Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Review

Polyphenols and their potential role to fight viral diseases: An overview

María Fernanda Montenegro-Landívar, Paulina Tapia-Quirós, Xanel Vecino, Mònica Reig, César Valderrama, Mercé Granados, José Luis Cortina, Javier Saurina

Chemical Engineering Department, Escola d’Enginyeria de Barcelona Est (EEBE), Universitat Politècnica de Catalunya (UPC)-BarcelonaTECH, C/Eduard Maristany 10–14, Campus Diagonal-Besòs, 08930 Barcelona, Spain
Barcelona Research Center for Multiscale Science and Engineering, Campus Diagonal-Besòs, 08930 Barcelona, Spain
Chemical Engineering Department, School of Industrial Engineering-CINTECX, University of Vigo, Campus As Lagoas-Marcosende, 36310 Vigo, Spain
Department of Chemical Engineering and Analytical Chemistry, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain
CETAQUA, Carretera d’Esplugues, 75, 08940 Cornellà de Llobregat, Spain

HIGHLIGHTS

• Fruits and vegetables residues are a natural source of polyphenols.
• Polyphenols, from agri-food industry, present antiviral and antioxidant activities.
• Natural polyphenols could be used as a treatment/prevention against virus infection.
• Especially flavonoids are used for prevention/cure of diseases caused by viruses.
• Polyphenols with antiviral activity could be a novel strategy against SARS-CoV-2.

GRAPHICAL ABSTRACT

ABSTRACT

Fruits, vegetables, spices, and herbs are a potential source of phenolic acids and polyphenols. These compounds are known as natural by-products or secondary metabolites of plants, which are present in the daily diet and provide important benefits to the human body such as antioxidant, anti-inflammatory, anticancer, anti-allergic, antihypertensive and antiviral properties, among others. Plentiful evidence has been provided on the great potential of polyphenols against different viruses that cause widespread health problems. As a result, this review focuses on the potential antiviral properties of some polyphenols and their action mechanism against various types of viruses such as coronaviruses, influenza, herpes simplex, dengue fever, and rotavirus, among others. Also, it is important to highlight the relationship between antiviral and antioxidant activities that can contribute to the protection of cells and tissues of the human body. The wide variety of action mechanisms of antiviral agents, such as polyphenols, against viral infections could be applied as a treatment or prevention strategy; but at the same time, antiviral polyphenols could be used to produce natural antiviral drugs. A recent example of antiviral polyphenol application deals with the use of hesperidin extracted from Citrus sinensis. The action mechanism of hesperidin relies on its binding to the key entry or spike protein of SARS-CoV-2. Finally, the extraction, purification and recovery of polyphenols with potential antiviral activity, which are essential for virus replication and infection without side-effects, have been critically reviewed.

© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords:
Agri-food residues
Phenolic compounds
Antiviral activity
Antioxidant properties
Viral diseases
Polyphenol recovery

https://doi.org/10.1016/j.scitotenv.2021.149719
0048-9697/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Since ancient times, plants have played an important role for humanity, for example as food, clothing, perfumes and/or medicines (e.g., drugs in traditional medicine). Already in 1976, the World Health Organization (WHO) highlighted the need of scientific research in traditional medicine. Since then it has begun to put in value this type of medicine, as well as to investigate the efficacy of the mechanism of action and chemical bases of traditional herbal medicine for the development of new drugs, and also within the antiviral property that some plants possess (Ruwali et al., 2013; World Health Organization, 1978). Additionally, it is known that plants produce secondary metabolites such as polyphenols to protect themselves from the plethora of biotic and abiotic stresses. Biotic stress can be weeds, insect pests, fungi, and other microorganisms, whereas abiotic stresses can be physical and environmental conditions like salinity, drought, UV radiation, extreme temperatures, and toxic metals (Tuladhar et al., 2021). Polyphenols are not only involved in the defense mechanism of the plant system, but also, they have been found, for example, in the cell division, photosynthetic activity, reproduction, hormonal regulation, and nutrient mineralization mechanisms (Sharma et al., 2019). Thus, for instance, courmarins and tannins reduce stress on plants by repelling herbivores (Lattanzio, 2013).

Infections caused by viruses in humans are a critical and vitally important issue, as has been demonstrated during the last year with the 2019-nCoV disease. It is also stressed that polyphenols, specifically flavonoids, can act satisfactorily in various stages of the coronavirus entry and replication stages. Another example is catechin epigallocatechin-3-gallate (EGCG), present in green tea leaves, which inhibits replication of DNA viruses such as herpes simplex (oral dose of 800 mg), and HIV-1 (concentration ranging from 25 to 250 μmol/L), among others (Steinmann et al., 2013). Moreover, the half-maximal inhibitory concentration (IC50) of 47–73 μM of luteolin, hesperetin, and quercetin, among others flavonoids, can inhibit key proteins (PLpro, 3CLpro) involved in the infectious cycle of SARS coronavirus (Nguyen et al., 2012; Soukhova et al., 2004). More examples can be found as described below, where a list of some types of viruses could be inhibited by phytochemicals such as polyphenols. Of the diseases caused by harmful viruses where the use of polyphenols has been critically reviewed and shown an antiviral activity against them, kaempferol and quercetin, extracted from Broussonetia papyrifera, have shown activity against MERS-CoV and SARS-CoV-1 viruses; and hesperetin and naringenin block the replication of Sindbis virus. Thus, these are examples which, with future developments, could be approved as alternative treatments. In view of above, the main objective of this comprehensive review is to compile and evaluate the studies that have demonstrated the antiviral activity of polyphenols, the postulated mechanisms of action of polyphenols to defeat viruses as well as the synergy effect of antiviral and antioxidant.
| Type of virus | Disease characteristics | Alternative treatment with polyphenols | Conventional treatment |
|--------------|-------------------------|----------------------------------------|-----------------------|
| Respiratory infections | | | |
| Influenza virus (A, B and C) | Annually responsible for high mortality in both humans and animals worldwide | 1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC50 of 2.36 μM) purified from Echinacea purpurea | NA inhibitors and M2 protein channel blockers after infection, while prophylaxis is mainly in the use of vaccines |
| Respiratory tract infections | | 1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC50 of 2.36 μM) purified from Echinacea purpurea | NA inhibitors and M2 protein channel blockers after infection, while prophylaxis is mainly in the use of vaccines |
| Rhinovirus | | | |
| Respiratory tract infections in humans with outbreaks around the world, especially in winter | | 1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC50 of 2.36 μM) purified from Echinacea purpurea | NA inhibitors and M2 protein channel blockers after infection, while prophylaxis is mainly in the use of vaccines |
| Rotavirus | | | |
| Gastrointestinal infections | | 1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC50 of 2.36 μM) purified from Echinacea purpurea | NA inhibitors and M2 protein channel blockers after infection, while prophylaxis is mainly in the use of vaccines |
| Hepatitis virus (A, B and C) | Cause high morbidity and mortality around the world | 1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC50 of 2.36 μM) purified from Echinacea purpurea | NA inhibitors and M2 protein channel blockers after infection, while prophylaxis is mainly in the use of vaccines |
| Hepatitis B virus (HBV) | Cause high morbidity and mortality around the world | | |

