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# Pharmacological and Toxicological Aspects of *Cannabis sativa*: A Systematic Review

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**ABSTRACT**

*The use of Cannabis sativa and its components has been reported and spread, and it's in constant need of related studies. The molecular study of its properties has recently emerged with the discovery of an endogenous cannabinoid system. Popularly known as marijuana, Cannabis sativa has been receiving attention due to its therapeutic potential, but also for being the most popular illicit drug. Its use generates doubts among the lay people and health professionals, due mainly to its toxic effects commonly reported. The present paper is a Systematic Review which aims at researching the state-of-the-art knowledge of Cannabis sativa and its components, aiming at answering the following question: "Which are the Pharmacological and Toxicological Aspects of Cannabis sativa reported in literature?", using the databases Scielo, PubMed and Capes Journals, and the keywords: Cannabis sativa AND Cannabidiol AND Tetrahydrocannabinol. The criteria used were papers published between 2011 and 2016, in English, Portuguese and Spanish, which reported the information aimed at and were of open access. After the inclusion criteria had been applied, the selection went through three other phases: reading of titles, reading of abstracts and reading of full articles, respectively. At the end of such process, forty nine articles were selected. In general, the information searched was properly found, which contributed to consolidate the knowledge on the Pharmacological and Toxicological aspects of Cannabis sativa and opened perspectives for future researches.*

**Keywords**: *Cannabis sativa*; Cannabidiol; Tetrahydrocannabinol; Pharmacological and toxicological aspects

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## INTRODUCTION

The psychoactive substances have been consumed in several spheres and cultures with therapeutic, religious and recreational purposes. From the psychoactive drugs, *Cannabis sativa* (Cs) is one of the mostly consumed worldwide. *Cannabis sativa* is a bush from the *Moraceaes* family, which is able to live in tropical and temperate regions [1].

Concerning its medical use, with effects known for over 4 thousand years, Cs is used to relief symptoms related to cancer treatments, AIDS, multiple sclerosis and Tourette's syndrome, being its indications described in the medical practice, such as, analgesia and sedation, muscle relaxants, anticonvulsants, appetite stimulation, antipyretics and in the opioid detox treatments. Some oncologists advocate on the use of Cs as an antiemetic agent, that is, Cs can aid in chemotherapy, when the nausea and vomiting are refractory to other medications [1, 2].

The toxic effects of *Cannabis sativa* are divided into two groups: 1) the effects of the habit of smoking the plant and 2) those caused by the most important isolated substances (cannabinoids) [3].

Most researches show that Cs does not cause physical dependence (as cocaine, heroin, caffeine and nicotine do) and the suspension of its use does not generate drug withdrawal syndrome (like alcohol and heroin). However, its long term use may lead to psychological dependence, as well as lead to the consumption of other drugs. Thus, its use is dangerous due to the fact that the drug has powerful psychotropic and hallucinogenic properties.

The effects of *Cannabis sativa* on the body are linked to the cannabinoids. The cannabinoid components may be classified as therpene phenols and have not been isolated from any other plant or animal genus [4].
No other drug that may be potentially abused causes more debates than Cs. Its prevailing use is only less than alcohol and tobacco, licit substances in Brazil [5].
According to the World Health Organization (2000), the demand for psychoactive substances increased significantly over the last decades. Thus, it is necessary to obtain a greater set of information on the effects of *Cannabis sativa*, taking into account the theme's great coverage and importance, updating the knowledge with information from recent studies [5].
The present paper is a systematic review which consists of a summary of the results of researches related to a specific problem. These reviews are designed to be methodical, explicit and reproduced, serving to guide the development of projects, indicating new pathways for future investigations and identifying which research methods were used on a certain area [6].
In face of this, this study aims at knowing the pharmacological and toxicological aspects of *Cannabis sativa*, assessing the data found in the literature, after a bibliographic survey.

