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Rooibos, a supportive role to play during the COVID-19 pandemic?

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ABSTRACT

This article presents the potential health benefits of Rooibos to be considered a support during the COVID-19 pandemic. The recent pandemic of COVID-19 has led to severe morbidity and mortality. The highly infectious SARS-CoV-2 is known to prime a cytokine storm in patients and progression to acute lung injury/acute respiratory distress syndrome. Based on clinical features, the pathology of acute respiratory disorder induced by SARS-CoV-2 suggests that excessive inflammation, oxidative stress, and dysregulation of the renin angiotensin system are likely contributors to the COVID-19 disease. Rooibos, a well-known herbal tea, consumed for centuries, has displayed potent anti-inflammatory, antioxidant, redox modulating, anti-diabetic, anti-cancer, cardiometabolic support and organoprotective potential. This article describes how Rooibos can potentially play a supportive role by modulating the risk of some of the comorbidities associated with COVID-19 in order to promote general health during infections.

1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current Coronavirus disease 2019 (COVID-19) pandemic. This particularly infectious virus has been confirmed in more than 150 countries and cases are still steadily growing despite public health interventions (Lewnard and Lo, 2020, Fang et al., 2020) and the sustained demands of COVID-19 on health systems is likely to cause a shortage of hospital resources (Emanuel et al., 2020). Elderly patients and patients with comorbidity disorders including pulmonary disease, cardiac disease, kidney disease, diabetes, and hypertension have been associated with greater mortality rates, suggesting highly susceptible and/or vulnerable groups within the infected population (Shi et al., 2020, Patel and Verma, 2020). Clinical symptoms of COVID-19 are non-specific but an important distinguishing factor is a rapid progression to acute respiratory distress syndrome (ARDS) (Rodriguez-Morales et al., 2020).

SARS-CoV-2 retains the characteristic coronavirus structure with spike proteins that facilitate viral entry via angiotensin-converting enzyme 2 (ACE2) and viral envelope fusion with target cell membranes (Shereen et al., 2020). Consequently, it had been hypothesised that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19 (Fang et al., 2020, Diaz, 2020). This led to growing uncertainty from physicians and patients on what should be done regarding their hypertensive medications (Patel and Verma, 2020). In response, the Council on Hypertension of the European Society of Cardiology made the following statement, "The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should be discontinued because of the COVID-19 infection" (AHA, 2020). Furthermore, there is some evidence to demonstrate that treatment with ACEIs or ARBs can decrease the severity of pulmonary injury by SARS-CoV-2, with pre-clinical data suggesting a potential mechanism of benefit (Bavishi, Maddox et al., 2020).

Several vaccines are undergoing clinical trials as possible treatments, while other experimental interventions are in the early stages of development (Casadevall and Pirofski, 2020, Harrison, 2020). While the global research and development of an effective vaccine are unprecedented (Le et al., 2020), it will take time to produce, distribute, and administer (Emanuel et al., 2020) which further exacerbates the pandemic. Medicinal plant interventions have been used in previous

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ACE2, Angiotensin-converting enzyme 2; LPS, Lipopolysaccharide.

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coronavirus outbreaks, suggesting the tremendous potential of natural products to provide treatment for the ongoing COVID-19 pandemic (Lau et al., 2008, Li et al., 2005).

Plant derived polyphenols and their metabolites are bioactive compounds that display antioxidant, anti-inflammatory and immune regulatory properties (Luca et al., 2020). Epidemiological evidence strongly suggests that populations consuming high amounts of polyphenols are less likely to suffer from chronic metabolic disorders such as diabetes, obesity and cardiovascular complications (Boccellino and D'Angelo, 2020, Guasch-Ferré et al., 2017, Satija and Hu, 2018). Overall, available literature suggests that polyphenols are suitably positioned to play a multifaceted and beneficial role in the COVID-19 pandemic (Levy et al., 2020, Chojnacka et al., 2020). The use of botanicals as economically viable intervention strategies is gaining attention in underdeveloped countries, where the fight against poverty combined with the uncertain management of COVID-19 is considered as major hurdles in combatting the rampant spread of the virus.

Ethnopharmacology is practised in several countries and is regarded as one of the fastest growing scientific disciplines (Heinrich and Jäger, 2015), with several natural products inspiring the development of active ingredients in drug formulations (Mukherjee et al., 2010). Africa, especially southern Africa is gifted with a plethora of medicinal plants (Light et al., 2005, Karou et al., 2007). More than 80% of people on the African continent make use of these medicinal plants and herbals as traditional medicine and the WHO encourages African member states to promote and integrate traditional medical practices in their health system. Rooibos herbal tea brewed from *Aspalathus linearis (Burm.f.) R. Dahlgren, Fabaceae,* a fynbos plant part of the Cape Floristic Region (South Africa), is a popular, traditional tisane that has been consumed since the late 1700 s. It is customarily used for medicinal purposes and it contains a unique blend of bio-active phytochemicals (such as aspalathin, luteolin, quercetin and many more) reported to have potent antioxidant, anti-inflammatory and antimutagenic activities *in vitro* and *in vivo* (Snijman et al., 2009, Joubert et al., 2012, Joubert and de Beer, 2011, Standley et al., 2001, Lee and Bae, 2015, Chian et al., 2014, Wölfle et al., 2011, Kleemann et al., 2011; Marnewick et al., 2009; 2011). More pertinent to the current pandemic, Rooibos has displayed anti-hypertensive (through inhibition of ACE), anti-inflammatory, antioxidant, anti-diabetic, anti-viral, cardiometabolic - and organoprotective effects (Khan and Gilani, 2006, McKay and Blumberg, 2007, Yang et al., 2018, Nakano et al., 1997).

In the unfamiliar circumstances of COVID-19, legitimacy in the form of scientific evidence is lacking. Therefore, the impact of interventions relies upon extrapolations from the mechanisms of action of individual agents and/or published outcomes of data supporting their alleviating effects on illness. Based on the well-established bioactivities of Rooibos, we hypothesise its use as a potential support strategy during the current pandemic for persons infected with SARS-CoV-2 or at higher risk for contracting this virus.

2. Relation between ACEIs/ARBS and COVID-19 – Rooibos as a potential intervention

The SARS-CoV-2 life cycle describes the steps and changes the virus undergoes from its first contact with a target cell to the production of new infectious viral particles that can initiate the next round of replication and infection (Shereen et al., 2020). Wrapp *et al* recently reported that SARS-CoV-2 induces cellular internalization by binding to the catalytic domain of ACE2 via viral spike protein (Wrapp et al., 2020), this process initiates a conformational modification in the S protein, allowing proteolytic digestion by type II transmembrane serine proteases, leading to viral and cell membrane fusion (Hoffmann et al., 2020).

