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HESPERIDIN. I. MECHANISM OF ACTION AND ANTIVIRAL EFFECT AGAINST SARS-COV-2

BY

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Abstract. In the ever-evolving landscape of the 2019 Coronavirus Disease (COVID-19) pandemic, the Centres for Disease Control and Prevention (CDC) diligently monitor the frequent emergence of new variants of the virus. This review delves into the intricate structural configuration of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), its mechanisms of infection, and certain treatment options. Amid the various strategies for preventing and treating COVID-19, the significance of nutrition remains somewhat underestimated. Foods contain a vast array of substances, with specific compounds exhibiting antiviral properties and contributing to immune regulation and cellular defence against oxidative stress. In this overview, we focus on a specific compound - hesperidin, found in citrus fruits, renowned for their vitamin and flavonoid content. Hesperidin exhibits promising results in combating SARS-CoV-2, highlighting the potential of phytochemical interventions, including nutrition, alongside conventional therapies.

Keywords: COVID19, SARS-CoV-2, Hesperidin, Antiviral, Anti-inflammatory.

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1. Introduction

The World Health Organization (WHO) declared the outbreak of 2019 Coronavirus Disease (COVID-19) on January 30, 2020, marking the start of a global public health emergency. This declaration came in response to the virus's rapid spread, extending beyond its initial epicentre in Wuhan, Hubei, China, where numerous cases of pneumonia with unknown origin were being reported (WHO, 2020). By employing high-throughput metagenetic RNA sequencing on lower respiratory tract samples, scientists quickly identified and named the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This name was chosen due to its 79% nucleotide sequence similarity with the original SARS-CoV virus that emerged in 2003 (Mohanty *et al*., 2020). As of October 12, 2023, a WHO situation report indicates that SARS-CoV-2 had infected over 771 million individuals worldwide and resulted in more than 6,94 million deaths. The global scale of this pandemic has presented significant challenges for most countries (WHO, 2023; Al-Hatamleh *et al*., 2020).

While numerous approaches to prevent and treat COVID-19 have been explored, the role of nutrition has been overlooked. Within the realm of nutrition, we aim to focus particularly on citrus fruits, renowned for their rich vitamin and flavonoid content. Hesperidin stands out, as a compound extracted from *Citrus mitis*, *Citrus unshiu*, *Citrus sinensis*, *Citrus aurantium*, *Citrus juno*, *clementines*, limes, lemons, and grapefruits (Ur Rehman *et al*., 2021; Lee *et al*., 2020), showcasing promising antiviral properties with a good safety and efficacy profile in all study stages (*in silico*, *in vitro*, and *in vivo*), making it a possible treatment option for COVID-19 patients.

2. SARS-CoV 2 – structure and infection mechanism

SARS-CoV-2 falls into the category of enveloped viruses with a diameter of approximately 120 nanometers, containing a positive-sense single-stranded RNA genetic structure.

The virus's ARN is made of fourteen open reading frames (ORFs) organized into two segments. The initial two-thirds of the viral genome, beginning from the 5'-end, contains ORF1a and ORF1ab, which are directly translated into two polyproteins, *pp1a* and *pp1ab*, by the host cell's ribosomes. These polyproteins are further processed by viral proteases, including Papain-like Cystein protease (PLpro) and Main protease (Mpro), resulting in 16 non-structural proteins (Nsp1 to Nsp16) (Yan *et al*., 2022). Among these non-structural proteins, Nsp15 is worth mentioning as an essential enzyme in RNA processing and degradation, also serving as a viral immune evasion mechanism (Kim *et al*., 2020).

The remaining one-third of the genome relies on RNA-dependent RNA Polymerase for its expression and replication. This segment contains the information needed to produce structural proteins, such as the spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). These structural proteins are important for the assembly of new virus particles. Subgenomic RNAs use the host cell's transcription and translation process to create structural and accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10) (Yan *et al*., 2022).

In the final stages of viral replication, RNA and structural proteins combine to form mature viral particles, which are then released through exocytosis, continuing the infection cycle within the host cells.

