Joints for joints: cannabinoids in the treatment of rheumatoid arthritis

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Purpose of review
An increasing number of patients with rheumatoid arthritis (RA) are using cannabis to treat their symptoms, although systematic studies regarding efficacy in RA are lacking. Within this review we will give an overview on the overall effects of cannabinoids in inflammation and why they might be useful in the treatment of RA.

Recent findings
Peripherally, cannabinoids show anti-inflammatory effects by activating cannabinoid type 2 receptors (CB_2) which decrease cytokine production and immune cell mobilization. In contrast, cannabinoid type 1 receptor (CB_1) activation on immune cells is proinflammatory while CB_1 antagonism provides anti-inflammatory effects by increasing β_2-adrenergic signaling in the joint and secondary lymphoid organs. In addition, the nonpsychotropic cannabinoid, cannabidiol (CBD) demonstrated antiarthritic effects independent of cannabinoid receptors. In addition to controlling inflammation, cannabinoids reduce pain by activating central and peripheral CB_1, peripheral CB_2 receptors and CBD-sensitive noncannabinoid receptor targets.

Summary
Cannabinoids might be a suitable treatment for RA, but it is important to target the right receptors in the right place. For clinical studies, we propose a combination of a CB_2 agonist to decrease cytokine production, a peripheral CB_1 antagonist to prevent detrimental CB_1 signaling and to support anti-inflammatory effects of CB_2 via activation of β_2-adrenergic receptors and CBD to induce cannabinoid-receptor-independent anti-inflammatory effects.

Keywords
cannabidiol, cannabinoid, cytokines, rheumatoid arthritis, tetrahydrocannabinol

INTRODUCTION

Cannabis has been used for millennia as treatment for a wide variety of diseases such as depression, impotence, arthritis and kidney stones [1]. From the beginning of the 19th century until its complete ban in the United States in 1970, the psychopharmacological effects of cannabis were described in detail and phytocannabinoids were included in many pharmaceutical products. Significantly, the opioid sparing effect of cannabinoids was already known at the beginning of the 20th century and therefore, the plant was also used to treat opioid dependence [1].

Cannabis sativa contains over seventy different cannabinoids, with tetrahydrocannabinol (THC) and the nonpsychotropic cannabidiol (CBD) being the most prominent and best characterized [2]. Although THC mainly binds and activates the two cannabinoid receptors in humans, cannabinoid type 1 and 2 receptors (CB_1 and CB_2), CBD acts as a negative allosteric modulator at CB_1 and CB_2, limiting the effects of THC, but it also binds and activates several transient receptor potential (TRP) ion channels, orphan G-protein coupled receptors (GPCRs) and it is involved in serotonergic neurotransmission [3▪,4▪,5,6▪▪,7,8]. Most effects of cannabis formulations are attributed to activation/modulation of CB_1 and CB_2. Although CB_1 is the predominant cannabinoid receptor in the central nervous system, CB_2 is distributed mainly in the periphery with high expression in immune cells [9,10]. In the central nervous system, cannabinoid

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KEY POINTS

- CB_2 activation mediates anti-inflammatory effects in RA by decreasing immune cell migration and cytokine production.
- CB_1 activation promotes proinflammatory effects in immune cells, but reduces pain and depression.
- CB_1 antagonists provide anti-inflammatory effects by enhancing β_2-adrenergic signaling in arthritis.
- CBD is effective in reducing inflammation and pain and might enhance the efficacy of therapeutic drugs.
- A cannabinoid-based RA therapy would preferentially activate CB_2, inhibit CB_1 peripherally and include CBD to target noncannabinoid pathways.

receptors regulate neurotransmitter release and, depending on their concentration, modulate inhibitory and excitatory neurotransmission [11,12▪]. Peripheral effects of cannabinoids include modulation of pain pathways, cytokine and immunoglobulin production, control of immune cell migration and control of glucose/energy supply [13–18,19▪▪,20].

