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Medicinal Plants as Potential Inhibitors of SARS-CoV-2: A narrative review on antiviral and immunomodulatory properties

Plantas Medicinais como Potenciais Inibidores do SARS-CoV-2: Uma revisão narrativa sobre propriedades antivirais e imunomoduladoras

Plantas Medicinales como Inhibidores Potenciales del SARS-CoV-2: Una revisión narrativa sobre propiedades antivirales e inmunomoduladoras

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has highlighted the urgent need for effective therapeutic strategies. While antiviral drugs have been developed, the emergence of viral variants and the limitations of current treatments reinforce the necessity of exploring alternative approaches. Medicinal plants, known for their bioactive compounds with antioxidant, anti-inflammatory, and antiviral properties, have gained attention as potential inhibitors of viral replication. This article presents a narrative review study that seeks to examine the antiviral potential of plant extracts against SARS-CoV-2, focusing on key species such as *Perilla frutescens*, *Punica granatum* L., *Nerium oleander*, *Scutellaria baicalensis*, and *Vitis vinifera*. These extracts have demonstrated promising inhibitory effects on critical viral mechanisms, including RNA replication,

protease activity (e.g., $3CL^{Pro}$), and viral entry into host cells. The study also discusses the immunomodulatory effects of these compounds, particularly in reducing cytokine storm-related inflammation, a hallmark of severe COVID-19 cases. Furthermore, some plant-based extracts, such as *Perilla frutescens*, show potential synergistic effects when combined with conventional antivirals like remdesivir. Despite promising *in vitro* and *in vivo* results, further preclinical and clinical studies are necessary to validate the efficacy and safety of these natural compounds. Given their accessibility, safety, and broad-spectrum antiviral properties, medicinal plant extracts represent a valuable avenue for the development of novel therapies against COVID-19 and other emerging viral infections. This review underscores the need for continued research into plant-derived bioactives as potential candidates for integrative antiviral strategies.
Keywords: Antiviral; Phytochemicals; COVID-19; Cytokines; Medicinal plants; SARS-CoV-2.

Resumo

A pandemia da doença do coronavírus de 2019 (COVID-19), causada pelo coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), destacou a necessidade urgente de estratégias terapêuticas eficazes. Embora medicamentos antivirais tenham sido desenvolvidos, o surgimento de variantes virais e as limitações dos tratamentos atuais reforçam a necessidade de explorar abordagens alternativas. As plantas medicinais, conhecidas por propriedades antioxidantes, anti-inflamatórias e antivirais, ganharam atenção como potenciais inibidores da replicação viral. Este artigo apresenta um estudo de revisão narrativa que procura examinar o potencial antiviral de extratos vegetais contra o SARS-CoV-2, focando em espécies-chave como *Perilla frutescens*, *Punica granatum* L., *Nerium oleander*, *Scutellaria baicalensis* e *Vitis vinifera*. Esses extratos demonstraram efeitos inibitórios promissores sobre mecanismos virais críticos, incluindo a replicação do RNA, a atividade de proteases (e.g., $3CL^{Pro}$) e a entrada viral nas células hospedeiras. O estudo também discute os efeitos imunomoduladores desses compostos, especialmente na redução da inflamação associada à tempestade de citocinas, um dos principais fatores de gravidade da COVID-19. Além disso, alguns extratos vegetais, como *Perilla frutescens*, mostram efeitos sinérgicos quando combinados com antivirais convencionais, como o remdesivir. Apesar dos resultados promissores *in vitro* e *in vivo*, são necessários mais estudos pré-clínicos e clínicos para validar a eficácia e a segurança desses compostos naturais. Dada sua acessibilidade, segurança e propriedades antivirais de amplo espectro, os extratos de plantas medicinais representam um caminho valioso para o desenvolvimento de novas terapias contra a COVID-19 e outras infecções virais emergentes. Esta revisão reforça a necessidade de pesquisas contínuas sobre bioativos vegetais como potenciais candidatos para estratégias antivirais integrativas.
Palavras-chave: Antiviral; Compostos fitoquímicos; COVID-19; Citocina; Plantas medicinais; SARS-CoV-2.

