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# Tapping the nutraceutical potential of industrial hemp against arthritis and diabetes - A comprehensive review

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ABSTRACT

The incidence of non-communicable diseases (NCDs) is rising at an alarming rate. Arthritis not only affects the joints but can also affect surrounding organs, which is a key factor in causing disability that impairs quality of life quality. Moreover, systemic inflammation associated with arthritis contributes to diabetes in the future. The adverse effects of pharmacological treatment and the increased incidence of joint problems have led to a strong interest in preventive medicine, compared to natural food, as an alternative approach. Among these, industrial hemp is a promising candidate with a wide array of bioactive components. Despite the concerns regarding hemp, no one can ignore its potential as an excellent antioxidant, immunomodulatory, and anti-inflammatory agent with vasodilatory properties. By affecting various molecular and cellular pathways, hemp (seed, oil, or extract) can scavenge free radicals, lower proinflammatory cytokines, inhibit T cell proliferation, and reduce immune cell migration and adhesion. Cannabidiol (CBD) may improve these functions by activating the cannabinoid type 2 receptor (CB2). Therefore, this review article provides in-depth mechanistic insight into the potential of industrial hemp against NCDs, particularly arthritis and diabetes, to achieve sustainable development goals (SDGs target # 3.4). It can be a therapeutic strategy in the current era due to the balanced ratio of linolenic acid to linoleic acid, CBD, and other bioactive components. Purposely, the legalization of hemp as an agricultural product and the market for its food ingredients is expanding. Moreover, its role in managing NCDs has gained interest as several states have legalized its use. There needs to be more thorough, controlled studies proving industrial hemp's therapeutic value for several diseases. Further, given the increased awareness regarding industrial hemp, prospective controlled trials assessing its effectiveness are needed.

## 1. Introduction

Chronic diseases, generally known as non-communicable diseases (NCDs), are medical conditions with a protracted course and slow progression. Behavioral, physiological, genetic, and environmental factors are responsible for NCDs. Moreover, they are the main cause of death worldwide, causing 71% of all deaths annually (UN, 2015; Wang & Wang, 2020; WHO, 2013). According to World Health Organization (WHO), 80% of all deaths in the globe and nearly 47% of fatalities in Asia will be caused by NCDs (UN, 2015; Wang & Wang, 2020; WHO,

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2013). In 2015, the 2030 Agenda of the United Nations identified NCDs as a major health dilemma. SDG 3 includes target 3.4, which aims to reduce one-third of NCD mortality by 2030 (Thakur, Nangia, & Singh, 2021; UNDP, 2015). SDGs are the United Nations Sustainable Development Goals, also called global goals, which are a worldwide appeal to end poverty, preserve the planet, and ensure that all people enjoy peace and prosperity by the end of 2030 (UNDP, 2015).

The key risk factors for NCDs are poor eating habits, alcohol abuse, physical inactivity, and smoking (Shazmeen Haq et al., 2021; Tian, Mclaughlin, Verma, Chinoy, & Heald, 2021). Furthermore, inflammation is prominent in advancing chronic diseases like diabetes and cardiovascular and autoimmune diseases (Abbas et al., 2023; Egea et al., 2022; Niu, Li, Zhang, & Zhou, 2023; Rakha et al., 2022). This review paper aims to cover two common NCDs, *i.e.*, arthritis and diabetes. Arthritis is a highly prevalent chronic health issue and a main cause of disability. The word "arthritis" derives from the Greek letters "arthron" and "ites", which signify the swelling of the joints. It is an inflammatory, chronic autoimmune condition that causes pain, edema, and stiffness in the synovial joints. There are over 100 types of arthritis, and the most prevalent are gout, osteoarthritis (OA), psoriatic arthritis, rheumatoid arthritis (RA), and fibromyalgia (Khaleghi, 2020). Moreover, the disease causes bone erosion and joint damage and substantially affects the patients' bodily function, emotional state, and life quality (Malm, Bergman, Andersson, Bremander, & Larsson, 2017; Tahir, Khan, Ashraf, Adan, & Mubarik, 2023). Many complex neuropathological factors lead to disease development, defined as a 'mosaic of autoimmunity' consisting of genetic, hormonal, immunological, and environmental risks, with varying combinations and various disease outcomes (Shoenfeld & Isenberg, 1989). The linked co-morbidities, including a higher risk of diabetes, obesity, and cardiovascular disease (CVD), contribute to a decrease in life expectancy (Kose, Karali, Bodur, Cekic, & Kilic, 2024; Lindhardsen et al., 2011). Surprisingly, a 61% risk of diabetes increases with the development of arthritis (Verma et al., 2021). Diabetes is a multifactorial, chronic, progressive metabolic condition and insulin resistance (Liu et al., 2023).

Moreover, persistent hyperglycemia is the hallmark of diabetes. It affects 537 million adult patients worldwide, and it is anticipated that by 2030, this amount will increase to 643 million and 783 million by 2045 (IDF, 2021; Li et al., 2022; Rasheed et al., 2022). Thus, due to its high prevalence, diabetes has gained attention on a global scale. Not only is it a chronic condition, but it also poses a serious threat to life. Correspondingly, it may result in other serious illnesses like eye damage, renal failure, and heart problems, which in turn cause blindness and foot ulcers (Centorame et al., 2022; Firtin et al., 2023; Mariam et al., 2023). In type 1 diabetes, β-cells become unable to produce sufficient insulin, but in the case of type 2 diabetes, the cells fail to react to insulin (Aarthy et al., 2021; Akhtar et al., 2023). Owing to sudden shifts in eating habits and lifestyle behaviors, their prevalence is growing in developing countries relative to the developed world.

Furthermore, in later stages, lifestyle-related disorders remain a threat to severe outcomes. Adequate and balanced food consumption (adding plants to the diet) has been the secret to a healthy life (Indahsari, Aristanto, & Rio, 2020; Muddassir & Al-Zahrani, 2022; Rakha et al., 2023; Xie, Wang, Cao, Chen, & Lin, 2022). The treatment of these diseases must be economical and beneficial. Nationally, arthritis-related medical costs were 140 billion dollars 2013, which is 2117 dollars in extra medical costs per adult in the USA (CDC, 2013). Additionally, each year, 4237 billion is directly spent on the medical cost of diabetes, signifying a huge burden on the economy (ADA, 2018). According to the United Nations Conference on Trade and Development (UNCTAD), the rising awareness of hemp's benefits in the international market could strike $ 18.6 billion by 2027 – approximately quadruple in 2020 (UNCTAD, 2022). Moreover, at a CAGR of 21.6%, the industrial hemp market is expected to rise from $6.8 billion to $18.1 billion from 2022 to 2027 (MarketsandMarkets, 2022). Consequently, CBD and other hemp products have seen a boom that could not only be beneficial financially for people who seek out hemp products for health purposes but also a hard-hit sector of the economy, such as farmers.

In this regard, the use of a remedial plant is important. Hemp has been documented to have antioxidant, anticonvulsant, and immunomodulatory properties (Hartsel, Eades, Hickory, & Makriyannis, 2016; Iftikhar et al., 2021; Mukhametov, Mamayeva, Yerbulekova, & Aitkhozhayeva, 2022; Rashid et al., 2023). Additionally, hemp-based foods, nutritional supplements, and nutraceuticals are cheap and promising solutions for the increasing population, and their commercial usage and export can be helpful for the growing economy of Pakistan (Fomo, Madzimbamuto, & Ojumu, 2020; Ghazwani et al., 2023). Despite this, interest in natural bioactive components is rising because they are reliable sources of medicine and drug discovery for people concerned about their health (Al-Saeed et al., 2023; Mohamed & Hassan, 2023; Mohammad, Kamil, Tawfeeq, & Ahmed, 2023). Epidemiological studies showed a strong relationship between a high dietary intake of phytochemicals, especially polyphenols, and a reduction in the prevalence of chronic illnesses (Mohamadi et al., 2023; Rakha et al., 2023; Samtiya, Aluko, Dhewa, & Moreno-Rojas, 2021; Wani et al., 2022). In this association, industrial hemp is renowned. Hemp (*Cannabis sativa* L.*)* is a member of the Cannabaceae family. It is regarded as the oldest to be farmed because of its extensive history of cultivation (6000 years), supported by archaeological data. However, it is challenging to pinpoint its precise origin (Wimalasiri et al., 2021). Most scientists concurred that this plant originated in central Asia. The domesticated variety of *C. sativa* L. is grown widely worldwide, including in the United States (US), Africa, Europe, and Canada. It is a versatile crop with a low environmental effect that may be used in different industries, *i.e.*, agriculture, food production, construction, cosmetics, and pharmaceuticals (Irakli et al., 2019) (Fig. 1).

The global production of hempseed is 102,416 tons (FAOSTAT, 2020). China's share in 2015 was approximately 55%. Canada is the second largest producer of cannabis seeds, with more than 25% of the world's production (Filimonova, Matys, Skvortsova, & Valiullina, 2022). According to a report of FAO Stat 2018, by area, the largest producers are Canada (555,853 ha), France (12,900 ha), and North Korea (21,247 ha) (Horne, 2020). Around 70 different hemp types are currently subjected to commercial production and distribution regulations in the European Union (Pavlovic et al., 2019). The cultivars of hemp used to make cannabidiol (CBD) are different from those used to make fiber or seeds.

Additionally, the CBD concentration is higher in female flowers. Despite the knowledge gap in the industry's advancement, numerous farmers around the United States are attempting to cultivate CBD hemp. More research must be done on CBD hemp cultivars grown under various conditions to achieve higher CBD levels while keeping tetrahydrocannabinol (THC) below 0.3 % (Adesina, Bhowmik, Sharma, & Shahbazi, 2020). There is a positive outlook for increasing interest in hemp farming for CBD. The later flowering revealed a positive correlation with the CBD content; nonetheless, 83% of the variation in CBD was due to the genetic effects (Campbell, Berrada, Hudalla, Amaducci, & McKay, 2019). Recently, (Calzolari et al., 2017) found that increased irrigation slightly improved the CBD content, which seems that high rainfall increased the CBD content. Industrial hemp is a versatile plant that has the potential to reduce the impact of carbon footprint and can be cultivated with little or no use of chemical pesticides or fertilizers (Nath, 2022).

Generally, the chemical composition of cannabis varies within the varieties. Thus, chemotaxonomic classification characterizes different genotypes into chemotypes according to the concentration of cannabinoids and their concentration (Piluzza, Delogu, Cabras, Marceddu, & Bullitta, 2013). Besides genotypes, the production and buildup of cannabinoids are affected by environmental conditions and crop management practices, including biotic stresses, light, temperature, fertilizers, plant structure, water availability, and plant density (Song, Saloner, Fait, & Bernstein, 2023). For instance, in the Xinma hemp variety, it was


**Fig. 1.** Industrial hemp in various dietary and supplemental forms.

found that blue light in high amounts stimulated the growth and buildup of THC and CBD. Ultraviolet-B irradiation has also been responsible for the increased THC content in specific varieties of cannabis (Wei et al., 2021). Nitrogen, potassium, and phosphorous-based fertilizers (nitrogen, potassium, and phosphorus) alter the buildup of secondary metabolites (Song et al., 2023). Generally, higher availability of nitrogen and potassium inclines reduces the concentration of terpenoids and cannabinoids. Thus, it is suggested to use nitrogen, potassium, and phosphorous at 160 mg/L, 60 mg/L, and 5–15 mg/L levels, respectively, to keep a higher content of secondary metabolites in the breeds of medicinal cannabis (Saloner & Bernstein, 2021, 2022). Different pruning techniques influence the chemical constituents of cannabis plants (Topaz'cultivar) (Danziger & Bernstein, 2021). Salinity has also shown an effect on the buildup of metabolic end-product metabolites in cannabis because exposure to increased salt concentrations decreased the yield and effectiveness of the "Nordle" cultivar (Yep, Gale, & Zheng, 2020). The relative proportions of Δ9-THC and CBD revealed that these compounds are rarely affected by external factors such as climate change, making them useful for differentiating cannabis genotypes via different chemotaxonomic markers (Staginnus, Zörntlein, & de Meijer, 2014). Over and above, the ratio of THC versus CBD of cannabis for evolving plant materials is crucial in the selection of genotypes appropriate for industrial and medicinal applications (Fischedick, Hazekamp, Erkelens, Choi, & Verpoorte, 2010).

The thirteen hemp varieties were taken to assess the impact of genotype on the physicochemical and antioxidant aspects of hempseed. The crude protein, crude oil, crude fiber, and ash content in the tested hemp seeds were 26.48–32.03%, 28.03–33.23%, 28.78–36.55%, and 5.43%–6.32%, respectively. Physical analysis showed that compared to the standard weight of 44 Ibs/bu, a relatively low-test weight of 36.85 lbs/bu was observed. About 80% of unsaturated fatty acids were present in hempseed oil. In hydrolysates from different hempseed varieties, a great variation was shown in the DPPH scavenging activities (0.37–28.78%). This study offers a complete understanding of the potential of hemp as a new crop in agricultural systems (Xu, Zhao, et al., 2021).

Several genetic and environmental factors influenced the quality parameters of hemp seeds. Thus, hemp seed (Finola cultivar) grown at three locations within two years (2013–2014) in Slovakia (Borovce, Vígľaš-Pstruša, Milhostov) were selected to assess the impact of the environment on the chemical composition of hemp seed. Findings revealed that the average content of total dietary fiber, proteins, and lipids was 36.10 ± 1.92%, 24.66 ± 0.55%, and 32.05 ± 0.42%, respectively. About 75% of fatty acids in oil were linoleic, α-linolenic, and oleic. The total dietary fiber, lipids, and fatty acids content were notably influenced by the year of cultivation. In contrast, the maturity of seeds influenced proteins, gadoleic, and arachidonic acids. Moreover, the growing location also significantly affected the content of all these primary metabolites (Lančaričová et al., 2021).

The processing of hemp seed produced a wide array of products. Milling dehulled or whole seeds into flour leads to separating nutrient-rich oil and protein fractions. Furthermore, phytochemical extracts are gaining attention for their role in health and nutrition (Rupasinghe, Davis, Kumar, Murray, & Zheljazkov, 2020). Microwave processing improved the yield of oil and vitamins (carotenoid and tocopherol %) but did not change the composition of fatty acid and increased resistance to oxidation (Oomah, Busson, Godfrey, & Drover, 2002). Similar quality oil (fatty acid composition) was extracted from hemp seed using supercritical $CO_2$, cold pressing, or solvent extraction; however, supercritical extraction yielded oil with a higher amount of tocopherol but a lesser pigment than cold-pressed oil. Due to the high temperature, tocopherol contents were lost in solvent-extracted hemp seed oil but contained a moderate level of pigments compared to the other two methods (Aladić et al., 2015). Additionally, a comparison was performed between conventional and novel approaches for phytochemicals extraction, and results revealed that oil obtained from the ultrasound-assisted method contains a higher amount of polyphenols and flavonoids and extracts with increased antioxidant capacity (Teh & Birch, 2014). Over and above, these extracts are used for designing health-promoting functional foods (Rupasinghe et al., 2020).

Targeting inflammatory pathways as part of a plan to prevent or control arthritis and its consequences has stimulated interest due to a better knowledge of the mechanisms linking inflammation to diabetes and related disorders. Research must prioritize both prevention and management due to the rise in the prevalence of NCDs, especially arthritis and its consequences, such as diabetes. Although hemp and medicinal cannabis are both members of *C. sativa* L. plant species, they grow differently and have different phytochemical compositions. Agricultural hemp cannot have more than 0.3% THC content (Acosta & Almirall, 2021).

Moreover, hempseed is a good fiber, oil, protein, and micronutrient source (Xu, Li et al., 2021). Also, "cannabinoids" with various medicinal characteristics are in higher demand. Cannabis used for illicit purposes is referred to as marijuana, while industrial varieties are known as industrial hemp. The largest research institutions in the world are currently engaged in scientific research to find hemp varieties with low

THC content and unique particular genotypes in cannabis plants (Salami et al., 2020). The conventional drugs that have been associated with adverse effects and lead to other health issues should be replaced by natural food ingredients that not only have the potential to reduce the risk but also can treat the diseases. There is a dire need to explore the health benefits of more food ingredients commonly used in our households. Moreover, Pakistan, committed to SDGs, strives to meet the global health target, poverty alleviation, and sustainable development (Decouttere, De Boeck, & Vandaele, 2021; Hossain et al., 2021).

Thus, this article aims to gather evidence of the recent advances of hemp for its use against NCDs with special reference to arthritis and diabetes in the context of SDGs (target # 3.4) while highlighting gaps and future research on this high-value plant. Based on the data of different intervention studies and clinical trials, this pioneered review exploits the benefits of industrial hemp, either supplements or its active components against arthritis and diabetes. In this context, literature was reviewed by using advanced options of search on Google Scholar, Science Direct, PubMed, and Scopus with the subsequent Keywords: Cannabis, hemp or industrial hemp, SDGs, sustainable plant, polyphenols, nutritional composition, or CBD or benefits of hemp or hempseed, NCDs, hempseed oil or inflammation, or diabetes, or arthritis, joints, association of diabetes and arthritis.

### *1.1. History and driving barriers to hempseed consumption*

In North America, hemp was cultivated as a staple crop from the middle of the 18th century till the 1930s. It was categorized as "marijuana" in the 1930s, and the Narcotics Control Act prohibited its production in Canada (Tang, Ten, Wang, & Yang, 2006). The United States industrial hemp cultivation area and industry substantially declined after the 1937 Marijuana Tax Act (Deitch, 2003). However, the ban was temporarily removed when World War II broke out because no other fiber sources were available (Callaway, 2004). As a key historical note, the US Department of Agriculture (USDA) created a video, "Hemp for Victory," to encourage farmers to cultivate hemp. After this war, the restriction was reinstated, and investment in the sector declined as they were switched to other crops (Farinon, Molinari, Costantini, & Merendino, 2020). Industrial hemp was still produced to some extent in China, Eastern Europe, France, and Spain, in contrast to North America, where it was illegal to do so. Hemp production declined in Europe and America in the late 19th century. Additionally, following World War II, synthetic fibers like polyester, acrylic, and nylon became major competitors in the late 1930s and 1940s (Deitch, 2003).

