Macedonian pharmaceutical bulletin, 68 (Suppl 2) 21 - 22 (2022)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2022.68.04.005
Short communication

Flavonoids and Possible COVID-19 Integrative Considerations

Pawan K. Agrawal

Natural Product Inc., 7963 Anderson Park Lane, Westerville, OH-43081, USA

Despite vaccine developments, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is constantly evolving and multiple newer variants of concern (VOC) such as Delta and Omicron have emerged. Viral infection happens when a virus inserts its genetic code into the host cell, forcing it to replicate, which then spreads more viral genomic material and usually leads to the death of the host cell. This process can happen at enormous rates, which leads to viral fever affecting primarily the respiratory tract system, harmful inflammation and excessive aberrant immunological responses as the body's immune system tries to seek out and destroy viral material and, at a later stage, to potentially deadly complications.

COVID-19 treatment still remains largely supportive with an urgent need to identify effective anticoronaviral drugs that can prevent the virus from entry and/or replicating or clearing cells in which the virus has already entered. Effective treatments with antivirals can help slow the spread of a person's infection, potentially reducing the length and severity of symptoms. Thus, safe and effective antivirals responsible for restricting viral entry and/or disruption of the replication (inhibiting the specific proteins responsible for copying the virus' genetic material) process are a crucial part of the pandemic response. An attractive approach is repurposing drugs already licensed for other diseases, and flavonoids represent an important group of phytopharmaceuticals.

Flavonoids, ubiquitous groups of polyphenolic compounds, are abundantly present in fruits and vegetables, are integral constituents of the diet (Agrawal, 1989), and may exert a wide range of beneficial effects on human health, including protection against cancer, allergies, metabolic and inflammatory disorders, and cardiovascular diseases, as well as for their antiviral benefits.

The antiviral significance has attracted attention as several computational methods have shown that several flavonoids exhibit significant binding to multiple regions of SARS-CoV-2 [spike protein, host cell angiotensin-converting enzyme 2 (ACE2) receptor and proteases, such as papain-like protease (PL^{pro}), main protease (M^{pro}), also referred to as the 3-chymotrypsin-like protease ($3CL^{pro}$), and RNA-dependent RNA polymerase (RdRp).

Quercetin (3,3',4',5,7-pentahydroxyflavone), a dietary flavonoid, is well-known to ameliorate chronic diseases and aging processes in humans, and its antiviral properties have been investigated in numerous studies. *In silico* and *in vitro* studies demonstrated that quercetin can interfere with various stages of the coronavirus entry and replication cycle. Various studies have suggested that quercetin, in combination with, for example, vitamins C and D, may exert a synergistic antiviral action that may provide either an alternative or additional therapeutic/preventive option due to overlapping antiviral and immunomodulatory properties (Agrawal et al., 2020).

Rutin (quercetin-3-O-rutinoside) is abundantly present in various dietary sources such as buckwheat, onions, oranges, lemons, grapes, limes, berries, peaches, plums, apples, and tomatoes, as well as in drinks such as wine and black tea. Various computational studies, including *in silico* ones, have identified rutin as a potential hit, having prominent binding affinity to various regions of the coronavirus (Agrawal et al., 2021a).

Hesperetin (3´,5,7-trihydroxy-4´-methoxy-flavanone), and hesperidin (hesperetin-7-O-rutinoside) are abundantly present in citrus fruits. Docking studies have shown that hesperidin has a low binding energy, both with the SARS-CoV-2 "spike" protein, responsible for internalization, and also with the "PL^{pro}" and "M^{pro}" responsible for

*pkagrawal@naturalproduct.us

transforming the early proteins of the virus into the complex responsible for viral replication (Agrawal et al., 2021b).

Naringenin (4′,5,7-trihydroxy-flavanone), widely distributed in fruits and vegetables, is endowed with antiviral and other health beneficial activities, such as immune-stimulating and anti-inflammatory actions that could play a role in contributing, to some extent, to either preventing or alleviating coronavirus infection. Several computational studies have identified naringenin as one of the prominent flavonoids that can possibly inhibit internalization of the virus, virus-host interactions that trigger the cytokine storm, and replication of the virus 2 infection (Agrawal et al., 2021c).

Thus, flavonoid aglycones, such as quercetin, naringenin, and hesperetin, and their glycosides, rutin, naringin, and hesperidin, have low binding energies, both with the SARS-CoV-2 "spike" protein, responsible for internalization, and also with "PL^{pro}" and "M^{pro}" responsible for transforming the early proteins of the virus into the complex responsible for viral replication, suggesting that these could act as prophylactic agents by blocking several mechanisms of viral infections and replications, and thus helping the host cells to resist viral attack (Agrawal et al., 2020, 2021a-c, 2022)..

The aim of this presentation is to share some highlights from the past related to flavonoids, their anticoronaviral significance and our contributions by introducing "*Natural Product Communications* (*NPC*)" to serve the community of natural product researchers and its association with AMAPSEEC (Bankova, 2017) and Macedonian researchers (Petreska et al., 2011; Stefova, 2017).

References

Agrawal, P.K. ed. Carbon-13 NMR of Flavonoids. Elsevier, Amsterdam. 1989.

Agrawal, P.K., Agrawal, C., Blunden, G., 2020. Quercetin: antiviral significance and possible COVID-19 integrative considerations. Nat. Prod. Commun., 15(12), 1-10. https://doi.org/10.1177/1934578X20976293.

Agrawal, P.K., Agrawal, C., Blunden, G., 2021a. Rutin: A potential antiviral for repurposing as a SARS-CoV-2 main protease (M^{pro}) inhibitor. Nat. Prod. Commun., 16(4), 1-12. https://doi.org/10.1177/1934578X21991723.

Agrawal, P.K., Agrawal, C., Blunden, G., 2021b. Pharmacological significance of hesperidin and hesperetin, two citrus flavonoids, as promising antiviral compounds for prophylaxis against and combating COVID-19. Nat. Prod. Commun., 16(10), 1-15. https://doi.org/10.1177/1934578X211042540.

Agrawal, P.K., Agrawal, C., Blunden, G., 2021c, Naringenin as a possible candidate against SARS-CoV-2 infection and in the pathogenesis of COVID-19. Nat. Prod. Commun. 16(12), 1-16. https://doi.org/10.1177/1934578X211066723.

Agrawal, P.K., Agrawal, C., Blunden, G., 2022. Artemisia extracts and artemisinin-based antimalarials for COVID-19 management: Could these be effective antivirals for COVID-19 treatment? Molecules, 27, 3828. https://doi.org/10.3390/molecules27123828.

Bankova, V., (Guest Editor), 2017. NPC-CMAPSEEC issue. Nat. Prod. Commun., 12, 153-318.

Petreska, J., Stefkov, G., Kulevanova, S., Alipieva, K., Bankova, V., Stefova, M., 2011. Phenolic compounds of mountain tea from the Balkans: LC/DAD/ESI/MS^n profile and content. Nat. Prod. Commun., 6, 21-30. https://doi.org/10.1177/1934578X1100600107.

Stefova, M., (Guest Editor), 2017. Polyphenols: Occurrence, roles and benefits. Nat. Prod. Commun., 12, 1673-1820.