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HEALTH SCIENCES

Protein-coding gene interaction network prediction of bioactive plant compound action against SARS-CoV-2: a novel hypothesis using bioinformatics analysis

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Abstract: This study aimed to verify the action of bioactive compounds from Brazilian plants on the leader genes involved in the SARS-CoV-2 pathway. The main human genes involved were identified in GeneCards and UNIPROT platforms, and an interaction network between leader genes was established in the STRING database. To design chemo-biology interactome networks and elucidate the interplay between genes related to the disease and bioactive plant compounds, the metasearch engine STITCH 3.1 was used. The analysis revealed that SMAD3 and CASP3 genes are leader genes, suggesting that the mechanism of action of the virus on host cells is associated with the molecular effects of these genes. Furthermore, the bioactive plant compounds, such as ascorbate, benzoquinone, ellagic acid, and resveratrol was identified as a promising adjuvant for the treatment inhibiting CASP3-mediated apoptosis. Bioactive plant compounds were verified as the main pathways enriched with KEGG and related to viral infection, assessments/immune/infections, and cell proliferation, which are potentially used for respiratory viral infections. The best-ranked molecule docked in the CASP3 binding site was rutin, while the SMAD3 binding site was resveratrol. In conclusion, this work identified several bioactive compounds from Brazilian plants showing potential antiviral functions that can directly or indirectly inhibit the new coronavirus.

Key words: CASP-3, cerrado plant, coronavirus, COVID-19, medicinal plant, SMAD.

INTRODUCTION

On November 3, 2020, the World Health Organization declared the spread of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic, representing a high risk for countries with vulnerable health systems (Sohrabi et al. 2020). Given the continued lack of effective drugs or vaccines against SARS-CoV-2, the scientific community and general population have begun to search for both prevention and treatment alternatives, including the use of medicinal plants. Although phytotherapeutic medicines can be beneficial, they should be used with caution until consistent studies can confirm their effectiveness. In addition, the critical nature of the COVID-19 pandemic requires new research strategies that go beyond conventional antiviral treatments (Zhang et al. 2020a, Ling 2020, Luo et al. 2020, Xu et al. 2020a).

Historically, herbal medicines have played an essential role in the prevention and control of various diseases, including providing alternative treatments for the prevention and management of new acute respiratory tract infections (Luo et al. 2020, Ren et al. 2020a). Medicinal plant extracts have been found to exert antiviral properties in animal models and *in vitro* studies, especially against the H1N1, H3N1, and H5N1 viruses, through potent action in the early stages of viral replication (Rajasekaran et al. 2013, Sornpet et al. 2017). Phytotherapy is considered to be an alternative or complementary approach, mainly because its biochemical active components and action mechanisms have not been completely characterized (Kumar et al. 2020). In some countries, the integration of herbal and allopathic medicines has been used as a dominant treatment strategy in areas affected by new serious infectious diseases (Kohn et al. 2015, Dhama et al. 2018, Wang et al. 2020).

Despite technological advances in drug research, many challenges remain in the identification of potential therapeutic substances derived from plants, such as understanding molecular targets and biological effects (Barabási & Oltvai 2004, Marinho et al. 2020). Prior to pre-clinical assays, drug–protein interaction networks and molecular docking served as important bioinformatics tools for initial studies investigating the possible targets and molecular pathways of new drugs (Kumar et al. 2020, Marinho et al. 2020). Computational screening for potential drug candidates against the main SARS-CoV-2 protease revealed 40 pharmacophore-like structures of natural compounds from diverse chemical classes that exhibited better docking affinities compared to the known ligands (Andrade et al. 2020).

The application of a bioinformatics approach to health research studies has made a large amount of data available, including human genome data, the molecular structures of drugs, in silico simulations of drug interactions, drug targets, and biological mechanisms. This method demands the integration of data from various fields both within and outside of biology (Spirin & Mirny 2003). Several bioinformatics tools allow us to incorporate genomic data from different sources into biological interaction networks, including protein–protein interaction networks (PPINs), metabolic, signaling, and transcriptional regulation, and chemical–protein interaction networks (CPINs) (Rosvall & Sneppen 2003, Siegal et al. 2007).

Based on these bioinformatics applications and the emerging need to identify potential antiviral substances to mitigate SARS-CoV-2 infection, we conducted an in silico study using a molecular interaction network to investigate the bioactive compounds derived from Brazilian plants, their biological processes, target human genes, and likely routes of action to combat SARS-CoV-2.

MATERIALS AND METHODS

To survey the main human genes involved in the occurrence of COVID-19, we performed a preliminary study using the GeneCards (www.genecards.org) and UNIPROT (https://covid-19.uniprot.org/) platforms. To identify the human genes related to SARS-CoV-2 through GeneCards, descriptors “spike” and “new coronavirus” were used.

Next, we utilized the Search Tool for the Retrieval of Interacting Genes (STRING) database as a reference for this work (http://version10.stringdb.org/). The goal of STRING is to organize and make PPIN data available, including direct (physical) and indirect (functional) associations (Szklarczyk et al. 2019). The STRING input information was collected from the GeneCards and UNIPROT platforms.

In the STRING database, we assigned confidence scores greater than 0.900 for each interaction network. The selected sources of data were as follows: genomic neighborhood (neighborhood), gene fusion (fusion), co-occurrence between species (co-occurrence), co-expression in the same or other species (co-expression), experimental data (experimental), databases (database), and data mining in the literature (text mining). In the final configuration of STRING, we used the maximum number of interactors to show no more than 50 interactors for the first and second shells. In the network analyses, we also used a combined score (combined_score), which was the result of weighting between the values assigned to each source.

From the STRING-generated interaction network of genes related to COVID-19, we calculated the leader genes, which are genes that presented the highest weighted number of links (WNL). The number of edges (metabolic relationships between proteins) associated with a node (protein) determines its degree. Thus, the greater the number of node edges, the greater its degree (Barabasi & Oltvai 2004).

Leader proteins or genes are good targets for molecular interventions, especially when associated with important metabolic pathways, since their inactivation can disrupt much of the surrounding network, thereby interfering with metabolic functions. As the nodes of the interaction network tend to establish groupings, we clustered the proteins according to the highest WNL (leader gene clusters). In biological networks, it is common to have functional groupings that are represented as groups in the network (Barabasi & Oltvai 2004). For this process, we used k-means clustering, followed by one-way analysis of variance (ANOVA) ($P < 0.001$).

