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Review

Potential of germanium-based compounds in coronavirus infection

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The first germanium compounds which exhibited immunomodulatory and antiviral effects were sesquioxane-type germanates. To date, more than a dozen compounds containing germanium have been synthesized and are being actively studied. They include germanium carboxylates and citrates, complexes of germanium with resveratrol, daphnetin, mangiferin, chrysin, quercetin, ascorbic and nicotinic acids, amino acids, gamma-lactones, germanium-containing spirulina, yeast and others. Germanium-based compounds have shown the ability to influence the replication of various DNA/RNA viruses, stimulate the body's natural resistance, prevent the development of metabolic intoxication of various origin, increase the efficacy of vaccines, and prevent the development of excessive accumulation of reactive oxygen species, which plays a decisive role in the development of inflammatory response caused by a viral infection. It seems reasonable to say that germanium-based complex compounds effectively contribute to the preservation of high-energy bonds in the form of ATP, optimize the activity of metabolic processes by re-oxygenation, and exhibit antimicrobial activity. The purpose of this review is to summarize the pharmacological potential of various germanium-based compounds studied nowadays, taking into account their mechanisms of action, and to analyze their prospects in the development of integrated approaches in the prevention and treatment of SARS-CoV-2 infection.

Keywords: germanium, organic germanium, SARS-CoV-2, COVID-19

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INTRODUCTION

The study of the causative agent of the severe acute respiratory syndrome (SARS), the outbreak of which has swept the world since 2019, allowed for the identification of a new virus, which was defined by the International Committee on Virus Taxonomy as SARS-coronavirus-2 (SARS-CoV-2) (1), and the disease caused by SARS-CoV-2. It can affect patients of all ages and manifest itself as an asymptomatic carrier state, acute respiratory

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infections or pneumonia and has been officially recognized by the WHO as COronaVIrus Disease (COVID-19) (2).

The literature describes various mechanisms of pathogenesis of COVID-19, from interaction with the angiotensin-converting enzyme 2 receptor and trans-membrane serine proteases 2, cathepsin L and furin, or possible involvement of the myeloid compartment (3) to dysregulation of adaptive immunity (4), including a cytokine storm (5), which in severe cases causes an acute respiratory distress syndrome (6). Several recent reports mention the occurrence of lymphopenia (7), increased activity of cluster of differentiation (CD) 8 T-cells compared to CD4 T-cells (8), and functional depletion of cytotoxic lymphocytes (9).

People infected with the SARS-CoV-2 virus experience a phenomenon described as "quiet" or "happy" hypoxia, characterized by the absence of visible functional disorders with low blood oxygen saturation (10). According to some reports, saturation parameters can decrease to the range of 50–80 % without causing complaints, whereas in healthy people the saturation is at least 95 %. A mysterious finding can be dangerous as the patient does not feel much discomfort, but the level of oxygen in his/her lungs is so low that it can cause a rapid loss of consciousness or even death (11, 12).

Some authors believe that the onset of severe damage to organs, primarily the lungs, depends on the activation of the oxidative stress mechanism, which is associated with innate immunity (13). Overproduction of reactive oxygen species (ROS) and deprivation of antioxidant mechanisms result in oxidative damage to healthy cells (14) and enhance the host's inflammatory response to the virus (15), which are critical for viral replication and the development of subsequent disease symptoms (16). Complications observed in patients with COVID-19, such as hypoxemia, bilateral pneumonia or acute respiratory distress syndrome can result in pulmonary edema and pulmonary failure, arrhythmias, shock, acute heart damage, liver dysfunction, renal failure, secondary infections (7), neurological and neurodegenerative disorders (17), coagulation dysfunction (18) and affect lifestyle (19).

Like other viruses, SARS-CoV-2 has many potential natural intermediate and final hosts, which pose serious problems for the prevention and treatment of viral infection (20, 21). While our understanding of COVID-19 pathogenesis is advancing rapidly through global research efforts of unprecedented proportions, there is still scientific debate on both the accuracy of diagnosis and prevention and treatment of the disease in different populations.

