

Cannabisness PTY LTD and the Vaal University of Technology

Investigation of selected cannabinoids and cannabimimetic compounds against COVID-19 and PIMS

Mtunzi, F., Venter, H., Chiririwa, H., and Augustyn, W.G.

Department of Chemistry, Vaal University of Technology, Sebokeng Campus, Gauteng, South Africa

1. INTRODUCTION

The viral pneumonia known as SARS-CoV-2 also referred to as COVID-19 was first discovered in the city of Wuhan, China in December 2019 and has swept the globe devastating both the health care systems and economies of countries across the world [1].

The African Center for Disease Control (Africa-CDC) recently released the following information: "As of 9 am EAT 12 May 2020, a total of 66,373 COVID-19 cases and 2,336 (CFR: 4%) deaths have been reported in 53 African countries. This is about 2% of all cases reported globally. The distribution of cumulative cases (proportion of %-global cases) from the WHO reporting regions (excluding Africa) are as follows: Eastern Mediterranean Region 244,923 (6%), European Region 1,731,606 (43%), Region of the Americas 1,702,451 (42%), South-East Asia Region 100,881 (3%) and Western Pacific Region 161,622 (4%)" [2].

First -line responders are extremely concerned by the fact that some COVID-19 infected patients' progress from mild symptoms to critical condition in a very short period of time, whilst most the patients remain in a mild condition [3].

Hospitals in the USA have seen patients arriving with mild symptoms and within 72 hours the patients were in need of critical care and life supporting mechanical ventilating

systems. It is estimated that 80% of COVID-19 fatalities was observed in the elderly and people with compromised immune systems and underlying conditions remained at highest risk [4]. Research suggests that Cytokine Release Syndrome (CRS) also referred to as Cytokine Storms (CS) might be a main contributing factor to the rapid progression from mild to critical condition and possibly contributes to the high fatality rate in severe COVID-19 patients. The objectives of this research therefore are to:

- Investigate and develop a phytocannabinoid/cannabimimetic treatment as an Integrative Anti-inflammatory treatment for the control of the cytokine release Syndrome (CRS) in High Risk COVID-19 Patients.

- Investigate and develop a phytocannabinoid/cannabimimetic Integrative Anti-inflammatory treatment for the management of Pediatric Inflammatory Multi-System Syndrome (PIMS).

Medical doctors in The United States of America (USA) and the United Kingdom (UK) made observations and indeed alerted the scientific community with regards to an increasing number of children who are presented with Pediatric Multi-system Inflammatory Syndrome (PIMS) [6]. Amid the ongoing COVID-19 pandemic, Governor Andrew Cuomo recently announced that New York State is notifying 49 other states across USA of emerging cases of COVID-19 related illness in children. The State is currently investigating 85 reported cases in New York where children, predominantly school-aged, are experiencing symptoms similar to an atypical Kawasaki disease or toxic shock-like syndrome possibly linked to COVID-19 [7].

In the UK an urgent alert released by the North Central London Clinical Commissioning Group and the Pediatric Intensive Care Society indicated that the symptoms have been observed in both children who have tested positive and negative for COVID-19, suggesting an unknown pathogenic infection might be responsible. This PIMS-like condition also overlaps with a wide differential including e.g. Kawasaki's Disease, other vasculitides, toxic shock syndrome, Haemophagocytic Lymphohistiocytosis, malignancies, myocarditis, or other infection of viral or non-viral aetiology [8]. It is therefore imperative that our South African Scientists join the world in trying to establish and understand the pathways that the pathogen utilizes and how the pathogen can be prevented or controlled in children before the infections becomes unmanageable.

2. OUR RESEARCH AND APPROACH

Our researchers are currently investigating and developing an integrative phytochemical treatment in targeting the control of COVID-19 induced pro-inflammatory responses. We are focused on inhibiting Tumor Necrosis Factor Alpha (TNF α) and the Interleukin 6 (IL6) pathways, whilst investigating the immuno modulation and antiviral properties of the cannabis Sativa derived phyto-constituents.