The endogenous ligands for CB_1 and CB_2 are termed endocannabinoids with 2-arachidonylglycerol (2-AG) and anandamide (AEA) being the most prominent compounds [21,22]. Like phytocannabinoids, the action of endocannabinoids is not restricted to cannabinoid receptors but they also modulate TRP channels, gamma-aminobutyric acid receptors and several GPCRs [8,23,24]. Although the effects of exogenous cannabinoids are long lasting, endocannabinoids are rapidly (within minutes) inactivated enzymatically. Fatty acid amide hydrolase (FAAH) is the main degrading enzyme for AEA, while 2-AG is deactivated by monoacylglycerol lipase amongst others [25,26]. Significantly, AEA and 2-AG can also be metabolized by oxygenases, especially cyclooxygenase-2 (COX-2), yielding novel compounds with a pharmacology different from the parental endocannabinoids [27]. This mechanism might be especially important in (chronic) inflammatory situations where endocannabinoid metabolism might be diverted to COX-2, which is upregulated by proinflammatory cytokines [28]. In line with this, dual inhibitors for FAAH and COX-2 have been developed that synergize in increasing endocannabinoid levels [29].

Due to their anti-inflammatory effects, (endo-)cannabinoids have been considered as a potential therapy for the treatment of rheumatic diseases. However, at the moment there is no significant evidence for the efficacy of cannabinoid-based drugs in the treatment of rheumatoid arthritis (RA), although it is included in the list of conditions eligible for receiving medical cannabis in Canada and several US states and the majority of patients with arthritis reported beneficial effects of the drug, for example less pain and an opioid-sparing effect [30,31▪,32]. Although human data are lacking, cannabinoids have been used in animal models of arthritis providing evidence for their clinical efficacy [33–36]. In this review, we discuss possible antiarthritic effects of cannabinoids and we hypothesize that cannabinoids might also help controlling RA-associated comorbidities (e.g. insulin resistance, hypertension) which is of special importance as they contribute to the increased mortality of RA patients [37].

DIRECT EFFECTS OF CANNABINOIDS ON THE IMMUNE SYSTEM: IT CAN GO EITHER WAY

RA is characterized by immune cell infiltration into the joint, augmented cytokine and chemokine production by resident fibroblasts and macrophages and cartilage destruction by matrix degrading enzymes [38,39]. Consequently, current RA therapeutics (including glucocorticoids) often interfere with cytokine production or signaling but are often associated with side effects related to infection or immune disturbances [40–42]. Therefore, reduction of proinflammatory cytokine production and signaling without an overt risk of infection would be a preferable treatment of RA. In vitro data and results from animal experiments suggest that cannabinoids might help with just that. Early studies in the 1970s already demonstrated that THC inhibits macrophage function [43,44]. In later experiments, it was demonstrated that CB_2 is the target receptor in macrophages to mediate anti-inflammatory effects. CB_2 reduces the activation of the NLRP3 inflammasome and subsequent IL-1β release, enhances clearance of apoptotic cells and generally decreases cellular activation in response to tumor necrosis factor (TNF) or lipopolysaccharide (LPS) [45–48]. Recently, the importance of CB_2 in RA development was emphasized by the finding that a loss-of function gene polymorphism increased the risk for disease 10 fold [49▪]. In addition, inhibiting AEA degradation with subsequent increase in CB_2 activation reduced arthritis score and progression in a mouse model of mice with collagen-induced arthritis [36]. In contrast to CB_2, CB_1 induces proinflammatory effects by promoting macrophage M1 polarization, generation of reactive oxygen species, fibrosis and enhancing TLR4 signaling [50,51▪▪, 52,53]. This might be prevented by the use of CB_1

antagonists, but unfortunately, brain penetrable CB_1 antagonists, like rimonabant, demonstrated psychiatric side effects which led to discontinuation of the drug [54]. This was followed by the development of peripherally restricted CB_1 antagonists which might circumvent these central side effects [55].

Similar effects of cannabinoids have been demonstrated with cells from the adaptive immune system. In T cells, proliferation, differentiation and nuclear factor kappa-light-chain-enhancer of activated B cells activity were inhibited, while in B cells, migration, cellular energy supply and response to T-cell-independent antigens were modulated by CB_2 activation [56–59].

