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Research Article

Cannabidiol in Rheumatological Diseases: Collection of Clinical and Experimental Data: A Systematic Review

Gökhan Doğukan Akarsu1[1]*, Rukiye Höbek Akarsu1[2], Meral EKIM1[3]

[1] Yozgat Bozok University School of Health Services, Department of Pharmacy Services

[2] Yozgat Bozok University, Faculty of Health Sciences, Department of Nursing

[3] Yozgat Bozok University Faculty of Health Sciences, Department of Nutrition and Dietetics

***Corresponding Author:** Gökhan Doğukan Akarsu, Yozgat Bozok University School of Health Services, Department of Pharmacy Services.

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Abstract

The aim of this systematic review is to evaluate the results of cannabidiol (CBD) in rheumatological studies. This study is a systematic review prepared according to the PRISMA checklist and Cochrane guideline. Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest databases were made by scanning English articles published between 2000-2023. "CBD, Cannabidiol, Hemp, Rheumatic Diseases, Rheumatoid Arthritis, gout, systemic lupus, fibromyalgia, Osteoarthritis, acute rheumatological fever, rheumatologic" etc. words and combinations are used. According to the results of the study, there was not enough research in the literature to evaluate the effectiveness of CBD in rheumatological diseases. Studies have shown that CBD is effective in reducing pain. In a study, it was stated that CBD caused a decrease in the levels of inflammatory markers IL6 and TNFα, and there was no change in liver function tests and kidneys. It is necessary to determine the effectiveness of CBD in rheumatological diseases. Conducting controlled clinical trials after being evaluated with experimental animal models will contribute to the literature and guide future research.

Key words: cbd; cannabis; hemp; rheumatologic disease; treatment

Introduction

Cannabidiol (CBD) is a type of cannabinoid derived from the cannabis plant. Cannabidiol can also be synthesized in the living body through the endocannaboid system [1]. When it comes to cannabis, the first thing that comes to mind is that it is a prohibited substance and has a drug nature. For this reason, it has always been kept out of sight. As a result of developing researches, it has been determined that tetrahydrocannabinol (THC) constitutes the psychoactive part of cannabis. CBD has no psychoactive properties. On 22/01/2021, the US Food and Drug Administration (FDA) reported that it approved the use of CBD in its pure form for the use of epileptic seizures [2].

Similarly, although the licensing procedures vary from country to country in the European continent, there is no general ban on the use of CBD depending on the THC content.

With the relaxation of restrictions, research is increasing and the effectiveness of CBD in some signaling pathways, disease indications and during the inflammatory response can be evaluated. In some studies, it has been reported that CBD has some positive effects against some diseases, including rheumatic diseases.

Autoimmune diseases can be organ specific or affect more than one organ. Rheumatic diseases, which are among these diseases, are a type of disease that reduces the quality of life of patients with the disease, reduces their comfort, and causes them to encounter situations that remind themselves frequently for the rest of their lives [3].

Some of the rheumatic diseases are rheumatoid arthritis, osteoarthritis, acute rheumatic fever, fibromyalgia and gout. These diseases are heterogeneous diseases with high morbidity and mortality rates [4].

The treatment of rheumatic diseases varies according to the type of the disease, and since it is not possible to cure the disease, slowing and stopping its progression is the best technique available at the moment. Although many different studies continue to be carried out to cure the disease, a fully effective remedy has not yet been found.

There are studies in the literature examining the effect of CBD on rheumatological diseases. It was aimed to compile the methods used in proportion to the dose and duration of these studies in human and animal subjects and to determine the effect of CBD by comparing the experimental results.

Materials and methods

Type of Research

This study is a systematic review prepared according to the PRISMA checklist and Cochrane guideline [5-6].

Research Strategy

CBD is a group of molecules obtained from the cannabis plant and can also be produced in the living body through the endocannaboid system. Studies have evaluated the effect of CBD against rheumatological diseases. In this systematic review, the results of the stated effect in human and animal experimental groups will be evaluated depending on the method, daily dose, dosage form and treatment duration.

Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest databases were made by scanning English articles published between 2000-2023. "CBD, Cannabidiol, Hemp, Rheumatic Diseases, Rheumatoid Arthritis, gout, systemic lupus, fibromyalgia, Osteoarthritis, acute rheumatological fever, rheumatologic" etc. words and combinations are used.

The summaries of 184 studies that formed the universe published between 2000-2023 were systematically examined, and then 8 studies that were suitable for the purpose of the study and examined the effects of CBD on Rheumatological Disease formed the sample of the study (Figure 1).

Although all searches were done by a single reviewer, full-text review and data abstraction were done in duplicate. Experimental and clinical studies examining the effects of CBD on Rheumatological Diseases were included when scanning articles. Studies examining the combined efficacy of other molecules were not included.

Inclusion criteria;

• Full text accessible,

• In the field of CBD and Rheumatological Diseases,

• About Rheumatological Diseases,

• Studies published in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Index Copernicus, Pubmed, Cochrane Library, Proquest database center between 2000-2023 were included.

In this study, PICOS;

- (P: Population): Animal and human with Rheumatological Diseases
- (I: Intervention): Creatures using CBD
- (C: Comparison): Creatures that do not use CBD
- (O: Outcomes): The effects of CBD on Rheumatological Diseases
- (S: Study design): Experimental and clinical studies using CBD for Rheumatological Diseases were included.

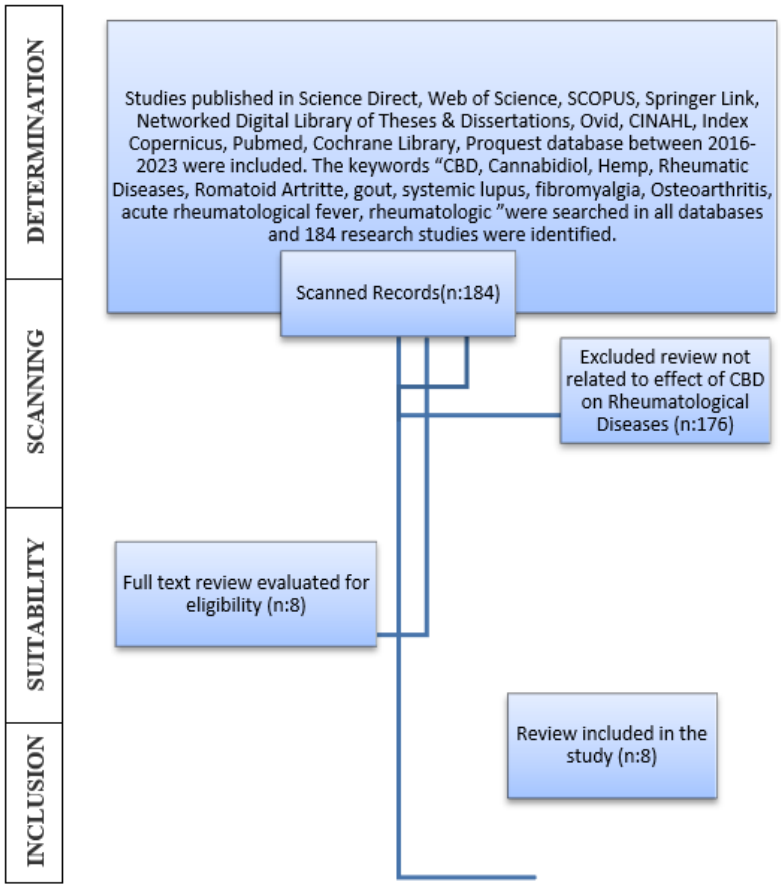

Figure 1: Prisma Flow Chart

Limitation of the study

Reviews that are not included in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Index Copernicus, Pubmed, Cochrane Library and Proquest databases and that are not recorded in the system are not included.

