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Cannabinoids as Potential Therapeutic Agents for Kidney and Liver Toxicity

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Abstract

Cannabinoids have many important properties, such as anti-inflammatory, antioxidant, and neuroprotective effects that make cannabinoids have promising effects to reduce kidney and liver toxicity. There are some conditions, such as oxidative stress and fibrosis, as well as inflammation, that are associated with nephrotoxicity and hepatotoxicity. Cannabinoids showed the ability to reduce these effects. According to numerous experimental investigations and preclinical models, these compounds appear to play a part in controlling inflammation and cell death by activating certain receptors and regulating cellular pathways. However, to assure the safety and effectiveness of cannabinoids, further research is required to develop dose regimens and comprehend medication interactions. Measurements such as the cannabinoid optimal dosages, frequency, and duration of cannabinoid treatment need to be addressed carefully.

Keywords:
Cannabinoids, nephrotoxicity, hepatotoxicity, the endocannabinoid system, delta-9-tetrahydrocannabinol, cannabidiol

1. Introduction

Cannabinoids are a group of compounds that mostly have effects on the nervous system and the immune system, and these compounds are commonly found in the cannabis plant [1]. In recent years, many researchers have focused on studies of these compounds because of their promising results on many conditions and diseases [1, 2]. One of these compounds, cannabidiol (CBD), has been shown in many research studies to treat different central nervous system (CNS) disorders, such as epilepsy [4], improving vocal learning [5], reducing anxiety [6], and depression [7]. In addition to cannabidiol, there is another compound called delta-9-tetrahydrocannabinol (Δ-9-THC) that showed positive results in relieving pain and nausea [8]. These compounds also showed their ability to produce neuroprotective effects and reduce inflammation [9].

Cannabinoids were also found to act by targeting the endocannabinoid system (ECS), and this system has a prominent role in regulating many physiological functions, including pain, appetite, mood, and immunity [10, 11]. There are several molecules and receptors found in the ECS that interact with cannabinoids, including endocannabinoids which are the cannabinoids that our body produces on its own [10, 11].

In the early 1990s, researchers were investigating the effects of THC when they discovered the ECS [12]. They discovered that THC binds to cannabinoid type 1 (CB1) receptors in the brain [13]. Afterward, the G protein-coupled receptor 55 (GPR55) and the cannabinoid receptor 2 (CB2) were discovered [14]. Among the endocannabinoid receptors discovered, there are also enzymes discovered that degrade cannabinoids, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [15], as well as transport proteins like fatty acid binding proteins (FABPs), which carry endocannabinoids and exogenous cannabinoids throughout the body. [16].

As the body requires, endocannabinoids regulate different physiological processes. In the body, two-arachidonoylglycerol (2-AG) and anandamide are well-known endocannabinoids. 2-AG has been found to be the most common endocannabinoid in the brain and is involved in many physiological processes, including mood regulation [15].

When endocannabinoids are released will interact with the CB1 receptor and activate a series of signaling pathways and physiological processes, this activation will decrease the level of pain, while in the immune system, the endocannabinoids will interact with the CB2 receptor will help to reduce inflammation [17].

2. Cannabinoid's effect on nephrotoxicity and hepatotoxicity

Although cannabinoids have been associated with psychoactive effects, many recent studies are concerned with their effects on reducing kidney and liver toxicity. This review will focus on the potential of cannabinoids to reduce or treat hepatotoxicity and nephrotoxicity by exploring the mechanisms of action, experimental evidence, and clinical studies.

2.1. Cannabinoids effect on nephrotoxicity

2.1.1 Overview of nephrotoxicity and its causes

Nephrotoxicity is a condition when the kidneys are unable to perform their normal functions due to different causes, including toxic substances exposure [18]. Because of the diversity of functions carried out by the kidneys, such as filtering blood,

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eliminating waste products from our body, and controlling fluid and electrolytes, these functions will be affected when the kidneys have nephrotoxicity and will lead to a wide variety of serious health implications [19].

There are many causes for nephrotoxicity, including drugs such as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and chemotherapy drugs [19]. These drugs may affect the normal functions of the kidney, like limiting blood flow or interfering with filtration [19]. In addition, exposure to heavy metals such as mercury, lead, and pesticides [21] can cause nephrotoxicity because they will attack kidney cells interfering with the transportation of crucial molecules throughout kidney membranes [19]. In addition to exposure to some drugs and heavy metals, some diseases may affect kidney functions and cause nephrotoxicity, such as diabetes and high blood pressure [22]. Different symptoms can appear in patients suffering from nephrotoxicity, such as decreased urine output, swelling, and fatigue; the severity of these symptoms depends on conditions and causes [18]. To prevent or at least reduce the incidence of nephrotoxicity, it is necessary to reduce people's exposure to toxic substances and monitor kidney function for people at risk [19]. It is also very necessary for researchers and scientists to strive to find a treatment or way to treat patients suffering from nephrotoxicity because the kidneys are one of the main and important organs in the human body.