Next, using the STITCH platform, we set up an interaction network between the leader genes related to COVID-19 and bioactive chemical compounds from Brazilian plants. This tool (http://stitch.embl.de/) allowed for the visualization of the physical connections among different proteins and chemical compounds. Each protein–chemical connection (edge) showed a degree of confidence between 0 and 1.0 (1.0 indicates the highest confidence). The parameters used in the STITCH program were as follows: all prediction methods enabled, no more than 10 interactions, a medium degree of confidence (0.400), and a network depth equal to 1. The input information for STITCH included the leader genes obtained from STRING and a list of bioactive components from Brazilian plants. We selected approximately 210 substances from a bibliographic survey of recognized medicinal use plants by the Brazilian Cerrado and used them to screen for molecules bind to proteins codded by the leader genes through computational resources against human genes and proteins involved with structure and pathogenesis of SARS-CoV-2.

To identify PPINs and CPINs, we entered each bioactive plant compound into the STITCH platform. Bioactive plant compounds that were not present in STITCH or those that did not show any protein connections were excluded from the analysis.

In addition to performing CPIN analysis, STITCH was used to predict pathway enrichment. The enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways ($P < 0.01$), Gene Ontology (GO) analyses in three categories (biological process, molecular function, and cellular component), PFAM protein domains, and INTERPRO protein domains were downloaded.

GOLD 2020 (Jones et al. 1997) was used to calculate the flexible docking between CASP3 (PDBid: 3H0E), SMAD3 (PDBid: 5XOC), and

selected ligands using the very flexible search parameter. The natural ligand structures were obtained from the ZINC15 (Sterling & Irwin 2015) and PubChem (Kim et al. 2021) repositories.

The GOLD program uses a genetic algorithm that propagates multiple copies of flexible ligand models at the active site of the receptor. The CASP3 binding site was defined by the position of a known inhibitor bound to the binding site cysteine (Havran et al. 2009). The SMAD3 binding site was defined by the most probable pocket using DeepSite (Jiménez et al. 2017). All selected ligands were submitted to 10 iterations in the binding site using a genetic algorithm. The resulting interaction energies between ligands and receptors were represented by the ChemPLP score that was used to rank the molecule poses.

RESULTS AND DISCUSSION

The initial analysis of the interaction network between human genes linked to COVID-19 showed a list of 17 candidate genes and 109 genes after expanding the network, as represented in the interactome map in Figure 1. In this network, caspase 3 (CASP3) and mothers against

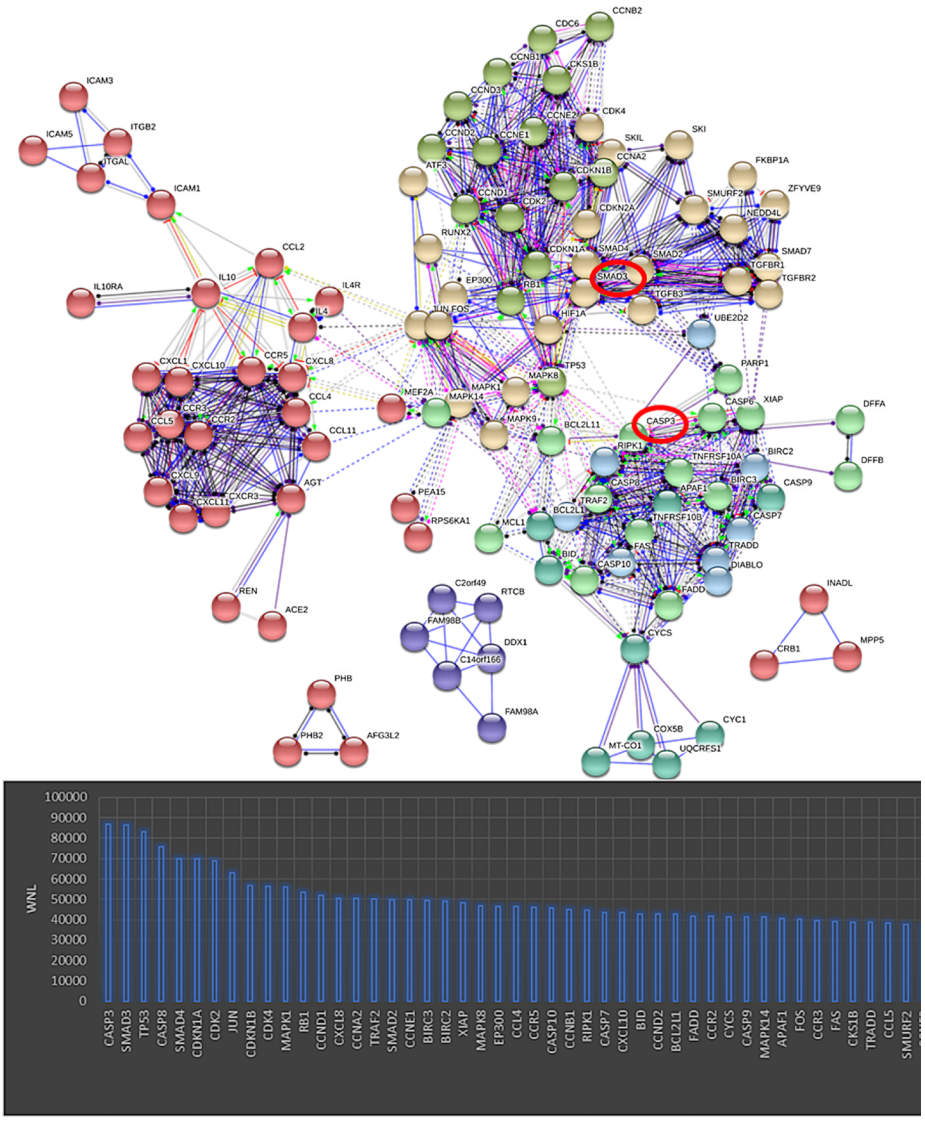


Figure 1. Leader genes in the protein interaction network between genes related to the SARS-CoV-2 infection. (a) protein interaction network with the leader genes circulated in red. (b) The graph representing the distribution of genes according to the WNL (Weighted Number of Links).

decapentaplegic homolog 3 (SMAD3) genes were identified as leader genes due to a large number of connections and shorter distances between nodes (Spirin & Mirny 2003, Barabási & Oltvai 2004). These nodes represent the control points of the network (Rosvall & Sneppen 2003, Barabási & Oltvai 2004). Evolutionarily older proteins have more connections than recent proteins (Barabási & Oltvai 2004). This empirical discovery demonstrates a preference for forming new connections with evolutionarily old proteins (Barabási & Oltvai 2004), emphasizing that nodes with a greater number of connections may play important biochemical functions in cells (Siegal et al. 2007).

In an interaction network, clusters are groups of molecules (nodes) that work together to perform a biological function; in other words, they represent common biological processes (Barabási & Oltvai 2004). The leader genes connect with two motifs or clusters. Thus, these genes command two distinct groups of protein-coding genes to develop a specific action. In this study, the CASP3 and SMAD3 leader genes were identified to predict the SARS-CoV-2 mechanism of action in host cells.

