Received: 22 February 2022 | Revised: 14 March 2022 | Accepted: 15 March 2022

DOI: 10.1002/msc.1636

CLINICAL ARTICLE

WILEY

Cannabinoids in rheumatology: Friend, foe or a bystander?

Nibha Jain[1,2] | Arumugam Moorthy[2,3,4,5]

[1]Department of Rheumatology, University of Leicester, Leicester, UK

[2]University Hospitals of Leicester NHS Trust, Leicester, UK

[3]College of Life Sciences, University of Leicester, Leicester, UK

[4]Tamil Nadu Dr MGR Medical University, Chennai, India

[5]New Vision University, Georgia

Correspondence
Arumugam Moorthy, Department of Rheumatology, University Hospitals of Leicester NHS Trust, Leicester, UK; College of Life Sciences, University of Leicester, Leicester, UK.
Email: moorthyarumugam@hotmail.com

Abstract

Objectives: Cannabinoids have gained popularity recently with special emphasis on their use for chronic pain. Although NICE guidelines advise against their usage for management of chronic pain, almost all rheumatologists encounter a few patients in their daily practice who either use them or are curious about them.

- We reviewed the mechanism of action of cannabinoids, current knowledge about their role in rheumatology and potential drug interactions with common drugs used in Rheumatology.
- We attempted to answer the question "If cannabinoids are friend, foe or just a mere bystander?"

Methods: We adhered to a search strategy for writing narrative reviews as per available guidelines. We searched PubMed with the search terms "Cannabinoids", "Rheumatology" and "Chronic pain" for published articles and retrieved 613 articles. The abstracts and titles of these articles were screened to identify relevant studies focusing on mechanism of actions, adverse effects and drug interactions. We also availed the services of a musculoskeletal librarian.

Results: Despite the NHS guidelines against the usage of cannabinoids and associated significant stigma, cannabinoids are increasingly used for the management of pain in rheumatology without prescription. Cannabinoids act through two major receptors CB1 and CB2, which are important modulators of the stress response with potential analgesic effects. Their role in various rheumatological diseases including Rheumatoid arthritis, Osteoarthritis and Fibromyalgia have been explored with some benefits. However, in addition to the adverse effects, cannabinoids also have some potential interactions with common drugs used in rheumatology, which many users are unaware of.

Conclusion: While the current studies and patient reported outcomes suggest cannabinoids to be a "friend" of rheumatology, their adverse events and drug interactions prove to be a "Foe". We were unable to arrive at a definite answer for our question posed, however on the balance of probabilities we can conclude cannabinoids to be a "foe". Under these circumstances, a disease and drug focussed research is need of the hour to answer the unresolved question.

KEYWORDS
cannabinoids, chronic pain, complementary medicine, drug interaction of cannabinoids, fibromyalgia, medical cannabis

1 | INTRODUCTION

Recently there has been a lot of interest among patients and clinicians regarding the use of cannabinoids for management of chronic pain in rheumatology. Presently, there is limited research on therapeutic indications particularly in pain due to chronic rheumatological conditions. Despite frequent discussions in the media about the use of cannabinoids as therapeutic option in chronic pain, physician's perspective on using such therapies and their knowledge of cannabinoids are unknown.

Cannabinoids are licenced for use in certain medical conditions such as spasticity in adults with multiple sclerosis (MS), treatment-resistant epilepsy (Dravet and Lennox-Gastaut syndromes) and refractory vomiting secondary to chemotherapy (NICE, 2019). Cannabinoids are available both legally and through alternative sources in several forms such as cannabidiol (CBD) oils, tablets, cakes and coffee that are widely used by rheumatology patients.

Management of chronic pain is an integral part of rheumatology with limited options to date.

There is a need of the hour for alternative therapies which can modulate pain and enable a better quality of life in our patients. Many healthcare professionals come across patients asking about the efficacy of cannabinoids in the management of chronic pain with some sharing their personal or friends'/families' experience. Many clinicians have even faced patients requesting a prescription of cannabinoids. Guidelines in the United Kingdom still do not advocate the use of cannabinoids for management of chronic pain, as there is a paucity of research and randomised control trials (RCT).

NICE (NG144) does not recommend cannabis-derived products for the management of chronic pain in adults with the conclusion that the available evidence is modest in comparison to the high cost (NICE, 2019).

In the absence of any consistent guidelines and recommendations for cannabinoid usage in rheumatology, we performed a comprehensive literature search for evidence of the efficacy, tolerability and safety of cannabinoids, including mechanism of action and drug interactions with commonly used medications in rheumatology.

2 | METHODS

We undertook a detailed review of the use of cannabinoids in rheumatology including their mechanism of action, adverse effects and drug interactions.

We adhered to a search strategy for writing narrative review. We searched PubMed with the search terms 'Cannabinoids', 'Rheumatology' and 'Chronic pain' in articles published and retrieved 613 results. The abstracts and titles of these articles were screened to identify relevant studies and articles. Besides, we also took help from the musculoskeletal librarian of our department.

This review focuses on the mechanism of action of cannabinoids, current knowledge about their role in rheumatology, adverse effects and potential drug interactions.

2.1 | The legal status of cannabinoids in the United Kingdom

Cannabis are currently controlled drug as classified by the Misuse of Drugs Act 1971 (Crime, Policing and Fire Group (CPFG) Drugs and Alcohol Unit, 2018). Medical use of cannabis are legal in the United Kingdom for specific indications (CPFG Drugs and Alcohol Unit, 2018). The NHS guidance states that medical cannabis can be prescribed only with clear published evidence and when other options have been exhausted.

Initial prescription of cannabis-based medicinal products must be made by a specialist medical practitioner with a special interest in the condition being treated (NICE, 2019).

Subsequent prescriptions may be issued by another prescriber (including primary care) as part of a shared care agreement under the direction of the initiating specialist prescriber.

CBD, on the other hand, are classified as novel food substance since January 2019 and would require Food Safety Agency approval from 2021. They are legal for use and sale in the United Kingdom without the requirement of a doctor's prescription, provided these medications do not contain more than 1 mg tetrahydrocannabinol (THC; Food Standard Agency, 2021; Milando & Friedman, 2019).

Licences for CBD oils as medicine have not been granted; however, these products can still be sold as long as no claims about their medical benefits are made.

Sativex, which is a 50-50 mix of THC and CBD, has been approved for use in the United Kingdom as a treatment for spasticity associated with multiple sclerosis (CPFG Drugs and Alcohol Unit, 2018; NICE, 2019).

2.2 | Perception towards complimentary medicine

Complimentary medicine including cannabinoids are widely used across various specialities. In our cross-sectional survey on the use of complimentary medicine in rheumatology, 31.8% patients reported using alternative therapies for pain management (Tharakan et al., 2019).

One self-reported study on the prevalence of cannabinoid use in fibromyalgia patients reported 13% of all patients use cannabinoids, with 80% using herbal cannabis (marijuana), 24% using prescription cannabinoids, and three percent using both herbal cannabis and prescription cannabinoids (Ste-Marie et al., 2012).

2.3 | The stigma attached in the general population

There is a significant stigma attached to the use of cannabinoids. Most of it stems from negative addictive and psychological impact due to the THC component of cannabis. In a study exploring the experiences of therapeutic cannabinoid users, it was found that stigma arose significantly in interactions with family members and close friends, as well as from others in society (Bottorff et al., 2013).

These findings suggested complex and overlapping factors that result in stigmatisation experienced by cannabinoid users due to the ambiguous status of cannabis, lack of acknowledgement about medical cannabis and stigma associated with health disorders. While there is a gradual public acceptance, there continues to be a stigma at interpersonal and institutional levels (Bottorff et al., 2013). Stigma stems from external and internal sources. External sources include friends, family, healthcare providers and law enforcement, while the internal sources are that of guilt and discomfort related to using a medication that is often used illegally and for recreational purposes. Thus, there is an overt need for further research and education regarding the potential use of cannabinoids as therapeutic targets.