(continued on next page)
| Type of virus               | Specific virus    | Disease characteristics                                                                 | Conventional treatment                                                                 | Alternative treatment with polyphenols                                                                 | Reference                                                                 |
|----------------------------|-------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Neurologic infections      | Rabies virus      | Causes an acute and fatal neurological infection in humans and mammals                  | Disease can be prevented by vaccination                                                | Tannin pentagalloylgucose (PGG) (10 μM) for 24 h possess significant anti-RABV activity; PGG can reverse the expression of miR-455-5p (a microRNA whose excess production regulates host cell signalling pathways and innate immune responses) | (Fisher et al., 2018; Riedel et al., 2019; Tu et al., 2019)               |
| Polio virus                |                   | The virus drains into the cervical and mesenteric lymph nodes and then into the blood, causing a transient viremia | The incidence has been largely reduced especially by the use of a vaccine, but the disease is still endemic in Africa and Asia | Extract of Avicennia marina leaf, the IC_{50} was 145.7 μg/mL before and 314.3 μg/mL after attachment stages of virus replication, with a cytopathic effect of 50% in both stages | (Felipe et al., 2006; Racaniello, 2006; Zandi et al., 2009)               |
| Haemorrhagic fevers        | Dengue virus      | Causing a mild fever to haemorrhagic fever, nausea, joint pains, etc.                    | There are no effective vaccines, and the prevention options available for the control of the virus infection are very limited | Baicalein (IC_{50} was 7.14 μg/mL) potent antiviral agent against adsorption in the host and after entry viral replication, and IC_{50} of 1.55 μg/mL presents a virucidal effect | (Zandi et al., 2011, 2012)                                                |
| Sindbis virus              |                   | Cause of disease outbreaks in humans in South Africa and Northern Europe                 | There are no vaccines or therapeutic means                                               | Hesperidin and naringenin with a 50% inhibitory dose (ID_{50}) of 20.5 μg/mL and 14.9 μg/mL respectively, reaching 50% for hesperidin and up to 80% for naringenin of virus replication inhibition | (Ling et al., 2019; Paredes et al., 2003)                                 |
| Immune system infection    | Human immunodeficiency virus (HIV-1 and HIV-2) | Spreads through certain body fluids and attacks the immune system, destroying T lymphocytes. Thus, the body loses its ability to fight infections and diseases | Since HIV was discovered, there has been no preventive vaccine for virus infection, and the applied treatment is antiretroviral therapy drugs which help control the multiplication of HIV in infected patients | Tricyclic coumarin compound from Galphophilum brasiliense stem bark (IC_{50} was 8.44 μM) inhibits virus replication by suppressing nuclear factor-kappa B (a protein complex that controls DNA transcription) activation | (Bhatti et al., 2016; Häggblom et al., 2016; Kudo et al., 2013; Lin et al., 2014; Sundquist and Kräusslich, 2012) |
| Multisystem diseases       | Coxsackie virus   | Causes muscle injury, paralysis and death                                                 | There is no specific treatment or vaccine available                                     | Apigenin (IC_{50} of 9.7 mg/L) and ursolic acid (EC_{50} of 6.6 mg/L) extracted from Ocimum basilicum interfere with virus replication after infection | (Bedard and Semler, 2004; Chiang et al., 2005; Wong et al., 2013)           |
properties against viral diseases. Additionally, the extraction, purification and recovery technologies to produce polyphenols from natural products and/or agri-food waste are also evaluated, since they could be limiting steps for the application of polyphenol molecules as an alternative against viruses on a large scale.

1.1. Therapeutic tools against viral diseases

The type of virus diseases and the specific virus considered in the review are summarized in Table 1, and includes: i) respiratory infections: influenza virus, coronavirus, rhinovirus, and syncitial virus; ii) gastrointestinal infections: rotavirus; iii) hepatic infections: hepatitis virus, Epstein-Barr virus, human cytomegalovirus, and herpes virus; iv) exanthematous infections: varicella-zoster virus; v) neurologic infections: rabies virus and poliovirus; vi) haemorrhagic fevers: dengue virus and Sindbis virus; vii) immune system infections: human immunodeficiency virus; and viii) multisystem disease: coxsackie virus.

In view of the examples described in Table 1, there are a large number of viruses, which can affect human health to different extent. For this reason, it is important to identify new therapeutic and functional strategies using natural sources through bioactive compounds and, more specifically, polyphenols. Furthermore, it is worth noting that polyphenols extracted from plants can efficiently inhibit the different stages of replication of various viruses in a dose-dependent matter.

2. The potential of phenolic acids and polyphenols as antiviral agents

Plants not only have the function of feeding human beings, but have also been used since ancient times as a source of therapeutic agents. According to Naithani et al. (2008), up to 80% of the world population uses plants as alternative medicine for various reasons such as their well-known antiviral features. This claimed activity is due to a wide variety of bioactive compounds present, such as polyphenols, proteins, and terpenoids, among others (Kamboj et al., 2012). Although, polyphenols are common components of the human diet, it has been reported that polyphenols are also toxic due to their biocidal activity at intake concentrations between 1 and 5% of the total daily diet (Galanakis, 2018). Considering the significant amounts of compounds that a person must be consumed, being approximately between 0.025 and 1 g per day (Scalbert and Williamson, 2000), and their multitude activities, it should be noted that they could play an important role in the prevention of numerous diseases, including antivirals. However, it is necessary to consider that despite many promising results obtained in vitro or animal experiments, there is still not enough convincing evidence from human studies, especially with large populations. More research is needed to better understand the value of therapeutic polyphenols, dietary polyphenols, and in the context of their ability to prevent the progression of diseases caused by viruses (Koch, 2019; Martin, 2009; Yang et al., 2020).

The focus of this review is on phenolic compounds and polyphenols, which have a common structural feature consisting of the presence of one or more hydroxyl groups attached to a benzene ring. Polyphenols can be classified into different classes based on their chemical structure, ranging from simple to highly polymerized compounds. Their fundamental physiological functions deal with the growth and reproduction of plants, as well as protection against pathogenic organisms and ultraviolet radiation. In addition, polyphenols strongly influence the organoleptic characteristics of food products, such as color and flavor (Ignat et al., 2011).

Polyphenols are often classified into four main families, namely: phenolic acids, flavonoids, stilbenes and lignans (Saurina and Sentellas, 2015). The basic chemical structure and examples of these polyphenol families are collected in Table 2.

As shown in Table 2, polyphenols have a great structural diversity as a function of the number of phenol rings that they contain and the elements that bind these rings. Flavonoids are the largest and most studied group.

Phenolic acids possess a high antioxidant capacity and their medical properties, such as vasodilatory, antibacterial, antiviral, anticarcinogenic and anti-inflammatory, have been reported elsewhere (Oroian and Escriche, 2015).

An important derivation from hydroxybenzoic acids are the so-called hydrolysable tannins, which are mostly present as phenolic polymers with different molecular weights, from 500 to 3000 Da (Andronescu and Grumezescu, 2017). As their principal characteristic, tannins precipitate proteins, thus contributing to regenerate, for example, a burn tissue, besides their antimicrobial, antioxidant and antiviral properties (Hamiinuk et al., 2012). Their antiviral activity against Epstein–Barr virus DNA polymerase has been demonstrated, and especially those tannins extracted from mouse-tail plant (Phyllanthus myrtifolius) and chamber bitter (Phyllanthus urinaria) (Naithani et al., 2008).

Regarding flavonoids, they represent the largest amount of polyphenols (up to 60%) consumed in the human diet (Briglez Mojzer et al., 2016). Actually, more than 9000 different flavonoids have been reported, having important benefits on human health because of their antiviral, anti-inflammatory and anti-diabetic attributes (Zhang et al., 2015; Krych and Gebicka, 2013; Tian et al., 2013; Ragab et al., 2014).

| Class | Structure | Substitutions | Examples |
|-------|-----------|---------------|----------|
| Phenolic acids | R1: H, OH, OCH3 | R2: H, OH, OCH3 | Gallic acid, Vanillic acid, Procyanidin B1 |
| Hydroxybenzoic acids | R1: H, OH, OCH3 | R2: H, OH, OCH3 | Theegallin |
| Hydroxycinnamic acids | R1: H, OH, OCH3 | R2: H, OH, OCH3 | Caffeic acid, Ferulic acid, p-Coumaric acid, Rosmarinic acid |
| Flavonoids | R1: H, OH | R2: H, OH | Hesperidin, Naringenin, Quercetin, Kaempferol, Luteolin |
| Flavanols | R1: H, OH | R2: H, OH, OCH3 | Epicatechin, Epigallocatechin |
| Flavones | R1: H, OH | R2: H, OH, OCH3 | Cyanidin, Pelargonidin |
| Anthocyanidins | R1: H, OH | R2: H, OH, OCH3 | R3: H, OH | R4: H, OH | R5: OH, OCH3 | R6: H, OH | R6: H, OH |
| Catechins | R1: OH | R2-R3: H, OH | Genistein, Daidzein |
| Isoflavones | R1: R5: H, OH | Xanthohumol, Phloretin, Isosulphurpurin |
| Chalcones | R1-R5: H, OH | Enterodiol, Matairesinol |
| Lignans | R1-R2: H, OH | Resveratrol, Piceatannol |
| Stilbenes | R1-R4: H, OH, R5: H, OH | | |
Flavonoids have been studied against the type-1 and type-2 herpes simplex virus, and against the human immunodeficiency virus (HIV-1 and HIV-2) (Naithani et al., 2008).