## EXPERIMENTAL SECTION

The research was performed aiming at answering the question "Which are the Pharmacological and Toxicological Aspects of *Cannabis sativa* reported in literature?" The databases Scielo, PubMed and Capes Journals were used, through the following words: *Cannabis sativa*, Cannabidiol, tetrahydrocannabinol; from July to December 2016. As criteria of inclusion, the papers selected were published between 2011 and 2016, and written in English, Spanish or Portuguese. The selected papers would have to report the pharmacological and toxicological aspects of *Cannabis sativa* and allow an open access.
The following criteria were used for exclusion: 1) publication year; 2) paper title out of context; 3) abstracts out of context; 4) those who did not meet the other inclusion criteria or those of paid access.
Data analysis: the charts and data analyses were performed using the software Excel 2010.

## RESULTS AND DISCUSSION

From the keywords, 791 papers were found on the databases Scielo, PubMed and Capes Journals. After the first inclusion criterion, the publication year, the sample was reduced to 477 articles. The next step was title reading, with 113 papers selected; of those, 27 were excluded after the abstract reading, resulting in a sample with 86 papers, where 9 articles were found repeated in the databases, being then excluded. Therefore, there were 77 articles remaining for full reading, but 21 of those were excluded due to their paid access. After reading the 56 remaining papers, 7 were excluded for not containing the information aimed at to generate this review. The final sample ended up with 49 articles. The article selection process is presented in Figure 1.
Thus, from the sample with n = 49 publications, 31 (63%) provided information on the pharmacological aspects of Cannabis sativa, 4 (8%) dealt with the toxicological aspects of the plant and 14 (29%) reported both kinds of information.
Chart 1 displays how these pieces of information were divided among the selected studies.

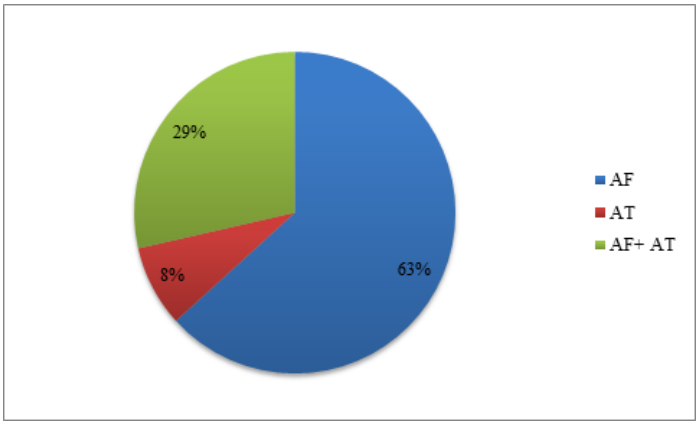


**Chart 1: Distribution of the information on Pharmacological Aspects (AF) and Toxicological Aspects (AT) of *Cannabis sativa* on the selected studies**

