

Review

Selenium-Containing Polysaccharides—Structural Diversity, Biosynthesis, Chemical Modifications and Biological Activity

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Abstract: Selenosugars are a group of sugar derivatives of great structural diversity (e.g., molar masses, selenium oxidation state, and selenium binding), obtained as a result of biosynthesis, chemical modification of natural compounds, or chemical synthesis. Seleno-monosaccharides and disaccharides are known to be non-toxic products of the natural metabolism of selenium compounds in mammals. In the case of the selenium-containing polysaccharides of natural origin, their formation is also postulated as a form of detoxification of excess selenium in microorganisms, mushroom, and plants. The valency of selenium in selenium-containing polysaccharides can be: 0 (encapsulated nano-selenium), IV (selenites of polysaccharides), or II (selenoglycosides or selenium built into the sugar ring to replace oxygen). The great interest in Se-polysaccharides results from the expected synergy between selenium and polysaccharides. Several plant- and mushroom-derived polysaccharides are potent macromolecules with antitumor, immunomodulatory, antioxidant, and other biological properties. Selenium, a trace element of fundamental importance to human health, has been shown to possess several analogous functions. The mechanism by which selenium exerts anticancer and immunomodulatory activity differs from that of polysaccharide fractions, but a similar pharmacological effect suggests a possible synergy of these two agents. Various functions of Se-polysaccharides have been explored, including antitumor, immune-enhancement, antioxidant, antidiabetic, anti-inflammatory, hepatoprotective, and neuroprotective activities. Due to being non-toxic or much less toxic than inorganic selenium compounds, Se-polysaccharides are potential dietary supplements that could be used, e.g., in chemoprevention.

Keywords: selenium-containing polysaccharides; Se-polysaccharides; Se-glycosides; selenates; Se-supplementation; organoselenium



Citation: Górska, S.; Maksymiuk, A.; Turło, J. Selenium-Containing Polysaccharides—Structural Diversity, Biosynthesis, Chemical Modifications and Biological Activity. *Appl. Sci.* **2021**, *11*, 3717. <https://doi.org/10.3390/app11083717>

Academic Editor: Ilaria Cacciotti

Received: 18 February 2021

Accepted: 9 April 2021

Published: 20 April 2021

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1. Introduction

Polysaccharides are macromolecules that are extremely interesting due to their remarkable structural diversity and, consequently, functional versatility. Their structure is much more complex than that of other natural macromolecules, proteins, and nucleic acids. Polysaccharides are composed of more than 10 monomers—monosaccharides; their number ranges from 11 up to several thousands. Polysaccharides may consist of a single type of monomer (homoglycans) or of different monomers (heteroglycans), and each unit can be linked to others in multiple ways. Consequently, they can form straight or branched chains, create cyclic forms, contain a protein component, lipid, etc. It can be therefore concluded that there is an infinite number of combinations of polysaccharide structures [1,2].

The result of the structural diversity of polysaccharides is their functional versatility. There are great differences in physical and chemical properties of polysaccharides, including solubility; viscosity; swelling capacity; resistance to acids, bases, and enzymes; and chemical character (acidic, basic, neutral) [1], which also contribute to their versatility.

Biological activity of polysaccharides is also diverse, as they possess a wide range of pharmacological activities: antioxidative, antitumor, antimicrobial, antiviral, anti-obesity, hypolipidemic, antidiabetic, hepato-protective, and others [3–5].

The modification of the polysaccharides' structure carried out by biotechnological or chemical methods may cause a significant change in their biological activity [6–9]. For example, incorporation of selenium (Se) in the polysaccharide molecules is one of the currently explored methods of modifying the structure and activity of these compounds [10–13].

Selenium is one of the trace elements that are of fundamental importance to human health, being part of the antioxidant enzymes that protect cells against the effects of free radicals [14–18]. It plays an important role in a number of biochemical functions in humans and animals, such as antioxidant, immune function, reproduction, and thyroid hormone metabolism. Selenium appears to be a key nutrient in cancer prevention and inhibition of HIV progression to AIDS [19–25]. The important health effect of selenium is related to its impact on the immune system. Numerous reports on the immunomodulatory and antiviral activity of preparations containing selenium show that supplementation with this micronutrient may be beneficial for both prevention and treatment of viral infections, including coronaviruses [26,27]. The mechanism by which selenium exerts antioxidant, anticancer, and immunomodulating activity differs from that of polysaccharides, but a similar pharmacological effect suggests a possible synergy of these two agents. This has led to a growing research interest in Se-polysaccharides in recent years, particularly the methods of incorporating selenium into the carbohydrate structure and the structure–activity relationship of these compounds.

The approach to the problem of the Se-polysaccharides presented in the current review is based precisely on the analysis of the structure of these compounds and related changes in biological activity. To our knowledge, an extensive analysis of the chemical structures of seleno-carbohydrates (with a broader analysis of possible ways of incorporating selenium into the sugar structure), and the reference of these data to the currently known selenopolysaccharides, has not yet been presented.

2. Biologically Active Polysaccharides—Structure and Function

In the recent decades, natural polysaccharides isolated from bacteria, algae, fungi, and higher plants have attracted attention in the fields of nutrition and medicine [28]. The reasons include their broad spectrum of biological and pharmacological activity combined with low toxicity and rare negative side effects [29]. Many of them have been used for hundreds of years in traditional medicine. Further, some of the natural polysaccharides are already used as auxiliary substances, drug carriers, blood substitutes, and pharmacologically active compounds [30–32].

The polysaccharides showing immunomodulatory and anti-tumor properties are of particular interest [4]. Biological activity of polysaccharides results from direct inhibition of the neoplastic cells survival (cytotoxic activity) and from indirect mechanisms involving the activation of the immune system (immunostimulating activity). Detailed characterization of the structure of polysaccharides showing immunomodulatory effect is challenging; however, the most frequently mentioned parameters include molecular weight, monosaccharide composition, type of glycosidic bond, degree of cross-linking, conformation of the molecule, and modification in the structure of the molecule (carboxymethylation, sulfonation, aminopropylation, hydroxyethylation, phosphorylation, element incorporation into the molecule) [13,33–37]. The higher the molecular weight of a polysaccharide, the greater its chance of effective binding to a receptor or binding protein, which triggers the immune response or tumor cell apoptosis [38]. According to the literature data, the polymers of glucose and mannose show the highest immunomodulatory activity [39], which can bind to the receptors specific to these polysaccharides [40].

Additionally, polysaccharides with a predominance of β -(1-6) glycosidic bonds show weaker activity than those with predominant β -(1-3) bonds in the main chain [41,42]. Both too low and too high a degree of branching of the molecule results in a decrease of the activity of the polysaccharide [43]. A greater number of side chains are associated with a tighter conformation of the helix, which makes polysaccharides difficult for the receptors to recognize [44]. Moreover, the degree of branching of the most biologically active β -(1-3)-

glucans is 0.20–0.33 [45]. Furthermore, the conformation of polysaccharides is related to the spatial arrangement of the atoms that determine the shape of the chain. The triple-helix conformation provides strong immunostimulatory effects of β -D-glucans by promoting the release of TNF- α by macrophage cells [46]. It must be admitted that the structure–activity relationships proposed by the above-cited authors work well only for a fairly homogeneous group of β -D-glucans, but not for all currently known immunoactive polysaccharides.

The section below describes the biological activity of the polysaccharides isolated from various natural sources.

2.1. Bacterial Polysaccharides

Bacteria have the ability to synthesize biopolymers, which are divided into intracellular polysaccharides (CPS) and extracellular polymeric substances (EPS) according to their localization and function in the cell [47]. The main function of CPS is the structural support of the bacterial cell wall, but EPS have strong antioxidant properties and application in cancer therapy, antimicrobial and antiviral activities, and antioxidant and cholesterol-lowering effects [48]. K5PS is a heparin-like envelope polysaccharide of *Escherichia coli* that inhibits the metastasis of human breast cancer and murine melanoma cells [49].

The source of bioactive polymers showing antiproliferation activity is *Paenibacillus polymyxa* rods, which secrete polysaccharides of the levan-type, consisting mainly of β -D-fructofuranosyl residues connected by 2,6-bonds with 2,1-branches [50]. Moreover, *Rhizobium* papillary bacteria contain polysaccharides with the structure of α -glucans and a skeleton composed of glucose molecules linked by 1,4-bonds with 1,6-branches, which inhibit the formation of neoplasms in mice [51].

In recent years, there has been an increased interest in curdlan, insoluble in water linear beta-1,3-glucan, a high-molecular-weight polymer of glucose, obtained for the first time from *Alcaligenes faecalis* [52]. Curdlan has anti-cancer and anti-inflammatory properties and also supports wound healing [53]; its reaction mechanism is based on the interaction with the dectin-1 receptor present in dendritic cells, macrophages, and monocytes. Further, it stimulates the immune system and enhances the phagocytosis process and production of TNF- α , IL-6, and ROS [54]. In addition, symbiotic polysaccharides of *Bacterioides fragilis*, presented in intestinal dendritic cells, activate CD4 T cells and stimulate the production of cytokines [55], while the polysaccharide from *Paenibacillus polymyxa* has an anti-proliferative effect, and its derivatives formed as a result of acetylation show even stronger biological activity [28].

A commercially used biopolymer is dextran, a high molecular weight water-soluble glucose polymer released by *Leuconostoc mesenteroides*. Dextran is used as a drug carrier to inhibit cancer cells and reduce the toxic effects of drugs [56].

Many cyanobacteria are able to release easily recoverable polysaccharides into the culture medium. Most cyanobacterial polysaccharides show an anionic nature, due to the presence of uronic acids and other charged groups such as pyruvyl or sulfate [57]. Numerous publications describe exopolysaccharides produced by cyanobacteria *Spirulina platensis*, considered by some researchers to be microalgae. Polysaccharides extracted from of *S. platensis* are water-soluble; it has been proven that they have antitumor, antioxidation, antiaging, and antiviral properties [58]. Rajasekar et al. investigated the structural characterization and bioactive potential of sulfated polysaccharides from *S. platensis* and isolated a fraction containing glucose, rhamnose, xylose, fucose, mannose, and galactose as main sugars with Mw of 1016 kDa [59].

2.2. Algal and Lichen Polysaccharides

Rather for practical reasons than according to the official taxonomy, algae, a complex group of photosynthetic organisms, are divided into multicellular marine organisms (red—Rhodophyta, brown—Phaeophyceae, and green—Chlorophyta, algae) and unicellular microalgae [60]. In general, the polysaccharides are the main components of algal biomass, and in contrast to terrestrial plants, the polysaccharides of all the marine algae are

sulfated [61]. Due to the large number of biologically active algal polysaccharides, only a few examples of structures, mainly with immunomodulatory and anti-tumor activity, will be described in this short section. This arbitrary choice is due to the main interest in the synergism of selenium and such polysaccharides.

Fucoidan is a polysaccharide isolated from various species of brown algae (Phaeophyceae), with a high pharmacological potential [62]: immunostimulating, anticancer, anticoagulant, antiviral, antibiotic, anti-inflammatory, and antioxidant activity [63,64]. The biological activity of fucoidan depends on the organisms from which it is isolated. It has been proven that *Fucus vesiculosus* polysaccharides inhibit the production of TNF- α , but fucoidans isolated from *Undaria pinnatifida* induced TNF- α , showing cytotoxic activity against a tumor cell line [65]. Additionally, fucoidans show activity towards bone marrow mononuclear cells (BMCs), protecting them against apoptosis [66]. There are two types of fucoidan molecules, containing a backbone of (1-3)-linked α -L-fucopyranose residues or (1-3)-linked α -L-fucopyranose and (1-4)- α -linked-L-fucopyranose residues [67]. Additionally, the molecules may be modified by linking with sulfate (VI) residues [68]. The structure of fucoidans includes monosaccharides such as fucose, galactose, glucuronic acid, mannose, or glucose [69]. Laminarans are 1,3- β -D-glucans, isolated from the brown algae *Saccarina cichorioides*, that have proven anti-cancer activity. Laminarans in combination with radiation therapy may have a positive effect on the treatment of human breast cancer [70].

Polysaccharides isolated from *Sargassum latifolium* have a specific cytotoxic activity against lymphoblastic leukemia [71]. Further sulfonated polysaccharides isolated from red seaweed *Champia feldmannii* have been shown to inhibit the development of sarcoma, in studies carried out with mice [72]. Moreover, carrageenans—sulfonated galactans derived from *Chondrus ocellatus*, linear high-molecular-weight water-soluble D-galactans, consisting of alternately arranged units of α -D-galactopyranose and β -D-galactopyranose, linked by 1,3- and 1,4-glycosidic bonds, increased the antitumor effect of fluoroaracil [73]. Since the high molecular weight of the native lambda-carrageenans decreases their solubility and limits their bioactivities, Zhou et al. obtained microwave-degraded low-molecular weight lambda-carrageenans, which could add the antitumor activities of 5-fluorouracil and improve the immunocompetence damaged by this chemotherapeutic [74].

One of the best-known representatives of the sulfonated polysaccharides, isolated from red algae, is porphyran isolated from *Porphyra capensis* or *Porphyra hairanensis*. A typical porphyran chain consists of alternating β -D-galactose, α -L-galactose-6-sulfate, and 3,6-dehydro- α -galactose units. Other sulfonated polysaccharides with similar structure, agarans, were isolated from *Polysiphonia strictissima*, *Polysiphonia abscissoides*, *Polysiphonia nigrescens*, and *Polysiphonia atterima*; however, the agaran backbone may be interrupted by different O-linked substitutions in addition to sulfate, including methyl and xylosyl groups. Sources of such polymers are also *Acanthophora spicifera* and *Gracilaria corticata* [75,76].

The major sulfonated polysaccharide isolated from green algae is ulvan. The structure of this polysaccharide is complex and includes sulfo-groups, rhamnose, xylose, glucuronic acid, and iduronic acid. The ulvan chain is comprised of rhamnose sulfate molecules linked by an α -1,4 bond of glucuronic or iduronic acid. In turn, the algae, *Codium fragile* and *Codium cylindrium*, contain even more complex and branched galactans [76].

The anti-cancer activity of marine microalgae has not yet been thoroughly investigated; however, it was reported that microalgae extracts (e.g., *Attheya longicornis*, *Chaetoceros socialis*, *Chaetoceros furcellatus*, *Skeletonema marinoi*, and *Porosira glacialis*) may be also a source of bioactive anti-cancer polysaccharides [77].

The polysaccharides isolated from lichens are mainly α -glucans, β -glucans, galactomannans, and complex heteroglycans. The first isolated lichen polysaccharides were lichenan and isolichenan from *Cetraria islandica*. Lichenan and pustolan, isolated from *Evernia prunastri*, and several polysaccharides obtained from *Cora pavonia* and *Collema leptosporum*, are classified as β -glucans, while isolichenan is a representative of α -glucans. The biological activities of lichens' polysaccharides are antiviral, antitumor, and immunostimulating [78]. It was also reported that lichenan and isolichenan-rich polysaccharide-fractions

have anti-tumor activity. Similar properties were found for polysaccharides isolated from *Usnea runescens* and *Lasallia pensylvanica*; moreover, polysaccharides derived from *Evernia prunastri* show activity against sarcoma 180 cells [79]. Lichenan and other lichen-derived β -glucans have an immunostimulating effect by inducing the release of cytokines, reactive oxygen species, and nitric oxide. These polysaccharides also stimulate the release of arachidonic acid metabolites involved in inflammatory reactions [80]. Moreover, it was confirmed that α -glucan from *Ramalina celastri* induces apoptosis and leads to cell death [79].

2.3. Fungal Polysaccharides

Several members of the Basidiomycota division (as well as some of the Ascomycota), often referred to as the “higher fungi”, can produce immunomodulating, hepatoprotective, antimicrobial, antioxidant, hypoglycemic, and hypolipidemic substances, which are usually β -glucans, but also heteroglycans or proteoglycans [81–84]. Numerous mushroom polysaccharides are considered biological response modifiers (BRMs) [85]. Fungal polysaccharides may be used as a non-invasive form of cancer treatment due to their ability to induce a non-specific response of the immune system against cancer cells. Further, this capacity is also evident against viral and bacterial infections and inflammation [86]. They stimulate macrophages, T lymphocytes, and NK cells to produce cytokines (TNF- α , IL-1b, IFN- γ), which have the ability to inhibit cancer cell proliferation and apoptosis [87]. The best polysaccharides tested for immunomodulatory properties were branched β -(1-3)-D-glucans, containing a backbone of β -(1,3)-D-glucose residues to which β -(1,6)-D-glucose side groups are linked via glycosidic linkages. The most well-studied immunomodulating branched β -D-glucans are lentinan from *Lentinula edodes* [88–90] and schizophyllan isolated from *Schizophyllum commune* [91,92]. The structures of lentinan and schizophyllan are similar, but the molar mass of lentinan is significantly higher: lentinan has an average molecular weight of around 500 kDa, while schizophyllan is in the range of 100–200 kDa. Both β -glucans acquire a triple helical conformation in solutions. They are also both used as immunological adjuvants during chemotherapy, radiotherapy, radio-chemotherapy, and hormone therapy for various malignant tumors. Although they do not have a direct cytotoxic effect on cancer cells, they are effective in treating cancer of the stomach, colon, lung, breast, and cervix in combination with conventional medications. Both glucans are non-toxic. Their action is more effective if given in the early stage of neoplastic disease development [93]. Many other fungi can biosynthesize immunoactive, branched β -D-glucans, mainly constituting the building blocks of their cell wall. They include: *Ganoderma lucidum* (ganoderan) [94–96], *Pleurotus ostreatus* (pleuran) [97,98] *Grifola frondosa* (grifolan) [99], and several others.

In addition to the above-described immunoactive, branched β -D-glucans, fungi produce numerous biologically active polysaccharides with different monosaccharide composition and types of glycosidic bonds: homo- and heteroglycans. For example, Ye et al. determined the structure of an immunoactive proteoglycan isolated from *G. lucidum* fruiting bodies, with a main chain of 1,6- α -galactopyranoside-, 1,2,6-trisubstituted- α -galactopyranoside-, 1,3-disubstituted- β -glucopyranoside-, and 1,4,6-tri-substituted- β -glucopyranoside-groups, with branches of 1- β -glucopyranoside- and 1- α -fucopyranoside-residues [100]. In turn, two immunostimulating heteroglycans have been isolated from *Agaricus blazei* fruiting bodies, which are composed of glucose, galactose, and mannose [101]. Moreover, *A. blazei* mycelium cultivated in liquid cultures excretes an extracellular antitumor proteoglycan with high molecular weight (1000–10,000 kDa), which was composed of mannose, glucose, galactose, and ribose groups [102]. One of the most successful therapeutic mushroom polysaccharides, which has been marketed as an anticancer drug (in combination with chemotherapy), krestin (polysaccharide-K, PSK) derives from the edible mushroom *Coriolous versicolor* (*Trametes versicolor*) [103]. It is a low-molecular-weight proteoglycan, containing glucose as a major monosaccharide, but other sugar residues are also present, such as mannose, fucose, xylose, and galactose. The main chain of PSK is made of β -(1,4)-glucopyranoside, with β -(1,6)-glucopyranosidic side-chains at

every fourth glucose unit [103,104]. Another source of therapeutic (immunomodulatory and antidiabetic) polysaccharides is the edible medicinal *Tremella* mushrooms. *Tremella* polysaccharides are composed of a linear backbone of α -(1,3)-D-rhamnose, with side groups of xylose and glucuronic acid. These polysaccharides are acidic, with a pH of 5.1–5.6 in aqueous solutions [105–107]. Extracellular acidic heteroglycans from filtrates of *Tremella* species, in turn, are characterized by an α -(1-3)-mannan backbone with β -linked side chains. They contain xylose, arabinose, mannose, galactose, glucose, and glucuronic acid residues [106].

Other examples are highly branched galactomannans, which have been purified from fruiting bodies of *Cordyceps sinensis*. Their main chain contains predominantly (1,2)- α -D-mannopyranose-groups, with branches of (1,3)-, (1,5)-, and (1,6)-linked D-galactofuranose and (1,4)-D-galactopyranose residues [108].

A list of so-called “medicinal mushrooms” capable of biosynthesis biologically active polysaccharides is long, and includes nearly 270 species [96]; therefore, it is impossible to list all types of active polysaccharides of fungal origin in a short paragraph in this review.

2.4. Plant Polysaccharides

Among the chief components of herbal medicines, polysaccharides are responsible for various pharmacological immuno-stimulatory, antiviral, antioxidant, antitumor, hepatoprotective, neuro-protective, and other potentials [109].

Numerous natural polysaccharides found in herbs, often components of the plant cell wall, are known to stimulate the human immune system. The activation of macrophages by plant polysaccharides results from recognition of polysaccharide by TLR4 (toll-like receptors), CR3, and scavenger receptors. The studies on the polysaccharides from *Aloe barbadensis* showed that acetylated mannan isolated from aloe has the ability to increase the production of monocytes [110]. In addition, *Astragalus membranaceus* polysaccharides (α -(1-4)-D-Glucans with α -(1-6)-branches) have the ability to inhibit the proliferation of tumor cells by regulating p53 expression. Additionally, they strongly induce the process of erythropoiesis through gene modulation, expression of γ -globin mRNA, and the synthesis of fetal hemoglobin [28]. Further, angelan is a pectin polysaccharide isolated from the roots of *Angelica gigas*, which reduces the adhesive capacity of neoplastic cells and has the ability to induce the maturation of dendritic cells [28], while fructan isolated from the root of *Achyranthes bidentata* shows a dose-dependent effect on the growth of Lewis lung cancer in vivo. Lower doses of this polymer inhibited tumor growth, as anti-tumor activity of *A. bidentata* is associated with inhibition of the tumor cell cycle. However, in higher doses, it can also cause stimulation of tumor growth due to NK dysfunction and an increase in the amount of interleukin-6 and TNF- α [111]. Polysaccharides isolated from *P. ginseng*, co-responsible for the biological activity of ginseng preparations, are mainly composed of starch-like glucans: α -D-(1,4)-glucans, 6-branched α -D-(1,4)-glucans, 3-branched α -D-(1,6)-glucans, α -D-(1,6)-glucans without side chains, and pectin, mainly composed of homogalacturonan, rhamnogalacturonan, and arabinogalactans [112,113].

It was reported that the PS, isolated from the root of *Panax ginseng*, can inhibit the proliferation of human bladder cancer T24 tumor cells and lactate dehydrogenase release. In addition, they have also significantly hampered cell migration and invasion. It was reported that polysaccharides isolated from *P. ginseng* induced the peritoneal macrophages (PMs) activity against K562, HL-60, and KG1 α cells. The mechanism was involved with increasing the expressions of CD68, increasing the level of TNF- α , interleukin-1 (IL-1), and IL-6 [114–116]. In a like manner, the polysaccharides and glycoproteins are compounds partly responsible for the immunostimulatory effect of *Echinacea* sp. The polysaccharides and glycoproteins, which have been isolated from *E. purpurea* and *E. angustifolia*, are inulin-type fructans, acidic arabinogalactans, arabinogalactan-protein complexes, rhamnoarabinogalactans, and xyloglucans [117].

3. Organoselenium Compounds

Selenocarbohydrates belong to organoselenium compounds, as they contain carbon-to-selenium chemical bonds. Organoselenium compounds include both natural metabolites of microorganisms, plants or animals (seleno amino acids, selenoproteins, selenosugars), and numerous synthetic compounds [118].

The toxicity and bioavailability of selenium strongly depend on its chemical form [119]. Numerous studies show that organic Se sources, such as selenomethionine, are assimilated more efficiently than inorganic Se, such as selenite, and inorganic Se species are more toxic than organic Se species. At the same time, naturally occurring Se compounds, such as animal and plant metabolites, are less toxic than artificial Se compounds [120,121]. Consequently, it can be predicted that Se-polysaccharides with a natural origin might be characterized by low toxicity and good selenium accessibility.

3.1. Physiological Functions of Se

Selenium is one of the key micronutrients required to maintain a cellular redox state as well as to control cell proliferation and survival. As a component of the amino acid selenocysteine, selenium is incorporated in about 35 selenoproteins [122]. Some of them have important enzymatic functions [123], but the roles of many others have not yet been fully elucidated [124]. The selenium-dependent enzymes with selenocysteine at the active site, such as glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases, have biological functions in oxidoreductions, redox signaling, antioxidant defense, and thyroid hormone metabolism [125]. Selenium also appears to be important for the methylation of DNA, which is known to control gene expression and thus proliferation and differentiation; however, the exact mechanism of this interaction is not yet known [126,127]. Selenium has additional important effects on the immune response that are not exclusively associated to enzymatic activity. Even in a selenium non-deficient population, the supplementation of this micronutrient appears to stimulate the immune response [128,129]. This may be attributed to the stimulation of many cellular immune functions, including increased natural killer cell activity, as well as protection against oxidative stress-induced damage to immune cells [130–132]. Selenium appears to be a key nutrient in cancer prevention, although reports on this subject are not clear [133,134]. Nevertheless, Se is important in the prevention and treatment of several viral infections including RNA viruses [135,136]: it boosts Th1-type host immunity against viral infections [137] and appears to prevent the evolution of more virulent strains of some viral pathogens [138,139].

3.2. Selenium Species, Bioavailability, and Effects of Excess and Deficiency

Selenium is an essential element with a narrow safety margin: essential to humans in trace amounts, but highly toxic when in excess. It has one of the narrowest ranges among all the elements between dietary deficiency (less than 40 µg/day) and toxic levels (over 400 µg/day) [140]. The recommended dietary allowance (RDA) of selenium for adults is 55 µg/day, according to the Linus Pauling Institute [141]. The tolerable upper intake level advised by the USA is 400 µg/day in the USA [142,143] and 300 µg/day in Europe [144]. However, the recommendations do not take into account that Se can be present in food (or food supplements) under different chemical forms, organic or inorganic. These forms differ in bioavailability and therefore exert different effects on the organism [145,146].

To address this problem, several methods are used to determine selenium bioavailability. These include the measurement of plasma selenium concentration, measurement of glutathione peroxidase (GPx) activity, and absorption–retention tests following intake of a specific dose of a selenium compound [147]. Plasma selenium is the most commonly measured biomarker, reflecting different levels of Se exposure that also respond positively to intervention. According to the Mayo Clinic Laboratories, the normal concentration of Se in adult human blood serum is 70 to 150 micrograms per liter [148]. This is indicative of the adequate dietary intake, above which selenium supplementation is not recommended.