COVID-19 is an infectious disease that is transmissible and potentially fatal. The exact mechanism whereby SARS-CoV-2 proteins induce apoptosis must be identified in order for targeted drugs to be developed (Ye et al. 2008). The results of this study suggest that the mechanism of action of the virus on host cells occurs via CASP3 and SMAD3.

CASP3 is part of the group of caspases that perform cell death signaling (Green & Llambi 2015). Among several functions, they are associated with the inhibition of type I interferon (IFN-I) production and apoptosis (Selvam et al. 2018, Ning et al. 2019, Gu et al. 2020).

Recent studies in mouse models have shown that the pathogenesis of SARS-CoV-2 is caused by high initial virus titers, resulting from a late response to IFN-I, which leads to recruitment of monocyte–macrophage inflammatory processes (MMIs) in the lungs, as well as the activation of the innate immune system response (Mckechnie & Blish 2020) resulting in cytotoxicity (Channappanavar et al. 2016).

In addition to activating the intracellular defense of pathogens, IFN-I acts on the development of innate and adaptive immunity (Deng et al. 2020). The induction of IFN-I production is associated with the production of double-stranded RNA inside the cell during viral replication. The degradation of messenger RNAs (mRNAs) and the inhibition of translation are the main antiviral effects of IFN-I, which consequently inhibits protein synthesis in the target cell, making it an inappropriate medium for viral replication (Liu et al. 2014, Barber 2015, Motwani et al. 2019, Sun et al. 2020).

The above process may be associated with the pathogenesis of SARS-CoV-2 and other betacoronaviruses, which use strategies to deregulate IFN-I-dependent immunity in the pathogens causing so-called cytokine storms (Acharya et al. 2020, Vabret et al. 2020). The deregulation of the IFN-I response suggests it plays a critical role in the pathogenicity of SARS-CoV-2 (Vabret et al. 2020). SARS-CoV open reading frames (ORFs) are accessory proteins related to innate immunity that limit interferon production mediated by ORF3 (Shi et al. 2019). The kinetics of systemic and local responses to IFN-I that occur during COVID-19, as well as their respective contributions to the pathogenesis and severity of COVID-19, remain unclear.

Experimental models have demonstrated that IFN-I is protective at the beginning of the disease but can subsequently participate in the pathological process (Channappanavar et al. 2016, 2019). Other events, such as the IFN-I-induced positive regulation of angiotensin-converting

enzyme 2 (ACE2) in the airway epithelium, may contribute to this effect (Ziegler et al. 2020). The production of interleukin 6 (IL-6) and IL-8 (Magro 2020) and other evasion mechanisms with viral factors antagonizing each step of the pathway, including PRR detection, cytokine secretion, and IFN-I signal transduction, are involved in a series of pathological changes in COVID-19 (Vabret et al. 2020).

Corroborating the action of IFN-I in disease pathology, a reduction in the multiplication rate of SARS-CoV-2 has been observed in cells infected experimentally and treated with IFN-I (Blanco Melo et al. 2020, Lokugamage et al. 2020), indicating the possibility of using IFN-I for therapeutic purposes (Vabret et al. 2020). It is likely that proteins from the IFN-induced transmembrane family (IFITM) inhibit the entry of SARS-CoV-2, as has been previously demonstrated for SARS-CoV-1 (Huang et al. 2011).

Apoptosis is a physiological mechanism that controls cell numbers during development and infection, including bacterial and viral infections (Wang 2001). Viruses have evolved strategies to either inhibit or stimulate host cell apoptosis depending on particular virus–host interactions. Many viruses encode either pro-apoptotic or anti-apoptotic proteins, which can specifically inhibit or delay apoptotic pathways, resulting in increased virus production. Apoptosis in the later stages of infection may also be advantageous in facilitating virus dissemination and limiting the host's inflammatory response (Zhou et al. 2017).

In coronavirus infections, apoptosis can occur in various host tissues, including lymphoid tissue, cardiac cells, alveolar epithelium, intestinal mucosa, kidney tubular cells, and nerve cells (Ye et al. 2008, Lim et al. 2016, Fung & Liu 2019, Centurión et al. 2020, Nani & Nima 2020, Chan et al. 2020, Huang et al. 2020a, Xu et al. 2020b, Fathi & Rezaei 2020). One of the ways of inducing apoptosis by SARS-CoV-2 is through the action of the viral protein ORFs that serve as both apoptosis and caspase activators in this pathology (Tsoi et al. 2014, Huang et al. 2020b). A previous study hypothesized that more investigations of ORF3a will help to shed light on the pathogenicity of SARS-CoV-2, as CASP3 was significantly elevated in the presence of ORF3a (Ren et al. 2020b). Furthermore, several cellular mechanisms and gene products, such as the SARS-CoV M and N proteins (Zhao et al. 2006, Tsoi et al. 2014), 3C-like protease (3CLpro) (Lin et al. 2006), and S1 protein, are capable of inducing apoptosis (Chen et al. 2018a) and play an important role in virus dissemination.

Although the pathogenesis of COVID-19 is not yet fully understood, we can utilize existing data on infections by other coronaviruses to interpret the hypotheses raised in the present study. Coronaviruses can infect a wide range of mammals and birds, but exhibit a marked tropism for epithelial cells of the respiratory and enteric tracts, as well as for macrophages (Reguera et al. 2014, Lee 2015), and most are capable of inducing apoptosis in infected host cells.

The cytoplasmic proteins of the SMAD family comprise a group of transforming growth factor beta (TGF-β) ligands and essentially act as transcription factors to activate or repress target genes (Hill 2016). SMAD3 also acts as an interferon regulator (Tamiya et al. 2013). SARS-CoV-infected patients display high levels of TGF-β (Morikawa et al. 2016), which may be related to the pathogenesis of betacoronavirus infections (Mo et al. 2020).

TGF-β/SMAD signaling plays a critical role in a variety of biological processes, including embryogenesis, homeostasis, disease pathogenesis, proliferation, apoptosis, migration, adhesion, extracellular matrix protein production, cytoskeletal organization, and performance in the immune system (Morikawa et

al. 2016, Oshima et al. 2019, Tzavlaki & Moustakas 2020). TGF-β is a cytokine involved in suppressive and inflammatory immune responses that act in the processes of innate and acquired immunity (Sanjabi et al. 2017). In addition, it operates in the presence of pro-inflammatory cytokines, such as IL-6 (Favell et al. 2010, Morikawa et al. 2016), which is produced in the early stages of nonspecific immunity (Baek et al. 2020) and is one of the main cytokines in the pathogenesis of SARS-CoV-2 (Zhang et al. 2020b). These findings may be related to the exacerbated production of cytokines described in SARS-CoV-2 infections (Chang et al. 2020).