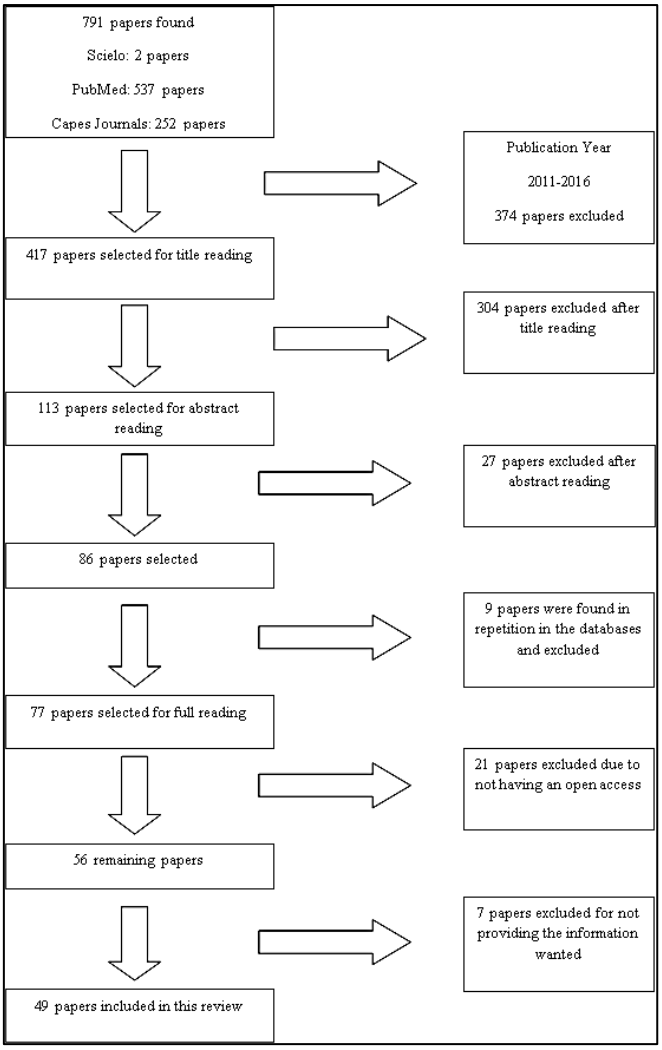


**Figure 1: Selection process of the published papers**

*Cannabis sativa* contains over 400 substances, from which approximately 60 are cannabinoids. The two most abundant and widely cited ones are the $\Delta^9$-tetra-hydrocannabinol - **THC**[1] ((−)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol), and the Cannabidiol - **CBD**[2] (2-[(1R,6R)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol).

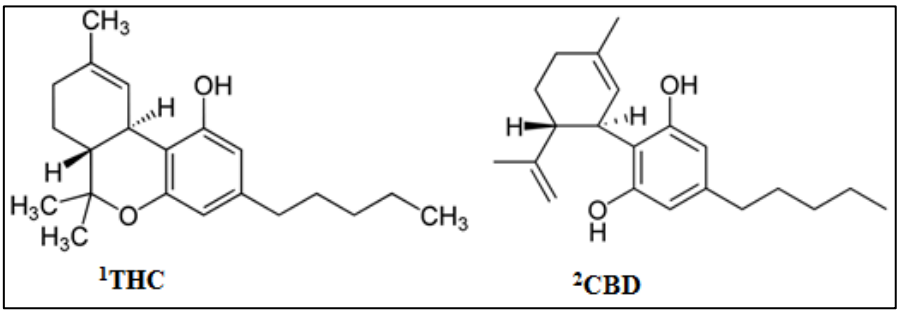


**Figure 2: Chemical structures of the most cited constituents of *Cannabis sativa,* for the period studied**

### *Cannabis sativa* (Cs)-pharmacological aspects

In this revision 9 papers are found reporting pharmacological aspects of *Cannabis sativa*, such as: analgesic, antiemetic, antispasmodic, anticonvulsant, antioxidant, anti-tumor and anti-inflammatory.
Such effects were reported in different frequencies, as shown in Chart 2.

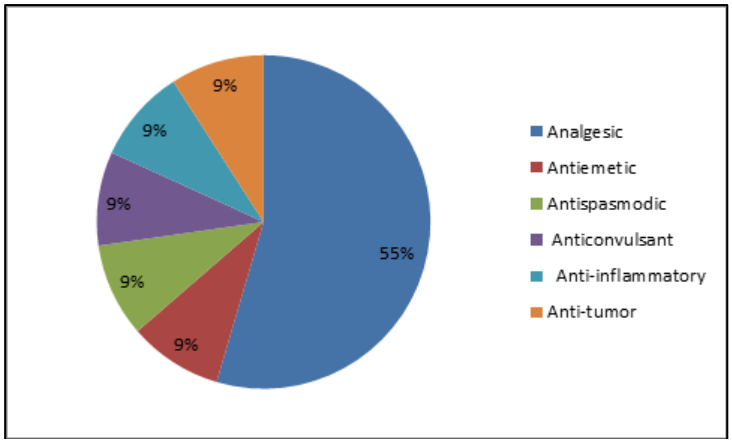


**Chart 2: Pharmacological aspects of *Cannabis sativa* (Cs)**

Brunt et al. (2014) reported the analgesic effect in a study with 102 patients, with an average of 53 years of age, under treatment for chronic pain and all of them showed therapeutic satisfaction.