When concentration of selenium is lower than the recommended 70 µg/L, the selenium intake is inadequate, and there is a risk of diseases related to selenium deficiency. In this case, supplementation of this element is recommended. Conversely, excessive selenium intake leads to a serum concentration higher than the recommended Se (over 150 µg/L⁻¹), and there is an increased risk of diseases related to selenium excess. The U-shaped relationship between the concentration of selenium in human serum and the biological effects expressed as disease risk is particularly interesting [17]. The optimal selenium serum concentration (70–150 µg/L) is indicative of the adequate dietary intake, in which case selenium supplementation is not recommended. Both the excess and deficiency of selenium have several common negative health effects, i.e., increased mortality, type 2 diabetes, and increased prostate cancer risk [18,149–151].

The complete list of the adverse health effects associated to an insufficient selenium intake and Se deficiency is wider and includes Keshan disease [152], Kashin–Beck disease [153], increased virus virulence [154], increased mortality [150], poor immune function [131], decreased fertility and reproductive health [17], thyroid autoimmune disease [155], cognitive decline and dementia [156], type-2 diabetes [149], prostate cancer risk [151], and colorectal cancer risk in women [157].

A selenium overdose can occur during chronic exposure to high levels of selenium in food and water. This may occur, for example, during regular snacking on Brazil nuts, which may contain up to 90 µg of selenium per nut, or participation in clinical trials where high doses of selenium are given for a long period of time [18], and overdose of Se food supplements [158]. The effects are similar for both organic and inorganic forms of selenium [144]. Symptoms of selenium overdose include hair loss, abnormal nails, nausea, vomiting, diarrhea, rash, fatigue, and nerve damage [159].

To summarize, the beneficial and harmful effects of selenium depend on its dose and form (speciation). The introduction of the new forms of selenium (e.g., selenopolysaccharides) to be used as selenium supplementation or treatment of various diseases requires extensive studies on the bioavailability, absorption, and metabolism of this element.

3.3. Organoselenium Natural and Synthetic Compounds

Natural organoselenium compounds are products obtained from the metabolism of bacteria, fungi, plants, and animals [160]. In the environment (soil, rocks, water), selenium is present in the inorganic forms, as selenate (SeO₄²⁻), selenite (SeO₃²⁻), elemental (Se), and selenide (Se²⁻) [161]. During the bioaccumulation in plants, fungi, and bacteria, the inorganic forms of selenium are incorporated into amino acids like selenomethionine, selenocystine, methylselenocystine, selenocystathionine, γ-glutamyl-Se-methylselenocysteine, and Se-adenosyl-selenohomocysteine [161]. These forms of selenium can also be methylated and form dimethylselenide, dimethyldiselenide, dimethyl selenone, methylselenol, and dimethyl selenyl-sulfide [162,163]. Several plant and mushroom species are known to be good Se-accumulators [164]; however, selenium is not considered an essential micronutrient for those organisms as it is for humans. Their ability to accumulate large amounts of organoselenium compounds may be the result of the detoxification process [165]. In humans, the inorganic forms of selenium are converted to selenocysteine and incorporated into selenoproteins or transformed into methylated metabolites, which are excreted through exhalation, urine, and faeces [166].

Mammals have no efficient mechanism of methionine synthesis. Therefore, they are also unable to synthesize selenomethionine, which is produced along with methionine in fungi and plants in quantities dependent on the amount of Se available. Consequently, selenomethionine, which can be incorporated nonspecifically in body proteins, constituting the main selenium store, must be supplied in the human diet.

Less known products of selenium metabolism are selenosugars. The major metabolite in humans (hepatic metabolite) is the selenosugar 1β-methylseleno-N-acetyl-D-galactosamine [167,168].

According to Kuehnelt et al., two other selenocarbohydrates may be present in human urine after ingestion of selenium supplements, and they are 1 β -methylseleno-D-galactosamine and 1 β -methylseleno-N-acetyl-D-glucosamine [169].

Several fungi and plant species, grown on the selenium-enriched substrates mainly as inorganic forms, such as sodium selenite, are able to incorporate selenium into the cell wall polysaccharides [170,171]. The knowledge about their structures is still fragmentary, and its current status will be presented in more detail in Section 5.

The number of known synthetic organoselenium compounds is incomparably greater than that of known natural compounds. In the past three decades, an exponential growth of organoselenium chemical studies was observed, as well as of the number of reactions and the variety of selenium compounds [172]. For example, organoselenium compounds were already used in organic chemistry as an electrophile, nucleophile, or even as a radical in chemo-, regio-, and stereo-selective reactions [173,174].

The most important types of synthetic organoselenium compounds are diorganodiselenides (R-Se-Se-R) [175,176], selenols (R-Se-H) [177], diorganoselenides (R-Se-R') [178,179], diorganoselenoxides (R₂Se = O) [180–182], selenenyl sulfides (R-Se-S-R') [183], organoselenium halides (R-Se-X, R₂SeX₂ and R₃SeX) [184], selenenic and selenonic acids (R-Se-OH, R-Se(O)-OH, R-Se(O)₂-OH) [185], and selenic and selenious acid aliphatic and aromatic and cyclic esters (alkyl and aryl selenates and selenites). In the last 20 years a great effort has been directed toward the synthesis of biologically active organoselenium compounds as potential antitumor agents [20,21,25,186–191], enzyme modulators [192], antioxidants [193–195], antimicrobials [196–202], antivirals [203–209], and cytokine inducers [210]. Among synthetic organoselenium compounds, selenosugars constitute a large group, which will be described separately in the next Section 4.

3.4. Selenium in Therapy and Chemoprevention—Traditional and Next Generation of Se Supplements

Due to the aforementioned beneficial health effects (Section 3.1), selenium compounds are used in prevention and treatment (as adjuvant) of various human diseases, such as several types of cancers, immune disorders, bacterial and viral infections, and cardiovascular diseases [211,212]. Nevertheless, the previously described U-shaped relationship between selenium dose and disease (Section 3.2) indicates that a daily intake of Se higher than that recommended leads to disease promotion.

The recommended plasma selenium concentration (an indicator of recent selenium intake) assures a balanced expression of bioactive selenoproteins, which act mainly as oxidoreductases, redox signal regulators, or thyroid hormone activators [213,214]. However, the overexpression of selenium enzymes and excess formation of bioactive selenium metabolites results in pathophysiological effects [214,215].

As stated above, selenium bioavailability depends largely on the form (organic versus inorganic) and the origin of the supplement (natural versus synthetic). However, the health implications of selenium intake are also related to its epigenetic effects [127,216]. All those factors suggest the need for a more personalized selenium supplementation; however, this approach is difficult to implement, as selenium preparations are freely available on the market as dietary supplements and nonprescription medicine.

Currently, the most widely used selenium supplements are (i) inorganic forms, such as sodium selenate and selenite; (ii) elemental selenium; and (iii) several organic selenium forms, such as selenomethionine and selenized yeast (rich in selenomethionine). Some reports describe other types of synthetic organic selenium supplements, such as phenylselenocysteine, methylseleninic acid, and selenocyanate [217,218]. These supplements, however, are not optimal and sometimes are even hazardous, given that selenium is easy to overdose on [160,219,220].

The search for selenium preparations with reduced toxicity, higher bioavailability, and controlled release led to the development of a “new generation” of selenium supplements [214]. Such next-generation selenium dietary supplements are based on selenium zerovalent nanoparticles encapsulated into polysaccharides [221] and selenium polysaccha-

rides [13,222]. These selenium forms are not yet officially used as selenium supplements; however, the available information suggests that they have a history of safe use [214]. The big advantage of these selenium species is the slow release of active selenium forms, which results in a low risk of overdose. Synergistic biological effects of polysaccharides and selenium [223] could also make them more suitable for personalized supplementation.

4. Selenosugars: How Selenium May Be Bound to the Carbohydrate Structure

Selenosugars are a complex group of organoselenium compounds. They differ considerably in the type of selenium binding, valency, and degree of oxidation. They can be classified as Se-alkylselenides and Se-arylselenides, selenopyranoses, selenofuranoses, selenoglycosides, selenonucleosides, selenoesters, and others. Selenosugars are derivatives of mono-, di-, oligo-, and finally, polysaccharides, that can be obtained by various methods (synthesis, biosynthesis, chemical modification of natural compounds), and differ in their biological activity. Several of them are currently being intensively studied as a non-toxic and highly bioavailable source of organic selenium [224].

Currently, the largest and best studied group of selenosugars are Se-monosaccharides and their derivatives. However, the exact knowledge of the structure and selenium bonding in many of the currently explored Se-polysaccharides is still missing. The following brief overview of the types of selenium bonding in selenosugars may be used for prediction of the probable structures of novel Se-polysaccharides.

4.1. Selenopyranoses and Selenofuranoses

Selenopyranoses and selenofuranoses are cyclic forms of carbohydrate derivatives, with the ring oxygen replaced by a selenium atom: a polyhydroxytetrahydroselenophene or selenane derivatives [224].

In general, selenopyranose and selenofuranose derivatives are obtained by chemical synthesis, starting from appropriate monosaccharides [225–227]. Most of them were synthesized as potent water-soluble selenium derivatives able to act as potential antioxidants with expected good oral bioavailability [228,229].

Numerous selenosugars have also been investigated for their capacity as glycosidase inhibitors. Glycosidases catalyze the hydrolysis of glycosidic linkages and are suitable targets for development of anti-type 2 diabetes, anticancer, and antiviral agents [230–232]. The selenosugars bearing selenium atoms in their ring positions, synthesized by Davies and Shiesser (2019) as part of the program aiming at developing powerful water-soluble antioxidants, are particularly interesting [233]. Several of them, as expected, proved to be powerful antioxidants. 1,4-anhydro-4-seleno-D-talitol (Figure 1c) seems to have a privileged structure: it acts not only as an efficient scavenger of multiple biologically important oxidants, but also exhibits the ability to repair damaged skin tissue, including accelerating healing of diabetic wounds, and is capable of decreasing endothelial dysfunction arising from diabetes [233].

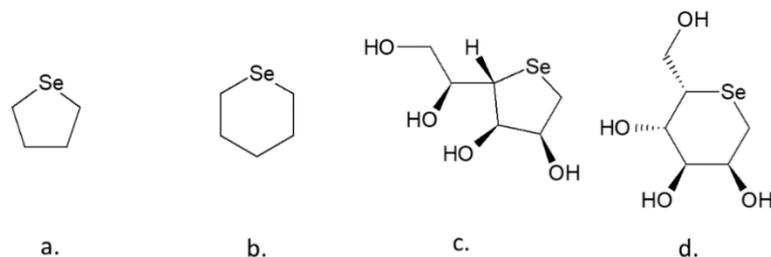


Figure 1. Structures of the tetrahydroselenophene (a), selenane (b), and some derivatives: 1,4-anhydro-4-seleno-hexofuranose (1,4-anhydro-4-seleno-D-talitol) (c) and 1,5-anhydro-5-seleno-hexopyranose (1,5-anhydro-5-seleno-D-mannitol) (d).

Se-nucleosides are a specific group of carbohydrates with selenium bound in the sugar backbone. They cannot be converted into the corresponding nucleotides due to hampered

capacity for enzymatic phosphorylation. Most of the Se-nucleosides are biologically not active; however, the selenonucleoside developed by Jeong et al. showed antitumor activity against paclitaxel-resistant prostate cancer [234,235]. Regarding the selenopyranose derivatives of natural origin, the polysaccharides containing selenium atoms in their ring positions were investigated using the XAS (X-ray absorption spectroscopy) method [39].

4.2. Se-Glycosides

Selenoglycosides are members of the selenosugar family in which the bridging oxygen of the glycosidic bond is replaced by selenium [236]. (Figure 2).

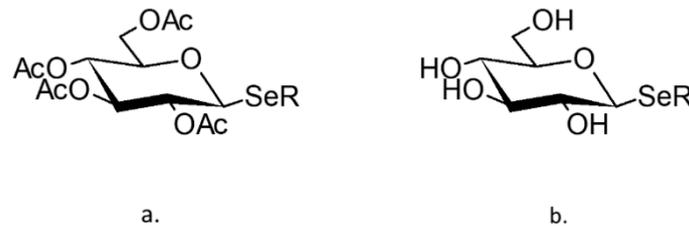


Figure 2. Se-alkyl-selenoglucoside in protected (a) and deprotected (b) form.

The Se-glycosidic bond is resistant to enzymatic hydrolysis; therefore, selenoglycosides can act as inhibitors of glycosidase enzymes [237,238]. This type of sugars found application in disaccharide and oligosaccharide synthesis as glycosyl donors, where an arylselenyl group introduced at the anomeric position functions during glycosylation as a leaving group (Figure 3).

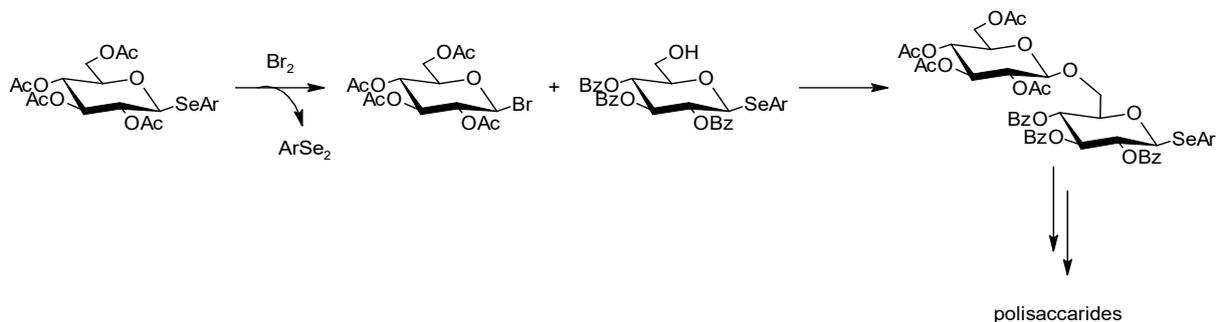


Figure 3. The application of selenoglycosides in polysaccharide synthesis. Bz—benzoyl group: $C_6H_5C(O)-$; Ac—acetyl group: $CH_3C(O)-$.

Using similar synthesis methods, it is possible to obtain selenodisaccharides in which the bridging oxygen of the glycosidic bond is replaced by selenium (Figure 4), as it happened in Nanami et al. experiment [239]; the first examples of the synthesized α -selenoglycosides that link to the carbon in the sugar ring were obtained.

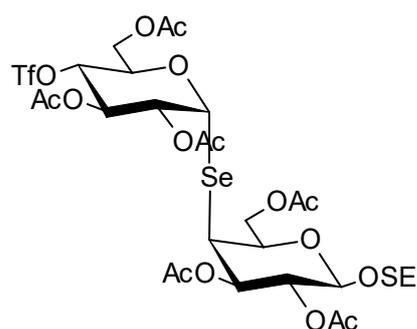


Figure 4. An example of a structure of the protected selenodisaccharide (Galp α (1 \rightarrow 4)Galp) synthesized by Nanami et al. [239]. SE-2-(trimethylsilyl)ethyl-group, Tf-trifluoromethanesulfonyl-(triflyl-) group.

Most of selenoglycosides are obtained by chemical synthesis. However, three natural selenoglycosides, identified as derivatives of galactosamine and glucosamine, have been detected in human urine [167–169]. Kobayashi et al. (2002) stated that selenium was excreted into mammals' urine in the form of these selenosugars, when selenium intake was lower than the toxic level [168] (Figure 5).

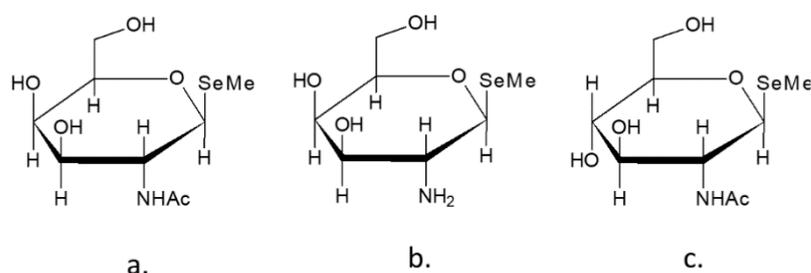


Figure 5. Three selenoglycosides detected as urinary selenium metabolites within the required to low-toxic range: (a) 1 β -methylseleno-*N*-acetyl-*D*-galactosamine, (b) 1 β -methylseleno-*D*-galactosamine, and (c) 1 β -methylseleno-*N*-acetyl-*D*-glucosamine.

Another example of natural Se-glycoside is a selenium metabolite in the liver—a glycoconjugated molecule with the unusual Se–S linkage, known as “hepatic metabolite A” [168] (Figure 6).

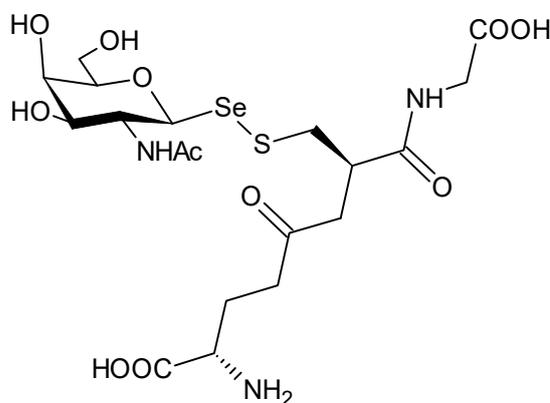


Figure 6. Hepatic metabolite A.

4.3. Se-Alkylselenides and Se-Arylselenides

Se-alkyl- and Se-arylselenides derived from carbohydrates contain an organoselenium moiety at the non-anomeric position of sugars [200,240,241] (Figure 7). Many of these synthetically obtained sugar derivatives show biological activity, e.g., antioxidant activity.

Further, Vargas et. al. (2015) reported synthesis of simple alkylseleno-carbohydrates with different sugar scaffolds. Screening of the selected compounds for antioxidant activity revealed that several of them express free radical scavenging activity and therefore can potentially prevent oxidative damage of proteins and lipids [242].

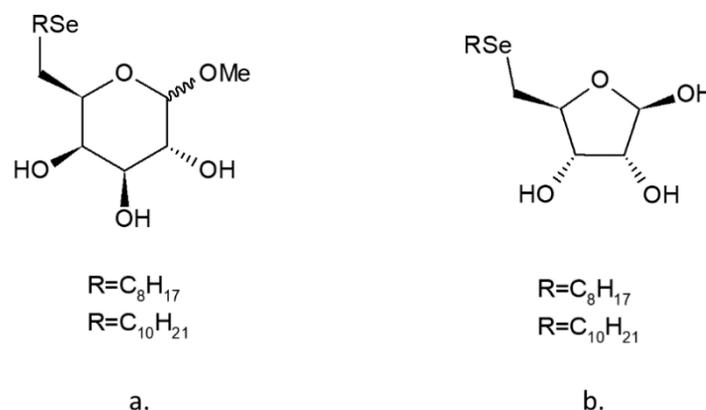


Figure 7. Examples of the alkylselenide structures derived from pyranose (a) and furanose (b), synthesized by Vargas et. al. [242].

4.4. Se-Esters

Carbohydrates, as polyhydroxy aldehydes or ketones, contain several hydroxyl groups that may react with an appropriate acidic compound, resulting in the formation of sugar esters. Among them are the selenious acid esters. The selenylation (esterification/acylation with selenious acid) reaction may be conducted, for example, using the $HNO_3-Na_2SeO_3$ method [243] (Figure 8).

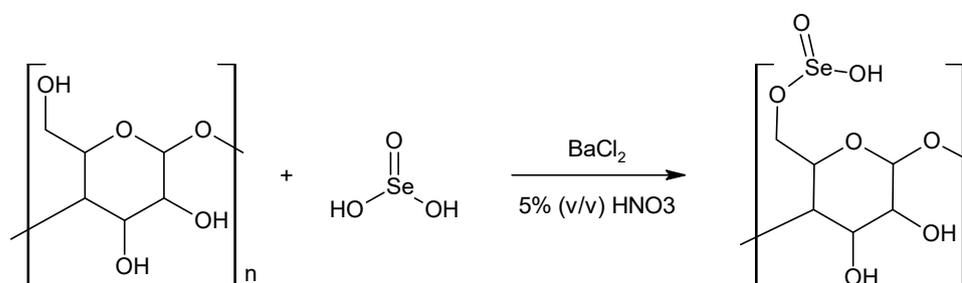


Figure 8. Formation of the selenious acid ester of carbohydrate.

Formation of the selenious acid sugar esters is a method widely used for the preparation of Se-polysaccharides containing selenium at the fourth oxidation state and will be further described in the next section (Section 5).

5. Selenium-Containing Polysaccharides

5.1. Divalent, Tetravalent, and Zerovalent Selenium in Polysaccharide Structure

The current literature shows that selenium in Se-polysaccharides may be di-, tetra-, or zero-valent, depending on the nature of the compound and the type of chemical bonds or interactions. Divalent selenium was found in selenoglycosides or selenopyranoses [13], tetravalent in selenites of polysaccharides (selenious acid esters) [244], and zerovalent in selenium nanoparticles encapsulated into polysaccharides [245]. However, the structures of numerous selenium-containing polysaccharides described in the literature have not been conveniently studied yet. Certain structural analyses were limited to examining only the amount of selenium bound to the polysaccharide structure, without taking into consideration its chemical environment. Moreover, conclusions regarding selenium binding (oxidation degree, chemical bonds, chemical environment) in some of the published reports

were based on insufficient data (e.g., only IR spectra). Unraveling the chemical environment of selenium in selenoorganic compounds requires advanced analytical methods. The principal techniques that should be used for the characterization of selenium-containing molecules are mass spectrometry, X-ray crystallography, Se NMR spectroscopy, X-ray absorption spectroscopy (XAS), and several others [118,214].

However, the structurally undefined Se-polysaccharides are a relevant research subject, as the introduction of selenium into their structure often has significant effects on the biological activity.

5.2. Se-Glycosides and Selenopyranoses

As explained in Section 4, in most of the selenosugars and their derivatives, e.g., selenopyranoses, selenofuranoses, selenoglycosides, selenonucleosides, and Se-alkylselenides, selenium is divalent. Most of the selenosugars containing divalent selenium are small molecules obtained by chemical synthesis. However, as previously described, four natural selenoglycosides, identified as derivatives of galactosamine and glucosamine, have been detected in human urine [167–169]. The results of research conducted by Kobayashi et al. [168] suggested that the major selenium metabolite in mammals urine is a selenoglycoside (Figure 5a). Therefore, since mammals are capable of selenium sugars biosynthesis, in which selenium is glycosidically bound, it is highly probable that plants, fungi, and microorganisms may also have such capability. In fact, multiple reports describe the ability of these organisms to accumulate selenium in the structure of polysaccharides.

The isolation of selenium-containing polysaccharides from fungi [13,108,246–249], algae, and microorganisms [250,251] has been widely described.

In a series of studies on selenium-enriched mycelial cultures of the medicinal mushroom *Lentinula edodes*, Turlo et al. proved that mycelium effectively accumulated Se from the cultivation medium enriched in sodium selenite [252,253] and that selenium was also incorporated into the mycelial polysaccharides [171,254]. Further, Malinowska et al. (2018) [39] isolated a selenium-containing polysaccharide-protein fraction from the Se-enriched mycelial cultures of *L. edodes* composed of glucose and mannose, containing 190 μg Se/g dry weight. X-ray absorption of fine structure (XAFS) spectra analysis in the near edge region (XANES) confirmed that selenium in the Se-polysaccharide structure is divalent and organically bound. The simulation analysis in the EXAFS (extended X-ray absorption fine structure) suggested that selenium is bound in a β -1,3-, α -1,4-glycosidic linkage or substitutes oxygen in a pyranosidic ring (Figure 9).

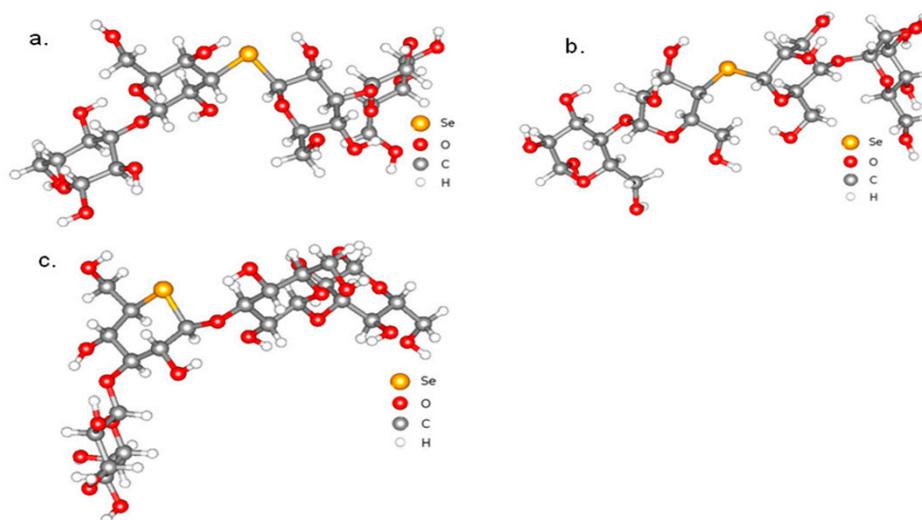


Figure 9. The hypothetical local structures around Se in Se-polysaccharide [39]: (a) 1,3-Se- β -D-glycosidic bond in glucan chain, (b) 1,4-Se- α -D-glycosidic bond in mannan chain, and (c) Se in glucopyranose ring.

According to the calculations performed with Gaussian 03 software, incorporation of selenium cause deformations in the polysaccharide structure, including change in bond lengths and torsion angles, and, as a result, disappearance of hydrogen bonds in the vicinity of the selenium atoms [13]. This modification may affect the interaction with specific polysaccharide receptors and introduce changes in the biological activity [11].

5.3. Se-Esters—Selenites and Diselenites of Polysaccharides

The esterification of polysaccharides with selenious acid results in formation of polysaccharide selenites, esters of selenious acid (Figure 8). Under appropriate conditions, practically all native polysaccharides, as polyhydroxy aldehydes or ketones, may react with H_2SeO_3 or Na_2SeO_3 in an acidic environment to yield the polysaccharide selenites. In these compounds, selenium is tetravalent and in the fourth oxidation state, so it retains the redox properties typical for this oxidation state [118]. Depending on the acylation method used and the degree of polysaccharide substitution (DS), the content of selenium in the polysaccharide molecule may be significantly different.

Currently, the selenylation of natural polysaccharides to selenious acid esters is a frequent method to obtain selenium-containing polysaccharides. The method most commonly used to obtain a selenite from a polysaccharide is using nitric acid and sodium selenite [255].