Finally, stilbenes (including curcuminoids) and lignans have been extensively studied because of their antioxidant properties, but their antiviral activity is not far behind. These compounds and their derivatives have been studied against viruses such as herpes simplex (type-1 and type-2), HIV, influenza, and human papilloma, among others (Naithani et al., 2008; Abba et al., 2015).

A list of polyphenols with antiviral activity, the type of virus against which they act, and their plant source is collected in Table 3.

As shown in Table 3, polyphenols with antiviral activity such as quercetin, rutin, hesperidin, apigenin, catechin, and morin are present in abundance in plants like fruits (e.g., berries, citrus fruits, tropical fruits), popular beverages (e.g., green tea, coffee), vegetables (e.g., spinach, beans, onions, olives), spices and herbs (e.g., turmeric, rosemary, ginger), which are consumed in the daily human diet (Brigelz Mojzer et al., 2016). Currently, the antiviral activity of various polyphenols makes their study more attractive; for example, 3 mg/kg body weight of curcumin, extracted and purified from turmeric, is sufficient to inhibit HIV (Praditya et al., 2019; Barthelemy et al., 1998; Haslberger et al., 2020).

Table 3: Summary of relevant polyphenols present in plants with antiviral activity according to the reviewed publications.

| Plant source | Polyphenol | Type of virus | Reference |
|--------------|------------|---------------|-----------|
| Berries, tea, almond, beans, tomato, Ficus carica, L., caps, caraway, cloves, cumin, Cardamom, Propolis, Oroxylum indicum | Kaempferol | Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus | (Naithani et al., 2008, Kamboj et al., 2012; Russo et al., 2020; Watson et al., 2013; Haminiuk et al., 2012) |
| | Chrysin | Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus | (Cheng and Wong, 1996; Kumar and Pandey, 2013; Cusnie and Lamb, 2005) |
| | Euphorbia cooperi, Morus alba, Rhus succedanea | Catechin | HIV, HSV-1 | (Kamboj et al., 2012; Kamboj and Lamb, 2005; El-Touny et al., 2018) |
| Citrus spp., cocoa, fish meat (H. cordata), Spondias mombin, Spondias tuberosa | Quercetin | Rabies virus, poliovirus, syncytial virus, HSV-2, respiratory syncytial virus, dengue virus, coronavirus | (Suárez et al., 2010; Silva et al., 2011; Zandi et al., 2011; El-Touny et al., 2018; Chiow et al., 2016) |
| Betula pendula, apple | Quercetin | Rabies virus, HSV-1, influenza virus | (Kumar and Pandey, 2013; Suárez et al., 2010) |
| | Rutin | Rabies virus, influenza virus, dengue virus | (Kamboj et al., 2012; Cusnie and Lamb, 2005) |
| | Hesperidin | Influenza virus, HSV, poliovirus, syncytial virus, SARS-CoV-2 | (Mhatre et al., 2020; Bellavite and Donzelli, 2020) |
| Chamomile, parsley, oregano, thyme, grapefruit, orange, onion, mango | Apigenin | HSV-1, HIV | (Kumar and Pandey, 2013; Kamboj et al., 2012) |
| | Naringin | Respiratory syncytial virus | (Kumar and Pandey, 2013) |
| | Caffeic acid | HIV, HSV | (Pommier et al., 2005; Sytar et al., 2021) |
| | Luteolin | HSV-1 and HSV-2 | (Naithani et al., 2008; Lopez-Lazaro, 2008) |
| Berries, pomegranate, walnuts, pecans | Ellagic acid | Dengue virus, hepatitis A and B | (Kang et al., 2006; Kamboj et al., 2012) |
| Grape, berries, peanuts | Resveratrol | Influenza A, hepatitis C virus, respiratory syncytial virus, varicella-zoster virus, Epstein-Barr virus, HSV, HIV | (Docherty et al., 2006; Mastronardino et al., 2015) |

2.1. Polyphenolic recovery from secondary sources

Phenolic compounds can also be obtained from by-products of plant processing, being cheap and easily available to recover them following a circular economy strategy (Tapia-Quirós et al., 2020; Montenegro-Landívar et al., 2021). In addition, the growing interest in polyphenols processing, being cheap and easily available to recover them following a conventional or combination of both extraction approaches by means of organic and/or aqueous solvents. For their subsequent purification implies a preliminary stage of clean-up and concentration by using sorption on resins, or pressure-driven membrane processes such as microfiltration (MF), ultrafiltration (UF), or reverse reverse osmosis (RO) followed by a final purification by using extraction chromatography (Bottino et al., 2020; Charcosset, 2016).

As mentioned, the commonest technique for polyphenols extraction is maceration (e.g., a solid-liquid process). For example, Edziri et al. (2012) used maceration for polyphenol extraction from Marrubium deserti. The dried product (250 g) was extracted with methanol, butanol, chloroform and ethyl acetate (using a feed to solvent ratio of 1:10) for an extraction time of five days. Results from antiviral activity tests concluded that the extracts with methanol and ethyl acetate showed significant antiviral activity against coxsackie B3 virus with IC50 of 100 and 135 μg/mL, respectively.

Magnetic agitation at 20 °C has been applied to recover active components from apple pomace (10 g) using 100 mL of 70% acetone and 80% methanol in darkness. The results showed that acetonic and methanolic extracts could inhibit the replication of HSV-1 and HSV-2 by more than 50% (Suárez et al., 2010).

The purification of plant extracts is, in general, a complex process and no single method is complete enough. It requires a combination and integration of them to achieve the highest separation and purification factors. A successful example is the study by Zahooor et al. (2020), who compared the separation efficiency of quercetin extracted from Rubus fruticosus by using RO and NF membranes. Quercetin is used against rabies virus, poliovirus, syncytial virus, and HSV-2, among other viruses (Suárez et al., 2010; Silva et al., 2011; Zandi et al., 2011; El-Touny et al., 2018; Chiow et al., 2016). The results obtained indicated that the RO membrane accomplished a quantitative recovery (e.g., >99%) of the drainage pipe, while NF membranes achieved a 95% of polyphenol recovery. The study showed that the cost of use the RO membranes is higher, due to the higher energy consumption than the use of NF membrane stage followed by a sorption stage of the remaining 5% of the permeate stream by using magnetic carbon nanocomposite.

It should be noted that the phenolic compounds recovered from extracts, such as kaempferol, luteolin, chrysin, gallic acid, ferulic acid, catechin, anthocyanins among others, could be used as a treatment and/or prevention against virus infection (Singh et al., 2020; Kumar and Goel, 2019; Watson et al., 2013; Marin et al., 2015).
2.2. Economic prospects of polyphenol recovery

Taking into account the different antiviral applications of polyphenol extracts, as well as the need to investigate innovative extraction and purification procedures, it is interesting to mention some examples of the economic evaluation of the recovery of polyphenols, which is also applicable to antiviral polyphenols.

The manufacturing cost (COM), expressed as €/kg per year, of the polyphenol extraction from raw material could be estimated using the methodology described by Turton et al. (2009), where five main costs must be taken into account: (i) fixed capital investment (FCI), (ii) cost of operating labour (COL), (iii) cost of utilities (CUT), (iv) cost of waste treatment (CWT), and (v) cost of raw material (CRM). Following this methodology, Vieira et al. (2013, 2017) compared the COM of extraction of jussara pulp (Euterpe edulis Martius) with strong antioxidant activity by ultrasonic assisted extraction (UAE) and agitated bed extraction (ABE) at lab scale. The UAE extracts presented a higher cost (∑5.2–137.2 €/kg) than the ABE extracts (∑72.5–139 €/kg). It was reported that the ABE and UAE extracts contained polyphenols such as kaempferol, luteolin, apigenin, catechin, epicatechin, caffeic acid and rimantadine, which may have medical applications (e.g., antiviral activity) (Galanakis, 2018). Therefore, the stability as well as their reactivity, synergism and bioavailability of polyphenols are the main aspects that must be taken into account in the recovery, processing, storage and consumption of phenolic compounds for their market applications.

