

# Effects of Cannabidiol (CBD) on the inflammatory response of patients with rheumatoid arthritis

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**Abstract** – With an increase in the understanding of rheumatoid arthritis (RA) in terms of genetic and environmental risk factors, the pathogenesis of the disease is still not entirely understood. Treatments focus on maintaining joint function, analgesia and immunosuppression, however, in some cases there is little to no response to therapeutic drugs, highlighting the need to explore further therapeutic treatments. Cannabidiol (CBD) has been studied for its potential anti-inflammatory properties with regards to inflammatory conditions, but with conflicting and limited research surrounding RA. The aim of this systematic review was to determine the effects of cannabidiol on the inflammatory response of patients with RA. Most recent findings, relevance and quality of available research has been analyzed following the principles of the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. An electronic literature search was conducted through PubMed, Google Scholar, ScienceDirect. The PICO framework, FINER, inclusion and exclusion criteria were considered to identify specific components within the studies. Four studies were identified as relevant after being assessed through the critical appraisal tool CASP. Two qualitative in vivo experiments on 58 humans and 54 rats. One in vivo study analyzed qualitative and quantitative data from 133 mice and a final study giving quantitative data from an in vitro experiment on macrophages. All participants were diagnosed with either acute or chronic rheumatoid arthritis, whilst receiving a variation of dosages and routes of administration, with a collation of data and observations from both before and after administration of the CBD treatment. The reviewed studies highlighted no significant adverse reactions from the use of the CBD therapeutics in the varying dosages and routes of administration. From these four studies there is evidence to suggest that there are benefits of CBD as a therapeutic in terms of inflammation, three of the studies specifically found a reduction in the inflammatory marker TNF- $\alpha$  caused by RA after administration of the various therapeutic interventions and dosages. There is a requirement for more human clinical trials to determine the anti-inflammatory properties, the safety, dosage, route of administration and efficacy of CBD in humans with RA.

**Keywords** – Phytocannabinoid; Rheumatoid arthritis; Inflammatory disease; Anti-inflammatory; Therapeutic intervention; Sativex®; Transdermal; Tumor necrosis factor alpha protein; Interferon gamma; Interleukin 10.

## 1. Background on cannabis sativa L. and rheumatoid arthritis

*Cannabis sativa* L. is an annual flowering herbaceous plant indigenous to Eastern Asia and for thousands of years it has been farmed for recreational, industrial, and medicinal purposes [1,]. Nowadays, its cultivation is regulated via legislation and laws in many counties across the world [3,4], however, some legalization has been seen in several countries such as Canada, Netherlands, and Spain [4,5].

The United Kingdom (UK) has yet to legalize cannabis and as a result it is still classified as a class B drug [4] whereby it is illegal to grow, possess, sell and distribute any plant of the genus cannabis, however, cannabidiol (CBD)/hemp oil and CBD/hemp supplements were deemed legal by the medicines and healthcare products regulatory agency (MHRA) in 2016 [6] and by 31<sup>st</sup> March 2021 the food standards agency (FSA) required the approval of a novel food application by any establishment selling such products [7]. A home office license is required to cultivate medicinal cannabis within the UK [5]. Medicinal use within the UK was approved in November 2018 and is used to treat Dravet, Lennox-Gastaut syndrome, chemotherapy induced sickness and multiple sclerosis via a National Health Service (NHS) prescription [5,8]. Cannabis plants themselves are complex, the *sativa* strain itself contains more than 120 naturally occurring phytocannabinoids [9]. These cannabinoids have been shown through

various studies to interact with the human cannabinoid system, specifically G-protein coupled receptors (GPCR's), cannabinoid receptor type 1 (CB<sub>1</sub>), cannabinoid receptor type 2 (CB<sub>2</sub>)(10,11), several transient receptor potential (TRP) ion channels as well as involvement in serotonergic neurotransmission [12-15]. CB<sub>1</sub> are predominantly found within the brain and the central nervous system [16] while CB<sub>2</sub> receptors are primarily found in immune system associated cells [17]. One phytocannabinoid found within *sativa* is CBD and although this has the capability of antagonising CB<sub>1</sub> and CB<sub>2</sub> receptors and activating transient receptor potential cation channel subfamily V member 1 (TrPV1) [18], it shows low binding affinity to the CB<sub>1</sub> and CB<sub>2</sub> receptors [16].