In 2009, Ji et al. described the use of this method to introduce selenium into polysaccharides isolated from *Cynomorium songaricum*. The maximum selenic content determined by ICP-AES was 2925 $\mu\text{g/g}$ [256]. In 2012, Wang et al. reported the synthesis of selenium-containing polysaccharides derivatives from *Artemisia sphaerocephala* polysaccharide with a high Se content (1703 $\mu\text{g/g}$) using $\text{H}_2\text{SeO}_3/\text{HNO}_3$ and BaCl_2 as a catalyst [244]. The C-6 substitution was predominant in selenized polysaccharide, as proven by Raman and $(13)\text{C}$ NMR spectroscopy. The authors have observed a sharp decrease in the molecular weight of the polysaccharide caused by a degradation of the polymer. The structure of obtained Se-polysaccharides was studied by using size exclusion chromatography combined with multi angle laser light scattering (SEC-MALLS) [257].

Several modifications of the above-described method for the acylation of natural polysaccharides have been described, using nitric acid and selenious acid [258], glacial acetic acid and selenious acid [259], glacial acetic acid and sodium selenite [258], or selenium oxychloride [259,260]. Using the above-described methods of selenylation, several research teams obtained biologically active selenites from plant, mushroom, and bacterial polysaccharides in the last decade. The examples include polysaccharides from *Hedysarum polybotrys* [261], *Cordyceps militaris* [262], *Catathelasma ventricosum* [263], *Enteromorpha prolifera* [264], *Lachnum* sp. [265], *Atractylodes macrocephala* [255], *Lentinula edodes* [266], *Lilium lancifolium* [267], *Codonopsis pilosula* [268], *Lycium barbarum* [269], *Astragalus* sp. [270], *Hericiium erinaceus* [271], *Glycyrrhiza uralensis* [272], *Epimedium* sp. [273], *Isatis indigotica* root [273], *Schisandra chinensis* [243], *Capparis spionosa* [274], *Cynomorium songaricum* [256], *Murus alba* [275], *Castanea mollissima* [276], *Rhizobium* sp. [277], *Artemisia sphaerocephala* [244], *Potentilla anserina* [278], *Lactococcus lactis* subsp. *lactis* [260], garlic [279], tea [280], and others.

In addition to the selenylation method used, the selenium content of selenylated polysaccharides (10^2 – 10^4 $\mu\text{g/g}$) [281] also depends on the structure and chemical character of the native polysaccharide. For example, using the same selenylation method, the ability to incorporate selenium into lily polysaccharides (11,770–39,780 $\mu\text{g/g}$) [267] was 26–88-fold higher than that of *Murus alba* polysaccharides (452 $\mu\text{g/g}$) [275].

Selenium polysaccharides obtained with those methods exhibit a broad spectrum of biological activity, e.g., antioxidant, antibacterial, anti-hyperlipidemic, anti-diabetic, antitumor, hepatoprotective, neuroprotective, anti-inflammatory, antifibrotic, immunomodulatory, and immunoenhancing activity. This subject will be widely discussed in a separate section (Section 7).

5.4. Polysaccharide Encapsulated Nanoselenium

Zero-valent selenium (0 oxidation state) in the form of selenium nanoparticles (SeNPs) has attracted research attention thanks to its high bioavailability, lower toxicity—it is lower than that of inorganic and organic forms of selenium (e.g., SeNPs have seven-fold lower toxicity than sodium selenite), and controlled Se release [214,282–285]. As a result, SeNPs carry a lower risk of excess Se supplementation.

According to the IUPAC definition, a nanoparticle is a particle of any shape with dimensions in the 1×10^{-3} to 1×10^{-1} micron range [286]. This wide range of nanoparticle sizes results in differences in their properties, with smaller particles showing a greater cellular intake and activity [287–289]. Hence, Desai et al., (1997) observed that in vitro absorption of 0.1 μm particles of SeNPs was found to be 2.5 and six times higher when compared to 1 and 10 μm particles, respectively [288]. Thus, when considering preparation of the potential drugs and dietary supplements, an appropriate particle size should be chosen. However, selenium in the form of nanoparticles is unstable and easily transformed into an inactive form [289], which necessitates the use of stabilizing agents in SeNPs solutions. These solutions may be stabilized and modified by various polymers, such as chitosan [290,291] and other polysaccharides [44,45,292–297], proteins [293,294], or their combinations [298–300].

The stabilizing agents, such as polysaccharides, may play a dual role in the SeNPs formulations, as they can also improve the bioavailability and biological activity due to the synergistic effect of SeNPs and polysaccharides [301]. Polysaccharide-stabilized SeNPs may be obtained by chemical methods, e.g., by reduction of selenites in the solution containing polysaccharides [302], or by biological and biotechnological methods—extraction from the plant, fungal, algal, or microbial material grown in media enriched in selenium compounds, preferably sodium selenite [303,304]. The reduction of selenium to elemental nanoselenium in organisms is thought to be a form of detoxification and elimination of selenium excess, where part of the reduced elemental selenium becomes linked to the polysaccharides in the cell wall of the cultured organism [39].

Polysaccharide-encapsulated nanoselenium may have a wide range of biomedical applications. It exerts antimicrobial activity [305], anticancer effects [306,307], enhanced hypoglycemic effect [308], protection against diabetic nephropathy [309], anti-inflammatory effect in arthritis [310], and antioxidant effects [311]; enhances wound healing effects [312] and anti-diabetic activity [44]; and improves fetal growth and hair follicle development [313].

6. Methods for Obtaining Selenium-Containing Polysaccharides

The low molecular weight selenosugars may be obtained by a biosynthesis, a multi-step, enzyme-catalyzed process occurring in living organisms, chemical modification of natural compounds (semisynthesis, i.e., partial chemical synthesis that uses chemical compounds isolated from natural sources as starting material) [314], or by a complete chemical synthesis from simple precursors [315,316]. Due to the enormous complexity of the polysaccharide molecules, not all of the above-mentioned methods are applicable to the preparation of the high-molecular weight polysaccharides and Se-polysaccharides: most of the methods of chemical synthesis of polysaccharides yield compounds with a limited molecular weight (typically $<10,000$ g/mol) [317]. The total synthesis of selenium polysaccharides has not yet been described. However, selenosaccharides with low molar mass (selenoglycosides) have already shown an application in the disaccharide and oligosaccharide synthesis that was described in Section 4 (Figure 3).

In conclusion: Se-polysaccharides may be obtained by extraction from natural products, mainly plants and fungi, but also from microorganisms, by biosynthesis with biotechnological methods or chemical modification of natural polysaccharides. A separate subject is the preparation of nanoselenium–polysaccharide complexes, i.e., nanoselenium particles stabilized (encapsulated) into polysaccharides. All these methods will be discussed below.

6.1. Extraction from Natural Products

As stated in the previous paragraph, chemical synthesis of high molecular-weight polysaccharides is practically impossible. Therefore, these compounds are either isolated from natural sources or obtained by biotechnological methods and, in certain cases, chemically modified.

Depending on the biological material from which the polysaccharides are extracted, slightly different extraction conditions have to be chosen [318] due to the different cell wall structure of bacteria, fungi, and plants. Polysaccharides are mostly soluble in water, but insoluble in organic solvents; therefore, water is the most common extraction medium [319] and the base solvent in the acid or alkali extraction and the enzymolysis method [320].

Basically, the Se-polysaccharides are isolated and purified using the same methods as non-selenium-enriched polysaccharides. Certain differences, observed in our research on the biosynthesis, extraction, and purification of these compounds, consist in different solubilities and limitations in the use of aggressive reagents in derivatization processes (strong acids and bases) due to the instability of some selenium compounds in such an environment [252,320]. As it has been observed, selenium polysaccharides have lower water solubility than non-selenated analogues, which thus affects their extraction efficiency [39].

In plants, breaking the cell wall with ultrasound or microwave methods is required prior to the polysaccharide extraction [321,322]. In mushrooms, on the other hand, the biologically active polysaccharides (mainly β -glucans) are components of the outer layer of the cell wall [323]. In this case the extraction of cell wall polysaccharides commonly involves a pre-extraction with 80% ethanol for elimination of low molecular substances [324].

However, apart from those slight differences, the basic extraction methods are similar and include hot water extraction, precipitation with alcohol (ethanol or methanol), deproteinization, and fractionation, utilizing different methods.

Taking into account the differences in the physical and chemical properties of the various polysaccharides (Se-polysaccharides), an appropriate extraction method should be chosen based on the structure and solubility (in water or alkali) of the target compounds.

During the extraction, a transition from gentle to aggressive extraction conditions (pH, temperature, pressure) is essential. This way the cell wall is gradually destroyed, resulting in the release of Se-polysaccharides from deeper cell wall layers. Procedures are often time-consuming and multiphasic [321].

The example procedure for the extraction of the active polysaccharides from mushroom cultures may involve the following steps. The initial water extraction is carried out with organic solvents, mainly ethanol, acetone, or a mixture of chloroform and methanol in order to remove non-polar compounds such as lipids, phenols, and terpenes. The next step is centrifugation, which produces a supernatant called cold water extract. The residue is then extracted in boiling water, and the biomass is isolated from the hot water extract by another centrifugation. The extraction is repeated to increase the yield [325]. The aqueous extraction residue is extracted with an aqueous base solution (with 2% NaOH or KOH solutions) at the boiling point [326]. The precipitate is separated by a centrifugation using NaBH_4 to protect against degradation of the end units of the polysaccharide chains. Exactly the same procedures were used to extract Se-polysaccharides from selenium enriched mycelium of *L. edodes* and *Hericium erinaceus* [11,13,39,249].

After the extraction, the polysaccharides are purified from proteins, amino acids, monosaccharides, phenolic derivatives, and other molecules. Protein contaminants are removed using a 20% trichloroacetic acid solution by an enzymatic process using a protease enzyme, by the Sevage method, or by extraction with a phenolic reagent [326].

Currently, in addition to the above described classical extraction methods, some modern methods of isolating polysaccharides have been used, e.g., pressurized liquid extraction (PLE), supercritical fluid extraction (SFE), ultrasound-assisted extraction (UEA), and microwave-assisted extraction (MAE) [326–328].

The extracted polysaccharide is in fact a polysaccharide fraction—a mixture of chains with different degrees of polymerization, sometimes varying monosaccharide composition, and chemical character. Therefore, fractionation and deep purification are necessary to obtain a homogeneous polysaccharide (Se-polysaccharide). Based on the purification techniques used, the methods can be divided into three categories: physical, chromatographic, and chemical precipitation. In most cases, the combination of several separation methods has to be employed to improve the purification results.

Fractional precipitation may be used to separate polysaccharides with large differences in solubility and molecular weight [329]. The long-chain quaternary ammonium salt chemical precipitation method may also be applied [318].

Chromatographic separation by column chromatography is also used, with several modifications, mostly as an anion-exchange column chromatography and gel column chromatography [330]. In most cases, anion-exchange chromatography is used in the first step, followed by gel column chromatography.

Design of the methods for extracting polysaccharide fractions from biological material may have to consider some unexpected factors. For example, significant differences were found between the structure of the cell walls of the mycelium of *L. edodes* cultured by biotechnological methods and the fruiting bodies of this fungus. These differences were expressed as a low chitin content and higher exopolysaccharide content in the mycelial cells, which determine the conditions for the polysaccharide extraction [171]. The enrichment of the mycelium with selenium also causes significant changes in the structure of the mycelial cell walls, which is related to the content of polyphenols. These differences also have an impact on the polysaccharides and ergosterol in the biomass extracts. Such differences significantly affect the extractability of Se-polysaccharides from the biological material [171].

6.2. Biotechnological Methods

When considering the biotechnological methods to obtain Se-polysaccharides, the cultures of plants, fungi, algae, or microorganisms are grown in media enriched with soluble selenium compounds. The culture is then used to isolate selenium-enriched polysaccharide fractions from the selenium-enriched biomass of the cultivated species (cell wall polysaccharides and endo-polysaccharides) or from the culture medium (exo-polysaccharides). In order to isolate and purify Se-polysaccharides from those cultured organisms, the methods used are the same as for other natural sources. As a result of the transport into the cell and following enzymatic processes, selenium compounds supplementing the medium may be incorporated into the structure of polysaccharides, as happens with plants or fungi grown on substrates enriched with selenium compounds. However, the biotechnological methods are in many aspects advantageous over the crops cultivation [331].

A major advantage is the shorter time of cultivation in bioreactors, which gives a significant reduction in the time needed to obtain a comparable biomass. Moreover, culturing in bioreactors is carried out under repeatable conditions, resulting in a stable composition of the grown biomass. This facilitates standardization of the preparations, for example for pharmaceutical use.

Biotechnological processes also use optimized composition of the culture media and physico-chemical conditions of the culture. This enables regulation of the metabolism of the cultivated organism and results in a significant increase in efficiency of the biologically active compounds. Finally, the technology of the biotechnological processes provides monitoring and maintenance of the biochemical and genetic identity of the strain cultivated in a fermenter.

However, there are also serious disadvantages of using of modern biotechnological methods when compared with crops cultivation or hydroponics. Primarily, not all species of plants and fungi are capable of growing as efficiently as cell, callus, or mycelial cultures in bioreactors. Moreover, the cultivation of plants (cell, callus, or tissue cultures) and higher fungi (mostly mycelial cultures) in bioreactors faces more challenges than the culture of single-celled organisms. Additionally, the use of biotechnological methods is mostly more expensive than crops. When using biotechnological methods of cultivation, the costs of specialized equipment and apparatus, energy, the required specific constituents of the culture media, highly specialized service, maintaining sterile conditions, etc., are relatively high. However, in the case of protected plants or fungi, plants growing slowly in crops, or hydroponic cultivation, coming from climatic zones/regions, where cropping is very difficult, the choice of the biotechnological methods is favorable. Biotechnological cultures of ginseng (*Panax ginseng* CA Mayer) are a good example. Field cultivation of *Panax ginseng* is a slow and laborious process; therefore, cell and tissue culture methods have been explored as potentially more efficient for ginseng biomass and its bioactive components production [332]. Regardless, the decisive factors in choosing the method of obtaining biological material, for example, for the polysaccharide isolation, are its implementability and of course the cost.

A great number of reports have been published on the preparation of Se-polysaccharides (exo- and endo-polysaccharides) by biotechnological methods. Only a few examples will be given below.

Selenium-containing polysaccharides were isolated from cultures of fungi, e.g., liquid cultures of *Hericium erinaceum* [13], stillage from *Cordyceps sinensis* [108], mycelia of *Catathelasma ventricosum* [246], *Poria cocos* mycelia [247], mycelium of *Pholiota dinghuensis* [248] and *Lentinula edodes* [249], *Pleurotus geesteranus* [333], and other microorganisms, such as *Spirulina platensis* [251], *Enterobacter cloacae* [250], *Pseudomonas* sp. [334], *Leuconostoc mesenteroides* [335], and many others.

6.3. Chemical Modification of Natural Polysaccharides

In order to improve the physico-chemical or biological properties of natural polysaccharides, various chemical modification methods, known as for functionalization or diversification, may be applied [336]. However, the basic properties of the polysaccharide should be maintained during chemical modification: the polymeric chain has to remain intact or, in case of its partial degradation, the products still have to be polysaccharides [337]. One of the widely used methods that may interfere with functionalization and/or diversification of polysaccharides is esterification or acylation with different reagents [336]. To our knowledge, acylation with selenious acid is currently the only method used for the chemical selenylation of natural polysaccharides (stabilization of SeNP with polysaccharides is strictly a non-chemical modification of the polysaccharide structure, and therefore will be discussed separately). In general, esterification involves the reaction of an alcohol (one of the saccharide hydroxyl groups) with an acylating agent. Regarding the diversification reactions, the extent of the process is evaluated by the degree of substitution (DS), defined as a number of substitutions per monomer unit [336]. The maximum DS depends on the structure of the polysaccharide and the type of the diversification reaction. For example, the polyglucopyranose has three hydroxyl groups per monomer that may be acylated; therefore, the maximum DS achievable by esterification of this polysaccharide would be 3 (Figure 10). In order to introduce a selenium-containing moiety into the polysaccharide molecule, maintaining the favorable redox properties of selenium in the oxidation state 4, the polysaccharides should be esterified with selenious acid.

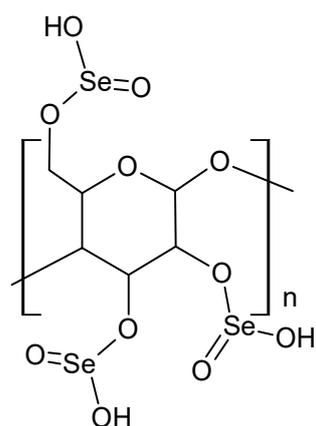


Figure 10. Theoretical structure of the polyglucopyranose with three hydroxyl groups per monomer acylated by selenious acid (DS = 3).

Assuming that the highest DS value for a linear selenite-polyglucan is 3 (Figure 10), it can be calculated that the theoretical highest amount of selenium accumulated in a molecule of such Se-polysaccharide is close to 48×10^3 mg/g. A similar DS value and theoretical maximum amount of accumulated selenium is for each hexose polymer (polyglucan). In principle, these values depend on the number of hydroxyl groups per mer of the polysaccharide and may be calculated theoretically for each glycan. This is only a theoretical value, because complete esterification of all hydroxyl groups of the polysaccharide is very unlikely; acylation of the primary hydroxyl group at the C-6 position of the monomer is preferred. In addition, the efficiency of the acylation reaction depends on the structure of the polysaccharide, including the spatial secondary and tertiary structure.

The most commonly used method to obtain the selenite-polysaccharide is the chemical reaction with nitric acid and sodium selenite [281]. The general procedure includes the following steps [281]: native polysaccharides are dissolved in nitric acid and react with sodium selenite in the presence of BaCl_2 . Then, the solution is neutralized with NaOH, and Ba^{2+} ions are removed by precipitation. The product is purified by dialysis, at room temperature, in a dialysis sack with 1 kDa ultrafiltration membrane, against distilled water [255], yielding the selenite-polysaccharide (selenylated polysaccharide). During the preparation of the selenites, several modifications of the acylation method may be carried out, including chemical reactions with nitric acid and sodium selenite [255,265,267–269,271,272,338–340], nitric acid and selenious acid [258], glacial acetic acid and selenious acid, glacial acetic acid and sodium selenite [258], and selenium oxychloride [260,261]. In order to improve the efficiency of selenylation, some additional techniques, such as microwave [341,342] and ultrasound [262], were already tested. For example, Wei et al. (2019) [343] observed some beneficial effects after using acidic ionic liquids as catalyst that promoted the selenylation of polysaccharides. Interestingly, their work showed that a controlled regulation of Se content and M_w (weight averaged molecular weight) could be achieved by adjusting anions in acidic ionic liquids [343].

In turn, based on the available literature [4,344], Huang et al. [345] suggested that it is also possible to obtain diselenite or cyclic forms of selenite-polysaccharides (Figure 11) by use of selenium oxychloride as acylating agent.

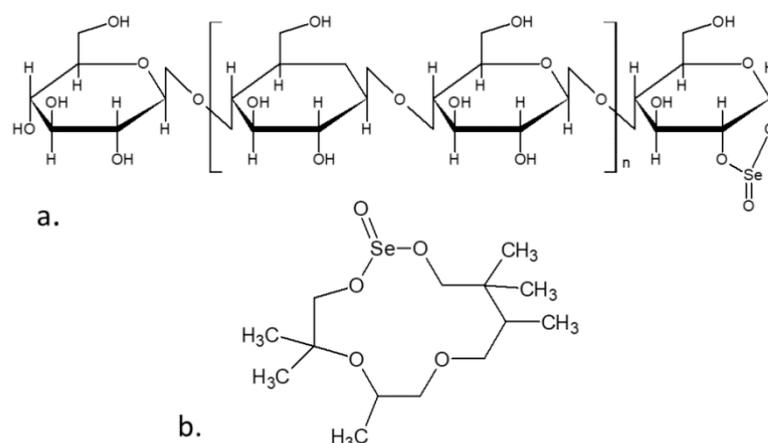


Figure 11. The proposed linear (a) and cyclic (b) structures of selenodextran (according to Huang et al. [345]).

6.4. Encapsulation of Nanoselenium Particles into Polysaccharides

Three methods for preparation of SeNPs are currently used: chemical synthesis [304], physical procedures [346], and biogenic methods utilizing enzymatic reactions in microorganisms, mushrooms, or plants [347]. The polysaccharide-stabilized SeNPs are currently obtained by chemical synthesis and biological and biotechnological methods.

Chemical methods using elemental nano-selenium employ the reduction of this element, mostly from the +4-oxidation state, with a reducing agent in the presence of a polysaccharide as a capping agent. Encapsulated nanoparticles form in a colloidal suspension of a characteristic red color. Some selenium precursors are selenious acid, sodium selenite, or sodium hydrogen selenite; reducing agents include ascorbic acid or reducing mono and disaccharides, like glucose and galactose [286,302,306–310,348–352]. The process is conducted in the presence of polysaccharides such as chitosan, glucomannan, acacia gum, carboxymethylcellulose, or other polysaccharides with different molecular properties and chain conformations [302,353]. The polysaccharides are used as stabilizers and coating agents to obtain stable and water-dispersible selenium nanoparticles.

The procedure to obtain encapsulated SeNPs is simple and includes several steps [354]: (1) adding a vitamin C solution to an aqueous solution of polysaccharides, and mixing uniformly; (2) adding dropwise, with mixing, a selenium dioxide solution or a selenite solution; (3) adding water to the solution to obtain a polysaccharide functionalized nano-selenium hydrosol. The product is stored in the form of sol in an aqueous solution.

Chemical methods of SeNPs preparation are more effective than biological and biotechnological methods; however, the risk of presence of toxic by-products unacceptable in medicinal preparations and dietary supplements led to the development of novel biogenic methods, typical of green chemistry. In green synthesis, a bioreductive capacity of plant extracts is utilized for preparation of selenium nanoparticles. The components of the complex plant extracts (among others polysaccharides) may act as good encapsulating stabilizing agents and facilitate the formation of stable colloidal nanoparticles [355]. Several plant extracts were used for the synthesis and stabilization of the SeNPs, e.g., tea extract [45], aqueous extract of *Allium sativum* [356], leaf extract of *Clausena dentata* [357], polysaccharide solutions extracted from *Undaria pinnatifida* [358], and leaf extract of *Terminalia arjuna* [359]. Biosynthesis of encapsulated SeNPs using plant extracts is inexpensive and does not require any special conditions [304].

Several organisms such as plants, fungi, or bacteria have the ability to convert some toxic ions to less toxic forms including metal precipitants or formation of NPs [360,361]. This capacity is based on the involvement of oxidoreductases in the detoxification process, in case of an excess of harmful factors in the environment. The ability to reduce excess amounts of selenium in the oxidation state +6 or +4 to elemental selenium, often to red selenium in the form of nanoparticles, has been observed in many organisms. Due to that

ability, the cultures of microorganisms or mushroom may be used for synthesizing SeNPs with an ecofriendly approach [362–365].

Several types of bacteria and cyanobacteria cultivated in submerged cultures have already been used for the biosynthesis of SeNPs, and these include *Escherichia coli* [366], *Enterobacter cloacae* [367], *Pseudomonas aeruginosa* [368], *Klebsiella pneumoniae* [369], *Zooglea ramigera* [370], *Lactobacillus casei* [371], *Streptomyces* sp. [372], *Arthrospira* [*Spirulina*] *platen-sis* [373], and many others. Further, fungal cultures may be used for in vivo synthesis of SeNPs. For example, several filamentous fungi species [374], yeast *Saccharomyces cerevisiae* [375], *Aspergillus terreus* [376], *Phanerochaete chrysosporium* [377], and even higher fungi such as *Lentinula edodes* [378] were already used. The list of species used for the production of SeNPs is much longer, and the species presented above should be treated as examples. The nanoselenium particles in fungal and microbial cultures may be present inside the cell or secreted into the culture medium. Depending on the location, they interact with either the components of the culture medium or the cytosol, leading to natural stabilization of SeNPs through the interactions with proteins and polysaccharides. Thus, SeNPs stabilized with polysaccharides can be obtained after extraction from the cultures of mushrooms or microbes enriched with high concentrations of selenium, as previously described for *L. edodes* mycelia [13]. When the selenium content in the *L. edodes* Se-polysaccharides was equal to 1045 µg/g, the X-ray absorption fine structure (XAFS) spectra analysis in the near edge region (XANES) confirmed that selenium in the Se-polysaccharides structure is zerovalent (at 0 oxidation state). The disadvantage of synthesis in vivo by macro- or microorganisms are the changes of the particle morphology and shape caused by the diversity of the reducing enzymes in organisms [289].

7. Biological Activity of Se-Polysaccharides

Natural Se-polysaccharides are not common, and the selenium content in their molecules is very low. Therefore, there is a growing interest in the synthesis of polymers with a high selenium index [262]. In the process of chemical modification of polysaccharides, the ability of organisms to absorb the microelements present in the culture medium has been used. Hence, the best way to improve that absorption is the enrichment of the culture medium with inorganic selenium (e.g., sodium selenite), leading to the incorporation of the element into the biopolymer structure and turning it into an organic form. Selenium compounds resulting from the time-consuming biotransformation method in fungi, bacteria, plants, and algae are attracting increasing attention due to their high bioavailability and low toxicity [13,262]. These selenated polysaccharides can thus serve not only as a new source of selenium, but also as compounds with a new, higher bioactivity. Se-polysaccharides show a higher immunomodulating, anticancer, antioxidant, and hepatoprotective bioactivity in relation to the native polysaccharides [10,281] due to the synergistic effect of selenium and polysaccharides (despite their different mechanisms of action) [11,39]. In general, along with the increase in selenium content, the bioactivity of the modified polysaccharide also increases, but this relation is still a subject of research. The following subsections outline the biological activity of Se-polysaccharides isolated from bacteria, algae, fungi, and plants.

7.1. Bacterial Se-Polysaccharides

Selenium-enriched exopolysaccharide isolated from *Enterobacter cloacae* culture medium increased the proliferation of lymphocytes in mice, indicating that it might be used as an immunomodulator to increase the cellular and humoral immune response [250]. In addition, studies by Lu et al. on *Enterobacter cloacae* confirmed the immunological activity of Se-polysaccharides after administration of 840 mg/kg in broilers [12]. Further, Se-polysaccharides isolated from *Lactococcus lactis* showed a stronger effect on the immune system than non-selenated polysaccharides, which was manifested by enhanced macrophage phagocytosis and hemolytic complement activity in mice [379]. *Pseudomonas* PT-8 is another strain used in the biosynthesis of selenium-rich polymers. The obtained

Se-exopolysaccharides (SePEPS) showed higher antioxidant and antiradical activity when compared to the unmodified biopolymers [334]. In turn, the Se-polysaccharides isolated from selenium-enriched cultures of cyanobacterium, *Spirulina platensis*, showed strong biological activity, dependent on the concentration and chemical form of selenium. It was discovered that Se-polysaccharide fraction had a protective effect against cadmium-induced toxicity in vitro and in vivo—in a rat model. The protective effect for Se-polysaccharide was superior compared to the reference polysaccharide or Na₂SeO₃ alone. The authors hypothesize that this effect may be due to the covalent bonding of selenium to polysaccharide [380]. The results of another study confirmed that supplementing *S. platensis* with selenium increases the production of phycocyanins in the bacterial cells [381], and that those products showed antioxidant, anti-inflammatory, and antitumor properties, including against a very aggressive non-small-cell lung carcinoma (NSCLC). The last was investigated in vitro on three typical NSCLC cell lines, NCI-H1299, NCI-H460, and LTP-A2; however, without the control (normal cell line) [382,383]. On the other hand, Zhu et al. found that the Se-polysaccharides isolated from *S. platensis* reduce the symptoms of sodium dextran sulfate-induced colitis in mice [384].