The purpose of this study was to review the literature and analyze the mechanisms of possible therapeutic activity of germanium-containing compounds in order to further optimize prevention and develop comprehensive methods to combat COVID-19.

Systematic content analysis using the main online databases (PubMed, Google Scholar, MEDLINE, UpToDate, Embase and Web of Science) was used.

GERMANIUM-CONTAINING COMPOUNDS WITH POTENTIAL THERAPEUTIC VALUE

Sesquioxane-type germanium compounds

The most studied and well-known germanium-containing compound is Ge-132 or carboxyethylgermanium sesquioxide, or poly-*trans*-[(2-carboxyethyl) germasesquioxane, [$(GeCH_2CH_2COOH)_2O_3$] (also known as repagermanium, propagermanium or proxiger-

manium) (Fig. 1a) (22). It showed antioxidant properties *in vitro* in the liver tissues by reducing the activity of NADPH oxidases and xanthine oxidase and increased activity of superoxide dismutase and catalase (23), changed oxidative properties of bilirubin in the bile (24), influenced sensitivity of plasma low-density lipoproteins to oxidation and the morphology of atherosclerosis in the aorta and coronary artery (25), reduced intensity of DNA strand breaking, malondialdehyde levels and increased activity of superoxide dismutase and catalase in the liver (26).

The results of Ge-132 effects on the processes of oocyte maturation demonstrated changes in mRNA expression associated with the nuclear factor erythroid 2-related factor 2 gene and the pro-apoptotic Bax gene; a decrease in the levels of intracellular reactive oxygen species and apoptosis intensity caused by oxidative stress in the oocytes during their maturation (27). The results of other recent studies suggested the mechanism of Ge-132 immunomodulatory and antioxidant effects *via* changes in the expression of more than 1200 genes associated with transport proteins, antioxidant activity, lipid metabolism, ATP synthesis and apoptosis (28). Data on increased mRNA expression, fibroblast proliferation and collagen fiber formation associated with a decrease in edema (29) can be taken into account in the development of comprehensive approaches to the restoration of damaged epithelium. In addition, it was suggested that Ge-132, comprising three oxygen atoms, is an effective electron donor. It amalgamates with free radicals and eliminates them from the body through excretion (30).

Activation of CD4, CD8 T-cells and natural killer (NK) cells, as well as induction of the production of several cytokines induced by Ge-132, suggest this compound as a non-specific immunomodulator for the treatment of patients with chronic hepatitis B (31).

In water, Ge-132 is hydrolyzed to 3-(trihydroxygermyl)propanoic acid (Fig. 1b), which can interact with *cis*-diol-containing compounds of the nucleic acids (32), inhibit the expression of the genes associated with cell death and inflammatory response and exhibit antioxidant properties, which, according to the authors, are not associated with direct absorption of ROS (33).

In early studies in mice infected with an adapted strain of influenza A subtype H2N2, the antiviral activity of Ge-132 was demonstrated through an increase in the number of surviving animals and survival days, as well as a decrease in the titer of the virus in the lung tissues. Since no *in vitro* virucidal or virostatic activity of Ge-132 was detected, these protective effects in mice against influenza virus could be manifested through the immunomodulatory activity of this compound, *i.e.*, an increase in the activity of NK cells (34). Similar immunological effects, including an increase in the activity of NK cells, were observed in the later studies in dogs with adenocarcinoma (35).

