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Review

Selenylated plant polysaccharides: A survey of their chemical and pharmacological properties

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ABSTRACT

Polysaccharides from plants and fungi are considered nowadays as powerful pharmacological tools with a great therapeutic potential. In the meantime, efforts have been addressed to set up effective chemical modifications of naturally occurring polysaccharides to improve their biological effects as well as to positively modify some key parameters like solubility, bioavailability, pharmacokinetic, and similar. To this concern much attention has been focused during the last decade to the selenylation of natural polysaccharides from plants, algae, and fungi, the use of which is already encoded in ethnomedical traditions. The aim of this review article is to provide a detailed survey of the in so far reported literature data and a deeper knowledge about the state of the art on the chemical and pharmacological properties of selenylated polysaccharides of plant, algal, and fungal origin in terms of anti-oxidant, anti-cancer, anti-diabetic, and immunomodulatory activities. In all cases, literature data revealed that selenylation greatly improved such properties respect to the parent polysaccharides, indicating that selenylation is a valid, alternative, and effective chemical modification of naturally occurring carbohydrates.

1. Introduction

Polysaccharides represent one of the main classes of biopolymers in all living organisms together with proteins, lipids, and polynucleotides. Polysaccharides are particularly abundant in the plant and fungi kingdoms where they are used as fundamental structural elements, other than for energy reserve purposes. Polymers like cellulose, hemicelluloses, pectins, chitins, chitosan, alginates, and hyaluronic acid are basic constituents of plants and fungi cell walls. In animals, polysaccharides play crucial roles in several important biological processes like cell-cell communication, embryonic development, bacterial and/or viral infections, and modulation of the immune system. During the last decade the natural kingdom has been re-considered as a valuable source of alternative remedies to encompass the drawbacks and difficulties of therapeutic means currently at disposition for several acute and chronic diseases affecting humans and animals. Plants, fungi, protozoa, and bacteria have been "classically" in so far seen as sources of biologically active specialised metabolites (e.g. terpenes, polyphenols, alkaloids, glycosides, etc.), but during the last twenty years also polysaccharides of the same origin have attracted much interest due to their pharmacological effects and potential as laxative, anti-diabetic, anti-inflammatory, anti-oxidant, immunomodulatory, anti-cancer, anti-bacterial, and anti-viral agents (Liu et al., 2015a; b). In this context, also polysaccharides modified by chemical synthesis have been investigated. In most cases such structural changes led to significant improvements of the pharmacological activity. This is the case of Se-modified plant and fungal polysaccharides. Selenium is nowadays well recognized as an important micronutrient for humans and animals. It is for example contained in selenocysteine, considered as the 21st aminoacid, which in turn is a component of about 30 enzymes, among which glutathione peroxidase and thioredoxine reductase. Other reported biological activities include its capacity to boost immune responses, and anti-oxidant, anti-cancer, anti-metal poisoning, and anti-diabetic effects (Santi and Bagnoli, 2017). Se-containing polysaccharides of natural origin are biosynthesized by a very restricted number of plants and fungi like *Cucurbita pepo* L. ("pumpkin", Cucurbitaceae), *Codonopsis pilosula* Nannf. ("dangshen", Campanulaceae), *Ganoderma lucidum* (Curtis) P. Karst ("reishi", Ganodermataceae), *Astragalus membranaceus* Moench. ("huang qi", Fabaceae), *Flammulina velutipes* (Curtis) Singer ("enokitake", Marasmiaceae), and *Auricularia auricula-judae* (Bull.) J. Schröt. ("jelly ear", Auriculariaceae). However, in all cases the Se content is very low ($< 8\,\mu g/g$) even in the case of plants and fungi