Physiologically, ACE2 is a member of the renin-angiotensin-aldosterone system (RAAS). Concisely put, the RAAS is essential to the regulation of blood pressure (BP) control by acting in the cardiovascular and renal systems. Conversely, aberrant RAAS activation promotes many adverse cellular processes implicated in systemic damage through hemodynamic actions, cytokines and intracellular signalling pathways, and plays a crucial role in the pathogenesis of hypertension. In the RAAS, angiotensin (Ang) I is converted to Ang II by ACE (homologue of ACE2). Angiotensin II facilitates vasoconstrictive, proinflammatory, and pro-oxidative effects by binding to the Ang II type 1 receptor (AT1R). Angiotensin-converting enzyme 2 converts Ang II to Ang 1–7, which binds to Mas receptor (MasR) and mediates numerous beneficial actions, including vasodilation, anti-inflammatory, antioxidant and anti-apoptotic effects. Thus, the ACE2/Ang 1–7/MasR axis has counter-balancing actions to the ACE/AngII/AT1R axis (Fig. 1) (Tikellis and Thomas, 2012, Velkoska et al., 2016).

As previously discussed, SARS-CoV-2 penetrates the cell through ACE2 which is located on the surface of type II alveolar cells (this may explain the widespread respiratory symptoms (ARDS) in COVID-19 patients) as well as other cell types, such as those of the heart, kidney, liver, gastrointestinal tract (especially the oesophagus, stomach, colon, ileum, and rectum), and bladder (Sanchis-Gomar et al., 2020). Because ACE2 is a functional receptor for SARS-CoV-2, it has been hypothesized that increased levels of ACE2 through administration of ACEIs/ARBs may increase the risk of severe and fatal COVID-19. This idea is grounded in part on the findings in some studies that ARBs and ACEIs may increase ACE2 levels (Sanchis-Gomar et al., 2020), and that hypertension is one of the most important factors associated with poor prognosis of COVID-19 infection (Wu et al., 2020, Zhang, Dong et al., 2020, Qin et al., 2020). Such considerations contributed to the perceived potential influence of ACEIs and ARBs on poor outcomes in patients with COVID-19 despite no clinical evidence.

Recently, a tentative suggestion to utilise available and clinically-used angiotensin receptor 1 (AT1R) blockers as a treatment for COVID-19 has been put forth (Sun et al., 2020). This is based on AT1R antagonists blocking internalization, proteolytic degradation, and ubiquitination of ACE2. As such, this pathway represents a mechanism by which established drugs could prevent COVID-19 viral entry (Gurwitz, 2020, Sanchis-Gomar et al., 2020). However, it remains unknown whether preventing ACE2 internalization would be effective at attenuating infections by SARS coronaviruses, and further studies are urgently needed to clarify this mechanism (Sanchis-Gomar et al., 2020). In an earlier study, the *in vitro* treatment of HEK293T cells with Ang II enhanced ACE2 ubiquitination, mediated by AT1R, was found to stimulate ACE2 lysosomal degradation (Deshotels et al., 2014) (which might prevent interaction of the SARS-Co-V2 with ACE2 catalytic site). Conversely, binding of SARS-CoV-2 to ACE2 may attenuate residual ACE2 activity, tilting the ACE/ACE2 balance to a predominant ACE/Ang II/AT1 signalling axis, in which Ang II may then foster pulmonary vasoconstriction, pro-inflammatory and oxidative organ damage (Zhang and Baker, 2017, Sanchis-Gomar et al., 2020).

Rooibos may help mitigate some of these adverse effects of Ang II based on its ability to significantly inhibit ACE with maximum inhibition at 30–60 min (min) and persisting for about 60 min after participants consumed an acute dose of fermented rooibos (Persson et al., 2010, Persson, 2012, Persson et al., 2006). According to the kinetic study, Rooibos probably inhibits ACE activity using a mixed inhibitor mechanism. It also seems that Rooibos uses the same enzyme kinetic mechanism as the clinically used and established ACE inhibitor enalaprilat (mixed type inhibitors) (Persson, 2012). Rooibos contains a unique blend of flavonoids including, aspalathin (only found in Rooibos), nothofagin, rutin, orientin, isovitexin, isoorientin, vitexin and quercetin. Since flavonoids are acknowledged as metal chelators, a possible mechanism for Rooibos phytochemicals is to bind to the Zn^{2+} at the active site of ACE, thereby inhibiting the enzymes ability to convert the inactive angiotensin I to form the active angiotensin II (Persson, 2012). Given the similar pathway of action, it can be hypothesized that Rooibos may ameliorate lung damage caused by angiotensin II in COVID-19 patients.

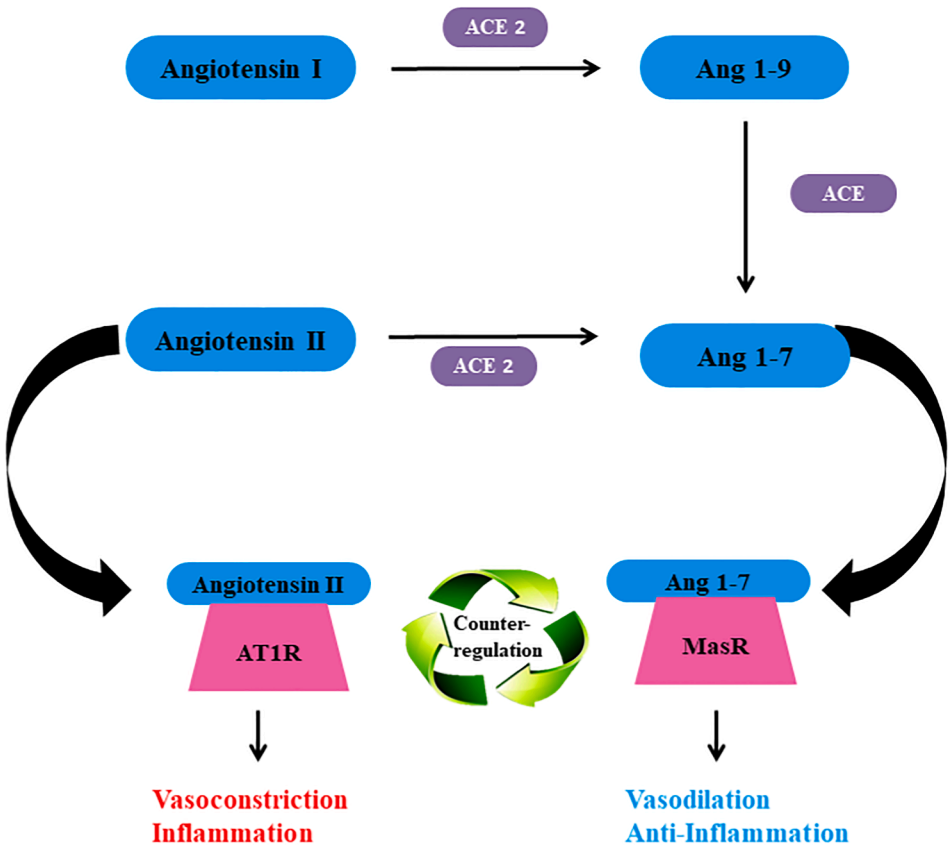

Fig. 1. Brief schematic representing ACE homologue activity and recruited pathways.