Trials based on non-specific cannabis strains containing THC/CBD in varying forms such as oils, capsules and sprays suggest analgesic therapeutic potential [19,20] and its alteration of lymphocyte function [21], therefore, could CBD be considered an option in terms of therapeutic treatment for inflammatory diseases, specifically rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disease associated with progressive inflammation, causing disability and systemic complications. It is thought that in the UK alone that for every 10,000 people 3.6 women and 1.5 men will have the disease [22]. Rheumatoid arthritis primarily affects the proximal and metacarpal interphalangeal joints and wrists causing deformities [23]; however, it can affect any joint in the body [24], whereby autoantigens cause an immune response which is characterized as synovitis, bone/cartilage erosion and angiogenesis [25,26].

Autoantigens are recognized by antigen presenting cells (APC) that migrate to the lymph nodes and activate cluster of differentiation 4<sup>+</sup> thymus cells (CD4<sup>+</sup> T-cells), these co-stimulate the bursa of fabricius cells (B-cells), which induce proliferation and class switching to plasma cells. The plasma cells produce autoantibodies against the patient's own antigens and migrate to joint tissues [27].

Macrophages enter the synovial compartment and release tumor necrosis factor alpha protein (TNF- $\alpha$ ), interleukin 1 (IL-1) and interleukin 6 (IL-6) cytokines [25-27]. These stimulate and activate the fibroblast like synoviocytes (FLS), therefore inducing proliferation. Stimulation of osteoclast activity leads to bone erosion. Many cells found within the synovial fluid are responsible for the feedback loops seen [25-27]. There is no cure for rheumatoid arthritis, however, there is an increase in the understanding of the pathogenesis which has led to the formulation of several different types of therapeutic drugs: nonsteroidal anti-inflammatory drugs (NSAID's) which help to manage the inflammation, disease modifying anti rheumatic drugs (DMARD's) and corticosteroids which both aim to suppress inflammation [28]. These drugs, however, are not effective for everyone and some patients experience side effects [29]. With existing studies on the effects of CBD in the human body [30,31], there is ever more knowledge suggesting its benefits, yet in spite of this, the mechanisms surrounding how this occurs is still not fully recognized. Certain drugs have been manufactured for a variation of diseases such as: cesamet® (used for the side effects seen with chemotherapy) [32], marinol® (for use as an appetite stimulator for AIDs/HIV patients and chemotherapy induced nausea) [33], sativex® (for use in multiple sclerosis spasticity) [8] and epidyolex® (for children and adults with epilepsy) [8]. This suggests there is scope for further therapeutic drug manufacturing and the review will look to determine whether CBD does/ doesn't have an effect on the inflammatory response caused by rheumatoid arthritis.

## 2. Hypothesis, aims and objectives

### 2.1 Hypothesis

**Null hypothesis:** There is no evidence that CBD can provide an anti-inflammatory response in a population with rheumatoid arthritis.

**Hypothesis:** There is clear evidence that CBD can provide an anti-inflammatory response in a population with rheumatoid arthritis.

### 2.2 Aims

The purpose of this review will be to systematically determine, whilst using specific research questions to minimize bias, whether or not CBD and its derivatives have any effect on the inflammatory response caused by rheumatoid arthritis and whether CBD could be considered as an alternative therapeutic choice for the treatment of rheumatoid arthritis inflammation by clinical practitioners.

### 2.3 Objectives

- 1) Systematically review the findings, relevance, and quality of research to generate new knowledge with existing data.
- 2) To use inclusion/ exclusion criteria to find the most suitable studies that will give reliable and consistent results.

3) Critically analyze whether CBD or its derived products provide a link to support or reject the hypothesis.

