



## An Overview of Pomegranate Peel: A Waste Treasure for Antiviral Activity

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### ABSTRACT

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Agricultural waste has always been a global problem that causes environmental pollution, and thanks to the efforts of scientists, this agricultural waste has become not a neglected product, but rather a source of many effective chemical compounds that have industrial, pharmaceutical and food applications. Viral disease therapy has attracted a great deal of scientific interest worldwide. Therefore, the pace of research is increasing for effective and safe treatment. The potential inhibitory activity of pomegranate peel extract polyphenols against virus for effective viral disease therapy has attracted a great deal of scientific interest. The aim of this review was to present an overview of the pomegranate peel effects on viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Influenza virus, Norovirus, Adenovirus, Herpes simplex virus, Coronavirus disease (COVID-19). Pomegranate is consumed as fresh fruit and juice for its reported health benefits as antioxidant, antidiabetic, hypolipidemic, antibacterial, anti-inflammatory, antiviral, anticarcinogenic activities, and improves cardiovascular as well as oral health. The health benefits of pomegranate have been attributed to its wide range of phytochemicals, which are predominantly polyphenols, ellagitannins, anthocyanins, and other polyphenols. Instead of the pomegranate peel being a neglected product, it is considered as a promising antiviral agent which also offers other health benefits without side effects.

**Keywords:** Human Virus, Pomegranate peel extract, Antiviral effect, Plant active components.

### Introduction

The goal of scientists has always been to search seriously for an antiviral treatment. Previous studies have acknowledged the high content of phenols in pomegranate<sup>1,2</sup> and showed that extracts of different parts of the pomegranate have many biological activities such as antimicrobial, antiviral, antioxidant, anti-inflammatory, anti-diabetic, anti-heart, and anti-cancer.<sup>3</sup> Pomegranate fruits are used in traditional medicine and medicine for its effectiveness in treating liver failure, dry cough, facial swelling, skin itching, and jaundice. Also, pomegranate peel is useful in treating sore throats, gastrointestinal worms and diarrhoea. Due to the availability of nutraceutical products and high content of active compounds in the fruits and peel, it is used to fight diseases such as adenovirus infection.<sup>4</sup> The therapeutic potential of pomegranate peel is attributed to the chemical compounds with biological activity such as tannins, ellagic acid, gallic acid,

catechins, flavonoids, and anthocyanins.<sup>3,5-8</sup> Pomegranate peel also contains a variety of polysaccharides, organic acids, alkaloids, polyphenols, fatty acids, vitamins, etc.<sup>4,9</sup> Several studies on pomegranate have reported that the pomegranate peel represents approximately 30% of the fruit,<sup>9</sup> and that it is a good source of tannins, flavonoids and phenolic compounds such as punicalagin (ellagitannin), gallic acid, ellagic acid, catechins, and chlorogenic, caffeic, and ferulic acids and that these compounds act as antioxidants, anti-inflammatory, antineoplastic, anti-bacterial, and anti-viral.<sup>9-15</sup>

Hence their increased use as ingredients in herbal products and nutritional supplements. Moreover, the highest total phenolic content was detected in pomegranate peel in comparison with juice and seeds.<sup>16</sup> Thus, our review focuses on highlighting the therapeutic uses of pomegranate waste to benefit from beneficial health bio-activities rather than as a neglected waste. One of the results obtained by Corao<sup>17</sup> is that pomegranate peel extract inhibits  $\alpha$ -glucosidase and human leukocyte elastase activity, thus impairing viral binding and penetration by disrupting the glycosylation of viral glycoproteins. In another study, it was shown that pomegranate extracts have antiviral effects against the human immunodeficiency virus (HIV) as a result of blocking the binding of HIV-1 gp 120 envelope glycoprotein, which prevents the interaction of HIV-1 with CD4 receptors, thereby reducing viral infection.<sup>18</sup>

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## Materials and Methods

This review was conducted based on previous scholarly works, which were accessible online and published in English. The source includes Google Scholar, PubMed, ResearchGate and Scopus, and other platforms for reviews and studies related to the aim of this work. The search terms included viruses, pomegranate peel, humans, infection, and other related terminologies.