3. COVID-19 cytokine storm syndrome and modulation of hyperinflammation with Rooibos

Viral infections prompt a swift and coordinated innate immune response as the first line of defence; however, when the immune response is dysregulated, it often results in hyperinflammation, and may even cause death (Shaw et al., 2013). Although no direct link was found for the involvement of proinflammatory cytokines and chemokines in lung pathology during COVID-19, the changes in laboratory parameters, including elevated serum cytokine, chemokine levels, and increased neutrophil-to-lymphocyte ratio in infected patients, were correlated with the severity of the disease and adverse outcomes, suggesting a possible role for hyperinflammatory responses or a "cytokine storm" in COVID-19 pathogenesis (Mehta et al., 2020, Qin et al., 2020). Respiratory failure from ARDS is the foremost cause of mortality in COVID-19 patients but mortality may also be driven by viral hyperinflammation. This is based on predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, which included elevated ferritin and interleukin (IL)-6 (Ruan et al., 2020). Furthermore, secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-appreciated, hyperinflammatory syndrome distinguished by sudden inception and fatal hypercytokinaemia often resulting in multi-organ failure (Huang et al., 2020, Seguin et al., 2016). Key features of sHLH and a cytokine profile similar to sHLH is associated with COVID-19 disease severity. Such features include increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α (Huang et al., 2020).

Current management of COVID-19 is supportive which makes the identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles imperative to address the immediate need to reduce the rising mortality (Mehta et al., 2020). Based on this a multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765) (Mehta et al., 2020, McGonagle et al., 2020, Zhang, Zhao et al., 2020). When considering Rooibos in experimental models of disease and elevated levels of inflammation, encouraging results regarding the attenuation of circulating cytokine levels and reduced inflammatory responses have been reported by a number of authors (Baba et al., 2009, Smith and Swart, 2016, Katengua-Thamahane et al., 2014, Lee and Bae, 2015, Ku et al., 2015).

While Rooibos is regarded as having anti-inflammatory activity, not many studies have focused on the mechanisms behind this anti-inflammatory property. The data to date seem to support that Rooibos tea consumption is associated with both a reducing pro-inflammatory cytokine signalling (Katengua-Thamahane et al., 2014, Smith and Swart, 2016) and heightened secretion of the anti-inflammatory cytokine, IL-10 (Smith and Swart, 2016). In a rodent model of lipopolysaccharide (LPS)-induced damage, 4 weeks of pre-injury, Rooibos consumption, prepared as a tisane at the same concentration customarily consumed by humans, resulted in significantly lower TNF-α and IL-6 levels in hepatic tissue (Ajuwon et al., 2014). The active constituents of Rooibos responsible for these effects were highlighted in a murine model of sepsis, induced by administering high mobility group box 1 (HMGB1), an ubiquitous nuclear protein, the Rooibos constituents nothofagin and aspalathin specifically, were shown to decrease levels of IL-6, TNF-α and active NFκB (Lee and Bae, 2015). Similarly, in a rat model of colorectal cancer, supplementation with orientin – another constituent of Rooibos – was again linked to lower TNF-α, IL-6 and NF-kB, as well as lower levels of inflammatory enzymes iNOS and COX-2 (Thangaraj and Vaiyapuri, 2017). In terms of anti-inflammatory outcome, Rooibos exposure was reported to significantly increase IL-10 production by ovalbumin-challenged murine splenocytes in culture (Ichiyama et al.,

2007).

Messina *et al* recently reported on the supportive role dietary interventions may play in COVID-19 infected patients by improving the infection outcomes and perhaps even preventing the infection. They focussed on an important aspect in metabolic disease, i.e. adiponectin and improving the levels thereof to attenuate inflammation (Messina et al., 2020a). As IL-6, a proinflammatory cytokine is produced by adipose tissue during various viral infections of the pulmonary tract, these authors suggest the role that dietary interventions can play in improving the levels of adiponectin, an important regulator of the cytokine response (Messina et al., 2020a). When considering Rooibos and its main phenolic constituent, aspalathin, Son *et al* reported the prevention of a decreased serum level of adiponectin in a diabetic mouse model and concomitant increase in adiponectin serum levels by dietary feeding of aspalathin in these animals (Son et al., 2013). Another indirect method to increase adiponectin levels has been shown to include the use of ACE-inhibitors (Messina et al., 2020b). Previously we have discussed the ability of Rooibos to inhibit ACE after 30–60 min of consuming 500 mL of traditional Rooibos by the study participants (Persson et al., 2010).

These pre-clinical and clinical lines of evidence suggest that the use of Rooibos as a dietary supportive measure may effectively reduce the levels of pro-inflammatory cytokines, and potentially lower levels of inflammation in patients.

4. COVID-19 and oxidative distress – Rooibos and its antioxidant potential as a dietary support

Oxidative stress as described by the "redox pioneer", Helmut Sies in 1985 entails "a disturbance in the pro-oxidant – antioxidant balance in favour of the former" (Sies and Sies, 1985) and more recently the concepts of oxidative eustress or distress were introduced describing the effect on the cellular redox balance to either be positive and maintain cellular homeostasis (oxidative eustress) or negative where the result is the induction of detrimental damage (oxidative distress) to important cellular molecules such as lipids, DNA and proteins (Niki, 2016). Oxidative stress is important for viral replication and the subsequent virus-associated disease (Khomich et al., 2018) with the link between hyperinflammation and oxidative stress well established (Gill et al., 2010, Serasanambati and Chilakapati, 2016). Although clinical evidence supporting the link between oxidative stress (in this case distress) and COVID-19 pathogenesis is lacking, outcomes from laboratory and experimental animal models suggest that a compromised endogenous antioxidant defence system and the enhanced production of cellular oxidants, such as ROS, have a critical role to play, also in the outcome of this respiratory disease (Delgado-Roche and Mesta, 2020). Using a Toll-like receptor 4 (TLR4) mutant mouse model, Imai et al concluded that in conjunction with innate immunity pathways, oxidative stress pathways are critical to control the outcomes of acute lung injury (Imai et al., 2008). Together, when signalling pathways involving oxidative stress, transcription factors such as NF-kB and Toll-like receptors are triggered by pathogenic viruses, the host inflammatory response is amplified, causing severe lung injury (Delgado-Roche and Mesta, 2020).