The virus enters the cells by attaching its surface spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptors found on various tissues, including type I and type II alveolar epithelial cells in the lungs, the gastrointestinal tract, and kidneys, following the priming of the spike proteins by transmembrane serine protease 2 (TMPRSS2) through cleavage (Al-Hatamleh *et al*., 2020; Hoffmann *et al*., 2020). While most patients experience mild symptoms, some develop severe lung injuries and thromboembolic complications due to the systemic inflammatory response syndrome (Mohanty *et al*., 2020; Masi *et al*., 2020).

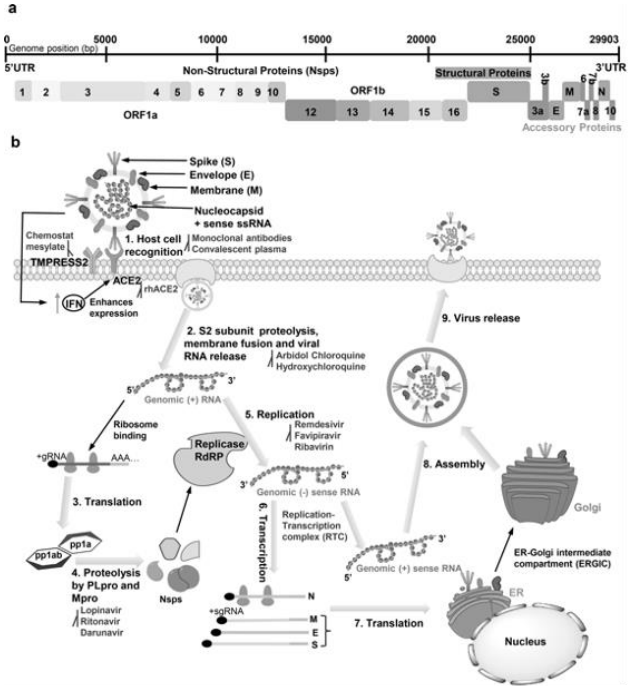

Fig. 1 – Stages of SARS-CoV-2's Replication Process (Yan *et al*., 2022)

As a result, standard treatment typically involves multiple approaches, including anti-inflammatory therapy (such as Ibuprofen, which has been shown to decrease the likelihood of immunological complications as "cytokine storms") (Giollo *et al*., 2020; Soy *et al*., 2020), antiviral therapy (including Nirmatrelvir, Ritonavir, Remdesivir, and Molnupiravir) (NHS, 2023), and monoclonal antibodies (for example, Sotrovimab or Casirivimab combined with Imdevimab). These monoclonal antibodies target distinct regions of SARS-COV-2's spike protein, effectively preventing its evasion from the immune system (NHS, 2023; Matthews, 2020).

3. Hesperidin

Hesperidin (HD; 3,5,7-trihydroflavanone-7-rhamnoglucoside) is a flavonoid glycoside found in various citrus fruits, including *Citrus mitis*, *Citrus unshiu*, *Citrus sinensis*, *Citrus aurantium*, *Citrus juno*, clementines, limes, lemons, and grapefruits (Ur Rehman *et al*., 2021; Lee *et al*., 2020).

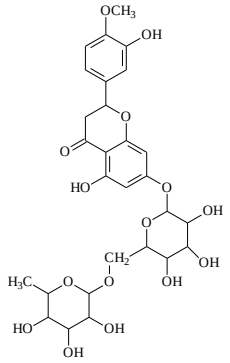

Fig. 2 – Hesperidin chemical structure.

Hesperidin is found in orange peel up to 14%, having the higher amount among flavonoids, the amount of hesperidin being related to the maturation of the fruit (Barthe *et al*., 1988). Citrus fruits also contain a small amount of hesperidin (hesperidin aglycone) (Londono-Londono *et al*., 2010, Monteiro de Lima Marsiglia *et al*., 2023).

Food Agriculture Organization estimated that, in 2019, 143,755,600 tons of citrus were produced, which produced huge amounts of wastes and by-products (Krivosija *et al*., 2023; Monteiro de Lima Marsiglia *et al*., 2023).

Hesperidin is found in great amounts in albedo, membranes and pith and is almost non-existent in leaves, juice and seeds. In seeds hesperidin concentration increase after germination (Barthe *et al*., 1988).