Resumen

La pandemia de la enfermedad por coronavirus 2019 (COVID-19), causada por el coronavirus del síndrome respiratorio agudo grave 2 (SARS-CoV-2), ha resaltado la necesidad de estrategias terapéuticas eficaces. Aunque se han desarrollado antivirales, la aparición de variantes y las limitaciones de los tratamientos actuales refuerzan la necesidad de explorar enfoques alternativos. Las plantas medicinales, conocidas por sus propiedades antioxidantes, antiinflamatorias y antivirales, han atraído atención como posibles inhibidores de la replicación viral. Este artículo presenta un estudio de revisión narrativa que busca examinar el potencial antiviral de los extractos vegetales contra el SARS-CoV-2, centrándose en especies clave como *Perilla frutescens*, *Punica granatum* L., *Nerium oleander*, *Scutellaria baicalensis* y *Vitis vinifera*.". Estos extractos han mostrado efectos inhibidores sobre mecanismos virales críticos, incluyendo la replicación del ARN, la actividad de proteasas (e.g., $3CL^{Pro}$) y la entrada viral en células huésped. El estudio también analizo los efectos inmunomoduladores de estos compuestos, especialmente en la reducción de la inflamación asociada a la tormenta de citocinas en casos graves de COVID-19. Además, algunos extractos, como *Perilla frutescens*, muestran efectos sinérgicos con antivirales convencionales, como remdesivir. Apesar de resultados prometedores *in vitro* e *in vivo*, se requieren estudios preclínicos y clínicos para validar su eficacia y seguridad. Dada su accesibilidad y propiedades antivirales, los extractos vegetales representan una vía valiosa para el desarrollo de nuevas terapias contra la COVID-19 y otras infecciones virales emergentes. Esta revisión enfatiza la importancia de seguir investigando bioactivos vegetales como candidatos para estrategias antivirales integrativas.
Palabras clave: Antiviral; Fitoquímicos; COVID-19; Citocinas; Plantas medicinales; SARS-CoV-2.

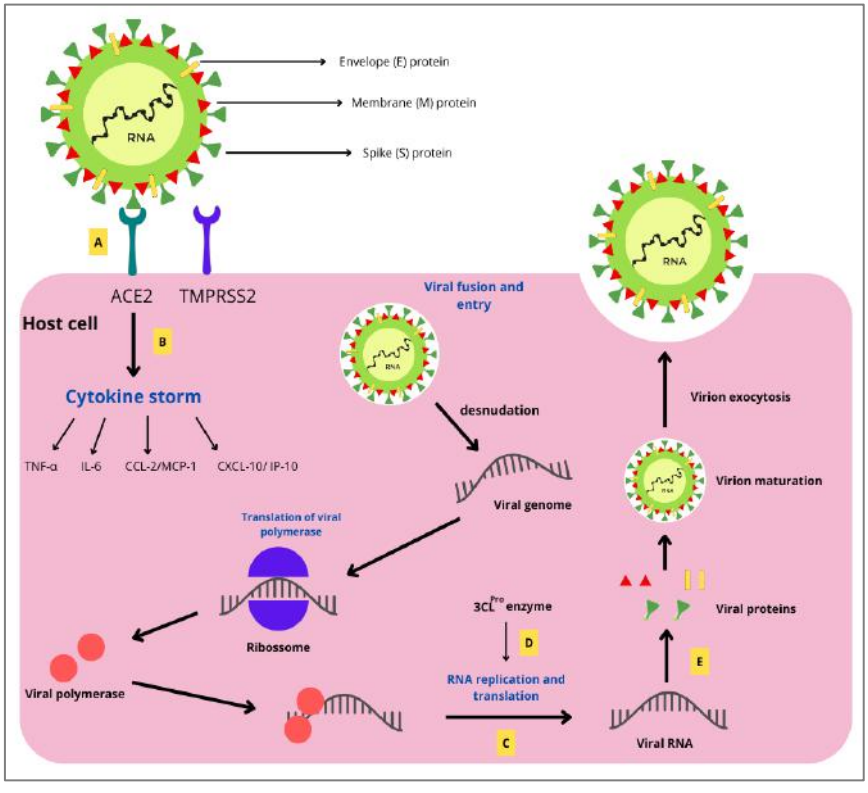
1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2, has transformed the global dynamics of public health and highlighted the importance of new therapeutic strategies. Since the onset of the pandemic, efforts have been directed toward developing effective treatments to reduce the morbidity and mortality associated with the disease. However, the emergence of viral variants and the limitations of available antiviral drugs underscore the need to explore alternative approaches for infection control (Zhou et al., 2016; Lin et al., 2016).

Medicinal plants have been widely used throughout history as a source of bioactive compounds with diverse therapeutic properties. Among the key benefits attributed to these compounds are their antioxidant, anti-inflammatory, and antiviral activities, which play an essential role in the prevention and treatment of infectious diseases. Plant extracts rich in phenols, flavonoids, and other secondary metabolites have been associated with the ability to inhibit specific viral proteins and modulate inflammatory responses, making them a promising alternative in global health scenarios (Chen et al., 2005; Martins et al., 2016; Godos et al., 2020).

Recent studies have highlighted the potential of various plants in combating enveloped viruses, including SARS-CoV-2. Compounds derived from species such as *Scutellaria baicalensis*, *Perilla frutescens*, and *Punica granatum* L. have demonstrated the ability to inhibit key processes in the viral life cycle, such as RNA replication, the action of essential proteases (e.g., $3CL^{Pro}$), and viral entry into host cells (Figure 1). Moreover, these substances have shown potential in reducing the cytokine storm, a hallmark of severe COVID-19 cases (Liu et al., 2021; Moradi et al., 2020). Such findings underscore the therapeutic and preventive value of these compounds in addressing viral diseases.