In addition to the aforementioned recent data (23, 33), the antiviral activity of Ge-132 was observed in cytomegalovirus infection model back in the 1980-90s (36), immunomodulatory activity, including the mechanisms involving macrophages and/or T-cells, in the experimental tumor models of ascites in mice (37, 38) and the transformation of T-lymphocytes in chicken infected with Marek's virus (39), as well as the ability to influence interferon synthesis (40–43). Ge-132 may be useful as an inducer of counter-suppressive T-cells in immunocompromised individuals, who have suppressive T-cell. Elimination of suppressor T-cells in immunocompromised hosts can result in an increased resistance to various opportunistic infections (44). There is evidence that Ge-132 was able to reduce the manifestations of oxidative stress during the use of steroid anti-inflammatory drugs (45),

to restore the properties of leukocytes and stabilize their membranes (46), to improve cell metabolism (47) and to enhance the production of interferon (IFN)-α/β in mice infected with influenza virus (48). Although Ge-132 did not suppress *in vitro* multiplication of various DNA or RNA viruses, its oral administration increased the survival rate in animals and decreased the manifestations of symptoms of *Herpes simplex virus* type I (HSV-1) infection through the induction of cytotoxic T-lymphocytes against antigen HSV-1, reduced the intensity of symptoms of vaccinia virus infection by the number of pocks on the tail and enhanced IFN-γ induction in mice treated with *Mycobacterium bovis* (49).

Some authors consider neglect of the potential clinical use of this unique germanium compound to be very hasty (50), and despite contradictory data on its effects in the body (51), there are some very convincing results regarding the low toxicity of germanium--organic polymers of the germsesquioxane type (52).

Other germanium-based compounds

Bis(pyridine-2,6-dicarboxylate)germanium. – Bis(pyridine-2,6-dicarboxylate) germanium (Fig. 1c) is a component of the drug Maxidin 0.4, which is prescribed for the treatment and prevention of viral infections in small animals (53). The drug has immunomodulatory and antiviral effects, stimulates the body's natural resistance, increases the activity of the effector cells of the immune system, exhibits a pronounced interferonogenic activity, stimulating the synthesis of both early (mainly IFN-α/β) and late (mainly IFN-γ) interferon, blocking the translation of viral proteins, significantly enhances the functional activity of macrophages – phagocytosis, chemotaxis, oxidative metabolism and lysosomal activity (53, 54). In addition, bis(pyridine-2,6-dicarboxylate) germanium had a prophylactic value in metabolic intoxication during the period of various immunodeficiencies (55).

Germanium nanocarboxylate. – Germanium nanocarboxylate is a component of Hermakap, a trace element supplement, which, when administered for 5 days before and after vaccinations against viral diseases in birds, resulted in an increase in specific antibodies against infectious bursal disease, infectious bronchitis in chicken and group immunity to Newcastle disease (57). When this drug was used in calves, the activation of hematopoiesis and restoration of the structure of this system was observed in terms of leukocyte, segmented neutrophil and eosinophil levels, lymphocyte content, in a significant increase in total protein and its gamma-globulin fraction, as well as in phagocytic activity of the neutrophils (58).

Aluminosilicate mineral germanium. – The studies of Germanium Biotite, a supplement containing the aluminosilicate mineral germanium, showed an increase in the immune response to the aphthous fever vaccine (59), an increase in the proliferative response of lymphocytes and lysozyme activity (60) and preventive effects against respiratory disease in cattle (61).

Given the ability of SARS-CoV-19 to be transmitted from animals to humans, the prevention of the latter's morbidity can play an important role in the prevention of pandemics.

Nanogermanium citrate. – Its use in the experiment had a protective effect on thymus and lymph node cells, reducing their DNA damage and death, which may be mediated by the observed certain normalization of neutrophil functions (62). An improvement in the parameters of the immune and antioxidant systems was confirmed by the bottom content