SMAD3 participates in the regulation of sensitivity to apoptosis induced by TGF-β and is indispensable for the maintenance of vascular integrity (Itoh et al. 2012), which may also be associated with the "cytokine storms" observed in COVID-19 patients (Chang et al. 2020). The deregulation of the TGF-β/SMAD pathway regulated by SMAD2 and SMAD3 is responsible for tissue fibrosis (Hu et al. 2018). The presence of pulmonary fibrosis in COVID-19 (Morikawa et al. 2016, Liu et al. 2019, Sheng et al. 2019, Mo et al. 2020) may be due to the excessive activation of TGF-β production by viral infection and constitutes one of several serious complications in patients infected with SARS-CoV-2 (Sun et al. 2020).

Thrombocytopenia in COVID-19 may be associated with other pathological processes in addition to the action of TGF-β (Xu et al. 2020b, Zulfiqar et al. 2020, Menter et al. 2020, Fox et al. 2020), such as low levels of low IFN-α, which is also responsible for suppressing the expression of transcription factors that regulate megakaryopoiesis, thereby inhibiting megakaryocyte maturation (Zhang et al. 2020c). Following the effects of TGF-β and IFN-α on the population of megakaryocytes, the defense and maintenance of vascular integrity exercised by blood platelets is also affected (Rayes et al. 2019, Ribes et al. 2020), compromising hemostasis and plasma coagulation, and protecting the pulmonary alveoli epithelium (Washington et al. 2020).

The deregulation of the TGF-β/SMAD pathway is responsible for tissue fibrosis, the regulators of which are SMAD2 and SMAD3 (Hu et al. 2018). Pulmonary fibrosis observed in COVID-19 patients (Morikawa et al. 2016, Liu et al. 2019, Sheng et al. 2019, Mo et al. 2020) may occur due to the excessive activation of TGF-β production by viral infection and is a serious complication of the disease (Sun et al. 2020). As a result, therapies aimed at inhibiting the fibrogenic effect of TGF-β are needed (Luo et al. 2014).

Given that this study aimed to investigate a possible activity of bioactive chemical compounds isolated from Brazilian plants for targeting genes involved in SARS-CoV-2 infection, we first performed a literature search of the main chemical compounds isolated from these plants. Then, using the STITCH platform, we constructed an interaction network between these compounds and the identified leader genes related to COVID-19. Figure 2 shows the potential interactions between the selected bioactive compounds and the leader genes CASP3 and SMAD3. Resveratrol had the highest combined score. However, as shown in Table I, ascorbate was the only component found to exert an inhibitory effect and negatively regulate CASP3. This effect may be the most appropriate since the virus promotes cell apoptosis via CASP3, among other mechanisms. Despite the consistency of resveratrol, this compound had inhibitory, activating, downregulating, and upregulating effects.

An *in vitro* study showed that SARS-CoV was able to induce apoptosis in Vero cells from the kidney in a virus replication-dependent

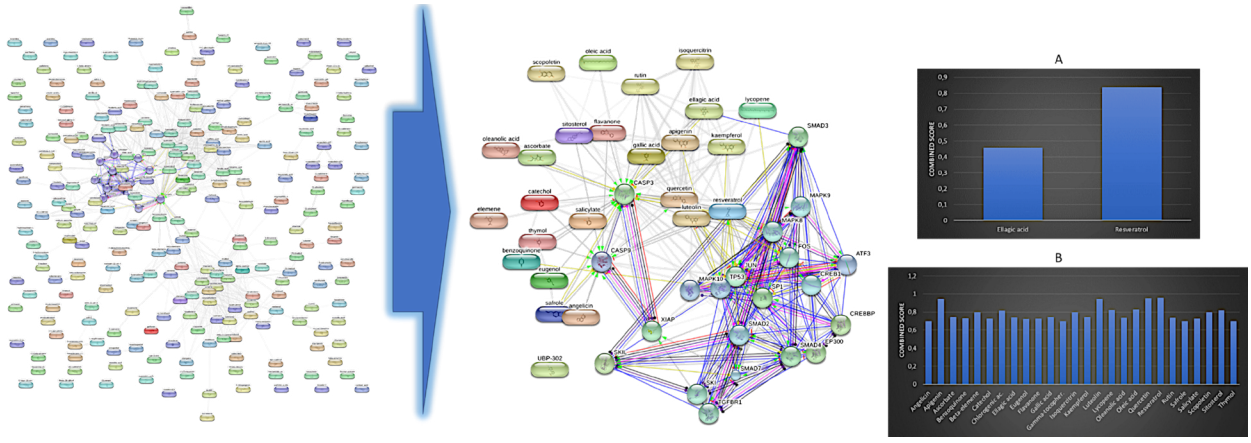


Figure 2. Chemical-protein interaction network, showing the possibilities of interactions between bioactive chemical compounds from Brazilian plants and the CASP3 and SMAD3 leader genes. The network was expanded to show the leader genes and their interactions with bioactive plant compounds. Graphs a and b show the combined scores of the bonds of the chemical compoundswi th the SMAD3 and CASP3 genes, respectively.

manner. Additionally, B-cell lymphoma 2 (Bcl-2) down regulation, CASP3 activation, and Bax upregulation were identified as molecular changes promoted by the virus. These preliminary data provide important information about both the pathogenesis and potential antiviral targets of SARS-CoV-2 (Ren et al. 2005). In this sense, our in silico analysis revealed that ascorbate and other bioactive plant compounds may serve as potential chemical substances for inhibiting CASP3 expression. It is believed that the modulation of apoptosis is relevant to diseases caused by various viruses. As presented in Table I, in addition to resveratrol, the compounds ascorbate, benzoquinone, and ellagic acid can perform this function.

Ascorbic acid (vitamin C) is a potent antioxidant, the properties of which have been proposed to prevent and mitigate the effects of COVID-19 in infected patients (Wimalawansa 2020). It is also associated with immune health (Carr & Maggini 2017), antimicrobial activities (Mousavi et al. 2019, Colunga et al. 2020), and antiviral action (Kim et al. 2013). Furthermore, ascorbic acid has been shown to inhibit CASP3 activation, cleavage, and apoptotic gene expression (Abu Zeid et al. 2018). In addition to its effects on CASP3, ascorbic acid protects cell DNA from attack by generated reactive oxygen species, decreasing the effects on host tissues (Park et al. 2018). Our in silico results suggest that ascorbic acid may be a potential therapeutic agent for combating SARS-CoV-2 by inhibiting the CASP3-mediated apoptosis of host cells.