Although THC regulates several aspects of adaptive and innate immunity, an involvement of cannabinoid receptors is questionable as high concentrations of THC were necessary to elicit anti-inflammatory effects and effects were not shown to be inhibited by CB_1/CB_2 antagonists [60–63]. Although the mechanism of action is still unclear, CBD and its analogues demonstrated promising results in combating chronic inflammation in RA [33,35]. CBD induces regulatory T cells, activates and desensitizes several TRP ion channels, ligates peroxisome proliferator-activated receptor-γ and binds several other orphan GPCRs which might explain its complex pharmacology [4▪,7,64–66]. Like CBD, endocannabinoids engage several cellular targets other than cannabinoid receptors and some anti-inflammatory effects are attributed to activation of noncannabinoid related pathways [67].

When considering direct therapeutic effects of cannabinoids for the treatment of RA, it can be concluded that CB_2 agonists induce beneficial anti-inflammatory effects by downregulating pro-inflammatory cytokine production and reducing mobilization and migration of immune cells to sites of inflammation CB_1 agonists promote proinflammatory signaling and noncannabinoid, but endocannabinoid and phytocannabinoid (CBD)-sensitive receptors mediate anti-inflammatory effects.

In this respect, a combination of a CB_2 agonist and a peripherally restricted CB_1 antagonist together with CBD would hypothetically be an optimal combination to combat excessive inflammation and cytokine production in RA. Significantly, compounds with both, agonistic action at CB_2 and antagonistic action at CB_1, have already been described but not yet tested in models of chronic inflammation [68]. Similar therapeutic effects might be achieved by combining an endocannabinoid degradation inhibitor (preferentially a FAAH inhibitor) with a CB_1 antagonist.

INDIRECT ACTIONS OF CANNABINOIDS: TARGETING COMORBIDITIES IN RHEUMATOID ARTHRITIS

In addition to having direct effects on immune cells, cannabinoids might exert many additional effects on chronic inflammation via modulation of the sympathetic nervous system (SNS) and its neurotransmitters. It has already been demonstrated that anxiolytic and antidepressant effects or side effects of cannabinoids are dependent on the modulation of noradrenergic and serotonergic neurotransmission [12▪]. In addition, the beneficial effects of CB_1 antagonism in a murine model of arthritis was dependent on intact β2-adrenergic signaling and CB_1 was found to form dimers with β2- adrenergic receptor [69,70].

Many RA patients suffer from comorbidities such as depression and cardiovascular events and it has been shown that hypertension and osteoporosis correlate with disease activity [71,72]. Decreased parasympathetic and an increase in sympathetic activity is one cause for the development of these conditions and, as they counteract neurotransmitter imbalances, cannabinoids might help in this respect [73–75]. In animal models, systemic activation of the SNS at the early phase of arthritis constitutes a proinflammatory signal as it mobilizes leukocytes, increases antigen uptake/presentation and provides energy to the immune system [76]. In addition, direct anti-inflammatory effects of sympathetic neurotransmitters on immune cells in the joint are blunted due to the repulsion of sympathetic nerve fibers from the site of inflammation [77]. In the later phase of the disease, compensatory, catecholamine-producing cells appear in the joint whose ablation aggravates experimental arthritis [78]. The question arises, how would cannabinoids interfere with the SNS in RA?