Boychuk et al. (2015) state that the use of *Cannabis sativa* for chronic neuropathic pain has the same efficacy of other medications, for instance, the opioids. Birdsall et al. (2016) mention in their study the work of Whiting, which is a systematic review and meta-analysis of *Cannabis sativa* for medical use that includes a total of 79 tests and 6462 participants, and had as a result the discovery that Cs has proven to be a moderate quality drug for treatment of chronic pain.

According to Benbadis et al. (2014), the mechanism through which Cs mediates the pain seems to be through the CB1 and CB2 cannabinoid receptors, once they are found in the central and peripheral regions of the nervous system, respectively. They also report that several test models in animals, of neuropathic pain induction, have shown that cannabinoids may relief hyperalgesia and allodynia.

Baron (2015) reports in his paper a survey done with patients treating migraine and other headache disturbances with Cs and the results show that the effects were similar or greater to those with painkillers such as ergotamine and aspirin. The antiemetic effect of Cs has also been reported by the study of Birdsall (2016), in which a research with cancer treatment patients and marijuana users reported subjectively the benefits of the plant in controlling the nausea and vomiting. The antispasmodic function assigned to *Cs* has been observed by Koppel (2015) when assessing surveys from 630 patients seen with movement disorders, being 25% under the use of marijuana, and 31% of those were benefited in resting tremors, bradykinesia (45%), and dyskinesia (14%).

Case report studies such as Rosenberg et al.'s (2015), describe the anticonvulsant effect of *Cs*, reporting cases such as that of one patient whose seizures were not controlled by Phenobarbital or Phenytoin, but had less tonic-clonic seizures when using Cs from 2 to 5 times a day. Such a study reports, also, about a survey performed via telephone, in a treatment center for epilepsy, with adult patients, in which the most active Cs users reported beneficial effects over seizures (severity reduced by 68%, and 54% less incidence), after daily use of *Cs*, and 24% patients believed marijuana to be an effective therapy for epilepsy; no patient has reported crise worsening with the use of Cs.

Ruhaak et al. (2011) have proved the anti-inflammatory potential of *Cannabis sativa* in their work . An in vitro test with *Cs* samples acting on the enzymes COX-1 and COX-2 demostrated inhibition on the production of prostaglandins. A probable anti-tumor action was pointed out in the work of Birdsall et al. (2016), reported by the antiproliferative and antiangiogenic activities in *in vitro* and *in vivo* tests in several cancer models. In this study, the cannabinoids signaled regulation of cell survival, invasion, angiogenesis and metastasis; and they were also involved in a mechanism which activates the apoptosis.

### *Cannabis sativa* (Cs)-toxicological aspects

Concerning the toxicological aspects of *Cs*, 6 papers described the following toxic potentials: possibility of causing psychotic symptoms (hallucinations, euphoria, paranoia, depersonalization, loss of judgment), dizziness, anxiety, motor coordination deficit and cognition impairment. Chart 3 shows the frequencies with which the toxicological aspects were reported.