It can also increase the expression of mitochondrial antiviral signaling (MAV) genes in SARS-CoV infections, which play an important role in inducing IFN production in the innate immune response (Shi et al. 2014), as well as in H1N1 and H3N2 influenza virus infections (Cai et al. 2015, Kim et al. 2013), indicating its pharmacological potential (Carr 2020, Hernández et al. 2020) as a supplement for the treatment of viral infections.

Benzoquinone also has an inhibitory effect on apoptosis in cancer cells by acting on pro-apoptotic proteins (Radhakrishnan et al. 2011). Recent studies have demonstrated that quinone molecules inhibit the effect of the 3CLpro protease in SARS-CoV, which is responsible for proteolytic processes in functional proteins essential for viral replication (Ryu et al. 2010, Park et al. 2016). However, its specific effects on CASP3, as well as the apoptosis and inhibition

Table I. Effects of bioactive compounds from Brazilian plants on the CASP3 and SMAD3 target proteins.

TARGET PROTEIN: CASP3							
Bioactive compounds	**Action/effects**			**Action/Types**			
	Upregulation	**Downregulation**	**Unspecified**	**Activation**	**Inhibition**	**Transcriptional regulation**	**Binding**
Angelicin	x			x			
Apigenin	x			x			
Ascorbic acid		x			x		
Benzoquinone	x	x		x	x		
β-elemene			x				
Catechol	x			x			
Ellagic acid	x	x	x	x	x	x	
Eugenol	x			x			
Flavanone	x			x			
Gallic acid	x		x	x		x	
γ-tocopherol							
Isoquercitrin			x				
Kaempferol			x				
Luteolin	x			x			
Lycopene			x				
Oleanolic acid	x		x	x		x	
Oleic acid			x				
Quercetin	x		x	x		x	
Resveratrol	x	x	x	x	x	x	
Rutin	x			x			
Safrole	x		x	x		x	
Salicylate	x			x			
Scopoletin			x				
Sitosterol	x			x			
Thymol	x			x			
TARGET PROTEIN: SMAD3							
Ellagic acid							x
Resveratrol			x			x	

of the INF-I pathways, were not found in the literature.

Ellagic acid has anti-inflammatory and anti-apoptotic effects in several cell types (Chen et al. 2018b). In the immune system, ellagic acid acts in the regulation of pro-inflammatory and anti-inflammatory cytokines (Allam et al. 2016, Ben Saad et al. 2017), in addition to immunomodulatory action (Jantan et al. 2019), showing promising results against influenza viruses (Tran et al. 2017, Choi et al. 2018). Similarly, previous studies have revealed that an ellagic acid-derived colonic metabolite induced cytotoxicity in HepG2.2.15 cells, which was accompanied by CASP3 protein cleavage and the down regulation of the Bcl-2/Bax ratio (Qiu et al. 2018). This compound was able to significantly prevent OS, mitochondrial dysfunction, apoptosis, and inflammation

induced by methotrexate (Ebrahimi et al. 2019). Ellagic acid also curbed redox alterations by lowering the production of lipid peroxides and nitric oxide, as well as countering the elevation of antioxidant-reduced glutathione. In support of cell survival, ellagic acid inhibits testicular apoptosis by downregulating CASP3 protein expression (Arab et al. 2019).

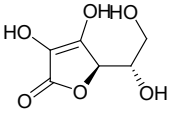
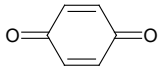
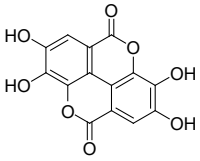
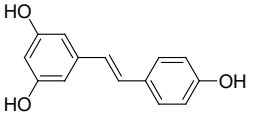
Polyphenol resveratrol is a potent antioxidant that has shown antiviral activity against several viruses (Marinella 2020), including MERS-CoV, wherein it experimentally inhibits MERS-CoV infection by acting on different pathways, such as protein N expression, as well as inhibiting CASP3 cleavage, thereby reducing the apoptosis characteristic of this infection (Lin et al. 2017). Resveratrol modulates the expression of TGF-β1, controlling growth or discontinuing scarring to significantly elevate the expression of TGF-β2 growth inhibitor mRNA with no changes in the expression levels of TGF-β1 and TGF-β3. These data suggest that resveratrol inhibits proliferation by altering growth modulating pathways (Lin et al. 2011, Wang et al. 2013, Sun et al. 2019). The role of resveratrol in modulating the TGF-β/SMAD pathway has been described in different cells (Huang et al. 2014, Chen et al. 2015, 2016), thus highlighting its potential to act on the pulmonary fibrosis observed in COVID-19.

A high intake of resveratrol may have a protective role, thereby upregulating ACE2, whereas a high intake of dietary fat may have a detrimental role, downregulating ACE2. As such, the biological plausibility of interactions between dietary fat and/or resveratrol and ACE2 gene variations in the modulation of SARS-CoV-2 illness severity has been examined (Horne & Vohl 2020). Resveratrol and quercetin were found to reduce viral propagation and/or counteract the effects of neuronal infection in an analysis of progeny virion production, neuronal viability, and neurodegenerative events during herpes simplex virus 1 (HSV-1) infection. In addition, the activators of the AMPK/Sirt1 axis were found to increase the viability of infected neurons, significantly reduce the supernatant viral titer, and regulate the expression levels of viral genes. More importantly, the pretreatment of neurons with resveratrol or quercetin significantly reduced the levels of cleaved and hyperphosphorylated CASP3 associated with HSV-1 infection (Leyton et al. 2015). Additional information on the aforementioned four compounds can be found in Table II.

Caspase inhibition as a treatment for excessive apoptosis, such as in neurodegeneration, appears to be easier with the use of classical small-molecule inhibitors. Preliminary experiments in animal models using non-selective caspase inhibitors, such as z-VAD (OMe)-CH2F, have shown *in vivo* efficacy in ischemic and hypoxic brain injury, as well as traumatic and excitotoxic brain damage. The same approach may be applied to SARS-CoV-infected cells to identify them for therapy (Endres et al. 1998, Holly et al. 1999, Schierle et al. 1999), given that two SARS-CoV proteins, ORF-6 and ORF-7a, seem to activate pro-apoptotic pathways via the CASP3-dependent pathway (Ye et al. 2008). In this context, it has been suggested that bioactive plant compounds, such as ascorbate, benzoquinone, ellagic acid, and resveratrol, can be used in the adjuvant treatment of COVID-19 by inhibiting CASP3-mediated apoptosis (Figure 3).

