

UNCOVERING THE POTENTIAL OF NARINGIN

Many viruses have three phases with respect to its replication and action on the human cells (19) being marked by:

Phase 1 - Entry of virus into the cell through the activation cell surface receptors. Ex viruses from coronavirus family uses cell surface receptor **Angiotensin-converting enzyme 2 (ACE2)** and Transmembrane serine protease 2 (TMPRSS2) in tissues of the respiratory tract. ACE-2 activation is considered to be responsible for the higher airway infection, as it is highly present in the respiratory tract. **Early control can be achieved by inhibiting entry of virus through ACE2.**

Phase 2 - Post entry inside the cell, intracellular replication of the virus through RNA dependent RNA polymerase (RDRP) followed by reinfection and increased virus transmission to adjacent cells. **Prevention of RDRP mediated viral replication can be a target to control progression of infection.**

Phase 3 - Response of the body to the viral infection popularly known as host's uncontrolled or controlled inflammatory immune responses which include increased inflammation may lead to collateral tissue damage or multi organ damage. **Hypothetically, the control of inflammation during inflammatory phase could help virus infected patients.**

Hence there is need of compounds which can act on one of these phases or all of these phases.

Flavonoids are a class of phenolic natural products, used traditionally for the treatment of various diseases including viral infection. Their potential inhibitory activity against various viruses including coronavirus family is documented and reported in various international journals.

NARINGIN

Naringin is a flavanone glycoside that displays strong anti-inflammatory and antioxidant activities. Naringin present in citrus fruits like grapefruit (43.5 mg/100 mL) and oranges (2.13 mg/100 mL) (1). Various international peer reviewed journal documented its analgesic, anti-oxidant, anti-inflammatory, anti-tumoral, and anti-viral effects (2-5).

The name Naringin is probably derived from the Sanskrit term "**narangi**" meaning "**orange**". The active metabolite of the Naringin is Naringenin and studied to have strong anti-viral action. The consumption of 8 mL/kg of orange juice increases naringenin plasma levels from 0 to 300 µg/L 4 h after ingestion (6).

Globally it has been studied in 12 clinical trials, out of which 06 clinical trials have been completed. Naringenin the active form of naringin is found to be safe even at 900 mg /

day dose and adverse events are less than the placebo. **Naringin** has shown strong anti-viral, anti-inflammatory and antioxidant activities.

ANTI-VIRAL PROPERTIES OF NARINGENIN

The documented and published data highlights **Naringin's** antiviral effect in pre-infection and post-infection (8). It's antiviral effect has been documented against various viruses, such as dengue (7,8), hepatitis C (3,9), zika (10), chikungunya (11), Semliki Forest (12), herpes simplex 1 and 2 (13), yellow fever (14), and human immunodeficiency virus (15), and SARS COV-2 (16).

Because of it's spectrum of activity Naringenin can be used against various viruses to prevent entry and control disease progression.

Inhibits viral entry inside the cell by inhibiting cell surface receptors

As corona family virus uses surface specific cellular receptors, the inhibition of activity of proteins like Transmembrane serine protease 2 (TMPRSS2) would be the potential way to reduce the entry corona family viruses inside cell.

Naringin was found to competitively inhibit cell surface protein mediated attachment of corona family virus to ACE 2 receptor thus inhibit viral entry and the progression of disease. (17)

Naringin has shown strong TMPRSS2 binding potential (17)

Naringenin has double action, it not only inhibits entry of virus but also postulated to inhibit viral replication via inhibition of M^{pro} and viral RNA dependent RNA polymerase (RDRP).