### Table 4

| Antiviral polyphenol                  | Plant source                        | Target virus       | Extraction technique | Purification technique | Study effectiveness against virus                                                                 | Results                                                                 | Scaling-up | Reference |
|--------------------------------------|-------------------------------------|--------------------|----------------------|------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------|------------|-----------|
| 1,2,3,4,6-Penta-O-galloyl-8-D-glucose (PGG) | Pomegranate                         | Influenza A (H1N1) | Maceration           | Sephadex LH-20 column  | EC50 2.36 ± 0.29 μg/mL of PGG 5 or 8 h upon infection | Significant inhibition virus release                                   | Lab scale   | (Liu et al., 2011) |
| Extract rich in polyphenols          | Magnolia officinalis bark            | Influenza A (H1N1) | PLE                  | –                      | In vivo oral administration (10 and 20 mg/kg) for 5 days                                      | Infected mice reduce the production of nitric oxide, pro-inflammatory cytokines, TNF-α and IL-6 | Pilot scale | (Wu et al., 2011) |
| Isoquercetin (isoquercetin glucoside form) | Hypericum perforatum, Equisetum arvense L | Influenza A (H1N1) | Maceration           | –                      | In vivo administrated intraperitoneal                                                         | Reduce virus titres and pathological changes in lungs of mice infected with influenza A (H1N1) by up to 20-fold at 1:500 (Equisetum arvense L) or 1:100 dilutions (Hypericum perforatum) at 24 h post-inoculation | Pilot scale | (Kim et al., 2010) |
| Baicalein                            | Scutellaria baicalensis root         | Influenza H1N1     | Maceration           | –                      | In vivo oral administration                                                                | Infected mice showed significant therapeutic activities, including death prevention and lung virus titre reduction | Pilot scale | (Xu et al., 2010) |
| Quercetin, kaempferol, myricetin, quercetin-3-O-galactoside, morin, apigenin, catechin, epicatechin, caffeic acid and rimantadine | Geranium sanguineum aerial roots | Influenza (H3N2) | Maceration           | Administered in aerosol way (dose 5.4 mg/mL)                                                | Around 70% was the protective index and the survival time was in a range of 2.9–4.9 days, the animal lung infectious virus titre was reduced in comparison with control | Pilot scale | (Serkedjjeva et al., 2008) |
| Epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC) and catechin gallate | Tea | Influenza | Maceration           | –                      | 76 adult persons around 65 years old gargling 200 mg/mL 3 times daily for 3 months         | The catechin-treated group have lower incidence of influenza infection than the control group | Pilot scale | (Yamada et al., 2006) |

However, the extraction yields of the three techniques were similar (PLE 11 ± 1, Soxhlet 12 ± 1 and LPSE 12 ± 1). On the other hand, Ioannou-Ttofa et al. (2017) determined that the total cost of the treatment of olive mill waste water through an integrated process using UF and NF membranes (UFZW-10/NF270) was 9.94 €/m³. The high-added value polyphenols present in this stream, like hydroxytyrosol, can be purified, and the cost can reach 14,900 to 20,900 €/kg.

Besides, it is worth noting that the approximately market value, according to the Sigma-Aldrich website, of 10 mg of kaempferol (≥90% purity) is 113 €, 10 mg of luteolin (≥98%) is 169 €, 10 mg of apigenin (≥97%) is 92 €, 10 g of quercetin (≥95%) is 44 €, 10 g of rutin (≥94%) is 24 € and 10 mg of hydroxytyrosol is 191 € (≥90%), but their purity can make them more expensive.

### 2.3. Stability, reactivity, synergism and bioavailability of polyphenols

Technically, polyphenols are extracted, purified and concentrated from plants using different techniques as described above, which can be processed into tablets or capsules for human consumption. However, polyphenols are unstable, prone to degrade and/or react with some elements (e.g., oxygen and metal ions during their processing and storage stages), resulting in changing structures and decreasing activities (e.g., antiviral activity) (Galanakis, 2018). Therefore, the stability as well as their reactivity, synergism and bioavailability of polyphenols are the main aspects that must be taken into account in the recovery, processing, storage and consumption of phenolic compounds for their market applications.

#### 2.3.1. Stability

Instability generally due to many polyphenols are sensitive to chemical, enzymatic and physical treatments, which are used in food...
processing. Chemical and enzymatic instability leads to changes such as oxidation or polymerization, among others, causing alterations on their nutritional and physical-chemical attributes. Physical instability leads to changes like phase separation, flocculation, etc. that can also alter their attributes (Joye and McClements, 2014; Zhang et al., 2020).

2.3.2. Reactivity
Another factor that influences polyphenols is their reactivity, as they can be enzymatically degraded and polymerized during food processing stages. One of the most notable enzymatic reactions is on color, taste and nutritional value of polyphenols, which can even cause significant economic problems due to their impact on quality and shelf life of the products (Galanakis, 2018).

2.3.3. Synergism
The synergism of polyphenols in plant extracts means that a combination of two or more of compounds creates a higher biological activity than when the extracts are analyzed relative to individual polyphenols isolated from the same extracts (Yao et al., 2012; Zhang et al., 2020). However, the commercial application of polyphenols is currently limited due to instability when exposed to light, heat or oxygen as well as low bioavailability. A solution of the limitations mentioned, it could be the encapsulation (Zhang et al., 2020). Long et al. (2015) showed that bioactive food compounds can produce synergistic effects, as they have been reported in traditional Chinese medicine research. Therefore, the synergism between polyphenols must be taken into account for the development of functional foods and thus promote human well-being and prevent diseases such as viral ones.

2.3.4. Bioavailability
Bioavailability plays an important role in terms of the biological properties of polyphenols, which makes it possible to understand the proportion of their absorption, digestion and metabolism after their entry into the circulatory system (Carbonell-Capella et al., 2014). Several epidemiological and experimental studies describe the protective role of polyphenols in diseases such as viral diseases, diabetes, inflammation, among others (Kumar and Goel, 2019). Scalbert and Williamson (2000) reported few human bioavailability studies showing that the amounts of intact polyphenols in urine vary from one to another polyphenols. For example, for quercetin glycoside the percentage found in excretion urine was between 0.3 and 1.4%, while in the case of hesperidin, it was 24.4%. Similar variations were also observed for naringin consumed with grapefruit juice depending on the individual (5 to 57%).

Hong et al. (2014) and Liang et al. (2017) demonstrated that EGC loading in nanoparticles constructed with zein a protein as zein or with a polysaccharide as chitosan, improved the stability of said polyphenols at the gastrointestinal level. Another study by Xue et al. (2014) using glycosylated casein nanoparticles to encapsulate EGC demonstrated the improvement of its physical stability during storage. Xue et al. (2018) encapsulated curcumin in zein-caseinate nanoparticles, and reported improved stability against UV radiation and heat treatments.

On the other hand, there has also been an interest in encapsulating combinations of polyphenols and taking advantage of their synergistic effects. For example, curcumin and resveratrol have been encapsulated within hyaluronic-coated lipid droplets, as they have similar mechanisms of action to inhibit tumor cell growth and antioxidant and antiviral effects (Nasr, 2016). Encapsulated polyphenols have been shown to have better chemical stability that non-encapsulated ones. However, after encapsulation no improvement in the bioavailability of polyphenols has been observed, as polyphenols can become indigestible. Therefore, the most appropriate administration system for the polyphenols and the food matrix used should be thoroughly evaluated case by case (Dueik and Bouchon, 2016).

