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Experimental Studies and First Retrospective Clinical Data Suggest a Possible Benefit of CBD in COVID-19

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Abstract

SARS-CoV-2 damages human cells and organs by multiple mechanisms. Intriguingly, preclinical studies have demonstrated that cannabidiol (CBD) may interact in many ways with virus entry and cell stress on one hand, and with inflammatory mechanisms affecting the lung and other organs on the other. A number of very recent *in vitro* and *in silico* studies demonstrate that CBD may be able to affect a high number of different proteins that are involved in the infection process, among them the Glucose Regulated Protein 78, heme oxygenase 1 (HO1), the virus-specific protease SARS-CoV-2 Mpro and apelin. Furthermore, a number of animal studies confirmed independently the anti-inflammatory and organ protective properties of CBD. As there is still no optimal treatment known, highly purified magisterial phyto-CBD has been included to a standard therapy for COVID-19 as an adjunct anti-inflammatory drug. A retrospective analysis of data of 30 patients hospitalised for COVID-19 and who received adjuvant low dose CBD (up to 300 mg/day), show a more pronounced reduction of virus load, normalisation of lymphocyte counts and of other abnormal laboratory parameters when compared to a non-matched group of patients who did not receive CBD.

Keywords: *Cannabidiol; CBD; Concomitant treatment; COVID-19; Drug repurposing; SARS-CoV-2*

Introduction

Infections with SARS-CoV-2 as well as fatality rates continue to increase despite of efforts to limit the pandemic. Even with the availability of vaccines, the virus will never go away. Mutations cause variants of the virus which may have an influence on infection mechanisms and on the efficacy of vaccines. Therefore, continued research on effective and well tolerated treatments as complementary strategy is mandatory. Since the beginning of 2020, a large number of drugs and combinations have been repurposed for COVID-19. They target widely differing mechanisms related to the infection process and/or to the innate response of the human organism. Many articles have argued also an eventual role of cannabidiol (CBD) and of other cannabinoids in the infection with SARS-CoV-2, but potential inhibitory effects of CBD on virus entry and cell stress have – to the best of our knowledge - never been summarised. In addition, no treatment results have been published so far despite that pharmaceutical grade phyto-CBD received marketing authorisation in the United States already in June 2018 and in the European Community in September 2019. Furthermore, CBD is freely available since many years for magisterial prescription in Austria and Germany; in some cases it is also reimbursed by the social insurance. Based on preclinical studies which are briefly summarised below, highly purified, magisterial phyto-CBD was added to a standard treatment for patients suffering from COVID-19. Observations were compared indirectly to a cohort of patients who did not receive CBD.

Preclinical Data Suggest a Potential Benefit of Cannabidiol in COVID-19

Cannabidiol (CBD) may interfere with the attack of SARS-CoV-2 on host cells by multiple mechanisms. The primary target of SARS-CoV-2 is the membrane-bound angiotensin-converting enzyme 2 receptor (ACE2), whereby the spike protein (S) functions as "door opener". ACE2 is expressed by most cell types, although in varying densities. Recently, 13 of 22 cannabis extracts high in CBD were shown to down-regulate ACE2 receptor expression and ACE2 protein levels in artificial 3D models of oral, airway, and intestinal human tissues [1]. Theoretically, this would limit SARS-CoV-2 virus entry and disease progression. Unfortunately, pure CBD was not included in this study, and other phyto-compounds may have contributed to the effects. Co-localised with ACE2 is another enzyme, the membrane-bound transmembrane protease serine subtype 2 (TMPRSS2), known to activate *in vitro* and *in vivo* a wide range of viruses such as influenza and corona viruses including SARS-CoV-2 [2]. This enzyme is found specifically in cells of the secretory epithelium of airways, and cleaves (primes) the spike protein of SARS-CoV-2, thus facilitating fusion with the host cell. As extracts high in CBD inhibited also TMPRSS2 in the study mentioned above, this may reduce virus invasion further [1]. Apart from TMPRSS2, SARS-CoV-2 can utilise other proteases for priming as well, namely cathepsin B and L (CatB/L) and furin. As a multiplicity of cleavage mechanisms increases the efficacy of infection by SARS-CoV-2, the simultaneous inhibition of proteases used by the

