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Ecocience
INTERNATIONAL JOURNAL

Vol.5, No. 8, enero-junio 2023

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Ecocience International Journal
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DOI: https://doi.org/10.35766/j.ecocience

ECOCIENCE INTERNATIONAL JOURNAL, 5 (8), ENERO-JUNIO 2023, es una Publicación semestral editada por CORPORACIÓN UNIVERSITARIA CIFE S.C. (www.cife.edu.mx), Calle Tabachín, 514, Bellavista, 62140, Cuernavaca, Morelos, México.Tel. (01)777 243 8320.Sitio Web: www.cife.edu.mx/ecocienceE-mail: forhum@cife.edu.mx

Director Editorial: Dr. Josemanuel Luna-Nemecio

Reserva de Derechos al Uso Exclusivo No. 04-2022-051714010000-102, ISSN: 2992-6998 ambos otorgados por el Instituto Nacional del Derecho de Autor. Responsable de la última actualización de este número, Unidad de Desarrollo Tecnológico de la Corporación Universitaria CIFE S.C., Calle Tabachín, 514, Bellavista, 62140, Cuernavaca, Morelos, México: JUNIO 2022.

Ecocience International Journal
ISNN: 2992-6998

DOI: https://doi.org/10.35766/j.ecocience

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Vol 5. , No. 8, ENERO-JUNIO 2023

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Ecocience
INTERNATIONAL JOURNAL

https://doi.org/10.35766/j.ecocience.23583
ISNN: 2992-6998
Vol. 5, No. 8, 2023 | e23583 | enero-junio 2023
Recibido: Marzo, 13, 2023 | Aprobado: Mayo 11, 2023
Publicado: Junio 30, 2023

Cáscaras de frutas como vehículo para la disponibilidad de compuestos fenólicos con actividad contra el virus de la influenza

Fruit peels as a vehicle for the availability of phenolic compounds with anti-influenza virus activity

Resumen: La influenza es un virus que infecta las vías respiratorias causando altos índices de mortalidad. Las cáscaras de las frutas son estudiadas debido a la cantidad de compuestos fenólicos (PC) encontrados con funciones positivas a la salud. Se han aportado abundantes pruebas sobre el gran potencial de los PC contra diferentes virus que causan problemas de salud generalizados. Estas acciones dependen de la hidroxilación, la metoxilación y la alquilación de varios componentes del anillo polifenólico. Quercetina, ácido gálico, epigalocatequina, catequina son algunos PC que se les han analizado su actividad contra el virus de la influenza, bloqueando la entrada en las células huésped, inhiben la multiplicación del virus y protegen contra la sobreinfección. La gran variedad de mecanismos de acción de los PC contra las infecciones víricas podría aplicarse como estrategia de tratamiento o naturales. El presente trabajo es una revisión descriptiva centrada en las potenciales propiedades antivirales de los PC provenientes de la cáscara de frutas sobre el virus de la influenza.

Palabras clave: actividad antiviral; cáscara; compuestos fenólicos; gripe; resfriado

Abstract: Influenza is a virus that infects the respiratory tract causing high mortality rates. Fruit peels are studied due to the amount of phenolic compounds (PC) found with positive health functions. Abundant evidence has been provided on the great potential of PC against different viruses that cause widespread health problems. These actions depend on the hydroxylation, methoxylation and alkylation of several components of the polyphenolic ring. Quercetin, gallic acid, epigallocatechin, catechin are some PC that have been tested for their activity against influenza virus, blocking entry into host cells, inhibiting virus multiplication and protecting against superinfection. The wide variety of mechanisms of action of PC against viral infections could be applied as a treatment or prevention strategy; but at the same time, they could be used to produce natural antiviral drugs. The present work is a descriptive review focused on the potential antiviral properties of PC from fruit peel on influenza virus.

Keywords: *antiviral activity; catarrh; cold; peel; phenolic compounds*

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Conflicto de intereses
Mencionar posible conflicto de interés.