Furthermore, it is understood that apoptosis represents the host's defense against viral infection because the death of the infected cell prevents the spread of the virus. During viral infection, the main death mechanism for cells infected by viruses is mediated by cytotoxic T lymphocytes and natural killer cells (Danthi 2016). To ensure the success of this function, since many viruses develop anti-apoptotic

Table II. Additional information about Ascorbic acid, Benzoquinone, Ellagic acid and Resveratrol.

	Ascorbic acid	Benzoquinone	Ellagic acid	Resveratrol
Description*	A six-carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant.	1,4-Benzoquinone, commonly known as para-quinone, is a chemical compound with the formula C6H4O2. In a pure state, it forms bright-yellow crystals with a characteristic irritating odor, resembling that of chlorine, bleach, and hot plastic. This six-membered ring compound is the oxidized derivative of 1,4-hydroquinone. The molecule is multifunctional: it exhibits properties of a ketone, forming an oxime; an oxidant, forming the dihydroxy derivative; and an alkene, undergoing addition reactions, especially those typical for Î±,Î²-unsaturated ketones. 1,4-Benzoquinone is sensitive toward both strong mineral acids and alkali, which cause condensation and decomposition of the compound.	Ellagic acid is a natural phenol antioxidant found in numerous fruits and vegetables. The antiproliferative and antioxidant properties of ellagic acid have prompted research into its potential health benefits. It has been fraudulently marketed as having the ability to prevent and treat several human maladies, including cancer, but such claims have not been proven.	Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenolic phytoalexin. It is a stilbenoid, a derivate of stilbene, and is produced in plants with the help of the enzyme stilbene synthase. It exists as two structural isomers: cis-(*Z*) and trans-(*E*), with the trans-isomer shown in the top image. The trans-form can undergo isomerisation to the cis- form when heated or exposed to ultraviolet irradiation.
Structure*	 Ascorbic acid	 Benzoquinone	 Ellagic acid	 Resveratrol
Plants	Scientific name: *Annona coriacea* Mart.	Scientific name: *Ourateahexasperma* (A.St.-Hil.) Baill.	Scientific name: *Cochlospermumregium* (Mart. ex Schrank) Pilg.	Scientific name: *Ourateahexasperma*(A. St.-Hil.) Baill.
	Popular name: Pinha, araticum, cabeça-de-negro, pinha-miúda		Popular name: Algodão bravo,algodão-do-campo,algodão-do-mato,algodão-do-campo	
	Scientificname: *Annonasylvatica* A.St.-Hil.		Scientific name: *Terminaliaargentea* Mart. &Zucc.	
	Popular name: Araticum, articum	Popular name: Cabelo-de-negro	Popular name: Capitão-do-mato,capitão-do-campo,Pau-de-bicho	Popular name: Cabelo-de-negro
	Scientific name: *Eugenia punicifolia*(Kunth.) DC.		Scientificname: *Mesosphaerumsuaveolens* (L.) Kuntze	
	Popular name: murta, muta		Popular name: bamburral	
* Source: STRING DATABASE				

strategies, such as producing proteins capable of inactivating p53 or stimulating greater expression of Bcl-2, cytotoxic T lymphocytes have different mechanisms that are capable of leading to cell death via apoptosis (Pessayre et al. 1999). Thus, other bioactive compounds from plants, such as eugenol, gallic acid, quercetin, and apigenin, may present potential in the adjuvant treatment of COVID-19 by contributing to cell death through T lymphocyte-mediated apoptosis. Therefore, elucidating the pathogenesis mechanism of SARS-CoV-2 is necessary for the development of more accurate treatment strategies involving the use of phytotherapy.

In interatomic studies, one way to assess the quality of PPINs is by comparing the suggested interactions with the subcellular location or functional classes of the protein, such as GO analysis (Bader & Hogue 2002). This analysis assumes that the members of the interaction must belong to the same category, and the validity depends strongly on the choice of classes. In addition, the co-expression of the corresponding genes is used as an evaluation criterion (Kemmeren et al. 2002). Thus, the network shown in Figure 3 was set up to perform a topological analysis of the interactome made up of the leader genes, the four plant bioactive compounds that have the potential to inhibit CASP3-mediated apoptosis, and other important molecular mechanisms that contribute to the increased severity of COVID-19. The network was expanded to perform functional enrichment (Table III).

Another way to validate interactions is to associate proteins within a metabolic pathway through KEGG. Using enrichment analysis of the genes found with KEGG pathways, processes involving everything from cell control to other mechanisms of immortalization and immune

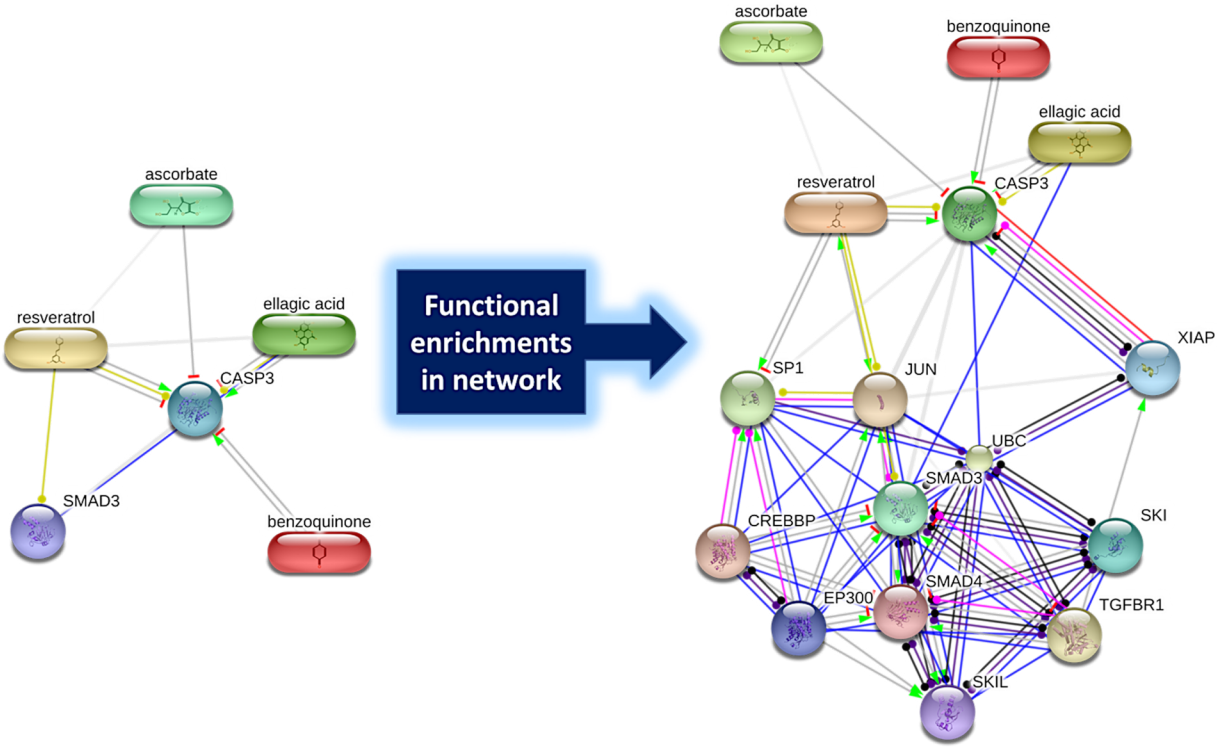


Figure 3. Interactome between leader genes (CASP3 and SMAD3) and bioactive compounds in plants (ascorbate, ellagic acid, benzoquinone, and resveratrol). On the right is the same network with functional enrichment.