Figure 1 - Interact sites of the plant products within the SARS-CoV-2 replication cycle. These compounds can inhibit the virus entry in the host cell (A), inhibit the cytokine storm (B), block important processes in the RNA replication (C), neutralize $3CL^{Pro}$ enzyme (D) or inhibit the viral protein synthesis (E). Plants products and interaction sites: Selected Plants Extracts (D), *Lianhuaqingwen* exerts (B); *Nerium oleander* (A); *Perilla frutescens* (A, C and E); *Punica granatum L* (A); *Prunella vulgaris* (A); *Scutellaria baicalensis* (A and D); Tri-Herbal Medicine Coronil (A and B); *Vitis vinifera* (A).



Source: Authors.

Another relevant aspect is the safety and accessibility associated with many of the plant extracts studied. In various cultures, plants such as chamomile, turmeric, and citrus fruit peels are widely consumed and recognized for their medicinal properties. This scenario reinforces the feasibility of their large-scale application, both as prophylactic measures and as adjuvants in antiviral therapies (Chen et al., 2005; Martins et al., 2016). However, while *in vitro* studies provide a promising foundation,

further investigations are needed to understand the underlying molecular mechanisms and validate the efficacy of these compounds in preclinical and clinical models.

Given the magnitude of the challenges posed by the COVID-19 pandemic, this study aims to contribute to scientific progress by exploring the antiviral properties of selected plant extracts against SARS-CoV-2. The research focuses on elucidating the mechanisms of action of these compounds, identifying potential viral inhibitors, and assessing their potential for the development of new therapeutic strategies. Considering the need for accessible and effective options, the findings of this study may offer valuable insights to address both the current health crisis and future pandemics caused by emerging viruses. This article presents a narrative review study that seeks to examine the antiviral potential of plant extracts against SARS-CoV-2, focusing on key species such as *Perilla frutescens*, *Punica granatum* L., *Nerium oleander*, *Scutellaria baicalensis* and *Vitis vinifera.*

2. Material and Methods

The present study was conducted as a narrative review (Rother, 2007). To achieve this, the studies included were retrieved through searches on the PubMed platform, provided by the National Library of Medicine, and the Scientific Electronic Library Online (SciELO). The article search utilized the following keywords: (1) SARS-CoV-2; (2) medicinal plants; (3) extracts; (4) antiviral. The inclusion criteria for the selected studies were as follows: (1) full-text articles; and (2) articles written in the English language.

3. Results and Discussion

3.1 Selected Plants Extracts

Background

Some extracts of plants inhibited the SARS-CoV-2 $3CL^{Pro}$ activity *in vitro* (Chen et al., 2005; Lin et al., 2005). Phenolic compounds have been extensively studied for their antioxidant capacity acting as free radical scavengers tested *in vitro* and using *in vivo* models (Martins et al., 2016). Then, diets rich in fruits and vegetables with high levels of these compounds are associated with a reduction in the risk of chronic inflammatory processes, thus lowering the risk of developing some degenerative and cardiovascular diseases and several types of cancer (Zhou et al., 2016; Lin et al., 2016; Godos et al., 2020). These materials have easy access, because they are used in many cultures. There is also a possibility about development of prophylactics or therapeutics vegetal extracts against COVID-19. Moreover, the comproved security of consume of these plants by humans indicates a potential use against COVID-19.

Methodology

Guijarro-Real et al. (2021), selected 17 plants foods and its derived products: peels of sweet orange (*Citrus sinensis*), lemon (*C. limon*), lime (*C. aurantiifolia*) and grapefruit (*C. paradisi*), aromatic herbs like celery leaves and celery stalks (*Apium graveolens*), parsley (*Petroselinum crispum*), dill (*Anethum graveolens*), sweet chamomile (*Marticaria chamomilla*), and dried oregano (*Origanum vulgare*), red onion (*Allium cepa*) and turmeric (*Curcuma longa*), a succulent plant aloe vera (*Aloe barbadensis*), brown mustard seeds (*Brassica nigra*), horseradish (*Armoracia rusticana*) and wasabi powder. Aqueous methanol was used to extract phytochemicals compounds of the samples. With an assay using fluorogenic substrate, the residual activity was measured, indicating possible inhibitors of SARS-CoV-2 (enzyme $3CL^{Pro}$). For determination of $3CL^{Pro}$'s activity, the plants extracts were diluted in an assay buffer with $3CL^{Pro}$.

Main findings

The lime peel and chamomile extracts were discarded, because it produced signal interferences. However, the coincubation of $3CL^{Pro}$ with chamomile extracts produced a reduction of the protease activity despite possible signal interference. From the other 15 extracts, seven demonstrated low inhibitory capacity and left a residual activity of protease over 70%. Included extracts: grapefruit, lemon, and orange fruit peels (72,4-82,8% of residual activities); red onion (80,9%); celery stalk (79,9%); horseradish (75%); and dill (73,1%). Other five materials showed an intermediate inhibitory capacity (35,5%): extracts of celery leaves (38%), parsley (42,8%) and oregano (46,3%); aloe vera leaves (54,8%); and wasabi powder (35,8%). The study found 3 extracts with a high inhibitory capacity: mustard seeds, wall rocket, and turmeric (0,0% of $3CL^{Pro}$ residual activity).

