Antiviral Effects of Quercetin through Zinc Ionophore Activity

Quercetin is an increasingly well-known plant compound with potent anti-inflammatory effects. The recent SARS-CoV-2 outbreak resulted in renewed research efforts focusing on its effects as a zinc-ionophore, increasing intracellular zinc concentrations and thus Quercetin working as an antiviral.

In this article, we explore the relationship between zinc, ionophores, antivirals, and their potential use in modern society.

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What are Quercetin's Antiviral Effects?

Quercetin is a plant bioflavonoid found in many types of fruits and vegetables. It has powerful antioxidant and anti-inflammatory effects and has recently been studied for its potent antibacterial and antiviral benefits. More about Quercetin can be read here and about Quercetin-3-O-rutinoside (Rutin) here.

Quercetin has been the subject of extensive research in recent years – pertaining primarily to its free-radical scavenging and antioxidant effects. Some preliminary research has pointed to potential anti-allergy effects (anti-histamine), while further research has pointed towards potential cancer-fighting properties.

In terms of antiviral research, the data is still somewhat limited to Quercetin's efficacy. A few studies have indicated that Quercetin has the ability to inhibit viral replication at various stages – with effects on several virus types, including respiratory viruses, influenza virus, parainfluenza virus, rhinovirus, and more.[1] [2]

Preliminary studies in South Korea and China have pointed to Quercetin's potential for inhibiting viral replication of SARS-CoV-2. In a review entitled "*Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2)*", researchers pointed out several key findings regarding Quercetin's potential effects against coronaviruses:[3]

- Inhibits the cleavage activity of MERS-3CLpro enzyme[4]
- Inhibits SARS-3CLpro activity [5]
- Inhibits the cellular entry of SARS-CoV [6]

While the data looks somewhat promising, it is important to keep in mind that this is very preliminary research, and much more extensive data is required before we can fully understand the significance of these effects in humans.

Nevertheless, Quercetin is currently in the recruiting phase of a clinical trial to establish its efficacy for the prophylaxis and treatment of COVID-19.[7]

What is an Ionophore?

An ionophore is an "ion carrier" – a molecule that facilitates the movement of electronically charged ions in and out of cell membranes. Ionophores are lipid-soluble and are typically biosynthesized by microorganisms. Their mechanism of transfer involves reversibly binding to ions and releasing them on one or the other side of a cell membrane.

There are two types of ionophores worth noting:

#1 Carrier ionophores

Carrier ionophores bind to an electrically charged ion and protect its charge while it is 'carried' through the cell membrane. These can be proteins or a wide range of other lipid-soluble molecules with properties that are capable of reversibly binding to an ion.

#2 Channel ionophores

Ionophores can form "ion channels" through the membrane, allowing the passage of a variety of ions that would otherwise not have been able to enter or exit the cell. These ion channels can thus be regulated and controlled. Examples of endogenous ion channels include lithium (Li+), calcium (Ca2+), magnesium (Mg2+), and potassium (K+) but there are many others.

In industry, ionophores are especially of interest in the development of antibiotics and other pharmaceuticals.

For example, antibiotics may have difficulty entering into cells if they are hydrophobic. Thus, pharmaceutical development often needs to make use of endogenous ionophores to facilitate the antibiotic entering through the cell membrane.

Antiviral Effects of Ionophores

Ionophores are not typically antibiotics in and of themselves. However, they do facilitate the movement of electrically charged molecules through cell membranes – and these charged molecules may have antibiotic properties.

However, some antibiotics – for example the macrolide group – do work as ionophores. The macrolide antibiotics help to facilitate the transfer of sodium

(Na+) or potassium (K+) through the cell membrane. High concentrations of sodium, potassium, as well as zinc, have been shown to have potent antibiotic effects.

This is especially interesting when looking at ionophores for zinc – like Quercetin and even some quinolone-based antimalarial treatments like Chloroquine.

Antiviral Activity of Zinc

How does Zinc prevent viral replication?

Zinc has long been known for its potential antiviral effects. For example, over-the-counter remedies containing zinc with vitamin C have been shown to reduce the duration and symptoms of the common cold.[8]

Since early 2020, researchers and the general public have become increasingly interested in the potential antiviral effects of zinc (Zn2+), as well as zinc ionophores.

Zinc is an essential trace element that supports growth and development in children, and a healthy immune system in adults. Research has found that approximately 10% of the human proteome (all the proteins in a human body) is comprised of zinc. Nevertheless, non-clinical zinc deficiency remains very common around the world.[9]

There are numerous mechanisms of action through which zinc acts against viruses in the human body. These include (but are not limited to):

- Inhibition of RNA binding
- Inhibition of RNA synthesis
- Inhibition of viral polyprotein cleavage
- Inhibition of viral replication
- Metallothionein-dependent inhibition of viral replication
- Virus inactivation

- Viral protease enzyme inactivation [7]

As you can see, zinc has a great many ways in which it helps to protect the body against viral infections. Furthermore, it is also a crucial factor in the body's immune response – for example by helping to:

- modulate IFN secretion
- improve cytokine potency
- improve receptor binding
- modulate signaling intermediates and pathway inhibitors.

Binding of Zinc to Quercetin & Polyphenols for Antiviral Effects

In response to the outbreak of SARS in 2010 and SARS-CoV-2 in 2019, researchers doubled down on efforts to understand the mechanisms and potentials of naturally-occurring zinc ionophores like Quercetin and other plant polyphenols.

This was especially interesting since zinc has previously been shown to inhibit coronavirus and Arterivirus RNA polymerase activity *in vitro*.[10]

In a 2014 publication, researchers demonstrated clearly that quercetin and a similar polyphenol (epigallocatechin-gallate) were capable of rapidly increasing labile zinc concentrations in mouse Hepa 1-6 cells and liposomes. The mechanism of action was found to be independent of plasma membrane zinc transporters.[11]

Following the first study, a 2016 publication examined fourteen polyphenols – including Quercetin – and their capacity to form complexes with zinc cations. The researchers used a liposome-assay method with zinc-sensitive fluorophore encapsulated liposomes and results confirmed that polyphenols have the capacity to transport zinc across a variety of lipid membranes.[12]

The full antiviral potential of the capacity for polyphenols like Quercetin to act as ionophores for zinc will only be understood after much more research is

conducted. However, at least for now, there seem to be some promising results pointing towards benefits against RNA-viruses, including the novel SARS-CoV-2 virus.

Summary

In summary, Quercetin is a plant polyphenol with numerous benefits in the human body. It works as a powerful antioxidant and one of many supplements that helps to support a healthy immune system. Recently, research has pointed to Quercetin's potential as a zinc ionophore – helping to increase the intracellular concentrations of Zn2+ by transporting the charged element through the cell membrane.

Zinc is well-known for its antibacterial and antiviral effects. Especially considering its effects on RNA-viruses, including the novel SARS-CoV-2 virus, zinc is of renewed interest to epidemiologists. There is promising evidence suggesting a protective antiviral effect when using Quercetin as a zinc ionophore. However, there is still a need for further research to fully understand the potentials and significance of these effects.

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