Canurta

White Paper

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Protease Inhibition

Introduction

From 2019 to the present day, viruses have been a frequent and pressing topic of discussion around the globe due to the current coronavirus disease 19 (COVID-19) pandemic. Since the beginning of its spread in 2019, the virus behind the disease, which is known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been responsible for close to 600 million cases and approximately 6,400,000 deaths according to the World Health Organization (2022). Given the severity of the virus and its contagious nature, scientists around the world have been working to find ways of controlling and limiting the spread of the virus as well as decreasing the effect of the virus on affected individuals.

Current efforts to mitigate damage include mRNA vaccines - for example, two doses of the BNT162b2 vaccine sold by Pfizer were found to produce 95% immunity against the virus (Polack et al. 2020). Despite this major step forward, the pandemic is ongoing and devastating effects heighten in waves. This may have to do with the fact that vaccine immunity only lasts up

to 6 months - for the BNT162b2 vaccine, immunity against the delta variant decreased from 93% to 53%, with immunity against other variants decreasing from 97% to 67% over four to five months (Tartof et al. 2021). It must also be noted that inequity in healthcare systems in different communities creates a divide that prevents global immunization. Lower income communities may not be able to purchase vaccines, or may face difficulty in the manufacturing, maintenance, and distribution of vaccines (Marshall 2022). Therefore, though vaccines are effective and important, they should not be the sole component of viral limitation. Another viral management strategy is the implementation of public health and safety measures. These include wearing face masks, maintaining a distance of 6 ft from others, and mandatory isolation for those who test positive (Government of Canada 2022). However, these measures are difficult to coordinate since compliance is not guaranteed - this was observed via 'anti-lockdown' protests against masks and vaccines that began in the summer of 2020 (Martin and Vanderslott 2021). Taking all aforementioned factors into consideration, many specialists predict that this virus will never be entirely eradicated, will likely remain endemic, and concur that we must instead focus our efforts on continued immunity, be it through booster shots or innovative and accessible novel approaches.

After the 2018 legalization of marijuana from cannabis plants in Canada, Akeem Gardner (founder of Canurta) began to conduct research into the healing capabilities and antiviral properties of hemp molecules. Hemp is

known as cannabis with under 0.3% tetrahydrocannabinol (THC), which is the main compound producing psychoactivity (Hilderbrand 2018). Canurta's research was focused on flavonoids, which are natural metabolites that have demonstrated antiviral, anti-inflammatory, and even anti-cancer properties (Panche et al. 2016). Over 20 flavonoids were identified in *Cannabis sativa* including cannflavin A, cannflavin B, cannflavin C, and luteolin (Bautista et al. 2021). Recent research indicates these flavonoids are capable of suppressing viruses via their inhibition of viral components known as proteases. The aim of this white paper is to review substantial support for protease inhibition as a therapeutic method and aims to make a case for the future development of a hemp-based supplement that fights viruses such as SARS-CoV-2, HIV, Hepatitis C, and other flaviviruses.

Background

With an urgent need to investigate alternative strategies for managing viruses, examining the viral life cycle and stopping replication holds great potential. The viral life cycle is generally divided into attachment, penetration, uncoating, biosynthesis, assembly, release, and maturation (Ryu 2017). First, the virus' bacterial vector (carrying encoded virus information) binds to the surface of the host cell. The virus then enters through receptor-mediated endocytosis or direct fusion; enveloped viruses (possessing a lipid bilayer membrane) can use either method whereas nonenveloped viruses (lacking

the additional membrane) use the former. Receptor-mediated endocytosis utilizes the host plasma membrane, allowing it to bud inward for intake of the virus. Direct fusion involves the fusion of the host membrane and virus membrane, allowing viral matter to pass between the merged membrane. The next step in the life cycle is uncoating, where the viral contents are released into the host cell. Subsequently , the viral can take over host cell machinery to replicate itself. Lastly, the host cell is lysed, or broken, and replicated viral particles are released into the host to carry on the cycle, after which they finish developing outside the cell through a series of developmental alterations.