virus would enhance the effectiveness of a blockade of cell invasion. Once attached to the receptors, fusion with the host cell membrane occurs as next step; further viral uptake is mediated by endocytosis. Another protein, supposed to act as co-receptor to facilitate the binding of SARS-CoV-2 to the host cell, is the Glucose Regulated Protein 78 (GRP78) [3,4]. GRP78 is a highly conserved protein normally residing inside the cell where it controls the correct folding of proteins. Under stress conditions such as virus multiplication, the expression of GRP78 is considerably increased, and GRP78 is actively translocated from the endoplasmic reticulum (ER) to the cell surface where it acts as co-receptor for spike protein. Indeed, levels of GRP78 were found to be significantly increased in COVID-19 patients [5]. In an *in vitro* model of cadmium (Cd)-induced neuronal toxicity, a low concentration of CBD (1 μM) significantly prevented the GRP78 increase and ER stress [6]. A reduced expression of GRP78 reduces also its translocation to the cell membrane and availability as co-receptor. Another protein potentially targeted by CBD is the virus-specific protease SARS-CoV-2 Mpro, (also known as nsp5 or 3CLpro) which cleaves the continuous viral polypeptide, generating non-structural proteins. Based on *in silico* and *in vitro* molecular docking studies it was found that CBD as well as other cannabinoids bind strongly to SARS-CoV-2 Mpro, resulting in a stable conformation [7]. In this study, CBD was the most potent out of five phyto-cannabinoids (cannabidiol, cannabidiolic acid, delta-9-tetrahydrocannabinol, delta-9-tetrahydrocannabinolic acid, cannabinol), and even more potent than the reference drugs lopinavir, chloroquine and remdesivir. Intriguingly, CBD may be able to bind also to the spike protein as has been demonstrated in a recent *in silico* study [8]. A further peptide possibly playing more than just one role in early infection is apelin. Apelin is a natural, ubiquitous anti-inflammatory peptide with vasodilatory and positive inotropic activities; it interferes with ACE2 [9]. With viral infection, apelin levels decrease. CBD (5 mg i.p./kg b.w., every other day for three injections), almost normalised levels of apelin in a mouse model where acute respiratory distress syndrome (ARDS) was induced by intranasal administration of polyinosinic:polycytidylic acid [Poly(I:C)], a synthetic analogue of double stranded RNA. In parallel, this reduced also symptoms of ARDS. As apelin serves as well as substrate for ACE2 it may compete with the binding of viruses [10]. The final step in the life cycle of CoV is viral shedding. Viruses can egress the infected cells by many ways; for SARS-CoV-2, an unconventional mechanism via lysosomal vesicles has been proposed recently [11]. However, it is currently unknown whether this represents the only and exclusive mechanism or not. Therefore, it is worth mentioning that in two different models, bacterial- and cancer cells [12,13], CBD was able to inhibit the release of exosomes and microvesicles *in vitro*. Another cannabinoid, the closely related delta-9-tetrahydrocannabinol (THC) decreased extracellular vesicles in the blood of macaques infected with Simian Immunodeficiency Virus (SIV) in a pharmacological dose of 0.18 mg/kg [14]. Furthermore, reduced plasma HIV-1 RNA viral loads have been observed in HIV-infected subjects with a heavy consumption of cannabis [15]. Taking all these observations together, it may be speculated that CBD could have an influence on the formation of virus-filled lysosomes and/or on the release of extracellular vesicles, although this still needs to be investigated. It should be remembered that CBD is a highly lipophilic substance which interferes with a wide range of membrane-bound receptors, ion channels and other targets [16]. Finally, lymphopenia, particularly of T-lymphocytes, is a well known characteristic of COVID-19. As natural killer cells play an important role in the immune response to virus infections, the observation that low doses of 2.5 mg CBD i.p./kg produced a significant increase in total numbers of NK- and NKT-cells in rats is particularly noteworthy [17].