system suppression were identified in the present study. For the four bioactive plant compounds, the verified main pathways enriched using KEGG included viral infection, assessments/immune/infections, and cell proliferation, highlighting their potential applicability in respiratory viral infections (Table III). Note that some of the bioactive compounds from the selected plants are already listed for use in viral infections.

Therefore, through an enrichment approach with KEGG pathways, we observed a high association of genes in the network "Pathways in Cancer." An enrichment analysis using GO terms revealed that the enriched ontologies for the "cell surface receptor signaling pathway" groups are essentially aimed at controlling the infection. Our observations demonstrate that the functional molecular category called "protein binding" involved most of the genes in the network. The most relevant cellular component was "nuclear lumen."

In the search for general domains and families, the PFAM database was utilized. In this platform, each family is manually refined and represented by two multiple sequence alignments, two HMM profiles, and an annotation file. For our analysis, we verified the SMAD3 and SMAD4 genes involved in the Mad homology 1 (MH1) and MH2 domains. A typical SMAD consists of a conserved N-terminal MH1 domain and a C-terminal MH2 domain connected by a proline-rich linker. The MH1 domain plays a key role in DNA recognition and facilitates the binding of SMAD4 to the phosphorylated C-terminus of R-SMADs to form an activated complex. The MH2 domain exhibits transcriptional activation properties (Makkar et al. 2009).

On the contrary, the Interpro platform (Mulder et al. 2005) searches against different databases of domains and families of proteins, integrating the services offered by Pfam, Uniprot, PROSITE, SMAR, PANTHER, PIRSF, SUPERFAMILY PRINTS, ProDom, GENE 3D, and TIGRFAMs. This database combines the different protein recognition methods and, in the absence of biochemical characterization, can be a reliable guide toward domain function (Quevillon et al. 2005). In this study, we verified the SMAD and Dwarfin-type domains.

The best-ranked molecule docked in the CASP3 binding site was rutin, while the SMAD3 binding site was resveratrol (Table IV). Seven molecules were unable to dock in the CASP3 binding site, probably due to problems with the ligand structures and/or incapacity to fit in the protein pocket.

We believe that the estimated anti-apoptotic and antiviral effects of the selected bioactive plant compounds are promising and deserve further investigation. Furthermore, we suggest that functional studies be carried out to verify the respective performances of ascorbate, benzoquinone, ellagic acid, and resveratrol in events that are also regulated by IFN-I and TGF-β, such as adaptive immunity, innate immunity, SARS-CoV-2 multiplication rate, thrombocytopenia, megakaryopoiesis, hemostasis, suppressive and inflammatory immune responses, processes for regulating apoptosis sensitivity, coagulation disorders, and pulmonary fibrosis (Figure 4).

Other bioactive compounds from plants that have not been highlighted by this analysis process may still have beneficial effects. However, this study aimed to provide a rational approach to the selection of herbal medicines with potentially high effectiveness in the treatment of SARS-CoV-2 and related viruses. Finally, the main step in the present approach was to propose a hypothesis that could be tested through future functional studies.

Table III. Categorization of genes according to their KEGG pathways, molecular functions, biological processes, cellular components, PFAM proteins domains, and INTERPRO proteins domains.

KEGG PATHWAYS				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
5161	Hepatitis B	5	1.41e-05	CASP3, CREBBP, EP300, JUN, SMAD4
5200	Pathways in cancer	6	1.41e-05	CASP3, CREBBP, EP300, JUN, SMAD4, XIAP
4350 TGF-beta signaling pathway		4	3.12e-05	CREBBP, EP300, SMAD4, SP1
5166	HTLV-I infection	5	7.35e-05	CREBBP, EP300, JUN, SMAD4, XIAP
4310	Wnt signaling pathway	4	0.000178	CREBBP, EP300, JUN, SMAD4
5016	Huntington s disease	4	0.000356	CASP3, CREBBP, EP300, SP1
5168	Herpes simplex infection	4	0.000356	CASP3, CREBBP, EP300, JUN
5203	Viral carcinogenesis	4	0.000356	CASP3, CREBBP, EP300, JUN
BIOLOGICAL PROCESS (GO)				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
GO.0007166	cell surface receptor signaling pathway	12	4.86e-07	CASP3, CREBBP, EP300, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC, XIAP
GO.0007165	signal transduction	11	0.00311	CASP3, CREBBP, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC, XIAP
GO.0071363	cellular response to growth factor stimulus	10	7.59e-09	CASP3, EP300, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC
GO.0007167	enzyme-linked receptor protein signaling pathway	9	2.83e-06	CASP3, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC
GO.0007179	transforming growth factor-beta receptor signaling pathway	8	4.38e-10	JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC
GO.0090092	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	7	1.56e-07	SKI, SKIL, SMAD3, SMAD4, TGFBR1, UBC, XIAP
GO.0017015	regulation of transforming growth factor-beta receptor signaling pathway	6	1.56e-07	SKI, SKIL, SMAD3, SMAD4, TGFBR1, UBC
GO.0009952	anterior/posterior pattern specification	5	9.86e-05	EP300, SKI, SMAD3, SMAD4, TGFBR1

Table III. Continuation.