### 3. Methodology

#### 3.1 Reduction of bias

No funding was required for the undertaking of this systematic review. The one researcher had no understanding of the topic pre-allocation; therefore, rigorous, and comprehensive research was required, furthermore, there was no pre-existing knowledge that could cause bias. Due to a single researcher undertaking the study selection, there is risk of bias, however, creating predefined methods, eligibility criteria, a summary of findings table and the critical analysis questions, will create uniformity between the studies and aims to minimize the bias. Any more than one researcher was beyond the scope of this review.

#### 3.2 Search strategy

A comprehensive search of published peer reviewed literature was performed through PubMed, Google Scholar, ScienceDirect, by using keywords and Boolean operators “CBD and arthritis,” “CBD or anti-inflammatory,” “CBD and rheumatoid arthritis,” “Cannabidiol anti-inflammatory properties,” “Cannabidiol oil and autoimmune diseases,” forwards and backwards citation tracking was applied to generate a wider range of literature.

#### 3.3 PICO

Using the PICO framework allowed for the creation of the research question (population, intervention, comparison, outcome) thus providing efficiency, allowing for identification of specific components and the ability to discard irrelevant studies promptly as approved by the Cochrane handbook for systematic reviews [34]. The results are given below in Table 1. The FINER criteria were also considered whilst formulating the research question, feasibility, interesting, novel, ethical and relevant- to produce a logically, relevant, and coherent result.

**Table 1.** The resulting PICO framework components.

Population-	In vitro/ vivo population displaying an inflammatory response to rheumatoid arthritis
Intervention-	By using a form of CBD intervention
Comparison-	Of the population not using the CBD intervention
Outcome-	The ineffectiveness/effectiveness of CBD as a therapeutic for inflammation

#### 3.4 Inclusion/ exclusion criteria

To reduce bias or ambiguity in the findings [34], inclusion and exclusion criteria were set out below in Table 2. Articles published in the English language were solely included as anything other was beyond the scope of the researcher’s abilities, however, this also prevented translational errors. Any studies performed before the year 2000 were disregarded for a more relevant and up to date finding of the literature. Published peer reviewed articles were used to improve the validity and quality of the review, whilst filtering out substandard research. A confirmed diagnosis of rheumatoid arthritis was included, however, no specific criteria surrounding how the disease diagnosis was defined, as this could unnecessarily force the exclusion of earlier studies. More recent studies may have different diagnostic criteria and could also differ between countries. The decision to include any age, gender, ethnicity, in vivo, in vitro, differing CBD therapeutic interventions, as well as synthetic CBD studies allowed for the exploration of a broader range of studies.

**Table 2.** The resulting inclusion and exclusion criteria.

Exclusion criteria-	Any language other than English. Any research before the year 2000
Inclusion criteria-	Published peer reviewed articles. A diagnosis of rheumatoid arthritis. No specific age, gender, or ethnicity. In vivo and in vitro studies. Any therapeutic intervention containing CBD, synthetic CBD

#### 3.5 Study selection

Initial studies were conducted by one researcher, using the key words and Boolean operators through the search

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engines mentioned above. The title and abstract of the studies were read, the inclusion/ exclusion criteria and the result of the PICO framework set out above were taken into consideration. The decision to retain/ exclude studies was solely made by the individual researcher. The studies were uploaded onto an excel spreadsheet [35], this is represented in table 3 below.