The chemical characterization of Rooibos directly led to the identification of several potential antioxidant molecules mainly due to its high content and unique polyphenol blend (Bramati et al., 2003, Krafczyk and Glomb, 2008). Thus, there is significant data showing that the antioxidant effects, among others of Rooibos, are likely to be beneficial in the COVID-19-induced oxidative stress and concomitant inflammatory response.

Cells employ intricate intracellular antioxidant defence systems to combat oxidative stress/distress. These include non-enzymatic and enzymatic antioxidant systems, both of which can be positively influenced by Rooibos. Rooibos exerts antioxidant activities *in vivo* and *in vitro* by scavenging free radicals, inhibiting ROS formation and/or supporting endogenous antioxidant defence systems. In an early study into the non-enzymatic antioxidant effects, normally healthy rats supplemented with Rooibos herbal tea (at a concentration customarily consumed by humans) showed increased redox status (reduced to oxidised ratio) of the endogenous antioxidant, glutathione, (increased GSH: GSSG ratio) in livers (Marnewick et al., 2003) and increased the activity of certain antioxidant enzymes (Baba et al., 2009, Hong et al., 2014). Furthermore, Rooibos was shown to scavenge the physiologically relevant reactive oxygen species, superoxide radical anion (O^{2-}) and hydroxyl radical (OH), thoroughly reviewed in (Joubert et al., 2008, Ajuwon et al., 2015). In a dietary intervention study, participants at risk for developing cardiovascular disease (linked to oxidative stress) consuming fermented/traditional Rooibos herbal tea daily for six weeks showed a significantly improved redox status for glutathione via increased levels of reduced GSH. These participants also had a significantly reduced level of circulating oxidative lipid damage (measured as conjugated dienes and malondialdehyde) (Marnewick et al., 2011). Therefore, Rooibos would be beneficial in controlling the induced inflammation and oxidative distress experienced in SARS-CoV-2 infected subjects (Fig. 2).

5. COVID-19 and associated cardiovascular metabolic co-morbidities – Rooibos organ protection

The presence of vulnerabilities/comorbidities increased the mortality risk of SARS-CoV-2. Cardiovascular comorbidities are common in patients with COVID-19 and such patients are at risk of increased severity of morbidity and increased mortality. In a cohort of 191 patients from Wuhan, China, hypertension was present in 30% (48% of non-survivors), diabetes mellitus (DM) in 19% (31% of non-survivors), and cardiovascular disease (CVD) in 8% (13% of non-survivors) (Qin et al., 2020). In a cohort of 138 hospitalized patients with COVID-19, comorbidities were similarly prevalent (46% overall, 72% in patients requiring an ICU), as were cardiovascular comorbidities: hypertension in 31% (58% in patients requiring an ICU), CVD in 15% (25% in patients requiring an ICU), and DM in 10% (22% in patients requiring an ICU) (Cheng et al., 2020). A recent meta-analysis of eight studies from China which included 46,248 infected patients, showed the most prevalent comorbidities were hypertension (17 ± 7%, 95% CI 14–22%) and DM (8 ± 6%, 95% CI 6–11%), followed by CVDs (5 ± 4%, 95% CI 4–7%) (Yang, Zheng et al., 2020). However, the mechanism of these associations has not been elucidated. Potential reasons include CVD being more prevalent in the elderly, elevated levels of ACE2, or a predisposition to COVID-19 (Clerkin et al., 2020). Moreover, COVID-19 can also cause damage to organs such as the heart, the liver, and the kidneys, as well as to organ systems such as the cardiovascular and the immune system (Cheng et al., 2020, Huang et al., 2020, Chen et al., 2020). Patients may eventually die of multiple organ failure, shock, ARDS, heart failure and renal failure (Chen et al., 2020, Wang et al., 2020). The scientific community should therefore pay attention to interventions that could play a supportive role in alleviating potential multi-organ injuries and the original comorbidities of the individual, which will support treatment regimens for COVID-19, especially in older and/or vulnerable patients.

Rooibos, widely available and consumed across the world (Van Wyk and Wink, 2018) may provide a supportive approach when dealing with specific comorbidities during this pandemic. Clinical evidence show that daily Rooibos consumption has a beneficial role in the context of CVD and oxidative stress modulation (Marnewick et al., 2011), with daily consumption of fermented rooibos (prepared as a herbal tea), by adults at risk for developing cardiovascular disease, resulted in significantly reduced serum oxidative stress, improved levels of HDL cholesterol and decreased levels of LDL cholesterol and triglycerides. Other studies (including *in vitro* and experimental animal studies) have provided substantial evidence of its myocardial protective effects (Dludla et al., 2014, Pantsi et al., 2011, Smith and Swart, 2018). As reviewed and put forward by Dludla and co-workers, Rooibos flavonoids can protect heart tissue from oxidative stress induced by hyperglycaemia. These authors proposed several mechanisms to play a role, including metabolic

