

# Medical cannabis and cannabidiol: A new harvest for Malawi

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## Abstract

In February 2020 parliament passed the Cannabis Regulation Bill (2020) which regulates the cultivation and production of industrial hemp and medical cannabis. The country will only fully benefit from this development if the medical and scientific community can take the lead in enabling the country to exploit the plant's potential to help address some of our economic and public health challenges. This special communication provides some basic information on cannabis and discusses its history and medical uses. Cannabidiol (CBD) has emerged as one of the most important cannabis-derived phytochemicals and has formed the basis for the growth of the medical cannabis industry. The scientific data on the mechanisms of the effects of CBD on the human neuroendocrine-immune network is reviewed and the first effective cannabis-based FDA-approved treatment for epilepsy discussed. Some clinical research that is being done on the antipsychotic and neuroprotective properties of CBD is also reviewed. A case is made for the potential of CBD as a neuroprotective adjunctive therapy for the prevention of neuropsychological sequelae associated with complicated malaria. The safety profile of CBD is reviewed and finally, the potential importance of the re-medicalization of cannabis-based therapies for the broader field of phytomedicine is pointed out.

**Keywords:** *Cannabis sativa*, industrial hemp, medical cannabis, marijuana, endocannabinoid, cannabidiol

## Background

On the 28th February 2020, the Malawi National Assembly passed the Cannabis Regulation Bill. The bill regulates the cultivation, propagation, production, processing, storage, exportation, importation, distribution and use of medical cannabis and industrial hemp. It is the culmination of over 20 years of lobbying efforts by Malawian advocates which resulted in adoption of a motion in the National Assembly in June 2016<sup>1</sup> to explore cannabis as an alternative crop to tobacco as well as the successful completion of industrial hemp cultivation trials at Chitedze Agricultural Research Station and other sites under the Ministry of Agriculture and private companies.

Within the region, similar legislation has passed in Uganda (2015), Lesotho, Zimbabwe, South Africa (2018) and Zambia (2019). Globally, there has been a resurgence of innovation, and commercialization related to cannabis and in recent years, a significant amount of scientific research and progress in medical uses of cannabis.

Medical publications about cannabis in Malawi have been limited to issues relating to marijuana use and its causes, consequences and associations. For health professionals, scientists and researchers in Malawi, it is important to be aware of the growing body of scientific data that has accrued around cannabis to be able to advance the discourse.

This special communication is aimed at providing some basic information and highlighting some of the potential medical benefits of cannabis. Special emphasis is placed on cannabidiol (CBD) which was historically the lesser known of the major cannabis derived compounds since it was thought to be non-psychoactive. In the last decade however, CBD has undergone an increase in popularity and significance with respect to medical uses of cannabis.

## Marijuana, industrial hemp and their current legal status

Cannabis is a genus of flowering plants mainly comprising two species, *sativa* and *indica*.

*Cannabis sativa* is the oldest recorded cultivated crop<sup>2</sup> and is grown for its fibre, seeds and flowers. The fibre produced by cannabis is referred to as hemp fibre and is used to produce many products such as rope, clothing, fabric, paper and building materials. The seeds of the cannabis plant are used as food for both humans and livestock and are pressed to produce oil. Hempseed oil is an important nutritional supplement and ingredient in soaps and cosmetics and many other products. The flowers of cannabis plants produce a thick and sticky resin. This resin is known to contain the psychoactive ingredient of marijuana,  $\Delta^9$ -tetrahydrocannabinol (THC). Cultivars of Cannabis grown as marijuana can contain anywhere from 2% to over 20% THC<sup>3</sup>.

Industrial hemp refers to cannabis that is bred specifically for the industrial uses of its derived products other than THC. Such varieties have been bred to have a very high fibre (30-40%) and seed content. In contrast to marijuana, these varieties have very low THC content and are consequently non-psychoactive. In Europe where there are established hemp industries the European Union (EU) standards for industrial hemp state that the THC content cannot exceed 0.2%<sup>4</sup> while a 1% THC content is acceptable in more tropical areas.