In 1998, the sixty-year ban on hemp cultivation was repealed, and the industrial hemp regulation program was implemented to strictly regulate Canada's hemp farming activities. Due to its link with medical cannabis, industrial hemp was culpable (Tang et al., 2006). If the dried plant material of hemp contains THC (more than 0.3 %), neither North America nor Europe will permit its sale (Acosta & Almirall, 2021). Some countries, like France, set this limit at 0.2% THC. Furthermore, State Agriculture Departments and "Institutions of higher education" in the USA were allowed to cultivate hemp as part of the program under the 2014 Farm Bill. Previously, all varieties and subvarieties of hemp were listed as Schedule I illegal substances. The Farm Bill 2018 authorized hemp and added it to the list of covered commodity crops for crop insurance (Rupasinghe et al., 2020). Globally, hemp is a crop that produces both grain and fiber. However, the extraction of CBD from hemp has recently made it one of the most valuable commodities. Hemp produced for CBD is becoming a substantial commercial crop in various US states.

Meanwhile, public perception of hemp has shifted in the Western world due to the growing usage of cannabis as a psychoactive substance. The distinction between "Industrial Hemp" and "drug hemp," however, continues to be poorly understood, especially in the general population. There is still a lack of knowledge and stigma around hemp, particularly among the community. Thus, research towards the potential benefits of hemp is still stigmatized by the negative beliefs about the drug type hemp, which discourages investment regarding industrial hemp. Meanwhile, the literature regarding the nutritional profile of hempseeds is present, but much research has not yet been done on the potential health benefits of hemp-based products (Farinon et al., 2020).

## 2. Nutritional and phytochemical composition

Hemp is getting attention due to its multiple bioactive compounds with many health benefits (Liu et al., 2022). Hempseed contains significant dietary fiber, minerals, vitamins, protein, and oil (Xu, Li et al., 2021). A study determined the chemical constituents of 29 distinct varieties of hemp seeds. All hempseed varieties exhibited significant differences for all measured parameters. Crude protein contents varied from 21.6 to 28.9%, and crude fat contents ranged from 21.1 to 35.7%, respectively. The three major fatty acids were oleic acid, linoleic acid, and α-linolenic acid, present in the following amounts: 11.08–17.81%, 52.79–57.13%, and 12.62–20.24%, %, respectively. In all the varieties, all indispensable amino acids were present, with arginine from 12.66 to 17.56 mg/100 g being the most abundant; however, lysine was limiting. The major macro mineral was potassium, which ranged from 509.96 to 1182.65 mg/100 g, and the concentration of micromineral iron was 5.06–32.37 mg/100 mg. All the cannabinoids were present in trace amounts, and THC was only found in the five varieties. Therefore, the chemical composition of whole seeds makes them appropriate to be incorporated into the diet of humans and animals (Arango et al., 2024). Furthermore, an in-vitro was designed to examine the metabolite profile and biological properties of ethanolic extracts of the stem and seed of hemp (Cheongsam cultivar). Results revealed that seed extract presented higher antioxidant and anti-inflammatory activity than stem extract (61.20% versus 38.73%). Likewise, the lipase inhibition due to seed was 76.14%, while due to stem was 61.61%. α-glucosidase inhibitory activity of seed extract was 83.70%, and stem extract was 70.19%. Overall, the seed extract exhibited higher inhibitor activity than the stem extract. Seed extracts also contained higher total phenolics, tannins, and saponins than hemp stems. The major polyphenolic compounds in hemp seed were quercetin, apigenin, and rutin 42.50 μg/g, 15.55 μg/g, and 5.22 μg/g, respectively. At the same time, ferulic acid, caffeic acid, and *p*-coumaric acid were present in trivial amounts in the following ratios: 1.71 μg/g, 0.25 μg/g, and 2.85 μg/g. The findings stated that 'Cheongsam' hemp seeds are a good source of bioactive compounds and hold anti-obesity, antioxidant, anti-diabetic, and anti-inflammatory properties, which could make them a promising functional item in the food industry (Aloo, Kwame, & Oh, 2023).

Apart from the stem and whole seeds, cold-pressed hemp seed oil (Finola cultivar) has been characterized by in vitro antioxidant activity and high-performance liquid chromatography (HPLC). It was found that Finola hemp seed oil exhibited high antioxidative activity against DPPH (146.76 mmol of TE/100 g oil), 2,2′- casino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) (695.2 μmol of TE/100 g oil), ferric-reducing antioxidant power (3690.6 μmol of TE/100 g oil), and inhibited the bleaching of β-carotene, scavenged a chemically formed peroxyl radical and manifested higher ferrous ion sequestrating activity. The obtained oil contained a significant amount of phenolic compounds, of which 2780.4 mg of QE/100 g total flavonoids were present. Overall, the oil manifested higher antioxidant activity as compared to lipophilic and hydrophilic fractions, which might depend on the phenolics of oil, particularly flavonoids, such as flavanols, flavanones, isoflavones, and flavonols (Smeriglio et al., 2016).

Industrial hemp inflorescences are a source of biomolecules with pharmaceutical interest. Thus, a study was undertaken to determine the anti-fungal effect of essential oils obtained from Futura 75, Eletta compana, and Carmagnola selezionata hemp varieties. Side by side, the inhibitory effects of the essential oil against tyrosinase, the production of prostaglandin E2 in isolated mouse skin cells, and human H1299 lung adenocarcinoma cells exposed with hydrogen peroxide ($H_2O_2$), and gene

expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). In the essential oils, *E*-caryophyllene and α-pinene were the major terpenes, while out of other terpenes, terpenophenol (cannabidiolic acid) was present in higher concentrations. Due to the presence of these compounds, it was observed that essential oils suppressed the growth of all evaluated fungi. Moreover, in isolated skin specimens, they prohibited synthesizing prostaglandin E2 induced due to hydrogen-peroxide in parallel with the intrinsic antityrosinase activity. At the same time, in H1299 cells, all examined oils also decreased the expression of ACE-2 and TMPRSS2 genes. Hence, these findings highlight using hemp essential oils for treating infectious diseases (Orlando et al., 2021). Numerous bio-actives with potential biological effects have been discovered that have made cannabis species the most vital plant in human history. These compounds include 100 cannabinoids, more than 120 terpenoids, 27 nitrogenous compounds, 34 glycosidic compounds, 50 hydrocarbons, 18 amino acids, 22 fatty acids, 25 non-cannabinoid phenols, 11 proteins, 13 ketones, 21 simple acids, 13 simple lactones and esters, 12 aldehydes, vitamin K, 11 steroids, 7 alcohols, and 9 trace elements (Hazekamp, Fischedick, Díez, Lubbe, & Ruhaak, 2010). Some biologically active components present in industrial hemp are mentioned in Fig. 2. Interestingly, 50 mg of hempseeds gives more than 100% of the daily dosage of vitamins E, D, and A and provides 50–100% of the daily magnesium, zinc, and copper intake. These values are derived from the "Dietary Supplement Ingredient Database" by the US Department of Agriculture (Andrews et al., 2018; USDA).

Data indicate that hemp was identified with 189 lipids (52 phospholipids and 80 sulfolipids). Solid-liquid extraction was performed using chloroform and methanol (1:1 v/v) to identify these compounds (Ding, Morozova, Scampicchio, Morini, & Ferrari, 2022). Furthermore, the graphitized carbon black solid phase extraction was performed to separate phospholipids and sulfolipids into different eluates. After extraction, the hemp extracts were evaluated by ultra-high-performance liquid chromatography hyphenated with high-resolution mass spectrometry, and lipids were analyzed by Lipostar (Antonelli et al., 2020) and 147 compounds from proanthocyanidins, phenolic acids, and flavonoids. Ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry was used to identify polyphenols and their derivatives with the help of Compound Discoverer software (Cerrato et al., 2020). Along with this, hemp has been found to contain a variety of cannabinoids, including cannabichromene (CBC), cannabielsoin cannabicyclol, cannabigerol (CBG), cannabinol, and cannabitriol (Gupta, Srivastava, & Lall, 2019). Despite this, their interaction with the endocannabinoid system, which contains ligands

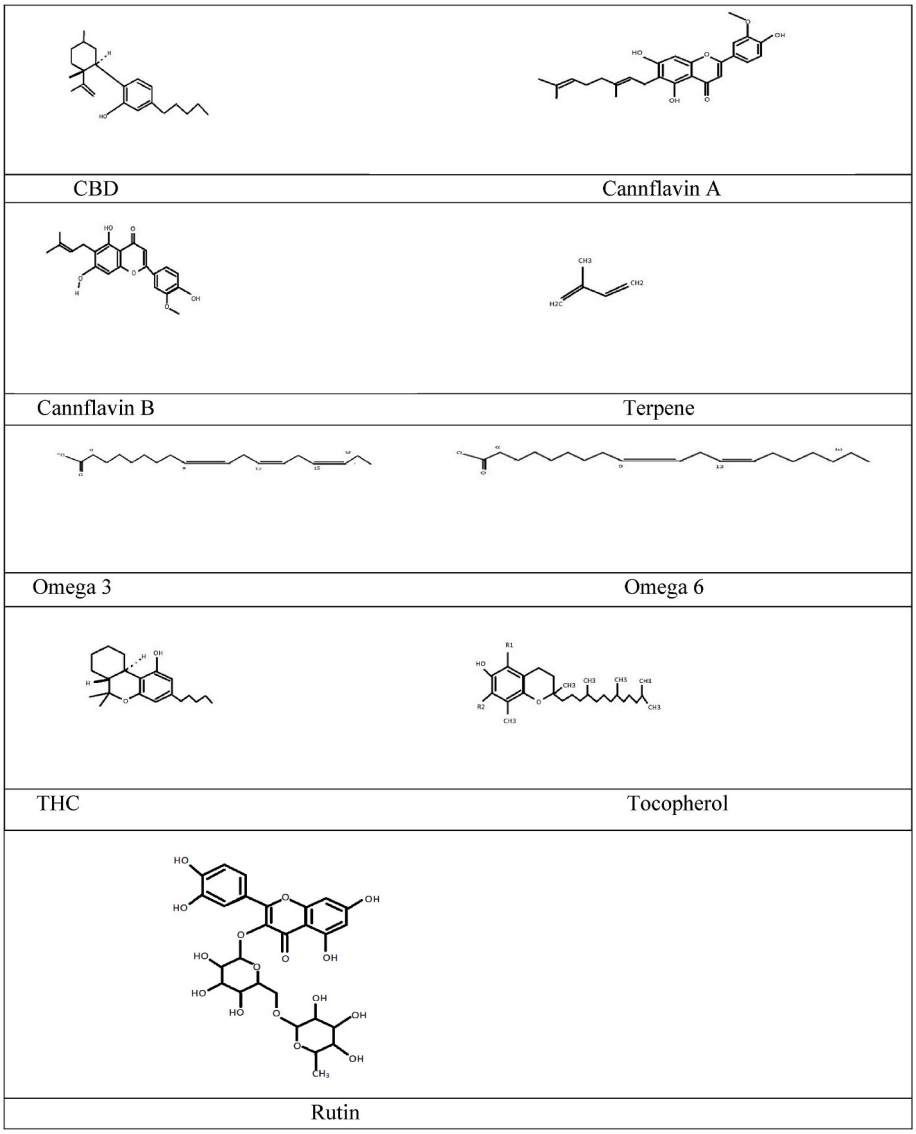


**Fig. 2.** Some biologically active components of industrial hemp.

(2-arachidonoylglycerol and anandamide) and two G protein-coupled receptors of cannabinoids (CB1 and CB2), can be used to explain some of their biological activity (Di Marzo & Piscitelli, 2015). Vitamin E is found in hemp oil and some other bioactive components, comprising polyphenols, phytosterols, carotenoids, minerals, and vitamins that improve the nutrient profile of the oil (Liang, Appukuttan Aachary, & Thiyam-Holländer, 2015). Tocopherols (0.1%), sterols (0.7%), and phenolic compounds in hempseed are effective for anti-inflammatory benefits (Xu et al., 2021; Yu, Zhou, & Parry, 2005). Table 1 shows the nutrient profile of industrial hemp. The whole seed comprises roughly 30 % carbohydrates, 25 % protein, 15% insoluble fiber, zinc, phosphorus, magnesium, carotene, potassium, iron, calcium, sulfur, and vitamins B3, B2, B1, B6, C, and E. The chemical composition of hempseed was determined by AOAC methods (Borhade, 2013). Moreover, the stalk of the plant is formed of multiple layers. The epidermis protects the stalk cells against humidity.

**Table 1**
The nutrient profile of industrial hemp.

| Main group | Nutritional profile | References |
|---|---|---|
| Carbohydrates | Dietary fiber, mainly insoluble (15%) | Farinon et al. (2020) |
| Protein | 60–80% are globulins, whereas albumins comprise most.<br>Whole seed contains 3.74–4.58% of glutamic acid followed by arginine (2.28–3.10%)<br>Sulfur-containing amino acids: methionine and cysteine. | Sun, Sun, Li, Wu, and Wang (2021)<br>Aluko (2017) |
| Fat | Unsaturated fatty acids (90%), out of which 70%–80% are PUFAs (50–60% omega 6 and 20–25% omega 3) | Abdollahi, Sefidkon, Calagari, Mousavi, and Mahomoodally (2020) |
| Vitamins | Vitamin A, D, E | Andrews et al. (2018) |
| Minerals | P, Mg, Na, K, Ca, Fe, Mn, S, Zn, Cu, | Leonard, Zhang, Ying, and Fang (2020) |
| Phytonutrients | Tocopherols, carotenoids, sterols | Leonard et al. (2020) |
| Phenolic compounds | **Hydroxycinnamic** (Caffeic acid, caffeic acid hexoside, chlorogenic acid, ferulic acid, *trans-p*-coumaric acid, *N*-trans caffeoyl tyramine, *N*-trans-caffeoyl octopamine, *N*-trans coumaroyloctopamine, *N*-trans-coumaroyltyramineae, *N*-trans-feruloyltyramineae, sinapic acid)<br>**Lignanamides** (Cannabisin B, cannabisin A, cannabisin D, cannabisin C, cannabisin E, cannabisin G, cannabisin F, cannabisin M, cannabisin O, cannabisin Q, cannabisin N, cannabisin A derivative, grossamidee)<br>**Hydroxybenzoic acid** (*P*-coumaroyl-tartaric acid, protocatechuic acid, caffeoyl-tartaric acid, gallic acid, *p*-hydroxybenzoic acid, hydroxytyrosol hexoside, hydroxybenzoic acid hexoside, and vanillic acid)<br>**Flavonoids** (Apigenin, catechin, daidzein, dihydro kaempferol hexoside, epicatechin, eriodictyol, eriodictyol-7-*O*-glucoside, genistein, hesperidin/ neohesperidin, isorhamnetin-*O*-hexuronide, isorhamnetin-*O*-rutinoside, kaempferol-*O*-hexoside, kaempferol-*O*-rutinoside, kaempferol-*O*-hexuronide, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-rutinoside, kaempferol hexuronyl methyl ester, naringenin, luteolin, naringin, naringerin-7-*O*-glucoside, quercetin-*O*-hexoside, quercetin, quercetin-*O*-hexuronid, rutin, quercetin-3-*O*-glucoside, and quercetin-3-*O*-rutinoside | Faugno et al. (2019)<br>Zhao, Wang, Li, Sun, and Wang (2022)<br>Smeriglio et al. (2016) |
| Anti-nutritional factors | Trypsin inhibitors, tannins, saponins, phytic acid, and cyanogenic glycosides | Burton, Andres, Cole, Cowley, and Augustin (2022) |

Besides, hemp hurds comprises 23.0% lignin, 25.0% hemicellulose, 44.0% alpha-cellulose, 4.0% extractives (pectin, proteins, oil, and amino acids), and 1.2% ash. The protein fraction was examined by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE). At the same time, HPLC determined the free amino acids, and pectin identification was done by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) method. Total ash, acid-insoluble lignin, and acid-soluble lignin were measured by TAPPI T 211 om-02 (ash determination method no.), TAPPI 222 om-06 (acid insoluble lignin determination method no.), TAPPI UM-250 (acid soluble lignin determination method no.) respectively (Gandolfi, Ottolina, Riva, Fantoni, & Patel, 2013). The roots of cannabis include triterpenoids, epifriedelanol (21.3 mg/kg), friedelin (12.8 mg/kg); carvone, alkaloids, dihydro carvone; *N*-(p-hydroxy-β-phenylethyl)-p-hydroxy-trans-cinnamamide (1.6 mg/kg); anhydrocannabisativine (0.3 mg/kg); cannabisativine (2.5 mg/kg) various sterols like campesterol (0.78%), sitosterol (1.5%), and stigmasterol (0.56%); as well as choline. All these components were identified by chromatographic analysis and their structure was determined by spectral analysis (Ryz, Remillard, & Russo, 2017). In addition, gucuronic acids, *C*-glycosides of apigenin and kaempferol were present in the leaves with a total amount of 3.8, 6.1, and 7.8 mg/g, respectively These compounds were identified with the HPLC coupled with Mass Spectrometry (Nagy, Cianfaglione, Maggi, Sut, & Dall'Acqua, 2019). Table 2 shows the composition of different parts of industrial hemp and their mechanism of action.