Viruses have some unique features that streamline this process - some viruses possess proteases, which are enzymes that carry out proteolysis. This process entails the breakage of the peptide bonds that hold together proteins via hydrolysis, which uses water molecules to break bonds through chemical reactions. Because of their nature and ability to break bonds, they are classified as enzymes, as denoted by the "-ase" suffix. The enzymes act on proteins within host cells as well as virus precursors, thus fast-tracking viral progression. Since the process is highly time-consuming, enzymatic catalysis evolved to speed up the viral cycle (Sojka et al. 2021). These catalysts have been around since the early stages of evolution and are evolved in all stages of the viral life cycle, from beginning to end (Bond, 2019). Proteases are able to achieve greater specificity of regions by recognizing cysteine, serine, and aspartic acid residues within conserved sequences (Steinkühler 2008).

As a key player in the viral life cycle, proteases have been outlined as strong targets for antiviral therapies over the last few decades. With prior success in other viruses, protease inhibition is now being explored as an alternative treatment to current/novel and highly relevant viruses. Canurta has made groundbreaking progress investigating different compounds in hemp and their various undiscovered functions, and future prospects for hemp as an antiviral therapy are highly promising.

COVID-19

SARS-CoV-2, the virus behind the COVID-19 pandemic, is a member of the coronavirus, or coronaviridae, family. These viruses are classified by spike proteins on their surfaces that give them their characteristic crowned appearances, hence the “corona-” prefix. SARS-CoV-2 was found to match over 80% of the RNA genome of the virus named severe acute respiratory virust (SARS-CoV, now labeled SARS-CoV-1), the agent behind the 2003 pandemic (Ghahremanpour et al. 2020). The positive-sense single-stranded enveloped RNA virus is spread through contact with expelled mucus and saliva droplets and takes effect by binding to angiotensin-converting enzyme 2 (ACE2), thus competitively inhibiting the receptor’s substrate known as angiotensin II (Hoffmann et al. 2020). The virus targets the respiratory system and produces symptoms including fever, loss of taste and smell, coughing, and in more serious cases can produce complications leading to death.

SARS-CoV-2 has two proteases; the first is the chymotrypsin-like cysteine protease, also known as the main protease (Mpro), and the second is the papain-like cysteine protease (PLpro). The hydrolysis catalyzed by these enzymes transforms polyproteins (covalently bonded proteins) coded by the virus RNA into essential proteins that assist in virus replication and packaging, thus it is hypothesized that protease inhibition would stop the virus from spreading (Ghahremanpour et al. 2020). This strategy stops the virus before it can cause widespread damage in the body as opposed to attempting to stop transmission - successful implementation should result in recovery from the virus without decreased quality of life due to detrimental symptoms of the virus. The strategy is especially advantageous due to the high transmissibility of COVID-19. The virus is deemed highly contagious and can be contracted by respiratory droplet transmission from close proximity to infected individuals, both of which are often difficult to be aware of and even more difficult to control. Its transmission from surfaces is less likely. The virus can even actively circulate in enclosed and unventilated buses for up to half an hour while maintaining full infectivity (Ren et al. 2020). Because of the highly infective nature of the virus and the shortcomings of public health measures as preventative strategies, the necessity of effective treatment has become of paramount importance, and protease inhibition appears to be an important mechanism for its achievement.

The main protease is of particular interest as an antiviral target and has been a promising area of study since the SARS outbreak of 2003. This protease recognizes a specific sequence of amino acids/residues (Leu-Gln-Ser-Ala-Gly) and cleaves the peptide bond between glutamine and serine of the 1ab polyprotein. Mpro is distinct from its fellow protease because of its ability to cleave after a glutamine residue; this quality allows for substrate specificity since no other human protease is known to cleave the glutamine residue within this sequence, making it an easy target. Alternatively, PLpro seeks ubiquitin's C-terminal sequence, but this sequence is not unique to PLpro and inhibitors could thus also interfere with host-cell proteases. As such, Mpro shows more promise than PLpro and other targets such as spike proteins, nucleoside triphosphatases, and RNA-dependent RNA-polymerases (Ullrich and Nitsche, 2020).