The limitations of the study are research on the effect of CBD on Rheumatological Diseases, accessing the same compilations with different keywords, and the low number of accessed articles. Other molecules studies are not included. If amount of THC more than 2% total medicine, it does not inclusion on data.

Ethical aspect of research

Ethical permission was not obtained because open access article were open to access were used in this systematic review. Reviews were selected by the researchers considering the PRISMA checklist.

Analysis of data

The data were evaluated using the data summary form prepared by the researchers. The data summary form includes the author, supervisor, year of the study, the purpose of the study and results of the studies. Data summary forms were evaluated independently by the researcher.

Results

The data obtained from the literature with the research are given in the table below. The table includes the name of the article, the year, the subject, the amount of CBD given and the brief results of the article (Table 1).

No	Article Name	Year	Model	CBD	Highlights
1	Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis	2017	Effect of CBD on Experimental Osteoartrit Model on Rats	100-300 ul	It has been reported that prophylactic treatment with CBD on the 1st and 3rd days after MIA induction prevents secondary allodynia, which is neuropathic pain, on the 14th day, does not increase the joint carrying capacity, reduces the inflammation due to MIA from the 7th day, and reduces the development of pain.
2	The use of cannabidiol in the treatment of pain related to scleroderma digital ulcers	2021	Effect of CBD on patient of scleroderma digital ulcers	55,2g	Patients with scleroderma digital ulcers were given CBD in olive oil and treated for 5.9±3.2 months. CBD has shown an effect from the first month and has been reported to be beneficial in reducing chronic pain.
3	Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis	2018	Effect of CBD on patient of osteoarthisis	500 mg	The gel containing 250 mg of synthetic CBD was applied twice a day to patients with osteoarthritis and a decrease in pain scores was reported after 12 weeks.
4	Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis	2006	Effect of CBD on rheumatoid arthritis patient	2,5 mg CBD	In patients with rheumatoid arthritis, oromucosal spray containing 2,5 mg of CBD was applied for 5 weeks and it was reported that the pain scores of the patients decreased after the treatment.
5	The Effect of Medical Cannabis on Pain Level and Quality of Sleep among Rheumatology Clinic Outpatients	2021	Effect of medical cannabis on chronic pain patient	Medical cannabis (include CBD)	According to the treatment results, although its effect against synovitis was low, it was evaluated that it had a greater effect on chronic pain.
6	Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial	2022	Effect of medical cannabis on osteoarthritis and psoriatic arthritis patients	Up to 30mg of CBD	It has been reported that CBD has no effect on chronic pain.
7	Oral Transmucosal Cannabidiol Oil Formulation as Part of a Multimodal Analgesic Regimen: Effects on Pain Relief and Quality of Life Improvement in Dogs Affected by Spontaneous Osteoarthritis	2020	Effect of CBD on osteoarthritis with dogs	2mg per kg	CBD has been reported to be effective in reducing pain associated with osteoarthritis in dogs.
8	A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain.	2020	Effect of CBD on patinet with osteoarthritis	CBD supplement in varying proportions	CBD; • Inflammation model created with croton oil in mice reduces TNFα and myeloperoxidase secretion in monocyte cell line, • It decreases LPS-induced TNFα and IL6 levels in a dose-sensitive manner, • When given orally, liposomal packaging increases bioavailability, • CBD given at a dose of 50 mg/day for 30 days did not change the ALT and Alpine levels of dogs. • It has been reported to increase the mobility and quality of life of dogs with osteoarthritis.

Table 1: Studies investigating the effect of CBD in rheumatic diseases.

1Holly et al. (2017), in their study, experimental osteoarthritis was induced by injection of 3 mg/50uL monoiodoacetate into the joints of rats, and 100-300 µl of CBD treatment was applied after the 1st and 3rd days. After the treatment, the joints were examined and the petal functions were evaluated using von Frey hair. The tissues were then evaluated under the electron microscope. As a result of the evaluation, it was stated that 300 µl of CBD in the treatment of experimental osteoarthritis induced with monoiodo acetate in rats reduced pain due to osteoarthritis [7].