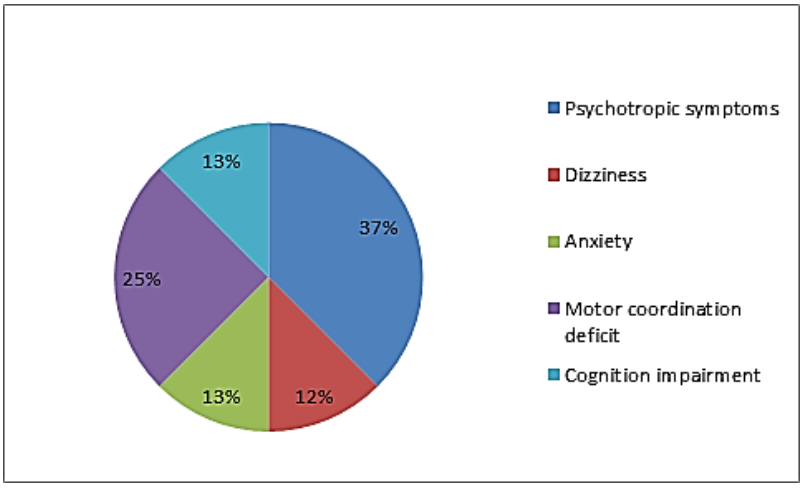


**Chart 3: Toxicological aspects of *Cannabis sativa***

The most cited chronic toxicological effects of Cs are the psychotic symptoms. Sirven (2014) reports that such symptoms are popularly and culturally narrated by potential Cs users. Whilst Birdsall et al. (2016) report the short term adverse effects of smoking Cs; these effects occur approximately 30 minutes after the consumption and last, generally, from 2 to 4 hours, namely: excitement, depersonalization, hallucinations, as well as loss of judgment and attention. Amsterdam et al. (2015) also reported that the use of Cs produces psychotic episodes in sensitive individuals or other psychiatric comorbidities bearers. And Chohan et al. (2016) reported dizziness as being a chronic effect.

Hoch et al. (2015) state that high doses of Cs on the long term, beginning in the adolescence, may be associated to the psychic dependence, anxiety and cognitive jeopardy.

Concerning the motor coordination deficit, Neavyn et al. (2014) reported that the acute intoxication due to Cs use jeopardizes the visual acuity and psychomotor reflexes. Such damages may be extrapolated for activities such as driving or operating machinery, being potentially dangerous.

Next, the specific results concerning pharmacological and toxicological aspects of THC and CBD, the most widely described cannabinoids from *Cs*, will be reported.

**$\Delta^9$-tetra-hydrocannabinol (THC) - Pharmacological Aspects**

After analyzing 14 papers, the following effects concerning pharmacological aspects of THC were found: analgesic, antispasmodic, anticonvulsant, antiemetic, neuroprotective and antineoplastic. Chart 4 displays the frequencies with which the information on these pharmacological effects of THC were provided.