Cannabinoids modulate the outflow of sympathetic neurotransmitters centrally and peripherally through CB_1 and in the early phase of arthritis or to postpone clinical symptoms, reduction of SNS activity might be beneficial [12▪]. Hypertension is a widespread problem in RA and it is often accompanied by insulin resistance and metabolic disturbances [79]. Activation of CB_1 reduces blood pressure and this effect was due to a reduction in noradrenergic tone [80]. Significantly, the consumption of cannabis is also associated with lower risk of metabolic syndrome and diabetes and might therefore prevent the RA-induced changes in metabolism [81]. This seems paradoxical as cannabis is known for its stimulating effect on food intake, but due to the partial agonsim of THC, it also acts as antagonist for endocannabinoids [82,83]. In addition, CB_1 desensitizes and downregulates rather quickly resulting in functional antagonism even in the presence of agonist although

the rate and speed of this process is dependent on cell type and context [84]. Although CB_1 agonism might have some beneficial effects in the treatment of RA comorbidities, CB_1 antagonists are better suited to directly target inflammation in RA. Indeed, it has been shown that the anti-inflammatory effect of peripherally restricted CB_1 antagonists is dependent on intact adrenergic signaling in the spleen. CB_1 antagonism increases adrenergic β_2 signaling which reduces TNF production and arthritis severity [70]. In addition, metabolic changes due to low level systemic inflammation in RA might be diminished with CB_1 antagonists. In fact, this has been observed in the treatment of obesity and CB_1 antagonists improved insulin levels, lowered blood glucose and promoted a lean phenotype [82]. Another mechanism by which CB_1 antagonism might contribute to an anti-inflammatory phenotype in RA is by increasing local norepinephrine levels in joint and spleen that allow β-adrenergic signaling [70,85]. Norepinephrine has higher affinity for proinflammatory α-adrenergic receptors than for β-receptors resulting in mostly proinflammatory α-effects under low levels of norepinephrine [86]. As sympathetic nerves are repelled from the joint in the course of RA, norepinephrine levels are low serving an α-adrenergic dependent, proinflammatory role [77]. Like in the LPS-induced arthritis mouse model [70], use of a CB_1 antagonist might be able to increase intraarticular norepinephrine concentrations due to disinhibition at sympathetic nerve terminals recovering anti-inflammatory β-adrenergic effects. Although not tested experimentally, catecholamine-producing cells that appear in the course of arthritis might also be modulated by cannabinoids. The presence of the monoamine transporter VMAT2 suggests that catecholamines are stored in vesicles in tyrosine hydroxylase positive, catecholaminergic cells and their release might be under the control of CB_1 just like their neuronal counterparts [87]. If this is true, CB_1 activation would counteract catecholamine release and promote α-adrenergic, proinflammatory effects while CB_1 inhibition would be beneficial by increasing catecholamine levels, thereby promoting β-adrenergic effects.

CANNABINOIDS AND PAIN

The reduction of neuropathic and cancer pain are known indications for the use of cannabinoids and three cannabis-based drugs (Nabilone, Sativex and Marinol) are used clinically for this purpose [88,89]. Although there are only very limited clinical data on the effect of cannabinoids on arthritic pain, reports from patients show that a significant number uses cannabis to treat their symptoms [90]. In addition one study investigated the effects of sativex, a combination of CBD and THC, in arthritis patients and this drug demonstrated a significant analgesic effect with mild adverse events like dizziness, but these did not lead to withdrawal from the study [91]. Although data from RA patients regarding cannabinoid effects are scarce, models of arthritic, inflammatory and neuropathic pain demonstrated a clear reduction of pain and allodynia when animals were treated with cannabinoids [92,93,94▪]. In addition, data from human cohorts suggest at least limited efficacy of cannabis-based products on neuropathic pain [95]. Cannabinoids modulate pain by activating CB_1 and CB_2 receptors but some compounds also directly ligate the nociceptors TRP vanilloid 1 (TRPV1) and TRP Ankyrin 1 (TRPA1) [92,94▪,96]. Although CB_1 desensitizes nociceptors like the capsaicin receptor TRPV1 directly, CB_2 might reduce pain by inhibiting proinflammatory cytokine production and immune cell infiltrates that promote nociceptor function [97]. In addition, it has been demonstrated that CB_2 activation induces the peripheral release of β-endorphin, which might contribute to CB_2-induced analgesia [98,99]. Furthermore, CB_2 might functionally interact with peripheral μ-opioid receptors to induce antinociception and animals treated with a CB_2 agonist along with morphine showed additive analgesic effects [100]. Although CB_2-mediated analgesia is peripherally restricted, CB_1 reduces pain by peripheral and central mechanisms [101]. TRPV1 is a direct target of cannabinoids but it is also an ionotropic receptor for endocannabinoids [97,102,103]. AEA is able to desensitize TRPV1 and animals with complete FAAH inhibition demonstrate increased pain thresholds and TRPV1 antagonists or desensitizing agonists resulted in decreased proinflammatory cytokine production by macrophages [104–107]. Cannabinoids also support opioid-induced analgesia and it has been demonstrated that a combination of low dose THC with morphine prevents μ-opioid receptor desensitization and provides superior pain relief [89,108].