CBD Likely Protects Cells and Organs Against SARS-CoV-2 Induced Damages *In Vivo*

Once the virus has hijacked the cell, viral RNA is released into the cytoplasm; transcription and replication starts whereby the virus uses extensively the machinery of the host for synthesising and assembling viral proteins. As has been mentioned, the infection causes oxidative stress of the endoplasmic reticulum (ER), the site of protein synthesis. CBD significantly prevented the ER stress and GRP78 increase in an *in vitro* model [6]. Also induced by oxidative stress is heme oxygenase 1 (HO1), a cytoprotective enzyme regulated by the nuclear transcription factor Nrf2 of which CBD is an indirect agonist via the peroxisome proliferator-activated receptor gamma (PPARγ) pathway. HO1 degrades heme, generating biliverdin/bilirubin, iron/ferritin, and carbon monoxide. It plays a critical role in the prevention of vascular inflammation and survival of endothelial cells. CBD (6 and 10 μM) increases *in vitro* Nrf2 and the expression of HO1, therefore mitigating the generation of ferritin [18,19]. Infections with viruses or bacteria induce the production of highly reactive oxygen species (ROS) in the mitochondria. As a result, lipid- and protein-peroxide products are formed which induce a strong inflammatory response which may end up in a cytokine release syndrome (CRS), also called "cytokine storm", even in the absence of (further) viral replication. CBD in low to moderate concentrations has demonstrated anti-inflammatory and immune-modulating properties in many models as has been reviewed recently [20]. It is cytoprotective, reduces oxidative cell stress by ROS, and protects against the cytokine release syndrome (CRS), whereby CBD acts as antioxidant via enzymatic as well as via non-enzymatic mechanisms (as radical scavenger). It stimulates on one hand the transcription of cytoprotective proteins by activating, although weakly, the nuclear factor Nrf2, and downregulates on the other the transcription of pro-inflammatory cytokines by inhibiting NFκB [21]. Consequently, this reduces the release of inflammatory cytokines such as IL-6, TNFα and IFNγ, as well as the release of LDH which is a marker of cellular damage.

Different Models Show that CBD Reduces the Inflammation of Airways and Protects Against Acute Respiratory Distress Syndrome (ARDS)

The endocannabinoid system (ECS) also plays a role in the immune-pathogenic response to viral infections. When mice were infected with respiratory syncytial virus (RSV) it was observed that the infection of airways significantly induced the expression of CB1 receptors in lung cells. Activation of CB1 receptors with JZL184, a selective indirect agonist, decreased immune cell influx and cytokine/chemokine production, and alleviated lung damage [22]. In another animal model, the "one lung-injury" model, inhibition of fatty acid amide hydrolase (FAAH) attenuated lung injury and improved ventilation [23]. Interference of CBD with FAAH indirectly increases levels of anandamide (AEA), a CB1 agonist, which may have protective effects against lung injury. This therapeutic potential of CBD for airway inflammation has been reviewed recently [24]. When ARDS was induced in mice by intranasal application of synthetic RNA, a low dose of CBD (5 mg/kg i.p., every other day for a total of three doses) downregulated the level of pro-inflammatory cytokines and improved clinical symptoms of ARDS [21]. In other murine models of lung injury,

CBD (20 mg i.p./kg) reduced lipopolysaccharide (LPS)-induced acute pulmonary inflammation[25,26]. Finally, in a mouse model of allergic asthma induced with ovalbumin, CBD (5 or 10 mg i.p./kg) improved lung mechanics, and decreased collagen fibre content in the airways, as well as the inflammatory and remodelling processes[27,28]. A particularly vulnerable group are patients with pulmonary arterial hypertension. Although uncommon with COVID-19, it is worth to mention that CBD (10 mg/kg/day) was able to reduce monocrotaline-induced pulmonary arterial hypertension in two animal models [29,30]. As lung injury in COVID-19 may be increased by hypoxic ischemic brain damage, brain-protective properties of CBD are of further importance.

