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Review

Selenium and COVID-19: A spotlight on the clinical trials, inventive compositions, and patent literature

Mohammed Kanan Alshammari, Waseem Fatima, Reem Ahmed Alraya, A. Khuzaim Alzarhaini, Mehnaz Kamal, Reem Saud Alshammari, Sarah Ayad Alshammari, Lina Mohammed Alharbi, Norah Saad Alsulaibie, Rakan Bijad Alosaimi, Syed Mohammed Basheeruddin Asdaq, Mohd. Imran

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Abstract

Selenium is an indispensable trace element for all living organisms. It is an essential structural component of several selenium-dependent enzymes, which support the human body’s defense mechanism. Recently, the significance of selenium in preventing/treating COVID-19 has been documented in the literature. This review highlights the clinical studies, compositions, and patent literature on selenium to prevent/treat COVID-19. Selenium exerts its anti-COVID-19 action by reducing oxidative stress, declining the expression of enzymes of SARS-CoV-2. The data of clinical studies, inventive compositions, and patent literature revealed that selenium monotherapy and its compositions with other nutritional supplements/drugs (vitamin, iron, zinc, copper, ferulic acid, resveratrol, spirulina, N-acetylcyesteine, fish oil, many herbs, doxy cycline, azithromycin, curcumin, quercetin, etc.) might be practical to prevent/treat COVID-19. The studies have also suggested a correlation between COVID-19 and selenium deficiency. This indicates that adequate selenium supplementation may provide promising treatment outcomes in COVID-19 patients. The authors foresee the development and commercialization of Selenium-based compositions and dosage forms (spray, inhalers, control release dosage forms, etc.) to battle COVID-19. We also trust that numerous selenium-based compositions are yet to be explored. Accordingly, there is good scope for scientists to work on developing novel and inventive selenium-based compositions to fight against COVID-19. However, there is also a need to consider the narrow therapeutic window and chemical interaction of selenium before developing selenium-based compositions.

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1. Introduction

The infection with SARS-CoV-2 (a RNA virus) causes contagious COVID-19, which has disastrously impacted the world’s demography [1]. The first case of COVID-19 emerged in December 2019, whereas the World Health Organization (WHO) announced it as a pandemic in March 2020 [1–3]. SARS-CoV-2 is transmitted through the respiratory droplets of the infected person and virus-contaminated surfaces/items [1]. The general symptoms of COVID-19 include fever, cough, sore throat, nasal congestion, headache, fatigue, pain in muscles/joints, loss of smell/taste, diarrhea, and breathlessness [1–4]. Most of the COVID-19 patients (about 80%) recover without hospitalization, about 15% get serious symptoms, and about 5% require intensive care [1,2]. The death-causing complications of COVID-19 comprise respiratory failure, septic shock, thromboembolism, and multiorgan failure [1,2]. As of June 27, 2022, the World Health Organization (WHO) reported 539,893,858 confirmed cases of COVID-19, 632,411,12 deaths due to COVID-19, and administration of vaccines comprises respiratory failure, septicaemia, thromboembolism, and multiorgan failure [1,2]. These issues forced scientists to develop new treatments and supportive therapy for COVID-19. Selenium is a recognized trace element and an essential nutrient for human health [13–16]. Recently, the importance of selenium in preventing/treating COVID-19 has been documented in the literature [17–27]. When writing this review, the authors believe that no publication covers the clinical studies, inventive composition, and patent literature of selenium to prevent/treat COVID-19 in a single document. This review fills this literature gap and will be valuable to scientists developing Selenium-based COVID-19 treatment.

2. Selenium

Selenium, designated as Se (atomic number 34), is known as a chemical element since 1818 [28]. This trace or essential micro-nutrient is one of the critical structural components of several selenium-dependent enzymes, including glutathione peroxidase 1 and 2 (control intracellular oxidative stress), glutathione peroxidase 4 (lowers lipid hydroperoxides), iodothyronine deiodinases (help in immunity building), methionine-S-sulfoxide reductase (regulate oxidative stress), thioredox reductase, selenoprotein H and T (regulates redox homeostasis), selenoprotein I (controls phospholipid biosynthesis), selenoprotein K (regulates lymphocyte activity and calcium signaling), selenoprotein P (relates to selenium status and its supply in the cell), selenoprotein S (regulates protein synthesis), and selenophosphate synthetase 2 (regulates biosynthesis of selenoproteins) [22,29–33]. Selenium is a more potent antioxidant than tocopherol, vitamin C, and beta-carotene [31,32]. Selenium and selenium-containing enzymes/proteins/food support the defense mechanism of the human body and play an essential biological role (antiviral, antioxidant, anti-inflammatory, immunity booster, etc.) for human health (Fig. 1) [32–37].