Of 2,000 oral drugs approved for research into Mpro inhibitors, 42 were determined to exhibit promising activity - 17 of those that showed the most compatible structures with Mpro were chosen for a kinetic assay and 14 of the 17 significantly inhibited protease activity (Ghahremanpour et al. 2020). Five oral drugs also exhibited half maximal inhibitory concentration (IC_{50}) values lower than 40 μM, which refers to the amount of substance needed to inhibit target activity by 50% (Ghahremanpour et al. 2020). This measure validates these five compounds as potent inhibitors. A table summarizing these findings is provided below (Table 1.0).

Table I Analysis of 17 compounds as inhibitors of Mpro (Ghahremanpour et al. 2020)

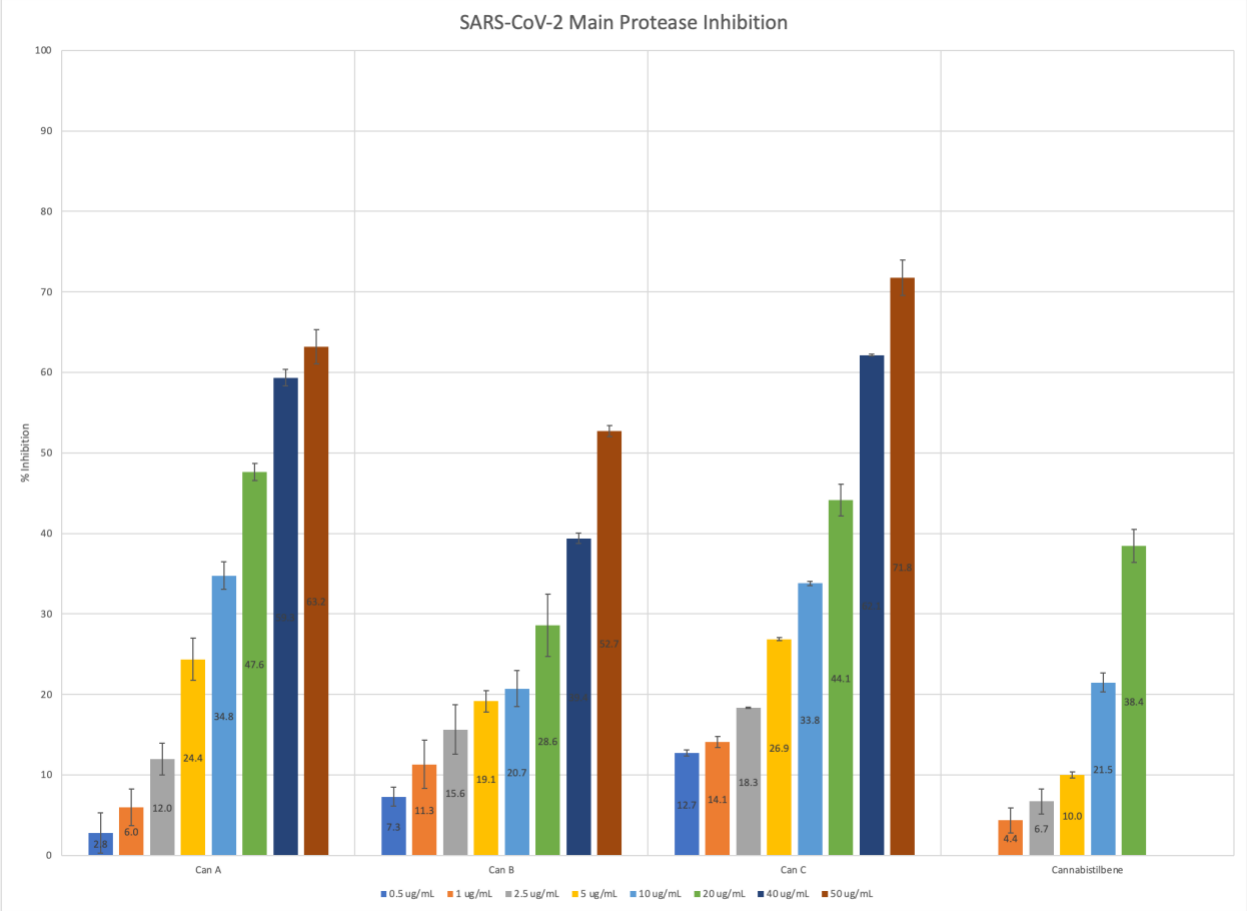
Compound	% Activity at 100 μM Concentration	IC_{50} (μM)
Manidipine	1	4.81 ± 1.87
Boceprevir	6	5.40 ± 1.53
Lercanidipine	8	16.2 ± 2.94
Efonidipine	18	38.5 ± 0.41
Bedaquiline	28	18.7 ± 4.20
Perampanel	43	100-250
Periciazine	55	250
Nelfinavir	64	250-600
Tipranavir	65	>600
Azelastine	69	20-100
Cinnoxicam	75	>600