7.2. Algal Se-Polysaccharides

The antioxidant and antitumor properties of selenium polysaccharides were also investigated in algae, such as *Sargassum fusiforme* (Harv) Setch. In mice with S₁₈₀ tumor, selenium-enriched polysaccharides reduced the level of malondialdehyde, while increasing the activity of catalase, superoxide dismutase, and glutathione peroxidase in the blood, liver, and heart cells [385]. Additionally, Se-polysaccharides isolated from *Ulva fasciata* showed antiproliferative activity against human lung cancer cells A549 [386]. The selenium nanoparticles encapsulated in *Ulva lactuca* polysaccharides have also been observed to reduce the symptoms of sodium dextran sulfate-induced colitis in mice [295].

Data on Se-polysaccharides in microalgae are very limited and concern mainly selenium metabolism in these organisms, as in the work cited below [387].

7.3. Fungal Se-Polysaccharides

Compounds isolated from *Hericium erinaceus* were modified in order to obtain Se-polysaccharides. In vitro studies have shown that the use of the modified polysaccharides induced morphological changes in dendritic cells, increasing the expression of the surface molecules, key for antigen presentation [271]. Additionally, the Se-polysaccharide isolated from the mycelium of *Ganoderma lucidum* showed a tenfold higher inhibitory effect on the proliferation of human cancer cell lines when compared to the natural polysaccharide [388]. Further, in a study conducted by Wang et al., Se-polysaccharides from *Hohenbuehelia serotina* were isolated after the esterification of the polysaccharide with selenious acid [389]. Again, it was shown that the chemically modified compound had a greater antioxidant capacity than the natural polysaccharide [251]. Furthermore, Se-polysaccharides can be obtained by supplementing the culture medium used in the biosynthetic process with selenium, as was the case of *Lentinula edodes* mycelial cultures, which accumulated selenium from the culture medium. The incorporation of selenium into the *L. edodes* mycelium increased the immunomodulatory activity of the produced Se-polysaccharides that showed no cytotoxic effects and increased the cell survival [171]. Moreover, the protection test against oxidative stress induced by the H₂O₂ exposure showed the antioxidant activity of a Se-polysaccharide fraction and the reference polysaccharides in HeLa cells. At the same time, the viability of cells treated with selenium polysaccharides was higher than that of the native polysaccharides, and the selenium polysaccharide fraction showed a greater effect on the modulation of the immune response [252].

7.4. Plant Se-Polysaccharides

The immunomodulatory properties of the natural garlic polysaccharides and those modified with selenium have been compared. The selenation process significantly increased

the bioactivity of the polysaccharides. Hence, Se-polysaccharides showed a stronger stimulating effect of the cellular and humoral immune system. Further, chickens administered these Se-polysaccharides showed a higher level of lymphocyte proliferation and a higher serum antibody titer along with a higher stimulation of Th1 helper lymphocytes to produce IFN- γ and IL-2 [280]. In addition, the native polysaccharides isolated from the roots of *Hedysarum polybotrys* also showed an immunomodulatory effect [261]. However, the research demonstrated that the *H. polybotrys* polysaccharides modified with selenium had a stronger antioxidant effect, reflected by the removal of superoxide and hydroxyl radicals [390]. In another study with a group of rats administered CCl₄, the biological activity of Se-polysaccharides isolated from the root of *Astragalus membranaceus* was compared with those of the natural polysaccharides. The results showed that selenopolysaccharides had a greater efficiency in increasing the activity of SOD, GPx, and MDA. Additionally, histopathological examination of the liver tissue of the rats confirmed the effectiveness of Se-polysaccharides in alleviating the inflammation and necrosis of hepatocytes, induced by the administration of CCl₄ by inactivating the Kupffer cells [270]. Research on selenium polysaccharides derived from *Pyracantha fortuneana* showed that they can enhance the cytotoxic effect of doxorubicin on human breast cancer cells in vitro [391]. Furthermore, investigation in Se-polysaccharides from *Platycodon grandiflorum* indicated that selenium-enriched biopolymers had the ability to protect against oxidative damage induced by hydrogen peroxide in the pheochromocytoma cells of rats [392]. In another study, tea was identified as another plant source of bioactive Se-polysaccharides, and its ability to inhibit the proliferation of S₁₈₀ in mice was reported to be significantly higher than that of the Se-yeast (Se-enriched *Saccharomyces cerevisiae*) [392]. Green tea Se-polysaccharides may have a positive effect in the treatment of human osteosarcoma and greater antioxidant activity when compared to the native polysaccharides [170].

8. Se-Polysaccharides—Perspectives

For nearly twenty years, the selenium-enriched polysaccharides have been attracting great interest among scientists and have become a subject of comprehensive research. As a result, a large number of selenium-containing polysaccharides of diversified structure, origin, selenium binding, and oxidation state were obtained with a range of experimental methods. The biological activity of these compounds was also a subject of detailed investigation.

These compounds had proven to be very promising in terms of the potential use in the selenium supplementation and in the adjunctive therapy of many diseases. Se-polysaccharides are characterized by a low toxicity and a slow release of selenium, which is a great advantage over the “traditional” selenium supplements. The incorporation of selenium into a molecule of biologically active polysaccharides significantly enhances their action, which suggests the synergy of selenium and polysaccharides.

The main weakness of the current research is the lack of a broader look at the problem of the relationship between the structure and activity of Se-polysaccharides, and especially, the impact of the selenium binding method into the polysaccharide molecule and its oxidation degree on its activity. The treatment of seleno-polysaccharides as a structurally homogeneous group of compounds whose activity is affected only by the amount of selenium introduced into the molecule, regardless of its chemical environment or the degree of oxidation, is in our opinion an inappropriate approach. For example, it is difficult to expect a similar antioxidant effect from Se-polysaccharides containing selenium in the second, fourth, or zero oxidation state. Selenium compounds are often antioxidants, but can also act as pro-oxidants depending on their redox properties.

To summarize, it is necessary to use the standard methods of medicinal chemistry in the research on the preparation and activity of selenium-containing polysaccharides. The study of the structure–activity relationship requires preparation of a series of compounds with methodically introduced structural changes. To take a simple example: one could biosynthesize a selenium analogue of a natural polysaccharide containing glycosidically

bound (divalent) selenium, then obtain a semisynthetic analog of the same polysaccharide containing ester-bound selenium (selenite with tetravalent selenium), and, finally, obtain selenium nanoparticles encapsulated with the same polysaccharide (zero-valent selenium) by a chemical or a biological method. A comparison of the activity of such selenium-containing analogues of a biologically active polysaccharide would provide conclusive data on the influence of “selenium” on the activity of the investigated polysaccharide. Of course, the study of the structure–activity relationship should consider the complex analysis of not only the primary structure of the Se-polysaccharide, but also the secondary and tertiary structure, which are very important in shaping biological activity other than simple redox properties. The published data shows that the incorporation of selenium into a polysaccharide molecule causes far-reaching deformation of the molecule. In case of the receptor activity (binding to the receptor), such changes are extremely important and should also be carefully investigated.

Regarding the wide scope and diversity of this research subject, the comprehensive research on the effect of selenium binding on the activity of Se-polysaccharides would require cooperation across various research centers, mostly specialized in certain methods of “selenating” polysaccharides.

Author Contributions: Conceptualization, S.G. and J.T.; writing—original draft preparation, S.G. and J.T.; writing—review and editing J.T.; visualization, A.M.; supervision, J.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study did not require ethical approval.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Cui, S.W. *Food Carbohydrates: Chemistry, Physical Properties, and Applications*; Taylor & Francis: Boca Raton, FL, USA, 2005; ISBN 978-0-8493-1574-9.
2. Diener, M.; Adamcik, J.; Sánchez-Ferrer, A.; Jaedig, F.; Schefer, L.; Mezzenga, R. Primary, Secondary, Tertiary and Quaternary Structure Levels in Linear Polysaccharides: From Random Coil, to Single Helix to Supramolecular Assembly. *Biomacromolecules* **2019**, *20*, 1731–1739. [[CrossRef](#)] [[PubMed](#)]
3. Yu, Y.; Shen, M.; Song, Q.; Xie, J. Biological Activities and Pharmaceutical Applications of Polysaccharide from Natural Resources: A Review. *Carbohydr. Polym.* **2018**, *183*, 91–101. [[CrossRef](#)] [[PubMed](#)]
4. Chen, F.; Huang, G. Preparation and Immunological Activity of Polysaccharides and Their Derivatives. *Int. J. Biol. Macromol.* **2018**, *112*, 211–216. [[CrossRef](#)] [[PubMed](#)]
5. Naqash, F.; Masoodi, F.A.; Rather, S.A.; Wani, S.M.; Gani, A. Emerging Concepts in the Nutraceutical and Functional Properties of Pectin—A Review. *Carbohydr. Polym.* **2017**, *168*, 227–239. [[CrossRef](#)]
6. Wang, X.; Wang, J.; Zhang, J.; Zhao, B.; Yao, J.; Wang, Y. Structure-Antioxidant Relationships of Sulfated Galactomannan from Guar Gum. *Int. J. Biol. Macromol.* **2010**, *46*, 59–66. [[CrossRef](#)]
7. Cunha de Padua, M.M.; Suter Correia Cadena, S.M.; de Oliveira Petkowicz, C.L.; Martinez, G.R.; Rodrigues Noletto, G. Galactomannan from *Schizolobium Amazonicum* Seed and Its Sulfated Derivatives Impair Metabolism in HepG2 Cells. *Int. J. Biol. Macromol.* **2017**, *101*, 464–473. [[CrossRef](#)]
8. Ferreira, S.S.; Passos, C.P.; Madureira, P.; Vilanova, M.; Coimbra, M.A. Structure-Function Relationships of Immunostimulatory Polysaccharides: A Review. *Carbohydr. Polym.* **2015**, *132*, 378–396. [[CrossRef](#)] [[PubMed](#)]
9. Xie, L.; Shen, M.; Hong, Y.; Ye, H.; Huang, L.; Xie, J. Chemical Modifications of Polysaccharides and Their Anti-Tumor Activities. *Carbohydr. Polym.* **2020**, *229*, 115436. [[CrossRef](#)]
10. Li, J.; Shen, B.; Nie, S.; Duan, Z.; Chen, K. A Combination of Selenium and Polysaccharides: Promising Therapeutic Potential. *Carbohydr. Polym.* **2019**, *206*, 163–173. [[CrossRef](#)]
11. Kaleta, B.; Górski, A.; Zagożdżon, R.; Cieslak, M.; Kaźmierczak-Barańska, J.; Nawrot, B.; Klimaszewska, M.; Malinowska, E.; Górka, S.; Turło, J. Selenium-Containing Polysaccharides from *Lentinula Edodes*—Biological Activity. *Carbohydr. Polym.* **2019**, *223*, 115078. [[CrossRef](#)]
12. Lu, Z.; Jin, M.; Huang, M.; Wang, Y.; Wang, Y. Bioactivity of Selenium-Enriched Exopolysaccharides Produced by *Enterobacter Cloacae* Z0206 in Broilers. *Carbohydr. Polym.* **2013**, *96*, 131–136. [[CrossRef](#)]

13. Malinowska, E.; Krzyczkowski, W.; Herold, F.; Lapienis, G.; Ślusarczyk, J.; Suchocki, P.; Kuraś, M.; Turlo, J. Biosynthesis of Selenium-Containing Polysaccharides with Antioxidant Activity in Liquid Culture of *Hericium Erinaceum*. *Enzyme Microb. Technol.* **2009**, *44*, 334–343. [[CrossRef](#)]
14. Tapiero, H.; Townsend, D.M.; Tew, K.D. The Antioxidant Role of Selenium and Seleno-Compounds. *Biomed. Pharmacother. Biomed. Pharmacother.* **2003**, *57*, 134–144. [[CrossRef](#)]
15. Roy, M.; Kiremidjian-Schumacher, L.; Wishe, H.I.; Cohen, M.W.; Stotzky, G. Supplementation with Selenium and Human Immune Cell Functions. I. Effect on Lymphocyte Proliferation and Interleukin 2 Receptor Expression. *Biol. Trace Elem. Res.* **1994**, *41*, 103–114. [[CrossRef](#)] [[PubMed](#)]
16. Dodig, S.; Cepelak, I. The Facts and Controversies about Selenium. *Acta Pharm.* **2004**, *54*, 261–276. [[PubMed](#)]
17. Rayman, M.P. Selenium and Human Health. *Lancet* **2012**, *379*, 1256–1268. [[CrossRef](#)]
18. Rayman, M.P. Selenium Intake, Status, and Health: A Complex Relationship. *Hormones* **2020**, *19*, 9–14. [[CrossRef](#)]
19. Murdolo, G.; Bartolini, D.; Tortoioli, C.; Piroddi, M.; Torquato, P.; Galli, F. Selenium and Cancer Stem Cells. *Adv. Cancer Res.* **2017**, *136*, 235–257. [[CrossRef](#)]
20. Fernandes, A.P.; Gandin, V. Selenium Compounds as Therapeutic Agents in Cancer. *Biochim. Biophys. Acta* **2015**, *1850*, 1642–1660. [[CrossRef](#)]
21. Kim, C.; Kim, S.-B.; Park, M.-S. Synthesis of Novel 3-Allylseleno-6-Alkylthiopyridazines: Their Anticancer Activity against MCF-7 Cells. *Arch. Pharm. Res.* **2014**, *37*, 452–458. [[CrossRef](#)]
22. Domínguez-Álvarez, E.; Gajdács, M.; Spengler, G.; Palop, J.A.; Marć, M.A.; Kieć-Kononowicz, K.; Amaral, L.; Molnár, J.; Jacob, C.; Handzlik, J.; et al. Identification of Selenocompounds with Promising Properties to Reverse Cancer Multidrug Resistance. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2821–2824. [[CrossRef](#)]
23. Yu, S.Y.; Zhu, Y.J.; Li, W.G.; Huang, Q.S.; Huang, C.Z.; Zhang, Q.N.; Hou, C. A Preliminary Report on the Intervention Trials of Primary Liver Cancer in High-Risk Populations with Nutritional Supplementation of Selenium in China. *Biol. Trace Elem. Res.* **1991**, *29*, 289–294. [[CrossRef](#)] [[PubMed](#)]
24. Hehr, T.; Hoffmann, W.; Bamberg, M. Role of sodium selenite as an adjuvant in radiotherapy of rectal carcinoma. *Med. Klin.* **1997**, *92* (Suppl. S3), 48–49. [[CrossRef](#)] [[PubMed](#)]
25. El-Bayoumy, K. The Protective Role of Selenium on Genetic Damage and on Cancer. *Mutat. Res.* **2001**, *475*, 123–139. [[CrossRef](#)]
26. Hiffler, L.; Rakotoambinina, B. Selenium and RNA Virus Interactions: Potential Implications for SARS-CoV-2 Infection (COVID-19). *Front. Nutr.* **2020**, *7*, 164. [[CrossRef](#)]
27. Chaturvedi, U.C.; Shrivastava, R.; Upreti, R.K. Viral Infections and Trace Elements: A Complex Interaction. *Curr. Sci.* **2004**, *87*, 1536–1554.
28. Zong, A.; Cao, H.; Wang, F. Anticancer Polysaccharides from Natural Resources: A Review of Recent Research. *Carbohydr. Polym.* **2012**, *90*, 1395–1410. [[CrossRef](#)] [[PubMed](#)]
29. Khan, T.; Date, A.; Chawda, H.; Patel, K. Polysaccharides as Potential Anticancer Agents—A Review of Their Progress. *Carbohydr. Polym.* **2019**, *210*, 412–428. [[CrossRef](#)] [[PubMed](#)]
30. Gopinath, V.; Saravanan, S.; Al-Maleki, A.R.; Ramesh, M.; Vadivelu, J. A Review of Natural Polysaccharides for Drug Delivery Applications: Special Focus on Cellulose, Starch and Glycogen. *Biomed. Pharmacother.* **2018**, *107*, 96–108. [[CrossRef](#)] [[PubMed](#)]
31. Kulicke, W.-M.; Heinze, T. Improvements in Polysaccharides for Use as Blood Plasma Expanders. *Macromol. Symp.* **2005**, *231*, 47–59. [[CrossRef](#)]
32. Sun, Y.; Jing, X.; Ma, X.; Feng, Y.; Hu, H. Versatile Types of Polysaccharide-Based Drug Delivery Systems: From Strategic Design to Cancer Therapy. *Int. J. Mol. Sci.* **2020**, *21*, 9159. [[CrossRef](#)]
33. Bohn, J.A.; BeMiller, J.N. (1→3)-β-D-Glucans as Biological Response Modifiers: A Review of Structure-Functional Activity Relationships. *Carbohydr. Polym.* **1995**, *28*, 3–14. [[CrossRef](#)]
34. Okazaki, M.; Adachi, Y.; Ohno, N.; Yadomae, T. Structure-Activity Relationship of (1,3,6)-β-D-Glucans in the Induction of Cytokine Production from Macrophages, in Vitro. *Biol. Pharm. Bull.* **1995**, *18*, 1320–1327. [[CrossRef](#)]
35. Surenjav, U.; Zhang, L.; Xu, X.; Zhang, X.; Zeng, F. Effects of Molecular Structure on Antitumor Activities of (1→3)-β-D-Glucans from Different *Lentinus Edodes*. *Carbohydr. Polym.* **2006**, *63*, 97–104. [[CrossRef](#)]
36. Ohno, N.; Miura, N.N.; Chiba, N.; Adachi, Y.; Yadomae, T. Comparison of the Immunopharmacological Activities of Triple and Single-Helical Schizophyllan in Mice. *Biol. Pharm. Bull.* **1995**, *18*, 1242–1247. [[CrossRef](#)] [[PubMed](#)]
37. Zhang, Y.; Li, S.; Wang, X.; Zhang, L.; Cheung, P.C.K. Advances in Lentinan: Isolation, Structure, Chain Conformation and Bioactivities. *Food Hydrocoll.* **2011**, *25*, 196–206. [[CrossRef](#)]
38. Leung, M.Y.K.; Liu, C.; Koon, J.C.M.; Fung, K.P. Polysaccharide Biological Response Modifiers. *Immunol. Lett.* **2006**, *105*, 101–114. [[CrossRef](#)] [[PubMed](#)]
39. Malinowska, E.; Klimaszewska, M.; Strączek, T.; Schneider, K.; Kapusta, C.; Podsadni, P.; Lapienis, G.; Dawidowski, M.; Kleps, J.; Górska, S.; et al. Selenized Polysaccharides—Biosynthesis and Structural Analysis. *Carbohydr. Polym.* **2018**, *198*, 407–417. [[CrossRef](#)]
40. Lombard, Y.; Giaimis, J.; Makaya-Kumba, M.; Fonteneau, P.; Poindron, P. A New Method for Studying the Binding and Ingestion of Zymosan Particles by Macrophages. *J. Immunol. Methods* **1994**, *174*, 155–165. [[CrossRef](#)]
41. Sakagami, H.; Aoki, T.; Simpson, A.; Tanuma, S. Induction of Immunopotential Activity by a Protein-Bound Polysaccharide, PSK (Review). *Anticancer Res.* **1991**, *11*, 993–999.

42. Tsiapali, E.; Whaley, S.; Kalbfleisch, J.; Ensley, H.E.; Browder, I.W.; Williams, D.L. Glucans Exhibit Weak Antioxidant Activity, but Stimulate Macrophage Free Radical Activity. *Free Radic. Biol. Med.* **2001**, *30*, 393–402. [[CrossRef](#)]
43. He, N.; Shi, X.; Zhao, Y.; Tian, L.; Wang, D.; Yang, X. Inhibitory Effects and Molecular Mechanisms of Selenium-Containing Tea Polysaccharides on Human Breast Cancer MCF-7 Cells. *J. Agric. Food Chem.* **2013**, *61*, 579–588. [[CrossRef](#)]
44. Liu, Y.; Zeng, S.; Liu, Y.; Wu, W.; Shen, Y.; Zhang, L.; Li, C.; Chen, H.; Liu, A.; Shen, L.; et al. Synthesis and Antidiabetic Activity of Selenium Nanoparticles in the Presence of Polysaccharides from *Catathelasma Ventricosum*. *Int. J. Biol. Macromol.* **2018**, *114*, 632–639. [[CrossRef](#)] [[PubMed](#)]
45. Zhang, W.; Zhang, J.; Ding, D.; Zhang, L.; Muehlmann, L.A.; Deng, S.-E.; Wang, X.; Li, W.; Zhang, W. Synthesis and Antioxidant Properties of Lycium Barbarum Polysaccharides Capped Selenium Nanoparticles Using Tea Extract. *Artif. Cells Nanomed. Biotechnol.* **2018**, *46*, 1463–1470. [[CrossRef](#)] [[PubMed](#)]
46. Satitmanwivat, S.; Ratanakhanokchai, K.; Laohakunjit, N.; Chao, L.K.; Chen, S.-T.; Pason, P.; Tachaapaikoon, C.; Kyu, K.L. Improved Purity and Immunostimulatory Activity of β -(1 \rightarrow 3)(1 \rightarrow 6)-Glucan from *Pleurotus Sajor-Caju* Using Cell Wall-Degrading Enzymes. *J. Agric. Food Chem.* **2012**, *60*, 5423–5430. [[CrossRef](#)] [[PubMed](#)]
47. Ercole, C.; Cacchio, P.; Botta, A.L.; Centi, V.; Lepidi, A. Bacterially Induced Mineralization of Calcium Carbonate: The Role of Exopolysaccharides and Capsular Polysaccharides. *Microsc. Microanal. Off. J. Microsc. Soc. Am. Microbeam Anal. Soc. Microsc. Soc. Can.* **2007**, *13*, 42–50. [[CrossRef](#)] [[PubMed](#)]
48. Yildiz, H.; Karatas, N. Microbial Exopolysaccharides: Resources and Bioactive Properties. *Process Biochem.* **2018**, *72*, 41–46. [[CrossRef](#)]
49. Borgenström, M.; Wärr, A.; Hiilesvuo, K.; Käkönen, R.; Käkönen, S.; Nissinen, L.; Pihlavisto, M.; Marjamäki, A.; Vlodavsky, I.; Naggi, A.; et al. O-Sulfated Bacterial Polysaccharides with Low Anticoagulant Activity Inhibit Metastasis. *Semin. Thromb. Hemost.* **2007**, *33*, 547–556. [[CrossRef](#)] [[PubMed](#)]
50. Liu, J.; Luo, J.; Ye, H.; Zeng, X. Preparation, Antioxidant and Antitumor Activities in Vitro of Different Derivatives of Levan from Endophytic Bacterium *Paenibacillus polymyxa* EJS-3. *Food Chem. Toxicol.* **2012**, *50*, 767–772. [[CrossRef](#)]
51. Zhao, L.; Chen, Y.; Ren, S.; Han, Y.; Cheng, H. Studies on the Chemical Structure and Antitumor Activity of an Exopolysaccharide from *Rhizobium* Sp. N613. *Carbohydr. Res.* **2010**, *345*, 637–643. [[CrossRef](#)]
52. Harada, T.; Fujimori, K.; Hirose, S.; Masada, M. Growth and β -Glucan 10C3K Production by a Mutant of *Alcaligenes faecalis* Var. *Myxogenes* in Defined Medium. *Agric. Biol. Chem.* **1966**, *30*, 764–769. [[CrossRef](#)]
53. McIntosh, M.; Stone, B.A.; Stanisich, V.A. Curdlan and Other Bacterial (1 \rightarrow 3)-Beta-D-Glucans. *Appl. Microbiol. Biotechnol.* **2005**, *68*, 163–173. [[CrossRef](#)]
54. Zhan, X.-B.; Lin, C.-C.; Zhang, H.-T. Recent Advances in Curdlan Biosynthesis, Biotechnological Production, and Applications. *Appl. Microbiol. Biotechnol.* **2012**, *93*, 525–531. [[CrossRef](#)]
55. Mazmanian, S.K.; Liu, C.H.; Tzianabos, A.O.; Kasper, D.L. An Immunomodulatory Molecule of Symbiotic Bacteria Directs Maturation of the Host Immune System. *Cell* **2005**, *122*, 107–118. [[CrossRef](#)]
56. Huang, S.; Huang, G. Preparation and Drug Delivery of Dextran-Drug Complex. *Drug Deliv.* **2019**, *26*, 252–261. [[CrossRef](#)] [[PubMed](#)]
57. De Philippis, R. Exocellular Polysaccharides from Cyanobacteria and Their Possible Applications. *FEMS Microbiol. Rev.* **1998**, *22*, 151–175. [[CrossRef](#)]
58. Wang, B.; Liu, Q.; Huang, Y.; Yuan, Y.; Ma, Q.; Du, M.; Cai, T.; Cai, Y. Extraction of Polysaccharide from *Spirulina* and Evaluation of Its Activities. *Evid. Based Complement. Alternat. Med.* **2018**, *2018*, 1–8. [[CrossRef](#)]
59. Rajasekar, P.; Palanisamy, S.; Anjali, R.; Vinosha, M.; Elakkiya, M.; Marudhupandi, T.; Tabarsa, M.; You, S.; Prabhu, N.M. Isolation and Structural Characterization of Sulfated Polysaccharide from *Spirulina Platensis* and Its Bioactive Potential: In Vitro Antioxidant, Antibacterial Activity and Zebrafish Growth and Reproductive Performance. *Int. J. Biol. Macromol.* **2019**, *141*, 809–821. [[CrossRef](#)]
60. Usov, A.I.; Zelinsky, N.D. Chemical structures of algal polysaccharides. In *Functional Ingredients from Algae for Foods and Nutraceuticals*; Elsevier: Cambridge, UK, 2013; pp. 23–86, ISBN 978-0-85709-512-1.
61. Aquino, R.S.; Grativol, C.; Mourão, P.A.S. Rising from the Sea: Correlations between Sulfated Polysaccharides and Salinity in Plants. *PLoS ONE* **2011**, *6*, e18862. [[CrossRef](#)] [[PubMed](#)]
62. Van Weelden, G.; Bobiński, M.; Okła, K.; van Weelden, W.J.; Romano, A.; Pijnenborg, J.M.A. Fucoidan Structure and Activity in Relation to Anti-Cancer Mechanisms. *Mar. Drugs* **2019**, *17*, 32. [[CrossRef](#)] [[PubMed](#)]
63. Fitton, J.H. Therapies from Fucoidan; Multifunctional Marine Polymers. *Mar. Drugs* **2011**, *9*, 1731–1760. [[CrossRef](#)]
64. De Jesus Raposo, M.; de Morais, A.; de Morais, R. Marine Polysaccharides from Algae with Potential Biomedical Applications. *Mar. Drugs* **2015**, *13*, 2967–3028. [[CrossRef](#)] [[PubMed](#)]
65. Yoo, Y.-C.; Kim, W.-J.; Kim, S.-Y.; Kim, S.-M.; Chung, M.-K.; Park, J.-W.; Suh, H.-H.; Lee, K.-B.; Park, Y.-I. Immunomodulating Activity of a Fucoidan Isolated from Korean *Undaria Pinnatifida* Sporophyll. *ALGAE* **2007**, *22*, 333–338. [[CrossRef](#)]
66. Byon, Y.Y.; Kim, M.H.; Yoo, E.S.; Hwang, K.K.; Jee, Y.; Shin, T.; Joo, H.G. Radioprotective Effects of Fucoidan on Bone Marrow Cells: Improvement of the Cell Survival and Immunoreactivity. *J. Vet. Sci.* **2008**, *9*, 359–365. [[CrossRef](#)] [[PubMed](#)]
67. Wu, L.; Sun, J.; Su, X.; Yu, Q.; Yu, Q.; Zhang, P. A Review about the Development of Fucoidan in Antitumor Activity: Progress and Challenges. *Carbohydr. Polym.* **2016**, *154*, 96–111. [[CrossRef](#)]