**Table 3.** A summary of the initial findings published from the years 2000-2023.

Author(s)	Title of article	Purpose or question	Type of study	Method	Design	Sample size
Sumariwalla PF, Gallily R, Tchilibon S, Fride E, Mechoulam R, Feldmann M.	A novel synthetic, non-psychoactive cannabinoid acid (HU-320) with anti-inflammatory properties in murine collagen-induced arthritis.	The potential of cannabinoid in mice	In vitro	0.01 to 10 g/ml, in vivo 0.5- 5 mg/kg.	Wasn't clearly stated in abstract	Wasn't clearly stated in abstract
Blake DR, Robson P, Ho M, Jubb RW, McCabe CS	Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis.	Assess sativex® for pain relief in rheumatoid arthritis (RA).	In vivo	Oromucosal Sativex®	Randomised double blind trial	58
Vela J, Dreyer L, Petersen KK, Arendt-Nielsen L, Duch KS, Kristensen S.	Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial.	To investigate the analgesic 12 12 week CBD treatment for Osteoarthritis.	In vivo	20-30mg or placebo daily for 12 weeks		129
Heineman JT, Forster GL, Stephens KL, Cottler PS, Timko MP, DeGeorge Jr BR.	A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis.	The potentials of CBD for thumb arthritis.	In vivo	Topical 1ml	Couldn't access	10
Hunter D, Oldfield G, Tich N, Messenheimer J, Sebree T.	Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis.	Safety and efficacy of CBD for osteoarthritis patients.	In vivo	500ml	Randomised double blind trial	320
Xu DH, Cullen BD, Tang M, Fang Y.	The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities.	Topical CBD oil for neuropathy	In vivo	250mg	Randomised	29
Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M	The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis.	CBD oil for CIA	In vitro in vivo combination	20, 10, 5 and 2.5 mg/kg	Both quantitative and qualitative data	133

Rajan TS, Giacoppo S, Iori R, De Nicola GR, Grassi G, Pollastro F, Bramanti P, Mazzon E.	Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages.	Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages.	In vitro	CBD and MOR alone and in combination	Quantitative	Macrophages
Hammell DC, Zhang LP, Ma F, Abshire SM, McIlwrath SL, Stinchcomb AL, Westlund KN.	Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis.	Transdermal CBD in rats for reduction in inflammation and pain.	In vivo	CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction	Qualitative data	54

**4. Results**

**4.1 Search results**

Further analysis of the studies from table 3 was carried out and it was determined that “Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial” and “Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis” would not be considered for the systematic review as although they both studied arthritic type diseases, they were not specifically rheumatoid arthritis. “A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis” study was also not considered for this review as full access was not available. “The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities” was also disregarded as this was in relation to diabetes.