In addition to CB_1 and CB_2, other pathways are involved in cannabinoid-induced nociception. It has been shown that the nonpsychotropic phytocannabinoid CBD promotes analgesia by activating serotonin $5\text{-}HT_{1a}$ and TRPV1 receptors while AEA provides additional analgesic effects via peroxisome-proliferator activated receptor α [109▪,110].

CONCLUSION: WHAT WOULD BE A PREFERABLE CANNABINOID-BASED TREATMENT FOR RHEUMATOID ARTHRITIS?

CB_1 activation is accompanied by central, psychotropic side effects but also by peripheral,

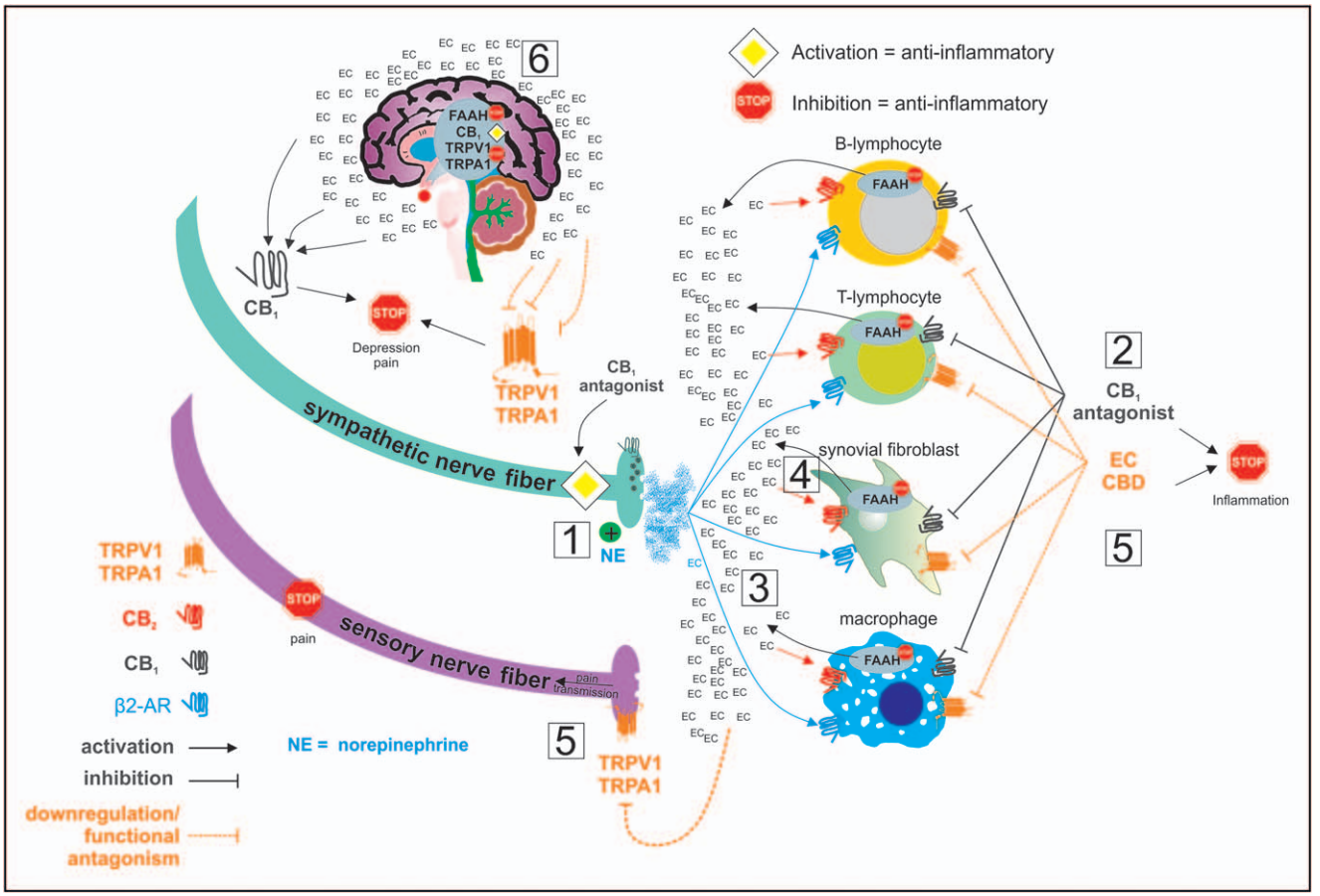

FIGURE 1. Consequences of a peripherally restricted cannabinoid type 1 receptor antagonist combined with cannabidiol and a fatty acid amide hydrolase inhibitor on arthritic pain and inflammation. (1) Use of a peripherally restricted cannabinoid type 1 receptor antagonist increases local norepinephrine release and promotes anti-inflammatory β2-adrenergic signaling (indicated by the yield sign). (2) In addition, proinflammatory cannabinoid type 1 receptor signaling on immune cells is inhibited while anti-inflammatory effects are enhanced (indicated by the stop sign). (3) Fatty acid amide hydrolase inhibition increases systemic endocannabinoid levels. (4) This is accompanied by an increase in anti-inflammatory cannabinoid type 2 receptor signaling in macrophages, synovial fibroblasts, B cells and T cells. (5) Endocannabinoids but also cannabidiol desensitize and therefore inhibit the nociceptors TRP vanilloid 1 (TRPV1) and transient receptor potential Ankyrin 1 (TRPA1) which supports antiinflammation in immune cells but also inhibit pain transmission in sensory nerves. (6) Fatty acid amide hydrolase inhibition also increases central endocannabinoid levels. This allows for central, cannabinoid type 1 receptor signaling and inhibition of TRP channels resulting in pain relief and attenuation of depressive symptoms. TRP, transient receptor potential.