## Results and Discussion

### Human noroviruses (HuNoV)

Norovirus is a highly contagious virus that infects all ages by contact with an infected person, consuming contaminated food or water and touching contaminated surfaces and then putting unwashed hands in the mouth.<sup>19</sup> Human norovirus is the most common enterovirus and causes about 19 to 21 million cases of vomiting and/or diarrhoea annually.<sup>20</sup> Pomegranate peel is high in phenolic compounds and tannins have beneficial health effects and broad biological activity. Ellagitannins and punicalagin and its derivatives are the main compounds potentially responsible for antimicrobial and antioxidant activity.<sup>21</sup> Also, ellagitannins and anthocyanins have a synergistic effect in enhancing the prevention of pathogens as antimicrobial and stimulate the growth of beneficial microbes in the human gut and antiviral properties against human noroviruses.<sup>22-25</sup> Hence the importance of pomegranate peel extracts and their practical importance in terms of they may be important natural additives for the food industry to improve safety, quality, food preservation and prevent food contamination.<sup>26,27</sup>

### Adenovirus

Adenoviruses (ADVs) are non-enveloped double-stranded DNA viruses of over 70 species (genotypes) of which seven are classified into human Adenovirus. The human adenovirus causes a number of diseases, and causes serious infections, especially in individuals with severe immunosuppression. Despite the risk of adenovirus infection, there is no approved anti-adenoviral therapy.<sup>28</sup> Whereas, no effective treatment or definitively approved drug has been developed for diseases associated with ADV. The drugs cidofovir and ribavirin are used against ADV.<sup>29</sup> Karimi *et al.*<sup>28</sup> showed that the extract of pomegranate peel had anti-adenoviral effect, and gallic acid had high anti-adenoviral activity and recommended pomegranate peel extract as a promising new anti-adenovirus agent.

### Influenza virus

Influenza virus is one of the most common human respiratory pathogens, which is associated with a high level of morbidity and mortality<sup>30,31</sup> and is therefore of public health concern. Although vaccination is an appropriate approach to influenza prevention, this method must be updated to be effective on new subtypes due to ongoing changes in influenza surface.<sup>30,31</sup> Due to the limited options for controlling and treating the disease, search for safe natural alternatives such as using herbal extracts of pomegranate peel becomes necessary. Moradi *et al.*<sup>30</sup> showed the high effect of pomegranate peel extract against influenza A virus, and recommended ethyl acetate fraction of pomegranate peel to prevent replication of the influenza A virus in the laboratory.

### Herpes simplex virus

The herpes simplex virus belongs to the family Herpes viridae family and infects humans,<sup>32</sup> leading to a range of diseases from simple uncomplicated mucocutaneous (e.g. cold sores) skin to more serious infections such as keratitis.<sup>32</sup> HSV-1 is the causative agent of cold sores and encephalitis, while HSV-2 is usually associated with anogenital infection.<sup>33</sup> Recently, drug-resistant strains of herpes appeared,<sup>34-36</sup> therefore, there is a need for new and more effective treatments for herpes simplex virus infection.<sup>33</sup> As demonstrated by the results of Houston *et al.*<sup>32</sup> study that pomegranate peel extract has potent antiviral activity against HSV-1 for the content of Punicalagin present in pomegranate peel extract. A similar conclusion was reached by Moradi *et al.*<sup>37</sup> in their study to evaluate the *in vitro* anti-HSV-1