## 3. Industrial hemp in the context of SDG's

The report, "Industrializing Hemp to Advance the United Nations' 17 SDGs,'" suggests that academic institutions are crucial in addressing the research gap about industrial hemp and exemplify its versatility for advancing global health. Given this, hemp is harvesting a new drive in areas such as agriculture, technology, energy, health care, policy-making, and more (GHI, 2022; Ostrowski, 2022a). The 2030 Agenda for SDGs represents a basic framework to support sustainable development (Grosso, Mateo, Rangelov, Buzeti, & Birt, 2020). Importantly, hemp, a gluten-free plant, is gaining recognition as a valuable and sustainable resource in the era of SDGs (Fig. 3). It offers numerous industrial outputs while having a reduced impact on the environment compared to other crops. Hemp's potential as a valuable industrial resource and its sustainability as a plant was initially hindered by misconceptions about marijuana, leading to limited cultivation and use at the industrial level. However, as the distinctions between hemp and marijuana have been clarified, the market of industrial hemp is experiencing rapid growth (Yano & Fu, 2023). By 2030, industrial hemp may be effectively used to help achieve the 17 SDGs of the United Nations (Ostrowski, 2022a). One notable aspect of hemp's sustainability is its cultivation process, which requires fewer pesticides and less water than crops like cotton. This characteristic reduces the environmental impact associated with agricultural practices (SDG 12: Responsible Consumption and Production) (Yano & Fu, 2023).

Regarding income, hemp cultivation can provide income opportunities for farmers, especially in rural areas where poverty is prevalent (SDG 8: Decent Work and Economic Growth) (Barnes, Parajuli, Leggett, & Suchoff, 2023). Hemp has been extensively recognized for eras in nearly every region, as well as by today's people across the globe, as a sustainable crop. From national to local levels, a significant % of poverty can be rapidly reduced in three fundamental ways through wide-scale adoption of hemp farming by quickly reducing unsustainable energy

**Table 2**
The composition of different parts of industrial hemp and their mechanism of action.

| Hemp parts | Nutritional composition | Mechanism | References |
|---|---|---|---|
| Hemp seed | 30 % carbohydrates, 25 % protein, 15% insoluble fiber, phosphorous, magnesium, carotene, potassium, sulfur, iron, calcium, and zinc, as well as vitamins B3, B2, B1, B6, C, and E | Hemp seed extract: Upregulated the markers of osteoblast formation, thus improving bone metabolism.<br>↑Microbial glycolytic activity of β-glucosidase and α- and β-galactosidase<br>↓Hepatic lipogenesis,<br>Improve blood sugar levels and the growth of healthy gut bacteria. | Borhade (2013)<br>(Maurotti et al., 2021; Opyd, Jurgoński, Fotschki, & Juśkiewicz, 2020) |
| Hemp stalk | 23.0% lignin, 25.0% hemicellulose, 44.0% alpha-cellulose, along with 4.0% extractives (pectin, proteins, oil, and amino acids), and 1.2% ash | Ethanolic extract of hemp stems both in-vivo and in-vitro:<br>↓Oxidative stress,<br>↓Inflammatory cytokines,<br>Normalized the activation of proapoptotic proteins,<br>Counteracts apoptosis. | (Gandolfi et al., 2013; Kim et al., 2022; Zimniewska, 2022) |
| Hemp root | Triterpenoids, epifriedelanol (21.3 mg/kg), friedelin (12.8 mg/kg); carvone, and dihydrocarvone; *N*-(p-hydroxy-β-phenylethyl)-p-hydroxy-trans-cinnamamide (1.6 mg/kg); anhydrocannabisativine (0.3 mg/kg); alkaloids, cannabisativine (2.5 mg/kg) and various sterols like campesterol (0.78%) sitosterol (1.5%), and stigmasterol (0.56%); as well as choline. | Hemp roots extract:<br>Improved blood glucose homeostasis,<br>Protect the function of islets in diabetic mice,<br>↓Cell apoptosis, ↓Inflammatory signaling induced by cytokine. In skeletal muscles, normalized the defects of insulin-signaling and regulate apoptotic response in the kidney and liver,<br>↓Proinflammatory cytokines (in vitro). | (Huang et al., 2023; Kim et al., 2023; Ryz et al., 2017) |
| Hemp leaves | Gucuronic acids and *C*-glycosides of apigenin and kaempferol with a total content of 3.8, 6.1, and 7.8 mg/g in leaves, respectively. | ↓Production of nitric oxide and inflammatory prostaglandins,<br>↓Biomarkers of inflammation,<br>↓α-glucosidase inhibition. | (Duangnin et al., 2017; Nagy et al., 2019; Suttithumsatid, Shah, Bibi, & Panichayupakaranant, 2022) |

and resource-based frictions, enhanced approach to regionally grown healthy and nutritious foodstuffs for both humans and livestock, establishing an infrastructure for carbon-neutral farming, processing, manufacturing and consumption with enormously positive economic and ecological impacts throughout every level human society (SDG 1: No Poverty) (Raihan & Bijoy, 2023). One noteworthy benefit of hemp is its capacity to produce and allot economic capital at the local, regional, and national levels. It is evidenced that this kind of financial growth can potentially strengthen education (SDG 4: Quality Education) (Raihan & Bijoy, 2023).

Hemp has a high nutritional value comparable to soy and provides various utilities through its various plant parts, including food, fiber, and construction materials. In the food industry, hemp protein has garnered attention due to its nutritional composition and functional properties. Recent research has explored its applications in various food processing methods. Hemp protein has been utilized in producing plant-based milk, meat, emulsifiers, fortification of gluten-free bread, and membrane formation. Promoting hemp agriculture and incorporating it into food systems can enhance nutrition and contribute to food security (SDG 2: Zero Hunger) (Yano & Fu, 2023). Hemp has been utilized traditionally for medical purposes. The plant contains cannabinoids, including CBD, which has shown potential in alleviating pain, reducing anxiety, and managing certain health conditions (SDG 3: Good Health and Well-being) (Hilderbrand, 2018). Additionally, hemp is known for absorbing pollutants and contaminants from the soil, including heavy metals (SDG 6: Clean Water and Sanitation) (Placido & Lee, 2022). The hemp biomass for the production process of biofuels, which are a renewable and cleaner alternative to fossil fuels, helps to reduce the emission of greenhouse gases emissions and promotes the transition towards a more sustainable energy system (SDG 12: Responsible Consumption and Production) (Ahmed, Islam, Mahmud, Sarker, & Islam, 2022).

Hemp is a regenerative plant that helps restore organic matter and degraded soil. Some specific strains of hemp are farmed specifically for phytoremediation (the usage of plants to remove pollutants from soil, water, or air) (SDG 15: Life on Land) (Raihan & Bijoy, 2023). The Cannabis plant can potentially lessen the discharge of harmful pollutants into the rivers and sea resulting from practices in agriculture such as cotton cultivation, topsoil degradation, and livestock farming (SDG 14: Life Below Water) (Raihan & Bijoy, 2023).

Hemp industrialization has a large and growing impact on the broader economy, from jobs to tax revenue to commercial real estate. At the early stage, industrialization affords a fresh opportunity to anchor equity and create structures for improving social, economic, and health gaps locally and globally. Thus, it makes a powerful framework for the mobilization of resources and the development of the infrastructure of hemp to advance equality (SDG 10: Reduced Inequalities) (Ostrowski, 2022b). The key benefit of industrial hemp is inherent in its ability to generate carbon-neutral alcohol and biodiesel. Applying hemp biofuel can significantly reduce the carbon emissions linked to human actions while offering environmentally friendly energy sources (SDG 7: Affordable and Clean Energy) (Raihan & Bijoy, 2023). The Cannabis plant has been originated to mitigate the adverse effects of climate change, such as global warming, by capturing carbon, substituting fossil fuels with hemp-derived biofuel, and reducing deforestation (SDG 13: Climate Action) (Raihan & Bijoy, 2023).

Moreover, this plant has the potential to help as a raw material to produce more than 20,000 consumer goods. The transition from traditional petroleum-based products (wood and plastic) to hemp is controlled, which has led to a greatly transformative era. In the milieu of development, exploiting a highly versatile multipurpose crop can produce a broader variety of vital resources such as medicine, housing, and clothing (SDG 9: Industry, Innovation, and Infrastructure) (Raihan & Bijoy, 2023). The implementation of a program intended to release individuals from jails who are in prison due to minor drug offenses and engaging them in various sectors of the hemp industry can contribute to

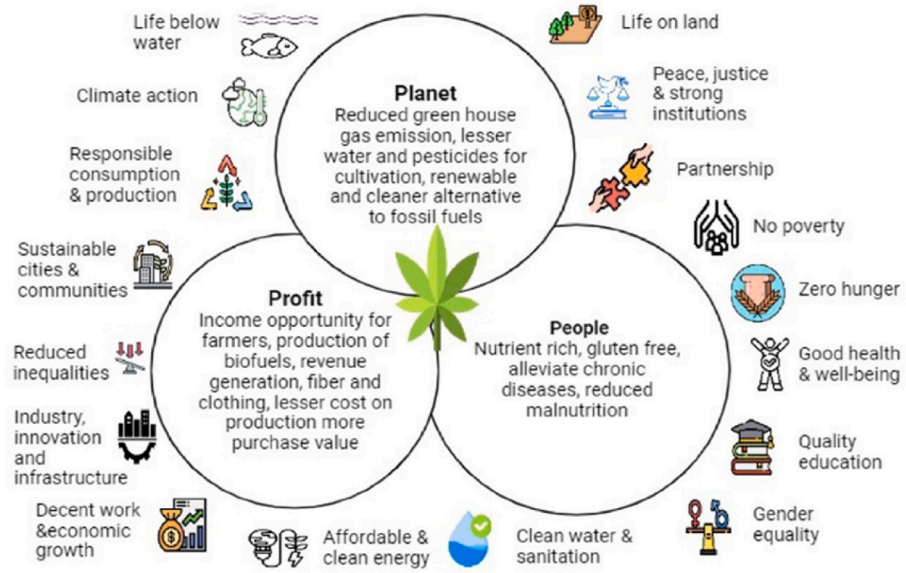


**Fig. 3.** Industrial hemp as an approach to sustainable development.

the ending of the worldwide operation against illicit narcotics (SDG: Peace, Justice, and Strong Institutions) (Raihan & Bijoy, 2023).

Over and above, hemp can make significant contributions to SDGs. It is important to note that achieving the SDGs requires a comprehensive and multi-faceted approach (SDG 17: Partnerships for the Goals). Collaboration between governments, industries, and communities is crucial for maximizing the potential of industrial hemp and integrating it effectively into sustainable development strategies (Moallemi et al., 2020; UN, 2016). This review unveils the novel therapeutic potential of industrial hemp in addressing arthritis and diabetes within the framework of SDG 3.4 (Fig. 4).

## 4. Inflammation: key risk factor in diabetes

Before discussing how inflammation is linked with diabetes, the etiology and pathophysiology of both diseases are detailed in the sections below.

### 4.1. Etiology of arthritis

The different types of arthritis have distinct kinds of etiology. The major contributive factors in osteoarthritis are advancing age, joint trauma, female sex, and obesity. Some genetic factors are mutated genes encoding types II, IV, V, and VI collagens (Reginato & Olsen, 2002; Siva, Velazquez, Mody, & Brasington, 2003; Wu, Fu, He, & Wang, 2023). On the other hand, RA is a systemic inflammation triggered due to autoimmunity. An interaction between the genetic factors such as human leukocyte antigen class II histocompatibility D related beta chain (HLADRB1) and environmental factors, i.e., smoking-induced stimulation and dysfunctional immune system, promotes inflammation in RA. Septic arthritis is a rarely seen acute arthritis in the general population. Still, some patients with predisposed risk factors, i.e., intravenous narcotics use, diabetes mellitus, weak immunity, rheumatoid arthritis, and older age, are at a greater risk. Moreover, it can often occur in patients with other autoimmune diseases, such as systemic lupus erythematosus

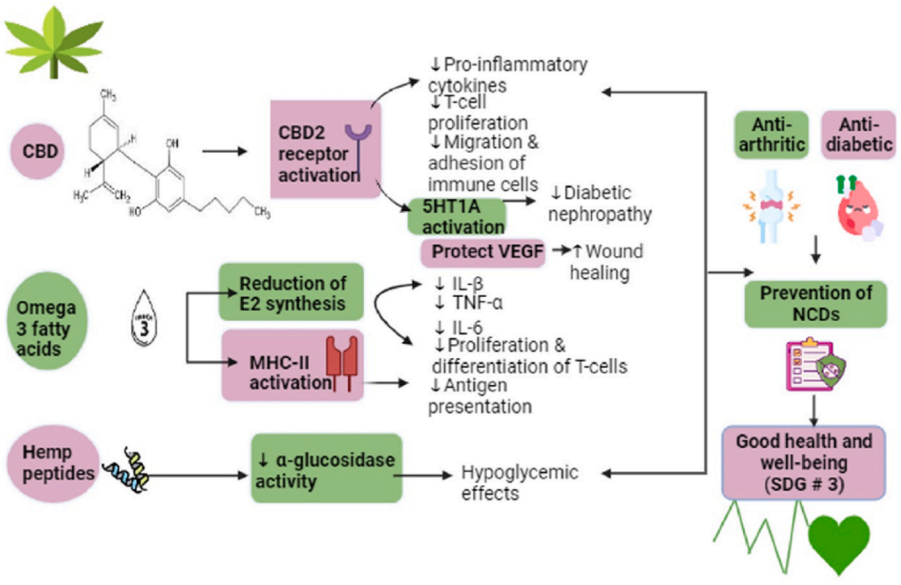


**Fig. 4.** The potential of industrial hemp against arthritis and diabetes within the context of SDG# 3.

(SLE) (Senthelal, Li, Ardeshirzadeh, & Thomas, 2018; Surianarayanan, Menon, Sundersingh, & Raja, 2024).

### 4.2. Pathophysiology of arthritis

In the synovium, many patients develop autoantibodies, which are produced by plasma cells before the development of the overt disease, and ultimately, autoimmunity is shifted towards immune-mediated inflammation (Floca et al., 2022; Klareskog, Rönnelid, Saevarsdottir, Padyukov, & Alfredsson, 2020). In RA, the synovium is infiltrated by innate immune cells (monocytes, mast, dendritic cells) and adaptive immune cells (B cells, T-helper 1, Th1; T-helper 17, Th17, and plasma cells), which activates the synovial fibroblast-like synovial cells (FSC). However, the synovium lacks neutrophils, which enter the synovial fluid from the blood (Cao et al., 2022; Fang, Zhou, & Nandakumar, 2020; Sultan, 2023).

Within the synovial compartment, chemokines and cytokines, *i.e.*, granulocyte-monocyte colony-stimulating factor (GM-CSF), interleukin-6 (IL-6), and tumor necrosis factor (TNF) stimulate the endothelial cells and attract immune cells (Derksen, Huizinga, & Van Der Woude, 2017). The FSC in the synovium tends to spread aggressively. Along with inflammatory cells, FSC produces receptor activators of nuclear factor kappa beta (RANKL), promoting osteoclast generation and resulting in bone erosion. Disease onset requires a second trigger, which, when established, stimulates the joint-to-joint migration of fibroblast-like synoviocytes (FLS), resulting in severe joint damage (Dong, Wang, Zhang, Cao, & Wu, 2022; Ji & Xu, 2022; López-Mejías et al., 2019).

The immune system, including innate and adaptive immunity, is involved. The innate immune response involves macrophages producing various substances, such as TNF, IL-6, IL-1, GM-CSF, IL-15, IL-18, IL-32, and chemokines, to promote tissue inflammation. Other cells, like endothelial cells and neutrophils, allow the movement of immune cells to the synovia and produce reactive oxygen intermediates, prostaglandins, and proteases, which leads to cartilage destruction (Fang et al., 2020; McInnes & Schett, 2011, 2017; Tang et al., 2023). Proinflammatory cytokines, PGDF, and chemokines activate the resident fibroblasts-like synoviocytes (FLS) to proliferate invasively and produce MMP and A disintegrin-like metalloprotease with thrombospondin type 1 motifs (ADAMTS). Moreover, TNF, IL-1, and IL-17 stimulate the chondrocytes to produce matric enzymes, and RANKL activation by osteoclasts plays a vital role in cartilage damage and bone erosions. TNF, leukotrienes, vasoactive amines, and proteases are produced by resident mast cells (Fang et al., 2020; Xia et al., 2023; Yin, Yan, Zheng, Wu, & Athari, 2023). The complement system is another innate immunity component triggered by rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA). These autoantibodies generate the C3a and C5a, which further attract and activate the pro-inflammatory cells like neutrophils, macrophages, and mast cells (Fang et al., 2020).

Adaptive immunity reacts to antigenic stimuli and triggers autoimmunity by modifying proteins such as citrullinated ones (Volkov, van Schie, & van der Woude, 2020). The interaction between T cells and B cells triggers the B cells (antigen-specific) to differentiate them into plasma cells that produce the RF and ACPA. These autoantibodies form the immune complexes that can initiate inflammatory reactions by stimulating the complement system (Fang et al., 2020). Some activated T cells set off the Th1 and Th17 cells to produce IL-17 (proinflammatory cytokine) that recruits other T cells and neutrophils. (Fang et al., 2020; McInnes & Schett, 2011; Wen et al., 2022; Zhu, Nai, Pan, Ma, & Zhou, 2023).

Over and above, the large amounts of cytokines in the synovial membrane play a crucial role in proliferating stronger inflammatory reactions, which in turn cause cartilage loss and bone erosions (Fang et al., 2020; Kondo, Kuroda, & Kobayashi, 2021; McInnes & Schett, 2011).

### 4.3. Etiology of diabetes

Diabetes is a serious public health issue, which consists of the two most common types of diabetes type 1 and diabetes type 2. Even though type 1 diabetes affects people of all ages, most individuals are diagnosed either around childhood or in their teens and early adulthood. Type 1 diabetes brings an autoimmune response to proteins of the islets of Langerhans (Holt, 2004). There is a strong relationship between type 1 diabetes and other endocrine autoimmunity disorders (Hussein & Gaafar, 2022; Ozougwu, Obimba, Belonwu, & Unakalamba, 2013).