2.4 | Forms of cannabinoids currently available

Cannabis plants (*Cannabis sativa*) are made up of more than 100 different cannabinoids, having different effects on the body with variable concentrations present in different parts of the plant. Their cultivation and utilisation can be traced back to 10,000 BC with the first evidence of their medicinal use as an analgesic in 4000 BC (Warf, 2014). Most common forms known are CBD and THC. THC is the component responsible for psychoactive effects. CBD does not have any psychoactive effect.

2.5 | Mechanism of action

2.5.1 | Pharmacokinetics

Knowledge of the pharmacokinetics of any drug is essential to understand the onset, magnitude and duration of their pharmacodynamic effects, to maximise therapeutic and minimise negative side effects.

Oral bioavailability of CBD are around 6% while smoking provides around 2%–56% (Huestis, 2007). Inhalation through a vapouriser has a rapid therapeutic effect, whereas oral ingestion has a slower but more sustained effect (Huestis, 2007).

When used topically, the permeability of CBD were found to be 10-fold higher than for THC. Similarly, Sativex (CBD: THC) when administered through oro-mucosally route, resulted in lower plasma levels of THC compared to inhalation at similar doses (Huestis, 2007). Transdermal delivery of cannabinoids bypasses the first-pass metabolism and have delayed onset with lower peak concentrations. The drug-abuse potential of cannabinoid transdermal patches are expected to be lower due to slow delivery of THC to the brain (Huestis, 2007).

CBD and THC metabolism are similar, with primary oxidation of C(9) to alcohol and carboxylic acid as well as side-chain oxidation in liver. They are subjected to first-pass metabolism. Unlike THC, a large proportion of CBD dose are excreted unchanged in the faeces (Huestis, 2007).

2.6 | Endocannabinoid system

The endocannabinoid system is an important modulator of the stress response with potential analgesic effects. This plays an important role in re-establishing equilibrium after stress or 'fight or flight' event. The reversal in equilibrium is the potential target for reducing pain and inflammation and hence a prospective therapeutic target in rheumatology.

The signalling system encompasses cannabinoid receptors, endocannabinoids (endogenous ligands of cannabinoid receptors) and enzymes regulating the biosynthesis and inactivation of endocannabinoids.

The molecules that affect cannabinoid or related receptors can be found in the following settings: endogenous ligands also known as endocannabinoids that are lipid mediators termed as eicosanoids (arachidonic acid derivatives); exogenous plant-derived phytocannabinoids and synthetic tricyclic terpenes (Table 1).

Currently, the most researched endocannabinoid ligands are arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG). AEA is largely synthesised by N- acyltransferase and N-acyl-phosphatidylethanolamine-hydrolysing phospholipase D. 2-AG is synthesised by diacylglycerol lipase. Degradation of these ligands occurs by hydrolysis or oxygenation. AEA is degraded by fatty-acid amide hydrolase (FAAH) and 2-AG is degraded by monoacylglycerol lipase. Cyclooxygenase-2, lipoxygenases or cytochrome P450 (CYP) enzymes, on the other hand, are responsible for oxygenation (Yamaori et al., 2012).

Cannabinoid receptors (CB) function through G proteins having an effect on the mitogen-activated protein (MAP) kinase pathway and inhibition of adenylyl cyclase activity. They activate potassium channels and inhibit voltage-gated sodium channels thereby inhibiting the neurotransmitter release at the synapse.

There are two primary receptors CB1 and CB2 with heterogeneous and sometimes opposite actions (Figure 1).

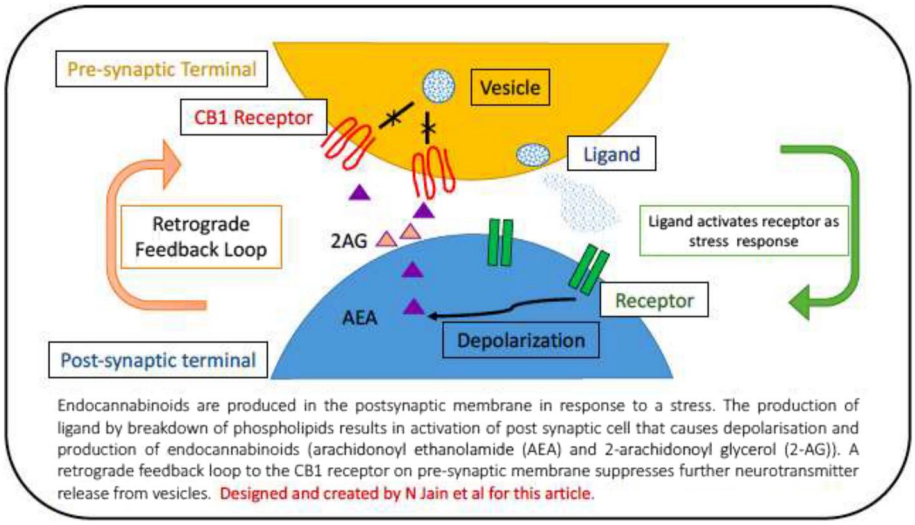

FIGURE 1 Endocannabinoid Signaling through Cannabinoid receptors

TABLE 1 Cannabinoid receptor ligands

1. Endogenous	• 2-Arachidonoyl glycerol (2-AG)—endogenous agonist of cannabinoid receptor 1 (CB1) and CB2
	• Anandamide arachidonoyl ethanolamide (AEA)—endogenous agonist of CB1 and CB2
2. Exogenous (phytocannabinoids)	• (–)-trans-Δ9-Tetrahydrocannabinol (THC)—primary psychoactive constituent.
	• Cannabidiol—non-psychoactive phytocannabinoid component
3. Synthetic tricyclic terpenes	• Nabiximols—natural THC and cannabidiol extracted from cannabis
	• Nabilone—synthetic cannabinoid resembling THC
	• Dronabinol—synthetic THC
	• JWH-015—CB2 agonist
	• JWH-133—CB2 agonist
	• HU-308—CB2 agonist
	• WIN 55,212-2 mesylate—CB1 and CB2 agonist
	• SR141716A—CB1 antagonist
	• VCE-004.8—Peroxisome proliferator-activated receptor-γ (PPARγ) and CB2 agonist
	• GP1a—CB2 agonist
	• O-1966—B2 agonist
	• Ajulemic acid—derivate of a non-psychoactive THC metabolite

2.6.1 | Cannabinoid receptor 1

CB1 is primarily present in the frontal cortex, basal ganglia and cerebellum. It is responsible for the psychotropic effects of cannabis. Other areas involved in motor control, memory and cognition express CB1 receptors (Guindon & Hohmann, 2009; Pagotto et al., 2006; Sido et al., 2015).

CB1 receptors are also found in chondrocytes and osteocytes derived from human joints. There are evidence that suggest CB1 facilitates the adhesion of fibroblast-like synoviocytes (FLSs) to fibronectin and reduce the migratory capacity of these cells. This may possibly decrease the cartilage destruction (Sido et al., 2015).

The effects of the CB1 receptor on the brain are mostly facilitated by retrograde signalling (also known as retrograde neurotransmission). Retrograde signalling is induced by the depolarisation of the postsynaptic cell, resulting in the postsynaptic production and release of endocannabinoids, which in turn activate presynaptic CB1 receptors (Castillo et al., 2012). Overall, CB1 activation exerts an inhibitory effect on the presynaptic cell (Figure 1).

2.6.2 | Cannabinoid receptor 2

CB2 receptors function similarly to CB1 and are mostly located peripherally on immunologic cells and musculoskeletal cells.

CB2 is primarily known for its expression on immune cells, chondrocytes, osteocytes, fibroblasts and FLSs (Aghazadeh Tabrizi et al., 2016; Gui et al., 2014).

2.6.3 | Other cannabinoid receptors

Transient receptor potential cation channel subfamily V member 1 (TRPV1) is a ligand-activated cation channel, regarded mainly as a pain receptor. It is expressed on the C-fibre and Aδ sensory neurons. Cannabinoids, including AEA, CBD and cannabigerol, have agonistic effects on TRPV1 (Pertwee et al., 2010). CB1 activation can cause reduction in TRPV1 activity leading to reduction in IL-6 secretion from sensitised FLSs, highlighting the potential connection between TRPV1, the endocannabinoid system and rheumatic diseases (Pertwee et al., 2010).