68. Lim, S.J.; Wan Aida, W.M. Extraction of Sulfated Polysaccharides (Fucoidan) from Brown Seaweed. In *Seaweed Polysaccharides*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 27–46, ISBN 978-0-12-809816-5.
69. Zhang, J.; Zhang, Q.; Wang, J.; Shi, X.; Zhang, Z. Analysis of the Monosaccharide Composition of Fucoidan by Precolumn Derivation HPLC. *Chin. J. Oceanol. Limnol.* **2009**, *27*, 578–582. [[CrossRef](#)]
70. Malyarenko, O.S.; Usoltseva, R.V.; Silchenko, A.S.; Ermakova, S.P. Aminated Laminaran from Brown Alga *Saccharina Cichorioides*: Synthesis, Structure, Anticancer, and Radiosensitizing Potential in Vitro. *Carbohydr. Polym.* **2020**, *250*, 117007. [[CrossRef](#)] [[PubMed](#)]
71. Gamal-Eldeen, A.M.; Ahmed, E.F.; Abo-Zeid, M.A. In Vitro Cancer Chemopreventive Properties of Polysaccharide Extract from the Brown Alga, *Sargassum Latifolium*. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2009**, *47*, 1378–1384. [[CrossRef](#)] [[PubMed](#)]
72. Lins, K.O.A.L.; Bezerra, D.P.; Alves, A.P.N.N.; Alencar, N.M.N.; Lima, M.W.; Torres, V.M.; Farias, W.R.L.; Pessoa, C.; de Moraes, M.O.; Costa-Lotufo, L.V. Antitumor Properties of a Sulfated Polysaccharide from the Red Seaweed *Champia Feldmannii* (Diaz-Pifferer). *J. Appl. Toxicol. JAT* **2009**, *29*, 20–26. [[CrossRef](#)]
73. Zhou, G. In Vivo Antitumor and Immunomodulation Activities of Different Molecular Weight Lambda-Carrageenans from *Chondrus Ocellatus*. *Pharmacol. Res.* **2004**, *50*, 47–53. [[CrossRef](#)]
74. Zhou, G.; Sheng, W.; Yao, W.; Wang, C. Effect of Low Molecular Weight Lambda-Carrageenan from *Chondrus Ocellatus* on Antitumor H-22 Activity of 5-Fu. *Pharmacol. Res.* **2006**, *53*, 129–134. [[CrossRef](#)] [[PubMed](#)]
75. Necas, J.; Bartosikova, L. Carrageenan: A Review. *Veterinárni Medicína* **2013**, *58*, 187–205. [[CrossRef](#)]
76. Jiao, G.; Yu, G.; Zhang, J.; Ewart, H. Chemical Structures and Bioactivities of Sulfated Polysaccharides from Marine Algae. *Mar. Drugs* **2011**, *9*, 196–223. [[CrossRef](#)]
77. Martínez Andrade, K.; Lauritano, C.; Romano, G.; Ianora, A. Marine Microalgae with Anti-Cancer Properties. *Mar. Drugs* **2018**, *16*, 165. [[CrossRef](#)] [[PubMed](#)]
78. Paulsen, B.S.; Olafsdóttir, E.S.; Ingólfssdóttir, K. Chromatography and Electrophoresis in Separation and Characterization of Polysaccharides from Lichens. *J. Chromatogr. A* **2002**, *967*, 163–171. [[CrossRef](#)]
79. Olafsdóttir, E.S.; Ingólfssdóttir, K. Polysaccharides from Lichens: Structural Characteristics and Biological Activity. *Planta Med.* **2001**, *67*, 199–208. [[CrossRef](#)] [[PubMed](#)]
80. Liu, J.; Willför, S.; Xu, C. A Review of Bioactive Plant Polysaccharides: Biological Activities, Functionalization, and Biomedical Applications. *Bioact. Carbohydr. Diet. Fibre* **2015**, *5*, 31–61. [[CrossRef](#)]
81. Chang, S.-T.; Wasser, S.P. The Role of Culinary-Medicinal Mushrooms on Human Welfare with a Pyramid Model for Human Health. *Int. J. Med. Mushrooms* **2012**, *14*, 95–134. [[CrossRef](#)] [[PubMed](#)]
82. Mizuno, M.; Nishitani, Y. Immunomodulating Compounds in Basidiomycetes. *J. Clin. Biochem. Nutr.* **2013**, *52*, 202–207. [[CrossRef](#)]
83. Wasser, S.P. Current Findings, Future Trends, and Unsolved Problems in Studies of Medicinal Mushrooms. *Appl. Microbiol. Biotechnol.* **2011**, *89*, 1323–1332. [[CrossRef](#)]
84. Giavasis, I. Production of microbial polysaccharides for use in food. In *Microbial Production of Food Ingredients, Enzymes and Nutraceuticals*; Elsevier: Amsterdam, The Netherlands, 2013; pp. 413–468, ISBN 978-0-85709-343-1.
85. Friedman, M. Mushroom Polysaccharides: Chemistry and Antiobesity, Antidiabetes, Anticancer, and Antibiotic Properties in Cells, Rodents, and Humans. *Foods* **2016**, *5*, 80. [[CrossRef](#)] [[PubMed](#)]
86. Moradali, M.-F.; Mostafavi, H.; Ghods, S.; Hedjaroude, G.-A. Immunomodulating and Anticancer Agents in the Realm of Macromycetes Fungi (Macrofungi). *Int. Immunopharmacol.* **2007**, *7*, 701–724. [[CrossRef](#)]
87. Reshetnikov, S.V.; Tan, K.-K. Higher Basidiomycota as a Source of Antitumor and Immunostimulating Polysaccharides (Review). *Int. J. Med. Mushrooms* **2001**, *3*, 34. [[CrossRef](#)]
88. Boon, H.; Wong, J. Botanical Medicine and Cancer: A Review of the Safety and Efficacy. *Expert Opin. Pharmacother.* **2004**, *5*, 2485–2501. [[CrossRef](#)] [[PubMed](#)]
89. Sullivan, R.; Smith, J.E.; Rowan, N.J. Medicinal Mushrooms and Cancer Therapy: Translating a Traditional Practice into Western Medicine. *Perspect. Biol. Med.* **2006**, *49*, 159–170. [[CrossRef](#)] [[PubMed](#)]
90. Yeung, K.; Gubili, J. Shiitake Mushroom (*Lentinula edodes*). *J. Soc. Integr. Oncol.* **2008**, *6*, 134–135.
91. Zhang, Y.; Kong, H.; Fang, Y.; Nishinari, K.; Phillips, G.O. Schizophyllan: A Review on Its Structure, Properties, Bioactivities and Recent Developments. *Bioact. Carbohydr. Diet. Fibre* **2013**, *1*, 53–71. [[CrossRef](#)]
92. Kumari, M.; Survase, S.A.; Singhal, R.S. Production of Schizophyllan Using *Schizophyllum Commune* NRCM. *Bioresour. Technol.* **2008**, *99*, 1036–1043. [[CrossRef](#)]
93. Giavasis, I. Bioactive Fungal Polysaccharides as Potential Functional Ingredients in Food and Nutraceuticals. *Curr. Opin. Biotechnol.* **2014**, *26*, 162–173. [[CrossRef](#)]
94. Bao, X.-F.; Wang, X.-S.; Dong, Q.; Fang, J.-N.; Li, X.-Y. Structural Features of Immunologically Active Polysaccharides from *Ganoderma Lucidum*. *Phytochemistry* **2002**, *59*, 175–181. [[CrossRef](#)]
95. Eo, S.-K.; Kim, Y.-S.; Lee, C.-K.; Han, S.-S. Possible Mode of Antiviral Activity of Acidic Protein Bound Polysaccharide Isolated from *Ganoderma lucidum* on Herpes Simplex Viruses. *J. Ethnopharmacol.* **2000**, *72*, 475–481. [[CrossRef](#)]
96. Wasser, S.P. Medicinal Mushrooms as a Source of Antitumor and Immunomodulating Polysaccharides. *Appl. Microbiol. Biotechnol.* **2002**, *60*, 258–274. [[CrossRef](#)] [[PubMed](#)]
97. Bergendiová, K.; Tibenska, E.; Majtan, J. Pleuran (β -Glucan from *Pleurotus Ostreatus*) Supplementation, Cellular Immune Response and Respiratory Tract Infections in Athletes. *Eur. J. Appl. Physiol.* **2011**, *111*, 2033–2040. [[CrossRef](#)] [[PubMed](#)]

98. Synytsya, A.; Míčková, K.; Synytsya, A.; Jablonský, I.; Spěváček, J.; Erban, V.; Kovářiková, E.; Čopíková, J. Glucans from Fruit Bodies of Cultivated Mushrooms *Pleurotus Ostreatus* and *Pleurotus Eryngii*: Structure and Potential Prebiotic Activity. *Carbohydr. Polym.* **2009**, *76*, 548–556. [[CrossRef](#)]
99. Boh, B.; Berovic, M. *Grifola Frondosa* (Dicks.: Fr.) S.F. Gray (Maitake Mushroom): Medicinal Properties, Active Compounds, and Biotechnological Cultivation. *Int. J. Med. Mushrooms* **2007**, *9*, 89–108. [[CrossRef](#)]
100. Ye, L.; Li, J.; Zhang, J.; Pan, Y. NMR Characterization for Polysaccharide Moiety of a Glycopeptide. *Fitoterapia* **2010**, *81*, 93–96. [[CrossRef](#)] [[PubMed](#)]
101. Biliaderis, C.G.; Izydorczyk, M.S. (Eds.) *Functional Food Carbohydrates*; Functional foods and nutraceuticals series; CRC Press: Boca Raton, FL, USA, 2007; ISBN 978-0-8493-1822-1.
102. Mizuno, T. Medicinal Properties and Clinical Effects of Culinary-Medicinal Mushroom *Agaricus Blazei* Murrill (Agaricomycetidae) (Review). *Int. J. Med. Mushrooms* **2002**, *4*, 14. [[CrossRef](#)]
103. Hobbs, C. Medicinal Value of Turkey Tail Fungus *Trametes Versicolor* (L.:Fr.) Pilat (Aphyllophoromycetidae). A Literature Review. *Int. J. Med. Mushrooms* **2004**, *6*, 195–218. [[CrossRef](#)]
104. Ooi, V.E.; Liu, F. Immunomodulation and Anti-Cancer Activity of Polysaccharide-Protein Complexes. *Curr. Med. Chem.* **2000**, *7*, 715–729. [[CrossRef](#)]
105. De Baets, S.; Vandamme, E.J. Extracellular Tremella Polysaccharides: Structure, properties and applications. *Biotechnol. Lett.* **2001**, *23*, 1361–1366. [[CrossRef](#)]
106. Khondkar, P. Composition and Partial Structure Characterization of Tremella Polysaccharides. *Mycobiology* **2009**, *37*, 286–294. [[CrossRef](#)]
107. Lo, H.-C.; Tsai, F.-A.; Wasser, S.P.; Yang, J.-G.; Huang, B.-M. Effects of Ingested Fruiting Bodies, Submerged Culture Biomass, and Acidic Polysaccharide Glucuronoxylomannan of Tremella Mesenterica Retz.:Fr. on Glycemic Responses in Normal and Diabetic Rats. *Life Sci.* **2006**, *78*, 1957–1966. [[CrossRef](#)]
108. Yang, S.; Zhang, H. Production of Intracellular Selenium-Enriched Polysaccharides from Thin Stillage by Cordyceps Sinensis and Its Bioactivities. *Food Nutr. Res.* **2016**, *60*, 30153. [[CrossRef](#)]
109. Li, T.; Peng, T. Traditional Chinese Herbal Medicine as a Source of Molecules with Antiviral Activity. *Antiviral Res.* **2013**, *97*, 1–9. [[CrossRef](#)] [[PubMed](#)]
110. Schepetkin, I.A.; Quinn, M.T. Botanical Polysaccharides: Macrophage Immunomodulation and Therapeutic Potential. *Int. Immunopharmacol.* **2006**, *6*, 317–333. [[CrossRef](#)] [[PubMed](#)]
111. Jin, L.-Q.; Zheng, Z.-J.; Peng, Y.; Li, W.-X.; Chen, X.-M.; Lu, J.-X. Opposite Effects on Tumor Growth Depending on Dose of *Achyranthes Bidentata* Polysaccharides in C57BL/6 Mice. *Int. Immunopharmacol.* **2007**, *7*, 568–577. [[CrossRef](#)] [[PubMed](#)]
112. Sun, L.; Wu, D.; Ning, X.; Yang, G.; Lin, Z.; Tian, M.; Zhou, Y. α -Amylase-Assisted Extraction of Polysaccharides from Panax Ginseng. *Int. J. Biol. Macromol.* **2015**, *75*, 152–157. [[CrossRef](#)] [[PubMed](#)]
113. Li, C.; Cai, J.; Geng, J.; Li, Y.; Wang, Z.; Li, R. Purification, Characterization and Anticancer Activity of a Polysaccharide from Panax Ginseng. *Int. J. Biol. Macromol.* **2012**, *51*, 968–973. [[CrossRef](#)]
114. Cheng, H.; Li, S.; Fan, Y.; Gao, X.; Hao, M.; Wang, J.; Zhang, X.; Tai, G.; Zhou, Y. Comparative Studies of the Antiproliferative Effects of Ginseng Polysaccharides on HT-29 Human Colon Cancer Cells. *Med. Oncol.* **2011**, *28*, 175–181. [[CrossRef](#)]
115. Tomoda, M.; Shimada, K.; Konno, C.; Sugiyama, K.; Hikino, H. Partial Structure of Panaxan A, a Hypoglycaemic Glycan of *Panax ginseng* Roots. *Planta Med.* **1984**, *50*, 436–438. [[CrossRef](#)]
116. Sun, L.; Peng, X.; Sun, P.; Shi, J.; Yuan, X.; Zhu, J.; Tai, G.; Zhou, Y. Structural Characterization and Immunostimulatory Activity of a Novel Linear α -(1 \rightarrow 6)-D-Glucan Isolated from Panax Ginseng C. A. Meyer. *Glycoconj. J.* **2012**, *29*, 357–364. [[CrossRef](#)] [[PubMed](#)]
117. Bergeron, C.; Gafner, S. Quantitative Analysis of the Polysaccharide and Glycoprotein Fractions in *Echinacea purpurea*. and *Echinacea angustifolia*. by HPLC-ELSD for Quality Control of Raw Material. *Pharm. Biol.* **2007**, *45*, 98–105. [[CrossRef](#)]
118. Jain, V.K. Chapter 1. An Overview of Organoselenium Chemistry: From Fundamentals to Synthesis. In *Organoselenium Compounds in Biology and Medicine*; Jain, V.K., Priyadarsini, K.I., Eds.; Royal Society of Chemistry: Cambridge, UK, 2017; pp. 1–33, ISBN 978-1-78801-029-0.
119. Soriano-Garcia, M. Organoselenium Compounds as Potential Therapeutic and Chemopreventive Agents: A Review. *Curr. Med. Chem.* **2004**, *11*, 1657–1669. [[CrossRef](#)]
120. Takahashi, K.; Suzuki, N.; Ogra, Y. Bioavailability Comparison of Nine Bioselenocompounds In Vitro and In Vivo. *Int. J. Mol. Sci.* **2017**, *18*, 506. [[CrossRef](#)] [[PubMed](#)]
121. Schrauzer, G.N.; Surai, P.F. Selenium in Human and Animal Nutrition: Resolved and Unresolved Issues. A Partly Historical Treatise in Commemoration of the Fiftieth Anniversary of the Discovery of the Biological Essentiality of Selenium, Dedicated to the Memory of Klaus Schwarz (1914–1978) on the Occasion of the Thirtieth Anniversary of His Death. *Crit. Rev. Biotechnol.* **2009**, *29*, 2–9. [[CrossRef](#)] [[PubMed](#)]
122. Rayman, M.P. The Importance of Selenium to Human Health. *Lancet* **2000**, *356*, 233–241. [[CrossRef](#)]
123. O'Dell, B.L. (Ed.) *Handbook of Nutritionally Essential Mineral Elements*; Clinical Nutrition in Health and Disease; Dekker: New York, NY, USA, 1997; ISBN 978-0-8247-9312-8.
124. Roussel, A.-M.; Anderson, R.A.; Favier, A. International Symposium on Trace Elements in Man and Animals. In *Trace Elements in Man and Animals 10*; Kluwer Academic Publishers: New York, NY, USA, 2006; ISBN 978-0-306-47466-8.

125. Schomburg, L.; Köhrle, J. On the Importance of Selenium and Iodine Metabolism for Thyroid Hormone Biosynthesis and Human Health. *Mol. Nutr. Food Res.* **2008**, *52*, 1235–1246. [[CrossRef](#)] [[PubMed](#)]
126. Zoidis, E.; Seremelis, I.; Kontopoulos, N.; Danezis, G.P. Selenium-Dependent Antioxidant Enzymes: Actions and Properties of Selenoproteins. *Antioxidants* **2018**, *7*, 66. [[CrossRef](#)]
127. Speckmann, B.; Grune, T. Epigenetic Effects of Selenium and Their Implications for Health. *Epigenetics* **2015**, *10*, 179–190. [[CrossRef](#)] [[PubMed](#)]
128. Broome, C.S.; McArdle, F.; Kyle, J.A.M.; Andrews, F.; Lowe, N.M.; Hart, C.A.; Arthur, J.R.; Jackson, M.J. An Increase in Selenium Intake Improves Immune Function and Poliovirus Handling in Adults with Marginal Selenium Status. *Am. J. Clin. Nutr.* **2004**, *80*, 154–162. [[CrossRef](#)]
129. Kiremidjian-Schumacher, L.; Roy, M.; Wishe, H.I.; Cohen, M.W.; Stotzky, G. Supplementation with Selenium and Human Immune Cell Functions. II. Effect on Cytotoxic Lymphocytes and Natural Killer Cells. *Biol. Trace Elem. Res.* **1994**, *41*, 115–127. [[CrossRef](#)]
130. Hoffmann, P.R. Mechanisms by Which Selenium Influences Immune Responses. *Arch. Immunol. Ther. Exp.* **2007**, *55*, 289–297. [[CrossRef](#)] [[PubMed](#)]
131. Avery, J.C.; Hoffmann, P.R. Selenium, Selenoproteins, and Immunity. *Nutrients* **2018**, *10*, 1203. [[CrossRef](#)]
132. Huang, Z.; Rose, A.H.; Hoffmann, P.R. The Role of Selenium in Inflammation and Immunity: From Molecular Mechanisms to Therapeutic Opportunities. *Antioxid. Redox Signal.* **2012**, *16*, 705–743. [[CrossRef](#)]
133. Vinceti, M.; Filippini, T.; Del Giovane, C.; Dennert, G.; Zwahlen, M.; Brinkman, M.; Zeegers, M.P.; Horneber, M.; D’Amico, R.; Crespi, C.M. Selenium for Preventing Cancer. *Cochrane Database Syst. Rev.* **2018**, *1*, CD005195. [[CrossRef](#)] [[PubMed](#)]
134. Evans, S.O.; Khairuddin, P.F.; Jameson, M.B. Optimising Selenium for Modulation of Cancer Treatments. *Anticancer Res.* **2017**, *37*, 6497–6509. [[CrossRef](#)] [[PubMed](#)]
135. Beck, M.A. Selenium and Host Defence towards Viruses. *Proc. Nutr. Soc.* **1999**, *58*, 707–711. [[CrossRef](#)] [[PubMed](#)]
136. Guillin, O.M.; Vindry, C.; Ohlmann, T.; Chavatte, L. Selenium, Selenoproteins and Viral Infection. *Nutrients* **2019**, *11*, 2101. [[CrossRef](#)]
137. Steinbrenner, H.; Al-Quraishy, S.; Dkhil, M.A.; Wunderlich, F.; Sies, H. Dietary Selenium in Adjuvant Therapy of Viral and Bacterial Infections. *Adv. Nutr.* **2015**, *6*, 73–82. [[CrossRef](#)] [[PubMed](#)]
138. Harthill, M. Review: Micronutrient Selenium Deficiency Influences Evolution of Some Viral Infectious Diseases. *Biol. Trace Elem. Res.* **2011**, *143*, 1325–1336. [[CrossRef](#)] [[PubMed](#)]
139. Louria, D.B. Undernutrition Can Affect the Invading Microorganism. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2007**, *45*, 470–474. [[CrossRef](#)] [[PubMed](#)]
140. Parr, R.M. *Trace Elements in Human Nutrition and Health*; Weltgesundheitsorganisation, FAO, Internationale Atomenergie-Organisation, Eds.; FAO: Geneva, Switzerland, 1996; ISBN 978-92-4-156173-0.
141. Micronutrients for Older Adults. 2014. Available online: <https://Lpi.Oregonstate.Edu/Mic/Life-Stages/Older-Adults> (accessed on 1 January 2021).
142. Goldhaber, S.B. Trace Element Risk Assessment: Essentiality vs. Toxicity. *Regul. Toxicol. Pharmacol. RTP* **2003**, *38*, 232–242. [[CrossRef](#)]
143. Pedrero, Z.; Madrid, Y. Novel Approaches for Selenium Speciation in Foodstuffs and Biological Specimens: A Review. *Anal. Chim. Acta* **2009**, *634*, 135–152. [[CrossRef](#)]
144. Institute of Medicine (U.S.) (Ed.) *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids: A Report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine*; National Academy Press: Washington, DC, USA, 2000; ISBN 978-0-309-06949-6.
145. Amoako, P.O.; Uden, P.C.; Tyson, J.F. Speciation of Selenium Dietary Supplements; Formation of S-(Methylseleno)Cysteine and Other Selenium Compounds. *Anal. Chim. Acta* **2009**, *652*, 315–323. [[CrossRef](#)]
146. Meltzer, H.M.; Norheim, G.; Bibow, K.; Myhre, K.; Holm, H. The Form of Selenium Determines the Response to Supplementation in a Selenium Replete Population. *Eur. J. Clin. Nutr.* **1990**, *44*, 435–446. [[PubMed](#)]
147. Thiry, C.; Ruttens, A.; Temmerman, L.; Schneider, Y.-J.; Pussemier, L. Current knowledge in species-related bioavailability of selenium in food. *Food Chem.* **2012**, *130*, 767–784. [[CrossRef](#)]
148. SES-Clinical: Selenium, Serum. Available online: mayocliniclabs.com (accessed on 1 January 2021).
149. Rayman, M.P.; Stranges, S. Epidemiology of Selenium and Type 2 Diabetes: Can We Make Sense of It? *Free Radic. Biol. Med.* **2013**, *65*, 1557–1564. [[CrossRef](#)]
150. Bleys, J.; Navas-Acien, A.; Stranges, S.; Menke, A.; Miller, E.R.; Guallar, E. Serum Selenium and Serum Lipids in US Adults. *Am. J. Clin. Nutr.* **2008**, *88*, 416–423. [[CrossRef](#)]
151. Duffield-Lillico, A.J.; Reid, M.E.; Turnbull, B.W.; Combs, G.F.; Slate, E.H.; Fischbach, L.A.; Marshall, J.R.; Clark, L.C. Baseline Characteristics and the Effect of Selenium Supplementation on Cancer Incidence in a Randomized Clinical Trial: A Summary Report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.* **2002**, *11*, 630–639.
152. Johnson, C.C.; Fordyce, F.M.; Rayman, M.P. Symposium on “Geographical and Geological Influences on Nutrition”: Factors Controlling the Distribution of Selenium in the Environment and Their Impact on Health and Nutrition. *Proc. Nutr. Soc.* **2010**, *69*, 119–132. [[CrossRef](#)]