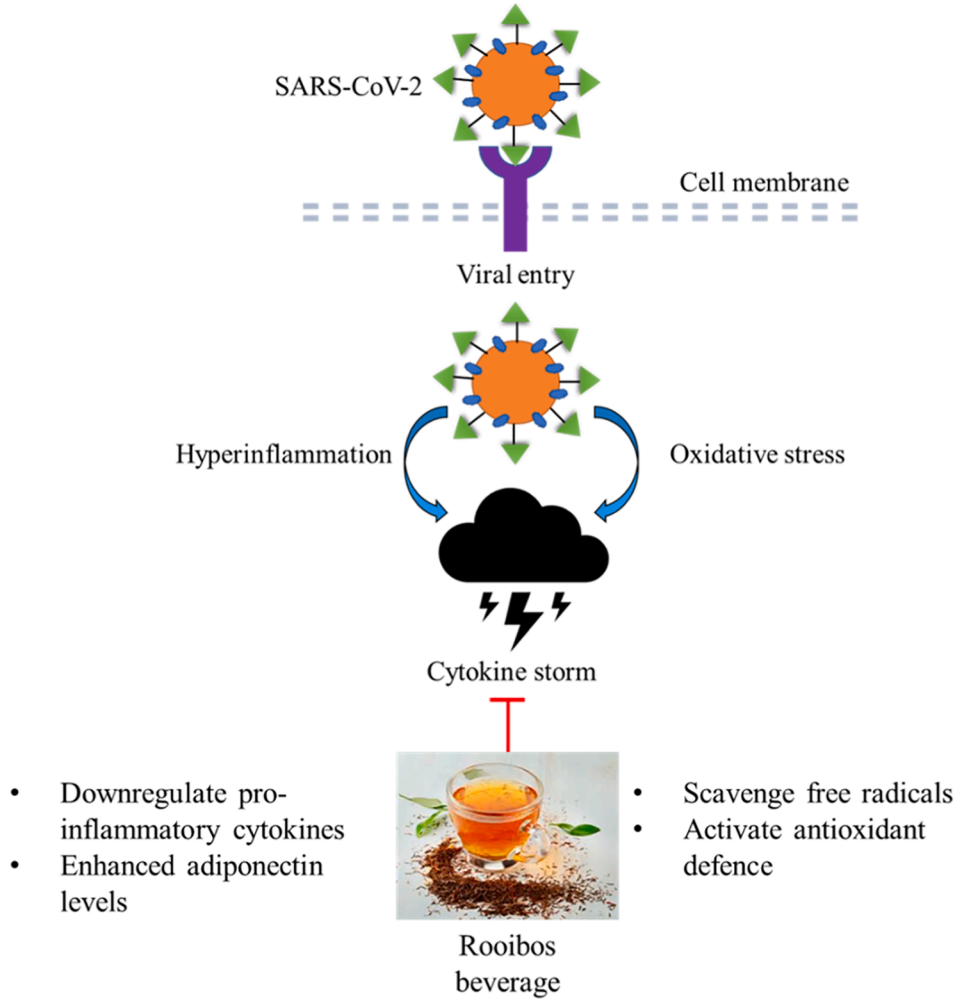

Fig. 2. Rooibos has the potential to modulate the cytokine storm induced by SARS-CoV-2 by various mechanisms.

signalling pathways, oxidative stress responses and mitochondrial stimulation (Dludla et al., 2017). The cardioprotective effects of Rooibos is highly pertinent to the current COVID-19 pandemic as infection with SARS-CoV-2 has been shown to elevate myocardial damage biomarkers (Bavishi, Bonow et al., 2020). Significant efforts are being made to elaborate on the underlying mechanisms of myocardial injury that have been noted in a significant number of infected patients as reviewed by (Babapoor-Farrokhran et al., 2020). Numerous lines of scientific evidence advocate for Rooibos to be of benefit – both as a preventative approach to CVD and as a complementary or supportive dietary approach to improve long-term prognosis in the COVID-19 vulnerable population.

Although ARDS is considered the main feature of COVID-19, a recent meta-analysis identified the high frequency of abnormal urine analysis and kidney dysfunction in COVID-19 patients (Yang, Jin et al., 2020). The overall incidence and degree of acute kidney injury (AKI) in SARS-CoV-2 infected patients is closely linked with the severity and prognosis of COVID-19. The authors of this work consider the renal tubule as the main part of injury and the aetiology of renal impairment in COVID-19 patients is likely to be diverse and multifactorial. Apart from direct attack by the SARS-CoV-2, hypoxia and hypercoagulability may also contribute to the occurrence of renal injury (Yang, Jin et al., 2020). Findings by Cheng and colleagues further showed that the prevalence of kidney disease on admission and the development of AKI during hospitalization in patients with COVID-19 is high and is associated with in-hospital mortality. Thus, clinicians should increase their awareness of kidney disease in patients with severe COVID-19 (Cheng et al., 2020). The nephroprotective effects of two Rooibos bio-actives, aspalathin and nothofagin were studied in a sepsis model. This study revealed decreased plasma levels of blood urea nitrogen, creatinine, urine protein, and lactate dehydrogenase in mice with caecal ligation and puncture -induced renal damage. Moreover, these two purified components inhibited NFκB activation and reduced the induction of nitric oxide synthase and excessive production of nitric acid. Both aspalathin and nothofagin treatment also reduced the plasma levels of NO, TNF-α, IL-6, and reduced lethality due to caecal ligation and puncture (CLP)-induced sepsis and markedly enhanced the antioxidant defence system by restoring the levels of superoxide dismutase, glutathione peroxidase, and catalase in the kidney tissues (Yang et al., 2018).

Diabetes is now known to be a key risk factor for developing severe COVID-19, and people with this condition are more likely to succumb to the viral infection. New laboratory and clinical evidence suggest that the virus damages insulin-producing cells, triggering diabetes in some people (Chee et al., 2020, Yang et al., 2010, Rubino et al., 2020). Rooibos may support people with problematic blood glucose levels, as a number of studies have reported Rooibos to have beneficial effects on glucose homeostasis through stimulating glucose uptake in muscle tissues and insulin secretion from pancreatic β-cells (Kawano et al., 2009) and enhancing the antioxidant status in diabetic models (Ulicna et al., 2006, Ayeleso et al., 2014). With the outcome of these studies, a supportive role by Rooibos, especially when considering the world-wide increasing number of pre-diabetic patients, is proposed.

6. Anti-viral activity of Rooibos – Relevance to the COVID-19 pandemic

Infectious diseases pose a global challenge, with developing countries being the most affected (Boutayeb, 2006, Jones et al., 2008). Phytochemicals are regarded as important sources of novel antiviral agents because they are easily accessible and have relatively few side effects (Potterat and Hamburger, 2008, Mukhtar et al., 2008). Consequently, there is growing interest in the use of traditional medicinal plants and their application as antiviral agents against SARS-Co-V2. A growing number of review and hypotheses articles have now been published in literature highlighting the potential of phytochemicals (polyphenolic constituents in particular) as alternate treatments for COVID-19. These compounds are proposed to interfere with the viral replication cycle, inhibit virus entry into cells or target the virus directly (Paraiso et al., 2020, Levy et al., 2020, Chojnacka et al., 2020).

Rooibos extracts have shown broad anti-viral activity against a diverse group of viruses such as the influenza virus (Rahmasari et al., 2017) and the human immunodeficiency virus (Nakano et al., 1997), however the active compounds responsible for these antiviral effects have not been elucidated. Although the exact mechanism of action is still unclear, these results suggest Rooibos may be a tangible agent in COVID-19 management. In line with this, two phytochemicals isolated from Rooibos have shown potential inhibitory effects on the SARS-Co-V-2 virus.

The Rooibos flavonoids, quercetin and luteolin were shown to inhibit SARS-CoV infection by stopping virus entry into Vero E6 cells with EC_{50} values of 83 μM and 10 μM, respectively. In the same study, luteolin was found to bind with high affinity to SARS-CoV S protein, suggesting an antiviral mechanism of action involving interference with the function of the S protein (Fig. 3) (Yi et al., 2004). While a more recent study identified quercetin to have a virus neutralizing effect by binding to the S protein (Pan et al., 2020). Furthermore, quercetin ($IC_{50} = 73$ μM) was shown as an inhibitor of $3CL^{pro}$ using *in silico* and *in vitro* approaches (Ghosh et al., 2020). $3CL^{pro}$ plays a vital role in polyprotein processing and virus maturation, and its direct targeting and inhibition has been touted as an effective first line defence against coronaviruses (Ullrich and Nitsche, 2020, Jin et al., 2020, Dai et al., 2020).

Recent work using a structure-based drug discovery approach have suggested vitexin and orientin (two compounds contained in Rooibos) to target "hot spot" residues on the SARS-Co-V-2 proteases that are necessary for viral replication (Alagu Lakshmi et al., 2020). The authors of this work believe that these compounds could serve as a promising platform for developing anti-COVID-19 drug(s). As a note of caution, *in silico* and *in vitro* attempts used for screening do not confirm the efficacy of the tested polyphenols against the human viral disease (Paraiso et al., 2020).