2.1.2. The potential role of cannabinoids as a protective agent against nephrotoxicity

Because nephrotoxicity has worried the medical field and caused many negative effects on the quality of life of many patients, researchers have sought to examine many compounds that are expected to treat or reduce the effect of this condition, one of them being cannabinoids. In a research published in the Journal of Pharmacology and Experimental Therapeutics, the effect of a non-psychoactive cannabinoid, cannabidiol (CBD), was examined on experimental animals have nephrotoxicity induced by cisplatin, and the results showed that CBD reduced kidney damage [23]. They found that CBD significantly reduces inflammation and oxidative stress in the kidney, which are important factors in the development of nephrotoxicity [23]. In addition, CBD shows a positive effect in reducing the nephrotoxicity caused by ischemia-reperfusion injury, which can cause inflammation and kidney damage in rats [24]. Moreover, CBD produced its ability to reduce inflammation and apoptosis in the kidneys [25]. These results suggest the potential of using CBD as protective kidneys against nephrotoxicity.

Likewise, delta-9-tetrahydrocannabinol (Δ-9-THC) has also been studied in reducing nephrotoxicity. The results of a study suggest that treatment with Δ -9-THC reduced kidney injury caused by ischemia-reperfusion injury and inflammation through the reducing oxidative stress in the kidney tissue [26]. In addition, Several studies have found that the ECS has a role in renal inflammation, oxidative stress, and fibrosis, which are key factors in nephrotoxicity development and progression [25, 27-29].

While the exact protective mechanisms of cannabinoids such as CBD, THC, as well as endocannabinoids against nephrotoxicity are not completely understood, it is believed that they produce this effect through various pathways that include promoting the regeneration of damaged cells in addition to the reduction of apoptosis, inflammation, and oxidative stress [28, 29].

Inflammation is one of the major factors contributing to renal disease, and various studies show that cannabinoids have anti-inflammatory effects. As well as their anti-inflammatory effect [23], cannabinoids can produce antioxidant effects which also help to produce a protective effect against nephrotoxicity. Oxidative stress is one of the main factors in the development and progression of nephrotoxicity [25]. Cannabinoids have been demonstrated to have potent antioxidant properties [30], which can help to reduce oxidative stress and protect the kidneys against nephrotoxicity.

In addition to these favorable effects of cannabinoids, cannabinoids also directly affect the cells of the renal tubules of the kidney. Studies have shown that cannabinoids help to reduce cell death (apoptosis) in the renal tubules, which will help to reduce the effect of nephrotoxicity [31, 32]. Demonstrated with endocannabinoids, they help to control pain which is a frequent symptom of kidney disease, and this effect is linked to CB2 receptor activation [15].

Overall, previous studies suggest that cannabinoids may have a beneficial protective effect against nephrotoxicity through their anti-inflammatory, antioxidant, and cell-protective properties. However, in order to fully understand the mechanisms underlying cannabinoids' potential protective effect against nephrotoxicity, further research is needed.

The endocannabinoid system and its negative impact on the kidneys

A negative effect on renal function may happen when CB1 receptors are activated and vice versa (positive effect for CB2 receptors) [27], [33]. Furthermore, Moradi et al. (2019) study found that endocannabinoids may have a role in patients with End-Stage Renal Disease who had higher levels of 2-AG in their blood compared to healthy control subjects [34]. Otherwise, the activation of CB1 receptors may have undesirable effects; however, antagonizing this receptor may produce beneficial effects.

2.2. Cannabinoids and liver toxicity:

2.2.1 Overview of hepatotoxicity and its causes

The liver is responsible for detoxification and metabolism, whereby its susceptibility to hepatoxicity is high. Hepatotoxicity is a condition where the liver suffers damage from exposure to certain substances such as drugs, for example, acetaminophen (paracetamol) [35] and antibiotics [36], or certain herbal and dietary supplements, for example, kava, black cohosh, and green tea extract [37]. In addition, heavy drinkers are more likely to develop hepatoxicity, which may lead to alcoholic hepatitis, alcoholic fatty liver disease, and cirrhosis [38]. This occurs because different mechanisms and processes are affected, including oxidative stress, inflammation, and disruption of liver metabolism [39].