Cytokines are proteins secreted by cells for intracellular signaling. Cytokines can act on their target cells in order to induce systemic or localized immune responses. A Cytokine Release Syndrome (CRS) or Cytokine Storm (CS) is the excessive and uncontrolled release of pro-inflammatory cytokines overloading the signaling systems, this inflammatory response could lead to tissue damage and organ failure. The major Cytokines involved in

the cytokine storms are interferon's, interleukins, tumor necrosis factor-alpha, colony-stimulating factors and chemokines. [9]

As a research group, we are also of the opinion that both our initial targets TNF α and IL6 are important pathways to start with in addressing CRS. TNF α is probably one of the best studied pathways of inflammation and a major contributor to the Cytokine Storms. Inflammation is a complex defense mechanism and immune response. Interleukin L-6 has a dual effect; at some levels it acts as a complex defense mechanism but in chronic and acute inflammation it acts as a pro-inflammatory. IL-6 expressions are mostly induced/activated by IL-1 β and TNF α , although there are different pathways or synthesis of IL-6 e.g. Prostaglandins, toll-like receptors, adipocytes, and stress response [10].

Corticosteroids are commonly used in the treatment of inflammatory diseases like rheumatoid arthritis [11]. The corticosteroid Dexamethasone is currently being utilized to treat COVID-19 induced inflammation and ARDS (acute respiratory distress syndrome) clinical settings [12], however the corticosteroid treatments remain controversial and the World Health Organization (WHO) warned against the use of corticosteroids outside of clinical trials [13]. A study recently compared the efficacy of alpha-humulene (obsolete name: alpha-caryophyllene), a cannabis derived phytochemical to the corticosteroid Dexamethasone in inhibiting inflammation by decreasing B1 receptor mRNA levels in vivo [14]. This comparison highlights the possibility of developing effective botanical derived phyto-chemical treatments that do not suffer from toxicity, adverse side effects and is safe to use for both adults and pediatrics alike.

The words cannabis and cannabinoids are synonymous with panpharmacon and miracle cures. There is unfortunately no clinical evidence yet that suggest that cannabis can be considered as a possible treatment or control of COVID -19. A recent article discusses the screening of Cannabis Sativa extracts by using artificial human 3D models, the authors suggest that phytocannabinoids could potentially modulate ACE2 gene expression and ACE2 protein levels addressing the pathway the COVID 19 virus uses to infect humans. [15] Our investigation and development approach is focused on the potent anti-inflammatory properties of cannabinoids and their immuno modulating and antiviral effects in order to prevent the CRS.

The anti-inflammatory properties of phytocannabinoids are well studied and are accepted to be potent anti-inflammatory compounds [16, 17, 18]. Research suggests that the Cannabinoid Acids (CA) are far more effective in targeting and inhibiting TNF α compared to their more neutral (decarboxylated) cannabinoid counterparts. As part of investigating into the anti-inflammatory properties of cannabis derived compounds, a study in the Netherlands in 2003 tested the efficacy of 8 phytocannabinoids with remarkable results. Studies with the most effective anti-inflammatory compounds namely, tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), cannabidiol (CBD), delta-9 Tetrahydrocannabinol (Δ 9-THC), cannabigerol (CBG), cannabinol (CBN) and cannabichromene (CBC) are well documented. Although it was found that all 8 phytochemicals exhibit anti-inflammatory properties and indeed inhibits TNF α it was the raw spectrum acids which had the most remarkable results as potent anti-inflammatory compounds [19].

Our proposed treatment will exclude THC as this compound showed lower efficacy inhibiting TNF α compared to other cannabimimetics. We are instead making use of THC's precursory volatile acid, THCA, as a major constituent in targeting TNF α . The absence of THC means that our treatment will exclude any psycho-active ingredient/constituent and the very low toxicity of phytocannabinoids makes the proposed treatment safe to utilize in the control of both pediatrics and adults with no suggested/expected adverse side effects.