Idarubicin	82	250-600
Clofamizine	88	>600
Talampicillin	90	250-600
Indinavir	100	NA
Cabergoline	100	NA
Lapatinib	100	NA

Based on these results, likely competitors of Canurta's product would be those in the market with the top 5 (most potent) inhibitors: manidipine, boceprevir, lercanidipine, efonidipine, and bedaquiline.

Research conducted by Canurta (2022) has provided insight into the Mpro inhibition activity by cannflavins. The study measured the percentage of Mpro inhibition by cannflavins A, B, and C, at concentrations ranging from 0.5-50 µg/mL concentrations, and estimated half maximal inhibitory concentration (IC_{50}) levels of each cannflavin. The results are provided below (Figure 1.0). Notably, cannflavin A provided up to 63.2% inhibition, cannflavin B up to 52.7%, and cannflavin C up to 71.8%. A significant finding is the IC_{50} levels - all three cannflavins were estimated to have IC_{50} levels below 40 µg/mL, thus making them as competent as the top five proposed inhibitors suggested by Ghahremanpour et al. (2020).

Figure 1.0 SARS-CoV-2 Mpro inhibition by cannflavins A, B, and C at varying concentrations.



An additional point of interest regarding cannflavins is their anti-inflammatory properties. Cannflavins offer a double-action antiviral and anti-inflammatory approach that can inhibit viral activity within cells while potentially decreasing inflammation of respiratory tract tissue to mitigate severity of COVID-19 symptoms.

Human Immunodeficiency Viruses

Human immunodeficiency virus (HIV) therapy is an excellent basis to build on for SARS-CoV-2 treatment prospects. HIV is a retrovirus passed on through sexual transmission, bodily fluid exchange, and pregnancy (from mother to child). Retroviruses are classified by their RNA genome, which is then converted to DNA and combined with host cell DNA. This single-stranded enveloped virus targets and weakens the host's immune system, attacking immune cells like dendritic cells, helper T cells, and macrophages. The specific helper T cells involved in this virus are CD4+ T cells, and critically low levels of this type of immune cell lead to decreased immunity and contribute to the development of acquired immunodeficiency syndrome (AIDS). Though there are two types of HIV viruses, the first (HIV1) is focused on in this paper due to its higher transmissibility, higher global prevalence, and more probable progression into AIDS (Nyamweya et al. 2013). HIV1 affects roughly 40 million people worldwide (World Health Organization 2022).

HIV has a high replication rate that gives rise, in turn, to a rapid mutation rate, allowing the virus to build resistance to drugs at a fast pace. As a result, treatment options are limited - scientists employed the protease inhibition method in an effort to variate approaches to the virus and found very positive results. The HIV1 protease is involved in the maturation phase of the viral cycle, which occurs after the virus is released into the host. Specifically, the protease was deemed crucial for transmissibility because of its ability to process gag and

gag-pol polyproteins (Gulnik et al. 2000). The protease is known as aspartic, meaning it has a catalytic site composed of an Asp-Thr-Gly sequence and is a competitive inhibitor. The protease uses flaps that open and close, allowing substrates to bind and blocking other substrates from binding (Sharma and Gupta 2017). Since HIV molecules are able to replicate rapidly and can simultaneously inhibit immune cells, combination therapy is often a necessity to combat the virus directly and overcome resistance. This creates a constant demand for new therapies and an opening for Canurta's hemp-based product to be used alongside traditional medicines to increase immunity through a multifaceted approach.