Moreover, hepatitis viruses A, B, C, D, and E [40] and some metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), are significant contributors to hepatoxicity, which will lead to longer-term and more severe complications, such as liver cirrhosis and hepatocellular carcinoma [41]. These are characterized by the accumulation of fat in the liver and subsequent inflammation, which can progress to liver fibrosis and cirrhosis [40, 41].

2.2.2 The potential role of cannabinoids as a protective agent against hepatotoxicity

As mentioned before, the mechanism of action of cannabinoids is highly dependent on the specific CB1 and CB2 receptors [42]. CB1 receptors are predominantly located in the brain as well as they are present in hepatocytes and hepatic stellate cells [43]. In comparison, CB2 receptors are primarily expressed in immune cells, such as Kupffer cells and hepatic stellate cells [44]. Once activated these receptors, various cellular processes such as inflammation, apoptosis, oxidative stress, and lipid metabolism are expressed in the liver [13], [43–45], providing hepatoprotective effects [44].

Preclinical studies using animal models have demonstrated that cannabinoids have hepatoprotective effects. These studies indicated that cannabinoids can attenuate liver inflammation and fibrosis, which are key contributors to the progression of liver diseases [44]

Its hepatoprotective effects could be due to the suppression of hepatic stellate cell activity by reducing the deposition of excess extracellular matrix proteins, which is the mechanism for preventing the development of liver fibrosis [44]. Furthermore, its anti-inflammatory properties reduce the release of stellate cells and inhibit the activation of immune cells in the liver [44], thereby limiting the progression of liver diseases [44]. Moreover, the antioxidant effects of cannabinoids act as scavengers of free radicals and inhibit the production of reactive oxygen species known to cause oxidative damage to liver cells, which helps to preserve healthy liver function [46].

Although the aforementioned research was preclinical, an increasing number of clinical investigations and human trials have lately offered insightful data. According to a comprehensive case control study conducted on a large population investigating any possible links between cannabinoid usage and NAFLD in the United States, the findings revealed a notable decrease in the prevalence of NAFLD among individuals who have used cannabinoids [47]. Observed in another five years long study, additional findings emerged revealing a 50% reduced risk of elevated steatosis for those who were coinfected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) and use of cannabis daily, indicating a significant association in this population. [48, 49].

3. Potential limitations and challenges in the use of cannabinoids for nephrotoxicity and hepatotoxicity

Currently, there are many studies suggesting the protective effects of cannabinoids against nephrotoxicity and hepatotoxicity [29]; however, the absence of standardized dosing and formulations for cannabinoids is a challenge. Due to the differences in absorption and metabolism between individuals, different components and formulations of cannabinoids can have extremely different effects on the human body [50]. The optimal dosage for their therapeutic application can be hard to identify due to their variation and may also lead to unpredictable side effects.

Another challenge would be the drug interactions between cannabinoids and other drugs, especially for patients who ingest medication daily. For those who already are in drug treatment for renal disease(s), ingesting cannabinoids may interact with other drugs used, such as diuretics and immunosuppressants [50, 51]. These interactions may cause unwanted adverse effects or reduce the cannabinoid and/or drug effects. Thus, careful monitoring and dose adjustment are required.

Finally, the use of cannabinoids in the legal and regulatory context can be difficult based on a country's requirements. In many parts of the world, legalizing cannabinoids for medical and/or recreational use has increased. However, their legal system is complicated and remains an evolving issue [52]. Due to this, the adoption of further research on cannabinoids, particularly on standardizing dosing, is slower restricting patient access. Therefore, more research is needed to fully understand the exact protective mechanisms of cannabinoids in human clinical trials to clarify and ensure the safety and effectiveness of cannabinoids for renal disease(s) [29].

4. Conclusion

In summary, the anti-inflammatory and antioxidant effects of cannabinoids can have promising results in working as a protective agent against nephrotoxicity and hepatotoxicity. Cannabinoids such as the CBD, THC, and the ECS interaction have the potential to module certain signaling pathways, regulate physiological processes, and reduce kidney and liver damage. However, more research is needed to fully understand the underlying protective mechanisms to combat challenges in standardized dosing and unknown potential drug interactions to curb legal regulations for the use of cannabinoids as therapeutic agents for kidney and liver-related disorders.

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