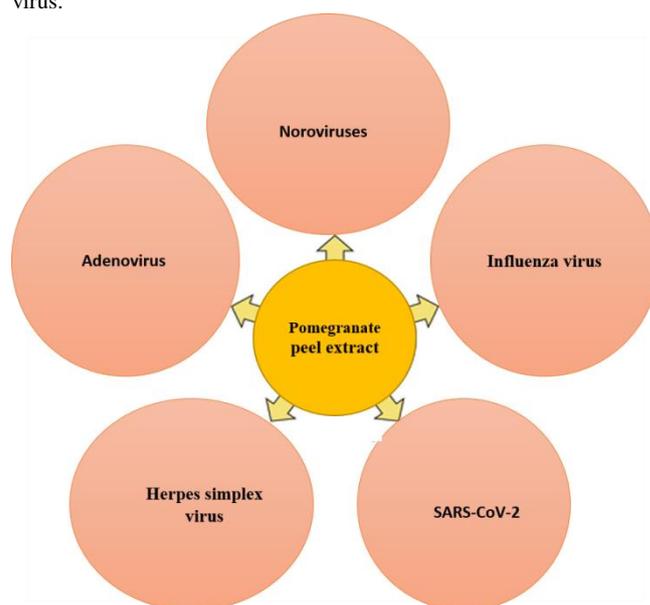
activity of pomegranate peel extract and revealed that pomegranate peel extract showed anti-HSV activity, due to its bioactive constituents. They added that pomegranate peel extract is a promising source of a medically important natural compound.

### Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Late in the year 2019, SARS-CoV-2 was first identified in Wuhan, China, and its unprecedented spread has led to it being one of the most serious epidemics in human history. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a zoonotic pathogenic virus, it is an enveloped positive-sense single-stranded RNA virus. Covid-19 is continuing to spread around the world, with 270 million confirmed cases and more than five million deaths across almost 200 countries.<sup>38</sup> While the infection usually causes only mild symptoms, some individuals develop severe illness that causes multiple organ damage.<sup>39,40</sup> As a consequence, scientists have been working tirelessly trying to discover effective preventive treatments and therapeutic agents.<sup>39</sup> Among the attempts made on plants and their active ingredients was pomegranate peel which contains biologically active compounds such as polyphenols, sesquiterpenes, and triterpenes, which potentially have antiviral activities.

Tito *et al.*<sup>39</sup> conducted a study for evaluating pomegranate peel extract and its efficacy against SARS-CoV-2 and the results obtained opened promising new opportunities for the development of effective and innovative therapies in the fight against SARS-CoV-2 from pomegranate peel. As the pomegranate peel extract is rich in bioactive molecules such as polyphenols that play vital roles in plant survival by protecting against pathogens such as bacteria, viruses and fungi. Studies have previously demonstrated the antiviral ability of some polyphenols against a range of viral infections, including influenza, Epstein-Barr virus, and herpes simplex virus.<sup>39</sup> Plant polyphenols could be a potential candidate for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) treatments.<sup>39</sup> The two polyphenols are punicalagin and theaflavin could be exploited as a strategy to prevent virus entry into human cells.<sup>39</sup> Also, curcumin, kaempferol, catechin, naringin, and quercetin may inhibit the activity and replication of SARS-CoV-2.<sup>39</sup>

This was evident in the study of Tito *et al.*<sup>39</sup> using pomegranate peel extract against SARS-CoV-2. It was shown that punicalagin is the most abundant polyphenol and represents 38.9% of all polyphenols, followed by pedunculagin (16.7%) and punicalagin (13.2%). Also, Tito and coworkers<sup>39</sup> showed that concentrations ranging from 0.04 mg/ml to 1 mg/ml for these compounds were up to 74% effective in inhibiting the virus. Moreover, the compounds punicalagin, punicalin and ellagic acid were the most effective compounds in inhibiting the virus.



**Figure 1:** Antiviral activity of pomegranate peel extract.

Therefore, the results showed that the polyphenols in pomegranate peel may play multiple biological roles in limiting the ability of SARS-CoV-2 to infect host cells and may pave the way for new ideas about how to reuse the by-products for medical and health care applications. This was explained that components in extracts obtained from pomegranate peel inhibit the binding of SARS-CoV-2 to the human host cell receptor and angiotensin-converting enzyme 2 (ACE2) *in vitro*. It also inhibited virus replicate and survive inside the host cell.<sup>39</sup> Studies have also indicated that the polyphenols in pomegranate peel such as ellagitannins, gallic acid, ellagic acid, and its glycosylated derivatives, and anthocyanins compounds have strong antioxidant activity and have protective activity against degenerative chronic diseases, such as some types of cancer, type 2 diabetes, atherosclerosis, and cardiovascular diseases.<sup>41-43</sup>