Multiple protease inhibitors were developed that structurally resemble protease substrates, namely saquinavir, lopinavir, and ritonavir. Saquinavir is sold under the brand names Fortovase and Invirase, and was proven to reduce viral activity without any adverse events and few side effects in general; it was tolerated well by HIV patients in clinical trials (Kitchen et al. 1995). Ritonavir followed closely and was first made available in 1996, proving to decrease the risk of AIDS development and lengthen patient lifespans in clinical trials (Cameron et al. 1998). Lopinavir came along in 2000 and is combined with Ritonavir, which decreases lopinavir metabolism, and combined trials inhibited viral replication in patients of all ages beginning at 6 months (Hurst and Faulds 2000). Each of these medications are among 10 approved by the US Food and Drug Administration (FDA) as HIV therapeutics that have reduced

fatality and improved quality of life through protease inhibiting agents (Sojka et al. 2021).

Not only does this discussion of HIV accredit protease inhibition as a successful and optimal antiviral approach, it also creates an exciting opportunity. Metabolite research found that Denbinobin is a stilbene present in *Cannabis sativa* that possesses anti-HIV1 properties by suppressing transcription and inhibiting a number of HIV1 developmental processes in the host (Sánchez-Duffhues et al. 2008). 12.5% THC cannabis was previously administered to patients to manage pain by inducing its psychoactive effect and was found to have a reasonable safety profile, yet no hemp (<0.3% THC) therapies have been tested as antivirals as of now (Ware et al. 2015). Research regarding the effect of cannabis on HIV1 and effect on fatality rates is currently limited (Lutge et al. 2013). As such, Canurta has an opportunity to make the historical first move and test the anti-HIV1 activity of a hemp-based oral supplement.

COVID and HIV

Fascinating new studies are looking into repurposing HIV protease inhibitors for COVID-19 patients. Since protease inhibition is an established successful treatment option, scientists were inspired to try repurposing proven effective drugs among similar single-stranded positive-sense enveloped viruses. After determining that HIV protease inhibitors interact with SARS-CoV-

2 proteases via in-silico studies, it was then found that the interaction between saquinavir and Mpro produced the strongest bond at -9.6 Kcal/mol (Ortega et al. 2020). It was then hypothesized that inhibitors of HIV proteases have the potential to reduce SARS-CoV-2 Mpro activity based on their exhibition of comparable, but notably higher, binding energies with Mpro compared to HIV proteases (Ortega et al. 2020).

There are some slightly contradictory results as of now regarding the effectiveness of HIV protease inhibitors against Mpro. A study conducted with adult individuals infected with SARS-CoV-2 found that there were no significant improvements after administration of lopinavir-ritonavir (Cao et al. 2020). However, another study found that adding lopinavir-ritonavir as an initial treatment to an established treatment regimen for SARS-CoV-1 decreased intubation rates as well as fatality rates in patients (Chan et al. 2003). These studies appear to outline a gap in research that calls into question whether or not traditional HIV inhibitors would be effective for SARS-CoV-2 and if they are worth exploring in future studies. From a new perspective, though, this gap can be seen as an opportunity. It is established that protease inhibition is highly effective with minimal side effects and it is clear that there is a link between viruses that allows for mutual therapies. A window is thus created for companies like Canurta to harness this information and offer novel therapeutics that can bridge the gap and provide a strong alternative.

Hepatitis C

Hepatitis C virus (HCV) protease inhibition can also be presented as an example to validate protease inhibition as an advantageous medicinal tactic. This virus affects roughly 58,000,000 people worldwide (Centers for Disease Control and Prevention 2021). HCV is a member of the Flaviviridae (or flavivirus) family, which are generally grouped by common size and structure. This enveloped single-stranded RNA virus targets hepatocytes, which are parenchymal tissue liver cells, through CD81 receptors. These receptors bind to one (E2) of two glycosylated proteins (E1, E2) that interact with receptors in order to enter host cells. The HCV protease, NS3/4A, is known to hydrolyze polyprotein precursors, resulting in the formation of structural and nonstructural proteins. Inhibitors of this protease mimic the amino acid sequence recognized by the enzyme, with 7 inhibitors currently approved by the FDA (including boceprevir) (LiverTox 2022). These inhibitors are not known to produce severe adverse events , but do result in dizziness, headaches, nausea, abdominal pain, diarrhea, and, in some cases, liver damage with rashes and fevers (LiverTox 2022). Similarities in substrate binding sites were also identified between HCV and SARS-CoV-2, and HCV inhibitors were predicted to possess the ability to bind to Mpro, yet antiviral activity detected was associated with the inhibition of PLpro (Bafna et al. 2021).