The selenium content in its sources hangs on the selenium levels in the soil. The selenium content in soil differs from country to country. For example, the selenium content in the soil is relatively low in Europe, Italy, New Zealand, China, and some parts of the USA [18]. The dietary requirement of selenium varies with age, gender, and health status of the individual [17,36] (Table 1). Intake of higher concentrations can cause selenium toxicity (selenosis) [17,36]. The average daily dose of selenium should not exceed 70 µg/day for adults, whereas a selenium dose of 400 µg/day may be toxic for an adult. The primary dietary bioavailable forms of selenium (≥ 90% bioavailability) are selenomethionine (SeMet) and selenocysteine (Sec) [32,33]. The inorganic forms of selenium (selenate [SeO₄]²⁻, selenite [SeO₃]³⁻, etc.) also have good bioavailability (60–70% bioavailability) but less than SeMet and Sec [31,38,39]. SeMet is absorbed from the intestine, whereas the inorganic forms of selenium
(selenate, selenite, etc.) are absorbed by the simple diffusion process. The absorbed selenium sources are converted to selenide (HSe\(^{-}\)) in the liver, which is utilized for the activation/generation of selenoenzymes [29,31,32,39–41]. The inorganic forms of selenium are utilized as supplements to manage selenium deficiency. The liver is the chief storing organ for selenium and supplies selenium to other tissues on a need basis [29,40,41].

Selenium is vital for the preservation of complete health. Its deficiency affects 0.5–1 billion people around the globe due to its poor intake [42]. A low selenium deficiency causes cognitive decline, involving confusion, anxiety, and depressive mood. The moderate to severe deficiency of selenium may lead to thyroid disorder, oxidative stress, deformity of bones (Kashin-Beck), weakness of heart muscles, myo-degenerative diseases, deficiency of vitamin E, infertility in men, prostate cancer, reduced adaptive immunity, increased chances of infection, neurological disorders, and Keshan disease [43]. Among these diseases, Keshan disease (weakness of heart muscles and cardiomyopathy) is endemic in Keshan, China, and is generally accompanied by Coxsackie B3 enterovirus infection [42–44]. One Chinese report has stated that selenium deficiency makes the individual more susceptible to COVID-19, whereas the supplementation of selenium decreases the cure time of COVID-19 patients. This report also stated a faster recovery of the COVID-19 patients with a higher hair selenium concentration [44]. Selenium deficiency can be managed by increasing the intake of selenium-rich food and its supplements [45]. However, selenium has a narrow therapeutic window [42]. Therefore, an excess intake of selenium or its supplements can cause toxicity (selenosis, garlic odor in the mouth, gastrointestinal upset, hair loss, fatigue, sloughing of nails, neurological damage, and irritability). The United States Food and Drug Administration (USFDA) recognized one such case of the selenium toxicity epidemic in 2008, wherein more than 200 individuals suffered from selenium toxicity due to nutritional supplements containing an excess of selenium [46].

2.1. USFDA approved selenium products

A search for the USFDA-approved selenium-containing products on the USFDA’s Orange Book database [47] was conducted on May 17, 2022. This search revealed eleven selenium products, out of which seven have been discontinued, and 4 are prescription products (Table 2) (Fig. 2). Two prescription products (Multrys and Selenium Acid) are used as a source of selenium for parenteral nutrition. In contrast, others are indicated to treat tinea versicolor/seborrheic dermatitis/dandruff and selenium deficiency.