This compound can be isolated from citrus peel by solid-liquid extraction using polar solvents (Monteiro de Lima Marsiglia *et al*., 2023), ultrasound

assisted extraction (Monteiro de Lima Marsiglia *et al*., 2023; Shorbagi *et al*., 2022), microwave assisted extraction (Londono-Londono *et al*., 2010; Shorbagi *et al*., 2022), extraction using supercritical fluids (CO_2) (Monteiro de Lima Marsiglia *et al*., 2023; Shorbagi *et al*., 2022).

Hesperidin was obtained by the removal of a rhamnose sugar from hesperidin, through acid hydrolysis of hesperidin (Londono-Londono *et al*., 2010), or by using glycosyl hydrolases (Cheng *et al*., 2021).

4. Bioactivity trials of Hesperidin

Prior to the COVID-19 pandemic, hesperidin gained renown in the medical field for its cardiovascular benefits. Its active metabolite, hesperidin (HT; 3',5,7-trihydroxy-4'-methoxyflavanone), has been shown to address risk factors associated with atherosclerosis, displaying antidiabetic, antihypertensive, anti-hyperlipidemic, antioxidative, and anti-inflammatory properties (Zanwar *et al*., 2014). In addition to its enhanced pharmacological activity, hesperidin, exhibit increased bioavailability, the smaller molecule facilitating its absorption in the small intestine (Cheng *et al*., 2021).

The antioxidant properties of Hesperidin against superoxide and hydroxyl radicals, coupled with its anti-inflammatory capabilities, may serve as a protective mechanism against cytotoxic damage induced by the virus (Bellavite *et al*., 2020). Apart from providing these non-specific means of protection against COVID-19, both HD an HT have a chemical structure that allows them to bind to key SARS-CoV-2 proteins, with promising results in docking simulations.

4.1. *In silico* studies

It has been previously showed that HD and HT specifically bind to TMPRSS2 and ACE2 (14), thereby disrupting their interaction with the spike protein, which is essential for SARS-CoV-2's cellular entry (Hoffmann *et al*., 2020). The energy values of TMPRSS2-HT, TMPRSS2-HD, ACE2-HT and ACE2-HD were −30.56, −7.2, −34.81 and −1.65 kcal/mol, respectively (Cheng *et al*., 2021).

Additionally, hesperidin exhibits a strong interaction with the receptor-binding site of SARS-CoV-2's Spike glycoprotein (Spike-RBD), characterized by a binding energy of -9.61 kcal/mol. This interaction involves a hydrogen bond with the aminoacid Tyr440 (Wu *et al*., 2020). But more importantly, it surpasses the binding strength of Nafamostat, a reference drug recognized for its inhibition of the virus's membrane fusion (Bellavite *et al*., 2020; Utomo *et al*., 2020). Moreover, when overlapping the ACE2-RBD complex with the hesperidin-RBD complex, was noticed that hesperidin obstructs the binding interface between Spike RBD and ACE-2 (Wu *et al*., 2020).

The main protease (Mpro), also known as 3-chymotrypsin-like protease (3CLpro), plays an essential role in the viral infection process, existing as a dimer in its active form (Wu *et al*., 2020). In a docking study, both chains A and B were individually examined for their compatibility with all 38 isomers of hesperidin. This investigation revealed that eight of these isomers bind strongly to both chains A and B of 3CLpro (Chen *et al*., 2020). They achieve this via hydrogen bonds with the amino acids THR24, THR25, THR45, HIS4, SER46, and CYS145 (Das *et al*., 2021). Notably, the binding energy of these isomers exceeds that of certain antiviral drugs like Lopinavir and Ritonavir (Hesperidin: -10.1 kcal/mol for chain A and -8.3 kcal/mol for chain B compared to Lopinavir: -8.0 kcal/mol for chain A and -6.8 kcal/mol for chain B and compared also to Ritonavir: -7.9 kcal/mol for chain A and -6.9 kcal/mol for chain B) (Bellavite *et al*., 2020; Chen *et al*., 2020).

Considering the vital role of these three proteins (the ACE-2 receptor, the receptor binding site of the spike protein and the main protease) in the survival, replication and infection of SARS-CoV-2, we can affirm that they are important targets involved in COVID-19 prevention and treatment strategies. Following the promising *in silico* results of HD and HT, which bind with a high affinity to these targets, it was appropriate to further explore their *in vitro* and *in vivo* promising effects.