This information further supports protease inhibition as an advantageous antiviral strategy but once again creates an opportunity for

improvement. As mentioned before, PLpro is not an ideal target due to the interference of host deubiquitinases by PLpro inhibitors. Therefore, if the success of HCV protease inhibitors for SARS-CoV-2 is contingent on inhibition of PLpro then this comes at a risk to patients and would likely produce greater side effects. For this reason, a natural supplement proven to inhibit Mpro (such as a cannflavin-based supplement) would be a safer alternative to repurposing HCV drugs for the treatment or prevention of COVID-19.

Though existing drugs are effective in countering Hepatitis C, the cost renders them inaccessible in lower-income communities, once again highlighting inequity in global healthcare (Chhatwal et al. 2016). Alternatively, a naturally-derived supplement that is easier to develop can resolve this issue. This is especially promising due to the ability of quercetin (a flavonoid in *Cannabis sativa*) to inhibit the NS3 protease of Hepatitis C, as discovered via an in-vitro catalysis assay (Bachmetov et al. 2012). In vivo studies with model systems also showed inhibition of NS3, suggesting that quercetin is an effective Hepatitis C inhibitor that suppresses RNA biosynthesis and prevents viral replication (Bachmetov et al. 2012). Other molecules in hemp exhibit specific antiviral activity that have not yet been leveraged , creating a major opportunity for the development of a novel therapeutic that would break boundaries and borders.

Canurta

Canurta's recent research is groundbreaking, as it provides some of the pioneering solid support for cannflavins as Mpro inhibitors, thus providing a strong foundation for marketing a hemp-based product targeting SARS-CoV-2 and other viruses. These findings also prove cannflavins to be on par with existing drugs - with an even playing field in a medical capacity, cannflavins offer a competitive advantage due to their herbal nature. It has been proven that consumers oftenprefer herbal alternatives to synthetic drugs, largely due to side effects of engineered drugs, which are responsible for roughly 8% of American hospitalizations annually (Karimi et al. 2015). Herbal medicines are traditionally regarded as holistic therapies that maintain bodily wellness as a whole. Canurta's molecules thus present a competitive advantage for those interested in natural therapies with scientifically sound, concrete proof. Protein engineering has allowed natural inhibitors to be refined to produce potent and highly specific thrombin, trypsin-fold, and Kunitz-domain-based protease inhibitors in the past (Drag and Salvesen 2010). Misconceptions may currently exist regarding the capabilities of natural products but promising research is coming to light in support of natural sources for protease inhibitors.

Since all of the drugs targeting proteases as inhibitory targets are oral drugs, it is most fitting for Canurta to develop an oral supplement with a marketed percent inhibition of under 40 µg/mL to compete with co-developing competition. As of now, the main competition on the market is

existing protease inhibitors, including saquinavir, lopinavir-ritonavir, and boceprevir. A table of common plant flavonoids covering their characteristics as SARS-CoV-2 therapeutics created by Abd El-Mageed et al. (2021) outlined that cannflavins, luteolin, naringenin, and apigenin (flavonoids found in *Cannabis sativa*) are shown to have moderate and high solubility respectively, gastrointestinal absorption, and no toxicity or carcinogenicity. These qualities make hemp-derived flavonoids an excellent alternative to existing protease inhibitors, as they should limit existing side effects.

Entering the Market

Next steps should entail assays to further elucidate antiviral action of these flavonoids before human trials - organizations like HUB Organoids are an excellent option for *in vitro* trials. HUB Organoids allows for the creation of "mini-organs in a dish" by cultivating stem cell replication and specialization (HUB Organoids 2022). Secondary assays also allow for dose-response studies to be conducted; though some information about concentrations has been conducted, further research should determine what doses are recommended to maximize antiviral activity with minimal negative side effects to the body. In-silico target predictions and imagining may not be necessary at this point, since published studies have already determined interactions exist between covered disease states' proteases and protease inhibitors, specifically flavonoids in Cannabis sativa. However, such studies may be repeated to form

a more cohesive and solid foundation to Canurta's research. After *in vitro* analyses are conducted to determine dose-amounts, clinical trials must be commenced.