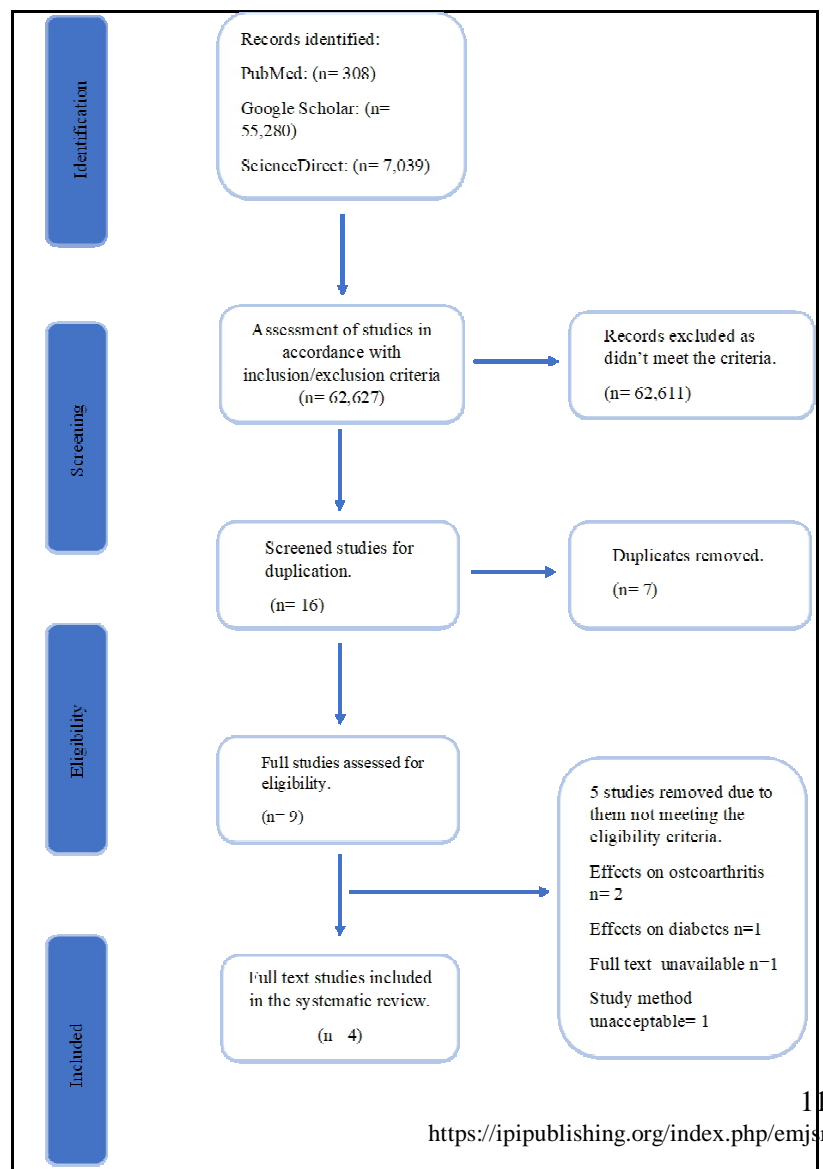
**4.2 PRISMA**

This systematic review was directed as a result of the preferred reporting items for systematic review and meta-analysis (PRISMA) statement(36). The protocols for searching are shown in Figure 1.

The original number of searches returned were 62,627 from PubMed 308, Google Scholar 55,286 and ScienceDirect 7,039. Of the 62,627 studies, 62,611 were excluded. Further screening allowed for the removal of 7 duplicates. 9 full studies remained and were reassessed for eligibility. 5 of these 9 studies were removed due to them not meeting the eligibility criteria. 2 were dismissed as they examined the effects on osteoarthritis and 1 other assessed the effects on diabetic patients, therefore that was also rejected. 1 was rejected due to the inaccessibility of the full study text. The 5th was removed because of an unacceptable study method. 4 studies remained and were deemed to be useful for looking at the effects of CBD on the inflammatory response of a population with rheumatoid arthritis.

**4.3 Critical appraisal**

A qualitative questionnaire sourced from the CASP (critical appraisal skills programme)



**Figure 0.** PRISMA flow diagram depicting the retrieval and selection of studies during different phases of the systematic review

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was used to assess the data from the remaining 4 studies and to highlight any that were weak and irrelevant and to be able to identify the more valuable, reliable, and relevant studies, as seen in table 4 [37]. Each question gave either a yes or no answer, indicated by a tick or cross, for each yes answer given, the study was awarded a point. The total of the points was collated from each study a score more than an 8 was considered extremely good, a score between 5-8 was considered good and a score below 5 was unsatisfactory.

**Table 4.** CASP table, the qualitative questionnaire identifying strengths and weaknesses of the remaining 4 studies.

	The non-psychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis.	Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis.	Transdermal cannabidiol reduces inflammation and pain related behaviors in a rat model of arthritis	Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages.
Was there a clear statement of the aims of the research?	✓	✓	✓	✓
Is a qualitative methodology appropriate?	✓	✓	✓	X
Was the research design appropriate to address the aims of the research?	✓	✓	✓	✓
Was the recruitment strategy appropriate to the aims of the research?	X	✓	✓	✓
Was the data collected in a way that addressed the research issue?	✓	✓	✓	✓
Has the relationship between researcher and participants been adequately considered?	✓	✓	✓	✓
Have ethical issues been taken into consideration?	X	✓	✓	✓
Was the data analysis sufficiently rigorous?	✓	✓	✓	✓
Is there a clear statement of findings?	✓	✓	✓	✓
How valuable is the research?	✓	✓		✓
Total	8	10	10	9

The study headed “The non-psychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis”, lost 2 points. Firstly, due to the process of participant selection, the recruitment process had been clearly explained, however, the reasoning behind the selection of the dependent variables such as the sex and age of the mice for the acute and chronic studies were not explicitly defined. There was a lack of clarity encompassing the number of animals used within this study but upon thorough reading, it became clear that after following all the variations of methods, there were over 100 mice used. Secondly, there were no discussions surrounding the ethics of the mice used within this study, with no evidence of an ethics committee being informed.