4.2. *In vitro* studies

All in-vitro cell studies must start with the assessment of the cytotoxicity of the tested compound, before their efficacy can be measured. In this case the cytotoxicity of HT and HD was assessed through a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay conducted on VeroE6 cells. This cell line is derived from monkey kidneys and is frequently employed in toxicology and pharmacology research. The half-maximal inhibitory concentration (IC50) was determined in a dose-dependent manner and was found to be 1491 μM for HT and 1435 μM for HD. These IC50 values, which are notably high, suggest a low likelihood of cytotoxicity (Cheng *et al*., 2021).

Regarding the efficacy of hesperidin, in the same study, Cheng et al. demonstrated that HD and HT inhibit cell infection in two cell lines: Beas 2B, isolated from human bronchial epithelium, and H460, a human non-small cell lung cancer cell line, by different variants of SARS-CoV-2. Additionally, in a Western blot analysis, they also observed a reduction in ACE2 and TMPRSS2 protein expression in cells treated with HT or HD (Cheng *et al*., 2021).

These promising results corroborate for further research, such as *in vivo* animal studies and clinical trials. These future studies aim to provide conclusive evidence regarding the effectiveness of this substances in approaching COVID-19 symptoms. It's worth mentioning that this product is not only economically advantageous but also widely available compared to alternative options. Its safety has been proved through a series of studies detailed in the following section.

4.3. *In vivo* safety studies

In a 2019 study by Li *et al*., Hesperidin (73%) was separated from a methanolic extract of dried citrus peel and characterized using Fourier Transform Infrared Spectroscopy (FTIR), and its concentration was standardized by High-Performance Liquid Chromatography (HPLC). Its acute and sub-chronic oral toxicities were assessed in Sprague-Dawley rats, showing a good safety profile. The Lowest Observed Adverse Effect Level, representing the smaller tested dose causing adverse health effects, was found to be 1000 mg/kg body weight while the median lethal dose (LD50) was 4837.5 mg/kg body weight (Li *et al*., 2019). Moreover, the parenteral way of administration, intraperitoneally in mice, has also been proven safe, as there was no observed adverse effect after daily injections of phosphorylated hesperidin at a dosage of 20 $mg \cdot kg^{-1}$ body weight for a duration of over 4 weeks (Sieve, 1952).

Another study in rats and primate, this time with a mixture of hesperidin and diosmin (known as the vasoprotective drug Daflon 500mg) did not show any reproductive or hematological side effects, with an LD50 of over $3g \cdot kg^{-1}$ body weight (Nagasako-Akazome, 2014). This same compound has also been proven safe in a in a double-blind, placebo-controlled study, performed on 100 patients, none of them reporting major adverse effects (Cospite, 1994).

Finally, a clinical trial has been made, enrolling 2,850 patients who were administered Daflon 500 mg (two tablets daily) for six weeks to a year. Side effects, primarily gastrointestinal or autonomic, led to only a 1.1% dropout rate, much lower than the 13.9% rate in the placebo group. Hemodynamic parameters (blood pressure) and various laboratory parameters, evaluating haematological, liver, kidney and metabolic functions remained stable even after a 1-year treatment (Meyer, 1994).

Overall, knowing that hesperidin has been already used as a traditional herbal medicine (Zanwar *et al*., 2014; Agrawal *et al*., 2021) and keeping in mind its favourable safety profiles both in animal and human studies, it appears to be a strong candidate to integrate into existing treatment protocols once its efficacy is fully proven in COVID-19 patients.

4.4. *In vivo* efficacy studies

For now, there are only a few efficacy studies that were conducted in similar conditions to those existing in COVID-19 patients. For example, knowing that SARS-CoV-2 is responsible for inducing acute respiratory distress, similar animal models would be worth investigating (Dupuis *et al*., 2022).

Therefore, in rats infected with the H1N1 virus, *in vivo* experiments illustrated that hesperidin efficiently alleviated lung dysfunction and inhibited pulmonary inflammation by reducing proinflammatory cytokines and the influx of inflammatory cells (Ding *et al*., 2017).