G protein-coupled receptor 55 (GPR55) is referred by some researchers as a 'CB3′ receptor. GPR55 was first discovered as an orphan G protein-coupled receptor, with evidence of its expression in the central nervous, immune and gastrointestinal systems as well as on articular surface tissues (Dunn et al., 2016).

Peroxisome proliferator-activated receptor-α (PPARα) is a fatty-acid-activated transcription factor. It is predominately expressed on skeletal muscles with some degree of hepatic expression, PPARα is also designated site of action for fibrates (fibric acid derivatives used in the treatment of hypercholesterolaemia; Pertwee et al., 2010). Apart from muscular and hepatic expression, PPARα is expressed on human chondrocytes and osteocytes (Dunn et al., 2016). An association between PPARα and the endocannabinoid system is verified by evidence that PPARα is stimulated by AEA, THC and WIN 55,212-2 mesylate (Pertwee et al., 2010).

To summarise, a fine balance exists between the effects of cannabis substances on CB1 and CB2 receptors, resulting either in psychoactive or immunomodulatory effects, respectively (Figure 2).

2.7 | Musculoskeletal pain

In a critical review of cannabinoids in the management of musculoskeletal pain (Maccarrone et al., 2015), 118 studies were included. Out of the studies included, 56% were observational with evidence of Level-II or below. Of these, 85 (72%) studies indicated cannabis treatment were effective, 17 (14%) demonstrated mixed effectiveness, 11 (9%) indicated that cannabinoids are not effective, and 5 (4%) studies demonstrated inconclusive or unclear findings. Majority studies (39%) demonstrated only mild-to-moderate adverse effects, and five studies (15%) demonstrated possible serious adverse effects. This systematic review highlights the relative paucity of high-quality evidence available on the use of cannabinoids for the management of musculoskeletal-related pain. There is a clear knowledge gap as most of the available literature mainly focuses on multiple sclerosis, fibromyalgia and spinal cord injury with a very few published studies in rheumatology.

2.8 | Cannabinoids in rheumatology

Evidence-based medicine regarding the use of cannabinoids in rheumatology is still sparse. The systemic review of four trials including two RCTs with nabilone in 71 fibromyalgia patients, one 4-week study of 30 spinal pain patients and a 5-week study with THC/CBD in 58 rheumatoid arthritis (RA) patients concluded the superiority of cannabinoids over controls (Fitzcharles et al., 2016). However, this conclusion was found to be inconsistent. It also highlighted cannabinoids are superior to placebo in neuropathic pain but not in pain due to rheumatic diseases. In studies with fibromyalgia patients, there was an improvement in pain on the Visual Analogue Scale with some improvement in the mental component of SF36. However, they concluded that the evidence for recommendations and policy are still insufficient, thus prompting the need for further research (Fitzcharles et al., 2016).

We did a detailed literature search for the role of cannabinoids in rheumatological diseases.

2.8.1 | Rheumatoid arthritis

CB2R activation might have immunomodulatory and anti-inflammatory effects in RA and the modulation of endocannabinoid metabolism might represent another target to control inflammation.

In a genetic sequence study on single nucleotide polymorphisms of CB2 cannabinoid receptor and functional consequences in humans, it was found that the presence of the polymorphisms at positions 63 (Q63R) and 316 produce alterations in the CB2 receptor functions (Carrasquer et al., 2010). Furthermore, the cannabinoid agonists WIN55212-2 and 2-arachidonoylglycerol (2-AG) had reduced efficacy in cells that expressed the polymorphic receptors as compared with the CB2 wild-type receptor. Therefore, it was suggested that the CB2 polymorphic receptors may contribute to the aetiology of certain diseases including systemic lupus erythematosus (SLE), myasthenia gravis, RA, osteoporosis and multiple sclerosis (Carrasquer et al., 2010). This study was followed by a preliminary study in Lebanese population that investigated the association between a common dinucleotide polymorphism, Q63R, in the CR2 genes (CNR2) and RA. Genomic DNA extraction followed by polymerase chain reaction was performed in 105 RA patients and 105 controls. The CNR2 was genotyped in a blinded fashion and showed significantly higher frequencies of the CB2-R63 variant in RA patients when compared with healthy controls. Moreover, RR carriers had more than 10-fold risk for developing RA, and QR carriers had more than threefold risk as compared with QQ carriers. Thus, this study demonstrates some role of CB2-Q63 R gene polymorphism in the

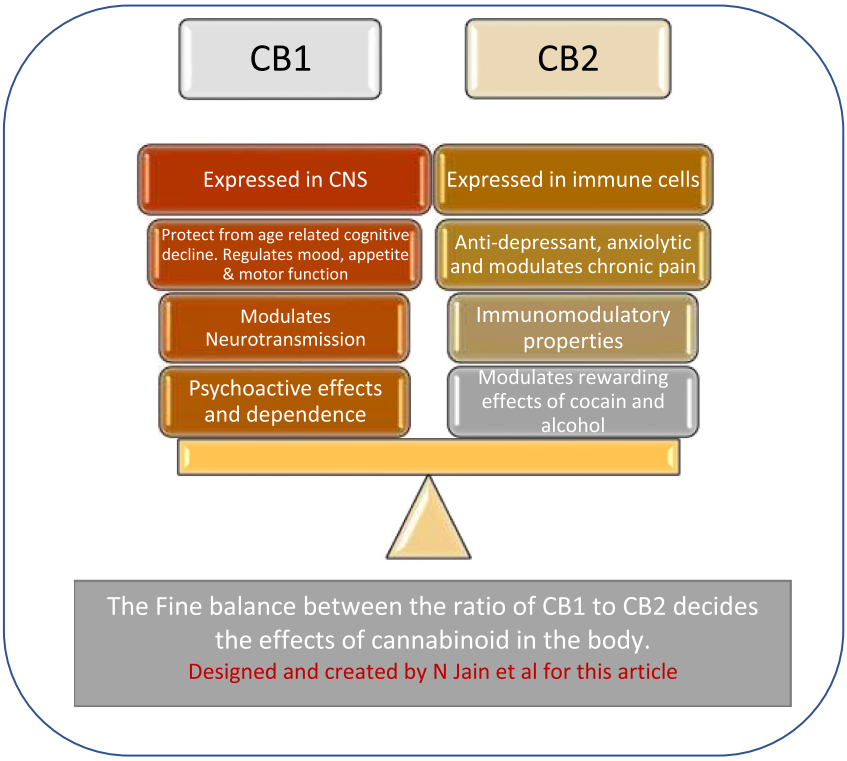

FIGURE 2 Difference in properties of cannabinoid receptors and fine balance between them

aetiology of RA, supporting their potential use as a pharmacological target for selective agonists in clinical practice (Ismail & Khawaja, 2018).

Expression of CB2R in synovial tissue and FLS have also been studied. The studies found that both the mRNA and protein expression of CB2R were present in synovial tissue and cultured FLS with a slightly higher level in RA patients as compared to OA patients. In cultured RA-FLS, the expression of CB2R was up-regulated on stimulation with IL-1β, TNF-α or lipopolysaccharide. It was concluded that in RA-FLS, the CB2R expression gets upregulated by the pro-inflammatory mediators, thereby negatively regulating the pro-inflammatory cytokines and matrix metalloproteinases production, suggesting the role of CB2R as a potential therapeutic target for RA (Gui et al., 2014).