Hence, studies focused on pomegranate peel extracts, which showed antibacterial and antiviral activity<sup>44</sup> and inhibition of influenza<sup>45</sup> and herpes virus<sup>32</sup>, and it can also be used successfully as antiviral agents against SARS-CoV2. It was found that the aqueous-alcoholic extract

obtained from pomegranate peel was able to inhibit the binding between SARS-CoV-2 S glycoprotein and ACE2 *in vitro*, indicating the potential of the extract in preventing SARS-CoV-2 entry into host cells. In addition to inhibiting the 3CL virus protease, this contributes to the possibility of using the extract as a natural remedy to enhance protection against SARS-CoV-2.<sup>39</sup>

Studies have indicated that plants are used for medicinal and health beneficial as a result of the large number of important plant-derived compounds under investigation for their potential therapeutic effects against SARS-CoV-2. Among those suggested are polyphenol compounds, such as curcumin, kaempferol, catechin, naringin, quercetin<sup>46</sup> or hesperidin, rutin, and diosmin<sup>47</sup> to inhibit the activity of the main SARS-CoV-2 protease and, consequently, viral replication.<sup>48</sup> It may be due to the binding of two polyphenols, punicalagin and theaflavin, to the S protein, the importance of which can be exploited as a strategy to prevent virus entry into human cells. Figure (2) show the flavonoids, tannins and phenolic acids identified in pomegranate peel extract.

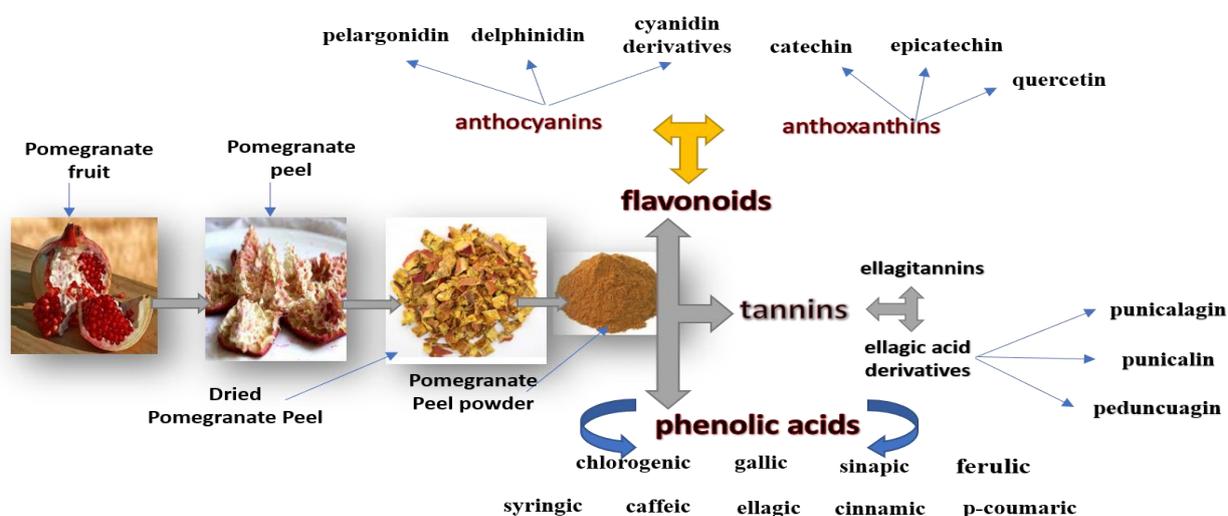


Figure 2: Major chemical constituents of pomegranate peel extracts.

## Conclusion

This review unravels that pomegranate is a natural rich source of vitamins, polyphenols, dietary fibre and many important compounds, making it a superfood due to its high antioxidant potential and other beneficial effects on human health. Pomegranate peels contain high concentrations of bioactive compounds with numerous bioactivities such as antiviral, antioxidant, antibacterial and anti-inflammatory activities. Pomegranate peel can be considered as an alternative antiviral agent which also offers other benefits to human health.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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