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COMMENTARY

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Hypothesis of zinc ascorbate as best zinc ionophore for raising antiviral resistance against Covid-19

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1 | INTRODUCTION

Under the current Covid-19 pandemic, there is a great and urgent need for compounds readily available against Covid-19 infection. Ideally, they should have minimal side effects, work as treatments or coadjuvants, and possibly be effective for prevention.

At present, millions of people worldwide could benefit from such treatments, and thousands could have their lives saved.

The purpose of this paper is to:

(1) Highlight the possibility that the compound zinc ascorbate could be the most readily available and effective zinc ionophore for the prevention and treatment of Covid-19;
(2) To solicit the scientific community for tests in vitro and clinical trials of zinc ascorbate against the SARS-CoV-2 virus and its Covid-19 infection.

1.1 | Zinc ionophores could inhibit SARS-CoV-2

The Covid-19 pandemic is a disease caused by the novel RNA coronavirus called SARS-CoV-2. Mild zinc deficiency is common in older adults, decreases immune function and could worsen Covid-19 outcome.[1]

The overall architecture of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRP), which is used by the virus for its replication, is similar to that of SARS-CoV, with a root-mean-square deviation value of 0.82 for 1078 Cα atoms.[2]

In 2010 it was shown that the combination of zinc ions (Zn^{2+}) and zinc ionophores at low concentrations inhibit replication of SARS-COV virus in cell culture, via inhibition of elongation of RdRP and reduction of RNA template binding.[3]

Due to the similarities between the RdRP of SARS-CoV and SARS-COV-2, it is reasonable to speculate that zinc ions with a zinc ionophore at low concentration, could also inhibit replication of SARS-COV-2 in cell culture.[4]

Several clinical trials are currently underway to test the effect of zinc supplementation in various forms, against SARS-COV-2 and Covid-19.[5] However no clinical trial has yet been registered for zinc ascorbate.

1.2 | Limits of zinc supplementation without zinc ionophores

Extracellular Zn^{2+} at low concentrations, like those in the human body, does not increase the intracellular concentration of Zn^{2+} enough to inhibit RNA virus's replication, since intracellular free Zn^{2+} concentration is kept at a relatively low level by metallothioneins.[3]

Inhibition on replication of SARS-COV virus in cell culture at low zinc concentration was achieved only thanks to a zinc ionophore: pyrithione.[3] Previously in fact it was shown that without zinc ionophores, high extracellular zinc concentrations are required to inhibit the replication of various RNA viruses.[3]

Accordingly, for a zinc compound to be potentially effective against Covid-19, it would need a marked zinc ionophore activity, and this is not documented for any zinc salt, except possibly for zinc ascorbate, as discussed in this article.

1.3 | Zinc ascorbate

The form of metal chelation influences the efficiency of metal transport across membranes,[6] and in cell culture, intracellular concentration of Zn^{2+} is increased more by extracellular Zn^{2+} presented as a complex of zinc ascorbate, rather than as other salts of zinc.[6] Specifically, the inhibition of cAMP accumulation by Zn^{2+} is more potent when the metal is presented as a complex of zinc ascorbate rather than as $ZnCl_2$, zinc citrate, and $ZnSO_4$.[6]

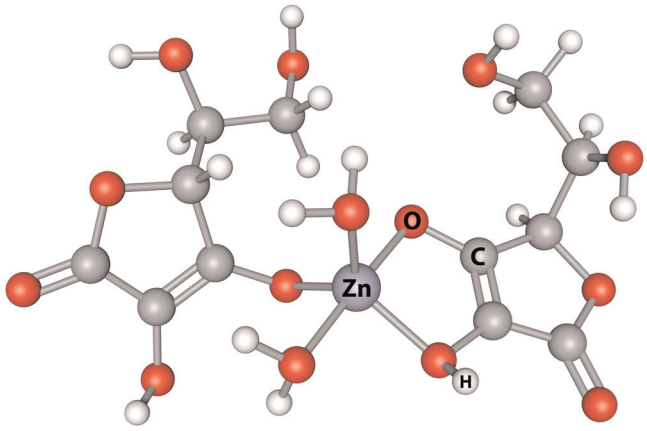

FIGURE 1 Molecular structure of zinc ascorbate.[8] The experimental and computational results agreed on fivefold coordination around Zn^{2+} where one ascorbate binds monodentately, the other bidentately, and two water molecules occupy the remaining sites of a distorted square pyramid[8]

Zinc ascorbate is the zinc salt of ascorbic acid.[7] It is a chelated compound that is produced by the combination of Zn^{2+} with vitamin C, and it is used worldwide as a dietary supplement, in which ascorbic acid enhances zinc absorption into cells.[5] The molecular structure of zinc ascorbate is shown in Figure 1[8] and its skeletal formula in Figure 2.[7]

1.4 | Zinc ascorbate differences with zinc plus vitamin C

Ascorbates are ascorbic acid derivatives, transported across cell membranes by proteins like the sodium-ascorbate cotransporters SVCT1 and SVCT2, and the membrane permeability to ascorbates contributes to a lesser degree to their transport.[9]

The ionophore activity of ascorbates such as sodium ascorbate and potassium ascorbate is likely due to the fact that sodium ions (Na^+) and potassium ions (K^+) are carried inside the cell by means of being linked to the ascorbate radical.[10] Ascorbic acid can in fact act as an ionophore for sodium and potassium, it is present as radical at physiological pH with the unpaired electron located in the C(4) region, and has a cyclic side-chain structure that can engulf also Na^+ or K^+, as a chelating agent, and can then transport these ions across membranes.[10]