The study named “Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages”, scored a nine. The CASP questionnaire used was a qualitative research tool, however, due to the nature of this study quantitative measures were recorded. Given the quality of the other questions included within the appraisal tool, it was felt that this questionnaire was best suited to this study and allowed for consistency between all four studies.

Both the studies headed “Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex®) in the treatment of pain caused by rheumatoid arthritis” and “Transdermal cannabidiol reduces inflammation and pain related behaviours in a rat model of arthritis” were awarded the full ten points. Both seek out

to interpret experiences of the research participants, albeit in differing ways to each other. The research strategy surrounding the participants has been considered. Discussions and reasoning were clear as to why individuals discontinued the studies. Ethical considerations were discussed, and both sought out ethical approvals from local committees.

The research design and goals for all four studies were clearly defined as well as their relevance and importance. Data method collection was clear and coherent with some biases discussed. Sufficient data led to clearly identified themes throughout the studies due to the in-depth analyses. These have helped establish a clear statement of findings, leading to discussions surrounding the value of their contributions with several gaps having been identified for further areas for research.

#### 4.4 Study characteristics and findings

Following on from the exclusions and critical appraisal analysis, four studies were retained. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS- The study design for Preliminary assessment of the efficacy, tolerability, and safety of a cannabis-based medicine (Sativex®) in the treatment of pain caused by rheumatoid arthritis [38] was a randomised five-week double blinded parallel study, assessing 58 positively diagnosed rheumatoid arthritis patients of varying sexes, ages, height, and weight, funded for by GW Pharmaceuticals. Patients experiencing severe cardiovascular, renal disorders, substance abuse, epilepsy and psychiatric conditions were not considered for the study. 31 patients were randomised to Sativex® with one withdrawal due to surgical procedure and 27 patients were placed on to the placebo with 3 patients withdrawing due to side effects. The study examined the intervention of an oromucosal spray administering 2.5mg of CBD and 2.7mg of THC, this was taken every day. Day 1 began with 1 spray, then every second day there was another spray added until 6 sprays in total were reached, this was then maintained for 3 weeks. The outcomes were measured using the short form McGill pain questionnaire (SF-MPQ) that required a numerical rating and the DAS28 which measures a disease activity score on 28 joints within the body. Significant improvements were observed in pain on movement, in the quality of sleep, pain at present and pain at rest, as well as in the DAS28 after administration of Sativex®. Many adverse effects were either mild or moderate i.e., dry mouth, dizziness, and 3 withdrawals were seen in placebo patients only.

Hammell DC, Zhang LP, Ma F, Abshire SM, McIlwrath SL, Stinchcomb AL, Westlund KN- Transdermal cannabidiol reduces inflammation and pain related behaviours in a rat model of arthritis(39) was an experimental study funded by the American Cancer Society, the aim of the study was to induce inflammation and pain via a complete Freund's adjuvant(CFA), introduce transdermal CBD and analyse the efficacy of the CBD treatment in male sprague-dawley rats. A total of 54 rats weighing between 260-280g were studied, 21 as controls and 23 received 100µl of CFA within one knee. All rats were individually enclosed, could continuously access a food source and were kept in a dark/light reverse cycle. On day 3 application of the mono-arthritis gel took place, gels of varying doses of CBD were rubbed into pre-shaved backs of the rats in quantities of 0.62mg, 3.1mg, 6.2mg and 62mg. Hind paw sensitivity was assessed prior and post day 3, 6.2 and 62.3mg/day dose showed best results. Knee joint inflammation was significant after 3 days post injection, upon application of the 6.2mg dosing, improvements were observed from an initial  $72.0 \pm 0.2\text{mm}$  down to  $65.6 \pm 1.0\text{mm}$  on day 7. A numerical score was used in all the rats induced with arthritis to determine pain via behavioral changes. The scores on day 3 were high (median 4) and following 4 days of treatment, the dosing of 6.2 and 62.3mg/day showed a significant improvement in pain related behaviour scores (1.5 median). Post euthanasia blood samples were collected, the transdermally absorbed CBD was determined good in the 0.62, 3.1 and 6.2mg dosing, they showed a linear pharmacokinetic profile, however, the 62.3mg dosing did not. A decrease of the synovial membrane thickness was observed in the dosage of 6.2mg/day, this was determined via excision of the synovial joint capsule membrane post euthanasia.