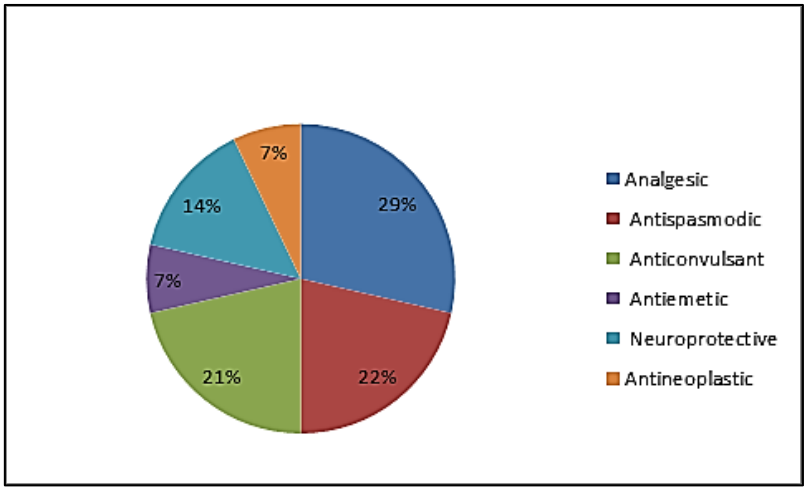


**Chart 4: Pharmacological Aspects of $\Delta^9$-tetra-hydrocannabinol (THC)**

For the analgesic effect played by THC, Lessa et al. (2016) report a study carried with multiple sclerosis patients where Dronabinol (synthetic THC) significantly decreased the chronic pain. Robson (2013) demonstrates the efficacy of THC and Nabilone (a synthetic equivalent of THC), in comparison with placebo, for the treatment of human neuropathic pain. In addition, Jensen et al. (2015) report similar analgesic effect of THC, orally administered, and Codeine when treating pains related to cancer. Pryce et al. (2014) refer to another study on patients with non-oncological chronic pain that had already been under treatment with opioids. It has been

discovered that the Dronabinol brought pain relief and it was better than the placebo given during the study. Concerning the antispasmodic effect of THC, a double-blind study using Nabilone has shown a significant decrease of Levodopa-induced dyskinesia in 7 patients and 2 patients reported an improvement of the dystonia during the time period they were off levodopa [12]. Bendabis et al. (2014) and Robson (2013) reported a major clinical trial in the United Kingdom, performed in early 2000 to assess the benefits of oral synthetic THC for the spasticity related to multiple sclerosis, being controlled by placebo, involving 630 patients. The THC didn't improve the spasticity on a primary endpoint, but showed benefits on the secondary endpoint, with positive reports on the spasticity and mobility.

The anticonvulsant effect of the THC is reported by Friedman & Devinsky (2015) which describe the activation of CB1 receptors with a consequent reduction of experimentally induced seizures [13]. Devinsky et al. (2014) state that the THC reduces the frequency and severity of the seizure crisis in a dose-dependent way. The antiemetic effect of the THC is reported in the article by Kramer (2015), which states that Dronabinol and Nabilone, two synthetic forms of THC, are the most studied for the treatment of secondary nauseas due to chemotherapy. These medications are already marketed in the United States. Concerning the neuroprotective activity of THC, a model study performed on rats with induced multiple sclerosis has demonstrated a significant reduction of the neurologic deficit, after the administration of THC [26]. Besides, Pryce et al. (2014) reported the antioxidative activity of THC, justifying the reduction of nervous cell deaths, due to the capture of toxic ions in the CNS. Pacher (2012) reported the antineoplastic effect of THC, assuring that in addition to other therapeutic effects, THC and endocannabinoids have shown potential in inducing the neoplastic cell death and inhibiting the proliferation and/or migration of malignant cell lineages in rats, as well as inhibiting the growth of certain kinds of tumors or tumor cell xenografts *in vivo*.

**$\Delta^9$-tetra-hydrocannabinol (THC)-toxicological aspects**

A total of 8 papers reported the toxicological aspects of the THC, namely: psychotic symptoms, anxiety, sedation, appetite increase and motor deficit.

Chart 5 shows the frequency of the toxicological aspects , being the property of initiating psychotic symptoms (34%) the most cited one.

