs ↑
Proliferation ↓
Apoptosis ↑
ROS production ↑
B cell
IL-8, CCL3, CCL4 ↓
IL-6, IL-10, TNF ↓
Apoptosis ↑
IgM/IgG ↑
Monocyte/
Macrophage
IL-10 ↓(ms)
IL-12, Il-6, TNF, G-CSF ↑ (ms)
CXCL10, IFN-β, TNF ↓ (hu)
IL-6, IL-1β ↓ (hu)
IL-6, IL-8, MCP-1, TNF, CCL2 ↑ (hu)
IL-10 ↑ (hu)
Apotosis ↑(hu)
Synovial
fibroblast
IL-6, IL-8, MMP-3 ↓
Cell death (necrosis) ↑

Fig. 3:


sensory nerve
inflamed synovial tissue
Lymphocyte
Monocyte
Erythrocyte
Substance P
CGRP
TRPV1
TRPA1
TNF
TNF receptor
1
2
3
3
4
5
6
CBD
CBD
leucocyte
extravasation
vasodilatation