Mechanism of action

The study used previous informations about inhibitors of SARS-CoV-2 $3CL^{Pro}$. Subsequently, the extracts were tested to see the potential of inhibition of this protease ($3CL^{Pro}$), which is essential in viral replication.

3.2 Lianhuaqingwen

Background

Lianhuaqingwen (LH) is a chinese medicine, made by 13 herbs, which showed a positive paper in the treatment of SARS-CoV-2. In addition, LH had demonstrated effects with a considerable range on a serie of influenza viruses, inhibiting the viral propagation and regulating immunology function, reaching therapeutic efficacy similar to Oseltamivir in the reduction of the course of infection by H1N1 virus (Duan et al., 2011; Ding et al., 2017; Lu 2020).

Methodology

In the study conducted by Lin et al. (2020), african green monkey kidney epithelial (Vero E6) cells and the human hepatocellular carcinoma cells were used. The SARS-CoV-2 was propagated in Vero E6 cells. Black powder of raw material of LH was dissolved in dimethyl sulfoxide (DMSO). The LH solution was diluted with serum-free and stored before using. Remdesiver was dissolved in DMSO. The cytotoxicity effects of LH in the Vero E6 cells and Huh-7 cells were evaluated. Monolayers of Vero E6 cells and Huh-7 cells were rinsed in 96-well plates with phosphate-buffered saline (PBS) followed by incubation with the indicated concentrations of LH. These cells were removed, and the formed crystals were dissolved. The monolayers of Vero E6 cells were cultivated in 96-well plates and inoculated with 100 $TCID_{50}$ of coronavirus strains. The inoculum was removed and, posteriorly, these cells were incubated with indicated concentrations of LH or with positive control of remdesivir. The monolayers of Vero E6 cells in 6 plates were infected with 50 plaque-forming units (PFU) of SARS-CoV-2. After incubation, the monolayers of these cells were covered with agar and incubated. Monolayers of Huh-7 cells in 12 plates were rinsed with PBS and exposed to coronavirus at a multiplicity of infection (MOI). The inoculum was removed and replaced with indicated concentrations of LH. Then, cells were harvested to the isolation of RNA and qPCR as described (Li et al., 2017). Ultrathin sections of incorporated cells were prepared and then observed with transmission electron microscopy.

Main findings

LH has demonstrated an unapparent cytotoxicity for both cell lines at concentrations up to 600 μg/mL. The positive control of remdesivir didn't show any kind of cytotoxicity to cells. LH inhibited viral replication of SARS-CoV-2 with a value of 411,2 μg/mL by CPE assay. Meanwhile, the treatment with LH after the infection had also an inhibitory effect dose-dependent on plaque formation of SARS-CoV-2 virus. There was a reduction in the quantity of virus in LH utilization and group control

with remdesivir. Results showed that high expressions of cytokines TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10 were considerably inhibited by the LH in a concentration-dependent way.

Mechanism of action

LH has a potent antiviral against SARS-CoV-2 virus with a value IC_{50} of 411,2 µg/mL. One slight deformations of virus particles were observed. The host cells infected with HCoV-229E and SARS-COV-2 elevated the liberations of cytokines like TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/ IP-10. This was inhibited by LH in a dose-dependent way.

3.3 *Nerium oleander*

Background

Oleandrin is a substance extracted from the oleander (*Nerium oleander*) plant and belongs to a class of compounds that are used to improve heart muscle working in patients with congestive heart failure. In addition, other therapeutic uses of oleandrin, such as cosmetic treatment of skincare problems (Benson et al., 2015) to the treatment of cancer (Pan et al., 2015; Newman et al., 2007; Newman et al., 2006), have been recognized. Actually, oleandrin is a unique lipid-soluble glycoside obtained in an isolated way from *N. oleander* and it has been recognized as the active principal ingredient in PBI-06150 and PBI-05204, used in some parts of clinical trials of patients with cancer. The group of compounds that oleandrin belongs is known as cardenolides. Recent reviews describe antiviral activities of cardenolides against cytomegalovirus, herpes simplex virus, coronaviruses, influenza virus, adenovirus, respiratory syncytial virus, Ebola virus and immunodeficiency virus (Amarelle; Lecuona, 2018; Newman et al., 2020). Furthermore, oleandrin has recently shown a strong antiviral response against HIV-1 and HTLV-1 (Singh et al., 2013; Hutchison et al., 2019). Studies suggest that oleandrin has potential against enveloped viruses.