7. Microbiota and Rooibos phytochemicals – Implications for COVID-19

Microbes that reside in the human gut are important regulators of host immune responses and have been shown to be disturbed by the SARS-CoV-2 virus. Poor prognosis is observed in COVID-19 patients with underlying co-morbidities and increased gut permeability and reduced gut microbiome diversity (Hu et al., 2020). Nutritional approaches for lowering the risk or alleviating the symptoms of COVID-19 have gained substantial attention. As a non-pharmacological complementary approach, dietary supplementation with nutraceuticals and probiotics is readily available with no or few side effects (Iddir et al., 2020, Infusino et al., 2020).

Dietary polyphenols are metabolized by intestinal and hepatic cells as well as colonic microbiota. The resulting metabolites may have an increased absorption rate than their parent compounds and exert beneficial effects in several organs. Thus, these microbial-derived metabolites have beneficial effects on the host. Furthermore, some of these phytochemicals can exhibit prebiotic effects, that can influence the gut microbiota and attenuate gastrointestinal complications reported in COVID-19 patients (Augusti et al., 2021). Such effects are attributed to improved intestinal homeostasis and immune responses as well as "reshaping" the gut microbiota (Maurer et al., 2019, Kawabata et al., 2019). These prebiotic-like effects are particularly relevant to SARS-CoV-2 therapy because COVID-19 patients displayed intestinal dysbiosis exemplified by a decrease in the diversity and abundance of gut microbiota (Gu et al., 2020, Zuo et al., 2020), which could present a potential target for the consumption of polyphenols. Supporting this hypothesis, a study in vervet monkeys suggest that fermented/traditional and unfermented/green Rooibos extracts and its major bio-active phenolic compound, aspalathin enhanced the relative abundance of beneficial butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Prevotella stercorea* and *Prevotella copri* (Mangwana, 2020).

The ACE2 receptors, which have been shown to mediate the entry of SARS-CoV-2 into cells (Shereen et al., 2020), are highly expressed in the gastrointestinal epithelial cells (An et al., 2021). The re-establishment of gut microbiota in gnotobiotic rats was shown to decrease colonic ACE2 expression compared to that in germ-free rats (Yang, Chakraborty et al., 2020), lending support that colonic expression of ACE2 is regulated by gut microbiota. Since Rooibos and its polyphenols increased the

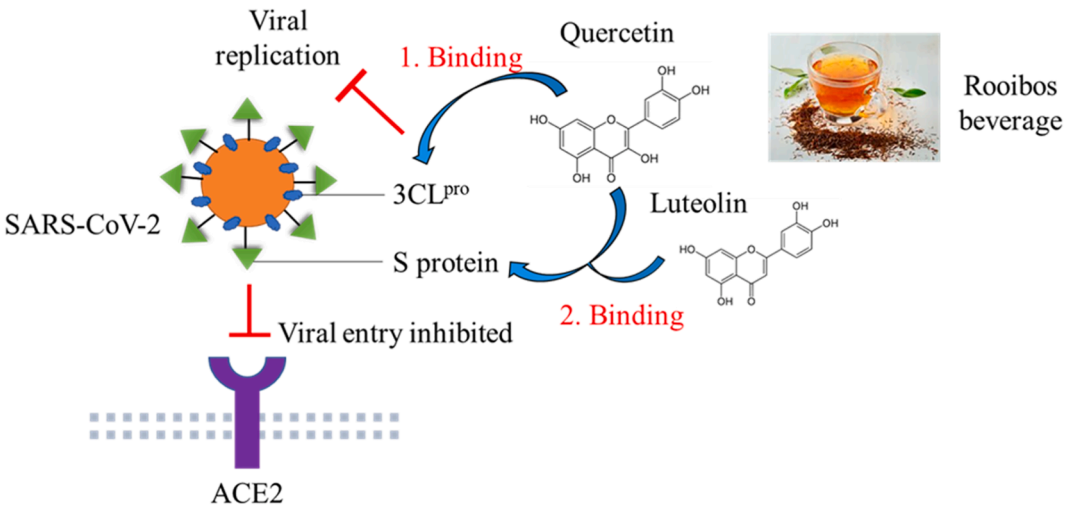

Fig. 3. Bioactive compounds present in Rooibos may (1) prevent viral replication by binding to a protease critical for the hydrolyses of viral polyproteins to produce functional proteins and/or 2) may also bind to the viral S protein inhibiting cell entry.

abundance and diversity of gut microbiota in favour of beneficial bacteria (Mangwana, 2020), reshaping of gut microbiota together with Rooibos' ability to inhibit this enzyme could modulate entry of SARS-CoV-2 into the host.

In addition, the reshaping of gut microbiota by Rooibos increases the production of short-chain fatty acids (SCFA), such as butyrate (Mangwana, 2020) which reduces pro-inflammatory cytokines while improving the systemic immune response after intestinal absorption (Koh et al., 2016). This mechanism will be of benefit as it may negate some of the effects associated with the "cytokine storm" in COVID-19 patients.

The phenolic compounds such as dihydro- chalcones, flavonols, flavanones, flavones, and flavanols present in Rooibos exert a myriad of biological activity (Breiter et al., 2011, Krafczyk et al., 2009, Krafczyk and Glomb, 2008). They require the gut microbiota to release the aglycone and enable colonic absorption (Amaretti et al., 2015). The role of the gut microbiota in the metabolism of aspalathin (the main and unique phenolic compound in green Rooibos) has not been fully characterised. However, data obtained from a complete crossover design human study with twelve healthy male volunteers indicates that the dihydrochalcone-, flavone-C-, and flavonol-O-glycosides contained in both the herbal tea and an isolated active fraction prepared from unfermented/green Rooibos, are bioavailable to a certain extent. Therefore, it is assumed that these flavonoids directly reach the large intestine. Consequently metabolism by intestinal bacteria, leads to low molecular weight ring fission products like phenolic acids (e.g. phloretic acid or 3,4-dihydroxyhydro-cinnamic acid (Breiter et al., 2011).

Other components of Rooibos have been better studied. In bioconversion experiments, the role of the gut microbiota and bifidobacteria in the release of the aglycones from two major rutinosides, hesperidin and rutin, was investigated. The microbiota removed rutinose from both rutin and hesperidin, however bioavailability was not determined in this study (Amaretti et al., 2015). A separate study revealed that the colonic microbiota break down rutin to liberate quercetin, some of which is absorbed via the colon and the remainder is bio-transformed into simpler phenolic acids (Parkar et al., 2013). Vitexin and isovitexin are flavonoids also found in Rooibos which are poorly absorbed in the gastrointestinal tract. They reach the colon where they are hydrolysed by the gut microbiome through deglycosylation and ring-opening of the heterocyclic C ring. It is probable that vitexin and isovitexin are degraded into small-molecule phenols and various aromatic acids such as phloretic acid (Zhang et al., 2007).