2Giuggioli et al. (2021), prepared a 10% CBD solution in olive oil for a group of 31 patients with scleroderma, an autoimmune disease, and administered orally 3 drops of this solution 2 times a day for 5.9±3.2 months. The amount of CBD administered daily is 55.2 g. It has been reported that some patients received prostanoid infusion (31/31), calcium channel blockers (24/31) and anti-endothelin (24/31) treatments during this period. According to research results, it has been reported that CBD is effective in reducing chronic pain and may be beneficial for dysphagia [8]..

3Hunter et al. (2018), in their study with 320 osteoarthritis patients, the patients were given a gel containing synthetic CBD for 12 weeks, and the gel containing 250 mg of CBD in each dose was applied twice a day, and it was reported that a decrease in pain scores was observed after the treatment [9].

4Blake et al. (2006), in their study with 58 patients, applied an oromucosal spray containing 2,7 mg of THC and 2,5 mg of CBD, and it was reported that after the treatment, it reduced pain during movement and during rest, and increased sleep quality [10].

5Habib et al. (2021) evaluated the use of medical cannabis by patients who applied to the hospital due to rheumatological disease and reported the results of the use of controlled medical cannabis contained in CBD. According to the results of medical cannabis use, it has been reported that patients with rheumatological disease have a decrease in pain and an increase in sleep quality [11].

6Vela et al. (2022) evaluated the effectiveness of CBD in patients with hand osteoarthritis and psoriatic arthritis. It was reported that the participants in this study were given 10 mg of CBD for 2 weeks, then the dose was increased to 20 mg for 2 weeks, and those who did not have a decrease in pain were increased to 30 mg after 4 weeks, and the treatment

was continued for 12 weeks. According to the results of the study, it was reported that CBD was not statistically effective in reducing pain.[12].

7Brioschi et al. (2020), 21 dogs with osteoarthritis were tried to be treated by giving 2 mg of CBD per kg and its effectiveness in pain was evaluated. According to the results of the study, CBD was found to be effective in reducing pain in dogs.[13].

8Verrico et al. (2017) reported striking results in their mouse, dog and human study.

1. The inflammation model created with croton oil in mice reduces TNFα and myeloperoxidase secretion in the monocyte cell line, which is important for predicting the responses of CBD to diseases,

2. CBD reduces LPS-induced TNFα and IL6 levels depending on the dose given,

3. CBD changes the bioavailability of oral, topical or liposomal packaging, CBD given at a dose of 50 mg/day for 30 days does not change the ALT and ALP levels of dogs,

4. CBD has been reported to increase the range of motion and quality of life of dogs with osteoarthritis [14].

Discussion

CBD is a molecule that can be obtained from the cannabis plant, as well as produced synthetically and in the living system through the endocannabinoid system, and shows its effect by binding to the CB1 and CB2 receptors. There is a lot of research done on CBD against different diseases. Some of these have been shown to be effective in psychiatric diseases, obesity, Alzheimer's, cardiovascular diseases, Parkinson's, other neurodegenerative diseases, sleep disorders and various cancers. [15-23].

In addition to all these effects, it has been evaluated that it can affect some immune system disorders together with the CB1 and CB2 receptors it activates, contributing to the literature. Rheumatological diseases are an autoimmune disease associated with chronic inflammation. In the group of rheumatological diseases, there are rheumatoid arthritis, osteoarthritis, systemic lupus erythematous, acute rheumatic fever, fibromyalgia, myofascial pain, gout diseases. Today, intensive research continues to treat these diseases. However, although it is not possible to revert the disease in current methods, it is tried to slow down the rate of disease progression and to keep the comfort of life at the best possible level by reducing the pain.