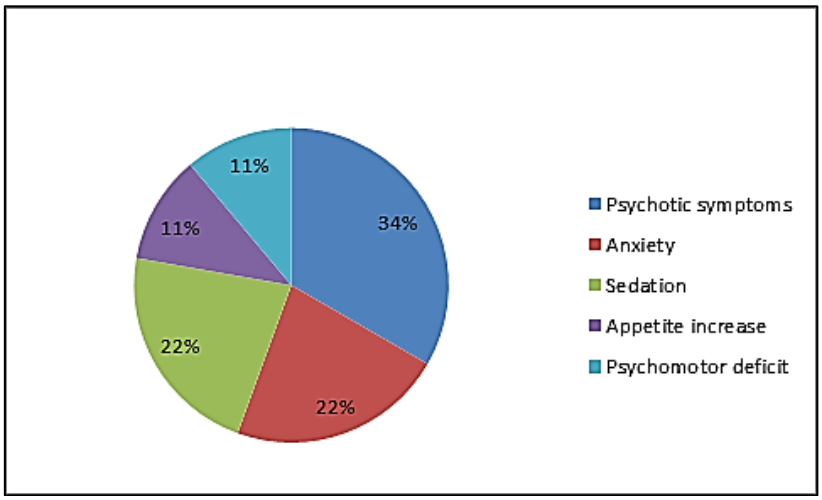


**Chart 5: Toxicological Aspects of the $\Delta^9$-tetra-hydrocannabinol (THC)**

A research performed with the administration of 10 mg of THC and placebo demonstrated that the THC triggers negative behavioral effects and psychotic symptoms and increases the level of anxiety and sedation [28]. Manseau & Goff (2015) state that the psychotic effects of THC are well established. A Cs preparation containing a greater content of THC is capable of initiating an increase on appetite and on anxiety symptoms [7, 29]. In order to demonstrate the psychomotor deficits caused by THC, the decrease in the development of tasks has been shown, while the individuals were under the influence of different doses of oral THC (cannabis milk containing 16.5 or 45.7 mg of THC) or 20 mg of dronabinol [18].

**Cannabidiol (CBD)-pharmacological aspects**

The Cannabidiol (CBD) is a very important cannabinoid of *Cannabis sativa* and it has been widely studied, mainly because its mechanism of action is not yet fully understood. CBD doesn't seem to present affinity with the cannabinoid receptors. Cannabidiol was the most cited cannabinoid in the collected studies, as well as its pharmacological effects. After analyzing the studies, a total of 27 papers reported the pharmacological aspects of CBD, assigning to it: psychomotor improvements and analgesic, anti-inflammatory, antispasmodic, anticonvulsant, anti-tumor, neuroprotector, anxiolytic, antidepressant and antineoplastic effects.

These effects have been reported with different frequencies, being the anticonvulsant function the most cited one (27%), as shown in Chart 6.

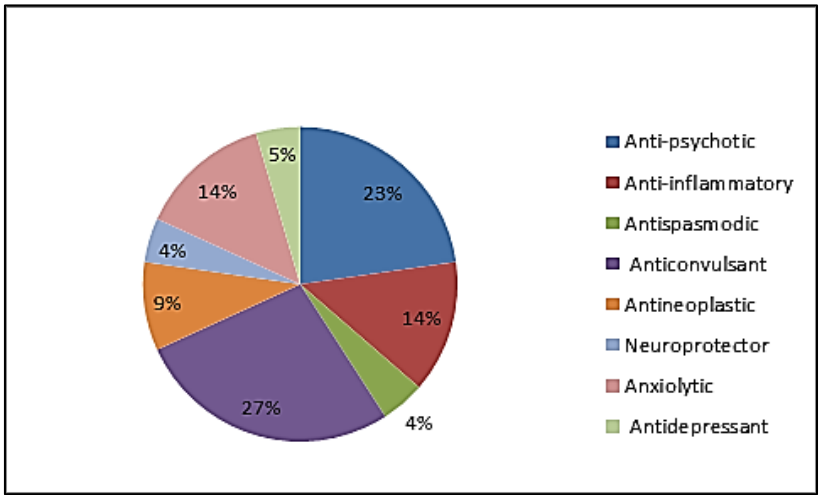


**Chart 6: Pharmacological Aspects of Cannabidiol**

The anticonvulsant effect was the most reported one in the papers, well described in a random study performed with adults, resulting in the decrease of seizures [30].

Still on the anticonvulsant effects, in a research with children bearing severe epilepsy, which received CBD-rich extracts, the evolution of the clinical condition to "free of crisis" and/or reduction of the crisis frequency has been reported [23,31]. Rosenberg et al. (2015) have pointed out the need for greater random clinical trials to better assess the role of CBD in the seizure crisis control, for through a meta-analysis its anticonvulsant therapeutic potential has been evidenced, with high tolerability and low toxicity.