3. Antiviral activity of polyphenols
The antiviral activity of different polyphenols has the target of interacting directly with viral particles, but this binding will depend on the nature of the virus (DNA or RNA virus) (Sundararajan et al., 2010; Palamara et al., 2005; Liu et al., 2011). Another characteristic of antiviral polyphenols is that they can exert the activity during intracellular replication, which may be attributed to antioxidant features of phenolic groups, thus inhibiting the oxidation of cells by the replication of some viruses (Sundararajan et al., 2010; Fraternali et al., 2009).

Many natural polyphenols have provided research results and are becoming an important target in the development of some drugs to combat viruses, thanks to their wide availability, inexpensive production and, above all, their low side-effects (Kumar and Goel, 2019; El-Toumy et al., 2018). This is the case with the virus that is currently attacking the entire world, the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which causes the 2019-nCoV disease transmitted person-to-person (Kampf et al., 2020).

As of June 2021, a total of nearly 171 million confirmed cases have been reported, including almost 4 million deaths worldwide since the start of the outbreak (World Health Organization, 2020). Due to the high infectivity and mortality rate of SARS-CoV-2, there is an opportunity to use the great amount of information on plants used in the Traditional Chinese Medicine (TCM) to be used to treat symptoms related to SARS (homology of SARS-CoV and SARS-CoV-2), considering that natural polyphenols could inhibit SARS-CoV-2 (Mehany et al., 2021). According to Wang et al. (2020) and Chojnacka et al. (2020), the entry of SARS-CoV-2 into the host cells (lung epithelium) is facilitated by a trimeric glycoprotein, called the spike protein (protein S), located in the capsid of the virus (outer envelope). SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as a receptor for binding to host cells. The protein S is hydrolysed by endosomal proteases, such as cathepsin or transmembrane cellular serine protease 2 (TMPRSS2), which results in membrane fusion. After the virus enters the host cell, it produces new RNA and the proteins that form its envelope. The binding of SARS-CoV-2 to the receptor ACE2 may depend on several factors, such as variants in the virus protein S that promote the efficiency of their interaction. In the replication and transcription, the main protease 3CLpro and papain-like protease (PLpro) are involved. The therapeutic targets to protect the human body from the entry, replication and transcription of the SARS-CoV-2 virus are the receptor with the proteases cutting spike protein and the proteases. Polyphenols with antiviral activity (e.g., flavonoids such as kaempferol, quercetin, and naringenin, see Table 3) have been developed as protease inhibitors, helping to stop virus infection (e.g., HIV, MERS and SARS) (Paraiso et al., 2020). Current studies show that some extracted polyphenols have antiviral activity, specifically as protease inhibitors. Park et al. (2016) used 95% ethanol to extract chalcones from Angelica keiskei that showed inhibition of protease 3CLpro as well as non-competitive inhibition of protease PLpro of SARS-CoV with IC50 values of 11.4 and 1.2 μM, respectively. Also Park et al. (2017) extracted polyphenols with ethanol from Broussonetia papyrifera with potential anti-coronaviral agents, which inhibit 100% PLpro (the IC50 was 3.7 μM) protease. Recent studies, such as Yudi Utomo and Meliyanto (2020), reported that hesperidin and naringenin, among other citrus flavonoids, and polyphenols from Curcuma spp., such as curcumin, bind strongly to the 3CLpro substrate, the binding domain of SARS-CoV-2, while interacting with the receptor ACE2 and protein S. Khalifa et al. (2020a) demonstrated that anthocyanidins, such as cyanodelphine, phacelianin, techoflin and gentiodelphin, authentically interact with the receptor binding site of SARS-CoV-2-3CLpro. Khalifa et al. (2020b) found that pedunculagin, castalin and 20tercatain, which are tannins, strongly interact with the SARS-CoV-2 receptor binding site. Other polyphenols such as sinigrin, with IC50 of 217 μM, and hesperidin, with IC50 of 8.3 μM, contained in the water extract of the root of Isatis indigotica, have also been shown to be anti-SARS-CoV-2-3CLpro (Xu et al., 2020). These studies triggered
that some polyphenols could be used as effective and above all natural anti-2019-nCovid components. Even, the Chinese Health Commission officially confirmed that natural medicine (e.g., TCM) should be used in combination with conventional medicine for the treatment of 2019-nCovid patients, and currently experimental research is focused on the therapeutic potential of polyphenols against SARS-CoV-2 (Yang et al., 2020). Table 5 collects a summary of the antiviral activities of recent studies of natural polyphenols and their mechanism of action against SARS-CoV-2.

Although Table 5 present more in silico experiments that predict promising results, more in vitro and in vivo studies are needed to evaluate the mechanism of action of polyphenols against SARS-CoV-2. Most of the studies were carried out in silico, current technology to predict drug behavior, accelerating the detection rate, since it allows screening many drugs and reduction of the cost of laboratory work, limiting clinical trials to the best candidates.

Recently has been discovered that hesperidin (which is a flavonoid) easily binds to key proteins of the SARS-CoV-2, due to its physicochemical structure (see Table 2) (Adem et al., 2020; Chen et al., 2020; Das et al., 2021; Joshi et al., 2020; Wu et al., 2020; Yudi Utomo and Meiyanto, 2020). These authors investigated if hesperidin is able to bind with a low binding energy. The lower energy required, the stronger and more specific the binding will be in therapeutic terms. Wu et al. (2020) tested hesperidin as a potent antiviral agent. The binding of hesperidin to the spike protein was effective in superimposing the ACE2-receptor binding domain (RBD) on the hesperidin-RBD complex, where a clear overlap of the spike protein was effective in superimposing the ACE2-receptor binding domain (RBD) on the hesperidin-RBD complex. Wu et al. (2020) confirmed that hesperidin can interrupt the ACE2 with RBD. Another low-energy binding site for hesperidin against SARS-CoV-2 is the main protease. This enzyme is called 3CLpro or Mpro and is the target of many chemical antiviral drugs. Das et al. (2021) studied the molecular coupling of the interaction between hesperidin and Mpro. The binding energy of hesperidin with hydrogen bonds to various amino acids (e.g., THR24, THR45, HIS4, SER46, etc.) was estimated as −37.7 kJ/mol. Finally Joshi et al. (2020) identified that hesperidin binds strongly to the main SARS-CoV-2 protease, and also to the ACE2-receptor.

Regarding vitro analysis, Suru et al. (2021) confirmed that pomegranate peel extract and its main polyphenols, such as punicalin and punicalagin, have a great capacity to attenuate the binding of the SARS-CoV-2 glycoprotein S to the ACE2 receptor. The most pronounced in vitro activity was observed in pomegranate peel extract, suggesting a possible synergistic effect of polyphenols, allowing their possible therapeutic application for 2019-nCovid.

On the other hand, there are few in vivo studies investigating the antiviral effect of polyphenols against this novel virus. Deng et al. (2020), studied Pudilan Xiaoyan Oral Liquid (EC₅₀ of 1.078 mg/mL), a traditional Chinese medicine containing four herbs: Indigowoad root (Isatis indigotica), Bunge Corydalis (Corydalis bungeana), Mongolian Dandelion (Taraxacum mongolicum), Scutellaria Amoena (Scutellaria baicalensis) as well as more than 180 compounds (e.g., polyphenols

**Table 5**

| Polyphenol | Source | Mechanism of action | Analysis study | Reference |
|-----------|--------|---------------------|---------------|-----------|
| Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin gallate, zingerol, gingerol, and alicin | Medicinal plants | Block the enzymatic activity of SARS-CoV-3CLpro | In silico | (Khaerumanns et al., 2020) |
| Malvidin, peonidin, petunidin, petargonidin, cyanidin and malvidin | Pimpinella anisum L | Binding affinities to 3C-like protease of SARS-CoV-2 (virus replication) | In silico | (Hasan et al., 2020) |
| Hesperetin, myricetin, caflalone, linebacker | Medicinal plants | High affinity to protein S, helicase and protease sites on the CE2 receptor (in silico analysis); in vitro analysis shows potential efficacy of hesperidin against SARS-CoV-2 | In silico and in vitro | (Ngwa et al., 2020) |
| Baicalin and baica | Scutellaria baicalensis | Down-regulators of the TMPRSS-2 expression. | In silico and in vitro | (Da Silva Antonio et al., 2020) |
| Polyphenol extract | Scutellaria baicalensis and Oroxylum indicum | In vitro (Signer et al., 2020) | In vitro | (Signer et al., 2020) |

**Fig. 1.** Virus replication and polyphenol targets (adapted from Pommier et al., 2005; Kamboj et al., 2012).
such as chrysirin, apigenin, rutin among others), which exhibited potent anti-SARS-CoV-2 activity in infected hACE2 mice. In another study, Schettig et al. (2020) reported that a nebulized formulation of quercetin (20 mg/mL) and N-acetylcysteine (100 mg/mL) greatly alleviated the respiratory symptoms of SARS-CoV-2 in a patient treated with hydroxychloroquine and antibiotics. This demonstrates the importance of conducting further clinical (in vivo) studies to evaluate the potential of polyphenols as an adjuvant or primary therapy for 2019-nCovid.