153. Xiong, Y.M.; Mo, X.Y.; Zou, X.Z.; Song, R.X.; Sun, W.Y.; Lu, W.; Chen, Q.; Yu, Y.X.; Zang, W.J. Association Study between Polymorphisms in Selenoprotein Genes and Susceptibility to Kashin-Beck Disease. *Osteoarthritis Cartilage* **2010**, *18*, 817–824. [[CrossRef](#)]
154. Beck, M.A.; Handy, J.; Levander, O.A. Host Nutritional Status: The Neglected Virulence Factor. *Trends Microbiol.* **2004**, *12*, 417–423. [[CrossRef](#)] [[PubMed](#)]
155. Wu, Q.; Rayman, M.P.; Lv, H.; Schomburg, L.; Cui, B.; Gao, C.; Chen, P.; Zhuang, G.; Zhang, Z.; Peng, X.; et al. Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 4037–4047. [[CrossRef](#)] [[PubMed](#)]
156. Akbaraly, T.N.; Akbaraly, N.T.; Hingler-Favier, I.; Carrière, I.; Arnaud, J.; Gourlet, V.; Roussel, A.-M.; Berr, C. Plasma Selenium over Time and Cognitive Decline in the Elderly. *Epidemiol. Camb. Mass* **2007**, *18*, 52–58. [[CrossRef](#)] [[PubMed](#)]
157. Hughes, D.J.; Fedirko, V.; Jenab, M.; Schomburg, L.; Méplan, C.; Freisling, H.; Bueno-de-Mesquita, H.B.a.; Hybsier, S.; Becker, N.-P.; Czuban, M.; et al. Selenium Status Is Associated with Colorectal Cancer Risk in the European Prospective Investigation of Cancer and Nutrition Cohort. *Int. J. Cancer* **2015**, *136*, 1149–1161. [[CrossRef](#)]
158. Morris, J.S.; Crane, S.B. Selenium Toxicity from a Misformulated Dietary Supplement, Adverse Health Effects, and the Temporal Response in the Nail Biologic Monitor. *Nutrients* **2013**, *5*, 1024–1057. [[CrossRef](#)]
159. MacFarquhar, J.K.; Broussard, D.L.; Melstrom, P.; Hutchinson, R.; Wolkin, A.; Martin, C.; Burk, R.F.; Dunn, J.R.; Green, A.L.; Hammond, R.; et al. Acute Selenium Toxicity Associated with a Dietary Supplement. *Arch. Intern. Med.* **2010**, *170*, 256–261. [[CrossRef](#)]
160. Klayman, D.L.; Günther, W.H.H. *Organic Selenium Compounds: Their Chemistry and Biology*; The Chemistry of Organometallic Compounds; Wiley-Interscience: New York, NY, USA, 1973; ISBN 978-0-471-49032-6.
161. Lenardão, E.J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*; Springer International Publishing: Cham, Switzerland, 2018; ISBN 978-3-319-92404-5.
162. Hansen, D.; Duda, P.J.; Zayed, A.; Terry, N. Selenium Removal by Constructed Wetlands: Role of Biological Volatilization. *Environ. Sci. Technol.* **1998**, *32*, 591–597. [[CrossRef](#)]
163. Frankenberger, W.T., Jr. *Selenium in the Environment*; CRC Press: Boca Raton, FL, USA, 1994; ISBN 978-0-824-478993-0.
164. Shanker, A.K. Countering UV-B Stress in Plants: Does Selenium Have a Role? *Plant Soil* **2006**, *282*, 21–26. [[CrossRef](#)]
165. White, P.J. Selenium Accumulation by Plants. *Ann. Bot.* **2016**, *117*, 217–235. [[CrossRef](#)]
166. Mattmiller, S.A.; Carlson, B.A.; Sordillo, L.M. Regulation of Inflammation by Selenium and Selenoproteins: Impact on Eicosanoid Biosynthesis. *J. Nutr. Sci.* **2013**, *2*, e28. [[CrossRef](#)]
167. Ogra, Y.; Ishiwata, K.; Takayama, H.; Aimi, N.; Suzuki, K.T. Identification of a Novel Selenium Metabolite, Se-Methyl-N-Acetylselenohexosamine, in Rat Urine by High-Performance Liquid Chromatography–Inductively Coupled Plasma Mass Spectrometry and–Electrospray Ionization Tandem Mass Spectrometry. *J. Chromatogr. B Analyt. Technol. Biomed. Life. Sci.* **2002**, *767*, 301–312. [[CrossRef](#)]
168. Kobayashi, Y.; Ogra, Y.; Ishiwata, K.; Takayama, H.; Aimi, N.; Suzuki, K.T. Selenosugars Are Key and Urinary Metabolites for Selenium Excretion within the Required to Low-Toxic Range. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15932–15936. [[CrossRef](#)] [[PubMed](#)]
169. Kuehnelt, D.; Kienzl, N.; Traar, P.; Le, N.H.; Francesconi, K.A.; Ochi, T. Selenium Metabolites in Human Urine after Ingestion of Selenite, L-Selenomethionine, or DL-Selenomethionine: A Quantitative Case Study by HPLC/ICPMS. *Anal. Bioanal. Chem.* **2005**, *383*, 235–246. [[CrossRef](#)] [[PubMed](#)]
170. Wang, Y.; Li, Y.; Liu, Y.; Chen, X.; Wei, X. Extraction, Characterization and Antioxidant Activities of Se-Enriched Tea Polysaccharides. *Int. J. Biol. Macromol.* **2015**, *77*, 76–84. [[CrossRef](#)] [[PubMed](#)]
171. Turlo, J.; Gutkowska, B.; Herold, F.; Dawidowski, M.; Slowiński, T.; Zobel, A. Relationship between Selenium Accumulation and Mycelial Cell Composition in *Lentinula Edodes* (Berk.) Cultures. *J. Toxicol. Environ. Health A* **2010**, *73*, 1211–1219. [[CrossRef](#)] [[PubMed](#)]
172. Abel, E.W.; Stone, F.G.A.; Wilkinson, G. *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Pergamon: Oxford, UK; New York, NY, USA, 1995; ISBN 978-0-08-040608-4.
173. Iwaoka, M. Nucleophilic Selenium. In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; pp. 53–109, ISBN 978-3-527-64194-9.
174. Back, T.G. Selenium: Organoselenium Chemistry. In *Encyclopedia of Inorganic Chemistry*; King, R.B., Crabtree, R.H., Lukehart, C.M., Atwood, D.A., Scott, R.A., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 2006; p. ia214, ISBN 978-0-470-86078-6.
175. Bhasin, K.K.; Arora, E.; Mehta, S.K.; Klapoetke, T.M. Preparation and Characterization of Symmetrical Bis[4-Chloro-2-Pyrimidyl] Dichalcogenide (S, Se, Te) and Unsymmetrical 4-Chloro-2-(Arylchalcogenyl) Pyrimidine: X-Ray Crystal Structure of 4-Chloro-2-(Phenylselanyl) Pyrimidine and 2-(p-Tolylselanyl)-4-Chloropyrimidine. *J. Organomet. Chem.* **2011**, *696*, 835–840. [[CrossRef](#)]
176. Hodage, A.S.; Phadnis, P.P.; Wadawale, A.; Priyadarsini, K.I.; Jain, V.K. Synthesis, Characterization and Structures of 2-(3,5-Dimethylpyrazol-1-Yl)Ethylseleno Derivatives and Their Probable Glutathione Peroxidase (GPx) like Activity. *Org. Biomol. Chem.* **2011**, *9*, 2992–2998. [[CrossRef](#)]
177. Zade, S.S.; Singh, H.B. Synthesis of Organoselenium Compounds. In *PATAI'S Chemistry of Functional Groups*; Rappoport, Z., Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2012; p. pat0706, ISBN 978-0-470-68253-1.
178. Panda, A. Chemistry of Selena Macrocycles. *Coord. Chem. Rev.* **2009**, *253*, 1056–1098. [[CrossRef](#)]

179. Milton, M.D.; Khan, S.; Singh, J.D.; Mishra, V.; Khandelwal, B.L. A Facile Access to Chalcogen and Dichalcogen Bearing Dialkylamines and Diols. *Tetrahedron Lett.* **2005**, *46*, 755–758. [[CrossRef](#)]
180. Krafft, F.; Vorster, W. Ueber Umwandlung des Diphenylsulfons in Diphenylsulfid und Diphenylselenid. *Berichte Dtsch. Chem. Ges.* **1893**, *26*, 2813–2822. [[CrossRef](#)]
181. Ariyoshi, K.; Aso, Y.; Otsubo, T.; Ogura, F. Application of bis(*p*-methoxyphenyl)selenoxide as an oxidizing agent of kornblum oxidation. *Chem. Lett.* **1984**, *13*, 891–892. [[CrossRef](#)]
182. Kelly, A.M.; Rosini, G.P.; Goldman, A.S. Oxygen Transfer from Organoelement Oxides to Carbon Monoxide Catalyzed by Transition Metal Carbonyls. *J. Am. Chem. Soc.* **1997**, *119*, 6115–6125. [[CrossRef](#)]
183. Wessjohann, L.A.; Schneider, A.; Abbas, M.; Brandt, W. Selenium in Chemistry and Biochemistry in Comparison to Sulfur. *Biol. Chem.* **2007**, *388*, 997–1006. [[CrossRef](#)] [[PubMed](#)]
184. Kumar, S.; Helt, J.-C.P.; Autschbach, J.; Detty, M.R. A New Reaction for Organoselenium Compounds: Alkyl Transfer from Diorganoselenium(IV) Dibromides to Alkenoic Acids To Give γ - and δ -Lactones. *Organometallics* **2009**, *28*, 3426–3436. [[CrossRef](#)]
185. Reich, H.J.; Jasperse, C.P. Organoselenium Chemistry. Preparation and Reactions of 2,4,6-Tri-Tert-Butylbenzeneselenenic Acid. *J. Org. Chem.* **1988**, *53*, 2389–2390. [[CrossRef](#)]
186. Tanaka, T.; Kohno, H.; Murakami, M.; Kagami, S.; El-Bayoumy, K. Suppressing Effects of Dietary Supplementation of the Organoselenium 1,4-Phenylenebis(Methylene)Selenocyanate and the Citrus Antioxidant Auraptene on Lung Metastasis of Melanoma Cells in Mice. *Cancer Res.* **2000**, *60*, 3713–3716. [[PubMed](#)]
187. Rao, C.V.; Cooma, I.; Rodriguez, J.G.; Simi, B.; El-Bayoumy, K.; Reddy, B.S. Chemoprevention of Familial Adenomatous Polyposis Development in the APC(Min) Mouse Model by 1,4-Phenylene Bis(Methylene)Selenocyanate. *Carcinogenesis* **2000**, *21*, 617–621. [[CrossRef](#)] [[PubMed](#)]
188. Rao, C.V.; Wang, C.Q.; Simi, B.; Rodriguez, J.G.; Cooma, I.; El-Bayoumy, K.; Reddy, B.S. Chemoprevention of Colon Cancer by a Glutathione Conjugate of 1,4-Phenylenebis(Methylene)Selenocyanate, a Novel Organoselenium Compound with Low Toxicity. *Cancer Res.* **2001**, *61*, 3647–3652.
189. Koketsu, M.; Yang, H.O.; Kim, Y.M.; Ichihashi, M.; Ishihara, H. Preparation of 1,4-Oxaselenin from AgNO₃/LDA-Assisted Reaction of 3-Selena-4-Pentyn-1-One as Potential Antitumor Agents. *Org. Lett.* **2001**, *3*, 1705–1707. [[CrossRef](#)] [[PubMed](#)]
190. Lu, J.; Jiang, C.; Kaeck, M.; Ganther, H.; Ip, C.; Thompson, H. Cellular and Metabolic Effects of Triphenylselenonium Chloride in a Mammary Cell Culture Model. *Carcinogenesis* **1995**, *16*, 513–517. [[CrossRef](#)] [[PubMed](#)]
191. Da Cruz, E.H.G.; Silvers, M.A.; Jardim, G.A.M.; Resende, J.M.; Cavalcanti, B.C.; Bomfim, I.S.; Pessoa, C.; de Simone, C.A.; Botteselle, G.V.; Braga, A.L.; et al. Synthesis and Antitumor Activity of Selenium-Containing Quinone-Based Triazoles Possessing Two Redox Centres, and Their Mechanistic Insights. *Eur. J. Med. Chem.* **2016**, *122*, 1–16. [[CrossRef](#)]
192. Hatfield, D.L. (Ed.) *Selenium: Its Molecular Biology and Role in Human Health*, 2nd ed.; Springer: New York, NY, USA, 2006; ISBN 978-0-387-33826-2.
193. Roussyn, I.; Briviba, K.; Masumoto, H.; Sies, H. Selenium-Containing Compounds Protect DNA from Single-Strand Breaks Caused by Peroxynitrite. *Arch. Biochem. Biophys.* **1996**, *330*, 216–218. [[CrossRef](#)] [[PubMed](#)]
194. Beckman, J.S.; Beckman, T.W.; Chen, J.; Marshall, P.A.; Freeman, B.A. Apparent Hydroxyl Radical Production by Peroxynitrite: Implications for Endothelial Injury from Nitric Oxide and Superoxide. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 1620–1624. [[CrossRef](#)] [[PubMed](#)]
195. Chan, S.; Gerson, B.; Subramaniam, S. The Role of Copper, Molybdenum, Selenium, and Zinc in Nutrition and Health. *Clin. Lab. Med.* **1998**, *18*, 673–685. [[CrossRef](#)]
196. Alpegiani, M.; Bedeschi, A.; Perrone, E.; Franceschi, G. 2-Selenacephems and 1-Dethia-1-Selenapenems. *Tetrahedron Lett.* **1986**, *27*, 3041–3044. [[CrossRef](#)]
197. Stadtman, T.C. Selenocysteine. *Annu. Rev. Biochem.* **1996**, *65*, 83–100. [[CrossRef](#)]
198. Nozawa, R.; Yokota, T.; Fujimoto, T. Susceptibility of Methicillin-Resistant Staphylococcus Aureus to the Selenium-Containing Compound 2-Phenyl-1,2-Benzoisoselenazol-3(2H)-One (PZ51). *Antimicrob. Agents Chemother.* **1989**, *33*, 1388–1390. [[CrossRef](#)] [[PubMed](#)]
199. Lu, J.; Vlamis-Gardikas, A.; Kandasamy, K.; Zhao, R.; Gustafsson, T.N.; Engstrand, L.; Hoffner, S.; Engman, L.; Holmgren, A. Inhibition of Bacterial Thioredoxin Reductase: An Antibiotic Mechanism Targeting Bacteria Lacking Glutathione. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2013**, *27*, 1394–1403. [[CrossRef](#)]
200. Braga, H.C.; Stefani, H.A.; Paixão, M.W.; Santos, F.W.; Lüdtkke, D.S. Synthesis of 5'-Seleno-Xylofuranosides. *Tetrahedron* **2010**, *66*, 3441–3446. [[CrossRef](#)]
201. Shakibaie, M.; Forootanfar, H.; Golkari, Y.; Mohammadi-Khorsand, T.; Shakibaie, M.R. Anti-Biofilm Activity of Biogenic Selenium Nanoparticles and Selenium Dioxide against Clinical Isolates of Staphylococcus Aureus, Pseudomonas Aeruginosa, and Proteus Mirabilis. *J. Trace Elem. Med. Biol.* **2015**, *29*, 235–241. [[CrossRef](#)]
202. Alberto, E.E.; Rossato, L.L.; Alves, S.H.; Alves, D.; Braga, A.L. Imidazolium Ionic Liquids Containing Selenium: Synthesis and Antimicrobial Activity. *Org. Biomol. Chem.* **2011**, *9*, 1001–1003. [[CrossRef](#)] [[PubMed](#)]
203. Cohen, J. AIDS Trials Ethics Questioned. *Science* **1997**, *276*, 520–523. [[CrossRef](#)]
204. Du, J.; Surzhykov, S.; Lin, J.S.; Newton, M.G.; Cheng, Y.C.; Schinazi, R.F.; Chu, C.K. Synthesis, Anti-Human Immunodeficiency Virus and Anti-Hepatitis B Virus Activities of Novel Oxaselenolane Nucleosides. *J. Med. Chem.* **1997**, *40*, 2991–2993. [[CrossRef](#)] [[PubMed](#)]

205. Chu, C.K.; Ma, L.; Olgen, S.; Pierra, C.; Du, J.; Gumina, G.; Gullen, E.; Cheng, Y.C.; Schinazi, R.F. Synthesis and Antiviral Activity of Oxaselenolane Nucleosides. *J. Med. Chem.* **2000**, *43*, 3906–3912. [[CrossRef](#)] [[PubMed](#)]
206. Sahu, P.K.; Kim, G.; Yu, J.; Ahn, J.Y.; Song, J.; Choi, Y.; Jin, X.; Kim, J.-H.; Lee, S.K.; Park, S.; et al. Stereoselective Synthesis of 4'-Selenonucleosides via Seleno-Michael Reaction as Potent Antiviral Agents. *Org. Lett.* **2014**, *16*, 5796–5799. [[CrossRef](#)]
207. Sartori, G.; Jardim, N.S.; Marcondes Sari, M.H.; Dobrachinski, F.; Pesarico, A.P.; Rodrigues, L.C.; Cargnelutti, J.; Flores, E.F.; Prigol, M.; Nogueira, C.W. Antiviral Action of Diphenyl Diselenide on Herpes Simplex Virus 2 Infection in Female BALB/c Mice. *J. Cell. Biochem.* **2016**, *117*, 1638–1648. [[CrossRef](#)]
208. Sahu, P.K.; Umme, T.; Yu, J.; Nayak, A.; Kim, G.; Noh, M.; Lee, J.-Y.; Kim, D.-D.; Jeong, L.S. Selenoacyclovir and Selenoganciclovir: Discovery of a New Template for Antiviral Agents. *J. Med. Chem.* **2015**, *58*, 8734–8738. [[CrossRef](#)] [[PubMed](#)]
209. Wang, J.; Wang, H.-Y.; Xia, X.-M.; Li, P.; Wang, K.-Y. Inhibitory Effect of Sulfated Lentinan and Lentinan against Tobacco Mosaic Virus (TMV) in Tobacco Seedlings. *Int. J. Biol. Macromol.* **2013**, *61*, 264–269. [[CrossRef](#)]
210. Mughesh, G.; du Mont, W.W.; Sies, H. Chemistry of Biologically Important Synthetic Organoselenium Compounds. *Chem. Rev.* **2001**, *101*, 2125–2179. [[CrossRef](#)]
211. Duntas, L.H.; Benvenga, S. Selenium: An Element for Life. *Endocrine* **2015**, *48*, 756–775. [[CrossRef](#)]
212. Jablonska, E.; Vinceti, M. Selenium and Human Health: Witnessing a Copernican Revolution? *J. Environ. Sci. Health Part C Environ. Carcinog. Ecotoxicol. Rev.* **2015**, *33*, 328–368. [[CrossRef](#)] [[PubMed](#)]
213. Labunskyy, V.M.; Hatfield, D.L.; Gladyshev, V.N. Selenoproteins: Molecular Pathways and Physiological Roles. *Physiol. Rev.* **2014**, *94*, 739–777. [[CrossRef](#)] [[PubMed](#)]
214. Constantinescu-Aruxandei, D.; Frîncu, R.M.; Capră, L.; Oancea, F. Selenium Analysis and Speciation in Dietary Supplements Based on Next-Generation Selenium Ingredients. *Nutrients* **2018**, *10*, 1466. [[CrossRef](#)] [[PubMed](#)]
215. Rocourt, C.R.B.; Cheng, W.-H. Selenium Supranutrition: Are the Potential Benefits of Chemoprevention Outweighed by the Promotion of Diabetes and Insulin Resistance? *Nutrients* **2013**, *5*, 1349–1365. [[CrossRef](#)] [[PubMed](#)]
216. Fernandes, J.; Hu, X.; Ryan Smith, M.; Go, Y.-M.; Jones, D.P. Selenium at the Redox Interface of the Genome, Metabolome and Exposome. *Free Radic. Biol. Med.* **2018**, *127*, 215–227. [[CrossRef](#)]
217. Kubachka, K.M.; Hanley, T.; Mantha, M.; Wilson, R.A.; Falconer, T.M.; Kassa, Z.; Oliveira, A.; Landero, J.; Caruso, J. Evaluation of Selenium in Dietary Supplements Using Elemental Speciation. *Food Chem.* **2017**, *218*, 313–320. [[CrossRef](#)]
218. Gosetti, F.; Frascarolo, P.; Polati, S.; Medana, C.; Gianotti, V.; Palma, P.; Aigotti, R.; Baiocchi, C.; Gennaro, M.C. Speciation of Selenium in Diet Supplements by HPLC–MS/MS Methods. *Food Chem.* **2007**, *105*, 1738–1747. [[CrossRef](#)]
219. Helzlsouer, M.S. Acute Selenium Intoxication in the United States. *Fed. Proc.* **1985**, *44*, 1670.
220. Clark, R.F.; Strukle, E.; Williams, S.R.; Manoguerra, A.S. Selenium Poisoning from a Nutritional Supplement. *JAMA* **1996**, *275*, 1087–1088. [[CrossRef](#)]
221. Skalickova, S.; Milosavljevic, V.; Cihalova, K.; Horoky, P.; Richtera, L.; Adam, V. Selenium Nanoparticles as a Nutritional Supplement. *Nutrition* **2017**, *33*, 83–90. [[CrossRef](#)]
222. Gao, Z.; Zhang, C.; Tian, C.; Ren, Z.; Song, X.; Wang, X.; Xu, N.; Jing, H.; Li, S.; Liu, W.; et al. Characterization, Antioxidation, Anti-Inflammation and Renoprotection Effects of Selenized Mycelia Polysaccharides from *Oudemansiella Radicata*. *Carbohydr. Polym.* **2018**, *181*, 1224–1234. [[CrossRef](#)] [[PubMed](#)]
223. Liu, M.; Jing, H.; Zhang, J.; Che, G.; Zhou, M.; Gao, Z.; Li, S.; Ren, Z.; Hao, L.; Liu, Y.; et al. Optimization of Mycelia Selenium Polysaccharide Extraction from *Agrocybe Cylindracea* SL-02 and Assessment of Their Antioxidant and Anti-Ageing Activities. *PLoS ONE* **2016**, *11*, e0160799. [[CrossRef](#)] [[PubMed](#)]
224. Mangiavacchi, F.; Coelho Dias, I.F.; Di Lorenzo, I.; Grzes, P.; Palomba, M.; Rosati, O.; Bagnoli, L.; Marini, F.; Santi, C.; Lenardao, E.J.; et al. Sweet Selenium: Synthesis and Properties of Selenium-Containing Sugars and Derivatives. *Pharmaceuticals* **2020**, *13*, 211. [[CrossRef](#)] [[PubMed](#)]
225. Storkey, C.; Davies, M.J.; White, J.M.; Schiesser, C.H. Synthesis and Antioxidant Capacity of 5-Selenopyranose Derivatives. *Chem. Commun. Camb. Engl.* **2011**, *47*, 9693–9695. [[CrossRef](#)] [[PubMed](#)]
226. Storkey, C.; Pattison, D.I.; White, J.M.; Schiesser, C.H.; Davies, M.J. Preventing Protein Oxidation with Sugars: Scavenging of Hypohalous Acids by 5-Selenopyranose and 4-Selenofuranose Derivatives. *Chem. Res. Toxicol.* **2012**, *25*, 2589–2599. [[CrossRef](#)] [[PubMed](#)]
227. Lucas, M.A.; Nguyen, O.T.K.; Schiesser, C.H.; Zheng, S.-L. Preparation of 5-Selenopentopyranose Sugars from Pentose Starting Materials by Samarium(II) Iodide or (Phenylseleno)Formate Mediated Ring Closures. *Tetrahedron* **2000**, *56*, 3995–4000. [[CrossRef](#)]
228. Ng, H.H.; Leo, C.H.; O'Sullivan, K.; Alexander, S.-A.; Davies, M.J.; Schiesser, C.H.; Parry, L.J. 1,4-Anhydro-4-Seleno-d-Talitol (SeTal) Protects Endothelial Function in the Mouse Aorta by Scavenging Superoxide Radicals under Conditions of Acute Oxidative Stress. *Biochem. Pharmacol.* **2017**, *128*, 34–45. [[CrossRef](#)]
229. Carroll, L.; Pattison, D.I.; Fu, S.; Schiesser, C.H.; Davies, M.J.; Hawkins, C.L. Catalytic Oxidant Scavenging by Selenium-Containing Compounds: Reduction of Selenoxides and N-Chloramines by Thiols and Redox Enzymes. *Redox Biol.* **2017**, *12*, 872–882. [[CrossRef](#)]
230. Kötzer, M.P.; Hancock, S.M.; Withers, S.G. Glycosidases: Functions, Families and Folds. In *Encyclopedia of Life Sciences (eLS)*; John Wiley & Sons, Ltd.: Chichester, UK, 2014; p. a0020548, ISBN 978-0-470-01590-2.
231. Gerber-Lemaire, S.; Juillerat-Jeanneret, L. Glycosylation Pathways as Drug Targets for Cancer: Glycosidase Inhibitors. *Mini Rev. Med. Chem.* **2006**, *6*, 1043–1052. [[CrossRef](#)]