pro-inflammatory effects on immune cells that limit their clinical use [50,111]. In contrast, CB_1 activation provides pain relief and improves mood and one possibility to selectively activate mostly beneficial CB_1 pathways is by the means of FAAH inhibition. It has been shown that in contrast to THC, FAAH inhibition does not produce adverse effects but still promotes antidepressive behavior and analgesia [112–114]. Peripheral FAAH inhibition shares some of the negative effects of CB_1 activation in respect of metabolic changes and should therefore be avoided [115]. To prevent peripheral CB_1 activation a FAAH inhibitor might be combined with a CB_1 antagonist. With this combination, anti-inflammatory effects would be augmented: FAAH inhibition elevates endocannabinoid levels in the brain that counteract depression and pain, while CB_1 antagonism in the periphery inhibits detrimental, pro-inflammatory CB_1 effects while boosting anti-inflammatory effects by increasing sympathetic nervous activity (Fig. 1). FAAH inhibition also enhances anti-inflammatory CB_2 signaling due to enhanced levels of AEA [36] (Fig. 1). In addition, CBD might be added to RA therapy, as it elicits antidepressive and anti-inflammatory effects independent of cannabinoid receptors and without psychotropic side effects. In arthritis animal models, CBD provided pain relief and reduced inflammatory

cell infiltrates into the joint [116]. Furthermore, CBD might boost the effect of antirheumatic drugs as it has been shown that it increases the uptake of chemotherapeutic compounds into cancer cells [7].

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Conflicts of interest

There are no conflicts of interest.

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