In order to demonstrate the CBD activity as antineoplastic, McAllister et al. (2015) state that CBD causes the inhibition of cancer cell aggressiveness, through the decrease in the production of the reactive species of oxygen in glioma stem cells (GSCs). They also report that the CBD is under assessment for the therapeutic treatment of cancer due to its potential capacity to inhibit metastasis [33]. Pacher (2012) reports wide evidences that the cannabinoids derived from plants, specially the Cannabidiol, are powerful inhibitors of the feasibility of prostate carcinoma *in vitro*. Yet through *in vitro* tests, it has been reported that this substance acts mainly through induction of apoptosis through the activation of the intracellular intrinsic pathways, which partially involves the antagonism of the transient receptor potential channel of cations of subfamily M member 8 (TRPM8) and has been followed by an elevation of the intracellular calcium [27].

In an experiment performed in rats in a laboratory with stress induction with further administration of CBD solutions, it was noticed that the stress symptoms had been restrained. And Campos et al. (2012) through a survey with some patients who used CBD demonstrated that this procedure controlled the anxiety of patients with social phobia with no previous treatment [34]. Concerning the anti-inflammatory potential of CBD, Burstein (2015) mentions that the substance was referred to as exhibiting anti-inflammatory activity in an arachidonic acid induced ear inflammation model in rats. He also reports that patients with oral administration of CBD (5-40 mg/kg), at least once a day, for three days, after some acute inflammation, have also assured the beneficial action of CBD over two inflammation symptoms: the swelling and the hyperalgesia [36]. Concerning the antispasmodic effect, the Cannabidiol presented an improvement of 20 - 50% in tremors, in an assessment made via video on 5 patients with Parkinson's disease [12]. Yücel et al. (2016) state that CBD has a neuroprotective potential, and have assured this through an analysis of imaging tests, which shows that the hippocampus volume is reduced on the long terms in Cs users, and that this atrophy may be restored following a long abstinence. However, those users of CBD-rich Cs did not show structural alteration on the hippocampus, in relation to the control group, and these results are consistent with the suggestion that CBD may be a neuroprotector, and perhaps this is due to its role in synaptic plasticity and/or neurogenesis [37]. CBD may also play the role of antidepressant, enabling the activation of 5-HT1A serotonergic receptors, thus suggesting that the CBD may also have antidepressant properties, since 5HT1A receptors module the responses to stress stimuli and are proposed to mediate the effects from antidepressant medicines [35].

**Cannabidiol (CBD)-toxicological aspects**

The toxicological aspects of CBD were hardly found or described in the studies used in this review. This may be related to the absence of psychoactive action and the non-activation of classic cannabinoid receptors. Only one paper reported a toxicological aspect of CBD, to which it was assigned the potential increase of the waking state. Despite the waking inducer effects caused by CBD, its data remain conflicting with those papers which

reported it as being anxiolytic, for example. The author states that a possible explanation could be in the differences described in the methodological procedures (route of administration, vehicles used, doses, themes, etc.). Yet, it is assured that the alert state induced by the CBD may be associated with an increase in the dopamine release [38].

## CONCLUSION

It was possible to consolidate the knowledge on the pharmacological and toxicological aspects of *Cannabis sativa*, from the data found in the literature chosen after the bibliographic survey. *Cannabis sativa* and its constituents have positive biological activities and pharmacological aspects. However, many of these activities occur through mechanisms of action that remain unknown, involving or not the endocannabinoid system. Besides, the existence of side or adverse effects was demonstrated, as well as some toxicological aspects, which sometimes may impair even more the explanation of such mechanisms.

It is also possible to conclude that *Cannabis sativa* and its cannabinoid constituents, THC and CBD, offer a wide variety of options to be studied, demanding the elaboration of new researches to explain the pharmacological aspects, for, in face of what has been said, such cannabinoids may aid the treatment and control of common diseases and comorbidities in the medical clinic, such as: anxiety, etc. Similarly, a deeper study of the toxicological aspects is necessary to promote a better control of them.

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