Financiamiento
Mencionar si el artículo recibió un apoyo económico

Agradecimientos
Mencionar los agradecimientos

Nota
Mencionar si el artículo forma parte o no

Cita sugerida (APA, séptima edición)
Mercado, G., Hernández, D. (2023). Cáscaras de frutas como vehículo para la disponibilidad de compuestos fenólicos con actividad contra el virus de la influenza. *Ecocience International Journal*, *5*(8), e23583. https://doi.org/10.35766/j.ecocience.23583

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Introduction

Influenza is an emerging acute respiratory disease caused by the virus belonging to the *Orthomyxoviridae* family, which enters through the respiratory tract causing problems in people of all ages, mainly in children, young people and the elderly, manifesting itself mainly in the winter season. This disease occurs with greater incidence in people who self-medicate. Therefore, viruses become resistant to antibiotics, increasing contagion and causing problems in the nose, throat, bronchial tubes and lungs, which can last approximately 14 days.

Most of those affected usually recover by self-medication or consumption of fruit juices, but the disease may recur more frequently and with other conditions, such as pneumonia or cause death. For this reason, it is important to point out that this disease does not have a cure so it is necessary to lessen the discomfort through rest, fluid intake, home remedies, gargling with warm salt water, cough drops and medications to relieve body pain. In this sense, alternatives are sought to obtain components that have the potential to reduce the ailment (Zhu, Fodor and Keown, 2023).

The peels are a resource because they have been proven to contain antiviral compounds, such as phenolic compounds (PC). Several studies have shown that these compounds can act by inhibiting the activity of viruses such as SARS-CoV-2, inovirus, adenovirus, coronavirus (Niño-Gutiérrez, 2021), metapneumovirus and influenza (Ninfali et al., 2020). Therefore, the present study consists of describing the importance of taking advantage of the pharmaceutical value of PC present in fruit peels and their antiviral properties.

Development

Influenza overview

Influenza, colloquially called flu, is an infection that is easily transmitted from person to person through respiratory secretions with the appearance of nasal congestion, sneezing, fluid, watery and abundant rhinorrhea, discomfort and itching in the throat, dry cough, muscle aches, headache, bronchial and, occasionally, in the lungs; having an approximate duration of 10 to 13 days with temperature ranging between 38 to 41°C (Krammer et al., 2018). This disease is transmitted by inhaling particles (<5 μm in diameter) suspended in the air affecting people at any age group, mainly children <2 years, elderly >65 years, pregnant women and patients with pathologies (chronic diseases, diabetes, neuropathies, cystic fibrosis, asthma, neoplastic diseases), so it has become a serious problem due to high morbidity and mortality. Nowadays, it is common to confuse between common cold and flu; although they share some symptoms, it is common to make the mistake of mentioning these pathologies indistinctly, so it is important to highlight the differences as described in Table 1 (Shie and Fang, 2019; Krammer et al., 2018).

Table 1.
Differences in symptoms between the common cold and the influenza

Symptomatology	*Cold*	*Influenza*
Incubation time (h)	48 – 72	18 - 36
Virus	Rinovirus y coranovirus	Infuenza
Aches and pain	Slight	Assiduous, usually severe

Onset	Sudden	Paulatine
Fever	Sporadic or almost null	Assiduous with 38 - 41°C, especially in infants
Chills	Sporadic	Frequent
Sneezing	Assiduous	Sporadic
Runny nose	First three days	Sporadic
Stuffy nose	Assiduous	Sporadic
Headache	Sporadic	Assiduous e intenso
Cough	Assiduous	Assiduous, can become intense
Myalgia	Sporadic	Assiduous
Low back pain	Assiduous	Assiduous
Odynophagia	Assiduous	Sporadic
Eye irritation	Assiduous	Sporadic
Fatigue or weakness	Sporadic	Usually lasting up to 3 weeks
Extreme exhaustion	Never	Within the first few days and Frequent
Chest discomfort	Mild to moderate	Assiduous

Source: Czubak et al., (2021).

Morphology and organization of the genome and coding proteins of the influenza virus

Influenza is found within the *Orthomyxoviridae* family, which refers to the affinity it has for mucin, a mucoprotein present in the mucus of various secretions, epithelial receptors, red blood cell membrane and serum. The virus is grouped into A, B, C, Thogovirus and Isavirus, being genus A the most common and leading with higher infection and incidence of morbi-mortality in humans due to the capacity of mutation and constant evolution, which leads to make resistant to antigenic (Zhu, Fodor and Keown, 2023). Influenza viruses of genus A and B have a variable appearance (spherical or filamentous) with an average diameter of 100 nm and 300 nm in length, while the structure of genus C is usually in the form of a cord of about 500 nm (Krammer et al., 2018).