The interactions between polyphenols and the gut microbiome should be considered when assessing potential health benefits. From these studies it is plausible that the microbiota contributes to the release of the aglycone from Rooibos polyphenols, but it remains to be clarified which bacterial species may exert a role in affecting the biotransformation *in vivo*. Studies are also needed to clarify if such metabolites contribute to enhanced bioavailability.

8. Bioavailability and bioactivity of Rooibos

Evidence emerging from recent scientific endeavours supports the ability of Rooibos phytochemicals to modulate numerous cellular and molecular targets (Lawal et al., 2019, Dludla et al., 2017, Mazibuko-Mbeje et al., 2019), hence its potential as an early intervention or possible therapeutic option to several diseases including certain cancers, diabetes and cardiovascular disease (Sasaki et al., 2018, Marnewick et al., 2009, Joubert and de Beer, 2011; Marnewick et al., 2011). Human studies looking at the health benefits of Rooibos and the bioavailability of Rooibos phytochemicals are scarce but reports have concluded that bioavailability is sufficient to elicit beneficial responses in humans (Marnewick et al., 2011).

Bioavailability studies conducted with humans showed that Rooibos flavonoids have poor bioavailability and are absorbed to a very low extent following consumption of Rooibos herbal tea (Stalmach et al., 2009, Breiter et al., 2011). Most of the Rooibos metabolites are excreted in the urine of humans within 5 h of consuming 500 mL of a fermented Rooibos ready-to-drink beverage (Stalmach et al., 2009). Key reasons affecting the low plasma and tissue levels of Rooibos phytochemicals may be due to poor absorption, fast metabolism, and systemic elimination. Indirect evidence of their absorption through the gut barrier is the increase in the antioxidant capacity of plasma and/or the improved glutathione redox status after the consumption of aqueous Rooibos extracts by human volunteers (Breiter et al., 2011, Villaño et al., 2010; Marnewick et al., 2011), while direct evidence on the bioavailability of a few major phenolic compounds has been obtained by measuring their concentrations in plasma and urine after the ingestion of Rooibos herbal tea (Stalmach et al., 2009, Breiter et al., 2011). A human study with twelve healthy male volunteers found that on average a total of 0.76 nmol of flavonoids were detected during their peak concentration after intake of the Rooibos. Despite the comparable intake of total flavonoids, the quantified amounts were higher after administration of the Rooibos (0.76 nmol) compared to an isolated active fraction (0.41 nmol). The authors suggest that matrix and synergistic effects may be responsible for these results (Breiter et al., 2011) and supports the synergism of Rooibos polyphenolic constituents over Rooibos monomeric compounds.

The maintenance of a high concentration of Rooibos constituents in plasma was shown to be beneficial in a randomised, cross-over controlled clinical trial following a 12-week intervention study design. Marnewick and co-workers (2011) concluded that that consuming six cups of the fermented/traditional Rooibos daily for six weeks significantly improved the redox status and other biochemical parameters in adults at risk for developing cardiovascular disease with no adverse effects reported by study participants (Marnewick et al., 2011). This work suggests that the optimal benefit of Rooibos requires a repeated ingestion of the bio-active polyphenols over time. These results suggest that despite its poor bioavailability, Rooibos still displayed high functional bio-activity.

The dihydrochalcone-C-glucosides, aspalathin and nothofagin were identified to be the main phenolic compounds present in the aqueous extract prepared from unfermented/green Rooibos used to determine the bioavailability and metabolism of Rooibos flavonoids in healthy male volunteers and to identify the metabolites (Breiter et al., 2011). HPLC–MS/MS, revealed seven metabolites of aspalathin and nothofagin in the urine samples, as well as intact aspalathin and nothofagin. Moreover, glucuronidated, sulphated, methylated, both methylated and glucuronidated aspalathin, and glucuronidates of the aglycones of aspalathin and nothofagin were detected (Breiter et al., 2011). The authors of this work showed low bioavailability of free aspalathin in comparison to its metabolites, particularly methylated aspalathin. They suggested that methylation of aspalathin is a significant conjugation pathway. The authors concluded that in correlation to the very low bioavailability of flavonoids in plasma samples, the unique consumption of Rooibos formulations did not increase the antioxidant capacity of volunteer blood and that *ex vivo* antioxidant capacity may not be adequate as a sole parameter to assess the physiological activity of flavonoids and that *in vivo* study methods must be implemented to gain better insight into the efficacy of flavonoids (Breiter et al., 2011). This finding is in contrast with findings from Villaño and co-workers where consumption of an acute dose of either green or fermented Rooibos caused a significant increase in the plasma antioxidant capacity of the participants when using the FRAP assay, reaching a peak at 1 h post-consumption (Villaño et al., 2010).

9. Rooibos and possible drug interactions

As with most herbal preparations/extracts the likelihood of herb-drug interactions remains a concern (Williamson, 2003). Although two previous case reports showed the potential adverse effects on the liver by Rooibos, one in an individual diagnosed with a low-grade B-cell

malignancy, Waldenström's macroglobulinemia whom were also taking pharmaceutical drugs (Sinisalo et al., 2010), and another with a history of stage 3 chronic kidney disease whom consumed a mixture of Rooibos and another herbal, buchu (Engels et al., 2013), Rooibos is largely thought to be safe when consumed as a tisane (Marnewick et al., 2011) by apparently healthy individuals. In this study, an average increase in some of the hepatic enzymes associated with pathology were noted, but these may not be of clinical importance, as the values are still within the normal reference ranges, however this could indicate that some of the volunteers had uncharacteristic reactions to Rooibos (Marnewick et al., 2011).

Studies reporting on the metabolism of Rooibos and its polyphenols are in its infancy, but data does exist for its potential to affect drug metabolism via the inducible drug metabolizing cytochrome P450 (CYP) enzymes. These enzymes are primarily responsible for the metabolism of drugs and phytochemicals in organs such as the liver, kidney and intestines. Several conventional drugs are metabolized by specific enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) fitting into the subfamilies CYP1, CYP2, and CYP3 (Cupp and Tracy, 1998, Kong et al., 2011). Metformin, a first-line anti-diabetic drug, is metabolized by CYP2C11, CYP2D1, and CYP3A1/2, while glyburide and pioglitazone, other known hypoglycemic drugs, are metabolized by CYP2C9, CYP3A4, and CYP2C8. Atorvastatin used to treat hypercholesterolemia is metabolized by CYP3A4. Inhibition of these specific CYPs by phytochemicals can affect the pharmacodynamics of these drugs, leading to toxicity or, alternatively, reduced efficacy (Ogu and Maxa, 2000, Sprouse and van Breemen, 2016). When drugs and phytochemicals compete for the same receptor site, it can alter the pharmacodynamic properties of those drugs and phytochemicals. The reasons being that the more potent CYP inhibitor will exert control over the weaker inhibitor, thus resulting in decreased metabolism of the respective substrate (Ogu and Maxa, 2000).