If polyphenols are analyzed in depth as traditional anti-2019-nCovid therapeutics on humans, they could be innovative and effective, or even against other lethal viral diseases. The use of medicinal plants containing antiviral polyphenols, still has some risks and needs massive and additional experiments.

3.1. Antiviral mechanism

The mechanism of polyphenols deals with the prevention of the entry of the virus into the host cell. This was the case of the proanthocyanidins extracted from Rumex acetosa, which inhibited the entry of the influenza type A virus in its first critical phase (Daglia, 2012). Fig. 1 shows the scheme of the target sites of the antiviral mechanism of some polyphenols (e.g., quercetin, morin, chrysin).

The general interest in polyphenols, as antiviral agents, is increasing because of the great advantages of using nature-derived compounds with almost no side-effects on human health (Naithani et al., 2008). Several studies have been done for discovering the antiviral mechanism of different polyphenols; Table 6 gives an overview of some of them.

As shown in Table 6, the polyphenols with antiviral properties may have different mechanisms of action, such as inhibiting the entry of the virus, an effect on replication, etc. (Haslberger et al., 2020). New trends in biotechnology and medicine, as well as new processing technologies, could help to optimise the solubility, administration and therapeutic activities to prevent infection by viruses (Patra et al., 2018; Thomford et al., 2018; Lin et al., 2014).

3.2. Relationship between antiviral activity and antioxidant properties

The study of the relationship between antiviral and antioxidant activities has not been explored in depth. Only a few studies report a comparative evaluation. It is worth mentioning that a high formation of free radicals leads to an imbalance in the oxidative metabolism at the mitochondrial level and, as a result, the vitality of the cells of each tissue is affected (Delgado-Roche and Mesta, 2020). This imbalance can be caused by various viruses (e.g., SARS-CoV-2, HIV, influenza virus) and leads to oxidative stress and helps the virus life cycle and eventually causes cell death (Bellavite and Donzelli, 2020).

Viral infection disrupts the defensive antioxidant mechanism of the human body, bringing inflammation and oxidative damage. Experimental animal models have achieved high levels of reactive oxygen species (ROS) and an alteration of innate antioxidant defenses during, for example, a SARS-CoV infection (van den Brand et al., 2014).

Therefore, the use of polyphenols with antiviral and antioxidant activities could be an alternative to prevent the onset of infection or development of viral disease. For example, Lin et al. (2002) reported that HSV-2 infection increases the amount of free radicals, and consequently causes immune response pathology. They used an ethyl acetate extract from Euphorbia thymifolia with antiviral and antioxidant activities (the IC50 was 7.72 ± 0.15 μg/mL) to inhibit HSV-2 growth in the kidney cell line.

As mentioned, many of the pathological effects of the viruses are not only directly related to viral replication, but also to the host response to infection (e.g., inflammation, oxidative stress, etc.) (Mateos-Martín et al., 2014; Bellavite and Donzelli, 2020). Therefore, the combination of antiviral therapy with the antioxidant properties could help favourably to combat the virus infection, reducing toxicity and preventing antiviral resistance.

4. Conclusions

Keeping in mind that diseases caused by viruses remain among the leading causes of morbidity and mortality, in both developed and developing countries, despite having conventional medicine, it is of interest to looking for alternative treatments more biocompatible for humans. As an example of alternative treatments, polyphenols are interesting and promising molecules that could be applied in the pharmaceutical sector. Polyphenols are secondary metabolites from plants which can also be extracted from agri-food residues. The bioactivities of polyphenols, like antioxidant capacity, as well as their mechanisms, such as forming stable radicals, delay and/or prevent oxidative stress-induced cellular damage and disease, are well defined and studied. However, in this comprehensive review, it has specifically shown the potential role of polyphenols with potential targets, such as antiviral activity, in the prevention of diseases caused by viruses. The state of the art indicates that there is not a single mechanism of action of polyphenols against viruses. Indeed, the antiviral mechanism of these bioactive compounds could be by antioxidant activities, viral entry or inhibition of viral reproduction, DNA inhibition among others.

Additionally, due to the complex polyphenol structure, new extraction, purification, formulation and processing technologies could help to improve the stability and bioavailability of antiviral polyphenols, as well as the administration protocols and the therapeutic effects as antiviral treatments. Thus, the use of plant extracts, as polyphenols, is postulated as useful for health, due to their synergistic effects, such as antioxidant, antiviral, anti-inflammatory, among others that must be considered and studied intensively. Therefore, future and more comprehensive studies of the antiviral activity of polyphenols against the SARS-CoV-2 coronavirus could provide an additional strategy, for example as a curative treatment in vaccines, to combat this pandemic that is causing the deadly disease 2019-nCovid.
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.

Acknowledgements

This research was supported by the R2M2 project (CTM2017-85346-R) financed by the Spanish Ministry of Economy and Competitiveness (MINECO) and by the Catalan Government (ref. 2017-SGR-312). Spain. Maria Fernanda Montenegro-Landívar thanks MINECO for her predoctoral fellowship (ref. PRE2018-083861). Paulina Tapia-Quirós thanks to The National Council of Science and Technology of Mexico (CONACYT) for her predoctoral fellowship. Xanuel Vecino acknowledges Spanish Ministry of Science and Innovation for her financial support under the project PID2019-103873R-I00.

References

Abba, Y., Hassan, H., Hamzah, H., Noorim, M.M., 2015. Antiviral activity of resveratrol against human and animal viruses. Adv. Virol. 2015. https://doi.org/10.1155/2015/184241.

Adem, S., Eyupoglu, V., Sarfraz, I., Rasul, A., Ali, M., 2020. Identi- 12688/f1000research.22457.2.

Beigelman, A., Zeiger, R.S., Mauger, D., Strunk, R.C., Jackson, D.J., Martinez, F.D., Morgan, W.J., Covar, R., Sfzer, S.J., Tassigi, L.M., Bacharier, B.L., 2014. The association between vitamin D status and the rate of exacerbations requiring oral corticosteroids in 172, 171–177. https://doi.org/10.1016/j.jaci.2016.07.004.

Daglia, M., 2012. Polyphenols as antimicrobial agents. Curr. Opin. Biotechnol. 23, 174–181. https://doi.org/10.1016/j.copbio.2011.08.001.

Das, S., Sarmah, S., Lyden, S., Singha Roy, A., 2021. An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study. J. Biomol. Struct. Dyn. 39, 3347–3357. https://doi.org/10.1080/07391102.2020.1811530.

Delgado-Roche, L., Mesta, F., 2020. Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. Med. Res. Arch. https://doi.org/10.1016/j.ijar.2020.04.019.

Deng, Y., Kong, X., Qu, L., Yu, P., Liu, Q., Li, W., Qi, B., Bao, L., 2020. Therapeutic efficacy of pulidan xiaoyan Oral liquid (PDL) for COVID-19 in vitro and in vivo. Sing. Transduct. Ther. 5, 2–4. https://doi.org/10.1186/s41392-020-00176-0.

Docherty, J.J., Sweet, T.J., Bailey, E., Faith, S.A., Booth, T., 2006. Reservoir inhibition of vari- 

Cheynier, V., 2012. Phenolic compounds: from plants to foods. Phytochem. Rev. 11, 321–336. https://doi.org/10.1007/s11101-012-9242-8.