Another study showed CB2 expression upregulation in collagen-induced arthritis (CIA) mice synovium and bone tissues (Zhu et al., 2019). It also exhibited that CB2 selective agonist (JWH133) suppressed arthritis in mice by the decreasing synovial hyperplasia, inflammatory responses, cartilage damage, periarticular and systemic bone destruction. JWH133 treatment also decreased infiltration of pro-inflammatory M1-like macrophages. Activation of CB2 was shown to increase the expression of anti-inflammatory cytokine interleukin (IL)-10 and reduced the expression of pro-inflammatory cytokines, including tumour necrosis factor-α, IL-1β and IL-6. Also, JWH133 treatment reduced osteoclast formation and osteoclastic bone resorption. JWH133 inhibited RANKL-induced NF-κB activation in the osteoclast precursors and decreased pathological bone destruction in CIA mice via the inhibition of osteoclastogenesis and modulation of inflammatory responses (Zhu et al., 2019).

In another study, efficacy of cannabinoid receptor 2 (CB2) agonist JWH-015 using RA synovial fibroblasts (RASFs) and rat adjuvant-induced arthritis (AIA) model of RA was evaluated (Fechtner et al., 2019). It was shown that pre-treatment of human RASFs with JWH-015 markedly inhibited the ability of proinflammatory cytokine IL-1b to induce production of IL-6 and IL-8 and cellular expression of inflammatory cyclooxygenase- 2 (COX-2). JWH-015 was also found to be effective in reducing IL-1b - induced phosphorylation of TAK1 (Thr184/187) and JNK/SAPK in human RASFs. It was also shown that JWH-105 binds to the glucocorticoid receptor (GR), and knockdown of this GR using siRNA terminated JWH-015's ability to reduce IL-1b-induced IL-6 and IL-8 production. In vivo, administration of JWH-015 significantly reduced AIA in rats along with inhibition of bone destruction. This study has shown robust data on anti-inflammatory effects of CB2 agonist JWH-015 through GR and could be a potential adjunct therapy for the management of RA (Fechtner et al., 2019).

Multiple in vitro studies in mice models of RA and RA synoviocytes have shown anti-inflammatory effects of cannabinoids via different pathways. Anti-inflammatory effects of N-acylethanolamines in RA synovial cells was shown via a COX-2-dependent manner (Lowin et al., 2015). In a study by Selvi et al., while IL-1b-induced IL-6 and IL-8 production were inhibited by CBagonist CP-55940, cytokine levels were unchanged when using CB1 and CB2 antagonists, suggesting the presence of alternative anti-inflammatory receptor (Selvi et al., 2008).

The only available clinical study on the use of cannabinoids in RA was done in 58 patients who were treated with the oro-

mucosal spray Sativex and compared to placebo over a 5-week period (Blake et al., 2006). This parallel RCT compared active RA patients on a stable dose of DMARDs. Thirty-one of the eligible patients were randomised to Sativex and 27 to placebo. This study revealed significant improvement in pain assessed using VAS ($p = 0.018$), DAS28 score ($p = 0.02$) and sleep in the active drug group. Limitation of the study included a short follow-up (<6 months) and no clear information on the blinding method. The study was included in the NICE appraisal on the use of cannabinoids in the management of chronic pain.

In clinical practice, there is a lack of robust clinical RCT on the use of cannabinoids. Recently, a double-blinded, randomised, placebo-controlled study of CBD, followed by an open-label add-on of THC has been proposed in RA and spondyloarthritis patients. The oral treatment with CBD in the experimental group will be compared with placebo in a control group for 12 weeks, followed by an observational 12-week period with an open-label add on of THC in the primary CBD non-responders (Hendricks et al., 2019).

2.8.2 | Dermatomyositis

Lenabasum (JBT-101, anabasum), a synthetic, oral preferential CB2 agonist was studied in a double-blinded, 16-week phase 2 RCT of adult DM patients, predominantly having skin involvement with minimal muscle activity (Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI] = 14). Lenabasum was given to 11 patients of DM with 22 controls in two escalating dose levels. Study reported greater improvement in CDASI damage index, to patient-reported global skin disease and overall disease assessments than placebo. No serious, severe or unexpected adverse events (AEs) related to lenabasum were noted (Werth et al., 2018).

2.8.3 | Osteoarthritis

Currently, no formal RCT study about the use of cannabinoids as a disease-modifying anti-osteoarthritis drug exists. As analgesia, a potent FAAH inhibitor, PF-04457845 indicated no significant difference observed in pain control compared to placebo. While PF-04457845 was found to increase AEA in these patients, however, it did not produce any significant analgesic effect (Huggins et al., 2012).

Table 2 innumerates pre-clinical studies of cannabinoids in OA for reducing joint pain. In a recent animal study on Freund's adjuvant-induced monoarthritis knee joint model of rats (Hammell et al., 2016), the efficacy and adverse effects of transdermal CBD were evaluated. They reported significant reduction in joint swelling and pain with decreased immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. No evident side effects were reported. They concluded therapeutic potential of CBDs for pain relief and inflammation in OA.

2.8.4 | Fibromyalgia

In one of the first studies involving 40 patients with FM with a study period of 6 weeks, it was found that nabilone was associated with statistically significant improvements in pain and function with a 2-point reduction in pain score and 12-point reduction in Fibromyalgia Impact Questionnaire score (Skrabek et al., 2008).

Research Institute-Hospital del Mar in Barcelona conducted a trial in 2011 with 28 patients of FM in each group with and without use of cannabinoids. They found the effectiveness of cannabinoids in several symptoms including pain and muscle rigidity (Fiz et al., 2011). However, the small sample size and the short duration of study impede unprejudiced conclusions. The National Academies of Sciences, Engineering and Medicine (United States) concluded there is currently moderate-grade evidence supporting the effectiveness of cannabinoids for the treatment of fibromyalgia (National Academies of Science, Engineering, and Medicine, 2017).

2.8.5 | Psoriasis

Endocannabinoids have been implicated in the pathogenesis of psoriasis. They (AEA, 2-AG) have been found to be expressed in the skin (Wilkinson & Williamson, 2007). AEA inhibits keratinocytes proliferation and promotes cell death through CB1 and TRPV1 activation and Ca influx (Toth et al., 2011). AEA has also shown to downregulate the expression of keratins K6 and K16, which are over-expressed in psoriasis (Ramot et al., 2013). THC and cannabinoids have been shown to reduce the proliferation of keratinocytes (Wilkinson & Williamson, 2007).

There are ongoing research into the possible efficacy of cannabinoids in reducing inflammation in psoriasis (Milando & Friedman, 2019). It could potentially be an innovative topical/oral treatment option for psoriasis.

2.8.6 | Systemic sclerosis

Modest data exist regarding endocannabinoids in SSc. Expression of both CB1 and CB2 in dermal fibroblasts (DFs) has been shown to be increased with their activation inducing inhibition of the transdifferentiation of DFs in myofibroblasts and specialised fibroblasts thereby decreasing the pro-fibrotic behaviour (Garcia-Gonzalez et al., 2009).

Among the many receptors mediating intracellular cascade of the endocannabinoid system, PPAR-γ is of relevance in SSc. Administration of ajulemic acid (AJA), a non-psychoactive synthetic analogue of THC was shown to bind to PPAR-γ and reduce dermal and pulmonary fibrosis thus acting both as an anti-fibrotic and as anti-inflammatory agent (Garcia-Gonzalez et al., 2016). It was also shown to indirectly inhibit NF-κB translocation from cytoplasm to the nucleus thus resulting in reduced production of pro-inflammatory

TABLE 2 Summary of preclinical studies of cannabinoids for the improvement of joint pain in OA

Model	Compound	Mechanism of action	Result	Reference
MIA model of OA (rat)	Arachidonyl-2-chloroethylamide (ACEA)	CB1 agonist	The reduced firing of joint afferent fibres	Schuelert and McDougall (2008)
MIA model of OA (rat)	GW405833	CB2 agonist	Reduced weight-bearing deficits and sensitised joint afferent fibres	Schuelert et al. (2010)
MIA model of OA (rat)	URB597	FAAH inhibitor	Reduced weight-bearing deficits and attenuated firing of joint afferent fibres	Schuelert et al. (2011)
MIA model of OA (Mouse)	URB597	FAAH inhibitor	Acute treatment reduced joint inflammation. The prophylactic treatment prevented mechanical allodynia and nerve damage.	McDougall et al. (2017)
MIA model of OA (rat)	Cannabidiol (CBD)	Phytocannabinoid	The reduced firing of joint afferent fibres. Reduced secondary mechanical allodynia and weight-bearing deficits. Reduced joint inflammation. The prophylactic treatment prevented nerve damage.	Philpott et al. (2017)
MIA model of OA (rat)	JWH-133	CB2 agonist	Reduced osteoarthritis pain-related behaviour.	Burston et al. (2013)

Abbreviations: CB1, Cannabinoid receptor 1; CB2, Cannabinoid receptor 2; FAAH, fatty acid amide hydrolase; MIA, monoiodoacetate; OA, osteoarthritis.

cytokines, metalloproteases, and acute-phase proteins (Gonzalez et al., 2012; Lucattelli et al., 2016).