The influenza virus has a lipid envelope in which hemagglutinin (HA), neuraminidase (NA) and small amounts of M2 protein are embedded. Inside is the matrix protein, which surrounds the viral genome, coated by proteins (PB1, PB2 and PA) that make up the RNA polymerase and the NP nucleoprotein. The viral genome comprises 13,588 nucleotides that are fragmented by the viral genome comprises 13,588 nucleotides, which is fragmented by eight single-stranded RNA segments of different sizes (890 to 2,350 nucleotides) and encodes eleven viral proteins. The genome can undergo variations in the type of H and N proteins, this causes RNA segments to be exchanged between two or more different viruses in the same cell, giving rise to new variants (Medina and

García-Sastré, 2011). For this reason, there are currently >120 virus strains, the most frequent being Rhinovirus which prevails in autumn and spring and Coronavirus in late autumn and winter (Zhu, Fodor and Keown, 2023).

The glycoprotein HA is found to express approximately 80% of viral surface glycoproteins forming homotrimers of cylindrical shape. Each homotrimer is confirmed by a fibrous stalk, which at one end inserts into the viral membrane, while at the other end is the globular domain with three binding sites for sialic acid. Thus, sialic acid defines the particular tropism of influenza viruses due to the specificity that different virus strains have for different types of sialic acid bonds with the preceding galactose in the carbohydrate chain. Thus, HA binds to sialic acid residues attached to galactose via 2,6-galactoside linkages. Epithelial cells lining the human trachea have mainly α2,6-linked carbohydrates (Noda, 2011). The HA1 subunit is responsible for binding to sialic acid-containing receptors, which affinity determines their pathogenicity in human cells. The HA2 subunit participates in the fusion between the viral membrane and the endosomal membrane. The endosome containing the virion is acidified causing a conformational change in HA2 that allows the strangulation of the viral and endosomal membranes, releasing the ribonucleoprotein into the cytoplasm (Jones, Le Sage and Lakdawala, 2020; Noda, 2011).

On the other hand, NA has the function of cleaving the bonds between HA and sialic acid in order to release the virion from the infected cell. NA is found on the surface of the virion forming a homotetramer, each monomer is composed of a cytoplasmic domain, a transmembrane region, a hypervariable stalk, and a globular head that has the catalytic domain of this enzyme, with highly conserved regions in its active site. Other functions of NA include preventing the aggregation of released virions and breaking the N-acetyl-neuraminic acid bonds of the mucus so that the virus can establish itself in the upper respiratory tract (Krammer et al., 2018).

Once the virus has bound to its receptor in the cell, it enters the cytoplasm by endocytosis and the low pH of the endosome causes a change in the conformation of the virus hemagglutinin protein, which favors the fusion of the cell and viral membranes, allowing the viral particle to enter the cytoplasm of the cell. The acidic pH within the endosome favors the dissociation of the ribonucleoproteins associated with the viral genome. The M2 protein allows the entry of protons into the viral particle and releases the viral genome, which enters the cell nucleus and initiates its transcription and replication. The viral messenger RNA is translated to form the corresponding proteins, and finally the new viruses assemble in the cell cytoplasm and exit by budding through the plasma membrane, which has been previously modified by the insertion of the viral proteins HA, NA and M2 (Kausar et al., 2021).

Antiviral treatment

The drugs focus on inhibiting NA activity and stopping viral shedding and disease development. Drug treatment for influenza virus has been shown to reduce the severity and days of symptoms. There are two classes of antivirals for the treatment of influenza, adamantanes and NA inhibitors. The adamantanes block the M2 protein ion channel so that they inhibit the intracellular release of the virus; while the viral NA inhibitors prevent the release of viruses into the respiratory tract and their subsequent dissemination (Swierczynska, Mirowska-Guzel, Pindelska, 2022; Kausar et al., 2021).

The influenza virus can resist the drug causing a decrease in the effectiveness of its dose, due to the substitution of a histidine for a tyrosine at position 275 of the NA gene. This mutation does not affect susceptibility to zanamivir since the NA molecule has a different genetic basis. Therefore, there are other antiviral treatments that are not as widely used, for example ribavirin, which inhibits iniosine-monophosphate, oligonucleotides that interfere with viral RNA translation, interferon

inducers and nonstructural protein gene (NS1) inhibitors. It has also been suggested that the combination of antivirals can be administered, but there is scientific evidence on their effectiveness against influenza virus (Swierczynska, Mirowska-Guzel and Pindelska, 2022).