Cheng, H.W., Phoon, M.C., Putti, T., Tan, B.K.H., Choy, W.T., 2016. Evaluation of antiviral activities of Houttuynia cordata thunb. extract, quercetin, quercetin and cinamos- in against norovirus and dengue virus replication. Asian Pac J Trp Med 5, 1–7. https://doi.org/10.1016/j.aptem.2013.02.002.

Choi, H.J., Song, J.H., Bhattacharyya, L.R., Bae, S.H., 2010. Anti-human rhinovirus activity of gal- 

Chou, K.H., Phoon, M.C., Putti, T., Tan, B.K.H., Choy, W.T., 2016. Evaluation of antiviral ac- 

Chipman, A., Zoller, S.H., Weller, L.M., Schultze, J., 2017. The role of polyphenols in human health and food systems: a mini-review. Front. Nutr. 5, 1–9. https://doi.org/10.3389/fnut.2017.000087.

Crushoe, S., Rami, S., Tate, J.E., Parashar, U.D., Svensson, L., Hagbom, H., Franco, M.A., Greenberg, H.B., O’Ryan, M. Kang, G., Desselberger, U., Estes, M.K., 2017. Rotavirus infection. Nat. Rev. Dis. Prim. 3. https://doi.org/10.1038/nrdp.2017.83.

Cushnie, T.P.T., Lamb, A.J., 2005. Antimicrobial activity of flavonoids. Int. J. Antimicrob. Agents 26, 343–356. https://doi.org/10.1016/j.ijantimicag.2005.09.002.

Da Silva Antonio, A., Moreira Wiedemann, L.S., Veiga-Junior, V.F., 2020. Natural products’ role against COVID-19. RSC Adv. 10, 23379–23393. https://doi.org/10.1039/ 

dela F. Montenegro-Landívar, P. Tapia-Quirós, X. Vecino et al. Science of the Total Environment 801 (2021) 149719
Hasan, A., Nahar, N., Jannat, K., Afroz, T., Jahan, R., Rahmatullah, M., 2020. In Silico Studies on Phytochemicals of Pimpinella Anisum L. (Apiaceae) as Potential Inhibitors of SARS-CoV-2 3C-Like Protease 6640.

Liang, J., Yan, H., Wang, X., Zhou, Y., Gao, X., Puligundla, P., Wan, X., 2017. Encapsulation of epigallocatechin gallate in zein/chitosan nanoparticles for controlled applications in fruit and vegetable. Food Chem. 231, 19–24. https://doi.org/10.1016/j.foodchem.2017.02.106.

Lin, C.C., Cheng, H.Y., Yang, C.M., Lin, T.C., 2002. Antioxidant and antiviral activities of Eu- phorbia thymifolia L. J. Biomed. Sci. 9, 656–664. https://doi.org/10.1023/A:1012067281.

Lin, L.T., Hsu, W.C., Lin, C.C., 2014. Antiviral natural products and herbal medicines. J. Tradit. Complement. Med. 4, 24–35. https://doi.org/10.1016/j.jtcm.2014.06.008.

Ling, J., Smura, T., Lundström, J.O., Petterson, J.H.-O., Sironen, T., Vapalahti, O., Landvik, A., 2014. J. Food. Nutr. Res. 93, 1719–1738. https://doi.org/10.1128/jvi.00620-19.

Liu, X., Giong, J., Xiang, Y.F., Guo, C.W., Ge, F., Yang, C.R., Zhang, Y.J., Wang, Y.F., Kitzao, K., 2011. Antiviral activity and possible mechanisms of action of pentagalloylglucose on influenza A virus. Arch. Virol. 156, 1359–1369. https://doi.org/10.1007/s00705-011-0989-9.

Liu, D.X., Jiang, J.Q., Fung, T.S., 2020. Human coronavirus-229E, -OC43, -NL63, and -HKU1. Ref. Modul. Life Sci. 43, 1–3. https://doi.org/10.1007/978-0-387-82519-1-x.

Long, F., Yang, H., Xu, Y., Has, H., Li, P., 2015. A strategy for the identification of combina-
torial bioactive compounds contributing to the holistic effect of herbal medicines. Sci. Rep. 5, 1–11. https://doi.org/10.1038/srep12361.

Lopez-Lazaro, M., 2008. Distribution and biological activities of the flavonoid luolin.

Mhatre, S., Srivastava, T., Naik, S., Patravale, V., 2020. Antiviral activity of green tea and Epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded nanoparticles prepared from chitosan and polysaccharide. J. Agric. Food Chem. 62, 12603–12609. https://doi.org/10.1021/acs.jafc.2c00521.

Mhatre, S., Smith, W.S., Wang, X., Hossain, Z., Eng, V.T., Cui, L., Lin, T., Amin, S., 2016. Development of an optimized hyaluronic acid-based lipidic nanoemulsion for targeted delivery of SARS-CoV-2 3C-like protease. J. Pharm. Anal. 10, 1–10. https://doi.org/10.1016/j.jphana.2019.07.008.

Mhatre, S., Palamara, A.T., Nencioni, L., Aquilano, K., De Chiara, G., Hernandez, L., Cozzolino, F., Ciriolo, M.R., Caraci, E., 2015. Identi-
fication and valorization of olive mill wastewater. Water Res. 114, 1–10. https://doi.org/10.1016/j.watres.2017.02.002.

Mhatre, S., Torres, J.L., 2014. Identi-
fication of polyphenols from an antiviral Chamaecrista nictitans extract using high-resolution LC-ESI-MS/MS. J. Agric. Food Chem. 60, 5501–5506. https://doi.org/10.1021/jf403794p.

Mhatre, S., Shrestha, S., Kassinos, D., 2017. Treatment ef-
ciency and economic feasibility of biological oxida-
tion and membrane bioreactor for the treatment of domestic waste water. Bioresour. Technol. 235, 1–13. https://doi.org/10.1016/j.biortech.2016.11.010.

Mhatre, S., Shrestha, S., Kassinos, D., 2017. Treatment ef-
ciency and economic feasibility of biological oxida-
tion and membrane bioreactor for the treatment of domestic waste water. Bioresour. Technol. 235, 1–13. https://doi.org/10.1016/j.biortech.2016.11.010.

Motran, R., Giri, H.L., 2009. Polyphenols as dietary supplements: a double-edged sword. Nutr. Diet. 66, 255–263. https://doi.org/10.1111/j.1440-1690.2008.00575.x.

Muñoz, E., 2014. Introduction and dispersal of sindbis virus from Central Africa to Europe. J. Virol. 93, https://doi.org/10.1128/jvi.00620-19.

Park, J.Y., Ko, J.A., Kim, D.W., Kim, Y.M., Kwon, H.J., Jeong, H.J., Kim, C.Y., Park, K.S., Lee, W.S., Ryu, Y.B., 2016. Chalcones isolated from Angélica keiskei inhibit cytost}
proteases of SARS-CoV-2, Enzyme Inhib. Med. Chem. 31, 23–30. https://doi.org/10.3109/14757366.2014.10003215.

Pathan, E.K., Shinde, K.H., Shinde, K.S., Park, K.H., Ryu, Y.B., Lee, W.S., 2017. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protein inhibitors. J. Enzyme Inhib. Med. Chem. 32, 504–512. https://doi.org/10.1007/s10529-016-9825-7.

Patra, J.K., Sahu, A.K., Kar, P., Sadhukhan, S., 2020. Plant-derived natural polyphenols as antiviral agents. J. Nutr. Food Environ. Anal. 51, 23–46. https://doi.org/10.1007/s00701-019-09139-9.

Pacreau, S., Fraceto, L.F., Campos, E.V.R., Diaz-Torres, L.A., Grillo, C.M., 2021. Bioactive Polyphenols Pore-Granate Extract Polyphenol Antioxidants Satisfy the SARS-CoV-2 s-glycoprotein Binding Ability to ACE2 Receptor: In Silico and in Vitro Studies. 114.