2.8.7 | Systemic lupus erythematosus

Research on the role of cannabinoids in SLE is limited. In a unique study measuring cannabinoid levels in SLE patients, it was found that plasma levels of 2-arachidonoylglycerol were significantly increased in SLE patients compared to controls ($p = 0.0059$). These high levels were associated with lower disease activity. No differences were found in AEA, its congeners N-palmitoylethanolamide (PEA) and N-oleoyl ethanolamide (OEA) concentrations. On analysing the gene expression of enzymes and receptor targets of cannabinoids including functional activity, it was found that 2-AG metabolism is deranged in SLE patients. Therefore, we noted some evidence of the role of cannabinoids in SLE (Navarini et al., 2018).

2.8.8 | Immune thrombocytopenic purpura

In a study on ITP, 190 children with ITP and 600 healthy controls were evaluated. The study assessed the missense variant (CAA/CGG; Q63 R) of the gene encoding the CR2 (GeneID 1269) was evaluated. The allelic frequencies and genotype distribution of this polymorphism was significant in patients compared to the control. On comparing acute and chronic ITP patients a significant over representation of the RR genotype and the R allele was observed for the chronic form. The relative odds ratio of the risk of developing chronic form was more than double in ITP children homozygous for the variant (Rossi et al., 2011).

2.9 | Adverse effects of medicinal Cannabinoids

In a systemic review of medical cannabinoids, it was found that the most consistent effects of medical cannabinoids are its AEs (Allan et al., 2018).

It is imperative to make a distinction between recreational and medicinal cannabinoid compounds. While most cannabis products share similarities, those abused for recreational purposes tend to be highly potent thus having more AEs. However, this distinction was not made when the adverse effects of cannabis were studied.

A detailed review of systemic effects is shown in Table 3. Common adverse effects of cannabinoids include dizziness, nausea, dry mouth, tachycardia and agitation. They are associated with dependence and addiction, mediated via the rewarding effects of CB1 receptors. Research is still in its infancy with regards to adverse effects of selective cannabinoids having predilection towards CB2 receptors.

In a systemic review on the use of cannabinoids for pain, spasticity and vomiting, it was shown that the adverse effects caused more patients to stop treatment (number needed to harm [NNH] was 8–22). AEs included dizziness, confusion, sedation and dissociation. 'Feeling high' was reported in 35%–70% of users (Allan et al., 2018).

Due to multi-systemic battery of AEs, the Canadian Rheumatology Association (Fitzcharles et al., 2019) came up with a position

TABLE 3 Systemic adverse events noted with cannabis use

System	Effect	Ref
Nervous system	Moderate-grade evidence accumulated thus far indicates that cannabis consumption can cause acute impairment of learning, attention and memory.	National Academies of Science, Engineering, and Medicine (2017)
	In a study published in 2017 of 5115 volunteers followed over 25 years, deficit in memory was exhibited, which also demonstrated a relationship between lifelong cannabis consumption and poor performance in cognitive tests examining verbal memory, processing speed and executive function.	Auer et al. (2016)
	Two systematic reviews published in 2013 concluded that chronic cannabis consumption can result in anatomical changes in the brain. In one of these systematic reviews, an examination of 43 imaging studies led to the conclusion that chronic cannabis use can alter the structure of the cerebellum, medial temporal cortex and frontal cortex.	Batalla et al. (2013)
	Following these findings, the second systematic review concluded that chronic cannabis consumption might lead to a reduction in hippocampal size.	Rocchetti et al. (2013)
Mental health	Paranoia or psychosis is especially related to the higher concentration of THC in some strains of herbal cannabis. Immediate psychiatric effects include agitation, suicidal thoughts, acute psychosis and anxiety.	Moreira et al. (2009) Zhang and Ho (2015)
	Indeed, a substantial body of evidence supports the association between cannabinoids and the development of psychosis and schizophrenia. Other mental health disorders are less strongly associated with the use of cannabinoids. Moderate-quality evidence suggests that cannabinoid use slightly increases the risk of depressive disorders. A moderate level of evidence also suggests an increased incidence of suicidal ideation, suicide attempts, suicide completion and social anxiety among cannabinoid users. Contrary to these findings, cannabinoid use is only weakly associated with the development of bipolar disorder, anxiety disorders (apart from social anxiety) and increased symptoms of anxiety.	National Academies of Science, Engineering, and Medicine (2017)
Addiction	Although cannabinoids are commonly considered to be non-addictive, epidemiological studies indicate that 9% of adult users will develop cannabinoid dependence.	Anthony et al. (1994)
Cardiovascular system	Tachycardia and hypotension.	Tait et al. (2015)
	Temporal relationship to an increased risk of myocardial infarction and reduced exercise capacity of those with angina pectoris.	Thomas et al. (2014)
Respiratory system	High doses of THC-containing products are associated with an increased risk of developing respiratory irritation, wheezing and morning phlegm as well as frequent episodes of chronic bronchitis.	Ware et al. (2015)
	There is a debate regarding the evidence for risk for lung cancer. A recent pooled analysis of over 2000 lung cancer cases showed an overall OR for all lung cancers for habitual versus non-habitual or never users as 0.96 (95% CI 0.66–1.38), and an OR of 1.73 (95% CI 0.75–4.00) for adenocarcinoma. On at least 50 occasions, the use of cannabis was found to double the risk of lung cancer when studied over a 40-year period for Swedish military conscripts (hazard ratio 2.12, 95% CI 1.08–4.14).	Zhang et al. (2015) Callaghan et al. (2013)
Prenatal exposure	Only limited evidence links prenatal cannabis use with anaemia in the mother and with the placement of new-born babies in intensive care units. However, substantial evidence do corroborate an association between cannabinoid consumption during pregnancy and low birthweight in new-born babies.	National Academies of Science, Engineering, and Medicine (2017)
	A study published in 2016 addressed the late outcomes of prenatal cannabis exposure from a different approach by using imaging modalities. In the study, functional MRI was used to compare	Smith et al. (2016)

TABLE 3 (Continued)

System	Effect	Ref
	neurophysiological functioning in 16 young adults exposed to cannabinoids in utero and 15 young adults with no prenatal cannabinoid exposure. The imaging results demonstrated a difference in blood flow between the two groups during the performance of tasks related to executive function, although task performance was similar in both group.	
Mortality	The French Addict Vigilance Network identified 35 vascular events spontaneously reported between 2006 and 2010 attributable to cannabis use, with 26% resulting in death.	Jouanjus et al. (2014)
Children and adolescents	Risk of cannabis poisoning due to an accidental overdose in children leading to respiratory distress is of special concern.	National Academies of Science, Engineering, and Medicine (2017)
	Compared with adult cannabis users, individuals who start to use cannabis during adolescence perform poorly in cognitive tests, exhibiting deficiencies in memory, attention, inhibition and verbal fluency. Furthermore, cannabis consumption during adolescence has been associated with a decline in IQ score, possibly accounting for a drop of as many as 8 points.	Meier et al. (2012) Volkow et al. (2014) Curran et al. (2016)

TABLE 4 Interactions of cannabinoids with drugs specifically used in rheumatology

Drugs	Interaction	Result	Ref
Corticosteroids	CYP3A inhibition by cannabinoids	Decrease clearance of steroids and increased systemic effects	Katz-Talmor et al. (2018)
NSAIDs	CYP2C9 and CYP3A4 inhibited by cannabinoids	Increased levels of drug	Wilson-Morkeh et al. (2020)
Tofacitinib	CYP3A4 and CYP2C19	Increased serum levels. Dose reduction by 5 mg once daily advised.	Madden et al. (2018)

statement for medical cannabis for rheumatology patients. They advocate contraindication on the usage of cannabinoids in patients <25 years of age, having an allergic reaction to any products of cannabinoids, in pregnancy or during breastfeeding and in those with history of psychotic illness, substance abuse disorder, previous suicide attempts or suicidal ideation. They recommend caution in elderly patients, patients with unstable mental health disease, current moderate or severe cardiovascular or pulmonary disease or patients working in settings requiring high levels of concentration or those receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs.