In a phase 2, randomized, double-blind, placebo-controlled clinical study conducted at the Montreal Heart Institute, the effects of hesperidin (1000 mg once daily) and placebo were compared on COVID-19 symptoms in 216 non-vaccinated COVID-19 patients after 14 days. Daily administration of hesperidin showed a reduction in symptoms such as: cough, fever and shortness of breath, with anosmia persisting in both patient groups at the 14-day mark. These initial results even if promising, should be followed by further investigation which initiate treatment earlier, extend its duration, and use higher dosages (Dupuis *et al*., 2022).

5. Conclusions

In conclusion, as the COVID-19 pandemic continues to evolve, with new variants being continuously discovered, the understanding of the structural and replicative mechanisms of SARS-CoV-2 has greatly expanded. Many of these steps have now been pinpointed as potential targets for conventional therapies, including antiviral agents and monoclonal antibodies. However, amid COVID-19 research strategies, the role of nutrition has regrettably been underestimated.

Citrus fruits, renowned not only for their vitamin C content, but also for their valuable phytochemicals, notably hesperidin, have just recently come into the spotlight. Hesperidin has indeed emerged as a promising candidate, primarily known for its cardiovascular properties. Recently, its potential to interact with crucial viral targets has been the focus of extensive *in silico*, *in vitro* and *in vivo* studies. The results have been promising, with three key viral targets coming to the forefront: ACE2, the main protease, and the RBD-spike proteins, making it a viable option for further investigation. As we look ahead, we eagerly anticipate more comprehensive studies that will help us unlock the full potential of hesperidin in the fight against COVID-19. This versatile phytochemical offers a promising avenue that complements traditional therapies, ultimately contributing to a more holistic approach in our battle against this global health challenge.

REFERENCES

Agrawal P.K., Agrawal C., Blunden G., *Pharmacological Significance of Hesperidin and Hesperetin, Two Citrus Flavonoids, as Promising Antiviral Compounds for Prophylaxis Against and Combating COVID-19*. Natural Product Communications; SAGE Publishing, https://doi.org/10.1177/1934578x211042540 (2021).

Al-Hatamleh M.A.I., Hatmal M.M., Sattar K., Ahmad S., Mustafa M.Z., De Carvalho Bittencourt M., Mohamud R., *Antiviral and Immunomodulatory Effects of Phytochemicals from Honey against COVID-19: Potential Mechanisms of Action and Future Directions*. Molecules, **25**(21), 5017, https://doi.org/10.3390/molecules25215017 (2020).

Bellavite P., Donzelli A., *Hesperidin and SARS-CoV-2: New Light on the Healthy Function of Citrus Fruits*, Antioxidants, **9**(8), 742, https://doi.org/10.3390/antiox9080742 (2020).

Barthe G.A., Jourdan P.S., Mcintosh C.A., Mansell R.L. *Radioimmunoassay for the quantitative determination of hesperidin and analysis of its distribution in Citrus Sinensis*, Phytochemistry, **27**(1), 249-254 (1988).

Chen Y.W., Yiu C.P., Wong K.Y., *Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates*, F1000Research, https://doi.org/10.12688/f1000research.22457.2 (2020).

Cheng F.J., Huynh T.K., Yang C., Hu D.W., Shen Y., Tu C., Wu Y., Tang C., Huang W.C., Chen Y., Ho C.Y., *Hesperidin Is a Potential Inhibitor against SARS-CoV-2 Infection*. Nutrients; **13**(8), 2800, https://doi.org/10.3390/nu13082800 (2021).

Cospite M., *Double-blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids*, Angiology, 45(6 Pt 2):566-73, https://pubmed.ncbi.nlm.nih.gov/8203789/ (1994).

Das S., Sarmah S., Lyndem S., Singha Roy A., *An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study*, Journal of Biomolecular Structure and Dynamics, **39**, 9, https://doi.org/10.1080/07391102.2020.1763201 (2021).

Ding Z., Sun, G., Zhu Z., *Hesperidin Attenuates Influenza a virus (H1N1) Induced Lung Injury in Rats through its Anti-Inflammatory Effect*. Antiviral Therapy, **23**(7), 611-615, https://doi.org/10.3851/imp3235 (2017).