In zinc ascorbate, the ionophore activity of the ascorbate on its linked Zn^{2+}, being the main difference with unchelated zinc plus vitamin C, could explain the substantially higher inhibitory properties of zinc ascorbate compared to vitamin C and zinc, measured by Iinuma and Tsuboi.[11] In fact, compared to zinc and vitamin C, zinc ascorbate has significant superoxide dismutase-like activity.[11] Also, the minimum inhibitory concentrations of zinc ascorbate against *Staphylococcus aureus* and *Escherichia coli* are lower than those of ascorbic acid and zinc.[11]

It is likely that supplementing zinc plus vitamin C, where the ascorbic acid is not linked to the zinc ion, ascorbate does not act as a carrier of Zn^{2+}across the cell membrane, thus not performing any zinc ionophore activity. For these reasons supplementation of zinc ascorbate should be considered potentially more effective than zinc plus vitamin C against Covid-19.

1.5 | Hypothesis that zinc ascorbate could inhibit SARS-CoV-2

Since zinc ascorbate enhances Zn^{2+} absorption into cells, causing a bigger and quicker increase in intracellular Zn^{2+} concentration compared to all other currently tested forms of zinc supplements and to the zinc plus vitamin C, I hypothesize that supplementation of oral or intravenous zinc ascorbate could be effective in the prevention and treatment of Covid-19, by inhibition of SARS-CoV-2 replication, due to the higher intracellular Zn^{2+} concentration.

Currently, some clinical trials are underway with zinc plus vitamin C against Covid-19[5] but none with zinc ascorbate. It is timely for zinc ascorbate to be tested against Covid-19 both in vitro and in clinical trials, and to study the effects of the increase in membrane transport and intracellular Zn^{2+} concentration following its oral and intravenous supplementation.

1.6 | Advantages of zinc ascorbate over drugs and vaccines

Zinc ascorbate would have the advantage over drugs and vaccines of being a supplement already available worldwide. It would have the potential to reach more people and more quickly than drugs and vaccines, especially in many third world countries.

Zinc ascorbate would have also other advantages specifically over vaccines:

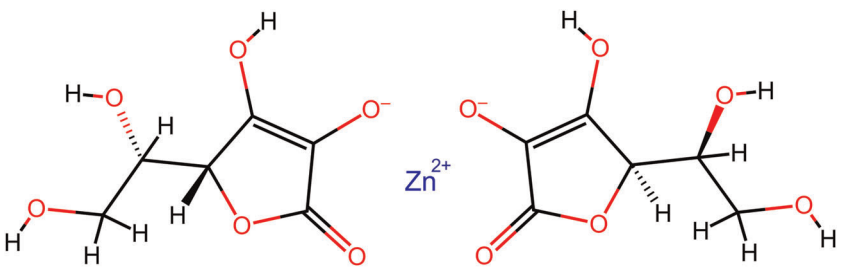

FIGURE 2 Skeletal structural formula of zinc ascorbate[7]

(1) It could be mass-produced more easily and widely than vaccines;
(2) Its effectiveness would likely be not as subject to virus variants like that of vaccines, due to SARS-COV-2 mutations, like the ones in the spike protein, which can cause vaccine resistance[12];
(3) It could be distributed without having to be necessarily stored in refrigerators, hence without having to maintain a cold chain, reaching so a wider number of people worldwide.

Zinc ascorbate would have then other specific advantages on possible drugs:

(1) It could be orally supplemented prophylactically, contrary to most drugs;
(2) It would have no considerable side effects at the typical dosages.[13]

1.7 | Considerations on a clinical trial of zinc ascorbate for Covid-19

Zinc ascorbate should be tested both in vitro and in vivo against SARS-COV-2.

Zinc ascorbate supplementation is already used in diabetes and glycemic control in humans.[14]

A clinical trial is highly feasible, and it could benefit so many people, that it should be carried out as early as possible, for the potential of prevention and therapy of Covid-19 disease.

More than one dosage should be tested, of which one should be the Tolerable Upper Intake of the recommended dietary allowances of zinc, both for prevention and treatment.[15]

Another dosage to be tested, for people who are positive to the virus, could be the one necessary to reach normal levels of zinc in the blood, following a test of zinc blood levels.

1.8 | Gastrointestinal absorption of oral zinc ascorbate and supplementation suggestions

The European Food Safety Authority evaluated that zinc ascorbate can be assumed to be dissociated in the stomach.[13]

This aspect requires further research and could pose a challenge for the correct absorption of the intended amount of zinc ascorbate in the intestine.

A possible solution could be to temporarily reduce stomach acidity with water[16] and to accelerate transit of zinc ascorbate out of the stomach to the small intestine with water and food. For example, zinc ascorbate could be ingested with a small amount of water on an empty stomach, then followed immediately by a full glass of water and possibly a meal, thus reducing temporarily stomach acidity and at the same time accelerating transit of zinc ascorbate out of the stomach to the small intestine, with the effect of a reduction of zinc ascorbate dissociation in the stomach.

In addition, given the recent studies which have shown the potential benefit of vitamin D supplementation against Covid-19,[17] it is suggested that a branch of the trial with zinc ascorbate + vitamin D be tested.

2 | CONCLUSIONS

(1) Based on current research it is reasonable to consider that zinc ascorbate has the potential to contribute to the prevention and treatment of Covid-19 by raising antiviral resistance to SARS-CoV-2;
(2) Tests in vitro and clinical trials for Covid-19 prevention and treatment with zinc ascorbate are strongly recommended and should start immediately;
(3) Potential advantages over drugs and vaccines are discussed, with supplementation suggestions.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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