More recently, the term medical cannabis has become popular. Medical cannabis includes all varieties of cannabis which are grown specifically for medicinal purposes and may include varieties with varying levels of THC and other cannabinoids such as CBD. The legality of different types of medical cannabis is determined by the legislative framework prevailing in the country and may vary from low THC

varieties to marijuana varieties that can be used for both medical and recreational purposes.

In Malawi, prior the new act of 2020, legislation related to cannabis was covered the Noxious Weeds Act of 1936 and the Dangerous Drugs Act of 1956 together with their Regulations.

Under these laws, cultivation of cannabis was made illegal. However provisions were made for the use of cannabis for industrial, food and medicinal purposes. Regulations enabled certain persons to be authorized to acquire, possess and supply cannabis under license for research and medical purposes. However, these laws did not distinguish between different varieties of cannabis and lacked a workable framework for effective regulation.

The Cannabis Regulation Bill of 2020 clearly distinguishes between marijuana (which remains illegal), industrial hemp and medical cannabis. It establishes a Cannabis Regulation Authority responsible for licensing and regulating the legal forms of cannabis and sets out framework for requirements and enforcement of all matters related to cannabis. The functional details of all of these aspects will be contained in regulations which are currently being drafted.

### Historical medical uses of cannabis

Cannabis has been used medicinally for millennia. It has been used by healers in ancient China and India, by ancient Greek and Roman doctors, by Arab doctors during the Middle Ages and by British Victorian and continental European physicians<sup>5</sup>. In Africa the oldest recorded uses of medicinal cannabis date back to ancient Egypt where it was used in suppositories for relieving the pain of haemorrhoids<sup>6</sup> and as a treatment for sore eyes<sup>7</sup>. During colonial times, European travellers documenting their travels in Africa found well-established traditions of cannabis use entrenched in many African cultures with religious and medical uses prominent<sup>8,9</sup>. In Malawi, there is much anthropological evidence that cannabis (known locally as *chamba*) has been a part of the culture since ancient times. This is seen in traditions such as curing the bud by tightly wrapping it in banana leaf (the so-called Malawi Cob) and the use of the term “*chamba cha makolo*” to denote an ancient tradition<sup>10</sup>. *Chamba* was traditionally used in treatment of anthrax, dysentery, fevers, malaria and treatment of snake bites<sup>11</sup>.

European medicine was slow in recognizing the medicinal value of cannabis with the first major description of its actions only happening in 1839<sup>12</sup>. Since then it has reportedly been used for: controlling nausea and vomiting, treating cholera and rabies, diminishing muscle spasms, stimulating appetite, lowering intraocular pressure in glaucoma, relieving phantom limb pain and other pain syndromes, alleviating menstrual cramps, promoting uterine contractions in labour, treating addiction and withdrawal symptoms, preventing seizures and reducing anxiety<sup>13</sup>. Cannabis was very widely used by American doctors during the early twentieth century as well as by English doctors until the 1970's. The passage of the Marijuana Tax Act (1937) in the US and later on, the UN Convention on Narcotics made cannabis illegal in most places by the middle of the 20th century which meant that cannabis based remedies could not be effectively studied using modern methodologies such as randomised clinical studies. In 1971 an overhaul of the British Pharmaceutical Codex resulted in the removal of a variety of non-evidence-based remedies including cannabis. In the US where cannabis

therapy had been widely used in the treatment of epilepsy, its use diminished with the introduction of phenobarbital (1912) and phenytoin (1937)<sup>14</sup>. Currently there is a resurgence in the development of cannabis based medicines driven by research on biomedical and molecular properties and activities of cannabis. Medical cannabis is currently either being used or being investigated in the treat a long list of conditions including: epilepsy, Huntington disease, Parkinson's disease, pain relief, Alzheimer's disease, multiple sclerosis pain, inflammatory bowel disease, sleep disorders, arthritis, glaucoma, eating disorders, asthma, anxiety, stress, addiction, PTSD, cancer and protection of the brain after stroke<sup>15</sup>.