Dupuis J., Laurin P., Tardif J., Hausermann L., Rosa C., Guertin M.C., Thibaudeau K., Gagnon L., Cesari F., Robitaille M., Moran J., *Fourteen-Day Evolution of COVID-19 Symptoms during the Third Wave in Nonvaccinated Subjects and Effects of Hesperidin Therapy: A Randomized, Double-Blinded, Placebo-Controlled Study*, Evidence-based Complementary and Alternative Medicine, Hindawi Publishing Corporation, https://doi.org/10.1155/2022/3125662 (2022).

Giollo A., Adami G., Gatti D., Idolazzi L., Rossini M., *Coronavirus disease 19 (Covid-19) and non-steroidal anti-inflammatory drugs (NSAID)*, Annals of the Rheumatic Diseases; BMJ, **80**, 2, https://doi.org/10.1136/annrheumdis-2020-217598 (2020).

Hoffmann M., Kleine-Weber H., Schroeder S., Krüger N., Herrler T., Erichsen S., Schiergens T.S., Herrler G., Wu N.H., Nitsche A., Müller M.A., Drosten C., Pöhlmann S., *SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor*. Cell; Cell Press., **181**, 2, https://doi.org/10.1016/j.cell.2020.02.052 (2020).

Kim Y.C., Jedrzejczak R., Maltseva N., Wilamowski M., Endres M., Godzik A., Michalska K., Joachimiak A., *Crystal structure of Nsp15 endoribonuclease NendoU from SARS-CoV-2*, Protein Science; Wiley-Blackwell, https://doi.org/10.1002/pro.3873 (2020).

Krivosija S., Jerkovic I., Nastic N., Zloh M., Joric S., Banozic M., Aladic K., Vidovic S., *Green pathway for utilisation of orange peel dust and in silico evaluation of pharmacological potential*, Microchemical Journal, **193**, 1-13, 109132 (2023).

Lee B.K., Hyun S., Jung Y., *Yuzu and Hesperidin Ameliorate Blood-Brain Barrier Disruption during Hypoxia via Antioxidant Activity*. Antioxidants, **9**, 9, https://doi.org/10.3390/antiox9090843 (2020).

Li Y., Kandhare A.D., Mukherjee A., Bodhankar S.L., *Acute and sub-chronic oral toxicity studies of hesperidin isolated from orange peel extract in Sprague Dawley rats*. Regulatory Toxicology and Pharmacology, **105**, https://doi.org/10.1016/j.yrtph.2019.04.001 (2019).

Londono-Londono J., Rodrigues de Lima V., Jaramillo C., Creczynski-Pasa T., *Hesperidin and hesperitin membrane interaction: Understanding the role of 7-O-glycoside moiety in flavonoids*, Archives of Biochemistry and Biophysics, **499**, 6-16 (2010).

Masi P., Hékimian G., Lejeune M., Chommeloux J., Desnos C., Pineton De Chambrun M., Martin-Toutain I., Nieszkowska A., Lebreton G., Bréchot N., Schmidt M., Edouard Luyt C., Combes A., Frere C., *Systemic Inflammatory Response Syndrome Is a Major Contributor to COVID-19–Associated Coagulopathy*, Circulation, 142(6), 611-614, https://doi.org/10.1161/circulationaha.120.048925 (2020).

Matthews D.B., *A cocktail of antibodies for COVID-19 therapy*, Nature Reviews Immunology, **20**(10), 591-591, https://doi.org/10.1038/s41577-020-00431-9 (2020).

Meyer O.C., *Safety and Security of Daflon 500 mg in Venous Insufficiency and in Hemorrhoidal Disease*, Angiology, **45**(6_part_2), 579-584, https://doi.org/10.1177/000331979404500614 (1994).

Mohanty S.K., Satapathy A., Naidu M.M., Mukhopadhyay S., Sharma S., Barton L.M., Stroberg E., Duval E.J., Pradhan D., Tzankov A., Parwani A.V., *Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19) – anatomic pathology perspective on current knowledge*, Diagnostic Pathology, **15**(1), https://doi.org/10.1186/s13000-020-01017-8 (2020).