The functional groups and chemical structure of polyphenols play an important role in their metabolism. Most xenobiotics including dietary polyphenols can bind to CYP3A4 as substrates. Flavonoids, common in the diet, are responsible for the modulation of the clinically relevant CYP2C8, CYP2C9, and CYP3A4 enzymes (Basheer and Kerem, 2015). This variation can alter drug metabolism through fluctuations in CYP enzymes expression or activity, thus altering the plasma concentration of co-administered chronic medications. Patel et al. (2016) investigated the effects of fermented and unfermented Rooibos extracts, and two of the major bioactive compounds, Z-2-(β-d-glucopyranosyloxy)-3-phenylpropenoic acid and aspalathin, on recombinant CYP450 enzymes. Both the unfermented and fermented Rooibos extracts inhibited the activity of CYP2C8 and CYP3A4. Both extracts dose- and time-dependently inhibited CYP2C8 activity, but only time-dependently inhibited CYP2C9. CYP3A4 showed concentration-dependent inhibition by aspalathin, fermented and unfermented Rooibos. These findings suggest that Rooibos-drug interactions may arise when extracts are co-administered with hypoglycemic drugs such as thiazolidinediones, sulfonylureas, and the dyslipidemic drug, atorvastatin (Patel et al., 2016). However, it is important to note that very high concentrations of polyphenolic compounds, ranging from 30 to 400 μM were used in these experiments, not easily achieved in humans when consuming it as a "cup-of-tea" (Fantoukh et al., 2019, Patel et al., 2016).

While this review has motivated largely for the beneficial effects of Rooibos, it is plausible that pharmacokinetic interactions may occur when co-consumed with COVID-19 and comorbidity treatment drugs. The combination of an aspalathin-rich green Rooibos extract with pioglitazone and atorvastatin was shown to significantly improve glycemia, and subsequently improve hepatic steatosis in an obese diabetic mouse model. However, despite these improvements, increased expression of genes involved in lipogenesis, cholesterol, and fatty acid transport, β-oxidation, and synthesis and storage of fatty acids, may exacerbate the hepatotoxic effects of atorvastatin (Patel et al., 2021). The affiliated use of herbal and conventional drugs heightens the possibility of clinically significant herb-drug interactions (HDIs). It was shown that the number of HDI reports has gradually increased since 2000, with a primary focus on tumorigenesis and diseases of the circulatory system. Most of these investigated pharmacokinetic reactions, with fewer reports investigating pharmacodynamics (Choi et al., 2016). Therfore to improve the safety of herbal drug practice the probability for HDI should be determined in the pre-clinical safety assessment phase of the drug development process. An increase in clinically relevant research is paramount as the present information on HDI is insufficient for clinical applications (Ghosh et al., 2018).

When considering the experimental data related to potential side-effects, the intricacy of the topic and the need for individualized characterization in this context becomes apparent. However, it is possible that Rooibos may recompense due to its specific beneficial bioactivities based on *in vivo* studies (Kawano et al., 2009, Ayeleso et al., 2014) and clinical trials (Marnewick et al., 2011, Persson et al., 2010). Rooibos was shown not to compromise the organism's ability to respond to disease conditions and suggests Rooibos to be a potential low-risk, dietary supplementation, and supportive strategy for everyone during this pandemic and perhaps more so for those with identified comorbidities. It is recommended for people taking therapeutic drugs to err on the side of caution when considering adding any herbal and/or medicinal plant components to their daily regime and to disclose it to their physician. Future investigations into pharmacokinetic interactions would be beneficial to further test the scientific support for advocating Rooibos consumption as a beneficial aid in the COVID-19 pandemic.

10. Role of natural beverages in the fight against COVID-19

Beverages prepared from different parts of plants (seeds, leaves, stems etc.) are becoming increasingly popular amongst health conscious consumers (Chandrasekara and Shahidi, 2018). Commonly and globally consumed beverages such as teas and coffee are being hypothesised as possible interventions for the current COVID-19 pandemic (Chowdhury and Barooah, 2020, Semiz and Serdarevic, 2020). The polyphenols present in these naturally occurring beverages are renowned for their health benefits in metabolic and cardiovascular diseases (Reis et al., 2019, Wolfram, 2007) which are often observed as co-morbidities in COVID-19 patients. Evaluation of green tea polyphenols using *in silico* approaches show its direct inhibitory effect on SARS-CoV-2 virus by binding to the S protein (Ghosh et al., 2020). To date no dependable plant-based clinical trial has been conducted on COVID-19.

This article presents a strong case for the inclusion of Rooibos herbal tea as part of a daily health regime to support in the management of COVID-19 and adds to the growing body of literature supporting the use of polyphenolic-rich beverages in the current pandemic.

11. Consequences and conclusion

Oxidative stress is causally involved in the development of some chronic diseases (CVD and diabetes) and inflammatory responses, that increase the risk of a severe outcome from COVID-19. Rooibos and its phytochemical constituents are increasingly under scientific inquiry for their potential beneficial effects on health. These beneficial effects are, in part related to the potent antioxidant and redox modulatory potential, underscoring the preventative and protective roles against poor health and disease. Specific effects relating to metabolic diseases include protection against oxidative distress and inflammation as well as maintaining glucose homeostasis.

The bioactivity of Rooibos is multi-faceted with numerous beneficial targets. Several lines of scientific evidence as discussed in this article, suggest Rooibos to be of considerable benefit as a supportive approach in the current pandemic. Rooibos has a low toxicity profile and although the direct evidence for a Rooibos application in COVID-19 is currently unclear, numerous animal models and increasing human studies have documented its efficacy and safety in several relevant chronic non-

communicable diseases, such as CVD and diabetes, oxidative distress, and inflammation as a support for general health and well-being. Its use during this pandemic by those with and without co-morbidities, as part of their daily health regime, could be highly beneficial. However, further clinical studies are required to validate this hypothesis.

Considering all the empirical evidence, it is rational to employ Rooibos as a support of general health during the COVID-19 pandemic. Studies suggest that it has potent antioxidant, antiviral and immunomodulating effects, which enhances the body's natural defence system. However, it must be noted that Rooibos is not a drug or substitute for clinical treatment of COVID-19. To validate the clinical relevance of Rooibos selection, additional studies are needed to evaluate its use treating not only COVID-19 but also the common cold and other respiratory disorders.

12. Ethics statement

This paper does not conduct research on humans or animals.

CRediT authorship contribution statement

Naeem Sheik Abdul: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jeanine L. Marnewick:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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