Rajan TS, Giacoppo S, Iori R, De Nicola GR, Grassi G, Pollastro F, Bramanti P, Mazzon E- Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages(40) was an experimental study funded by research funds 2015 of istituto di ricovero e cura a carattere scientifico (IRCCS) "Centro Neurolesi Bonino-Pulejo", Messina, Italy. The aim of the study was to compare the outcome of CBD and moringin (MOR) in combination and alone on Lipopolysaccharide (LPS) stimulated murine macrophages and determine if there were any antioxidative and anti-apoptotic effects. The murine macrophages were derived from cell line RAW 264.7, the cells did not exceed 30 passages and were cultured in single layers. E-coli (Escherichia coli) LPS was used to stimulate the cells to induce inflammatory responses and then the cells received either CBD (2.5 or 5µm) or MOR (2.5 or 5µm) or CBD-MOR (2.5 or 5µm + 2.5 or 5µm) for 24 hours. Untreated LPS cells containing varying doses of CBD, MOR, Glucomoringin and myrosinase were used as controls. Immunocytochemistry results showed negative staining for TNF-α after receiving CBD and CBD-MOR in macrophages induced with LPS, as well



as positive staining for IL-10 in macrophages induced with LPS after receiving CBD and CBD- MOR combination. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M- The non-psychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis<sup>(41)</sup> was an experimental study which received funding from the Arthritis research campaign of Great Britain, the basis of the study was to determine the possibility of CBD as a therapeutic treatment in collagen induced arthritis (CIA), whilst investigating the mode of action. The acute model studied male DBA/1 mice aged between 8 to 12 weeks old who received transdermal 100µg injection of type II collagen. The chronic model analysed 6-week-old female DBA/1 mice who had also received a transdermal 100µg injection of type II collagen and then latterly at 15 days another 100µg was administered via transdermal injection. CBD was initiated at the first clinical sign of arthritis in both the acute and chronic model. Acute- Administration via an intraperitoneal injection (IP) daily for ten days in varying dosages, 20 mg/kg, 10 mg/kg, 5 mg/kg, and 2.5 mg/kg at a ratio of CBD: ethanol (1:1), there were n = 23 control mice which received the vehicle of ethanol in saline. An oral treatment was also studied at an acute level after the onset of clinical symptoms with an oral administration of a CBD and olive oil combination at varying dosages of 10 mg/kg, 25 mg/kg, and 50 mg/kg for 10 days. 6 controls were also studied after receiving olive oil. Chronic- Administration via an IP daily for 5 weeks in a 10 mg/kg and 5 mg/kg dose of CBD and controls received vehicle. Oral treatment was again studied and delivered at a dosage of 2.5mg/kg each day from Monday- Friday and a comparative was made against controls that were fed olive oil. The systemic administration outcomes showed there was a small effect on CIA after receiving 20 mg/kg and 10 mg/kg. In the chronic study the 5 mg/kg IP CBD was best at suppressing arthritis. Oral suppression of acute CIA was seen via a dosage of 25 mg/kg. Whilst the chronic model also saw a suppression in the progression over a 4-week period with a dosage of 25 mg/kg. Synovial cells saw a reduction in TNF being released after a 10-day period of receiving 5 mg/kg IP CBD.