Pyott, S., Prakash, A.K., 2015. Resistance of herpes simplex virus (HSV-1) to nucleoside analogues: mechanisms, prevalence, and management. Antimicrob. Agents Chemother. 59, 459–472. https://doi.org/10.1128/AAC.02615-10.

Plotkin, S., Orenstein, W., Offit, P., 2012. Vaccines: expert consult. 6th ed. Saunders.

Pomeranz, Y., Johnson, P., Thomas, J., 2005. New insights to HIV/AIDS. Rev. Nutr. Drug Dev. 4, 236–248. https://doi.org/10.1080/166072404900000006.

Prati, D., Kirchhoff, L., Bruning, J., Rachmannawi, H., Steinmann, J., Steinmann, E., 2019. Anti-infective properties of the golden spice curcumin. Front. Microbiol. 10, 1–16. https://doi.org/10.3389/fmicb.2019.01310.

Racaniello, V.R., 2006. One hundred years of poxvirus pathogenesis. Virology 349, 4–16. https://doi.org/10.1016/j.virology.2005.09.015.

Ragab, F.A., Yahya, T.A.A., El-Naa, M.M., Arafa, R.K., 2014. Design, synthesis and structure-activity relationship of novel semi-synthetic flavonoids as antiproliferative agents. Eur. J. Med. Chem. 82, 506–520. https://doi.org/10.1016/j.ejmech.2014.06.007.

Riedel, C., Vasishtan, D., Pratap, R., 2018. Protective effects of Bacillus subtilis on adenovirus infection in vitro and in vivo. Virology 520, 102–109. https://doi.org/10.1016/j.ejmech.2014.06.007.

Ruskin, C., Schwab, L., Pratap, R., 2018. Protective effects of Bacillus subtilis on adenovirus infection in vitro and in vivo. Virology 520, 102–109. https://doi.org/10.1016/j.ejmech.2014.06.007.

Scalbert, A., Williamson, G., 2000. Dietary intake and bioavailability of polyphenols. Am. J. Clin. Nutr. 72, 1455S–1461S. https://doi.org/10.1093/ajcn/72.5.1455.

Scardapane, S., Moccia, S., Spagnuolo, C., Tedesco, I., Russo, G.L., 2020. Roles of polyphenols for the prophylaxis and therapy of COVID-19. Antioxidants 9, 1074. https://doi.org/10.3390/antiox91101074.

Sekeredjiva, J., Serkedjieva, J., Gegova, G., Mladenov, K., 2008. Protective effects of Bacillus subtilis on adenovirus infection in vitro and in vivo. Virology 520, 102–109. https://doi.org/10.1016/j.ejmech.2014.06.007.

Saurina, J., Granados, M., 2020. Olive mill and winery wastes as viable sources of bioactive compounds: a study on polyphenols recovery. Antioxidants 9, 1074. https://doi.org/10.3390/antiox91101074.

Saurina, J., Sentellas, S., 2015. Determination of phenolic compounds in food matrices: application to characterization and authentication. Fast Liq. Chromatogr. Spectrom. Methods Food Environ. Anal. 517, 547–557. https://doi.org/10.1002/fcm2.2014040013.

Sekeredjiva, J., Georgova, G., Mladenov, K., 2008. Protective efficacy of an aerosol preparation, obtained from Geranium sanguineum L., in experimental influenza infection. Farmacia 63, 160–163. https://doi.org/10.1016/j.farm.2008.07.017.

Shahidi, F., Ambigaipalan, P., 2015. Phenolics and polyphenolics in foods, beverages and foods. In: Food Science and Technology. https://doi.org/10.1186/s40694-015-0192-9.

Singh, S., Sk, M.F., Sonawane, A., Kar, P., Sadhukhan, S., 2020. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm. Sin. B 10, 766–788. https://doi.org/10.1016/j.apsb.2020.02.008.

Spring Harb. Perspect. Med. 2. https://doi.org/10.1101/cshperspect.a006924.

Suntarajezan, A., Ganapathy, R., Huan, L., Dunlap, J.R., Webby, R.J., Kotwal, G.J., Sangster, M., 2015. Influenza virus strain variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. Antivir. Res. 88, 1–9. https://doi.org/10.1016/j.antiviral.2014.12.005.

Sundquist, W.J., Kräusslich, H.G., 2012. HIV-1 assembly, budding, and maturation. Cold Spring Harb. Perspect. Med. 2. https://doi.org/10.1101/cshperspect.a005924.

Sukowati, C.H., El-Khobar, K.E., Ie, S.I., Anfuso, B., Muljono, D.H., Tiribelli, C., 2016. Significance of hepatitis virus infection in the oncogenic initiation of hepatocellular carcinoma. World J. Gastroenterol. 22, 1497–1512. https://doi.org/10.3748/wjg.v22.i23.1497.

Sundararajan, A., Ganapathy, R., Huan, L., Dunlap, J.R., Weebly, R.J., Kotwal, G.J., Sangster, M., 2015. Influenza virus strain variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. Antivir. Res. 88, 1–9. https://doi.org/10.1016/j.antiviral.2014.12.005.
Yang, Y., Islam, M.S., Wang, J., Li, Y., Chen, X., 2020. Traditional chinese medicine in the
treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review
and perspective. Int. J. Biol. Sci. 16, 1708–1717. https://doi.org/10.7150/ijbs.45538.
Yao, Y., Luong, T.N., Leplik, M., Aftab, N., Tong, V.H., Veira, A., 2012. Synergism of antioxi-
dant phytochemicals: comparisons among purified polyphenols and dietary-plant
extracts. Acta Hortic. 939, 121–127. https://doi.org/10.17660/ActaHortic.2012.939.15.
Yudi Utomo, R., Meiyanto, E., 2020. Revealing the potency of citrus and galangal constitu-
tents to halt SARS-CoV-2. Infection 2, 1–8. https://doi.org/10.20944/pre-
prints202003.0214v1.
Yugo, D.M., Hauck, R., Shivaprasad, H.L., Meng, X.J., 2016. Hepatitis virus infections in
poultry. Avian Dis. 60, 576–588. https://doi.org/10.1637/11229-070515-Review.1.
Zahoor, M., Shah, A.B., Naz, S., Ullah, R., Bari, A., Mahmood, H.M., 2020. Isolation of quer-
cetin from Rubus fruticosus, their concentration through NF/RO membranes, and re-
covery through carbon nanocomposite. A pilot plant study. Biomed Res. Int. https://
doi.org/10.1155/2020/8216435.
Zandi, K., Taberzadeh, M., Yaghoubi, R., Tajbakhsh, S., Rastian, Z., Fouladvand, M., Sartavi,
K., 2009. Antiviral activity of Avicennia marina against herpes simplex virus type 1
and vaccine strain of poliovirus (an in vitro study). J. Med. Plants Res. 3, 771–775.
Zandi, K., Teoh, B.T., Sam, S.S., Wong, P.F., Mustafa, M., Abubakar, S., 2011. Antiviral activity
of four types of bioflavonoid against dengue virus type-2. Virol. J. 8, 1–11. https://doi.
org/10.1186/1743-422X-8-960.
Zandi, K., Teoh, B.T., Sam, S.S., Wong, P.F., Mustafa, M., Abubakar, S., 2012. Novel antiviral
activity of baicalein against dengue virus. BMC Complement. Altern. Med. 12. https://
doi.org/10.1186/1472-6882-12-214.
Zhang, X., Huang, H., Zhan, X., Lv, Q., Sun, C., Li, X., Chen, K., 2015. Effects of flavonoids-rich
chinese bayberry (Myrica rubra sieb. et zucc.) pulp extracts on glucose consumption
in human HepG2 cells. J. Funct. Foods 14, 144–153. https://doi.org/10.1016/j.jff.2015.
01.030.
Zhang, L., Mc Clements, D.J., Wei, Z., Wang, G., Liu, X., Liu, F., 2020. Delivery of synergistic
polyphenol combinations using biopolymer-based systems: advances in physico-
chemical properties, stability and bioavailability. Crit. Rev. Food Sci. Nutr. 60, 2083–2097.
https://doi.org/10.1080/10408398.2019.1630358.