232. Kónya, Z.; Bécsi, B.; Kiss, A.; Tamás, I.; Lontay, B.; Szilágyi, L.; Kövér, K.E.; Erdódi, F. Aralkyl Selenoglycosides and Related Selenosugars in Acetylated Form Activate Protein Phosphatase-1 and -2A. *Bioorg. Med. Chem.* **2018**, *26*, 1875–1884. [[CrossRef](#)]
233. Davies, M.J.; Schiesser, C.H. 1,4-Anhydro-4-Seleno-D-Talitol (SeTal): A Remarkable Selenium-Containing Therapeutic Molecule. *New J. Chem.* **2019**, *43*, 9759–9765. [[CrossRef](#)]
234. Jeong, L.S.; Tosh, D.K.; Choi, W.J.; Lee, S.K.; Kang, Y.-J.; Choi, S.; Lee, J.H.; Lee, H.; Lee, H.W.; Kim, H.O. Discovery of a New Template for Anticancer Agents: 2'-Deoxy-2'-Fluoro-4'-Selenoarabinofuranosyl-Cytosine (2'-F-4'-Seleno-Ara-C). *J. Med. Chem.* **2009**, *52*, 5303–5306. [[CrossRef](#)]
235. Jeong, L.S.; Choi, Y.N.; Tosh, D.K.; Choi, W.J.; Kim, H.O.; Choi, J. Design and Synthesis of Novel 2',3'-Dideoxy-4'-Selenonucleosides as Potential Antiviral Agents. *Bioorg. Med. Chem.* **2008**, *16*, 9891–9897. [[CrossRef](#)]
236. Kumar, A.A.; Illyés, T.Z.; Kövér, K.E.; Szilágyi, L. Convenient Syntheses of 1,2-Trans Selenoglycosides Using Isoselenuronium Salts as Glycosylselenenyl Transfer Reagents. *Carbohydr. Res.* **2012**, *360*, 8–18. [[CrossRef](#)] [[PubMed](#)]
237. Mehta, S.; Mario Pinto, B. Phenylselenoglycosides as Novel, Versatile Glycosyl Donors. Selective Activation over Thioglycosides. *Tetrahedron Lett.* **1991**, *32*, 4435–4438. [[CrossRef](#)]
238. Mehta, S.; Pinto, B.M. Novel Glycosidation Methodology. The Use of Phenyl Selenoglycosides as Glycosyl Donors and Acceptors in Oligosaccharide Synthesis. *J. Org. Chem.* **1993**, *58*, 3269–3276. [[CrossRef](#)]
239. Nanami, M.; Ando, H.; Kawai, Y.; Kokets, M.; Ishihara, H. Stereoselective Synthesis of Various α -Selenoglycosides Using in Situ Production of α -Selenolate Anion. *Tetrahedron Lett.* **2007**, *48*, 1113–1116. [[CrossRef](#)]
240. Braga, A.L.; Severo Filho, W.A.; Schwab, R.S.; Rodrigues, O.E.D.; Dornelles, L.; Braga, H.C.; Lüdtke, D.S. Synthesis of Selenium- and Tellurium-Containing Nucleosides Derived from Uridine. *Tetrahedron Lett.* **2009**, *50*, 3005–3007. [[CrossRef](#)]
241. Braga, H.C.; Wouters, A.D.; Zerillo, F.B.; Lüdtke, D.S. Synthesis of Seleno-Carbohydrates Derived from D-Galactose. *Carbohydr. Res.* **2010**, *345*, 2328–2333. [[CrossRef](#)]
242. Vargas, J.P.; Pinto, L.M.; Savegnago, L.; Lüdtke, D.S. Synthesis of Alkylseleno-Carbohydrates and Evaluation of Their Antioxidant Properties. *J. Braz. Chem. Soc.* **2015**. [[CrossRef](#)]
243. Yue, C.; Chen, J.; Hou, R.; Liu, J.; Li, X.; Gao, Z.; Liu, C.; Wang, D.; Lu, Y.; Li, H.; et al. Effects of Selenylation Modification on Antioxidative Activities of Schisandra Chinensis Polysaccharide. *PLoS ONE* **2015**, *10*, e0134363. [[CrossRef](#)] [[PubMed](#)]
244. Wang, J.; Zhao, B.; Wang, X.; Yao, J.; Zhang, J. Synthesis of Selenium-Containing Polysaccharides and Evaluation of Antioxidant Activity in Vitro. *Int. J. Biol. Macromol.* **2012**, *51*, 987–991. [[CrossRef](#)]
245. Wang, L.; Li, C.; Huang, Q.; Fu, X. Biofunctionalization of Selenium Nanoparticles with a Polysaccharide from Rosa Roxburghii Fruit and Their Protective Effect against H₂O₂-Induced Apoptosis in INS-1 Cells. *Food Funct.* **2019**, *10*, 539–553. [[CrossRef](#)]
246. Liu, Y.; Sun, J.; Rao, S.; Su, Y.; Li, J.; Li, C.; Xu, S.; Yang, Y. Antidiabetic Activity of Mycelia Selenium-Polysaccharide from *Catathelasma Ventricosum* in STZ-Induced Diabetic Mice. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2013**, *62*, 285–291. [[CrossRef](#)]
247. Jin, Y.; Zhang, L.; Zhang, M.; Chen, L.; Cheung, P.C.K.; Oi, V.E.C.; Lin, Y. Antitumor Activities of Heteropolysaccharides of *Poria Cocos* Mycelia from Different Strains and Culture Media. *Carbohydr. Res.* **2003**, *338*, 1517–1521. [[CrossRef](#)]
248. Gan, D.; Ma, L.; Jiang, C.; Xu, R.; Zeng, X. Production, Preliminary Characterization and Antitumor Activity in Vitro of Polysaccharides from the Mycelium of *Pholiota Dinghuensis* Bi. *Carbohydr. Polym.* **2011**, *84*, 997–1003. [[CrossRef](#)]
249. Savic, M.; Klimaszewska, M.; Bamburowicz-Klimkowska, M.; Suchocki, P.; Niksic, M.; Szutowski, M.; Wroczynski, P.; Turlo, J. A Search for the Optimum Selenium Source to Obtain Mushroom-Derived Chemopreventive Preparations. *Int. J. Med. Mushrooms* **2016**, *18*, 279–289. [[CrossRef](#)]
250. Xu, C.L.; Wang, Y.Z.; Jin, M.L.; Yang, X.Q. Preparation, Characterization and Immunomodulatory Activity of Selenium-Enriched Exopolysaccharide Produced by *Bacterium Enterobacter Cloacae* Z0206. *Bioresour. Technol.* **2009**, *100*, 2095–2097. [[CrossRef](#)]
251. Li, Z.-Y.; Guo, S.-Y.; Li, L. Bioeffects of Selenite on the Growth of *Spirulina Platensis* and Its Biotransformation. *Bioresour. Technol.* **2003**, *89*, 171–176. [[CrossRef](#)]
252. Turlo, J.; Gutkowska, B.; Herold, F. Effect of Selenium Enrichment on Antioxidant Activities and Chemical Composition of *Lentinula Edodes* (Berk.) Pegl. Mycelial Extracts. *Food Chem. Toxicol.* **2010**, *48*, 1085–1091. [[CrossRef](#)]
253. Turlo, J.; Gutkowska, B.; Herold, F.; Klimaszewska, M.; Suchocki, P. Optimization of Selenium-Enriched Mycelium of *Lentinula Edodes* (Berk.) Pegler as a Food Supplement. *Food Biotechnol.* **2010**, *24*, 180–196. [[CrossRef](#)]
254. Turlo, J.; Gutkowska, B.; Herold, F.; Gajzlerska, W.; Dawidowski, M.; Dorociak, A.; Zobel, A. Biological Availability and Preliminary Selenium Speciation in Selenium-Enriched Mycelium of *Lentinula Edodes* (Berk.). *Food Biotechnol.* **2011**, *25*, 16–29. [[CrossRef](#)]
255. Liu, J.; Chen, X.; Yue, C.; Hou, R.; Chen, J.; Lu, Y.; Li, X.; Li, R.; Liu, C.; Gao, Z.; et al. Effect of Selenylation Modification on Immune-Enhancing Activity of *Atractylodes Macrocephala* Polysaccharide. *Int. J. Biol. Macromol.* **2015**, *72*, 1435–1440. [[CrossRef](#)]
256. Zhang, J.; Wang, F.-X.; Liu, Z.-W.; Zhang, S.-T.; Zhang, Y.-Y.; Liang, J.-Y.; Wang, Y.-P. Synthesis and Characterisation of Seleno-Cynomorium Songaricum Rupr. Polysaccharide. *Nat. Prod. Res.* **2009**, *23*, 1641–1651. [[CrossRef](#)]
257. Wang, J.; Li, Q.; Bao, A.; Liu, X.; Zeng, J.; Yang, X.; Yao, J.; Zhang, J.; Lei, Z. Synthesis of Selenium-Containing *Artemisia Sphaerocephala* Polysaccharides: Solution Conformation and Anti-Tumor Activities in Vitro. *Carbohydr. Polym.* **2016**, *152*, 70–78. [[CrossRef](#)]
258. Gao, Z.; Chen, J.; Qiu, S.; Li, Y.; Wang, D.; Liu, C.; Li, X.; Hou, R.; Yue, C.; Liu, J.; et al. Optimization of Selenylation Modification for Garlic Polysaccharide Based on Immune-Enhancing Activity. *Carbohydr. Polym.* **2016**, *136*, 560–569. [[CrossRef](#)]

259. Liu, L.; Pan, D.; Zeng, X.; Li, H. Effect of Selenium-Enriched Exopolysaccharide Produced by *Lactococcus Lactis* Subsp. *Lactis* on Signaling Molecules in Mouse Spleen Lymphocytes. *Food Funct.* **2013**, *4*, 1489–1495. [[CrossRef](#)]
260. Pan, D.; Liu, J.; Zeng, X.; Liu, L.; Li, H.; Guo, Y. Immunomodulatory Activity of Selenium Exopolysaccharide Produced by *Lactococcus lactis* Subsp. *Lactis*. *Food Agric. Immunol.* **2015**, *26*, 248–259. [[CrossRef](#)]
261. Huang, G.-C.; Lee, C.-J.; Wang, K.-T.; Weng, B.-C.; Chien, T.-Y.; Tseng, S.-H.; Wang, C.-C. Immunomodulatory Effects of Hedysarum Polybotrys Extract in Mice Macrophages, Splenocytes and Leucopenia. *Molecules* **2013**, *18*, 14862–14875. [[CrossRef](#)]
262. Zhu, Z.-Y.; Liu, F.; Gao, H.; Sun, H.; Meng, M.; Zhang, Y.-M. Synthesis, Characterization and Antioxidant Activity of Selenium Polysaccharide from Cordyceps Militaris. *Int. J. Biol. Macromol.* **2016**, *93*, 1090–1099. [[CrossRef](#)]
263. Liu, Y.; You, Y.; Li, Y.; Zhang, L.; Yin, L.; Shen, Y.; Li, C.; Chen, H.; Chen, S.; Hu, B.; et al. The Characterization, Selenylation and Antidiabetic Activity of Mycelial Polysaccharides from Catathelasma Ventricosum. *Carbohydr. Polym.* **2017**, *174*, 72–81. [[CrossRef](#)] [[PubMed](#)]
264. Lv, H.; Duan, K.; Shan, H. Selenylation Modification of Degraded Polysaccharide from Enteromorpha Prolifera and Its Biological Activities. *J. Ocean Univ. China* **2018**, *17*, 445–450. [[CrossRef](#)]
265. Surhio, M.M.; Wang, Y.; Xu, P.; Shah, F.; Li, J.; Ye, M. Antihyperlipidemic and Hepatoprotective Properties of Selenium Modified Polysaccharide from *Lachnum* Sp. *Int. J. Biol. Macromol.* **2017**, *99*, 88–95. [[CrossRef](#)]
266. Ren, G.; Li, K.; Hu, Y.; Yu, M.; Qu, J.; Xu, X. Optimization of Selenizing Conditions for Seleno-Lentinan and Its Characteristics. *Int. J. Biol. Macromol.* **2015**, *81*, 249–258. [[CrossRef](#)]
267. Hou, R.; Chen, J.; Yue, C.; Li, X.; Liu, J.; Gao, Z.; Liu, C.; Lu, Y.; Wang, D.; Li, H.; et al. Modification of Lily Polysaccharide by Selenylation and the Immune-Enhancing Activity. *Carbohydr. Polym.* **2016**, *142*, 73–81. [[CrossRef](#)]
268. Chen, W.; Chen, J.; Wu, H.; Gou, Y.; Hu, F.; Liu, L.; Gao, X.; Zhang, P. Optimization of Selenylation Conditions for a Pectic Polysaccharide and Its Structural Characteristic. *Int. J. Biol. Macromol.* **2014**, *69*, 244–251. [[CrossRef](#)]
269. Qiu, S.; Chen, J.; Chen, X.; Fan, Q.; Zhang, C.; Wang, D.; Li, X.; Chen, X.; Chen, X.; Liu, C.; et al. Optimization of Selenylation Conditions for Lycium Barbarum Polysaccharide Based on Antioxidant Activity. *Carbohydr. Polym.* **2014**, *103*, 148–153. [[CrossRef](#)] [[PubMed](#)]
270. Hamid, M.; Liu, D.; Abdulrahim, Y.; Liu, Y.; Qian, G.; Khan, A.; Gan, F.; Huang, K. Amelioration of CCl₄-Induced Liver Injury in Rats by Selenizing Astragalus Polysaccharides: Role of Proinflammatory Cytokines, Oxidative Stress and Hepatic Stellate Cells. *Res. Vet. Sci.* **2017**, *114*, 202–211. [[CrossRef](#)]
271. Qin, T.; Ren, Z.; Huang, Y.; Song, Y.; Lin, D.; Li, J.; Ma, Y.; Wu, X.; Qiu, F.; Xiao, Q. Selenizing Hericium Erinaceus Polysaccharides Induces Dendritic Cells Maturation through MAPK and NF- κ B Signaling Pathways. *Int. J. Biol. Macromol.* **2017**, *97*, 287–298. [[CrossRef](#)] [[PubMed](#)]
272. Lian, K.-X.; Zhu, X.-Q.; Chen, J.; Liu, G.; Gu, X.-L. Selenylation Modification: Enhancement of the Antioxidant Activity of a Glycyrrhiza Uralensis Polysaccharide. *Glycoconj. J.* **2018**, *35*, 243–253. [[CrossRef](#)]
273. Li, X.; Hou, R.; Yue, C.; Liu, J.; Gao, Z.; Chen, J.; Lu, Y.; Wang, D.; Liu, C.; Hu, Y. The Selenylation Modification of Epimedium Polysaccharide and Isatis Root Polysaccharide and the Immune-Enhancing Activity Comparison of Their Modifiers. *Biol. Trace Elem. Res.* **2016**, *171*, 224–234. [[CrossRef](#)]
274. Ji, Y.-B.; Dong, F.; Lang, L.; Zhang, L.-W.; Miao, J.; Liu, Z.-F.; Jin, L.-N.; Hao, Y. Optimization of Synthesis, Characterization and Cytotoxic Activity of Seleno-Capparidopsis Polysaccharide. *Int. J. Mol. Sci.* **2012**, *13*, 17275–17289. [[CrossRef](#)]
275. Chen, C.; Zhang, B.; Fu, X.; Liu, R.H. A Novel Polysaccharide Isolated from Mulberry Fruits (*Morus alba* L.) and its Selenide Derivative: Structural Characterization and Biological Activities. *Food Funct.* **2016**, *7*, 2886–2897. [[CrossRef](#)]
276. Li, H.; Wang, Y.; Wang, C.; Zhang, S.; Li, S.; Zhou, G.; Wang, S.; Zhang, J. Extraction, Selenylation Modification and Antitumor Activity of the Glucan from Castanea Mollissima Blume. *Glycoconj. J.* **2017**, *34*, 207–217. [[CrossRef](#)]
277. Ding, G.-B.; Nie, R.-H.; Lv, L.-H.; Wei, G.-Q.; Zhao, L.-Q. Preparation and Biological Evaluation of a Novel Selenium-Containing Exopolysaccharide from Rhizobium Sp. N613. *Carbohydr. Polym.* **2014**, *109*, 28–34. [[CrossRef](#)]
278. Zhao, B.; Zhang, J.; Yao, J.; Song, S.; Yin, Z.; Gao, Q. Selenylation Modification Can Enhance Antioxidant Activity of Potentilla Anserina L. Polysaccharide. *Int. J. Biol. Macromol.* **2013**, *58*, 320–328. [[CrossRef](#)]
279. Qiu, S.; Chen, J.; Qin, T.; Hu, Y.; Wang, D.; Fan, Q.; Zhang, C.; Chen, X.; Chen, X.; Liu, C.; et al. Effects of Selenylation Modification on Immune-Enhancing Activity of Garlic Polysaccharide. *PLoS ONE* **2014**, *9*, e86377. [[CrossRef](#)]
280. Wang, D.; Zhao, Y.; Sun, Y.; Yang, X. Protective Effects of Ziyang Tea Polysaccharides on CCl₄-Induced Oxidative Liver Damage in Mice. *Food Chem.* **2014**, *143*, 371–378. [[CrossRef](#)] [[PubMed](#)]
281. Cheng, L.; Wang, Y.; He, X.; Wei, X. Preparation, Structural Characterization and Bioactivities of Se-Containing Polysaccharide: A Review. *Int. J. Biol. Macromol.* **2018**, *120*, 82–92. [[CrossRef](#)]
282. Shi, L.; Xun, W.; Yue, W.; Zhang, C.; Ren, Y.; Shi, L.; Wang, Q.; Yang, R.; Lei, F. Effect of Sodium Selenite, Se-Yeast and Nano-Elemental Selenium on Growth Performance, Se Concentration and Antioxidant Status in Growing Male Goats. *Small Rumin. Res.* **2011**, *96*, 49–52. [[CrossRef](#)]
283. Wang, H.; Zhang, J.; Yu, H. Elemental Selenium at Nano Size Possesses Lower Toxicity without Compromising the Fundamental Effect on Selenoenzymes: Comparison with Selenomethionine in Mice. *Free Radic. Biol. Med.* **2007**, *42*, 1524–1533. [[CrossRef](#)]
284. Zhang, J.; Wang, X.; Xu, T. Elemental Selenium at Nano Size (Nano-Se) as a Potential Chemopreventive Agent with Reduced Risk of Selenium Toxicity: Comparison with Se-Methylselenocysteine in Mice. *Toxicol. Sci. Off. J. Soc. Toxicol.* **2008**, *101*, 22–31. [[CrossRef](#)] [[PubMed](#)]

285. Zhang, J.S.; Gao, X.Y.; Zhang, L.D.; Bao, Y.P. Biological Effects of a Nano Red Elemental Selenium. *BioFactors Oxf. Engl.* **2001**, *15*, 27–38. [[CrossRef](#)] [[PubMed](#)]
286. Vert, M.; Doi, Y.; Hellwich, K.-H.; Hess, M.; Hodge, P.; Kubisa, P.; Rinaudo, M.; Schué, F. Terminology for Biorelated Polymers and Applications (IUPAC Recommendations 2012). *Pure Appl. Chem.* **2012**, *84*, 377–410. [[CrossRef](#)]
287. Torres, S.K.; Campos, V.L.; León, C.G.; Rodríguez-Llamazares, S.M.; Rojas, S.M.; González, M.; Smith, C.; Mondaca, M.A. Biosynthesis of Selenium Nanoparticles by *Pantoea Agglomerans* and Their Antioxidant Activity. *J. Nanoparticle Res.* **2012**, *14*, 1236. [[CrossRef](#)]
288. Desai, M.P.; Labhassetwar, V.; Walter, E.; Levy, R.J.; Amidon, G.L. The Mechanism of Uptake of Biodegradable Microparticles in Caco-2 Cells Is Size Dependent. *Pharm. Res.* **1997**, *14*, 1568–1573. [[CrossRef](#)]
289. Hosnedlova, B.; Kepinska, M.; Skalickova, S.; Fernandez, C.; Ruttkay-Nedecky, B.; Peng, Q.; Baron, M.; Melcova, M.; Opatrilova, R.; Zidkova, J.; et al. Nano-Selenium and Its Nanomedicine Applications: A Critical Review. *Int. J. Nanomed.* **2018**, *13*, 2107–2128. [[CrossRef](#)]
290. Zhang, C.; Zhai, X.; Zhao, G.; Ren, F.; Leng, X. Synthesis, Characterization, and Controlled Release of Selenium Nanoparticles Stabilized by Chitosan of Different Molecular Weights. *Carbohydr. Polym.* **2015**, *134*, 158–166. [[CrossRef](#)]
291. Chen, W.; Li, Y.; Yang, S.; Yue, L.; Jiang, Q.; Xia, W. Synthesis and Antioxidant Properties of Chitosan and Carboxymethyl Chitosan-Stabilized Selenium Nanoparticles. *Carbohydr. Polym.* **2015**, *132*, 574–581. [[CrossRef](#)]
292. Sun, Y.; Nie, Y.; Wang, Z.; Hua, C.; Wang, R.; Gao, J. Biomacromolecule-Directed Synthesis and Characterization of Selenium Nanoparticles and Their Compatibility with Bacterial and Eukaryotic Cells. *Nanosci. Nanotechnol. Lett.* **2017**, *9*, 1987–1991. [[CrossRef](#)]
293. Xu, D.; Yang, L.; Wang, Y.; Wang, G.; Rensing, C.; Zheng, S. Proteins Enriched in Charged Amino Acids Control the Formation and Stabilization of Selenium Nanoparticles in *Comamonas Testosteroni* S44. *Sci. Rep.* **2018**, *8*, 4766. [[CrossRef](#)]
294. Liu, C.; Fu, Y.; Li, C.-E.; Chen, T.; Li, X. Phycocyanin-Functionalized Selenium Nanoparticles Reverse Palmitic Acid-Induced Pancreatic β Cell Apoptosis by Enhancing Cellular Uptake and Blocking Reactive Oxygen Species (ROS)-Mediated Mitochondria Dysfunction. *J. Agric. Food Chem.* **2017**, *65*, 4405–4413. [[CrossRef](#)]
295. Zhu, C.; Zhang, S.; Song, C.; Zhang, Y.; Ling, Q.; Hoffmann, P.R.; Li, J.; Chen, T.; Zheng, W.; Huang, Z. Selenium Nanoparticles Decorated with *Ulva Lactuca* Polysaccharide Potentially Attenuate Colitis by Inhibiting NF-KB Mediated Hyper Inflammation. *J. Nanobiotechnol.* **2017**, *15*, 20. [[CrossRef](#)]
296. Liao, W.; Yu, Z.; Lin, Z.; Lei, Z.; Ning, Z.; Regenstein, J.M.; Yang, J.; Ren, J. Biofunctionalization of Selenium Nanoparticle with *Dictyophora Indusiata* Polysaccharide and Its Antiproliferative Activity through Death-Receptor and Mitochondria-Mediated Apoptotic Pathways. *Sci. Rep.* **2015**, *5*, 18629. [[CrossRef](#)] [[PubMed](#)]
297. Ping, Z.; Liu, T.; Xu, H.; Meng, Y.; Li, W.; Xu, X.; Zhang, L. Construction of Highly Stable Selenium Nanoparticles Embedded in Hollow Nanofibers of Polysaccharide and Their Antitumor Activities. *Nano Res.* **2017**, *10*, 3775–3789. [[CrossRef](#)]
298. Wu, H.; Zhu, H.; Li, X.; Liu, Z.; Zheng, W.; Chen, T.; Yu, B.; Wong, K.-H. Induction of Apoptosis and Cell Cycle Arrest in A549 Human Lung Adenocarcinoma Cells by Surface-Capping Selenium Nanoparticles: An Effect Enhanced by Polysaccharide-Protein Complexes from *Polyporus Rhinoceros*. *J. Agric. Food Chem.* **2013**, *61*, 9859–9866. [[CrossRef](#)] [[PubMed](#)]
299. Wu, H.; Li, X.; Liu, W.; Chen, T.; Li, Y.; Zheng, W.; Man, C.W.-Y.; Wong, M.-K.; Wong, K.-H. Surface Decoration of Selenium Nanoparticles by Mushroom Polysaccharides-Protein Complexes to Achieve Enhanced Cellular Uptake and Antiproliferative Activity. *J. Mater. Chem.* **2012**, *22*, 9602. [[CrossRef](#)]
300. Hong, A.; Rao, L.; Zhuang, M.; Luo, T.; Wang, Y.; Ma, Y. Chitosan-Decorated Selenium Nanoparticles as Proteins Carriers to Improve the in Vivo Half-Life of the Peptide Therapeutic BAY 55-9837 for Type 2 Diabetes Mellitus. *Int. J. Nanomed.* **2014**, 4819. [[CrossRef](#)]
301. Bai, Y.; Wang, Y.; Zhou, Y.; Li, W.; Zheng, W. Modification and Modulation of Saccharides on Elemental Selenium Nanoparticles in Liquid Phase. *Mater. Lett.* **2008**, *62*, 2311–2314. [[CrossRef](#)]
302. Zhang, S.-Y.; Zhang, J.; Wang, H.-Y.; Chen, H.-Y. Synthesis of Selenium Nanoparticles in the Presence of Polysaccharides. *Mater. Lett.* **2004**, *58*, 2590–2594. [[CrossRef](#)]
303. Shoeibi, S.; Mashreghi, M. Biosynthesis of Selenium Nanoparticles Using *Enterococcus Faecalis* and Evaluation of Their Antibacterial Activities. *J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. GMS* **2017**, *39*, 135–139. [[CrossRef](#)] [[PubMed](#)]
304. Ramamurthy, C.; Sampath, K.S.; Arunkumar, P.; Kumar, M.S.; Sujatha, V.; Premkumar, K.; Thirunavukkarasu, C. Green Synthesis and Characterization of Selenium Nanoparticles and Its Augmented Cytotoxicity with Doxorubicin on Cancer Cells. *Bioprocess Biosyst. Eng.* **2013**, *36*, 1131–1139. [[CrossRef](#)] [[PubMed](#)]
305. Stevanović, M.; Filipović, N.; Djurdjević, J.; Lukić, M.; Milenković, M.; Boccaccini, A. 45S5Bioglass[®]-Based Scaffolds Coated with Selenium Nanoparticles or with Poly(Lactide-Co-Glycolide)/Selenium Particles: Processing, Evaluation and Antibacterial Activity. *Colloids Surf. B Biointerfaces* **2015**, *132*, 208–215. [[CrossRef](#)] [[PubMed](#)]
306. Yanhua, W.; Hao, H.; Li, Y.; Zhang, S. Selenium-Substituted Hydroxyapatite Nanoparticles and Their in Vivo Antitumor Effect on Hepatocellular Carcinoma. *Colloids Surf. B Biointerfaces* **2016**, *140*, 297–306. [[CrossRef](#)]
307. Yang, X.; Zhang, W.; Zhao, Z.; Li, N.; Mou, Z.; Sun, D.; Cai, Y.; Wang, W.; Lin, Y. Quercetin Loading CdSe/ZnS Nanoparticles as Efficient Antibacterial and Anticancer Materials. *J. Inorg. Biochem.* **2017**, *167*, 36–48. [[CrossRef](#)]
308. Yin, J.; Hou, Y.; Yin, Y.; Song, X. Selenium-Coated Nanostructured Lipid Carriers Used for Oral Delivery of Berberine to Accomplish a Synergic Hypoglycemic Effect. *Int. J. Nanomed.* **2017**, *12*, 8671–8680. [[CrossRef](#)]