Methodology

In the study conducted by Plante et al. (2021), SARS-CoV-2 strain was used to infect Vero E6 cells. After the infection, tissue culture supernatants were collected, clarified, aliquoted and stored. There were made stocks of genetic material of this virus, which were identical to the original stock, without deletions or mutations. Then, Vero CCL81 cells were used for the prophylactic and therapeutic assays, being submitted to infection, washing and incubation. Vero E6 cells were used for plaque assays. Vero CCL81 cells were submitted to an application of oleandrin and analyzed with a control group to quantify the toxicity of this substance. Levels of lactic dehydrogenase were analyzed. After the incubation of Vero cells, the supernatants from plaque assays were collected to construct the genome copy measurement. Extracted RNA was tested for SARS-CoV-2 by qRT-PCR following a previously published assay (Harcourt et al., 2020). For the *in vivo* experiments, four-week-old female golden Syrian hamsters were used for the determination of safety. Each experimental group had 5 hamsters. The *in vivo* treatment regimen included a model solution of PBI-06150 containing oleandrin. Different groups of animals were dosed with extract containing each of the different oleandrin concentrations, or vehicle control, by sublingual route. A subset of hamsters from each group was euthanized at days 7 and 21 post-treatment. Lungs, brain and heart tissues were collected and analyzed. Nasal turbinates were collected, homogenized and aliquots were stored. Tissues were examined by a veterinary pathologist in a blinded manner. Levels of ALP and ALT were measured to analyze the cytotoxicity effect of oleandrin. A virus quantification was performed in nasal turbinates of these groups of animals.

Main findings

Prophylactic oleandrin (as the active principal ingredient in PBL-06150) administration exhibited potent antiviral activity against SARS-CoV-2, with an 800-fold reduction in virus production, and a 0.1 µg/ml concentration resulted in a greater

than 3000-fold reduction in infectious virus production. Therapeutic (post-infection) treatment up to 24 h after SARS-CoV-2 infection of Vero cells also reduced viral titers, causing greater than 100-fold reduction as measured at 48 h, and the 0.05 µg/ml concentration resulting in a 78-fold reduction. Concentrations of oleandrin up to 10 µg/ml were well tolerated in Vero cells. Results about *in vivo* experiments have demonstrated evidence of the safety and efficacy of defined *N. oleander* extract (PBL-06150), which was administered to golden Syrian hamsters in a preparation containing as high as 130 µg/ml of oleandrin. Compared to administration of control vehicle, PBI-06150 provided a statistically significant reduction of the viral titer in the nasal turbinates.

Mechanisms of action

The oleandrin from *N. oleander* has an ability to inhibit functioning of Na/K-ATPase which changes ion flux across membranes (Fozzard; Sheets, 1985) and then creates an ion imbalance across cellular and perinuclear membranes. This inhibition is made by a blockade of ATP binding sites.

3.4 Perilla frutescens

Background

The *Perilla frutescens* is an herb plant that belongs to a mint family, Lamiaceae (Pandey; Bhatt, 2008; Zhou et al., 2014). It's commonly known as perilla, beefsteak plant, purple mint, perilla mint, Korean perilla, Chinese basil, Zisu (in China) and Shiso (in Japan), (Asif, 2011; Yu et al., 2017). The biology activity of *P. frutescens* is expressed through the benefits of the diverse biochemistry compounds' presence in human health, as antioxidant, antibacterial and antifungal activity, anti-allergic effect, antidepressant, anti-inflammatory and antitumor activity (Ahmed, 2018). In this study, the antiviral effect of perilla leaf extract was tested against cells infected by SARS-CoV-2.

Methodology

Tang et al. (2021) used Vero E6, human hepatocellular carcinoma (Huh7), human rhabdomyosarcoma (RD) and Calu-3 cells. These cell lines were infected with SARS-CoV-2. The leaf extract of *P. frutescens* was added between 3 and 0 h before the entry of virus; in 10, and from 0 to 24 h, after viral adsorption. The infected cells were harvested collectively after 24 h since the beginning. RNA viral synthesis and the viral protein expression were analyzed with qPCR and Western blotting. Remdesivir was the positive group control to the simulation of infection as negative control. At the end, an assay of combination analyzed a potential efficacy jointly with remdesivir and *P. frutescens* extract.

Main findings

The leaf extract of *P. frutescens* demonstrated an inhibition of SARS-CoV-2 virus entry in a dose-dependent manner, as indicated in human lung alveolar cell lines, Calu-3. Concentrations non cytotoxic block viral RNA and protein synthesis. Therefore, the vegetal products also significantly reduced cytokine proinflammatory expression induced by viral replication. Therefore, the combination of *P. frutescens* with remdesivir demonstrated an additional efficacy against SARS-CoV-2.

Mechanism of action

The products of *P. frutescens* could inhibit viral protein synthesis and its replication while inactivating the virion. These products blocked the entry of SARS-CoV-2 in the host cells and reduced the quantity of viral RNA in the culture cells. Finally, *P. frutescens* also was capable to inhibit influenza virus, which suggests a capacity of inhibition against RNA virus.