2.10 | Drug interactions

There are concerns regarding drug interactions of commonly used medications with cannabinoids. Currently, the data on cannabinoids and CYP450 are through in vitro studies and human data are still insufficient. However, pending further data, cannabis are presumed to act as substrate of CYP3A4, CYP2C9 and CYP2C19 (Hryhorowicz et al., 2018; Stout & Cimino, 2014; Yamaori et al., 2011). Therefore, they have potential interactions with many commonly used drugs. Table 4 gives details of interactions with drugs specifically used in routine rheumatology clinical practice.

Cannabinoids also inhibit CYP2D6, which is crucial for the biotransformation of tramadol to its active metabolite, thereby affecting its plasma concentration (Wilson-Morkeh et al., 2020). Likewise, amitriptyline is metabolised by the hepatic cytochrome P450 isozymes CYP2D6, CYP2C19, CYP3A4, CYP1A2 and CYP2C9. They are all inhibited by cannabinoids thus increasing their plasma levels and risk of QT prolongation and anticholinergic effects. Concomitant use of cannabinoids with gabapentin and pregabalin may cause additive sedative effects.

Drugs which have not shown any predictable interactions with cannabinoids include methotrexate, hydroxychloroquine, sulfasalazine, mycophenolate mofetil, mesalazine, adalimumab, etanercept, abatacept, infliximab or rituximab. Similarly, no significant interactions have been anticipated with IL-1 or IL-6 receptor antagonists (Wilson-Morkeh et al., 2020).

3 | CONCLUSION

Currently only limited evidence on therapeutic implications of cannabinoids as immune-modulatory targets in rheumatology exists as there is a paucity of robust data from clinical trials. Increasing awareness and patients' demand for cannabinoids in managing chronic rheumatic conditions should prompt researchers to explore

further in this area. Evidence on the efficacy of cannabinoids primarily comes from patient-reported outcome measures, which are very much subjective. Knowledge is still lacking about the efficacy, dosing and drug interactions of cannabinoids. Medical professionals in their routine clinical practice face patients seeking advice and demanding NHS prescription for cannabinoids. Inadequate knowledge and insufficient evidence often results in lack of confidence among treating physicians. With available information on significant interaction with CYP450, it is imperative treating physicians should be aware of various aspects of cannabinoid usage in clinical practice. The available data on immune cells and efficacy are promising; however, the studies are small or pre-clinical. Inconsistency in current medical literature restrict developing clear clinical guidelines and recommendations about cannabinoids use in routine clinical practice. The increasing availability, accessibility and legalisation of cannabinoids highlight the necessity for further large-scale RCTs.

Preliminary available evidence do suggest cannabinoids as being '*Friends*' of rheumatology, however, reported drug interactions and AEs make them '*Foe*'. In certain chronic pain conditions like fibromyalgia and OA, cannabinoids do act as '*Bystander*' and need further robust scientific evaluation.

We attempted to answer the question posed but struggled. On the balance of probabilities, with clear lack of tangible data and evidence, we concluded cannabinoids as '*foe*' in rheumatology. We do believe a robust structured research is need of the hour to answer the unanswered questions in this interesting and ever-expanding area.

AUTHOR CONTRIBUTION

Authors equally contributed in the concept and writing up this article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Arumugam Moorthy https://orcid.org/0000-0001-5903-1125

REFERENCES

Aghazadeh Tabrizi, M., Baraldi, P. G., Borea, P. A., & Varani, K. (2016). Medicinal chemistry, pharmacology, and potential therapeutic benefits of cannabinoid CB 2 receptor agonists. *Chemical Review*, *116*, 519–560.

Allan, G. M., Finley, C. R., Ton, J., Perry, D., Ramji, J., & CrawfordKolber, K. M. R. (2018). A systematic review of systematic reviews for medical cannabinoids. *Canadian Family Physician*, *64*(2), e78LP–e94LP. http://www.cfp.ca/content/64/2/e78.abstract

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, *2*, 244–268.

Auer, R., Vittinghoff, E., Yaffe, K., Künzi, A., Kertesz, S. G., Levine, D. A., Albanese, E., Whitmer, R. A., Jacobs, D. R., Sidney, S., Glymour, M. M., & Pletcher, M. J. (2016). Association between lifetime marijuana use and cognitive function in middle age. *JAMA Internal Medicine*, *176*, 352.

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J. A., Nogué, S., Torrens, M., Pujol, J., Farré, M., & Martin-Santos, R. (2013). Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLoS One*, *8*, e55821.

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*, *45*, 50–52.

Bottorff, J. L., Bissell, L. J., Balneaves, L. G., Oliffe, J. L., Capler, N. R., & Buxton, J. (2013). Perceptions of cannabis as a stigmatized medicine: A qualitative descriptive study. *Harm Reduction Journal*, *10*(2), 2. https://doi.org/10.1186/1477-7517-10-2

Burston, J. J., Sagar, D. R., Shao, P., Bai, M., King, E., Brailsford, L., Turner, J. M., Hathway, G. J., Bennett, A. J., Walsh, D. A., Kendall, D. A., Lichtman, A., & Chapman, V. (2013). Cannabinoid CB2 receptors regulate central sensitization and pain responses associated with osteoarthritis of the knee joint. *PLoS One*, *8*, e80440. https://doi.org/10.1371/journal.pone.0080440

Callaghan, R. C., Allebeck, P., & Sidorchuk, A. (2013). Marijuana use and risk of lung cancer: A 40-year cohort study. *Cancer Causes Control*, *24*, 1811–1820.

Carrasquer, A., Nebane, N. M., Williams, W. M., & Song, Z. H. (2010). Functional consequences of nonsynonymous single nucleotide polymorphisms in the CB2 cannabinoid receptor. *Pharmacogenetics and Genomics*, *20*(3), 157–166.

Castillo, P. E., Younts, T. J., Chávez, A. E., & Hashimotodani, Y. (2012). Endocannabinoid signalling and synaptic function. *Neuron*, *76*, 70–81.

Crime, Policing and Fire Group (CPFG) Drugs and Alcohol Unit. (2018). *Home Office Circular 2018: Rescheduling of cannabis-based products for medicinal use in humans*. Retrieved December 5, 2018, from http://assets.publishing.service.gov.uk

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J. A., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience*, *17*, 293–306.

Dunn, S. L., Wilkinson, J. M., Crawford, A., Bunning, R. A. D., & Le Maitre, C. L. (2016). Expression of cannabinoid receptors in human osteoarthritic cartilage: Implications for future therapies. *Cannabis and Cannabinoid Research*, *1*, 3–15.