2.2. Selenium and COVID-19

SARS-CoV-2 penetrates the human cells via Angiotensin-converting enzyme 2 receptor (ACE-2) [2–4]. This initiates the discharge of pro-inflammatory substances, cytokine storm, acute respiratory distress syndrome (ARDS), and oxidative stress in the human body [2–4]. The replication of SARS-CoV-2 takes place through 3CL\(_{pro}\) (main protease enzyme) and RNA-dependent RNA-Polymerase (\(R_\text{R}_\text{N}\)) [2–4]. Selenium (selenoproteins and selenium-containing organic compounds) exerts its anti-COVID-19 action by decreasing the expression of ACE-2 receptor (prevents SARS-CoV-2 entry into the cell); lowering the release of pro-inflammatory substances (inhibits cytokine storm, oxidative stress, ARDS, etc.), and inhibiting the 3CL\(_{Pro}\) (main protease) of SARS-CoV-2 [17–24,26,27] (Fig. 3). Selenium also inhibits papain-like protease (\(P_\text{L}_{\text{pro}}\) of SARS-CoV-2, an essential enzyme for its replication [17,21]. One report also hypothesizes that selenium interacts with the sulfhydryl group of viral protein (disulfide isomerase) and changes the active sulfhydryl group to an inactive disulfide group. This also prevents the virus entry into the cell [19,20]. Selenium also has anti-thrombotic and anti-platelet effects, which also help combat symptoms and complications of COVID-19 [15,20,28].

2.3. Clinical trials/studies on selenium

A search for the selenium-related clinical studies (CS) was performed on the clinical trial database [48] on June 27, 2022, utilizing the keywords “selenium”, “selenium + COVID-19”, and “selenium + SARS-CoV-2”. This search revealed 369 CSs in which selenium has been/is being assessed clinically for many conditions/disorders,
including diseases related to infection, immunity, respiratory system, musculoskeletal system, blood, heart, diabetes, and cancer. This search also unveiled 13 CSSs for the prevention/treatment of COVID-19 employing selenium. However, in two CSSs, selenium was used as a comparator rather than an intervention. Accordingly, the summary of 11 CSSs is mentioned in Table 3.

It is evident from the data in Table 3 that selenium (as selenious acid) monotherapy and the nutritional supplement containing selenium/selenium yeast in combination with vitamins (A, C, and E), iron, zinc, copper, ferulic acid, resveratrol, spirulina, N-acetylcysteine, and vitamins are a target for research in the context of prevention/treatment of COVID-19. It can also be observed that the maximum number of clinical studies have been conducted in Turkey (4 studies), followed by Spain (3), France (2), the United States (1), and Saudi Arabia (1). Interestingly, only one study (NCT04798677) mentioned in Table 3 has been published, whereas the results of other studies have not been publicized yet.

The PubMed search also revealed two important studies involving selenium and COVID-19. One study on 50 COVID-19 patients proved a lower level of selenium in COVID-19 patients (77.8 ± 13.9 µg/L) in comparison to healthy individuals (91.7 ± 16.7 µg/L) [49]. This study also stated that a lower selenium concentration might increase the chances of getting SARS-CoV-2 infection or COVID-19 but is silent about the relationship between serum selenium levels and severity/mortality associated with COVID-19. Another study published the results of NCT04798677 [50]. The relevant information about NCT04798677 is mentioned in Table 3. This study demonstrated that supplementation of ABBC1 increased the level of selenium, zinc, CD4+ T cells, CD8+ T lymphocytes, IgG, and IgM compared to placebo. These findings confirm the immunity booster effects of ABBC1.

2.4. Patent literature

The patent literature search was performed on Sci-Finder, Espacenet, Patentscope, and USPTO databases on June 27, 2022 [51–55]. The keywords “selenium + COVID-19” and “selenium + SARS-CoV-2” were selected for patent searching on different patent databases (Espacenet, USPTO, Scifinder, and Patentscope).
The summary of the COVID-19 related CSs on selenium is provided in Table 3.