### Cannabinoids and their mechanisms of action

Of the more than 560 distinct compounds that have been isolated from cannabis species, the most important and abundant group are known as cannabinoids<sup>15</sup>. The best studied of these cannabinoids are THC and CBD. The psychoactive effects of cannabis are mediated by THC. Because of this, it was assumed that many of the therapeutic properties of cannabis were also mediated by THC and this resulted in CBD being largely ignored by many earlier researchers. This has changed dramatically over the years with the perception of CBD moving from an inactive cannabinoid to a drug with a wide spectrum of action throughout the neuroendocrine-immune network. A PUBMED search for cannabidiol generated 50 reports for the period 1999-2002, 225 reports for 2003-2007 and 1,205 reports for 2008 to 2014<sup>16</sup>.

Cannabinoids produce many of their effects through the endocannabinoid system via cannabinoid (CB) receptors. This system influences synaptic communication and modulates eating, anxiety, learning and memory, reward processing and growth and development<sup>17</sup>. The endogenous ligands of the CB receptors are collectively referred to as endocannabinoids (EC) and are known to modulate neuronal excitability<sup>18</sup>. Recent work has indicated that EC and EC-like compounds are present in human milk and play a role in establishing suckling responses in infants<sup>19</sup>. CB1 receptors are found primarily in the brain but also in several peripheral tissues. CB2 receptors are found mainly in immune and hematopoietic cells but can be upregulated in other tissues<sup>20</sup>. THC exerts its action by binding to CB<sub>1</sub>R and CB<sub>2</sub>R.

In contrast, CBD is able to exert some of its most important neural effects through some non-CB-R mechanisms<sup>21</sup>. CBD has a very wide range of targets which are reviewed by Watt and Karl<sup>22</sup>. CBD has low affinity for both CB<sub>1</sub>R and CB<sub>2</sub>R<sup>23</sup>, but has very strong neuromodulatory effects via the serotonergic receptor 5-hydroxytryptophan 1A (5HT-1A)<sup>21</sup> and enhances levels of EC<sup>24,25</sup>.

The discovery of the mechanisms of action of have led to further studies which illustrated the anxiolytic, immunomodulatory, anti-emetic, anti-psychotic, anti-oxidative and neuroprotective properties of CBD. The greatest potential value of CBD is in neuropsychology and neuropsychiatry. Even at low doses CBD is known to have beneficial physiological effects which promote and maintain health (anti-oxidative, anti-inflammatory, neuroprotection). The pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders is reviewed by Devinsky et al. (2014)<sup>26</sup>. The use of cannabinoid based therapies for the treatment of spasticity, pain and anorexia demonstrated to clinicians and pharmaceutical companies that it is possible to develop and commercialize cannabinoids for human disease.

## Anti-epileptic properties

In cases where traditional antiepileptic drugs had failed or had intolerable side effects many patients had turned to medical marijuana. Accounts of dramatic improvements with cannabis based products with high CBD:THC (e.g. >20:1) ratios sparked serious interest in rigorous scientific study of CBD as an anti-seizure medication<sup>27</sup>. The most significant advances have been made in the development of CBD as a treatment for children with Dravet syndrome (DS), an early onset “treatment resistant” severe epilepsy. Supported by good results in a series of pre-clinical studies<sup>28</sup>, the safety and effectiveness of a standardized oral solution of a 98% oil-based CBD extract called Epidiolex was successfully tested in an open label trial involving 214 children and young adults<sup>29</sup>. This culminated in a randomized, double-blind, placebo-controlled trial of CBD as a treatment for DS in 2017<sup>30</sup>. CBD was effective in reducing the frequency of convulsive seizures with 5% of patients becoming seizure free. Epidiolex is now considered to be at the forefront of cannabis based therapies and is Food and Drug Administration (FDA) approved for treatment of DS. There are plans to conduct similar trials for other forms of epilepsy since the neuroprotective activity of CBD is likely to have a similar effect<sup>26</sup>.