## 5. Discussion

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS- The study design for “Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex®) in the treatment of pain caused by rheumatoid arthritis”[38]: The funding for this study was sourced from a British pharmaceuticals company called GW Pharmaceuticals, they are responsible for the cultivation of cannabis extracts and the manufacturing of a drug called Sativex® therefore there is the possibility of a funding bias here. However, the study itself was methodical and comprehensive allowing for ease with regards to analysis and it is the first recorded controlled study of CBD used in humans who have rheumatoid arthritis. The numerical score of the SF-MPQ allowed for comparability of before and after the administration of Sativex®, this allowed for any changes to be measured and provided a simplistic approach to the data analysis.

Hammell DC, Zhang LP, Ma F, Abshire SM, McIlwrath SL, Stinchcomb AL, Westlund KN- Transdermal cannabidiol reduces inflammation and pain related behaviours in a rat model of arthritis [39]: A pain related behavioral scale was used on the rats as part of this study, however, it is acknowledged that this is subjective. This wasn't the main source of evidence in the study, this assessment was used to support the main body of findings. The study also took into consideration the possibility of psychoactive side effects and so behavioral observations were made before and after treatment.

Rajan TS, Giacoppo S, Iori R, De Nicola GR, Grassi G, Pollastro F, Bramanti P, Mazzon E- Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages [40]: The methodology for this study was clearly explained, the experiments were repeated 3 individual times due to triplicates being made, therefore, the study gives for a more thorough data collection and analysis. There was no significant antioxidative protection or anti-apoptotic effects observed in LPS induced macrophages, however, this wasn't concluded.

Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M- The non-psychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis [41]: Male mice were solely used for the acute studies and only received the bovine CII, whereas the female mice were solely used for the chronic study and only received the mouse CII. There was also no explanation as to why and so there is a potential for sampling bias. Throughout the final discussions of this study, the findings were related back to their research question. The study was also candid in terms of an unexplained result for the bell-shaped dose dependence.



## 6. Conclusion

### 6.1 interpretation of the evidence

Some of the key features amidst the 4 studies suggest there is both supporting and dismissive evidence of their findings. Malfait, Rajan and Hammell have all identified that the inflammatory marker TNF- $\alpha$  saw a reduction after the therapeutic intervention of CBD, although with varying dosages; Malfait 5mg, Rajan 5 $\mu$ m and Hammell 6.2 and 62mg/day. However, Malfait could not suppress TNF from macrophages or RAW cells, whereas Rajan was able to achieve this in the murine macrophages that were derived from cell line RAW 264.7.

Blake found a suppression of pain on movement after an oromucosal administration of 6 sprays in the ratio 2.7mg of THC and 2.5mg CBD. Rajan observed another result seen in the LPS macrophages treated with CBD and CBD/MOR, positive staining was observed for the anti-inflammatory marker IL-10, suggesting anti-inflammatory properties in response to CBD and/ MOR and noted CBD might act preferably via TrPV1 receptors. Malfait also discovered there was a suppression of IFN- $\gamma$  after IP administration of 5mg/kg CBD. Malfait, Blake and Hammell saw no significant adverse reaction from the use of the CBD therapeutics in the varying dosages. From findings from these four studies suggest there are benefits of CBD as a therapeutic in terms of inflammation, three of the studies specifically found a reduction in TNF- $\alpha$  caused by rheumatoid arthritis and one study found an increase in the anti-inflammatory cytokine IL-10.

### 6.2 Any potential for future studies

What is clear from the findings is that there is a need for global support in the funding for randomised human control trials across all sexes, ages, and races with varying doses before CBD can be considered as a therapeutic option by clinical practitioners for the treatment of rheumatoid arthritis induced inflammation. To date there is only one human trial which is included within this review, therefore, there is a limitation on research with gaps in the knowledge surrounding cannabinoids and their potentiality with regards to rheumatoid arthritis. Future studies will allow researchers to build upon and collaborate with the evidence already available. With the potential for improving and gaining further knowledge on the mechanisms of CBD and providing an avenue for drug development to aid in the reduction of inflammation seen in rheumatoid arthritis. Three further studies have been identified as a promising potential for a wider range of data, NCT04911127, not expected to be completed by June 2024. NCT04269993, completion is due Nov 2023. Also, a third trial, EudraCT 2017-004226- 1[42].

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