### Table 3
Summary of the COVID-19 related CSs on selenium.

| Short title / objective / intervention | Primary purpose (Allocation/Type; Status; Phase; Number enrolled; Results; Comparison group; Primary outcome) | NCT number (Sponsor; Location; Start date; Completion date) |
|---------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Selenium efficacy among hospitalized COVID-19 patients (Loading dose of seleniumic acid infusion (2000 µg) on day 1, and maintenance dose (1000 µg per day) for 2–14 days along with standard care) | Treatment (Randomized; Not yet recruiting; 2; 100; Not available; Standard care + placebo; Mean change in the ordinal scale and rate of hospital discharges(deaths)) | NCT0469579 (Christus Health and Pharco Pharmaceuticals; United States; August 15, 2021; December 15, 2021) |
| Evaluation of the plasma concentration of micronutrients (selenium, zinc, copper, etc.) in elderly COVID-19 patients and its correlation with the prognosis of COVID-19 | Observation (Cohort; Completed; Not mentioned; 229; Not available; COVID-19 patients of > 50 years; The plasma concentration of selenium, zinc, copper, and vitamin A, D, and E) | NCT04877509 (Hospices Civils de Lyon; France; March 1, 2020; May 1, 2021) |
| Assessment of the ABBC1 (a nutritional supplement containing selenium and zinc) benefits among volunteers taking influenza and COVID-19 vaccine. The supplementation starts 30 and 35 days after taking the influenza, and COVID-19 vaccine, respectively. | Other (Randomized; Recruiting; Not applicable; 90; Published; Influenza/COVID-19 vaccine + placebo; Change in the immune response and selenium/zinc level after supplementation) | NCT04798677 (AB Biotek; Spain; October 29, 2020; July 2021) |
| To determine the serum concentration of trace elements (selenium, zinc, copper, etc.) in COVID-19 patients before starting the treatment and to compare the results with a healthy individual | Efficacy of micronutrient supplements (once a day oral supplementation comprising vitamins, iron (5 mg), zinc (10 mg), selenium (110 mg), and copper (0.9 mg)) in lowering hospital admissions of COVID-19 patients | NCT04694716 (Izmir Bakircay University; Turkey; January 6, 2021; August 15, 2021) |
| Reducing the COVID-19 severity by utilizing once a day oral capsule comprising selenium (15 µg), zinc (7.5 mg), vitamin A (1500 mcg), vitamin C (250 mg), and vitamin E (90 mg) for 7–14 days | Supportive Care (Randomized; Recruiting; 2/3; 40; Not available; Cellulose-containing placebo capsules; Change in the serum level of ferritin, Interleukin-6, C-reactive protein, Tumor necrosis factor-α, and monocyte chemoattractant protein 1) | NCT04323228 (King Saud University; Saudi Arabia; September 1, 2020; December 30, 2020) |
| Understanding the change in the serum concentration of trace elements (selenium, zinc, magnesium, copper, etc.) in COVID-19 patients and after COVID-19 treatment | Observational (Cohort; Completed; Not mentioned; 15; Not available; Not mentioned; Change of the levels of Trace Element at baseline and discharge) | NCT04694703 (Izmir Bakircay University; Turkey; January 6, 2021; August 29, 2021) |
| Determination of the oxidative stress indicators (Superoxide dismutase and malondialdehyde), trace elements (selenium, zinc, potassium, sodium, magnesium, and copper), and quality of life among healthy women before and COVID-19 vaccine | Screening (Not applicable; Not yet recruiting; Not applicable; 20; Not available; Not mentioned; Change of the levels serum trace elements) | NCT04751669 (Fundació Institut Germans Trias i Pujol; Spain; April 1, 2021; December 31, 2021) |
| Determination of the oxidative stress indicators (Superoxide dismutase and malondialdehyde), trace elements (selenium, zinc, potassium, sodium, magnesium, and calcium), and quality of life among healthy men before and COVID-19 vaccine | Screening (Not applicable; Not yet recruiting; Not applicable; 20; Not available; Not mentioned; Change of the levels serum trace elements) | NCT04751695 (Izmir Bakircay University; Turkey; February 2021; April 2021) |
| Determination of the concentration of trace elements (selenium, zinc, and magnesium) along with other parameters to assess their involvement in the generation of fatigue associated with COVID-19 | Diagnostic (Non-Randomized; Recruiting; Not applicable; 102; Not available; Not mentioned; Voluntary maximum force reduction) | NCT04363606 (Centre Hospitalier Universitaire de Saint Etienne; France; May 27, 2020; December 2022) |

Organic compounds. Most patent applications are filed in the United States and China (Fig. 4). The patent applications are also filed in Europe, Russia, France, Germany, the United Kingdom, India, and Columbia.