## Antipsychotic properties

Cannabidiol is currently being used for the treatment of a variety of conditions including psychiatric disorders such as schizophrenia and dementia<sup>31</sup>. Systematic reviews of the antipsychotic properties of CBD in humans and the effect of CBD on cognitive function are provided by Iseger & Bossong, (2015)<sup>27</sup> and Osborne et al., (2017)<sup>32</sup> respectively and Watt & Karl, (2017)<sup>22</sup> have conducted a mini review of the in vivo evidence for therapeutic properties of CBD for Alzheimer’s disease.

Cannabidiol has the ability to counteract psychotic symptoms and cognitive impairment associated with acute THC administration and may lower the risk of developing cannabis –related psychosis. Five small scale clinical studies with CBD treatment of patients with psychotic symptoms all showed improvement of symptomology or psychometric test performance with no side effects. Several pre-clinical mouse models demonstrate improvements in recognition, social recognition and spatial memory in Alzheimer’s disease but there are no human clinical trials to date<sup>32</sup>.

## Neuroprotection from trauma and infectious diseases

Trauma and infections of the CNS result in neurologic dysfunction. Two pre-clinical studies in murine ischemia models showed CBD is strongly neuroprotective and can attenuate and prevent learning and memory deficits induced by brain hypoxia<sup>32–34</sup>. Three pre-clinical studies in murine models of hepatic encephalopathy (HE) from liver failure showed CBD improved spatial learning and memory and working memory deficits<sup>35–37</sup>.

In Malawi, cerebral malaria (CM) is the most common complication in *Plasmodium* infection. A prospective study of survivors of CM in Blantyre, The Blantyre Malaria Project Epilepsy Study (BMPEs)<sup>38</sup> found that almost a third of retinopathy-positive CM survivors developed epilepsy or other neurological sequelae such as disruptive behavioural disorders and neurodisabilities. Neuroprotective clinical trials aimed at maintaining normothermia and seizure control are warranted. Notably, previous trials that have attempted to

achieve seizure control using phenobarbital in paediatric CM have been associated with increased mortality likely due to respiratory suppression as a side effect of the drug<sup>39</sup>.

There has been no human study to evaluate CBD in CM. However, Campos et al., (2015)<sup>40</sup> evaluated the effects of CBD in a murine model of CM. Mice were challenged with *Plasmodium berghei* ANKA and treated with CBD. Mice were also treated with Artesunate. Cytokines and neurotrophins in the prefrontal cortex and hippocampus were also measured. Challenged mice displayed memory deficits and increases in anxiety-like behaviours at the peak of disease and after the clearance of the parasitemia. Both of these effects were prevented by CBD treatment.

Treatment with CBD resulted in an increase in Brain Derived Neurotrophic Factor (BDNF) expression in the hippocampus which is associated with the improvement of cognitive performance<sup>41,42</sup>. The treatment also resulted in decreased levels of proinflammatory cytokines in the hippocampus which are related with improved memory and less behaviour impairment<sup>43,44</sup>.

This mechanism of protection involving regulation of neurogenesis and neuroinflammatory markers can be extended to murine hepatic encephalopathy model, where CBD chronic treatment restored BDNF levels and decreased the mRNA expression of the type-1 TNF- $\alpha$  receptors in the brain<sup>36</sup>. An intravital microscopy study showed that CBD reduced vascular changes, CNS leukocyte migration and TNF- $\alpha$  expression induced by the administration of LPS in rodents<sup>45</sup>.

Taken together, the evidence suggests that CBD may be a promising candidate as an adjunctive therapy in combination with various antimicrobial agents to prevent brain damage and neurological outcomes of various infections in humans

## Safety

Anecdotal evidence has suggested that CBD has a favorable side effect profile, which may improve compliance and adherence to treatment. From the numerous clinical studies that have since been performed on CBD, its safety, even at high doses, has been proven in the context of various medical conditions. The 39th Meeting of the World Health Organization’s Expert Committee on Drug Dependence in Geneva held from 6-10 November 2017 found that there is no evidence of recreational use of CBD or any public health related problems associated with the use of pure CBD<sup>46</sup>.