3.5 Punica granatum L.

Background

Pomegranate (*Punica granatum* L., Punicaceae family) is a well-known fruit and traditionally used to treat different chronic diseases such as diabetes type 2 (Banihani et al., 2013; Grabež et al., 2020), atherosclerosis (Al-Jarallah et al., 2013; Akhtar et al., 2015), cardiovascular diseases (Sohrab et al., 2019), inflammatory diseases (Danesi; Ferguson, 2017) and cancer (Orgil et al., 2014). Extracts of the pomegranate peel are rich with phytobiotics like hydrolysable tannins, flavonoids, anthocyanins and other phenols. Recent studies *in vitro* showed an antiviral effect of pomegranate peel extract (PoPEx) on influenza virus which is associated with inhibition of viral absorption and RNA transcription (Moradi et al., 2019; (Moradi et al., 2020).

Methodology

In the study by Tito et al. (2021), protein active sites, protein-ligand interactions, and binding affinities of selected protein targets with umifenovir, lopinavir, camostat, and selected PoPEx compounds were analyzed. The proteins S glycoprotein, ACE2, furin, and TMPRSS2 were selected as key proteins involved in SARS-CoV-2 internalization and considered relevant therapeutic targets. The selected protein targets were analyzed for druggable regions, and pocket sites with favorable volume, surface area, and drug-likeness scores were evaluated based on their constitutive amino acid residues.

Main findings

The results revealed that all PoPEx's compounds formed complexes more stable with furin. This was the only protein target analyzed that formed complexes with lower energy with all the ligands compared to the positive control. In this way, has an emphasis on the inhibitory potential of polyphenols PoPEx.

Mechanism of action

PoPEx's ligands interact through hydrogen ligations with residuals of amino acids in the active site of S glycoprotein. Punicalin demonstrated the strongest interaction with S glycoprotein with free binding energy and formation of hydrogen bond with Ser 371 amino acid. Punicalagin was another PoPEx constituent with more stable binding conformation than lopinavir. Among all analyzed targets, ACE2 was the only one that formed the most stable complex with lopinavir. All the PoPEx's ligands tested demonstrated a significant affinity of ligation in the active site predicted to ACE2 with all complexes ligand-protein stabilized through hydrogens bonds.

3.6 Prunella vulgaris

Background

P. vulgaris is a medical plant that belongs to the Lamiaceae family, which is distributed, mainly, in the east of United States, China, Europe and northwestern Africa (Gray, 1821; Fisher, 1932). Since antiquity, it's been used by chinese medicine to treat ulcers and inflammations, because of its hypotensive, antibiotic, antirheumatic, antiviral and antioxidant effects (Chiej, 1984; Duke, 1985; Rasool et al., 2010). The herb is compound by an aqueous extract (NhPV), which is constituted by the polysaccharide prunelin, shows a significant antiviral activity against HIV, HSV and Ebola virus (Tabba et al., 1989; Zheng, 1990; Rasool et al., 2010). Moreover, another compound, Suramin, demonstrated to have an efficacy as inhibitor of HIV (De Clercq, 1987) and also reduced viral loads of chikungunya virus (CHIKV) in infected mice (Kuo et al., 2016).

Methodology

Ao et al. (2021) evaluated the effects of *P. vulgaris* extract using human embryonic kidney cells (HEK293T) and kidney epithelial cells (Vero E6 and Vero cells). About *P. vulgaris*'s fruitspike, it was dried and soaked in deionized water and boiled. After this, it was cooled supernatant and centrifuged, filtered through a cellulose acetate membrane and lyophilized. The resulting dark brown residue was dissolved in deionized water and stored. To produce pseudotyped viruses SARS-CoV-2 SP, was used a transfecting HEK293T cells with pCAGGS-SARS-CoV-2-SP, pCAGGS-SARS-CoV-2-SPΔC and HIV vector. Then, after centrifugation, a varied concentration of NhPV extracts and Suramin was added to the Vero cells. A trypan blue assay was used to determine the effect of NhPV or Suramin on the cell viability and its cytotoxicity.

Main findings

NhPV is capable to prevent and block SARS-CoV-2 infections in Vero cells. About Suramin, it was observed that it inhibited, in the first stages, the infection by SARS-CoV-2 virus and inhibited the entry of degenerative effects caused by the infection. When used together, phytotherapeutic effects are potentiated.

Mechanism of action

It is believed that it has a relation to the time between the infection and the administration of the compound, because when these substances are administered together in one hour before the infection the effects were higher than three hours after the infection. This suggests the Suramin and NhPV acts in the entry of infection in the cell.

3.7 Scutellaria baicalensis

Background

Scutellaria baicalensis is a spice of plant of Lamiaceae family, listed in the Chinese Pharmacopeia, 2015 Edition, ("Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China," 2015) and European Pharmacopoeia, 10th Edition, (European Pharmacopoeia., 2019). It is indicated in the treatment of diarrhea, hypertension, hemorrhage, insomnia, inflammation and respiratory infections (Zhao et al., 2016). Its dried roots have been used in traditional medicine, known as Huang-Qin, for more than two millennia (Han et al., 2007). Derivatives of *S. baicalensis*, pure or mixing composition, were approved in antiviral use, as in the case of HIV, ZIKA, H1N1 and DENV, and against infection in the upper tract, in China (Qiao et al., 2016).