### 3. Discussion
Selenium is an essential structural part of many necessary enzymes (selenoproteins), which are implicated in developing a solid defense mechanism for the human body [17–24]. Most selenoproteins help prevent viral infections and positively impact immunity due to their anti-inflammatory and antioxidant nature [17–19]. It is documented that selenium deficiency makes an individual vulnerable to SARS-CoV-2 infection and is linked with the cure rate of COVID-19 patients [17,19,49]. Selenium deficiency also relates to the pathogenicity of the virus [22]. As stated above, the content of selenium in the soil is relatively low in Europe, Italy, China, and some other countries. A literature search on Espacenet (selenium + COVID-19 = 22 hits; selenium + SARS-CoV-2 = 26 hits), USPTO (selenium + COVID-19 = 25 hits; selenium + SARS-CoV-2 = 27 hits), Sci-finder (selenium + COVID-19 = 19 hits; selenium + SARS-CoV-2 = 22 hits), Patentscope (selenium + COVID-19 = 25 hits; selenium + SARS-CoV-2 = 21 hits) explored many patent applications. The duplicate patents/patent applications of the same patent family were removed. The patents/patent applications that did not explicitly claim or did not exemplify the use of selenium or its composition to prevent/treat COVID-19 were excluded. The summary of the finalized patent application is provided in Table 4.
Summary of the patent applications claiming the use of selenium to prevent/treat COVID-19.