Almost 90% of cases of diabetes are of type 2 diabetes (insulin resistance). Typically, it occurs in those above 45 years. However, other risk factors such as high caloric diet, physical inactivity, oxidative stress, inflammation, and obesity are making it more common in children, teens, and young adults. Insufficient insulin synthesis in the pancreas, insulin resistance in different organs such as the liver and muscles, and cells like fat cells are the predominant causes of type 2 diabetes. Due to a combined effect of inadequate insulin secretory response and resistance to its action can result in hyperglycemia (high blood glucose level) (Ozougwu et al., 2013; Shalaby, Ghandour, & Emam, 2022).

### 4.4. Pathophysiology of diabetes

A combination of both genetic and environmental factors causes type 1 diabetes. It most commonly results from autoimmune destruction of insulin-producing β-cells in the pancreas. Eisenbarth proposed that in genetically susceptible individuals, ecological factors like enteroviruses, diet, or toxins might trigger T-cell-dependent autoimmunity (Devendra, Liu, & Eisenbarth, 2004). They were established by measurable antibodies to insulin autoantibody and glutamic acid decarboxylase. Insulitis with gradual β-cell destruction leads to pre-diabetes and then overt disease. These patients are also prone to other autoimmune diseases. Genome-wide association studies and meta-analysis have revealed that forty genetic loci have been linked with type 1 diabetes (Barrett et al., 2009). These genetic loci located in the major histocompatibility (HLA) region are related to an increased risk of developing type 1 diabetes, and this is approximately 5% if there is a first-degree relative with the disease and slightly higher if the affected one is the father rather than the mother. To date, interventional trials in those genetically at risk are unsuccessful in delaying the onset or preventing type 1 diabetes. (Jabeen, Malik, Mir, & Rasool, 2023; Wherrett & Daneman, 2009).

Chronic excessive caloric intake is the primary pathogenic event in genetically and epigenetically susceptible people that drives the development of type 2 diabetes (Colagiuri et al., 2011; Ji & Zhang, 2022; Prentki & Nolan, 2006). The following metabolic disturbances are vital for type 2 diabetes development: inability of islet β -cells to recompense for the excessive energy, increased secretion of glucagon and decreased response of incretin hormone, impaired enlargement of the adipose tissue subcutaneously, hypoadiponectinaemia, adipose tissue inflammation, increased endogenous production of glucose, and development of peripheral insulin resistance. Prominently, the excessive is not carefully deposited into subcutaneous adipose tissue, such that it has to be deposited elsewhere in the visceral adipose tissue and “ectopic” storage in organs, such as the liver, heart, skeletal muscle, and pancreas, which causes extensive tissue damage (Kahn, 2003; Meier & Nauck, 2010; Nolan & Prentki, 2008; Stefan et al., 2008; Unger & Scherer, 2010; Wajchenberg, 2000).

### 4.5. Rheumatoid arthritis (autoimmunity) link with diabetes: a mechanistic view

Medical research and technological advancements over the past 20 years have transformed how many diseases, especially chronic conditions like RA, are treated. Therefore, awareness regarding its pathology, the development of medications, and its relationship with numerous other chronic conditions, such as diabetes, have led to improvements in

the disease's management and therapy. The prevalence of diabetes is closely related to RA. It is also linked to inflammation brought on by inflammatory markers like *C*-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6). In the development of RA, TNF-α is a potent proinflammatory factor. It is essential in oxidative stress response, monocyte activation, synovial fibroblast proliferation, and prostaglandin release (Costa et al., 2016). By suppressing the signals of NF-κB and phosphorylation of insulin receptor substrate-1 (IRS-1), TNF-α inhibits insulin secretion and sensitivity (Copps & White, 2012). Thus, the TNF-α therapy preserved the pancreatic β cell function and decreased insulin resistance (van den Oever et al., 2021). The important mediators in insulin resistance induced by TNF-α are the protein tyrosine phosphatase 1 B (PTP-1B) and the suppressor of cytokine signaling-3 (SOCS3) (Liang, Xu, Peng, Pan, & Ye, 2014).

Increased circulation of IL-6 in the serum and synovia of RA patients decreased the glucose uptake and hepatic insulin sensitivity while improving the plasma insulin levels, hyperlipidemia, and hyperglycemia, which plays a significant role in the development of insulin resistance (McElvaney, Curley, Rose-John, & McElvaney, 2021). IL-6 is related to apoptosis of pancreatic β-cells in diabetic patients (Jansen et al., 2021). Moreover, it is responsible for inhibiting glucose transporter 4 (GLUT4) and reducing IRS-1, eventually promoting insulin resistance. The inhibition of the secretion of TNF-α by immune cells indirectly contributes to the diabetes risk (McElvaney et al., 2021; Rehman et al., 2017).

In blood monocytes, tissue-resident macrophages, dendritic cells, and IL-1β are formed, and their activation is promoted through the NOD-like receptor protein 3 (NLRP3) inflammasome/caspase-1 pathway (Giacomelli et al., 2016). IL-1β attracts white blood cells towards the joints and promotes the differentiation of osteoclasts, resulting in bone and cartilage damage, which inhibits the signaling of insulin by suppressing tyrosine phosphorylation of IRS-1 (Amarasekara et al., 2018; Aye, Jansson, & Powell, 2013; Kang, Huang, Mandrup-Poulsen, & Larsen, 2021). In RA patients, a long-term increase of serum IL-1β triggers the activation of nitric oxide synthase (NOS), which causes the dysfunction of $\beta$ cells (Giacomelli et al., 2016). Meanwhile, it promotes the apoptosis of pancreatic $\beta$ cells through the NF-κB-Fas/FasL (Factor-associated suicide/Factor-associated suicide ligand) pathway. It upregulates the expression of insulin inhibitor-SOCS (Liang et al., 2014) while downregulating the expression of peroxisome proliferator-activated receptor $\gamma$ (PPARγ) along with adiponectin (Kang et al., 2021; Liu et al., 2016). Therefore, these regulations decrease insulin sensitivity and glucose uptake (Liu et al., 2016).

The presence of serum autoantibody, including RF and *anti*-CCP, also called ACPA, is one of the major differentiating factors between RA and other inflammatory arthritis (Laurent et al., 2015; Sokolove et al., 2014; Takeuchi et al., 2017). These autoantibodies exhibit their effect on other cells via binding to the Fc receptor. Thus, stimulating these receptors on macrophages promotes the secretion of TNF-α through immune complexes containing ACPA and citrullinated fibrinogen (Derksen, Huizinga, & Van Der Woude, 2017). Inflammation is a major factor that may contribute to the insulin resistance induced by RF and ACPA. NLRP3 via the signaling of AKT (protein kinase B)/NF-κB is activated by ACPA, leading to the releases of IL-1β fiercely (Dong et al., 2020; Mostashari & Mousavi Khaneghah, 2024; Takeuchi et al., 2017; Umeda, Matsumoto, & Sumida, 2017). Additionally, ACPA also caused macrophages to generate large amounts of TNF-α. Thus, the inflammation occurred due to the autoantibodies hindering the sensing of glucose and signal transduction of insulin, ultimately leading to insulin resistance. (Dong et al., 2020; Recinella et al., 2020; Umeda et al., 2017).

Other proteins like CRP, thioredoxin domain-containing protein 5 (TXNDC5), retinol-binding protein 4 (RBP4), NLRP3, and serum complement C3 also promote insulin resistance. CRP promotes insulin resistance by regulating the insulin signaling pathway via the activation of the mitogen-activated protein kinase (MAPK) pathway or hindrance of IRS/PI3K/AKT signal pathways (insulin receptor substrate/phosphatidylinositol three kinase/AKT) (Neale, Batterham, & Tapsell, 2016; Xu, Morita, Ikeda, Miki, & Yamori, 2007). TXNDC5 is an important molecule for the intrinsic link between RA and diabetes. For a long time, it has been expressed as a diabetes susceptibility gene (Chawsheen, Ying, Jiang, & Wei, 2018). It promotes insulin resistance by suppressing the expression of insulin-like growth factor binding protein (IGFBP1) (Horna-Terrón, Pradilla-Dieste, Sánchez-de-Diego, & Osada, 2014). In RA, NLRP3 stimulates insulin resistance by implicitly activating the IL-1β-induced inflammation (Tannahill & O'Neill, 2011). On the other hand, RBP4, independent of its receptor, induces the expression of inflammatory cytokines and, hence, indirectly prevents insulin signaling through the activation of JNK and TLR4 pathways (Norseen et al., 2012). Increased levels of serum complement C3 are projected to contribute to the augmentation of systemic inflammation, strongly correlated with insulin sensitivity (Ahmad & Al-Domi, 2017; Mostashari & Mousavi Khaneghah, 2024; Ursini et al., 2018).

It is of utmost importance to know that the insulin resistance promoted by inflammation increases the level of RF in the blood. Hence, the severity of insulin resistance increases with higher activity of RA and vice versa (Rizvi et al., 2022; Tian et al., 2021). In addition, insulin resistance contributes to raised fat mass, disease activity, and the incidence of RA-related factors. Further, obesity, lifestyle choices, and the use of glucocorticoids as a treatment have all been linked to people with RA, which leads to type 2 diabetes in these individuals (Batrakova, Kartashova, Babaskina, & Pashanova, 2022; Han et al., 2022). Even though diabetes is more likely to be a comorbidity of arthritis, more research will be useful to strengthen the link between the two conditions (Dong, Liu, Yang, & Zhang, 2017). Fig. 5 shows the relationship of arthritis (autoimmunity) in the development of diabetes.

## 5. Industrial hemp, hempseed, and hempseed oil: a remedy against arthritis and diabetes

There is a growing need for"cannabinoid" products with wide therapeutic properties. An ancient herb with promising benefits has been found by pharmaceutical research, and it may be able to preserve our world in the third millennium. Over 25,000 distinct types of products have been created during the 6000 years since cannabis first appeared and are now used for a wide range of reasons. From 2.700 BC on, cannabis was utilized as medicine long after it was employed for fiber and seeds. In primitive times, cannabis was used to treat malaria, digestive problems, rheumatic pain, and female reproductive disorders. Due to the presence of high-quality fiber and low cost, hemp has been known as a rich source of fiber for many centuries (Salami et al., 2020). Besides, its role in managing NCDs has gained interest as several states have legalized its use. CBD oil has gained popularity as a therapeutic option for RA (Perrot & Trouvin, 2019).

The cardiovascular system contains the endocannabinoid system, which comprises endocannabinoids as well as cannabinoid type 1 (CB1) and type 2 (CB2) receptors (cannabinoids). In both humans and animals, endogenous and exogenous cannabis cause alteration in the cardiovascular system (Malinowska, Toczek, Pędzińska-Betiuk, & Schlicker, 2019). The endocannabinoid system modulates mood, pain, appetite, inflammation, energy, and fat metabolism, with a wide range of therapeutic applications against neuropsychiatric, neurological, and inflammatory disorders (Di Marzo, 2018).

The activation of the CB1 receptor can have pro-inflammatory effects, while CB2 activation can decrease inflammation. In this regard, CBD is a negative allosteric regulator of the CB1 receptor and a weak agonist of the CB2 receptor (Muller, Morales, & Reggio, 2019). Apart from this, CBD may improve anti-inflammatory effects through CB2 activation. Clinical trials have concluded that CBD can reduce the levels of inflammatory markers, inhibit T cell proliferation, induce T cell apoptosis, and reduce the migration and adhesion of immune cells (Atalay, Jarocka-Karpowicz, & Skrzydlewska, 2019; Jean-Gilles et al., 2015).

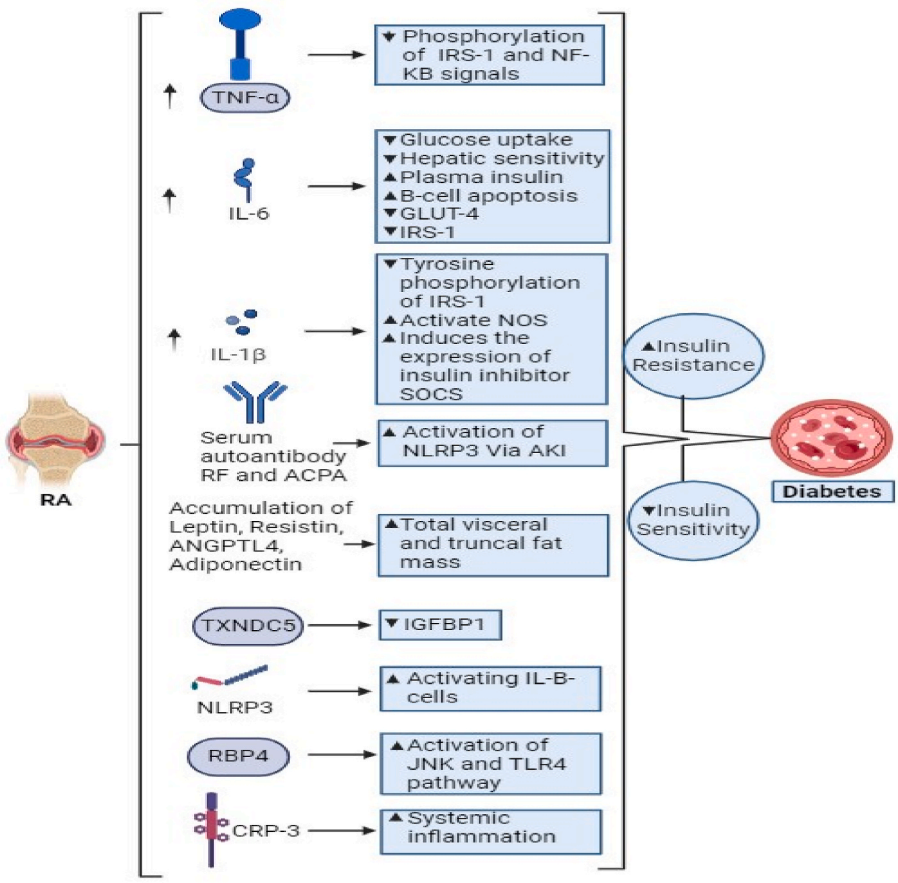


**Fig. 5.** A mechanistic view of arthritis (autoimmunity) linked with diabetes.

Due to the vasodilatory, antioxidant, anti-inflammatory, cardioprotective, and neuroprotective effects of CBD, it has been found to have a therapeutic role in managing stroke and cardiovascular complications of diabetes (Kicman & Toczek, 2020). Likewise, omega-3 fatty acids have been demonstrated to have anti-inflammatory effects and modulate the immune response, particularly in the context of autoimmune diseases such as RA. They compete with omega-6 fatty acids for enzymes involved in eicosanoid synthesis, producing less pro-inflammatory eicosanoids. Additionally, they can decrease the production of pro-inflammatory cytokines such as interleukin 1 beta (IL-1β), IL-6, and TNF-α. They can decrease the proliferation and differentiation of T cells that contribute to the autoimmune response. Omega-3 fatty acids may also reduce antigen presentation via MHC II, further modulating the inflammatory response. These effects suggest that omega-3 fatty acids have the potential as a therapeutic intervention for autoimmune diseases (Kostoglou-Athanassiou, Athanassiou, & Athanassiou, 2020). Terpenes, which give hemp its characteristic flavor and aroma, may also have various medically significant impacts (Rufino et al., 2015). Regardless, cannflavin A and B present in hemp inflorescence have a role in reducing prostaglandin E2 synthesis and thus show anti-inflammatory and antioxidant properties (Ijaz, Ishtiaq, Ehsan, Imran, & Zhu, 2022; Werz et al., 2014).

In type 2 diabetic rats, CBD has been demonstrated to induce vasodilation by activating the CB2 cannabinoid receptor (Wheal, Jadoon, Randall, & O'Sullivan, 2017). CBD has also been found to have therapeutic applications in diabetic neuropathy by activating 5-hydroxytryptamine receptor 1 A (5-HT1A receptors) (Jesus et al., 2019). Furthermore, it has been shown to accelerate the tissue repair process in a diabetic rat model by preserving the function of the endothelial growth factor (VEGF) (Yan et al., 2010). It also showed a substantial reduction in the development of destructive insulitis in pancreatic islets and the production of inflammatory cytokines (Weiss et al., 2006). Peptides are known to have a promising activity in managing blood glucose levels (Fig. 6). According to a study by Ren et al. (2016), novel -glucosidase inhibitory peptides serve as dietary components and functional food for treating hyperglycemia.

Regarding safety, few studies were performed to check CBD oil safety, and doses ranging from 300 mg/day for six months to 1200–1500 mg/day for four months were considered safe (VanDolah, Bauer, & Mauck, 2019). Thus, research with greater participants has reported side effects such as diarrhea, somnolence, decreased appetite, and increased levels of liver enzymes. In addition, drug-drug interactions have been reported from the CBD oil metabolism with the cytochrome P450 enzyme system, such as some epileptic medicines and warfarin. Finally, inconsistent branding of these types of products has included under-labeled THC and over-labeling of cannabidiol (CBD) content. Thus, adverse reactions due to the ingestion of these products have led to hospitalizations (VanDolah et al., 2019; Wiczek, 2020). The effects of both bioprocessed enzyme mixtures, yeast, and blends on the screening of nutrient and phytochemical content of hemp and their in-vitro digestion and metabolism were assessed. Results revealed that these bioprocessing treatments modulate the bioavailability of the screened phytochemicals. The EC-2 treatment (enzyme mixtures were prepared with the 0.01% (w/w) Fungamyl® 800 L, 0.14% (w/w) Viscozyme® L, 0.36% (w/w) Depol 740 L along with 0.01% (w/w) cellulase) improved the gastrointestinal (upper part) release of several plant metabolites in the in-vitro digestion model. However, the treatments did not affect the microbial metabolism of the hemp components (Fan et al., 2023).

Although hemp seeds are a good source of bioactive compounds, more information is needed about their bioavailability in tissues and excreta of animals feeding a diet supplemented with hemp seed cake.