To obtain approval as a COVID-19 therapeutic, results of clinical trials must be presented along with safety and efficacy reports, continuing reports on adverse side effects and other safety concerns after market introduction, production sustainability data, and a risk management plan (Government of Canada 2022). This process is extremely thorough and, though it does not take as long due to the current needs of the country, extensive clinical trials and research must be conducted and presented, after which a large panel of government officials from different departments and experts review evidence rigorously to ensure utmost safety and sustainability (Government of Canada 2022). Alternatively, immune health supplements are easier to market via independent organizations such as NSF - the certification process entails testing quality, sustainability, and safety by the organization to determine if the product meets their standards (NSF 2022). Specific hemp product certification verifies claims of action and ensures THC (and other contaminant) levels remain undetected (NSF 2022). Immune health supplements are also in high demand, with the market expecting to reach $31.5 billion USD in the next 6 years (Fortune Business Insights 2021). The general nutraceuticals and supplements market was valued at $353 billion USD as of 2019, seeing a 44% hike in the first wave of the pandemic alone

(Lordan 2021). This result was globally experienced; for example, vitamin sales were over 60% higher in March 2020 in the United Kingdom compared to March 2019, and up to 60% higher in France (Lordan 2021). Countries like Poland saw a rise in internet searches for supplements in the beginning of the pandemic as well (Lordan 2021). These trends outline an evident demand for immune health supplements including ones with antiviral activity.

Of the other disease states mentioned, HIV and Hepatitis C also come with big markets. The HIV market was valued at roughly $30.5 billion USD as of 2021 and is projected to grow by about $15 billion USD in the next 6 years (Fortune Business Insights 2021). The Hepatitis C drug market was worth close to $8 billion USD as of 2018 and is anticipated to remain relatively constant in the next 4 years (Fortune Business Insights 2021).

Dengue and Japanese Encephalitis Virus

Given the information above, there is great potential for research regarding the potential for flavonoids in the treatment of internationally relevant viruses such as Zika virus, Japanese Encephalitis virus, and Dengue virus. These viruses belong to the flavivirus class along with HCV. Since the active sites of inhibitors appear to be of a structure shared by multiple substrates and, HCV and fellow flaviviruses are grouped by similarity in structure, future research could show a link between protease inhibitors and the aforementioned viruses. As such, flavonoid supplements can be an

affordable and powerful tool in curbing viral spread across Asia. This will also address global inequity. As of now, treatment options currently sent to developing communities are often not utilized because manufacturing and transportation must be accessible (Marshall 2022). Flavivirus therapies currently available were also deemed costly to manufacture, and a need for new ideas exists (Krol et al. 2019). However, a natural supplement provides ease of manufacturing due to the accessible ingredients. It is recommended that further research be conducted to assess the viability of cannflavins as inhibitors of flavivirus proteases, and it is recommended that Canurta commence international relations to offer competent and cutting-edge therapies for flaviviruses.

Conclusion

The aim of this white paper was to review prior successes of protease inhibition as a foundation for the future development of hemp-based supplements. It has been well established that the strategy is a powerful tool for a range of different viruses, including HIV, HCV, and now SARS-CoV-2. This information can thus be used to produce therapeutics that continue to advance pharmacology by decreasing adverse effects and making health accessible for all. Canurta has the potential to create a naturally-derived product that boasts no current known toxicity nor carcinogenicity, and displays antiviral and anti-inflammatory effects. This naturally derived product has the potential to treat current and future viruses that are relevant in a

multitude of communities, ranging across more income and development levels than traditional medicines. Thus, Canurta can pave the path towards global equity in healthcare by providing an accessible and low-cost alternative to traditional medicines that provides immunity against a multitude of viruses. As this research indicates, Canurta is the one to watch over the coming few years.

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