Methodology

In the study conducted by Liu et al. (2021), a plasmid SARS-CoV-2 pET 3CL-21x was built, followed by a transformation to an expression of protein and purification with a nickel-nitrilotriacetic acid column and a gel filtration column. In the preparation of ethanolic extract of *S. baicalensis*, the substance was cut to extraction with ethanol. The $3CL^{pro}$ enzyme of SARS-CoV-2 suffered a dilution with an assay buffer to the desired concentration. Thr-Ser-Ala-Leu-Gln-pNA dissolved was added. After this, there was a process of molecular docking, followed by a culture of cells and virus, propagated in Vero cells. The cytotoxicity of the *S. baicalensis'*s extract and baicalein and antiviral activity of both against SARS-CoV-2 were analyzed.

Main findings

The ethanolic extract of *S. baicalensis* demonstrated promising ingredients against $3CL^{pro}$. Baicalein showed a potent capacity against $3CL^{pro}$ in SARS-CoV-2. The ethanolic extract of *S. baicalensis* and baicalein were able to inhibit the virus replication with a low cytotoxicity. Baicalein reduced the growth of the virus. According to experimental tests, some analogues

to baicalein such as scutellarin which inhibits $3CL^{pro}$ and scutellarin that showed an inhibitory activity. According to these tests, dihydromyricetin, quercetagetin and myricetin also inhibit SARS-CoV-2 $3CL^{pro}$ (Liu et al., 2021).

Mechanism of action

The baicalein binds well in the substrate binding site of $3CL^{pro}$ with its 6-OH and 7-OH, creating interactions between hydrogen bond and carbonyl group of L141 and amide group of G143. After this, catalytic residues H41 and C145 are covered by baicalein, acting in the inhibition. The inhibitors of $3CL^{pro}$ in the virus can be effective in the after-entry phase. Baicalein and ethanolic extract has activity in the after-entry and entry viral phase. It's inferred that *S. baicalensis* can interact with other viral targets or other hosts different than SARS-CoV-2 (Liu et al., 2021). Biodisponibility of baicalein can elevate its concentration in the lung tissue through intratracheal administration (Su et al., 2020).

3.8 Tri-herbal Medicine Coronil

Background

Coronil is tri-herbal medicine developed in India, focused to combat SARS-Cov-2. It´s made by enriched extracts of *Withania somnifera* Dunal, *Tinospora cordifolia* Miers and *Ocimum sanctum* L plants.

Methodology

In the study by Balkrishna et al. (2020), tablets of this substance were crushed into a fine powder and diluted in a solution of water and methanol. The samples were centrifuged and filtered. Were used six groups of 24 adult wild-type zebrafish in each group, which were maintained in a standard photoperiod and dark cycle. The infused oral feeds were prepared with powdered Coronil and Dexamethasone (DEX) diluted with PBS (Shin et al., 2010; Ducharme et al., 2015). Coronil and DEX were mixed and ground with a known quantity of fish feed and extruded to pellets of uniform size. The control group was fed by fish feed mixed with an equal volume of PBS without drug and extruded. Human alveolar epithelial (A549) cells were diluted in PBS for xeno-transplantation and injected intramuscularly to seed A549 cells at the posterior lobe of zebrafish swim bladder. Cytology of swim bladder was analyzed to confirm the A549 cell adherence to the swim bladder of zebrafish. After the 7-day period of xeno-transplantation, the fish were injected with the recombinant SARS-CoV-2 spike protein. This solution was injected to the site of xeno-transplant at the junction of the trunk and the caudal region, along the midline. With a Kaplan-Meier survival curve, survival and mortality of zebrafish in all groups were counted every day. The tank temperature was maintained with continuous heating and cooling from either side (Boltaña et al., 2013). In the examination for presence of skin hemorrhage, fish were euthanized, and images were captured on a glass slide before the dissection. About the *in vitro* cell-biology assay, before these experiments, the viability of human lung alveolar adenocarcinoma cell line, A549, was measured using Alamar blue reagent. The A549 cells were pre-treated with dilutions of Coronil followed by co-treatment with Coronil human IL-1β. Then, cell culture supernatant was collected and used for measuring the secretion of cytokines. About the secreted embryonic alkaline phosphatase-based NF-kB/AP-1 reporter assay, the serial dilutions of Coronil cited before were added to TNF-α cells and incubated. A reagent was applied to detect secretion of alkaline phosphatase.

Main Findings

Coronil inhibited SARS-CoV-2 spike protein, induced humanized zebrafish mortality, and rescued from behavioral fever. Morphological and cellular abnormalities along with granulocyte and macrophage accumulation in the swim bladder were restored to normal. Skin hemorrhage, necrosis and renal cell degeneration were also considerably attenuated by Coronil treatment, which has shown a potential use in SARS-CoV-2 infectivity.

Mechanism of action

Coronil has the capacity to inhibit IL-1β induced, IL-6 and TNF-α cytokine secretion in a nuclear factor-kappaB (NF-B) and activator protein-1 (AP-1) pathway, suggesting its immunomodulatory mode of action.