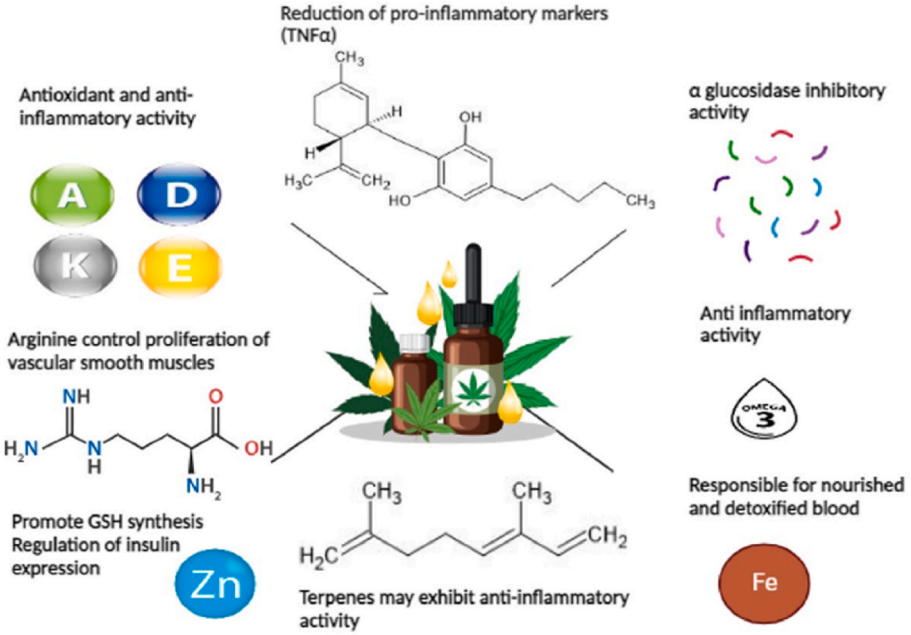


**Fig. 6.** Active components of industrial hemp and their mechanism.

Hemp seed cake at 0, 25, 50, 75, and 100 g/kg levels, respectively, was replaced for soybean meal in the diet of goats. Findings showed that, with the increased inclusion of hemp seed cake, the magnesium in urine, liver, and blood, as well as manganese and copper in the fecal matter, was increased linearly. However, selenium content in the liver and fecal matter decreased. The DPPH and ABTS assay also showed increased value in the blood, liver, and meat. At 50 g/kg dry matter in the blood and liver, the value of FRAP quadratically increased. Thus, it is suggested that the bioavailability of phytochemicals in the meat, liver, and blood can be improved by the inclusion of hemp seed cake about 100 g/kg replacing soybean meal in the forage of goats (Semwogerere, Chikwanha, Katiyatiya, Marufu, & Mapiye, 2024).

Cannabinoids may provide improved bioavailability and safety profiles via transdermal routes compared to other delivery routes. Thus, a single-arm, open-label study was conducted to determine the effect of a novel transdermal delivery system on the pharmacokinetics of CBD and THC. Blood was collected before giving the dose and after application of in 1:1 (100 mg CBD and 100 mg THC) at intervals of 10, 20, 30, and 45 min, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 12 h on the skin. It was indicated that CBD (123.36 ± 530.97/h) was absorbed at a faster rate in contrast to THC (71.5 ± 1142.19/h) but with similar terminal elimination rate constant 0.12 ± 0.029 and 0.13 ± 0.03/h, respectively. There were no psychotic effects, and the transdermal delivery of cannabinoids was safe and tolerable in the studied population (39.5 ± 7.37 years old and healthy humans) (Varadi et al., 2023).

A study was conducted in a clinical setting to measure the safety and effect of CBD on canine osteoarthritis-associated pain relief in dogs. CBD treatment was given for 6 weeks, followed by 6 weeks of different treatments. No differences were noted between groups at any time point in the documented outcome measures, *i.e.*, objective gait analysis, clinical metrology, and activity counts. However, some adverse events, including elevated liver enzymes and vomiting, were reported following CBD administration (Mejia, Duerr, Griffenhagen, & McGrath, 2021). Moreover, another study was conducted in dogs to assess the impact of a full-spectrum product comprising hemp extract and hemp seed oil in chronic maladaptive pain. It was observed that CBD extracted from hemp addition seems to positively influence dogs by reducing chronic maladaptive pain and improving the mobility of dogs and their life quality. A reduction in the dosage of gabapentin was also reported with the incorporation of the hemp oil extract. No side effects were reported during the 90-day trial; however, a significant increase in the alkaline phosphatase level was observed (Kogan, Hellyer, & Downing, 2020).

Similarly, a pharmacokinetics-based study was executed in dogs to determine the effect of oral transmucosal CBD, along with multimodal pharmacological treatment for chronic osteoarthritis-related pain. Pain severity and pain interference score were significantly lower in the treated group. Additionally, the quality-of-life index was higher. Promising results were shown due to the addition of oral transmucosal CBD. The addition of oral transmucosal CBD showed promising results. Thus, in the future, pharmacokinetics and long-term studies in larger populations are required to promote its inclusion in a multimodal pharmacological approach for canine osteoarthritis-associated pain (Brioschi et al., 2020).

Over the last two decades, in the United States, affirmative diagnoses of osteoarthritis have increased three times due to the growing rates of obesity and aging. Herein, CBD was evaluated for its ability to mediate the in-vitro production of proinflammatory cytokines and in murine models of induced inflammation. Further, they validated the ability of liposomal formulation to enhance the bioavailability in mice and humans. CBD was given in a separate form, and liposomal was encapsulated. In vitro and mouse models, CBD significantly reduced the production of proinflammatory cytokines IL-6 and TNF-a while increasing the levels of anti-inflammatory cytokine IL-10. In a dose-dependent manner, CBD significantly decreased pain and increased mobility among animals suffering from OA. The highest effective nonliposomal and liposomal CBD dose was 50 and 20 mg/day, respectively. Clinical chemistry, comprehensive metabolic profile, and hematocrit volume suggested no significant detrimental impact of CBD administration over the 4-week analysis period. Therefore, these findings support the safety and medicinal potential of hemp-based CBD for alleviating pain of arthritis and recommend future studies in humans (Verrico et al., 2020). Thus, a randomized, double-masked parallel-group study for 5 weeks in 58 patients of RA was conducted to evaluate the efficacy of a cannabis-based medicine (Sativex). In the final treatment week, the mean daily dose achieved was 5.4 actuations. The cannabis-based medicine showed significant improvement in quality of sleep, pain on movement, pain at rest, disease activity measure score, and findings of short form Mc-Gill pain questionnaire compared with placebo. At the same time, no effect on morning stiffness was reported. Moreover, Sativex treatment observed mild or intermediate adverse effects, and no

adverse events were linked to discontinuation, representing the benefits of clinical significance and presenting the need for detailed investigation (Blake, Robson, Ho, Jubb, & McCabe, 2006).

HempChoice® Hemp Oil Extract (extract of the aerial parts of hemp) primarily comprises 55–75% CBD, 1–15% other phytocannabinoids, and 1–15% terpenes. In the 90-day study, the extract showed no notable changes in food consumption, weekly body weight, daily weight gain, functional observational battery or motor activity assessment, abnormal clinical observations, mortalities, and ophthalmological changes. However, some changes were reported in the hematological and clinical chemistry markers that were considered reversible during the recovery period of 28 days. In addition, there were no macroscopic changes related to the exposure of the extract, but some histopathological changes restricted to adaptive changes in the liver were observed. However, these effects were not detected in the recovery group animals. Thus, in male and female Sprague Dawley rats, no observed adverse effect level for HempChoice® Hemp Oil Extract was determined to be 185.90 mg/kg/day (Dziwenka, Coppock, Davidson, & Weder, 2023).

Despite the advances in our understanding, the nutraceutical potential of hemp against arthritis and diabetes discloses the need for further research. Table 3 represents the different bioactive components and mechanism of action of Cannabis sativa ssp. Sativa and its different parts.

## 6. The anti-arthritic potential of industrial hemp

Arthritis is a degenerative disorder associated with human joints that can contribute to disability (Imtiaz, Shah, & urRahman, 2022). It leads to the swelling of the joints. About 50 million American adults are living with arthritis, the most frequent of which are degenerative arthritis (OA) and inflammatory arthritis (RA). By 2030, the prevalence is expected to rise to 67 million. Hammell et al. (2016) undertook a study to observe the potential of CBD against arthritis. After the induction of arthritis in rats, various dosages (0.6, 3.1, 6.2, or 62.3 mg/day) of CBD were administered every day in the form of gel and continued for four days. When CBD was applied topically to rats, immune cell infiltration, joint swelling, and inflammatory biomarkers were considerably reduced. Another investigation was carried out on dogs to examine the role of CBD oil in preventing osteoarthritis. Dogs who received CBD oil exhibited a notable decline in pain compared to those without treatment (Gamble et al., 2018). Moreover, a study was performed to exploit the antiarthritic potential of CBD. A questionnaire was developed to observe the perceived efficiency of CBD in treating arthritis. By using the internet (social media accounts, newsletters), a self-selected sample (n = 428) was collected. Findings exhibited significant improvement in pain (83%), sleep quality (66%), and physical function (66%). There were substantial improvements in physical activity in the osteoarthritic patients compared to the rheumatic group (Frane et al., 2022). A study was performed by Hunter, Oldfield, Tich, Messenheimer, and Sebree (2018) to evaluate the impact of CBD gel (250 mg) twice per day against OA in humans (n = 321) for 12 weeks. Results exhibited no notable changes between the two groups. Another study found the possible effect of CBD as an anti-inflammatory agent against neuroinflammation (Joffre et al., 2020). In a study, hemp seed oil phytol at 10–100 mM was used to observe its anti-inflammatory effects on human monocyte macrophages. Phytol revealed depletion of inflammatory markers, *i.e.*, IL-1, IL-6, and TNF-α, and improved anti-inflammatory properties in monocyte-macrophages in humans (Claro-Cala et al., 2022). Furthermore, the anti-rheumatic effects of hemp seed oil were observed using malignant human synovial sarcoma cell line (MH7A) of human fibroblast-like synoviocytes (FLSs) from RA patients. According to this research, hemp seed oil treatment showed apoptosis in MH7A cells, expressing CCAAT/enhancer binding protein (C/EBP) or homologous protein (CHOP) that acts as an anti-rheumatoid factor in MH7A cells (Jeong et al., 2014).

Similarly, a study proposed to assess the effects of two distinct dietary supplements, one of which contains hemp seed oil and the other containing hemp seed oil and terpenes, in reducing pain and improving the functions of joints in patients with knee osteoarthritis (KOA). Therefore, 38 patients of KOA were selected and subsequently sectioned into two cohorts. The control group received an oil-based supplement for 45 days. The treatment group simultaneously received a dietary supplement containing oil and terpenes. Patients were assessed at the start of the study ($T_0$) and the end of the intervention trial ($T_1$). Outcome measures included the Numeric Rating Scale (NRS) (for pain assessment), the Oswestry Disability Index (ODI) (for measuring functional disability), the Short-Form-12 (SF-12) (for assessing overall health-related quality of life), and the Knee Injury Osteoarthritis Outcome Score (KOOS) and Oxford Knee Score (OKS) for evaluating knee function. Both groups showed improvements in all outcome measures at $T_1$. However, the treatment group, which took both hemp seed oil and terpenes supplement, showed significantly greater improvements in NRS, KOOS, and OKS compared to the control group. It effectively improved joint function and pain in patients suffering from osteoarthritis. Subsequently, both supplements could be considered beneficial adjuvant treatment options for individuals suffering from KOA (Farì et al., 2023).

George, Saltman, Stein, Lian, and Zurier (2008) investigated the effects of ajulemic acid (AjA), a nonpsychoactive cannabinoid acid, on osteoclast differentiation and survival in RA. The findings illustrated that the simultaneous addition of AjA (at concentrations of 15 and 30 μM) and receptor activator of nuclear factor kappa beta (RANKL) profoundly impeded the progression of multinucleated osteoclasts (osteoclastogenesis) in a concentration-dependent manner. Furthermore, AjA restrained the growth of RAW264.7 monocytes and hindered further osteoclast formation. These effects were associated with apoptosis (programmed cell death), as evidenced by annexin V and propidium iodide staining, as well as caspase activity. Caspases 3 and 8 were induced in the osteoclast-like cells upon treatment with AjA, leading to their apoptotic cell death and protection against osteoclastogenesis. Moreover, the anti-inflammatory, anti-microbial, and anti-obesity properties of hexane extracts of hemp (*C. sativa* L.) seed were examined in research, particularly emphasizing the inflammation and lipogenesis caused by *Propionibacterium acnes* (*P. acnes*). Hemp seed hexane extract (HSHE) exerted an anti-microbial effect against the adverse consequences of P. acnes. By controlling MAPKs, NF-κB signaling, and HaCaT cells (immortalized human keratinocytes), HSHE demonstrated anti-inflammatory effects. HSHE regulates AMP-activated protein kinase (AMPK) and Akt kinase/Forkhead box O (AKT/FoxO1) signaling to control inflammation and lipid production. Additionally, HSHE stimulated collagen biosynthesis in vitro and decreased *P. acnes*-induced matrix metalloproteinase (MMP-9) activity and 5-lipoxygenase level. Due to its anti-inflammatory, antimicrobial, and collagen-promoting characteristics, it can be used against *Acne vulgaris* (Jin & Lee, 2018). According to research by Rossi et al., industrial hemp has an anti-inflammatory effect when used in the right amounts. This was seen in the cell lines of humans (Rossi et al., 2020). The anti-inflammatory compound CBD has been reported as a therapeutic remedy for methamphetamine-induced neuroinflammation (Majdi, Taheri, Salehi, Motaghinejad, & Safari, 2019). Applying CBD on macrophages like the oncogenic human monocyte cell line (U937), epithelial cells, and lung fibroblast cells in the human fetal lung (HFL-1) exhibits an anti-inflammatory effect (Muthumalage & Rahman, 2019). In silico analysis, thirteen anti-inflammatory compounds from *C. sativa*, *Withania somnifera,* and *Prunella vulgaris* were identified and evaluated for their potential to treat RA by targeting TNF-α. Findings showed anti-arthritic and anti-rheumatic qualities after a thorough literature review (Zaka, Sehgal, Shafique, & Abbasi, 2017).

In the realm of human nutrition, hempseed is becoming more and more well-liked, especially when it comes to essential fatty and amino acids. A study used an LPS-induced mouse model to check the *anti*-neuroinflammatory efficacy of phenylpropionamides TPA

**Table 3**
The bioactive components of industrial hemp and their mechanism.

| Active component | Method | Control | Mechanism and Result | References |
|---|---|---|---|---|
| Vitamin E | Female B6CBAF1, 7–8 weeks old mice,<br>Induction: LPS-induced inflammation,<br>Treatment: Vitamin *E*-supplemented diet. | | In mice, pretreatment with vitamin E reduced the effect of LPS on the expression of cytosolic ROS and IL-1$\beta$ mRNA and improved embryo viability.<br>Potent antioxidants with anti-inflammatory properties thus can be a helpful strategy in managing diabetes and boosting antioxidant capacity. | Mayorga, Iborra, Estany, and Martínez (2004)<br>Wallert, Börmel, and Lorkowski (2021) |
| Vitamin A | Male weanling rats (40–45 g),<br>Group 1, vitamin A–deficient diet (VAD),<br>Group 2, vitamin A sufficient (VAS) diet containing retinyl palmitate (1200 μg/kg diet),<br>Group 3 vitamin A supplemented containing retinyl palmitate (VASUP) (1200 μg/kg along with 300 μg retinyl palmitate in 0.25 mL of 1% glycerol in last 4 weeks),<br>Group 4 pair-fed (PF) the VAS diet rat in this group received the amount consumed by a VAD rat on the previous day/ | | Vitamin A deficiency induces colonic inflammation, ameliorated by supplementing vitamin A.<br>Immune system regulation and reduction in the activity of natural killer cells<br>Antioxidants, which protect against inflammation | (Reifen et al., 2002;<br>Yosaee, Fakhrabadi, and Shidfar (2016)<br>Gholizadeh et al. (2022) |
| Vitamin D | Randomized controlled trial (12 weeks)<br>Diabetic subjects receiving non-fortified drinks,<br>Diabetic subjects receiving vitamin D-fortified drinks. | | Vitamin D-fortified drinks decrease systemic inflammation in diabetic subjects by ameliorating inflammatory biomarkers like TNF-α.<br>Regulate the formation of GSH, ultimately reducing MCP-1 and IL-8 levels and diminishing oxidative stress and inflammation. | (Shab-Bidar et al., 2012; Shi, Karrar, Liu, Chang, & Wang, 2022) |
| Vitamin K | Lipopolysaccharide-induced inflammation in rats | Vitamin K-deficient rats | Vitamin K supplementation in rats suppressed the inflammation induced by lipopolysaccharide.<br>In adipose tissue:<br>↓Levels of inflammatory cytokines, *i.e.,* IL-1, TNF -α, and IL-6<br>↑Insulin sensitivity. | (Egawa et al., 2020; Ohsaki et al., 2006) |
| Fiber | Male Zucker rats (8 weeks old)<br>Lean and obese controls (standard diet)<br>Group 3 modified diet (hemp oil 4% of diet)<br>Group 4<br>modified diet (hemp seeds 12% of diet) | Lean and obese controls fed with a standard diet | Hempseed supplementation: ↑Microbial glycolytic activity ($\beta$-glucosidase and $\alpha$- and $\beta$-galactosidase) due to its high content of fiber fraction<br>Fiber fraction:<br>↑Production of cecal short-chain fatty acids, which, after absorption, improve the blood lipid profile and decrease the hepatic lipogenesis.<br>High fiber content can benefit blood sugar levels, the growth of healthy gut bacteria, and the decrease of the likelihood of intestinal cancer. | Opyd et al. (2020)<br>(House, Neufeld, & Leson, 2010; Karche, 2019) |
| Zinc | Male diabetic albino rats<br>Control group (standard diet),<br>Metformin treated group (250 mg/kg/day for 4 weeks),<br>Zn treated group,<br>(metformin + zinc (10 mg/kg/day for 4 weeks). | Metformin treatment | Zinc supplementation along with metformin:<br>↓Serum glucose and insulin and testicular levels of malondialdehyde and TNF-α<br>↑Serum levels of Zn, testosterone, and follicle-stimulating hormone, testicular total antioxidant capacity, and anti-apoptotic protein Bcl-2.<br>↓Formation of reactive oxygen species through various mechanisms.<br>The Nrf2 pathway, which is the principal mediator of the antioxidant defense system, is upregulated, thus promoting GSH synthesis, GPx activity, and other detoxification mechanisms. It may also have a role in the reduction of inflammatory cytokines.<br>Involve in fat and carbohydrate metabolism by initiating and regulating insulin expression. | (Aziz, Kamel, Mohamed, & Ahmed, 2018; Olechnowicz, Tinkov, Skalny, & Suliburska, 2018) |
| Copper | Control group,<br>Cu-treated group (non-diabetic)<br>Streptozotocin administered group (positive control) | | In the diabetic and non-diabetic groups, copper treatment:<br>↑Glutathione, thiobarbituric acid reactive substances levels, and total antioxidant | (Atari-Hajipirloo, Valizadeh, Khadem-Ansari, Rasmi, & Kheradmand, 2016; Civelek et al., 2010) |