Phenolic compounds in fruit peels

In order to search for natural and alternative sources of antiviral drugs and considering that pharmaceuticals require the incorporation of natural and efficient compounds for the reduction of these microorganisms, food matrices, including fruit peels, have been sought as a better option to obtain compounds that help against the influenza virus (Niño-Gutiérrez & Luna-Nemecio, 2021). These by-products represent alternatives for research and industrialization, preventing them from being discarded and causing a negative impact on the environment.

Thus, their use aims to recover their economic value through reuse, remanufacturing, redesign and recycling with the possibility of generating different alternatives in different areas (industry, cosmetics, pharmaceuticals, wastewater remediation) (Sadef et al., 2022). Multiple publications have reported the identification of different PC (Table 4), including hydroxybenzoic and hydroxycinnamic acid derivatives, as well as flavonoids with one or a high degree of polymerization of hydroxyl groups or functional derivatives (esters, methylates, glycosides) (Ninfali et al., 2020). For this reason, fruit peels have been awakening a great interest for their beneficial properties that they could exert on human health, among which this article focuses on the antiviral properties.

Antiviral activities of PC and their importance in pharmacology

Several experimental studies have sought to find the effectiveness of the antiviral activity of PC by inhibiting the genetic material of influenza virus. Catechins can minimize the infectivity of influenza A and B viruses in kidney cells and inhibit the interaction of the virus with the cell membrane when it invades a cell (Kuzuhara et al., 2009). Bang, et al. (2018) found that nepitrin, 6-hydroxyluteolin 7-O-*β*-D-glucoside and homoplantaginine from *Salvia plebeia* at concentrations of 50 μM inhibited NA, suggesting that the effectiveness is given by the hydroxyl group at C-5' and methoxyl at C-6. Also, these PC are able to inhibit the endonuclease activity of virus RNA polymerase (Kuzuhara et al., 2009). PC extracts from green tea-derived by-products suppress influenza virus replication in chickens and mice when supplied at concentrations of 10 g/kg (Lee et al., 2012). Flavonoids and certain tannins have also been reported to exhibit antiviral efficacy against respiratory syncytial virus, Flaviviridae, Retroviridae, Hepadnaviridae, Herpesviridae, Adenoviridae, Orthomyxoviridae y Picornaviridae (Ninfali et al., 2020; Steinmann et al., 2013).

On the other hand, there are other flavonoids called halo flavones, which have been little studied but have begun to be of interest due to their interest as antiviral agents. These compounds are synthetic flavonoids with the purpose of obtaining improvements in the pharmacological properties of non-fluorinated natural flavonoids. Few studies have shown that the incorporation of chlorine can significantly modulate the properties of a bioactive molecule, increasing the bioavailability of the compound by changes in its solubility, lipophilicity by trifluoromethyl grouping, metabolic stability, conformation, blocking in a biochemical mechanism by forming hydrogen bridge bonds, stabilizing peptide bonds, modification in the reactivity of adjacent functional groups by delaying enzymatic degradation (Badshah et al., 2021). As an example, chrysin is a flavone with great antiviral properties, however, it has low water solubility, poor absorption and is metabolized at high speed, which makes it difficult to exert effects via the intestinal/hepatic route. However, fluorinated derivatives of chrysin significantly changed the pharmacokinetic and pharmacodynamic properties by increasing the

biological activity (Zhu et al., 2019). 4',6-dichloroflavane is a potent inhibitor of rhinovirus; as well as other halogenated flavones that have been shown to have in vitro antiviral activity against poliovirus type 2, hepatitis A virus and astrovirus (Badshah et al., 2021). Therefore, ongoing studies with halo flavonoids will be key to providing a better understanding of their beneficial role in human health care.

Conclutions

The search for possible integrative strategies to prevent and reduce the spread of influenza. In this sense, fruit peel presents relevant antiviral activity, which could provide an opportunity to contribute to face this disease as a supplement or as a matrix to isolate phenolic compounds for the development of new drugs for the welfare and usefulness to society. In addition, opening studies to fluoroflavanes that allow us to approach the path of research to propose its possible pharmaceutical application in the future with the support of systematized research. Finally, in vivo assays are required to evaluate the effectiveness of the antiviral activity of phenolic compounds, as well as the effects and toxicity they may cause.

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