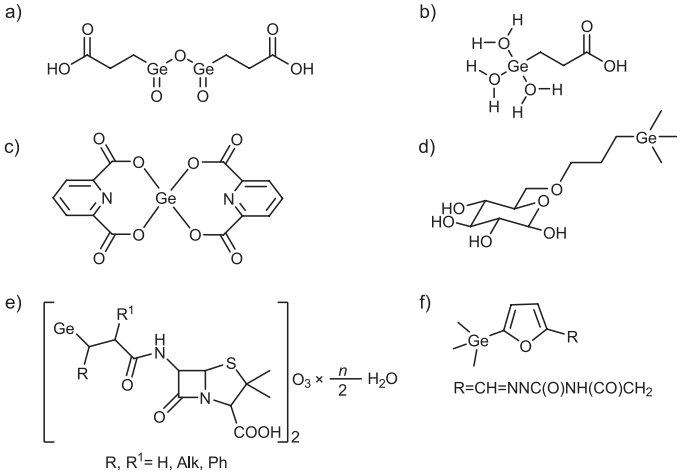

Fig. 1. Germanium-based compounds: a) Ge-132 or carboxyethylgermanium sesquioxide, propagermanium (22), b) 3-(trihydroxygermyl)propanoic acid (98), c) bis(pyridine-2,6-dicarboxylate) germanium (56), d) 6-*O*-[3-(trimethylgermyl)propyl]-*β*-D-glucopyranoside (72), e) β-lactam derivatives of germanium (48), f) trimethylgermanyl-furan (48).

of immune globulins, glycoproteins and the activity of antioxidant defence enzymes in pregnant rats (63), as well as immunological parameters and a decrease in the intensity of lipid peroxidation in infant rats (64).

1-Hydroxygermatranil citrate. – The findings of Liashenko *et al*. (65, 66) indicating the ability of 1-hydroxygermatranil citrate to enhance the effects of the Vaxigrip vaccine, may be of interest for the prevention of viral pandemics after COVID-19 and can be proposed as an adjuvant treatment after further studies.

Bio-germanium systems. – An increase in the activity of germanium-containing spirulina, compared to dietary spirulina, was observed in terms of plasma levels of IFN-γ and tumour necrosis factor (TNF)-α, an increase in the activity of catalase and glutathione peroxidase, as well as the level of oxidized glutathione in the liver under conditions of an experimental model of hepatitis (67).

Bio-germanium synthesized using a yeast culture process has shown immunostimulatory effects by increasing the cytotoxicity of NK cells and activating immunoglobulins, B cells and TNF-α in volunteers (68). Given the data on the low toxicity of germanium-enriched yeast (69), its ability to induce macrophage activation, thereby increasing their function (70), as well as its anti-inflammatory activity, partially associated with inhibition of arachidonic acid release and prostaglandin E_2 production in cancer basophilic cells (71), this supplement can also be considered in the process of complex modulation of immunological homeostasis during coronavirus infection.

6-O-[3-(trimethylgermyl)propyl]-beta-D-glucopyranoside. – 6-*O*-[3-(trimethylgermyl) propyl]-*β*-D-glucopyranoside (Fig. 1d) was a better inducer of IFN-γ than Ge-132, in animal studies (72).

Organogermanium poly-derivatives. – The anti-respiratory virus activity of organogermanium poly-derivatives, compared to ribavirin, has been confirmed *in vitro* (73).

There is evidence that β-lactam derivatives of germanium (Fig. 1e), in addition to inhibition of pathogenic microorganism growth, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, are able to exert a synergistic effect on β-lactam antibiotics (48).

Trimethylgermatril-furans (Fig. 1f) show high bacteriostatic activity against *Staphylococcus aureus* and *Escherichia coli* (48), which can be taken into account to prevent the development of complications of bacterial etiology.

Complexes of germanium with flavonoids, polyphenols, vitamins, amino acids and gamma-lactones. – The study of germanium-containing complexes with biologically active compounds is due to their ability to synergize the pharmacological activity of individual components of the complex, which was confirmed by the antioxidant activity of the Ge-resveratrol complex (Fig. 2a), the mechanism of action of which is associated with the presence of the -Ge-O- bond (74), complexes of germanium with polyphenols, namely, Ge-daphnitine (Fig. 2b) and Ge-mangiferin (Fig. 2c) (75), and chrysin-Ge (Fig. 2d) (76).