Bergamaschi et al., (2011)<sup>31</sup> reviewed 132 original studies on CBD’s safety and side effects. All studies consistently find CBD to be safe, that catalepsy is not induced and physiological parameters such as heart rate, blood pressure and body temperature are unaltered. Psychological and psychomotor functions are not adversely affected and neither are gastrointestinal transit and food intake. There is no toxicity and chronic use and high doses of up to 1,500 mg per day are well tolerated. Another review of clinical data and relevant animal studies related to the safety and side effects of CBD<sup>47</sup> noted that because of its importance as adjunct therapy more emphasis needs to be placed on clinical research which looks at CBD’s interaction with hepatic (drug)-metabolizing enzymes, such as those belonging to the cytochrome P450 family, drug-transporters and interactions with other drugs. CBD is metabolized, amongst others, via the CYP3A4 enzyme which is also involved in the metabolism of estimated 60% of clinically prescribed



drugs<sup>31</sup>. Various drugs such as ketoconazol, itraconazol, ritonavir and clarithromycin inhibit this enzyme. When co-administered with CBD this leads to slower CBD degradation and can consequently lead to higher CBD doses that are longer pharmaceutically active. In contrast, phenobarbital, rifampicin, carbamazepine and phenytoin induce CYP3A4 causing reduced CBD bioavailability. These interactions can have both positive and negative effects. For example, in a clinical study of children treated for epilepsy with clobazam and CBD the CBD interaction with isozymes CYP3A4 and CYP2C19 caused increased clobazam bioavailability, making it possible to reduce the dose of the anti-epileptic drug, which in turn reduced its side effects<sup>48</sup>.

Some of the parameters summarized by Bergamaschi et al., (2011), which were observed in animal experiments, are yet to be studied in humans<sup>49</sup>. Given that the endocannabinoid system also plays an important role in endocrine regulation, further research of CBD's off-target effects in this area is needed.

### Conclusions and future directions

Cannabidiol is an effective and safe therapeutic agent with the potential to help in addressing many of Malawi's public health challenges. It is a proven and approved anti-seizure therapy. The efficacy of CBD in models of neuronal injury, neurodegeneration and neuroinflammation suggest that it could also be effective in a wide range of conditions as a preventive or therapeutic agent. This is especially true for the cerebral malaria where pre-clinical data show CBD could be an effective adjunctive therapy for prevention of neurological sequelae. Taken together with its good safety profile, a case can be made for the consideration of clinical trials of CBD based therapies in Malawi. The commendable record of clinical research in malaria in Malawi and the commercial availability of high quality CBD formulations globally positions Malawi well to advance in this area.

Malawi is home to one of the most globally sought after Cannabis sativa strains but is yet to benefit in any meaningful way from this unique aspect of our natural heritage. An immediate priority has to be the development and production of CBD formulations from local cannabis varieties. The significant steps taken thus far in legislative reform, advocacy and awareness need to be built upon. Genetic studies and breeding would allow Malawi to develop high grade cannabis varieties with unique characteristics for medicinal uses. Registration of plant varieties and geographic indicators for strains from Malawi is key.

In recent years there has been increased focus on the importance of plant based therapies such as herbal and traditional medicines in public health. The scientific and medical community has responded proactively by focussing and mobilising research capacity and investment in the field. The Africa Centre of Excellence in Public Health and Herbal Medicine (ACEPHEM) is an example. The explosion of interest and investment in cannabis based phytochemicals could be a windfall for phytopharmaceuticals in general. Opportunities exist for cross pollination between the approaches and tools that have been developed for cannabis based medicines and those in the broader herbal medicine arena. Importantly, information gathered from the development of herbal medicines could give indications on the potential medicinal value of some of the other phytocannabinoids that are only now beginning to be investigated.

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