309. Kumar, G.S.; Kulkarni, A.; Khurana, A.; Kaur, J.; Tikoo, K. Selenium Nanoparticles Involve HSP-70 and SIRT1 in Preventing the Progression of Type 1 Diabetic Nephropathy. *Chem. Biol. Interact.* **2014**, *223*, 125–133. [[CrossRef](#)] [[PubMed](#)]
310. Malhotra, S.; Welling, M.N.; Mantri, S.B.; Desai, K. In Vitro and in Vivo Antioxidant, Cytotoxic, and Anti-Chronic Inflammatory Arthritic Effect of Selenium Nanoparticles. *J. Biomed. Mater. Res. B Appl. Biomater.* **2016**, *104*, 993–1003. [[CrossRef](#)]
311. Ramya, S.; Shanmugasundaram, T.; Balagurunathan, R. Biomedical Potential of Actinobacterially Synthesized Selenium Nanoparticles with Special Reference to Anti-Biofilm, Anti-Oxidant, Wound Healing, Cytotoxic and Anti-Viral Activities. *J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. GMS* **2015**, *32*, 30–39. [[CrossRef](#)]
312. Wu, X.; Yao, J.; Yang, Z.; Yue, W.; Ren, Y.; Zhang, C.; Liu, X.; Wang, H.; Zhao, X.; Yuan, S.; et al. Improved Fetal Hair Follicle Development by Maternal Supplement of Selenium at Nano Size (Nano-Se). *Livest. Sci.* **2011**, *142*, 270–275. [[CrossRef](#)]
313. Shi, L.; Yang, R.; Yue, W.; Xun, W.; Zhang, C.; Ren, Y.; Shi, L.; Lei, F. Effect of Elemental Nano-Selenium on Semen Quality, Glutathione Peroxidase Activity, and Testis Ultrastructure in Male Boer Goats. *Anim. Reprod. Sci.* **2010**, *118*, 248–254. [[CrossRef](#)] [[PubMed](#)]
314. Majhi, S.; Das, D. Chemical Derivatization of Natural Products: Semisynthesis and Pharmacological Aspects—A Decade Update. *Tetrahedron* **2021**, *78*, 131801. [[CrossRef](#)]
315. Armaly, A.M.; DePorre, Y.C.; Groso, E.J.; Riehl, P.S.; Schindler, C.S. Discovery of Novel Synthetic Methodologies and Reagents during Natural Product Synthesis in the Post-Palytoxin Era. *Chem. Rev.* **2015**, *115*, 9232–9276. [[CrossRef](#)] [[PubMed](#)]
316. Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim, Germany; New York, NY, USA, 1996; ISBN 978-3-527-29284-4.
317. Xiao, R.; Grinstaff, M.W. Chemical Synthesis of Polysaccharides and Polysaccharide Mimetics. *Prog. Polym. Sci.* **2017**, *74*, 78–116. [[CrossRef](#)]
318. Ren, Y.; Bai, Y.; Zhang, Z.; Cai, W.; Del Rio Flores, A. The Preparation and Structure Analysis Methods of Natural Polysaccharides of Plants and Fungi: A Review of Recent Development. *Molecules* **2019**, *24*, 3122. [[CrossRef](#)]
319. Zhang, H.; Chen, J.; Li, J.; Yan, L.; Li, S.; Ye, X.; Liu, D.; Ding, T.; Linhardt, R.J.; Orfila, C.; et al. Extraction and Characterization of RG-I Enriched Pectic Polysaccharides from Mandarin Citrus Peel. *Food Hydrocoll.* **2018**, *79*, 579–586. [[CrossRef](#)]
320. Song, Y.-R.; Sung, S.-K.; Jang, M.; Lim, T.-G.; Cho, C.-W.; Han, C.-J.; Hong, H.-D. Enzyme-Assisted Extraction, Chemical Characteristics, and Immunostimulatory Activity of Polysaccharides from Korean Ginseng (*Panax Ginseng Meyer*). *Int. J. Biol. Macromol.* **2018**, *116*, 1089–1097. [[CrossRef](#)]
321. Zhang, M.; Cui, S.W.; Cheung, P.C.K.; Wang, Q. Antitumor Polysaccharides from Mushrooms: A Review on Their Isolation Process, Structural Characteristics and Antitumor Activity. *Trends Food Sci. Technol.* **2007**, *18*, 4–19. [[CrossRef](#)]
322. e Silva, A.d.S.; de Magalhães, W.T.; Moreira, L.M.; Rocha, M.V.P.; Bastos, A.K.P. Microwave-Assisted Extraction of Polysaccharides from *Arthrospira (Spirulina) Platensis* Using the Concept of Green Chemistry. *Algal Res.* **2018**, *35*, 178–184. [[CrossRef](#)]
323. Sukhithasri, V.; Nisha, N.; Biswas, L.; Anil Kumar, V.; Biswas, R. Innate Immune Recognition of Microbial Cell Wall Components and Microbial Strategies to Evade Such Recognitions. *Microbiol. Res.* **2013**, *168*, 396–406. [[CrossRef](#)] [[PubMed](#)]
324. Choong, Y.-K.; Ellan, K.; Chen, X.-D.; Azuar Mohamad, S. Extraction and Fractionation of Polysaccharides from a Selected Mushroom Species, *Ganoderma lucidum*: A Critical Review. In *Fractionation*; Al-Haj Ibrahim, H., Ed.; IntechOpen: London, UK, 2019; ISBN 978-1-78984-964-6.
325. Segneanu, A.-E.; Szpile, F.; Vlazan, P.; Sfarloaga, P.; Grozesku, I.; Daniel, V. Biomass Extraction Methods. In *Biomass Now—Sustainable Growth and Use*; Matovic, M.D., Ed.; InTech: Rijeka, Croatia, 2013; ISBN 978-953-51-1105-4.
326. Ruthes, A.C.; Smiderle, F.R.; Iacomini, M. D-Glucans from Edible Mushrooms: A Review on the Extraction, Purification and Chemical Characterization Approaches. *Carbohydr. Polym.* **2015**, *117*, 753–761. [[CrossRef](#)] [[PubMed](#)]
327. Zhu, F.; Du, B.; Bian, Z.; Xu, B. Beta-Glucans from Edible and Medicinal Mushrooms: Characteristics, Physicochemical and Biological Activities. *J. Food Compos. Anal.* **2015**, *41*, 165–173. [[CrossRef](#)]
328. Villares, A.; Mateo-Vivaracho, L.; Guillamón, E. Structural Features and Healthy Properties of Polysaccharides Occurring in Mushrooms. *Agriculture* **2012**, *2*, 452–471. [[CrossRef](#)]
329. Zou, P.; Yang, X.; Huang, W.-W.; Zhao, H.-T.; Wang, J.; Xu, R.-B.; Hu, X.-L.; Shen, S.-Y.; Qin, D. Characterization and Bioactivity of Polysaccharides Obtained from Pine Cones of *Pinus Koraiensis* by Graded Ethanol Precipitation. *Molecules* **2013**, *18*, 9933–9948. [[CrossRef](#)] [[PubMed](#)]
330. Xie, J.-H.; Shen, M.-Y.; Nie, S.-P.; Liu, X.; Zhang, H.; Xie, M.-Y. Analysis of Monosaccharide Composition of *Cyclocarya paliurus* Polysaccharide with Anion Exchange Chromatography. *Carbohydr. Polym.* **2013**, *98*, 976–981. [[CrossRef](#)]
331. Turło, J. The Biotechnology of Higher Fungi—Current State and Perspectives. *Folia Biol. Oecologica* **2014**, *10*, 49–65. [[CrossRef](#)]
332. Wu, J.; Zhong, J. Production of Ginseng and Its Bioactive Components in Plant Cell Culture: Current Technological and Applied Aspects. *J. Biotechnol.* **1999**, *68*, 89–99. [[CrossRef](#)]
333. Sun, Y.; Zhou, C.; Huang, S.; Jiang, C. Selenium Polysaccharide SPMP-2a from *Pleurotus Geesteranus* Alleviates H₂O₂-Induced Oxidative Damage in HaCaT Cells. *BioMed Res. Int.* **2017**, *2017*, 1–9. [[CrossRef](#)]
334. Ye, S.; Zhang, J.; Liu, Z.; Zhang, Y.; Li, J.; Li, Y.O. Biosynthesis of Selenium Rich Exopolysaccharide (Se-EPS) by *Pseudomonas* PT-8 and Characterization of Its Antioxidant Activities. *Carbohydr. Polym.* **2016**, *142*, 230–239. [[CrossRef](#)]
335. Xing, H.; Du, R.; Zhao, F.; Han, Y.; Xiao, H.; Zhou, Z. Optimization, Chain Conformation and Characterization of Exopolysaccharide Isolated from *Leuconostoc Mesenteroides* DRP105. *Int. J. Biol. Macromol.* **2018**, *112*, 1208–1216. [[CrossRef](#)]
336. Cumpstey, I. Chemical Modification of Polysaccharides. *ISRN Org. Chem.* **2013**, *2013*, 1–27. [[CrossRef](#)]

337. Yalpani, M. A Survey of Recent Advances in Selective Chemical and Enzymic Polysaccharide Modifications. *Tetrahedron* **1985**, *41*, 2957–3020. [[CrossRef](#)]
338. Lee, J.-H.; Lee, Y.-K.; Chang, Y.H. Effects of Selenylation Modification on Structural and Antioxidant Properties of Pectic Polysaccharides Extracted from *Ulmus Pumila L.* *Int. J. Biol. Macromol.* **2017**, *104*, 1124–1132. [[CrossRef](#)] [[PubMed](#)]
339. Qin, T.; Chen, J.; Wang, D.; Hu, Y.; Wang, M.; Zhang, J.; Nguyen, T.L.; Liu, C.; Liu, X. Optimization of Selenylation Conditions for Chinese Angelica Polysaccharide Based on Immune-Enhancing Activity. *Carbohydr. Polym.* **2013**, *92*, 645–650. [[CrossRef](#)]
340. Gao, Z.; Liu, K.; Tian, W.; Wang, H.; Liu, Z.; Li, Y.; Li, E.; Liu, C.; Li, X.; Hou, R.; et al. Effects of Selenizing Angelica Polysaccharide and Selenizing Garlic Polysaccharide on Immune Function of Murine Peritoneal Macrophage. *Int. Immunopharmacol.* **2015**, *27*, 104–109. [[CrossRef](#)]
341. Yuan, B.; Yang, X.-Q.; Kou, M.; Lu, C.-Y.; Wang, Y.-Y.; Peng, J.; Chen, P.; Jiang, J.-H. Selenylation of Polysaccharide from the Sweet Potato and Evaluation of Antioxidant, Antitumor, and Antidiabetic Activities. *J. Agric. Food Chem.* **2017**, *65*, 605–617. [[CrossRef](#)] [[PubMed](#)]
342. Wang, J.; Yang, X.; Bao, A.; Liu, X.; Zeng, J.; Liu, X.; Yao, J.; Zhang, J.; Lei, Z. Microwave-Assisted Synthesis, Structure and Anti-Tumor Activity of Selenized *Artemisia Sphaerocephala* Polysaccharide. *Int. J. Biol. Macromol.* **2017**, *95*, 1108–1118. [[CrossRef](#)] [[PubMed](#)]
343. Wei, Y.; Zhao, Q.; Wu, Q.; Zhang, H.; Kong, W.; Liang, J.; Yao, J.; Zhang, J.; Wang, J. Efficient Synthesis of Polysaccharide with High Selenium Content Mediated by Imidazole-Based Acidic Ionic Liquids. *Carbohydr. Polym.* **2019**, *203*, 157–166. [[CrossRef](#)]
344. Chen, L.; Huang, G. The Antiviral Activity of Polysaccharides and Their Derivatives. *Int. J. Biol. Macromol.* **2018**, *115*, 77–82. [[CrossRef](#)]
345. Huang, S.; Yang, W.; Huang, G. Preparation and Activities of Selenium Polysaccharide from Plant Such as *Grifola Frondosa*. *Carbohydr. Polym.* **2020**, *242*, 116409. [[CrossRef](#)] [[PubMed](#)]
346. Quintana, M.; Haro-Poniatowski, E.; Morales, J.; Batina, N. Synthesis of Selenium Nanoparticles by Pulsed Laser Ablation. *Appl. Surf. Sci.* **2002**, *195*, 175–186. [[CrossRef](#)]
347. Jain, R.; Gonzalez-Gil, G.; Singh, V.; Hullebusch, E.D.V.; Farges, F.; Lens, P.N.L. Biogenic Selenium Nanoparticles: Production, Characterization and Challenges. In *Biotechnology*; Studium Press LLC.: New Delhi, India, 2014; Volume 10, pp. 365–394. [[CrossRef](#)]
348. Yu, B.; You, P.; Song, M.; Zhou, Y.; Yu, F.; Zheng, W. A Facile and Fast Synthetic Approach to Create Selenium Nanoparticles with Diverse Shapes and Their Antioxidation Ability. *New J. Chem.* **2016**, *40*, 1118–1123. [[CrossRef](#)]
349. Li, Y.; Lin, Z.; Guo, M.; Xia, Y.; Zhao, M.; Wang, C.; Xu, T.; Chen, T.; Zhu, B. Inhibitory Activity of Selenium Nanoparticles Functionalized with Oseltamivir on H1N1 Influenza Virus. *Int. J. Nanomed.* **2017**, *12*, 5733–5743. [[CrossRef](#)]
350. Cremonini, E.; Zonaro, E.; Donini, M.; Lampis, S.; Boaretti, M.; Dusi, S.; Melotti, P.; Lleo, M.M.; Vallini, G. Biogenic Selenium Nanoparticles: Characterization, Antimicrobial Activity and Effects on Human Dendritic Cells and Fibroblasts. *Microb. Biotechnol.* **2016**, *9*, 758–771. [[CrossRef](#)]
351. Piacenza, E.; Presentato, A.; Zonaro, E.; Lemire, J.A.; Demeter, M.; Vallini, G.; Turner, R.J.; Lampis, S. Antimicrobial Activity of Biogenically Produced Spherical Se-Nanomaterials Embedded in Organic Material against *Pseudomonas aeruginosa* and *Staphylococcus aureus* Strains on Hydroxyapatite-Coated Surfaces. *Microb. Biotechnol.* **2017**, *10*, 804–818. [[CrossRef](#)]
352. Wang, Q.; Webster, T.J. Nanostructured Selenium for Preventing Biofilm Formation on Polycarbonate Medical Devices. *J. Biomed. Mater. Res. A* **2012**, *100A*, 3205–3210. [[CrossRef](#)]
353. Yan, J.-K.; Qiu, W.-Y.; Wang, Y.-Y.; Wang, W.-H.; Yang, Y.; Zhang, H.-N. Fabrication and Stabilization of Biocompatible Selenium Nanoparticles by Carboxylic Curdlans with Various Molecular Properties. *Carbohydr. Polym.* **2018**, *179*, 19–27. [[CrossRef](#)] [[PubMed](#)]
354. Chen, T.; Wong, K.H.; Wu, H.L.; Zheng, W.; Wong, M.K.; Man, W.Y.C. Pleurotus Tuber-Regium Polysaccharide Functionalized Nano-Selenium Hydrosol with Anti-Tumor Activity and Preparation Method Thereof. U.S. Patent 9,072,669, 7 July 2015.
355. Husen, A.; Siddiqi, K.S. Plants and Microbes Assisted Selenium Nanoparticles: Characterization and Application. *J. Nanobiotechnology* **2014**, *12*, 28. [[CrossRef](#)] [[PubMed](#)]
356. Ezhuthupurakkal, P.B.; Polaki, L.R.; Suyavarana, A.; Subastri, A.; Sujatha, V.; Thirunavukkarasu, C. Selenium Nanoparticles Synthesized in Aqueous Extract of *Allium Sativum* Perturbs the Structural Integrity of Calf Thymus DNA through Intercalation and Groove Binding. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *74*, 597–608. [[CrossRef](#)] [[PubMed](#)]
357. Sowndarya, P.; Ramkumar, G.; Shivakumar, M.S. Green Synthesis of Selenium Nanoparticles Conjugated *Clausena Dentata* Plant Leaf Extract and Their Insecticidal Potential against Mosquito Vectors. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 1490–1495. [[CrossRef](#)] [[PubMed](#)]
358. Chen, T.; Wong, Y.-S.; Zheng, W.; Bai, Y.; Huang, L. Selenium Nanoparticles Fabricated in *Undaria Pinnatifida* Polysaccharide Solutions Induce Mitochondria-Mediated Apoptosis in A375 Human Melanoma Cells. *Colloids Surf. B Biointerfaces* **2008**, *67*, 26–31. [[CrossRef](#)] [[PubMed](#)]
359. Prasad, K.S.; Selvaraj, K. Biogenic Synthesis of Selenium Nanoparticles and Their Effect on As(III)-Induced Toxicity on Human Lymphocytes. *Biol. Trace Elem. Res.* **2014**, *157*, 275–283. [[CrossRef](#)] [[PubMed](#)]
360. Song, J.Y.; Kim, B.S. Rapid Biological Synthesis of Silver Nanoparticles Using Plant Leaf Extracts. *Bioprocess Biosyst. Eng.* **2009**, *32*, 79–84. [[CrossRef](#)]

361. Suresh, K.; Prabakaran, S.R.; Sengupta, S.; Shivaji, S. *Bacillus indicus* Sp. Nov., an Arsenic-Resistant Bacterium Isolated from an Aquifer in West Bengal, India. *Int. J. Syst. Evol. Microbiol.* **2004**, *54*, 1369–1375. [[CrossRef](#)]
362. Mandal, D.; Bolander, M.E.; Mukhopadhyay, D.; Sarkar, G.; Mukherjee, P. The Use of Microorganisms for the Formation of Metal Nanoparticles and Their Application. *Appl. Microbiol. Biotechnol.* **2006**, *69*, 485–492. [[CrossRef](#)]
363. Wang, T.; Yang, L.; Zhang, B.; Liu, J. Extracellular Biosynthesis and Transformation of Selenium Nanoparticles and Application in H₂O₂ Biosensor. *Colloids Surf. B Biointerfaces* **2010**, *80*, 94–102. [[CrossRef](#)]
364. Ingale, A.G. Biogenic Synthesis of Nanoparticles and Potential Applications: An Eco-Friendly Approach. *J. Nanomed. Nanotechnol.* **2013**, *4*. [[CrossRef](#)]
365. Oremland, R.S.; Herbel, M.J.; Blum, J.S.; Langley, S.; Beveridge, T.J.; Ajayan, P.M.; Sutto, T.; Ellis, A.V.; Curran, S. Structural and Spectral Features of Selenium Nanospheres Produced by Se-Respiring Bacteria. *Appl. Environ. Microbiol.* **2004**, *70*, 52–60. [[CrossRef](#)] [[PubMed](#)]
366. Kora, A.J.; Rastogi, L. Bacteriogenic Synthesis of Selenium Nanoparticles by *Escherichia Coli* ATCC 35218 and Its Structural Characterisation. *IET Nanobiotechnol.* **2017**, *11*, 179–184. [[CrossRef](#)] [[PubMed](#)]
367. Song, D.; Li, X.; Cheng, Y.; Xiao, X.; Lu, Z.; Wang, Y.; Wang, F. Aerobic Biogenesis of Selenium Nanoparticles by *Enterobacter Cloacae* Z0206 as a Consequence of Fumarate Reductase Mediated Selenite Reduction. *Sci. Rep.* **2017**, *7*, 3239. [[CrossRef](#)] [[PubMed](#)]
368. Kora, A.J.; Rastogi, L. Biomimetic Synthesis of Selenium Nanoparticles by *Pseudomonas Aeruginosa* ATCC 27853: An Approach for Conversion of Selenite. *J. Environ. Manag.* **2016**, *181*, 231–236. [[CrossRef](#)]
369. Fesharaki, P.J.; Nazari, P.; Shakibaie, M.; Rezaie, S.; Banoe, M.; Abdollahi, M.; Shahverdi, A.R. Biosynthesis of Selenium Nanoparticles Using *Klebsiella Pneumoniae* and Their Recovery by a Simple Sterilization Process. *Braz. J. Microbiol.* **2010**, *41*, 461–466. [[CrossRef](#)]
370. Srivastava, N.; Mukhopadhyay, M. Biosynthesis and Structural Characterization of Selenium Nanoparticles Mediated by *Zooglea Ramigera*. *Powder Technol.* **2013**, *244*, 26–29. [[CrossRef](#)]
371. Cavalu, S.; Prokisch, J.; Laslo, V.; Vicas, S. Preparation, Structural Characterisation and Release Study of Novel Hybrid Microspheres Entrapping Nanoselenium, Produced by Green Synthesis. *IET Nanobiotechnol.* **2017**, *11*, 426–432. [[CrossRef](#)]
372. Tan, Y.; Yao, R.; Wang, R.; Wang, D.; Wang, G.; Zheng, S. Reduction of Selenite to Se(0) Nanoparticles by Filamentous Bacterium *Streptomyces* Sp. ES2-5 Isolated from a Selenium Mining Soil. *Microb. Cell Factories* **2016**, *15*, 157. [[CrossRef](#)]
373. Zinicovscaia, I.; Chiriac, T.; Cepoi, L.; Rudi, L.; Culicov, O.; Frontasyeva, M.; Rudic, V. Selenium Uptake and Assessment of the Biochemical Changes in *Arthrospira (Spirulina) Platensis* Biomass during the Synthesis of Selenium Nanoparticles. *Can. J. Microbiol.* **2017**, *63*, 27–34. [[CrossRef](#)] [[PubMed](#)]
374. Ghareeb, M.M.; Wilkinson, S.C.; Gadd, G.M. Reduction of Selenium Oxyanions by Unicellular, Polymorphic and Filamentous Fungi: Cellular Location of Reduced Selenium and Implications for Tolerance. *J. Ind. Microbiol.* **1995**, *14*, 300–311. [[CrossRef](#)]
375. Zhang, L.; Li, D.; Gao, P. Expulsion of Selenium/Protein Nanoparticles through Vesicle-like Structures by *Saccharomyces Cerevisiae* under Microaerophilic Environment. *World J. Microbiol. Biotechnol.* **2012**, *28*, 3381–3386. [[CrossRef](#)] [[PubMed](#)]
376. Costa, C.R.L.d.M.; Menolli, R.A.; Osaku, E.F.; Tramontina, R.; de Melo, R.H.; do Amaral, A.E.; Duarte, P.A.D.; de Carvalho, M.M.; Smiderle, F.R.; Silva, J.L. da C.; et al. Exopolysaccharides from *Aspergillus Terreus*: Production, Chemical Elucidation and Immunoactivity. *Int. J. Biol. Macromol.* **2019**, *139*, 654–664. [[CrossRef](#)] [[PubMed](#)]
377. Espinosa-Ortiz, E.J.; Gonzalez-Gil, G.; Saikaly, P.E.; van Hullebusch, E.D.; Lens, P.N.L. Effects of Selenium Oxyanions on the White-Rot Fungus *Phanerochaete Chrysosporium*. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 2405–2418. [[CrossRef](#)] [[PubMed](#)]
378. Vetchinkina, E.; Loshchinina, E.; Kursky, V.; Nikitina, V. Reduction of Organic and Inorganic Selenium Compounds by the Edible Medicinal Basidiomycete *Lentinula Edodes* and the Accumulation of Elemental Selenium Nanoparticles in Its Mycelium. *J. Microbiol.* **2013**, *51*, 829–835. [[CrossRef](#)] [[PubMed](#)]
379. Guo, Y.; Pan, D.; Li, H.; Sun, Y.; Zeng, X.; Yan, B. Antioxidant and Immunomodulatory Activity of Selenium Exopolysaccharide Produced by *Lactococcus Lactis* Subsp. *Lactis*. *Food Chem.* **2013**, *138*, 84–89. [[CrossRef](#)] [[PubMed](#)]
380. Zhou, N.; Long, H.; Wang, C.; Zhu, Z.; Yu, L.; Yang, W.; Ren, X.; Liu, X. Characterization of Selenium-Containing Polysaccharide from *Spirulina Platensis* and Its Protective Role against Cd-Induced Toxicity. *Int. J. Biol. Macromol.* **2020**, *164*, 2465–2476. [[CrossRef](#)] [[PubMed](#)]
381. Chen, T.; Zheng, W.; Wong, Y.-S.; Yang, F.; Bai, Y. Accumulation of Selenium in Mixotrophic Culture of *Spirulina Platensis* on Glucose. *Bioresour. Technol.* **2006**, *97*, 2260–2265. [[CrossRef](#)]
382. Bannu, S.M.; Lomada, D.; Gulla, S.; Chandrasekhar, T.; Reddanna, P.; Reddy, M.C. Potential Therapeutic Applications of C-Phycocyanin. *Curr. Drug Metab.* **2020**, *20*, 967–976. [[CrossRef](#)]
383. Hao, S.; Yan, Y.; Li, S.; Zhao, L.; Zhang, C.; Liu, L.; Wang, C. The In Vitro Anti-Tumor Activity of Phycocyanin against Non-Small Cell Lung Cancer Cells. *Mar. Drugs* **2018**, *16*, 178. [[CrossRef](#)]
384. Zhu, C.; Ling, Q.; Cai, Z.; Wang, Y.; Zhang, Y.; Hoffmann, P.R.; Zheng, W.; Zhou, T.; Huang, Z. Selenium-Containing Phycocyanin from Se-Enriched *Spirulina platensis* Reduces Inflammation in Dextran Sulfate Sodium-Induced Colitis by Inhibiting NF- κ B Activation. *J. Agric. Food Chem.* **2016**, *64*, 5060–5070. [[CrossRef](#)]
385. Ji, Y.-B.; Dong, F.; Yu, M.; Qin, L.; Liu, D. Optimization of Synthesis of Seleno-*Sargassum fusiforme* (Harv.) Setch. Polysaccharide by Response Surface Methodology, Its Characterization, and Antioxidant Activity. *J. Chem.* **2013**, *2013*, 1–9. [[CrossRef](#)]

386. Sun, X.; Zhong, Y.; Luo, H.; Yang, Y. Selenium-Containing Polysaccharide-Protein Complex in Se-Enriched *Ulva Fasciata* Induces Mitochondria-Mediated Apoptosis in A549 Human Lung Cancer Cells. *Mar. Drugs* **2017**, *15*, 215. [[CrossRef](#)] [[PubMed](#)]
387. Araie, H.; Shiraiwa, Y. Selenium Utilization Strategy by Microalgae. *Molecules* **2009**, *14*, 4880–4891. [[CrossRef](#)] [[PubMed](#)]
388. Shang, D.; Li, Y.; Wang, C.; Wang, X.; Yu, Z.; Fu, X. A Novel Polysaccharide from Se-Enriched *Ganoderma Lucidum* Induces Apoptosis of Human Breast Cancer Cells. *Oncol. Rep.* **2011**, *25*, 267–272. [[CrossRef](#)]
389. Wang, L.; Li, X. Preparation, physicochemical property and in vitro antioxidant activity of zinc-Hohenbuehelia serotina polysaccharides complex. *Int. J. Biol. Macromol.* **2019**, *121*, 862–869. [[CrossRef](#)]
390. Yuan, C.; Wang, C.; Wang, J.; Kumar, V.; Anwar, F.; Xiao, F.; Mushtaq, G.; Liu, Y.; Kamal, M.A.; Yuan, D. Inhibition on the Growth of Human MDA-MB-231 Breast Cancer Cells in Vitro and Tumor Growth in a Mouse Xenograft Model by Se-Containing Polysaccharides from *Pyracantha Fortuneana*. *Nutr. Res.* **2016**, *36*, 1243–1254. [[CrossRef](#)] [[PubMed](#)]
391. Sheng, Y.; Liu, G.; Wang, M.; Lv, Z.; Du, P. A Selenium Polysaccharide from *Platycodon Grandiflorum* Rescues PC12 Cell Death Caused by H₂O₂ via Inhibiting Oxidative Stress. *Int. J. Biol. Macromol.* **2017**, *104*, 393–399. [[CrossRef](#)] [[PubMed](#)]
392. Cheng, L.; Chen, L.; Yang, Q.; Wang, Y.; Wei, X. Antitumor Activity of Se-Containing Tea Polysaccharides against Sarcoma 180 and Comparison with Regular Tea Polysaccharides and Se-Yeast. *Int. J. Biol. Macromol.* **2018**, *120*, 853–858. [[CrossRef](#)]