In the studies mentioned in the results section, it was a priority to conduct the research in a controlled manner, and it was aimed to objectively examine the dose and effect given in this way. Of these studies, only studies with human and animal subjects and investigating the effects on rheumatic diseases were examined. Those who were not under the control of the researcher or the amount of the dose given could not be clearly revealed were not included. Studies have also found sources indicating that CBD is given in different doses, and even in very high amounts, it does not cause a toxic effect [24].

This provides researchers with a wide range of motion to determine the amount of dose to be used. Because of the small amount of one-time effect and the possibility of interaction with food by researchers when administering CBD to the living, some studies have shown that it is administered as a PO, BID, or TID with or immediately after meals.

Gülhan (2013), Verbeeck (2009), Franz et al. (2013) and Yarur et al. (2014), it is aimed to have a high bioavailability of a molecule in the living body. It has been reported that liver, kidney and, if used orally, intestinal adequacy should be examined in order to achieve this [25-28].

Disturbances in these stages may reduce bioavailability and cause unwanted molecular accumulations.

Another method of administration of CBD can be said to be applied topically to the area. Some of the drawbacks of this application are that it can cause excessive sensitivity in the area and cause an allergic reaction. This may be due not only to the CBD, but also to the liquid/solid ingredients that render it liquid for administration, depending on the form in which the CBD is supplied. Or it can be caused by the interaction of these ingredients with CBD. Each of these is effective in the experimental phase and needs to be pre-tested or searched from the literature.

Topical application exists in many research methods. Especially in the dermis, epidermis and hypodermis layers that make up the skin tissue, the permeability of CBD should be created. If the area to be treated is in the epidermis and dermis layers, CBD should be able to act on this area. Especially due to the texture of the skin, the absorption and storage of lipid-based products from the skin can be easier. Molecules that pass from the skin to the vascular system are metabolized in the liver and activated for biological activities. Irregularities in these stages can create toxicity. The other event is that the metabolized CBD is filtered out of the nephrons with its passage from the blood to the kidneys. This stage is just as important as the first stage. Lodzki et al. (2003) reported that after transdermal application of the etosomal system to the abdomen of ICR mice for 72 hours, steady state levels were reached in about 24 hours. Transdermal administration of etosomal CBD has been reported to prevent inflammation and edema caused by basal-plantar injection of carrageenan in the same animal model [29].

In addition, changes in kidney function tests were investigated with oral administration of CBD, but it was known that no significant change was observed [30].

Conclusion

The absorption of a molecule into the body and its removal from the body by being metabolized actually informs the half-life of the molecule. The length of the half-life also means that it remains in circulation too much. Long half-life causes side effects to gradually increase.

For this reason, it reveals that the dose adjustment protocol should be done by considering all these variables. In the literature review, detailed kidney and liver function tests results of CBD have not been found depending on the oral treatment method, and this is a major deficiency for the literature. Although it was reported that there was no change in liver function tests as a result of topical application, the effects of this effect on long-term and overdose levels should be clearly demonstrated. Animal models may be good for this.

Another important issue is that due to the presence of drug interactions, the purification process should be applied and it should not be used together with other drugs. Wilson-Morkeh (2020) mentioned this issue in his study and mentioned that drug interactions can affect the results by creating false positivity or negativity [31].

As a result, no large literature has been found in the literature on the effect of CBD on rheumatological diseases, the effects it gives to the body and its pain relief effect, as well as stopping or reducing the direct inflammatory response. For this reason, topical or oral administration should be applied separately for each of the rheumatological diseases in animal models and general patient groups in which CBD is applied.

Declarations

Ethics approval and consent to participate Not required. Consent for publication Not required. Availability of data and materials All data is given in the article. For detailed information, please contact GDA.

Competing interests

We declare that we have no conflict of interest. Funding There is no funding source. Authors' contributions

All authors contributed equally to the article.

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