3.9 *Vitis vinifera*

Background

V. vinifera is a fruit plant and shows a big importance in studies related to different areas, such as investigation of specific family genes, resistant genes and studies of polyphenols. Following this way, many researches demonstrate the vine potential related to therapeutics effects by the presence of bioactives compounds (Duan et al., 2019; Batiha et al., 2020) associated with anti-bacterial (Squillaci et al., 2021), antiviral (Lee et al., 2017; Squillaci et al., 2021), hepatoprotective (Ammar et al., 2022), hypoglycemic (Fujita et al., 2018), cardioprotective (Kim et al., 2020) and antioxidant activity (Li et al., 2018; Squillaci et al., 2021).

Methodology

Through aqueous methanol, were prepared raw extractor of leaves of *V. vinifera* and, using a negative ionization, a chemistry profile analysis was made (Zannella et al., 2021). The cytotoxicity of *V. vinifera*'s molecules against used cells was determined by thiazolyl blue tetrazolium bromide. The antiviral activity identified was measured according to different therapeutic schemes, described in previous studies (Singh et al., 2020). Was observed that Vero were plated into 12-well cell culture plates in culture medium. After this, was done a dissolution of leave extract in Minimum Essential Medium (MEM) without Fetal Bovine Serum (FBS). The percentage of infectivity inhibition was obtained by counting the number of plaques in presence of extract related to those in control (only virus without extract). All experiments were realized in triplicate. In addition, were analyzed LC-MS of flavonoids, molecular network and spectral library search, cell language, cytotoxicity test and propagation of SARS-CoV-2 in Vero cells.

Main findings

The extract of *V. vinifera*'s leaves inhibited SARS-CoV-2 replication in its initial phases through pretreatment assay (extract incubated with virus and then added to the cells) at concentration 10 g/mL. Moreover, the extracted obtained from the leave made it possible to identify and characterize 35 flavonoids conjugates mostly derived from quercetin (Zannella et al., 2021).

Mechanism of action

The leaf extract prevents the binding of viral envelope with the cell membrane and all the subsequent stages of infection, which hinder a site interaction inside viral glycoprotein which is attributed to the fusion, as the Spike protein of SARS-CoV-2. Through reduction in the expression of S protein, the anti-receptor inserted in viral envelope essential to host cells binding by human receptor of angiotensin 2 converting enzyme (Conceicao et al., 2020; Zhao et al., 2020), the extract of *V. vinifera* represents a promising antiviral agent to the treatment of COVID-19 (Zannella et al., 2021).

4. Final Considerations

The COVID-19 pandemic has exposed significant vulnerabilities in global health systems and underscored the urgent need for innovative therapeutic approaches. Bioactive compounds derived from medicinal plants have proven to be a promising alternative due to their wide availability, safety, and diversity of therapeutic properties. This study revealed that plant extracts,

such as *S. baicalensis*, *P. frutescens*, *P. granatum* L., and *V. vinifera*, play crucial roles in inhibiting fundamental processes of SARS-CoV-2 replication, including host cell entry, inhibition of key enzymes such as $3CL^{Pro}$, and modulation of exacerbated inflammatory responses (Chen et al., 2005; Liu et al., 2021; Moradi et al., 2020; Zannella et al., 2021).

The findings of this study reinforce that the antiviral and immunomodulatory properties of these extracts not only contribute to reducing viral load but also offer strategies to mitigate severe complications of the infection, such as the cytokine storm, which is often associated with poor prognoses in hospitalized patients (Ding et al., 2017; Liu et al., 2021). Additionally, the use of therapeutic combinations, as observed with the interaction between *P. frutescens* and remdesivir, demonstrates the potential of these compounds in synergy with conventional antivirals, opening new possibilities for integrated interventions (Tang et al., 2021).

Although the findings present encouraging results, it is essential to advance with preclinical and clinical studies to validate the efficacy and safety of these compounds in humans. A detailed characterization of their molecular mechanisms of action and the evaluation of possible adverse effects are critical steps for translating laboratory findings into clinical practice (Martins et al., 2016; Zannella et al., 2021). Furthermore, factors such as the standardization of extracts, extraction methods, and effective concentrations must be considered, as they can directly influence therapeutic outcomes.

The potential impact of these compounds extends beyond addressing COVID-19. The knowledge generated from this study has broader implications, including the possibility of developing plant-based therapies for other emerging viral infections, such as respiratory and zoonotic viruses (Zhou et al., 2016; Ahmed, 2018). The integration of traditional practices, combined with modern science, could play a central role in building accessible and sustainable therapeutic strategies, particularly in regions where access to conventional medicines is limited.

In this context, the results presented here not only emphasize the relevance of medicinal plants in combating COVID-19 but also highlight their importance in a broader global public health scenario. The application of bioactive compounds as therapeutic agents or adjuvants not only expands the available options for managing viral infections but also offers a promising pathway to address future health crises, always with a focus on sustainability and accessibility (Chen et al., 2005; Moradi et al., 2020; Liu et al., 2021).

Conflict of Interest

The authors declare that there are no conflicts of interest.

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