| Patent application number (Applicant; Filing country; Publication date; Status) | Status (Family members as of June 27, 2022) | Summary of the claimed invention |
|---|---|---|
| WO2021263206A1 (Ghouwba Mohamed Samir Elsayed; United States; October 21, 2021) | Under examination (W02021216581A1) | A method of treating COVID-19 by administering a bolus dose (1000–6000 µg/day) of selenium in the form of its pharmaceutically acceptable form (selenium hydride, sodium selenite, selenic acid, selenium dioxide, SeMet, SeC, selenomethionine, dimethyl selenoxide, selenocystamine, selenomethyl SeC, selenated yeasts, etc.) followed by a continuous dose of selenium (1000–1600 µg/day), and monitoring the patient for certain parameters (levels of selenium, oxygen, enzymes, platelets, ferritin, total bilirubin, white blood cell counts, complete blood counts, interleukin-1, interleukin-6, tumor necrosis factor-alpha, SARS-CoV-2 polymerase chain reaction). The patent application states the utilization of selenium as an antioxidant, cytokine modulator, antiviral, immune booster, anti-apoptotic, and anticoagulant to treat/prevent COVID-19. This study provides prophetic examples for the intravenous/oral use of selenium (as Selenious Acid) to treat COVID-19 patients[56]. |
| US2022040228A1 (Prothione; United States; December 30, 2021) | Under examination (WO2022034549A1) | A micronutrient-based composition containing many nutrients (selenium, polyphenols, plant extracts, alkaloids, stilbenes, terpenes, volatile oils, vitamins, fatty acids, and amino acids) to treat COVID-19. This patent application demonstrates the effect of the selenium (2–500 µg) containing composition on the expression of the ACE-2 receptor and replication of SARS-CoV-2[58]. |
| WO2022035860A1 (HSA, Houn Simon; United States; February 17, 2022) | No national phase entry (None) | A composition containing fish oil (up to 20 g/day) and selenium (1000–10000 µg/day) to treat COVID-19. This composition may optionally contain coenzyme Q10. The patent application demonstrates apoptotic effects against SARS-CoV-2 and anti-inflammatory effects of the claimed composition against pro-inflammatory substances[59]. Seleniumopyrimidine-5’-triphosphate compounds[60]. |
| CN113004358A (Nisuo Weite Chengdu Biotechnology Company Limited; China; June 22, 2021) | Under examination (None) | Peptide nano-selenium compounds[61] |
| CN11291410A (Chen Yuxiang; China; June 8, 2021) | Under examination (None) | Selenium-based disinfectants[62] |
| CN11248823A (Baishan Fengshou Bee Products Technology Development Company Limited; China; June 9, 2020) | Application withdrawn (None) | A composition comprising glutathione precursor (glycine, l-cystine, and a glutamate source) and a selenium compound (SeMet, selenite, methyl SeC, or selenium nanoparticles)[57]. |
| US2022105110A1 (Lalvani Kartar Singh; Europe; April 7, 2022) | Under examination (None) | A selenium-enriched herbal composition comprising many herbs, including areca nut, cinnamon oil, and sweet potato[68]. |
| US2022042228A1 (Gaertner Frank; United States; February 10, 2022) | Under examination (None) | A composition comprising aspirin, promethazine, and nicinamide, which may optionally contain selenium, zinc, vitamins, etc.[63]. |
| CN113208020A (Guo Lifeng; China; August 6, 2021) | Under examination (None) | A composition consisting of zinc, elderberry fruit extract blend, vitamins (A, C, D3, B6, B12, folate), selenium, Echinacea, garlic allicin, and elderberry fruit extract[64]. |
| RU2763719C1 (Smart Aqua; Russia; December 28, 2021) | Patented case (None) | An immune booster liquid composition comprising vitamins (C, D3, B6, B12), succinic acid, selenium, zinc, magnesium citrate, and Bor[66]. Benzisoselenazolone derivatives[67] |
| CN113831302A (Shandong University; China; December 24, 2021) | Patented case (None) | A method of treating COVID-19 by administering a bolus dose (1000–6000 µg/day) of selenium in the form of its pharmaceutically acceptable form (selenium hydride, sodium selenite, selenic acid, selenium dioxide, SeMet, SeC, selenomethionine, dimethyl selenoxide, selenocystamine, selenomethyl SeC, selenated yeasts, etc.) followed by a continuous dose of selenium (1000–1600 µg/day), and monitoring the patient for certain parameters (levels of selenium, oxygen, enzymes, platelets, ferritin, total bilirubin, white blood cell counts, complete blood counts, interleukin-1, interleukin-6, tumor necrosis factor-alpha, SARS-CoV-2 polymerase chain reaction). The patent application states the utilization of selenium as an antioxidant, cytokine modulator, antiviral, immune booster, anti-apoptotic, and anticoagulant to treat/prevent COVID-19. This study provides prophetic examples for the intravenous/oral use of selenium (as Selenious Acid) to treat COVID-19 patients[56]. |
| CN112555162A (Song Jaoyu; China; March 19, 2021) | Under examination (None) | A composition comprising artemether, azithromycin, vitamin C, selenium, zinc, and vitamin D[71]. |
| CN11631404A (Chongqing Zhenminrun Technology Company Limited; China; September 8, 2020) | Under examination (None) | An immunity booster composition of Lactobacillus coryniformis, selenium, and zinc[72]. |
| CN11333667B (Zhejiang University of Technology; China; June 26, 2020) | Patented case (None) | A composition comprising artemether, azithromycin, vitamin C, selenium, zinc, and vitamin D[71]. |
| FR31092599A1 (Hamdan Sami; France; October 22, 2021) | Lapsed (None) | An immunity booster composition of Lactobacillus coryniformis, selenium, and zinc[72]. |
| DE202021105157U1 (Rittinghausen Reiner; Germany; October 13, 2021) | Under examination (None) | A composition obtained by combining curcumin powders, vitamin C, grape seed extract, quererin, vitamin D3, vitamin K2, zinc glutonate, Astragalus root extract, l-2Met, vitamin B12, vitamin A acetate, glutathione, Boswellia resin extract, potassium sorbate, stevia, and flavor (mango)[73]. A composition containing doxycycline and immunity booster (selenium, zinc, quererin, copper, vitamins, etc.)[74]. |
| WO2021255464A1 (Hahin Norman; United Kingdom; December 23, 2021) | No national phase entry (None) | A composition containing doxycycline and immunity booster (selenium, zinc, quererin, copper, vitamins, etc.)[74]. |
| US2021315910A1 (Stafford Vivi Robyn; United States; October 14, 2021) | Abandoned (None) | A composition of selenium, zinc, vitamin C, vitamin K2–7, and curcumin, which may optionally contain other vitamins (A, B, and D)[75]. Composition of vitamin C, vitamin D, and zinc, that may optionally contain other vitamins (A, B, and D)[76]. |
| WO2021191864A1 (Dound Yogesh; India; September 30, 2021) | No national phase entry (None) | Composition of selenium, zinc, vitamin C, vitamin K2–7, and curcumin, which may optionally contain other vitamins (A, B, and D)[75]. Composition of vitamin C, vitamin D, and zinc, that may optionally contain other vitamins (A, B, and D)[76]. |
| US11278528B2 (Hazar Sabine; United States; September 30, 2021) | Patented case (None) | Composition of selenium, zinc, vitamin C, vitamin K2–7, and curcumin, which may optionally contain other vitamins (A, B, and D)[75]. Composition of vitamin C, vitamin D, and zinc, that may optionally contain other vitamins (A, B, and D)[76]. |

(continued on next page)
Parts of the USA [18,42–44]. This fact may be one of the reasons that people of these regions suffered from COVID-19 more than other countries. Some immunopathological conditions (sepsis) are also there in which selenium deficiency is a marker. Patients suffering from such diseases are also prone to COVID-19 [19]. Older, hypertensive, diabetic, and immunocompromised people are susceptible to selenium deficiency, making these patients a high-risk group for developing COVID-19 [17–20].