CBD Reduces Neuroinflammation

Meanwhile, it has been reported repeatedly that SARS-CoV-2 shows brain-neurotropism. Several animal models have demonstrated that CBD may protect from neuroinflammation. CBD (5 mg i.p./kg) daily from days 1 to 7 post-infection demonstrated anti-inflammatory effects in a viral model of multiple sclerosis [31]. Treatment of U373-MG glial cells with low concentrations of CBD (0.5 μM) can enhance the secretion of the neuroprotective neurotrophin (NTF3) and the expression of insulin-like growth factor 1- (IGF-1) genes [32]. In addition, a large number of hypoxia-ischemia models have demonstrated that low doses of CBD (between 0.1 and 5 mg/kg) significantly reduced brain damage, neonatal hypoxia-ischemia induced myelination disturbances, haemodynamic impairment and functional deficits even if CBD was applied hours to days after the hypoxic event [33]. Intriguingly, brain hypoxemia, often silent, occurs also with COVID-19, potentially inducing long lasting sequelae even after remission. Furthermore, CBD mitigates *in vivo* widely differing forms of cardiomyopathies as has been shown in various animal models including ischemia/reperfusion arrhythmias, myocardial infarction, autoimmune myocarditis or diabetic cardiomyopathy (reviewed recently by [34,35]). This includes also a mouse model of doxorubicin-induced cardiotoxicity [36]. In most models, very low to moderate CBD doses between 0.05 and 10 mg/kg have been used. In short, based on a number of preclinical *in vitro* and *in vivo* studies, a benefit of CBD in protecting organs and in limiting the progression and severity of COVID-19 may be expected. Hypothetically, CBD could mitigate COVID-19 on two levels, the infection of cells by SARS-CoV-2, and the protection of host cells and organs against stress and overshooting inflammation ("cytokine storm"). Based on this, we included low dose, adjuvant CBD to the standard treatment for COVID-19 in our hospital where magisterial CBD is routinely used since many years, in a number of conditions and in accordance with relevant regulations.

Methods

Patients have been referred to our hospital by their treating physicians during the second wave of the pandemic in Austria, between September and November 2020. At admission, diagnosis of SARS-CoV-2 infection or COVID-19 respectively was confirmed by real time reverse transcriptase–polymerase-chain-reaction (RT-PCR), CT or X-ray imaging and included also routine laboratory tests. For the majority of PCR-test, the cycle threshold- (ct) value was also available. Patients received immediately oxygen as required and a standard treatment consisting of dexamethason 6 mg/d for 10 days, zinc-orotate 40 mg/d and vitamin C, 500 mg/d for the duration of their stay in the hospital. Patients who were severely ill, needing intubation, unable to swallow or to cooperate have been excluded. CBD was administered orally as a supportive, anti-inflammatory treatment, starting with twice 100 mg CBD/day during the first week, followed by 300 mg/day for the next two weeks. Capsules, each containing 100 mg, have been prepared by a local pharmacy. A limited amount of CBD (magisterial phyto-CBD, purity >99.8%) has been provided, free of charge, by Trigal Pharma GmbH, Vienna, Austria. At discharge, patients received an aliquot of CBD capsules for the remaining period. The local ethics committee had consented to the use of CBD. Other treatments including antibiotics were administered as needed. Patients also continued to receive their usual medication in case of concomitant disorders. All patients with a laboratory result before discharge and at least one further test result at admission were included in the analysis. Assessment was retrospectively; a cohort of 30 patients who received CBD was compared to 24 patients who received the same standard care except CBD as unmatched control group. None of the patients had a history of SARS-CoV-2 vaccination.