Taking into account the data on the interactions between SARS-CoV-2 and erythrocytes and their effect on the hemes and porphyrin, the quercetin-Ge_2 complex (Fig. 2e) is of interest, which is able to reduce oxidative damage to human erythrocytes and restore the morphology of the cell surface, the potential of the plasma membrane and intracellular levels of free Ca^{2+} (77).

The combination of organogermanium with ascorbic acid (Fig. 2f), in addition to significant antioxidant properties (78, 79), has demonstrated the ability to restore the barrier function of the skin, to reduce trans-membrane water loss and immunoglobulin E production in a model of chronic contact dermatitis (80), which can be useful in the development of complex approaches to restoration of epithelial tissue of the lungs in patients who suffered from COVID-19.

Antimicrobial activity and highly selective antibacterial action of germa-gamma-lactones (Fig. 2g) against Gram-negative bacteria (81) may be important for the prevention of opportunistic infections.

The immunomodulatory effects of germanium combinations with amino acids (bis-histidino germinate (Fig 2h), bis-methionino germanate (Fig. 2i) and bis-glutathiono germanate) (Fig. 2j) were studied in terms of *in vivo* interleukin-12 and IFN-γ levels, and the mechanism of these changes was determined as neurochemical (82). Among the compounds studied, bis-methionino germanate was found to be the best interferon inducer that improved immunological function.

Coordination compounds of germanium with organic bio-ligands. – The therapeutic potential of the coordination compounds of germanium with nicotinic acid (Fig. 2k) is expressed as the prevention of excessive accumulation of ROS, possibly through its superoxide dismutase activity (83), lipid (84, 85) and proteins peroxidation products (86), which play a key role in the development of inflammatory reactions caused by a viral infection.

Since oxidative stress plays an important role in the initiation and persistence of lung injury and inflammation, approaches combining ROS removal with inhibition of viral replication may be effective in modulating severe lung disease associated both with SARS-CoV-2 and other respiratory viral infections. In addition, given the pharmacological activity of