GO.0060395	SMAD protein signal transduction	4	3.37e-05	JUN, SKI, SMAD3, SMAD4
MOLECULAR FUNCTION (GO)				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
GO.0005515	protein binding	10	0.0438	CREBBP, EP300, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, TGFBR1, UBC
GO.0000988	transcription factor activity, protein binding	7	5.26e-05	CREBBP, EP300, JUN, SKI, SKIL, SMAD3, SMAD4
GO.0046332	SMAD binding	6	6.47e-09	JUN, SKI, SKIL, SMAD3, SMAD4, TGFBR1
GO.0001085	RNA polymerase II transcription factor binding	5	6.15e-06	CREBBP, EP300, JUN, SMAD3, SP1
GO.0001102	RNA polymerase II activating transcription factor binding	4	1.38e-05	CREBBP, EP300, JUN, SMAD3
GO.0070412	R-SMAD binding	3	0.000145	JUN, SMAD3, SMAD4
CELLULAR COMPONENT (GO)				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
GO.0031981	nuclear lumen	10	0.00449	CASP3, CREBBP, JUN, SKI, SKIL, SMAD3, SMAD4, SP1, UBC, XIAP
GO.0005654	nucleo plasm	8	0.0446	CASP3, JUN, SKI, SKIL, SMAD4, SP1, UBC, XIAP
GO.0005667	transcription factor complex	6	5.61e-05	CREBBP, EP300, JUN, SKI, SMAD3, SMAD4
GO.0000790	nuclear chromatin	5	0.000438	CREBBP, JUN, SMAD3, SMAD4, SP1
GO.0071141	SMAD protein complex	2	0.00132	SMAD3, SMAD4
PFAM PROTEINS DOMAINS				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
PF03166	MH2 domain	2	0.0103	SMAD3, SMAD4
PF03165	MH1 domain	2	0.0128	SMAD3, SMAD4

Table III. Continuation.

INTERPRO PROTEINS DOMAINS AND FEATURES				
Pathway ID	**Pathway description**	**Observed gene count**	**False discovery rate**	**Matching proteins in network (labels)**
IPR001132	SMAD domain, Dwarfin-type	2	0.00732	SMAD3, SMAD4
IPR013019	MAD homology, MH1	2	0.00732	SMAD3, SMAD4
IPR013790	Dwarfin	2	0.00732	SMAD3, SMAD4
IPR003619	MAD homology1, Dwarfin-type	2	0.011	SMAD3, SMAD4
IPR017855	SMAD domain-like	2	0.011	SMAD3, SMAD4
IPR008984	SMAD/FHA domain	2	0.0335	SMAD3, SMAD4

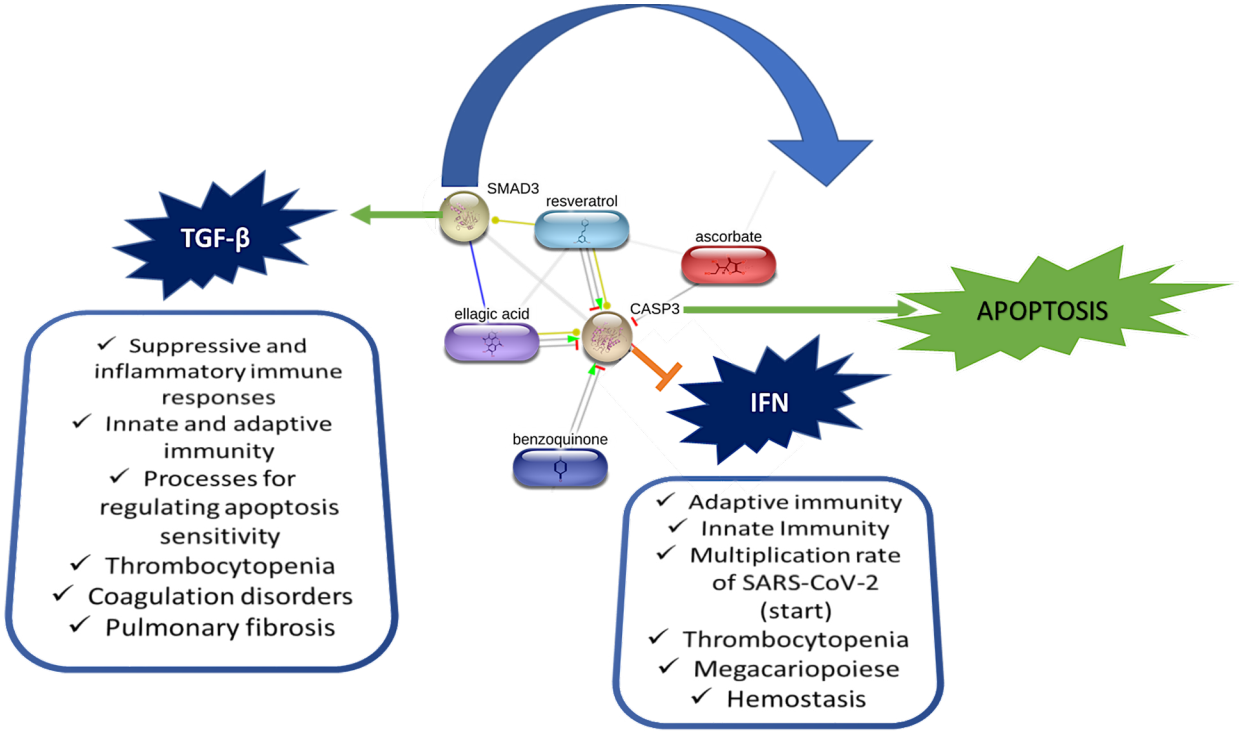


Figure 4. Representation of events that can be regulated by the action of the compounds ascorbate, benzoquinone, ellagic acid, and resveratrol on the leader genes CASP3 and SMAD3.

CONCLUSIONS

In conclusion, this work identified several bioactive compounds from Brazilian plants with potential antiviral functions that may directly or indirectly inhibit SARS-CoV-2, the virus that causes COVID-19. We hypothesized that the therapeutic effect of these bioactive plant compounds operates through interference in CASP3- and SMAD3-mediated apoptosis and other events that are also modulated by interferon and TGF-β. In addition, we proposed principles and methods of in silico analysis that

Table IV. Docking calculation for the main proteins and plant molecules.

CASP3	
Molecule	**ChemPLP score**
Angelicin	34,0
Apigenin	47,2
Ascorbic acid	28,8
Benzoquinone	-
β-elemene	47,3
Catechol	-
Ellagic acid	55,6
Eugenol	-
Flavonone	-
Gallic acid	41,4
γ-tocopherol	-
Isoquercitrin	66,3
Kaempferol	54,2
Luteolin	47,6
Lycopene	-
Oleanolic acid	82,2
Oleic acid	69,2
Quercetin	72,2
Resveratrol	65,5
Rutin	92,0
Safrole	48,9
Salicylate	55,6
Scopoletin	48,7
Sitosterol	-
Thymol	52,0
SMAD3	
Molecule	ChemPLP score
Resveratrol	65,8
Ellagic acid	50,2

can guide the screening of potential antiviral substances to combat COVID-19.

To summarize, our results support the use of medicinal plants and traditional medicine for the treatment of patients with COVID-19. These findings also provide an argument for the protection of Brazilian flora and support the diffusion and relevance of the country's natural assets in addressing a global problem.

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