(*continued on next page*)

**Table 3** (*continued*)

| Active component | Method | Control | Mechanism and Result | References |
|---|---|---|---|---|
| | Streptozotocin was administered, and the Cu-treated group (diabetic group) was administered. | | capacity<br>Impaired metabolism of elements like copper, iron, and zinc can promote the risk of type 2 diabetes in later stages of life. | |
| Iron | Effect of diets enriched with flax and hemp seeds on iron content of blood in lactating Alpine goats:<br>Group 1: Control group (control diet),<br>Group 2 (Diet supplemented with flaxseed),<br>Group 3 (Diet supplemented with hempseeds). | Control group and flaxseed-supplemented group | Iron content increased by 23% in control group (45 days in milk)<br>In the flaxseed-supplemented group, the iron in the blood increased by 36% and 62% (100 and 150 days in milk).<br>In the hempseed-supplemented group, iron in the blood increased by 33% and 67% (100 and 150 days in milk). | Reggiani and Russo (2016) |
| Phenylpropionamides | Lipopolysaccharide (LPS)-induced mouse model.<br>Control (1–3 weeks, 0.9% saline, 10 mL/kg/day),<br>Model (third week, 0.9% saline, 10 mL/kg/day)<br>TPA (1–3 week, 1, 2 g/kg/day),<br>Piracetam (2–3 weeks, 0.4 g/kg/day). | Piracetam (Drug) | TPA reduced LPS-induced hippocampal neuronal damage by reducing IL-1β, IL-6, and TNF-α levels. | Zhou, Wang, Ji, Lou, and Fan (2018) |
| Arginine | Hempseed cakes (cannabisin I) effect on mammal arginase.<br>Antioxidant activity (oxygen radical absorbance capacity). | Reference compound (*S*-(2-bromomethyl)-L-cysteine) | Cannabisins displayed arginase inhibition and antioxidant activity close to or better than the reference compounds.<br>Precursor for the synthesis of NO.<br>It acts as a crucial signaling messenger in the cardiovascular system. Plays a role in the control of homeostasis, leukocyte interactions with the arterial wall, platelets, fibrinolysis, and proliferation of vascular smooth muscle cells. | Bourjot, Zedet, Demange, Pudlo, and Girard-Thernier (2016)<br>Rodriguez-Leyva and Pierce (2010) |
| Omega-3 | Obesogenic mice,<br>Group 1 (control group; normal diet),<br>Group 2 (high fat/high sucrose obesogenic diet),<br>Group 3 (High fat/high sucrose obesogenic diet substituted with linseed),<br>Group 4 (High fat/high sucrose obesogenic diet substituted with hempseed. | A high fat/high sucrose obesogenic diet is substituted with linseed. | Hemp seed substitution alleviated diet-induced obesity-related increases in intestinal permeability.<br>No effects on markers of inflammation in epididymal adipose tissue<br>Both hemp seeds and linseeds were able to modify the expression of several endocannabinoidome genes<br>There is a higher abundance of Clostridiaceae 1 and Rikenellaceae in mice fed with hempseed than in the linseed or control diet.<br>Provide a significant proportion of leukotrienes and prostanoids with anti-thrombotic and anti-inflammatory effects.<br>Omega-6 and omega-3 fatty acids are used in eicosanoid synthesis.<br>Linolenic acid-derived eicosanoids inhibit platelet aggregation, whereas those derived from arachidonic acid are pro-inflammatory and pro-aggregatory. | Ben Necib et al. (2022) (Kostoglou-Athanassiou et al., 2020; Patterson, Wall, Fitzgerald, Ross, & Stanton, 2012) |
| Rutin | Rat C6 glioma cells and human U251 glioblastoma cells | DMSO (0.05%) | Rutin and its aglycone quercetin show anti-glioma effects that modulate the microglial inflammatory profile and may be perceived as an adjuvant against gliomas.<br>Showed anti-hyperglycemic, anti-inflammatory, hepatoprotective, and chemopreventive activities.<br>Exhibit insulinotropic properties. | (da Silva et al., 2020; Kittl et al., 2016) |
| GLA | In vivo study (mice)<br>A group; Evening primrose oil/hemp seed oil + rapamycin, B group; rapamycin, C group; Evening primrose oil/hemp seed oil, D group (Positive control autoimmune encephalomyelitis; EAE; treated with 1% ethyl alcohol diluted with distilled water), E group (negative control; no disease induction, no treatment). | Positive control, Negative control, Drug control (rapamycin). | Anti-inflammatory activity:<br>↑Expression of IL-4, IL-5, and IL-13 genes in lymphocytes,<br>↑Serum level of IL-4,<br>Increased % of GLA in the cell membrane of the spleen and blood. | (Rezapour-Firouzi, Mohammadian, Sadeghzadeh, & Mazloomi, 2020; Sergeant, Rahbar, & Chilton, 2016) |
| Peptide | Simulated gastrointestinal digestion | Acarbose (positive control) | Hemp seed protein treated via an Alcalase at 27.24% degree of hydrolysis showed higher α-glucosidase inhibitory activity than acarbose.<br>Retarded the metabolism of maltose, thus managing hyperglycemia. | Ren et al. (2016) |

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**Table 3** (*continued*)

| Active component | Method | Control | Mechanism and Result | References |
|---|---|---|---|---|
| CBD | (In vivo study on rats)<br>Dosage: 0.6, 3.1, 6.2, or 62.3 mg/day CBD in a gel for transdermal administration for 4 days | Vehicle control without CBD gel | In a dose-dependent manner, transdermal CBD gel showed:<br>↓Joint swelling,<br>↓Immune cell infiltration ↓limb posture scores,<br>↓Synovial membrane thickening.<br>Immunohistochemistry of the spinal cord and dorsal root ganglia showed:<br>↓Pro-inflammatory markers. | Hammell et al. (2016) |
| Tocopherol | Tocopherol determination by high-performance liquid chromatography | Canola, sunflower, and soybean oil | The tocopherol content in the oil is attributed to the high antioxidant activity of hemp seed oil (80–150 mg/100 g oil) as compared to canola oil (60–70 mg/100 g), sunflower oil (~90 mg/100 g) and soybean oil (~115 mg/100 g) which helpful in the prevention of degenerative diseases, such as Alzheimer's, certain types of cancer, and cardiovascular diseases.<br>They serve as antioxidants and stop unsaturated fatty acids from being oxidized. | (Blasi, Tringaniello, Verducci, & Cossignani, 2022; Irakli et al., 2019; Liang et al., 2015; Matthäus & Brühl, 2008) |
| Terpenes | Effect of β-myrcene and limonene on IL-1β simulated human chondrocytes cell line | Dimethyl sulfoxide (DMSO) 0.1% | Myrcene and limonene: ↓IL-1β-induced production of nitric oxide.<br>↓Expression of IL-1β-induced NF-κB, JNK, and p38 pathways, iNOS, and catabolic genes such as MMP-1 and MMP-13,<br>↑Expression of anti-catabolic genes, i.e., TIMP-1 and-3 by myrcene and TIMP-1 by limonene. | Rufino et al. (2015) |
| Cannaflavin A and B | In vitro study on different enzymes/assay cyclooxygenase 1 (COX-1 platelets), COX-1 cell-free, COX-2 monocytes, COX-2 cell-free,<br>(Calcium independent phospholipase A2 ($cPLA_2$) cell-free,<br>Prostaglandin E2 synthase 1 (mPGES-1 cell-free), (5-lipoxygenase (5-LO cell-free),<br>Polymorphonuclear leukocytes (5–10 PMNL A23187), 5–10 PMNL A23187 + AA<br>DPPH assay,<br>Cell viability assay. | Indomethacin, celecoxib, pyrrolidine, MK-86, Zileuton, BWA4C, ascorbate, Staurosporine with different indicated doses (20, 5, 10, 3, 0.3, and 50 μM, | Inhibit the production of pro-inflammatory prostanoids and leukotrienes at 10 μM.<br>(COX-1 platelets (26%), COX-1 cell-free (36%), COX-2 monocytes (56%),<br>COX-2 cell-free (35%),<br>cPLA cell-free (26%),<br>mPGES-1 cell-free (90%), 5-LO cell-free (88%),<br>5-10 PMNL A23187 (91%),<br>5-10 PMNL A23187 + AA (98%)<br>No effect was observed against DPPH and cell viability assay, | Cerino et al. (2021) |

Glutathione: GSH, Monocyte chemoattractant protein-1: MCP-1, Interleukine 8: IL-8, Interleukine 1: IL-1, Tumor necrosis factor-alpha: TNF-α, Interleukine 6: IL-6, Nuclear factor erythroid 2–related factor 2: Nrf2, Glutathione peroxidase: GPx, phenyl propionamide's: TPA, Lipopolysaccharide: LPS, Nitric oxide: NO, Nuclear Factor Kappa B: NF-κB, Mitogen-activated protein kinase pathway: p38, Inducible nitric oxide synthase: iNOS, Matrix metalloproteinase- 1 and 13: MMP-1 and MMP-13, Metallopeptidase inhibitor 1 and 3: TIMP-1 and-3, c-Jun N terminal kinase: JNK.

(phenylpropionamides) extract. TPA protected mice from harm and counteract the spatial and learning memory damage induced by LPS. In the LPS-induced animals, elevated levels of inflammatory markers such as TNF-α, IL-1, and IL-6 levels were decreased by TPA therapy. TPA also lessened the damage to mice's hippocampus neurons. This illustrates the hempseed's nutraceutical potential from a neuroprotective standpoint (Zhou et al., 2018). When pepsin hydrolyzes hempseed protein, two transepithelial-transported intestinal peptides, IGFLIIWV (H3) and WVSPLAGRT (H2), are produced. These peptides have an antioxidant impact on hepatocellular carcinoma (HepG2) cells. Also, these peptides are notable for altering the amounts of $H_2O_2$-induced lipid peroxidation and NO synthesis in HepG2 cells by inducible nitric oxide synthase pathways by stimulating the Nrf2, respectively (Cruz-Chamorro et al., 2022). Furthermore, it was discovered that CBD markedly increased anti-inflammatory pathways while significantly decreasing pro-inflammatory signaling and LPS-induced microglial cell migration (Kozela et al., 2010).

Osteoarthritis is a disease characterized by joint degeneration and underlying bone deterioration. A human trial was aimed to observe the impact of hemp seed flour-enriched pasta on indicators of bone development in individuals undergoing post-arthroplasty and also examined the effects of the extract of hemp seed on the RANKL, extracellular signal-regulated protein kinase (ERK1/2), Wnt/-catenin (protein) signaling, osteocalcin (OC), alkaline phosphatase, collagen type I alpha one chain (COL1A), and runt-related transcription factor 2 (RUNX-2) pathways. After six weeks, findings showed greater pain relief in individuals who regularly ate pasta. Hemp seed extract also upregulated the markers of osteoblast formation RUNX2, OC, COL1A, alkaline phosphatase (ALP), and downregulated RANKL compared to the control. Following the findings, hemp seed can improve bone metabolism both in vivo and in vitro trials and lessen pain in osteoarthritic patients after arthroplasty surgery. However, to support these preliminary findings, more clinical studies are required (Maurotti et al., 2021).

Musculoskeletal pain is frequently brought on by rheumatic disorders, which are known to produce inflammation and chronic pain (Dillmuth-Miller & Batson-Magnuson, 2020). Arthritic patients suffer from everyday pain, stiffness, immobility, and physical deformity. Additionally, Bruni et al. (2018) conducted a study in which transdermal and oral-mucosal routes were among the delivery techniques for CBD oil. The findings of their research recommended caution when using oils, tinctures, and vapors containing CBD to treat therapeutic pain because any benefits or health risks have not been established conclusively. They suggested caution even though the number of patients using CBD is increasing, and more investigation is still needed to check the safety parameters, efficacy, and quality of CBD (Bruni et al., 2018).

Moreover, Zurier, Rossetti, Burstein, and Bidinger (2003) examined

the effects of AjA, a non-psychoactive cannabinoid acid, on joint tissue damage and inflammation in adjuvant-induced arthritic rats. The study obtained peripheral blood monocytes (PBMs) and synovial fluid monocytes (SFMs) from healthy subjects and arthritis patients. These monocytes were treated with various concentrations of AjA 0–30 μM and then stimulated with lipopolysaccharide, a molecule that induces an immune response. The findings suggest that AjA can effectively reduce the production of IL-1β in human monocytes, which may contribute to its therapeutic effects in the animal model of arthritis. The suppression of IL-1β production was most pronounced at a concentration of 10 μM AjA, with a 50.4% reduction compared to untreated controls. However, AjA did not affect TNFα gene expression or secretion from PBMs. These findings deliver potential insight into the mechanisms favoring the benefits of AjA in reducing joint tissue damage and inflammation. AjA also exhibits its immunomodulatory reactions by apoptosis induced in activated osteoclasts, protecting them from osteoclastogenesis.

Furthermore, Miller and Miller (2017) acknowledged that many patients choose herbal cannabinoids as self-medication. Thus, it is imperative to check the role of cannabinoids in joint pain more thoroughly. Nonetheless, due to the limited research on the role of cannabinoids in individuals with rheumatic disorders, it is uncertain whether CBD alone is effective in providing analgesic benefits. Despite the numerous anecdotal patient reports, findings indicate that there is no conclusive affirmation about the use of CBD oil against joint pain because there are not enough thorough clinical investigations. In an in vitro investigation, the anti-arthritic activity of CBD was observed. By activating transient receptor potential cation channel subfamily (TRPA1) and mitochondrial target genes, CBD reduced cell survival and levels of MMP-3, IL-8, and IL-6 in rheumatoid arthritis synovial fibroblasts (RASF) and thus showed anti-arthritis effects (Lowin et al., 2020). Another study suggested that the anti-inflammatory compound 9-THC and CBD may be utilized to treat the neuroinflammation caused by the drug methamphetamine (METH) (Joffre et al., 2020).

Similarly, a study was conducted on patients with kidney transplants to observe the role of CBD (50 mg increased to 150 mg two times a day) in treating chronic pain. Results showed a reduction in self-reported pain in 6/7 patients after three weeks; it was noted that the causes of chronic pain (e.g., fibromyalgia, osteoarticular, neuropathic) varied across these individuals (Cuñetti et al., 2018). In a second research, CBD-rich hemp oil (150 mg/mL CBD/day for three months) was administered to twelve female volunteers with severe dysautonomic syndrome. The result showed a rise in the physical, vitality, and social functioning scores (Palmieri, Laurino, & Vadala, 2017).

A study focused on CBD targeting over 60 molecular pathways to cure OA. The findings revealed the role of PPAR-γ in modulating the therapeutic potential of CBD while increasing the expression of multiple transient potential receptor channels in heat hyperalgesia induced by the CBD. These results lay the foundation for cutting-edge CBD-based therapy with enhanced medicinal effects, which promotes the application of bioinformatic tools to anticipate the mechanism of CBD in various conditions (Mlost, Kędziora, & Starowicz, 2021).

β-Caryophyllene extracted from hemp is a CB2 agonist that modulates inflammation. Thus, a study was conducted to illustrate the therapeutic efficacy of β-caryophyllene and investigate the involvement of PPAR-γ in a collagen antibody-induced arthritis model. β-Caryophyllene (10 mg/kg/100 L) significantly hindered the adverse effect of the disease, decreased pro-inflammatory cytokines, and increased the anti-inflammatory cytokine IL-13 while reducing the expression of MMP 3 and 9 in joints. Additionally, it decreased the mRNA expression of COX2 and NF-kB mRNA and increased the effect of the PPAR-γ and PPAR coactivator-1 alpha. All in all, β-caryophyllene in human articular chondrocytes stimulated with LPS reduced the NF-kB activation and increased PPAR coactivator-1 alpha and PPAR-γ expression. These findings suggested that arthritis might be ameliorated by employing a cross-talk between CB2 agonist and PPAR-γ (Irrera et al., 2019). In a single-center randomized controlled trial, topical CBD (6.2 mg/mL with shea butter) treatment without adverse effects showed substantial improvements in thumb basal joint arthritis-related pain and disability (Heineman et al., 2022).

Additionally, the impact of non-stimulating cannabis extracts such as CBD oil and cannabigerol oil on pain and advanced OA in mice was investigated. The 12-week-old male C57BL/6 J mice either received a sham or invasive procedure, *i.e.*, surgical destabilization of the medial meniscus. Then, the mice were administered the cannabis extracts and vehicle. Both oils improved the gait of postoperative mice throughout the disease course. However, mechanical allodynia was not enhanced by any of the treatments. In contrast, they ameliorated the cold allodynia. The findings of the open field test stated that both interventional oils reverted the changes in the locomotion of mice and substantially reduced synovitis. The reduction of cartilage degeneration and chondrocyte loss in the expression of matrix metalloproteinase 13 and the increased number of anabolic chondrocytes were only caused by cannabigerol oil. Yet, CBD and cannabigerol oil did not ameliorate the subchondral bone remodeling in vehicle-treated mice. Thus, the research findings provide evidence for the nutraceutical potential of CBD oil and cannabigerol oil because both oils improve locomotion and gait and alleviate pain and inflammation. Nonetheless, the chondroprotective oil is the cannabigerol oil, which may offer greater efficacy in ongoing research in OA patients (Karuppagounder et al., 2023).