Monteiro de Lima Marsiglia W.I., de Sousa Cordado Oliviera L., Almeida R.L.J., Santos N.C., da Silva Neto J.M., Santiago A.M., Amorim de Melo B.C., da Silva F.L.H., *Thermal stability of total phenolic compounds and antioxidant activities of jaboticaba peel: effect of solvents and axtraction methods*, Journal of Indian Chemical Society, **100**, 100995 (2023).

Nagasako-Akazome Y., *Safety of High and Long-term Intake of Polyphenols*. Elsevier eBooks, https://doi.org/10.1016/b978-0-12-398456-2.00058-x (2014).

NHS, *Treatments for COVID-19*. nhs.uk. Retrieved October 17, 2023, from https://www.nhs.uk/conditions/covid-19/treatments-for-covid-19/ (2023).

Sieve B.F., *A New Antifertility Factor (A Preliminary Report)*, Science, **116**(3015), 373-385, https://doi.org/10.1126/science.116.3015.373 (1952).

Shorbagi M., Fayek N.M., Shao P., Farag M.A., *Citrus reticulata Blanco (the common mandarin) fruit: an updated review of its bioactive, extraction types, food quality, therapeutic merits and bio-waste valorization practices to maximize its economic value*, Food Bioscience, **47**, 101699 (2022).

Soy M., Keser, G., Atagündüz P., Tabak F., Atagündüz I., Kayhan S., *Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment*, Clinical Rheumatology, **39**(7), 2085-2094, https://doi.org/10.1007/s10067-020-05190-5 (2020).

Ur Rehman M.F., Batool A.I., Qadir R., Aslam M., *Hesperidin and naringenin*, *A* Centum of Valuable Plant Bioactives, 403-444, https://doi.org/10.1016/b978-0-12-822923-1.00027-3 (2021).

Utomo R.Y., Ikawati M., Meiyanto E., *Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection* Preprints, 2020030214, https://doi.org/10.20944/preprints202003.0214.v1 (2020).

WHO *Coronavirus (COVID-19) Dashboard*. (n.d.), WHO Coronavirus (COVID-19) Dashboard with Vaccination Data., https://covid19.who.int (2023).

WHO *Timeline - COVID-19*., https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19 Retrieved October 12, 2023 (2020).

Wu C., Liu, Y., Yang Y., Zhang P., Zhong W., Wang Y., Wang Q., Xu Y., Li M., Li X., Zheng M., Chen L., Li H., *Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods*, Acta Pharmaceutica Sinica B, **10**, 5, https://doi.org/10.1016/j.apsb.2020.02.008 (2020).

Yan W., Zheng Y., Zeng X., He B., Cheng W., *Structural biology of SARS-CoV-2: open the door for novel therapies*, Sig Transduct Target Ther **7**, 26 https://doi.org/10.1038/s41392-022-00884-5 (2022).

Zanwar A. A., Badole S. L., Shende P., Hegde M. V., Bodhankar S. L., *Cardiovascular Effects of Hesperidin*, Elsevier eBooks, https://doi.org/10.1016/b978-0-12-398456-2.00076-1 (2014).

HESPERIDINA. I. MECANISME DE ACȚIUNE ȘI PROPRIETĂȚILE ANTIVIRALE ÎMPOTRIVA SARS-COV-2

(Rezumat)

În peisajul în continuă evoluție al pandemiei de Coronavirus 2019 (COVID-19), Centrele de Prevenire și Control al Bolilor (CDC) monitorizează cu atenție apariția frecventă a noilor variante de virus. Această lucrare își propune să prezinte configurația structurală complexă a Coronavirusului Sindromului Respirator Acut Sever 2 (SARS-CoV-2), mecanismele sale de infecție și câteva variante de tratament. În ciuda diferitelor strategii de prevenție și tratament împotriva COVID-19, rolul nutriției rămâne oarecum subestimat. Pe de-o parte alimentele conțin o gamă largă de compuși, dintre care unii pot prezenta proprietăți antivirale, antioxidante și imunomodulatorii. Iar dintre alimente, citricele sunt renumite pentru conținutul lor ridicat în vitamine și flavonoide, precum hesperidina. Studiile recente arată rezultate promițătoare ale hesperidinei în combaterea infecției cu SARS-CoV-2, subliniind potențialul terapiilor non-farmacologice, inclusiv rolul nutriției, care ar putea completa terapiile convenționale în tratamentul COVID-19.