The adequate level of selenium in the human body avoids the cytokine storm owing to its anti-inflammatory and antioxidant effects, stops the doorway of SARS-CoV-2 into the human body by depressing the expression of ACE-2 receptors, and hindering the enzyme of SARS-CoV-2 (main protease and papain-like protease) [17–24,26,27]. The anti-thrombotic and anti-platelet activity of selenium is also reported [20]. Respiratory failure, septic shock, thromboembolism, and multiorgan failure are the foremost reasons for fatality among severe COVID-19 patients [2]. The studies suggest that selenium supplements (oral and intravenous) can improve the treatment outcomes of COVID-19 [17–20,56]. This effect may be due to the antiviral, antioxidant, anti-inflammatory, and anti-thrombotic effects of selenium [17–20]. The clinical study data of selenium (Table 3) also evidenced that selenium as a monotherapy and as a combination therapy with vitamins (A, C, and E), zinc, copper, iron, fericulic acid, resveratrol, spirulina, N-acetylcycteine, and vitamins may be adequate to prevent/treat COVID-19. The selenium compositions with herbal medicine (ginseng) and minerals (zinc) are also supposed to display beneficial antiviral effects on patients [19,21,22]. However, this effect needs confirmation. New variants of SARS-CoV-2 have been identified [13]. The efficacy of selenium against these variants is yet to be established.

The inorganic forms of selenium, like selenious acid (H₂SeO₃), and the combination of selenium with other nutrients/compounds are in clinical studies against COVID-19 (Table 3) [48]. The patent literature also discloses some selenium-containing compositions and organic compounds (organoselenium compounds) as antiviral/anti-COVID-19 agents (Table 4) [56–80]. Ebselen (Fig. 5) is an organoselenium compound that has demonstrated anti-SARS-CoV-2 activity and antioxidant/anti-inflammatory activity [18,20]. Ebselen has also been shown to hinder the main protease enzyme of SARS-CoV-2 [19]. This indicates that discovering more organoselenium compounds may be an option for developing drugs against COVID-19. The authors believe that the computational studies on already reported organoselenium compounds may also provide some potential lead compounds as anti-SAR-CoV-2 compounds. The patenting of new Selenium-based compositions and dosage forms (spray, inhalers, control release dosage forms, etc.) are also foreseeable to the authors.

The USFDA has approved two prescription products containing selenium to treat selenium deficiency (Table 2). These products are cheap and readily available [23]. Since selenium has promising anti-COVID-19 properties, its supplementation can be started in the initial phases of COVID-19. However, selenium has a narrow therapeutic window, and its unnecessary supplementation in individuals having adequate selenium concentration may cause toxicity [17,46]. Therefore, it is crucial to adhere to the optimal dose of selenium while starting selenium supplementation [17,22]. According to the postulated mechanism of selenium toxicity, selenium compounds like selenite react with the thiol group of proteins and generate selenotrisulfides. These selenotrisulfides produce superoxides and hydrogen peroxides that cause oxidative damage and symptoms of selenium toxicity [46]. Accordingly, the chemical interaction of selenium with other ingredients of its compositions must also be considered for safety and efficacy.

**Fig. 4.** Number of patent filings in different countries.
4. Conclusion

Selenium owns noticeable anti-COVID-19 activity. The data of clinical studies, inventive pharmacologic compositions, and patent literature support selenium’s prophylactic and therapeutic ability against COVID-19. However, there is a need to generate more evidence via randomized controlled clinical trials. The authors foresee the development and commercialization of Selenium-based composition to battle COVID-19 and other viral diseases. The therapeutic window of selenium is narrow and can also show chemical interactions with other excipients of the compositions. This makes it essential to consider these two factors before developing selenium-based compositions. We believe that countless selenium-based inventive antiviral and anti-COVID-19 compositions are yet to be explored. Accordingly, there is good scope for scientists to work on developing novel and inventive selenium-based compositions to fight against COVID-19 and other viral infections.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethical approval

It is not required for the review article.

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