Apart from oil, hemp leaf extracts were examined as an anti-inflammatory agent on synovitis in vitro. Results showed that in a dose-dependent manner, all hemp extracts reduced the production of NO and PGE2 and decreased the expressions of iNOS, COX-2, and IL-1β genes. These effects were probably related to the amount of sesquiterpenoids and THC. An extract from the Huai Hoi cultivar showed the most promising results. The hemp leaf extracts significantly reduced the biomarkers of inflammation. Hence, these extracts have a potential application to counteract inflammatory synovitis (Duangnin et al., 2017).

The role of myrcene and CBD in regulating pain and chronic joint inflammation in male Wistar rats was examined. The chronic arthritis in the right knee was induced by intra-articular administration of Freund's complete adjuvant. Findings revealed that applying myrcene (1 and 5 mg/kg subcutaneously) via cannabinoid receptor decreased joint pain and inflammation. However, the repeated treatment with myrcene did not affect joint damage or the formation of inflammatory cytokines. The combined therapy of myrcene and CBD (200 μg) substantially had the same effect as the myrcene alone. Thus, these results demonstrated that topical application of myrcene has the potential to reduce inflammation and pain in chronic arthritis, though it has no coactive effect with CBD (McDougall & McKenna, 2022).

The endocannabinoid system-based network pharmacology of anti-rheumatic processes was explored in a study by Nandi, Das, Dey, and Roy (2023). The results from these investigations revealed that the potential treatment mechanism for RA was responding to compounds containing oxygen and modifying peptidyl-amino acids. These biological activities supported the Rap1 signaling pathway, cancer, calcium signaling pathway, atherosclerosis, lipids, and neuroactive ligand-receptor interaction. In the context of RA, molecular docking showed that phytocannabinoids might integrate to target key proteins such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), serine/threonine kinase 1 (AKT1), mitogen-activated protein kinase 9 (MAPK9), protein kinase C delta (PRKCD), serine/threonine-protein kinase B-Raf (BRAF), insulin-like growth factor 1 receptor (IGF1R), and nitric oxide synthase 3 (NOS3). Considering the above results, future experimental studies on phytocannabinoid's systemic biological properties must verify the findings to date (Nandi et al., 2023).

Through in silico analyses, the compounds with protective effects against inflammation were categorized and screened out from plants and analyzed for RA by directing TNF-α. The molecular docking results revealed that alanine-22, glutamate-23, serine-65, glutamine-67,

tyrosine-141, leucine-142, asparagine-143, phenylalanine-144, and alanine-145 were the key interacting compounds for receptor-ligand interactions that presented utmost binding affinities, least binding energies, and efficient drug properties. Therefore, it is recommended that RA patients use reported compounds to cure RA by targeting TNF-α and opening new avenues for designing novel therapeutic targets (Zaka et al., 2017).

Besides, the anti-inflammatory effects of β-caryophyllene on monosodium urate crystals-induced acute gouty arthritis in vivo and silico were exploited. The bioinformatics methods and molecular docking analysis screened the specific influence of β-caryophyllene on different pathways involved in gout. β-Caryophyllene significantly decreases inflammation via reduced serum cytokine levels and protects the function of ankle joints. Additionally, in the synovial tissue, it inhibited the expressions ofNLRP3, Caspase-1, a speck-like protein comprising caspase domain (ASC) linked with apoptosis, toll-like receptor 4 (TLR4), myeloid differentiation primary response 88 (MyD88), p65, and IL-1β (Li & Yang, 2021).

Microarray-based gene expression profiling revealed that CBD elicits its immunomodulatory effects in activated memory $T_{MOG}$ cells by inhibiting the transcription of Th17, stimulating the exhaustion of T cells, promoting the anti-proliferative action of IFN cells, hindering antigen presentation, and inducing antioxidant effects mitigating inflammation. These findings suggest the mechanism by which CBD has anti-inflammatory effects and its beneficial effects in pathological memory T cells and autoimmune diseases (Kozela et al., 2016). Table 4 represents the summary of industrial hemp in different forms and their role in arthritis.

## 7. The anti-diabetic potential of industrial hemp

Two randomized cross-trials were conducted to evaluate the impact of protein isolated from hemp on the glycemic response by comparing it with soybean protein. Participants in both studies consumed the following diet: control, 20 g (hemp20), 40 g (hemp40), 20 g (soy20), and 40 g (soy40). In both tests, the glucose response varied from 0 to 200 min depending on the treatment and time by treatment. Contrary to the control group, hemp proteins, like soybean protein, showed a decline in blood glucose levels. In non-obese diabetic (NOD) mice, CBD has been demonstrated to reduce the incidence of diabetes (animal model). Intravital microscopy examined how experimental CBD therapy affected early pancreatic inflammation in type 1 diabetes (T1D) (Mollard, Mackay, Wang, Leon, & Jones, 2017). Female NOD mice aged seven weeks received prophylactic daily doses of 5 mg/kg CBD five times weekly for 10 weeks. CBD-treated NOD mice had a delayed onset of T1D and considerably lower levels of inflammation-related biomarkers in their pancreatic microcirculation (Lehmann et al., 2016).

A study highlights the potential beneficial effect of CBD in female NOD mice (11–14 weeks old), either in a dormant stage or with early signs of diabetes (after 14 weeks) for one month. T1D was induced in rodents by administering low doses of streptozotocin (MLDSTZ). CBD treatment significantly inhibits and delays destructive insulitis (inflammation of the islets of Langerhans in the pancreas) and the production of inflammatory T helper (Th1)-associated cytokines. They also exhibited a shift in immune response from Th1 dominance (proinflammatory) to Th2 dominance (anti-inflammatory). The treatment reduced proinflammatory cytokines IFN-γ and TNF-α levels while increasing the production of Th2-linked interleukins, *i.e.,* IL-4 and IL-10. CBD prevented the destruction of islets and reduced the infiltration of mononuclear cells in them, thereby preventing diabetes (Weiss et al., 2006).

It has been stated that CBD-treated rats (4 weeks) undergo significant prevention from diabetic retinopathy. Thus, CBD may be beneficial for controlling T1D due to its anti-inflammatory properties. (El-Remessy et al., 2006). In another study, 62 patients with diabetes received CBD either by mouth (100 mg, twice daily for 16 weeks) or a placebo (noninsulin treated). The results showed no alteration in high-density lipoprotein (HDL) concentrations after CBD administration compared to baseline (Jadoon et al., 2016).

In a study, the researchers aimed to investigate whether CBD treatment could improve metabolic dysfunctions in diabetic rats that were also subjected to chronic cerebral hypoperfusion. The diabetic male Wistar rats (350 days old) were given 10 mg CBD/Kg daily for 1 month. The outcomes demonstrated decreased total cholesterol levels, elevated insulin secretion, and reduced hyperglycemia aggravated by brain injury (Zorzenon et al., 2019). CBD lowers glucose levels in human coronary endothelial cells (Rajesh et al., 2007). In addition, it demonstrated a reduction in the prevalence of diabetes (Weiss et al., 2006). The therapeutic efficiency and potential limits of CBD in diabetic patients have not yet been understood. Inflammation and oxidative stress play a significant role in diabetes and its complications. Recent studies have shown strong evidence that the newly identified lipid signaling system (endocannabinoid system) may significantly impact the formation of lipid peroxides, inflammation, and tissue injury. The primary target for treating diabetes and its side effects may be the endocannabinoid system. CBD is a plant-based cannabinoid with antioxidant and anti-inflammatory properties (Horváth, Mukhopadhyay, Haskó, & Pacher, 2012).

Following this, a research investigation was carried out to find the connection between cannabis use and diabetes. A questionnaire was given to 17,967 men and women (18–84 years of age) who replied in 2002 to check for any new instances of diabetes and follow up for new cases in 2010. Potential confounders were age, gender, alcohol use, body mass index (BMI), physical inactivity, smoking, and employment. The outcomes showed no relationship between cannabis use and a reduction in diabetes. To reach more reliable results about cannabis use, further in-depth studies are required (Danielsson et al., 2016). Moreover, in a study, obese rats (n = 6) were administered hemp seeds (12% food) or hemp seed oil (4% diet) at the age of 8 weeks for a total of 4 weeks. In both interventions, hemp was unable to decrease obesity development despite the reduction in lipid peroxidation and cholesterol levels. However, when compared to hemp oil, dietary supplementation with hemp seed powder was more effective (Majewski & Jurgoński, 2021).

Furthermore, researchers examined how haloperidol and CBD affected fasting blood sugar (FBS) levels and body weight. CBD (5 mg/kg/day) combined with haloperidol (5 mg/kg/day) was given intraperitoneally (subchronic) for 21 days or intramuscularly (chronic) for three months. Oral CBD (5 mg/kg/day) was directed for 21 days. Weight and FBS were reduced by CBD, which was shown in the subchronic group treated with haloperidol (Kajero, Seedat, Ohaeri, Akindele, & Aina, 2022).

THC was demonstrated to restrict the action of insulin and its release in various experimental models. In type 2 diabetes, glucose uptake by cells is impaired due to insulin resistance. In cultured adipocytes, THC might increase the insulin-induced glucose uptake (Scherer & Buettner, 2009). By using insulinoma β-cells (RINm5F) from rats, it was demonstrated that CB1 and CB2 receptor agonists, through the mobilization of intracellular calcium via IP3 receptors and activation of phosphatidyl inositol– phospholipase-C pathway, stimulate the release of insulin as well as stimulated the secretion of insulin by strengthening the effect of lipooxygenase and by facilitating the metabolism of arachidonic acid (De Petrocellis et al., 2007; Matias et al., 2006).

Plants are promising therapeutics in herbal medicine, and extensive research is being conducted to determine their effectiveness against different diseases (Abdullah. *C. sativa* extract, with repeated administrations, increased the reduced glutathione level in the liver, decreasing lipid peroxidation and relieving mechanical allodynia in STZ-induced diabetic rats (Comelli, Bettoni, Colleoni, Giagnoni, & Costa, 2009). On the contrary, Sativex (which contains THC and CBD) found no significant difference in the ability of the cannabis-based product to alleviate neuropathic pain in a double-masked clinical trial. Of the record were the findings that depression affected the reference point of pain scores

**Table 4**
Role of industrial hemp in arthritis.

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| CBD | In vitro | | Antiarthritic activity of CBD | By activating TRPA1 and mitochondrial target genes in RASF CBD:<br>↓Cell survival and formation of IL-6/IL-8/M MMP-3 thus showed anti-arthritis effects.<br>Pre-treatment with TNF:<br>↑Cationic viability dye (PoPo3) intake in RASF | Lowin et al. (2020) |
| Hemp seed oil phytol | Human monocyte-macrophages | In vitro | Hemp seed oil phytol at 10–100 mM was used to observe its anti-inflammatory effects on human monocyte macrophages. | The acyclic alcohol fraction isolated from hempseed oil contains phytol in the 167.59 to 1.81 mg/kg range.<br>Phytol skewed the monocyte-macrophage plasticity (anti-inflammatory activity), non-classical CD14 + CD16++ monocyte phenotype, and macrophage M2 (CD200R high and MRC-1 high).<br>↓TNF-α, ↓IL-1, ↓IL-6. | Claro-Cala et al. (2022). |
| Hempseed oil and the UPR | MH7A human FLSs | In vitro | The anti-rheumatic effect of hempseed oil was checked in MH7A cells | In a time and dose-dependent manner, hempseed oil treatment:<br>↓Survival rate of MH7A cells.<br>Promoted apoptotic cell death.<br>↑Lipid accumulation and ↑intracellular reactive oxygen species (ROS), ↑major ER stress markers expression, ↑Glucose-regulated protein 78, ↑CHOP in hemp oil treated MH7A cells.<br>Co-treatment with the antioxidant Tiron abrogated the cytotoxic effects of hemp oil,<br>↓ROS level, Cell viability was recovered ↓, and Apoptotic cell death.<br>siRNA-mediated knockdown of CHOP prevented hemp oil-induced apoptosis | Jeong et al. (2014) |
| HSHE | HaCaT | In vitro | HSHE was examined in this work, with a particular emphasis on the inflammation and lipogenesis caused by *P. acnes*. HaCaT cells were treated with and without HSHE for 24 h at 37 °C in 5% $CO_2$. | HSHE effects on HaCaT:<br>↓Inducible nitric oxide synthase (iNOS), ↓Cyclooxygenase 2 (COX-2), ↓Production of NO, ↓Prostaglandin, ↓IL-1β, ↓IL-8.<br>Anti-inflammatory effects were regulated by NF-κB and MAPK signaling and abrupting the transfer of p–NF–κB towards the nucleus.<br>↓Phosphorylation of ERK and JNK, and their subsequent targets c-Fos and c-Jun.<br>↓Transactivation of AP-1<br>Biosynthesis of lipids and inflammation in sebocytes regulated via AMPK and AKT/FoxO1 signaling.<br>↓5-lipoxygenase level, ↓MMP-9 activity, In-vitro promoted biosynthesis of collagen. | Jin and Lee (2018) |
| Transepithelial-transported intestinal peptides, WVSPLAGRT (H2) and IGFLIIWV (H3) | In vitro (human hepatic cell line | | Cells were stimulated with 1 μg/mL LPS and then treated with 25 μM H3 or 100 μM H2 peptides to check anti-inflammatory properties. | WVSPLAGRT (H2) and IGFLIIWV (H3) exerted antioxidant activity in HepG2 cells.<br>Both peptides were revealed.<br>↓$H_2O_2$-induced ROS and lipid peroxidation Modulate the interferon-gamma (IFN-γ), TNF, IL-6, IL-10, and NO via mediating the pathways of Nrf2, NF-κB, and the iNOS pathways. | Cruz-Chamorro et al. (2022) |
| Hemp leaf extracts | In vitro (synovial fibroblast cell line SW982) | | | Results showed that in a dose-dependent manner, all hemp extracts:<br>↓Production of NO and PGE2<br>↓Expressions of iNOS, COX-2, and IL-1β genes<br>These effects were probably related to the amount of sesquiterpenoids and THC.<br>An extract from the Huai Hoi cultivar showed the most promising results. | Duangnin et al. (2017) |
| CBD | In vivo (rats) | Topically applied | 0.6, 3.1, 6.2, or 62.3 mg/day were administered daily in a gel for transdermal administration for four days | The effective doses were 6.2 and 62 mg/day.<br>In a dose-dependent manner, transdermal CBD gel showed:<br>↓Joint swelling, ↓Immune cell infiltration | Hammell et al. (2016) |

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**Table 4** (*continued*)

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| | | | | ↓Limb posture scores<br>↓Synovial membrane thickening.<br>Immunohistochemistry of the spinal cord and dorsal root ganglia showed:<br>↓Pro-inflammatory markers.<br>Paw withdrawal latency (PWL) improved to near baseline.<br>These doses did not alter the exploratory behavior, demonstrating limited effect on higher brain function. | |
| Myrcene and CBD | In vivo (male Wistar rats) | Subcutaneous route | Myrcene (1 and 5 mg/kg) and CBD (200 μg) | Findings revealed the local application of myrcene via cannabinoid receptor mechanism.<br>↓Repeated myrcene treatment did not affect joint pain, ↓Inflammation, or damage and cytokine production.<br>The combined treatment of myrcene and CBD (200 μg) substantially had no different effect from alone myrcene. | |
| β-caryophyllene | In vivo (mice) | Oral gavage | β-caryophyllene 10 mg/kg/100 μL daily for 14 days | β-caryophyllene (10 mg/kg/100 L) significantly hindered the adverse effects of the disease.<br>↓Pro-inflammatory cytokines, ↑Anti-inflammatory cytokine IL-13, ↓Joint expression of matrix metalloproteinases 3 and 9, COX2 and NF-kB mRNA expression, ↑Expression of the PPAR-γ and PPAR coactivator-1 alpha.<br>β-caryophyllene in human articular chondrocytes stimulated with LPS: ↓NF-kB<br>↑Activation PPAR coactivator-1 alpha and PPAR-γ expression.<br>These findings suggested that arthritis might be ameliorated through crosstalk between CB2 agonist and PPAR-γ. | Irrera et al. (2019) |
| CBD oil and cannabigerol oil | In vivo (mice) | Subcutaneous injection in the OA knee region | Vehicle (coconut oil)<br>CBD oil (20 mg/kg/day)<br>Cannabigerol oil (10 mg/kg/day)<br>were administered every other day. | Both oils restored the gait of postoperative mice throughout the disease course. No treatments improved mechanical allodynia, but cold allodynia was ameliorated.<br>In an open-field test, both interventions revealed changes in the locomotion of mice and substantially reduced synovitis.<br>The reduction of cartilage degeneration, chondrocyte loss, the expression of matrix metalloproteinase 13, and the increased number of anabolic chondrocytes was only because of cannabigerol oil.<br>Yet, CBD and cannabigerol oil did not ameliorate the subchondral bone remodeling in vehicle-treated mice. | Karuppagounder et al. (2023) |
| CBD oil | In vivo (dogs) | Orally | | Pharmacokinetics showed 4.2 h of an elimination half-life at both doses with no evident adverse effects.<br>Canine brief pain inventory and Hudson activity scores exhibited:<br>↓Pain, ↑activity, and ↓alkaline phosphatase in serum. | Gamble et al. (2018) |
| CBD | Human survey | Questionnaire | By using the internet (social media accounts, newsletters), a self-selected sample (n = 428) was collected. | CBD use was associated with 83% improvements in pain, 66% in physical function, and 66% in sleep quality.<br>Osteoarthritis, rheumatoid arthritis, or other autoimmune arthritis groups found improvements in physical function:<br>↓Pain (point reduction) favors the osteoarthritis group.<br>↓Pain (44%) in the overall cohort, ↓Cessation of other medications, ↓Anti-inflammatories, ↓Acetaminophen, ↓Opioids, and discontinuation of anti-inflammatories acetaminophen and opioids. | Frane et al. (2022). |
| Hemp seed extract and Hempseed pasta | Human (pilot study and in vitro) | | Effects of pasta enriched with hemp seed flour on | Hemp seed extract upregulated the markers of osteoblast formation, RUNX2, | Maurotti et al. (2021) |