Fechtner, S., Singh, A. K., Srivastava, I., Szlenk, C. T., Muench, T. R., Natesan, S., & Ahmed, S. (2019). Cannabinoid receptor 2 agonist JWH-015 inhibits interleukin-1β-induced inflammation in rheumatoid arthritis synovial fibroblasts and in adjuvant induced arthritis rat via glucocorticoid receptor. *Frontiers in Immunology*. https://www.frontiersin.org/article/10.3389/fimmu.2019.01027

Fitzcharles, M. A., Ste-Marie, P. A., Häuser, W., Clauw, D. J., Jamal, S., Karsh, J., Landry, T., Leclercq, S., Mcdougall, J. J., Shir, Y., Shojania, K., & Walsh, Z. (2016). Efficacy, tolerability, and safety of cannabinoid treatments in rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care & Research*, *68*(5), 681–688. https://doi.org/10.1002/acr.22727

Fitzcharles, M.-A., Zahedi Niaki, O., Hauser, W., & Hazlewood, G. (2019). Position statement: A pragmatic approach for medical cannabis and patients with rheumatic diseases. *Journal of Rheumatology*, *46*, 532–538. https://doi.org/10.3899/jrheum.181120

Fiz, J., Durán, M., Capellà, D., Carbonell, J., & Farré, M. (2011). Cannabis use in patients with fibromyalgia: Effect on symptoms relief and health-related quality of life. *PLoS One*, *6*(4), e18440. https://doi.org/10.1371/journal.pone.0018440

Food Standard Agency. (2021). *Cannabidiol (CBD) guidance: Business guidance on cannabidiol (CBD) as a novel food*. https://www.food.gov.uk/business-uidance/cannabidiol-cbd

Garcia-Gonzalez, E., Galeazzi, M., & Selvi, E. (2016). Can cannabinoids modulate fibrotic progression in systemic sclerosis? *The Israel Medical Association Journal*, *18*(3–4), 156–158.

Garcia-Gonzalez, E., Selvi, E., Balistreri, E., Lorenzini, S., Maggio, R., Natale, M. R., Capecchi, P.-L., Lazzerini, P.-E., Bardelli, M., Laghi-Pasini, F., & Galeazzi, M. (2009). Cannabinoids inhibit fibrogenesis in diffuse systemic sclerosis fibroblasts. *Rheumatology*, *48*(9), 1050–1056.

Gonzalez, E. G., Selvi, E., Balistreri, E., Akhmetshina, A., Palumbo, K., Lorenzini, S., Lazzerini, P. E., Montilli, C., Capecchi, P. L., Lucattelli, M., Baldi, C., Gianchecchi, E., Galeazzi, M., Pasini, F. L., & Distler, J. H. W. (2012). Synthetic cannabinoid ajulemic acid exerts potent anti-fibrotic effects in experimental models of systemic sclerosis. *Annals of the Rheumatic Diseases*, *71*(9), 1545–1551.

Gui, H., Liu, X., Wang, Z.-W., He, D.-Y., Su, D.-F., & Dai, S. M. (2014). Expression of cannabinoid receptor 2 and its inhibitory effects on synovial fibroblasts in rheumatoid arthritis. *Rheumatology*, *53*, 802–809.

Guindon, J., & Hohmann, A. G. (2009). The endocannabinoid system and pain. *CNS & Neurological Disorders – Drug Targets*, *8*(6), 403–421. https://doi.org/10.2174/187152709789824660

Hammell, D. C., Zhang, L. P., Ma, F., Abshire, S. M., McIlwrath, S. L., Stinchcomb, A. L., & Westlund, K. N. (2016). Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. *European Journal of Pain*, *20*(6), 936–948. https://doi.org/10.1002/ejp.818

Hendricks, O., Andersen, T. E., Christiansen, A. A, Primdahl, J., Hauge, E. M., Ellingsen, T., Horsted, T. I., Bachmann, A. G., Loft, A. G., Bojesen, A. B., Ostergaard, M., Lund Hetland, M., Krogh, N. S., Roessler, K. K., & Petersen, K. H. (2019). Efficacy and safety of cannabidiol followed by an open-label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: Protocol for a multicentre, randomised, placebo-controlled study. *BMJ Open*, *9*, e028197. https://doi.org/10.1136/bmjopen-2018-028197

Hryhorowicz, S., Walczak, M., Zakerska-Banaszak, O., Słomski, R., & Skrzypczak-Zielińska, M. (2018). Pharmacogenetics of cannabinoids. *European Journal of Drug Metabolism and Pharmacokinetics*, *43*(1), 1–12. https://doi.org/10.1007/s13318-017-0416-z

Huestis, M. A. (2007). Human cannabinoid pharmacokinetics. *Chemistry and Biodiversity*, *4*(8), 1770–1804. https://doi.org/10.1002/cbdv.200790152

Huggins, J. P., Smart, T. S., Langman, S., Taylor, L., & Young, T. (2012). An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain*, *153*, 1837–1846.

Ismail, M., & Khawaja, G. (2018). Study of cannabinoid receptor 2 Q63R gene polymorphism in Lebanese patients with rheumatoid arthritis. *Clinical Rheumatology*, *37*, 2933–2938. https://doi.org/10.1007/s10067-018-4217-9

Jouanjus, E., Lapeyre-Mestre, M., & Micallef, J. (2014). Cannabis use: Signal of increasing risk of serious cardiovascular disorders. *Journal of American Heart Association*, *3*(2), e000638.

Katz-Talmor, D., Katz, I., Porat-Katz, B., & Shoenfeld, Y. (2018). Cannabinoids for the treatment of rheumatic diseases—Where do we stand? *Nature Reviews Rheumatology*, *14*, 488–498. https://doi.org/10.1038/s41584-018-0025-5

Lowin, T., Apitz, M., Anders, S., & Straub, R. H. (2015). Anti-inflammatory effects of N-acylethanolamines in rheumatoid arthritis synovial cells are mediated by TRPV1 and TRPA1 in a COX-2 dependent manner. *Arthritis Research and Therapy*, *17*, 321. https://doi.org/10.1186/s13075-015-0845-5

Lucattelli, M., Fineschi, S., Selvi, E., Garcia Gonzalez, E., Bartalesi, B., De Cunto, G., Lorenzini, S., Galeazzi, M., & Lungarella, G. (2016). Ajulemic acid exerts potent anti-fibrotic effect during the fibrogenic phase of bleomycin lung. *Respiratory Research*, *17*(1), 49.

Maccarrone, M., Bab, I., Bíró, T., Cabral, G. A., Dey, S. K., Marzo, V. D., Konje, J. C., Kunos, G., Mechoulam, R., Pacher, P., Sharkey, K. A., & Zimmer, A. (2015). Endocannabinoid signaling at the periphery: 50 years after THC. *Trends in Pharmacological Sciences*, *36*, 277–296.

Madden, K., van der Hoek, N., Chona, S., George, A., Dalchand, T., Baldawi, H., Mammen, G., & Bhandari, M. (2018). Cannabinoids in the management of musculoskeletal pain. *JBJS Reviews*, *6*(5), e7. https://doi.org/10.2106/JBJS.RVW.17.00153

McDougall, J. J., Muley, M. M., Philpott, H. T., Reid, A., & Krustev, E. (2017). Early blockade of joint inflammation with a fatty acid amide hydrolase inhibitor decreases end-stage osteoarthritis pain and peripheral neuropathy in mice. *Arthritis Research and Therapy*, *19*, 106.

Meier, M. H., Caspi, A., Ambler, A., Harrington, H. L., Houts, R., Keefe, R. S. E., McDonald, K., Ward, A., Poulton, R., & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, E2657–E2664.

Milando, R., & Friedman, A. (2019). Cannabinoids: Potential role in inflammatory and neoplastic skin diseases. *American Journal of Clinical Dermatology*, *20*, 167–180. https://doi.org/10.1007/s40257-018-0410-5

Moreira, F. A., Grieb, M., & Lutz, B. (2009). Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: Focus on anxiety and depression. *Best Practice & Research: Clinical Endocrinology & Metabolism*, *23*(1), 133–144.

National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. The National Academies Press.

Navarini, L., Bisogno, T., Mozetic, P., Piscitelli, F., Margiotta, D. P. E., Basta, F., Afeltra, A., & Maccarrone, M. (2018). Endocannabinoid system in systemic lupus erythematosus: First evidence for a deranged 2-arachidonoylglycerol metabolism. *The International Journal of Biochemistry & Cell Biology*, *99*, 161–168.