Contacts:

Hennie Venter: +27 (0)79 609 6317 henniev@cannabisness.co.za

Prof. Fanyana Mtunzi: +27 (0)81 341 0579 fanyana@vut.ac.za

List of References

1. The SARS-CoV-2 outbreak: What we know. Di Wu et al. 2020
2. African Center for Disease Control: Coronavirus Disease 2019 (COVID-19) <https://africacdc.org/covid-19/>
3. Expert Recommendations for Tracheal Intubation in Critically ill Patients with Novel Coronavirus Disease 2019. Mingzhang Zuo et al. <http://cmsj.cams.cn/CN/10.24920/003724#1>
4. Outbreak Brief 17: COVID-19 Pandemic – Nancy Chow et al 2020- http://www.ecie.com.ar/images/paginas/COVID-19/4MMWR-severe_Outcomes_Among_Patients_with_Coronavirus_Disease_2019_COVID-19-United_States_February_12-March_16_2020.pdf
5. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Chi Zhang et al. 2020 <https://www.ncbi.nlm.nih.gov/pubmed/32234467>

6. Pediatric Intensive Care Society. PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease. April 27, 2020. Available at: <https://picsociety.uk/wpcontent/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf>
7. Amid ongoing COVID-19 Pandemic. Sen. Andrew M. Cuomo 10 May 2020 <https://www.governor.ny.gov/news/amid-ongoing-covid-19-pandemic-governor-cuomo-announces-new-york-notifying-49-other-states>
8. West Midlands Guidance for the early recognition, investigation and management of the Paediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARSCoV2 pandemic <https://kids.bwc.nhs.uk/wp-content/uploads/2020/05/PIMS-TS-Guidance-05-05-20-v1.pdf>
9. Into the Eye of the Cytokine Storm. JR. Tisoncik et al.2012 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426/pdf/zmr16.pdf>
10. Interleukin-6 and chronic inflammation C. Gaby 2006 <https://arthritis-research.biomedcentral.com/articles/10.1186/ar1917>
11. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. K. Saag et al.1994 <https://www.ncbi.nlm.nih.gov/pubmed/8109596>
12. COVID-19-associated ARDS Treated With Dexamethasone: Alliance Covid-19 Brasil III (CoDEX) <https://clinicaltrials.gov/ct2/show/NCT04327401>
13. WHO Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020 <file:///C:/Documents%20and%20Settings/User/My%20Documents/Downloads/WHO-2019-nCoV-clinical-2020.4-eng.pdf>
14. Sesquiterpenes from Essential Oils and Anti-Inflammatory Activity. e Sa et al. 2015 <file:///C:/Documents%20and%20Settings/User/Desktop/Covid-19/Sesquiterpenes%20from%20Essential%20Oils%20and%20Anti-Inflammatory%20Activity.pdf>

15. Anti-inflammatory cannabinoids in diet. J. Gertsch 2008
<https://www.ncbi.nlm.nih.gov/pubmed/19704783>
16. Cannabinoids as novel anti-inflammatory drugs. Nagarkatti et al. 2010.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828614/>
17. Cannabinoid-based drugs as anti-inflammatory therapeutics. [Thomas W. Klein](#) 2005 <https://www.nature.com/articles/nri1602>
18. Evaluation of anti-TNF- α activity of eight major cannabinoids isolated from Cannabis sativa. M. Iqbal et al. 2013
https://www.researchgate.net/publication/257637896_Phytochemicals_as_a_potential_source_for_TNF-a_inhibitors
19. Evaluation of anti-TNF- α activity of eight major cannabinoids isolated from Cannabis sativa. M. Iqbal et al. 2013
https://www.researchgate.net/publication/257637896_Phytochemicals_as_a_potential_source_for_TNF-a_inhibitors