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**Table 4** (*continued*)

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| | | | on osteoarticular pain and in vitro investigation of hemp seed extract on bone metabolism | OC, ALP, COL1A, Wnt/_-catenin, and Erk1/2 pathways and suppressed RANKL, thus improving bone metabolism in the Saos-2 cell line.<br>Hemp seed pasta consumption showed<br>↑Pain relief.<br>↓Serum bone-specific alkaline phosphatase (BALP) after six weeks | |
| CBD gel | Human | Transdermal | Twice per day (250 mg) against osteoarthritis in humans. Duration: 12 weeks (n = 321) | Results exhibited no noticeable changes between the ZYN002 and placebo groups. ZYN002 (250 mg/day) showed the worst knee pain reduction was _2.64, _2.83 for ZYN002 500 mg/day, and _2.37 for placebo.<br>In responder analysis, ZYN002 250 mg/day significantly outperformed placebo. Men treated with ZYN002 250 mg/day had a significantly greater decrease in average worst knee pain scores than placebo-treated men and greater performance in the responder analysis. The results were not statistically significant in women against average worst knee pain scores or responder analysis.<br>Adverse events were exceeded in 3% of patients on ZYN002 (application site dryness and headache). | Hunter et al. (2018) |
| CBD | Human (kidney transplant patients) | – | CBD (50 mg increased to 150 mg, twice a day) for three weeks | ↓Self-reported pain in patients after three weeks<br>Total pain improvement was observed in 2 patients.<br>No change in 1 patient.<br>Partial response in first 15 days in 4 patients | Cuñetti et al. (2018). |
| CBD-rich hemp oil | Human (females with somatoform and dysautonomic syndrome) | Sublingual | CBD-rich hemp oil (titrated up to 150 mg/mL CBD/day for three months) was administered. | A rise was observed in the physical scores, vitality, and social role functioning scores. Hemp oil showed:<br>SF-36 assessment showed:<br>↓Body pain | Palmieri et al. (2017) |
| CBD | Human (single-center randomized control trial | Topical application | Topical CBD (6.2 mg/mL with shea butter) | Topical CBD (6.2 mg/mL with shea butter) treatment without adverse effects showed substantial improvements in thumb basal joint arthritis-related pain and disability. | Heineman et al. (2022) |
| Phytocannabinoids | Bioinformatics based study | | | These analyses revealed that the underlying mechanisms of RA treatment were the processes like a response to compounds comprising oxygen and peptidyl-amino acid modification. These biological activities supported the Rap1 signaling pathway, cancer, calcium signaling pathway, atherosclerosis, lipids, and neuroactive ligand-receptor interaction.<br>In the context of RA, molecular docking showed that phytocannabinoids might integrate to target key proteins, including PIK3CA, AKT1, MAPK9, PRKCD, (BRAF), IGF1R, and NOS3. | Nandi et al. (2023) |
| Medicinal plants extracts | Bioinformatics-based study (in silico) | | | The docking analyses revealed that alanine-22, glutamate-23, serine-65, glutamine-67, tyrosine-141, Leucine-142, asparagine-143, phenylalanine-144, and alanine-145 were key compounds for receptor-ligand interactions that presented utmost binding affinities, least binding energies, and efficient drug properties. | Zaka et al. (2017) |
| β-caryophyllene | Bioinformatics and molecular docking (In silico and in vivo) | By oral gavage in rats | β-Caryophyllene (100 mg/kg)<br>Monosodium urate<br>+β-Caryophyllene (200 mg/kg)<br>Monosodium urate<br>+β-Caryophyllene (400 mg/kg)<br>MSU + Indomethacin (Ind: 5 mg/kg | β-caryophyllene significantly<br>↓Inflammation via reduced serum cytokine levels and protects the function of ankle joints. Additionally, in the synovial tissue, it inhibited the | Li and Yang (2021) |

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**Table 4** (*continued*)

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| | | | and β-Caryophyllene (400 mg/kg). Daily before the administration of monosodium urate | expressions of NLRP3, Caspase-1, ASC, TLR4, MyD88, p65, and IL-1β. | |
| CBD | Bioinformatics based study | | | Microarray-based gene expression profiling revealed that CBD elicits its immunomodulatory effects in activated memory $T_{MOG}$ cells by inhibiting the transcription of Th17, stimulating the exhaustion of T cells, promoting the anti-proliferative action of IFN cells, hindering antigen presentation, and inducing antioxidant effects mitigating inflammation. | Kozela et al. (2016) |

and that patients exhibited improvement of symptoms irrespective of the treatment regimen, which reveals the powerful link of depression with the understanding of pain (Selvarajah, Gandhi, Emery, & Tesfaye, 2010). Research in rat models of diabetes during the initial stages of diabetes demonstrated that CBD exerted protection against harm to the blood-brain barrier. This seems to be linked to a decrease in the expression of inflammatory factors, including TNF-α and adhesion molecules such as intercellular adhesion molecule (ICAM-1), among others (El-Remessy et al., 2006; Rajesh et al., 2007). Moreover, in Sprague Dawley diabetic rats, by blocking the nitration of tyrosine, CBD preserved the activity of glutamine synthesis and retinal neurons (El-Remessy, Khalifa, Ola, Ibrahim, & Liou, 2010).

CBD-rich hemp oil extract was studied for its effect on the adenosinergic system of left atria of obese type Zucker Diabetic rats. A daily dose of oil or vehicle via gavage was maintained at 60 mg/kg/day for one month. Results revealed that N6-cyclopentyl adenosine (poorly carried A1 adenosine receptor agonist) exhibited a notably weak response in the treated group. However, adenosine (rapidly metabolized and transported adenosine receptor agonist) elicited a strong response. All these effects of CBD were due to the accumulation of interstitial adenosine in the myocardium, which significantly increased adenosinergic activation that can be presumed during the prolonged treatment of oral CBD. Considering the above findings, all these effects were smaller than seemed, beyond the CBD-naïve level in every aspect (Viczjan, Zsuga, Varga, & Gesztelyi, 2022).

Apart from the role of cannabidiol from hemp leaves and inflorescence, a study was carried out to evaluate the anti-diabetic potential of ethanolic and aqueous extracts of hemp roots in insulin-deficient diabetic mice (streptozotocin (STZ)-induced). The administration of both extracts alleviated high blood glucose levels, improved homeostasis of glucose and islet function in diabetic mice, and decreased cell apoptosis and inflammatory signaling process in the pancreas. Additionally, the extracts normalized insulin signaling defects in skeletal muscles and apoptotic action in the liver and kidney. All these effects might be due to some active components such as vanillin, syringaldehyde apocynin, and methyl palmitate in both extracts. These results showed that hemp root extracts might protect against insulin-deficient diabetes. However, further studies are required to provide evidence for using hemp roots as a novel bioactive compound (Kim et al., 2023).

In a study by Guzmán-Flores, the therapeutic potential of *C. sativa* in type 2 diabetes was explored through molecular docking integrated with network pharmacology. Results revealed that four hub proteins, including proto-oncogene tyrosine-protein kinase Src (SRC), heat shock protein HSP 90-alpha (HSP90AA1), estrogen receptor (ESR1), and epidermal growth factor receptor (EGFR), that bind with the thirteen bioactive compounds of hemp such as cannabinol apigenin, luteolin arachidonic acid, caryophyllene, n-cis-feruloyl tyramine oxide, gamma-linolenic acid, oleic acid, gondoic acid, linoleic acid, linolenic acid, sitosterol, and stigmasterol and were involved in the responses linked with hormones, lipids, and stress. Additionally, the antidiabetic action was due to the insulin signaling, particularly the PI3K/Akt pathway, in which hypoxia-inducible factor 1 (HIF-1) and forkhead box O (FoxO) also play an essential role (Guzmán-Flores, Pérez-Vázquez, Martínez-Esquivias, Isiordia-Espinoza, & Viveros-Paredes, 2023).

The two major cannabinoids, namely CBD and THC, have been seemingly used as alternative medicine for diabetes treatment. However, their mechanisms of action yet remain unclear. Thus, a study was carried out to assess the α-glucosidase inhibitory activity of THC, CBD, and standardized cannabinoid extracts. The results of the enzyme-based in vitro assay on α-glucosidase reported that THC (IC50 values: 3.0 ± 0.37 μg/mL) and CBD (IC50 values: 5.5 ± 0.28 μg/mL) elicited a greater inhibitory activity as compared to the standard drug, acarbose (IC50 value: 488.6 ± 10.23 μg/mL). This inhibition was more due to the treatment of two standardized cannabinoid extracts (*C. sativa* leaf extract and *C. sativa* inflorescence extract) than alone THC and CBD. To conclude, this study provided the first indication that the standardized cannabinoid extracts comprising THC and CBD have potential applications as an α-glucosidase inhibitor as well as they showed exceptional pharmacokinetic profiles with minor toxicity in terms of tumorigenic and reproductive effects (Suttithumsatid et al., 2022). Moreover, considering the interaction between protein and phytochemicals (ligands) is vital for the pharmaceutical and food industries. The docking process showed that 7 phytochemicals-cannabichromene, cannabicyclol, friedelin, delta (9)-tetrahydrocannabinolic acid, kaempferol, cannflavin A, campest-4-en-3-one established the hydrogen and hydrophobic bonding with a great affinity with diabetes targeted human pancreatic α-amylase protein (BAJ). However, the mechanisms related to these effects require additional investigation for their role in structural-based drug design. These results are important and are a potential tool for the pharmacophore model near the active site pocket of alpha-amylase (Chauhan, Sharma, Durgapal, & Chandra, 2023). Table 5 represents a summary of industrial hemp in different forms and its role in preventing diabetes.

## 8. Conclusion

Cannabis (C. sativa) has been used for the treatment of inflammation for centuries, but in modern medicine, its use is hampered by a lack of scientific knowledge. Interestingly, industrial hemp is a nutrient-dense plant that contains essential amino acids, fiber, and some good antioxidants like iron, zinc, B vitamins, vitamin D, and vitamin E, as well as a balanced ratio of omega 3 to omega 6 fatty acids. Its unique phytochemical profile possesses antioxidants, immuno-modulatory, and anti-inflammatory properties. As CBD, essential fatty acid, hemp seed protein, and other bioactive components that are present in hemp may reduce the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, as well as the proliferation and differentiation of T cells that contribute to the autoimmune response. In diabetic rats, CBD induces vasodilation by activating the CB2 cannabinoid receptors and, thus, prevents beta cells from destruction. Cannflavin A and B showed

**Table 5**
The anti-diabetic potential of industrial hemp.

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| **CBD-rich hemp oil** | In vivo (Obese type Zucker Diabetic Fatty (ZDF) rats) | Oral gavage | Daily dose: 60 mg/kg/day CBD or vehicle via gavage for 4 weeks | N6-cyclopentyl adenosine exhibited a significantly weak action in the treated group. Adenosine elicited a significantly strong response. Accumulation of interstitial adenosine accumulation in the myocardium: increased ↑Adenosinergic activation that can be presumed during the prolonged treatment of oral CBD. | Viczjan et al. (2022) |
| **Ethanolic and aqueous extracts of hemp roots** | Streptozotocin (STZ)-induced insulin-deficient diabetic mice | Gavage by using an esophageal cannula | Non-STZ + vehicle, STZ + vehicle, STZ + hemp root water extract (150 mg/kg) STZ + hemp water extract (300 mg/kg) STZ + hemp root ethanol extract (150 mg/kg) STZ + hemp ethanol extract (300 mg/kg) | Administration of both extracts alleviated high blood glucose levels and improved glucose homeostasis and islet function. ↓Cell apoptosis and inflammatory signaling process in the pancreas. They normalized the hindrance of insulin signaling in skeletal muscles and apoptotic action in the liver and kidney. All these effects might be due to some active components such as vanillin, apocynin, methyl palmitate, and syringaldehyde in both extracts. | Kim et al. (2023) |
| **CBD** | In vivo (NOD mice) | Oral | Daily dose of 5 mg/kg CBD five times weekly for ten weeks. | CBD-treated NOD mice had a delayed onset of T1D and considerably lower levels of inflammation-related biomarkers in their pancreatic microcirculation. | Lehmann et al. (2016) |
| *C. sativa* **extract with high contents of CBD (64.5%)** | In vivo (STZ-induced diabetic rats) | Oral | Drug vehicle or eCBD (15 or 30 mg/kg), daily for 8 days, starting from day 28 after the induction. | The repeated administrations: ↑Reduced glutathione level in the liver, ↓Lipid peroxidation, Relieve mechanical allodynia. | Comelli et al. (2009) |
| **Hempseed extract and Hempseed oil** | Obese rats | Oral in diet | Hemp seeds (12%) or lipid hemp seed oil (4%) were given to obese rats (n = 6) at the age of 8 weeks for 4 weeks. | Triglycerides, and the estimated atherogenic parameters all decreased with hemp oil. Hempseeds showed improvement in vasodilation. Dietary supplementation with hempseeds was significantly more helpful than oil. | Majewski and Jurgoński (2021) |
| **Haloperidol CBD** | Rats | Oral | Haloperidol (5 mg/kg/day) was delivered intraperitoneally for 21 days (sub-chronic) or intramuscularly for 3 months (chronic), either on its own or before CBD (5 mg/kg/day). For 21 days, oral CBD (5 mg/kg/day) was given. | CBD showed a reduction in weight and FBS, which was observed in the subchronic group haloperidol groups. | Kajero et al. (2022) |
| **Hemp protein concentrate** | Humans (Adults) | Oral | Participants consumed the following diet: control, 20 g of hemp protein (hemp20), 40 g of hemp protein (hemp40), 20 g of soybean protein (soy20), and 40 g of soybean protein (soy40). | Hemp proteins like soy protein showed a reduction in blood glucose levels and insulin concentrations as compared to the control group. | Mollard et al. (2017) |
| **CBD** | Humans (pilot study) | Oral | Patients (n = 62) with type 2 diabetes received either oral CBD (100 mg, twice a day for 16 weeks) or a placebo (non-insulin treated). | CBD had a hepatoprotective impact by lowering hyperglycemia, increasing insulin secretion, and lowering total cholesterol levels. | Jadoon et al. (2016) |
| **CBD** | Humans (obese man) | Oral | A 62-year-old obese diabetic man (weight 113 kg) began taking 20 mg CBD daily for controlling blood glucose despite insulin degludec for 6 weeks. | The patient had no macrovascular complications of diabetes and had normal functioning of the hepatic and renal systems. CBD did not cause harm or deterioration of diabetes. | Mattes, Espinosa, Oh, Anatrella, and Urteaga (2021) |
| ***C. sativa*** | Bioinformatics based study | – | Molecular docking integrated with network pharmacology. | Four hub proteins including proto-oncogene tyrosine-protein kinase Src (SRC), heat shock protein HSP 90-alpha (HSP90AA1), estrogen receptor (ESR1), and epidermal growth factor receptor (EGFR), bind with the thirteen bioactive compounds of hemp such as cannabinol apigenin, luteolin arachidonic acid, caryophyllene, n-cis-feruloyl tyramine oxide, gamma-linolenic acid, oleic acid, gondoic acid, linoleic acid, linolenic acid, sitosterol, and stigmasterol and were involved responses related to hormones, lipids, and stress. The antidiabetic action was due to | Guzmán-Flores et al. (2023) |

(*continued on next page*)

**Table 5** (*continued*)

| Industrial hemp | Subject | Intervention form | Material and method | Result | References |
|---|---|---|---|---|---|
| | | | | modulation of the insulin signaling particularly the PI3K/Akt pathway, in which HIF-1 and FoxO also play an essential role. | |
| **Standardized cannabinoids extract from leaves and inflorescence** | Bioinformatics-based study (In silico) | – | – | The results of the enzyme-based in vitro assay on α-glucosidase reported that THC (IC50 values: 3.0 ± 0.37 μg/mL) and CBD (IC50 values: 5.5 ± 0.28 μg/mL) elicited a greater inhibitory activity as compared to the standard drug, acarbose (IC50 value: 488.6 ± 10.23 μg/mL). | Suttithumsatid et al. (2022) |
| ***C. sativa* phytochemicals** | Bioinformatics based study | – | – | The docking process showed that 7 phytochemicals- cannabichromene, cannabicyclol, friedelin, delta (9)-tetrahydrocannabinolic acid, kaempferol, cannflavin A, campest-4-en-3-one established the hydrogen and hydrophobic bonding with a great affinity with diabetes BAJ protein | Chauhan et al. (2023) |

anti-inflammatory properties by reducing prostaglandin E2 synthesis and regulating AMPK and AKT/FoxO1. Moreover, due to their glucosidase inhibitory activity, peptides are effective against diabetes. A growing body of knowledge suggests that industrial hemp (seed, oil, extract), due to its immunomodulatory, antioxidant, and anti-inflammatory activities, protects against osteoclastogenesis (bone degradation) and, thus, inflammation associated with arthritis and diabetes. However, it is important to note that while hemp has shown promising potential as a therapeutic agent, the research is still in its early stages. Findings suggest that currently, the evidence is still lacking in quality, quantity, and key factors concerning the efficacy and safety of hemp, especially hemp seed oil, for rheumatic diseases and diabetes. Further studies are needed to understand their efficacy for various medical conditions fully. Additionally, the use of hemp is a topic of ongoing debate, and the legal status of cannabis varies across different countries and jurisdictions.

## CRediT authorship contribution statement

**Amin Mousavi Khaneghah:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Conceptualization. **Rana Muhammad Aadil:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

## Data availability

No data was used for the research described in the article.

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