NICE. (2019). *Cannabis-based medicinal products*(NICE Guideline 144). www.nice.org.uk/ng144

Pagotto, U., Marsicano, G., Cota, D., Lutz, B., & Pasquali, R. (2006). The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocrine Reviews*, *27*, 73–100.

Pertwee, R. G., Howlett, A. C., Abood, M. E., Alexander, S. P. H., Di Marzo, V., Elphick, M. R., Greasley, P. J., Hansen, H. S., Kunos, G., Mackie, K., Mechoulam, R., & Ross, R. A. (2010). International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: Beyond CB1 and CB2. *Pharmacological Reviews*, *62*, 588–631.

Philpott, H. T., O'Brien, M., & McDougall, J. J. (2017). Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. *Pain*, *158*, 2442–2451.

Ramot, Y., Sugawara, K., Zakany, N., Toth, B. I., Biro, T., & Paus, R. (2013). A novel control of human keratin expression: Cannabinoid receptor 1-mediated signalling down-regulates the expression of keratins K6 and K16 in human keratinocytes in vitro and in situ. *PeerJ*, *1*, e40.

Rocchetti, M., Crescini, R., Borgwardt, S., Caverzasi, E., Politi, P., Atakan, Z., & Fusar-Poli, P. (2013). Is cannabis neurotoxic for the healthy brain? A meta- analytical review of structural brain alterations in non- psychotic users. *Psychiatry and Clinical Neurosciences*, *67*, 483–492.

Rossi, F., Mancusi, S., Bellini, G., Roberti, D., Punzo, F., Vetrella, S., Matarese, S. M. R., Nobili, R., Maione, S., & Perrotta, S. (2011). CNR2 functional variant (Q63R) influences childhood immune thrombocytopenic purpura. *Haematologica*, *96*(12), 1883–1885.

Schuelert, N., Johnson, M. P., Oskins, J. L., Jassal, K., Chambers, M. G., & McDougall, J. J. (2011). Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. *Pain*, *152*, 975–981.

Schuelert, N., & McDougall, J. J. (2008). Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis & Rheumatism*, *58*, 145–153.

Schuelert, N., Zhang, C., Mogg, A. J., Broad, L. M., Hepburn, D. L., Nisenbaum, E. S., Johnson, M. P., & McDougall, J. J. (2010). Paradoxical effects of the cannabinoid CB2 receptor agonist GW405833 on rat osteoarthritic knee joint pain. *Osteoarthritis and Cartilage*, *18*, 1536–1543.

Selvi, E., Lorenzini, S., Garcia-Gonzalez, E., Maggio, R., Lazzerini, P. E., Capecchi, P. L, Balistreri, E., Spreafico, A., Niccolini, S., Pompella, G., Natale, M. R., Guideri, F., Pasini, F. L., Galeazzi, M., & Marcolongo, R. (2008). Inhibitory effect of synthetic cannabinoids on cytokine production in rheumatoid fibroblast-like synoviocytes. *Clinical & Experimental Rheumatology*, *26*, 574–581.

Sido, J. M., Nagarkatti, P. S., & Nagarkatti, M. (2015). Role of endocannabinoid activation of peripheral CB1 receptors in the regulation of autoimmune disease. *International Reviews of Immunology*, *34*, 403–414.

Skrabek, R. Q., Galimova, L., Ethans, K., & Perry, D. (2008). Nabilone for the treatment of pain in fibromyalgia. *The Journal of Pain*, *9*, 164–173.

Smith, A. M., Mioduszewski, O., Hatchard, T., Byron-Alhassan, A., Fall, C., Fried, P. A. (2016). Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicology and Teratology*, *58*, 53–59.

Ste-Marie, P. A., Fitzcharles, M. A., Gamsa, A., Ware, M. A., & Shir, Y. (2012). Association of herbal cannabis use with negative psychosocial parameters in patients with fibromyalgia. *Arthritis Care & Research*, *64*(8), 1202–1208. https://doi.org/10.1002/acr.21732

Stout, S. M., & Cimino, N. M. (2014). Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: A systematic review. *Drug metabolism reviews*, *46*, 86–95.

Tait, R. J., Caldicott, D., Mountain, D., Hill, S. L., & Lenton, S. (2015). A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology*, *54*, 1–13.

Tharakan, C. S., Ungcharoen, N., Sabu, J., & Moorthy, A. (2019). THU0650 complementary and alternative medicine in rheumatology: A survey of its use for common rheumatological conditions among multi-ethnic patients in Leicestershire. *Annals of the Rheumatic Diseases*, *78*, 621.

Thomas, G., Kloner, R. A., & Rezkalla, S. (2014). Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. *The American Journal of Cardiology*, *113*(1), 187–190.

Toth, B. I., Dobrosi, N., Dajnoki, A., Czifra, G., Olah, A., Szollosi, A. G., Juhász, I., Sugawara, K., Paus, K., & Bíró, T. (2011). Endocannabinoids modulate human epidermal keratinocyte proliferation and survival via the sequential engagement of cannabinoid receptor-1 and transient receptor potential vanilloid-1. *Journal of Investigative Dermatology*, *131*(5), 1095–1104.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. B. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*, 2219–2227.

Ware, M. A., Wang, T., Shapiro, S., Collet, J.-P., Boulanger, A., Esdaile, J. M., Gordon, A., Lynch, M., Moulin, D. E., & O'Connell, C. (2015). Cannabis for the management of pain: Assessment of safety study (COMPASS). *The Journal of Pain*, *16*, 1233–1242.

Warf, B. (2014). High points: An historical geography of cannabis. *Geographical Review*, *104*, 414–438. https://doi.org/10.1111/j.1931-0846.2014.12038.x

Werth, V., Hejazi, E., Pena, S. M., Haber, J. S., Okawa, J., Feng, R., Gabre, K., Concha, J. S., Cornwall, C., Dgetluck, N., Constantine, S., & White, B. (2018). FRI0470 A phase 2 study of safety and efficacy of lenabasum (JBT-101), a cannabinoid receptor type 2 agonist, in refractory skin predominant dermatomyositis. *Annals of the Rheumatic Diseases*, *77*, 763–764.

Wilkinson, J. D., & Williamson, E. M. (2007). Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *Journal of Dermatological Science*, *45*(2), 87–92.

Wilson-Morkeh, H., Al-Abdulla, A., Sien, L., Mohamed, H., & Youngstein, T. (2020). Important drug interactions exist between cannabidiol oil and commonly prescribed drugs in rheumatology practice. *Rheumatology*, *59*(1), 249–251. https://doi.org/10.1093/rheumatology/kez304

Yamaori, S., Ebisawa, J., Okushima, Y., Yamamoto, I., & Watanabe, K. (2011). Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: Role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sciences*, *88*, 730–736.

Yamaori, S., Koeda, K., Kushihara, M., Hada, Y., Yamamoto, I., & Watanabe, K. (2012). Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metabolism and Pharmacokinetics*, *27*, 294–300.

Zhang, L. R., Morgenstern, H., Greenland, S., Chang, S. C., Lazarus, P., Teare, M. D., Woll, P., Orlow, I., & Cox, B. (2015). Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer*, *136*(4), 894–903.

Zhang, M. W., & Ho, R. C. (2015). The cannabis dilemma: A review of its associated risks and clinical efficacy. *Journal of Addiction*, *2015*, 707596.

Zhu, M., Yu, B., Bai, J., Wang, X., Guo, X., Liu, Y., Lin, J., Hu, S., Zhang, W., Tao, Y., Hu, C., Yang, H., Xu, Y., & Geng, D. (2019). Cannabinoid receptor 2 agonist prevents local and systemic inflammatory bone destruction in rheumatoid arthritis. *Journal of Bone and Mineral Research*, *34*, 739–751. https://doi.org/10.1002/jbmr.3637

How to cite this article: Jain, N., & Moorthy, A. (2022). Cannabinoids in rheumatology: Friend, foe or a bystander? *Musculoskeletal Care*, *20*(2), 416–428. https://doi.org/10.1002/msc.1636