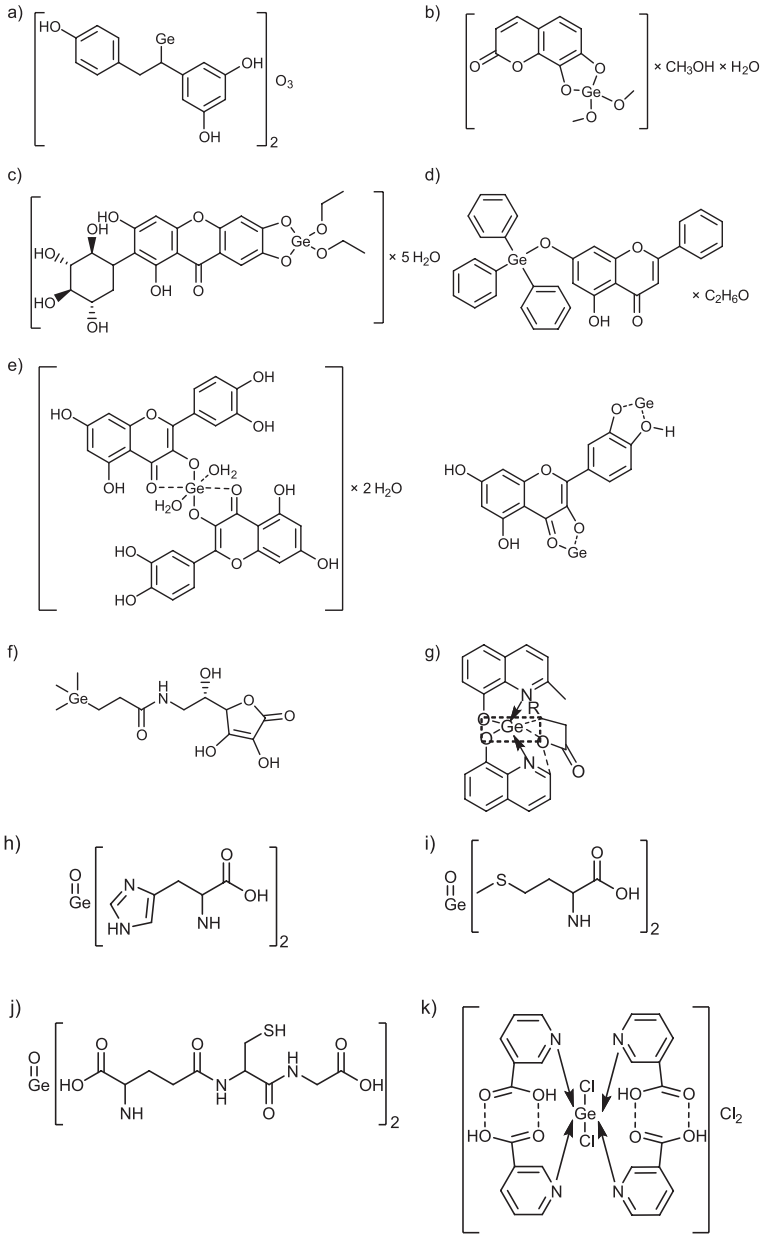

Fig. 2. Structures of germanium complexes with flavonoids, polyphenols, vitamins, amino acids and gamma-lactones: a) Ge-resveratrol (74), b) Ge-daphnitine (75), c) Ge-mangiferin (75), d) Ge-chrysin (76), e) Ge-quercetin (99) and Ge_2-quercetin (77), f) organogermanium with ascorbic acid (79, 80), g) germa-gamma-lactones (81), h) bis-histidino germanate (82), i) bis-methionino germanate (82), j) bis-glutathiono germanate (82), k) germanium complex with nicotinic acid (94).

nicotinic acid (87–89), further studies of germanium complex with nicotinic acid (86) seem promising. There are also reasons to assume that coordination compounds of germanium with nicotinic acid and nicotinamide, due to their membrane-protective activity, effectively contribute to the preservation of the levels of adenyl nucleotides, which are disrupted under conditions of exo- (90) and endo-toxemia (91, 92). In experimental re-oxygenation following hypoxia associated with hypercapnia, the coordination compounds of germanium showed the ability to stabilize the processes of oxygen uptake by the tissues by activating the main buffer systems of blood plasma, and also to optimize the level of metabolic processes by reducing the rate of O_2 extraction from the blood by the cells (93, 94). The data on the dose dependence of the antihypoxic effects of tartaric acid-based coordination compound of germanium with manganese (95) can also be taken into account in further studies of this group of compounds, and the *in vitro* anti-staphylococcal activity of the germanium complex with citric acid (96), and the effect of a number of germanium complexes with succinic, hydroxyethyliminodiacetic and iminodisuccinic acids on the synthesis and activity of collagenase enzymes, α-*N*-acetylgalactosaminidase and α-galactosidase (97) can play an important role in the prevention of opportunistic infections.

CONCLUSIONS

In this review, germanium-containing compounds of various structures and their main biochemical mechanisms of action are discussed. Hypotheses of their potential therapeutic activity in the development of complex approaches in the prevention and treatment of SARS-CoV-2 infection are proposed, including the effects on the reproduction of various DNA/RNA viruses, stimulation of the body's natural resistance, prevention of the development of metabolic intoxication of various etiologies, increased efficacy of vaccines, prevention of excessive accumulation of reactive oxygen species, preservation of high-energy bonds, as well as optimization of the activity of metabolic processes through re-oxygenation and antimicrobial activity. At the same time, despite the promising use of germanium-containing compounds for the development of approaches in the prevention and treatment of coronavirus infection, further comprehensive studies of the pharmacological mechanism of action of each of them are still required.

Abbreviations, acronyms, symbols. – ATP – adenosine triphosphate, CD cells – cluster of differentiation cells, IFN – interferon, NADPH – nicotinamide adenine dinucleotide phosphate, NK – natural killer, ROS – reactive oxygen species, SARS – severe acute respiratory syndrome, SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2, TNF – tumour necrosis factor

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