Results

Patient characteristics are summarised in Table 1. Patients of the CBD-group were younger (mean age 65.6 years versus 79.5 years), and the percentage of men was higher (57% vs. 42%). Comorbidities were

Table 1: Patient characteristics.

	Patients with CBD			Patients without CBD		
	Male	**Female**	**All**	**Male**	**Female**	**All**
N	17	13	30	10	14	24
Mean age (y)	63.8	67.8	65.57	72.6	84.43	79.5
Age range (y)	42-90	47-85	42-85	52-90	67-96	52-96
≤50 years	4	1	5	-	-	0
51-60	3	3	6	3	0	3
61-70	5	2	7	1	0	1
71-80	3	6	9	2	4	6
>80 years	2	1	3	4	10	14
Number of patients with at least one comorbidity	-	-	15	-	-	19
Disease onset to hospitalisation (d)	-	-	6.9	-	-	6.6
Duration of stay in the hospital (d)	-	-	8.7	-	-	9.0

d – days; y – years.

Table 2: Patients with abnormal laboratory values at admission and normal results at the last control in the hospital (n/N total).

Parameter (normal range)	All with CBD	All without CBD
PCR negative at discharge*	88.5% (23/26)	52.2% (12/23)
Lymphocytes (1.100-4.500/µl)	76.5% (13/17)	31.3% (5/16)
CRP (<0.50 mg/dl)	18.5% (5/27)	0% (0/21)
LDH (≤ 250 U/L)	30.8% (4/13)	0% (0/20)
Ferritin (30-400 ng/ml)	17.6% (3/17)	0% (0/7)
IL-6 (≤ 7pg/ml)	65.0% (13/20)	66.7% (6/9)

*Includes patients with a cycle threshold (ct)-value >30.0 (transmission considered to be unlikely); patients with a ct-value above 30.0 at admission or missing ct-values have been excluded.

frequent (CBD-group: 50% versus 79% in control patients); arterial hypertension was the most frequent concomitant disorder noted with 66.7% and 68.4% respectively. Sex and age are widely accepted risk factors for the course of COVID-19, with female sex and younger age favouring a better prognosis. The mean duration between onset of disease and hospitalisation was comparable (6.6 versus 6.9 days), as was the duration of hospitalisation (8.7 vs. 9.0 days).

Among the laboratory parameters which have been reported repeatedly as markers for COVID-19, the number of lymphocytes, the level of lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin and interleukin 6 (IL-6) have been analysed more closely as they may reflect the hypothetical mechanism of CBD. Results are summarised below (Table 2) and are presented as the number of patients with an abnormal value of the respective parameter at admission, and a normal test result at discharge, out of the total number of patients with values available for analysis.

As can be seen, the greatest differences concern the reduction of the infectiousness (ct-value, 88.5% vs. 52.2%), the normalisation of lymphocyte counts (76.5% vs. 31.3%), CRP-value (18.5% vs. 0%), LDH (30.8% vs. 0%) and ferritin (17.6% vs. 0%). This suggests an enhanced virus clearance, although results must be seen with caution due to the retrospective evaluation, the low number of patients and heterogeneity of groups. No adverse reactions occurred with concomitant CBD. In summary, a number of preclinical data suggest that CBD could have a broad-spectrum of beneficial properties in combating infections with SARS-CoV-2, by interfering with the attachment of SARS-viruses, reducing intracellular stress, boosting lymphocyte counts and alleviating inflammation. Preliminary observations in patients with COVID-19 could eventually support experimental results. However, our data on patients infected with SARS-CoV-2 are still very limited, and for many reasons they must be interpreted with caution. For a conclusive demonstration of the effectiveness of CBD in COVID-19, randomised controlled clinical trials would be necessary.

Author Contributions

RL: supervision, medical treatment, review,

MK: medical treatment,

SNS: medical treatment,

GN: consulting physicians, conceptualisation, writing the manuscript.

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Competing Interests

Authors declare no potential conflict of interest.

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