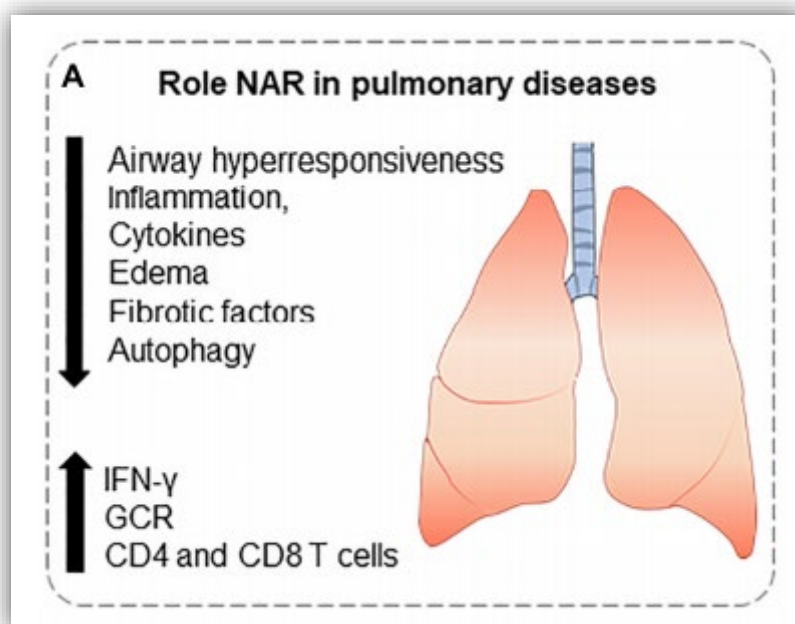
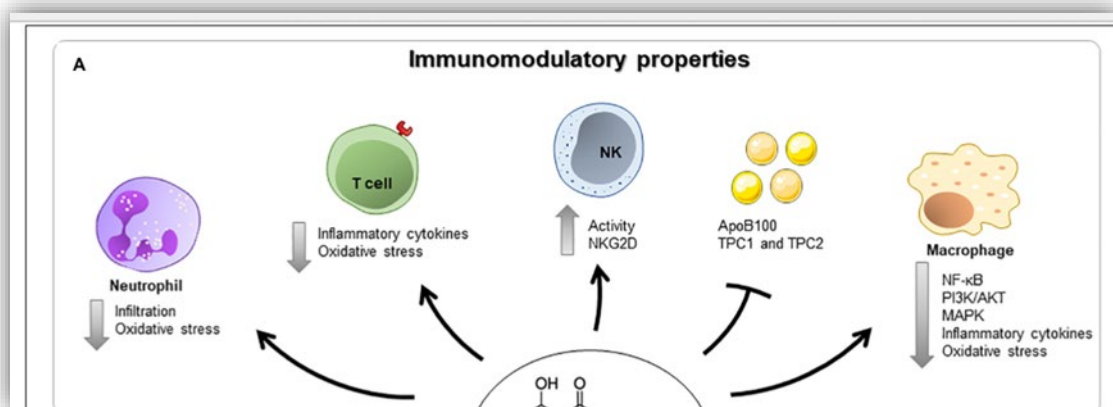
Its RDRP inhibition activity found to be comparable to Popular drug Remdesivir, a proven anti-corona virus agent. (17)

ANTI-INFLAMMATORY PROPERTIES OF NARINGENIN (18)

Inflammation is protective mechanism but hyper-inflammation may lead to permanent body organ damage. Post infection, pro-inflammatory mediators can regulate Inflammatory phase. There is strong evidence of the role of Naringin under inflammatory conditions due to a wide range of mechanisms as mentioned below.

1. Macrophages are important cells in the viral pathology, being able to sense and respond to pathogens and produce inflammatory cytokines and chemokines. Naringenin can reduce hyper activation of the macrophages by reducing various mediators responsible for inflammation in a dose-dependent manner. **Thus offers control over inflammatory process.**

2. Anti-inflammatory effect of Naringin have been demonstrated inside the body by reducing inflammatory various post inflammatory chemical messengers.
3. Naringin regulates key pathways responsible for the activation of the hyper-inflammatory process inside the body ex. nuclear factor kappa and mitogen-activated protein kinases (MAPK) activates body's defence and thus control disease by controlling early inflammation. (17)
4. It is observed that in Corona family virus infection, the level of neutrophil increases and thus, the ratio of neutrophil to leucocytes is used for the early detection of these infections. As these neutrophil aggravates inflammation, it is postulated that Naringenin reduces neutrophil induced inflammation, defensive cell (T cell) induced oxidative damage and can activate the interferon (INF) and enhance INF-I production. These INF helps body's defence system to identify infected cell early and destroy (18)



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