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Abbreviations

ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BHT	Butyl hydroxytoluene
CAT	Catalase
CREB	cAMP response element-binding protein
DPPH	Diphenyl pycryl hydrazyl
DSC	Differential scanning calorimetry
ERK	Extracellular signal-regulated kinase
FT-IR	Fourier transform infrared
GSH	Glutathione peroxidase
HDL	High density lipoprotein
ICP-AES	Inductively coupled plasma atomic emission spectrometry
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
i.m.	Intramuscular
i.p.	Intraperitoneally
JNK	c-Jun N-terminal kinase
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MDA	Malondialdehyde
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
ND	Newcastle disease
NF	Nuclear factor
NO	Nitric oxide
PARP	Poly(ADP-ribose)polymerase
rHBsAg	Recombinant hepatitis B virus surface antigen
ROS	Reactive oxygen species
Se-P	Selenylated polysaccharide
SOD	Superoxido dismutase
TNF	Tumor necrosis factor
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
Vis	Visible

grown in Se-rich soils, and by far not sufficient for human supplementation (Gao et al., 2016). Therefore, studies have been performed to establish methods to synthesize Se-P from the respective natural sources. The first approach consisted in adding inorganic Se, in most cases as Na_2SeO_3, to culture media of fungi, bacteria, algae, and other small plants. Although some successful cases have been reported, like those obtained with *A. membranaceus* (Li et al., 2014a; b), *Hericium erinaceus* (Bull.) Pers. ("lion's mane", Hericiaceae) (Malinowska et al., 2009), and *Catathelasma ventricosum* (Peck) Singer ("swollen-stalked cat", Tricholomataceae) (Wang et al., 2013), this kind of processes are restricted to a very narrow number of species, and the extraction, purification, and structural characterization of desired adducts is very complicated. Thus, the artificial selenylation of natural polysaccharides is nowadays considered as the best way to accomplish the overall process. The aim of this comprehensive review will be to provide a detailed survey of the in so far reported literature data on the chemical and pharmacological properties of Se-Ps deriving from polysaccharides of plant, algal, and fungal origin. The literature period covered goes from 2009 to 2018. Bibliographic searches in the mean internet databases like Scifinder, Medline, Scopus, ISI Web of Science, and Google Scholar indicated that to date more than 30 articles and patents on this topic have been issued. After a summary of the most effective synthetic and structural characterization methodologies, algae, fungal, and plants, grouped by their respective families in alphabetic order, will be examined. Finally, the major perspectives in the field with suggestions on possible topics to address novel research activities will be discussed.

2. Methodologies for the selenylation of natural polysaccharides and their structural characterization

The first chemical synthesis of a Se-P was performed in 1988 by Tang and Rui. These authors obtained selenylated carrageenan by the reaction of the parent polysaccharide with Se powder in water as the solvent. The main difficulty of this approach was the separation of unreacted Se by filtration under vacuum and the adjustment of the pH value necessary to get a complete crystallization of the desired Se-P. About ten years later (1997), Gong proposed the use of $SeOCl_2$ as a promoter for the selenylation of the glucane and dextrane fractions of *Astragalus* spp. polysaccharides. Although obtaining a high Se content and yield in the resulting adduct, the main inconvenience of this method is the use of a toxic, hazardous, harsh to handle, and highly polluting reagent like $SeOCl_2$ and also in this case difficulties in the recovery of the product from the reaction medium. The third and nowadays by far most accepted and employed methodology, due to its simple and mild conditions, feasibility, less environmental dangerous, and convenient product recovery, is the one reported by Qin and coworkers in 2013a, b. This consists in the use of a combination of diluted HNO_3 and Na_2SeO_3 to generate *in situ* H_2SeO_3 and to get the selective esterification of the more reactive primary OH group of monomers along the skeleton of the polysaccharide as depicted in Fig. 1.

In some cases, the addition of catalytic amounts of $BaCl_2$ speeds up the reaction kinetic. The one by Qin and coworkers has been the method to obtain all Se-Ps described in the paragraphs below, unless specified. Stating the degree of structural complexity, several methods to characterize the adducts resulting from a selenylation reaction have been proposed, and these include: particle size distribution analysis, Z potential, DSC analysis (Ji et al., 2013a), X ray diffraction (Ji et al., 2013b), mass spectrometry, atomic fluorescence spectrometry, and ICP-AES (Yuan et al., 2017). These three latters can be considered methods of choice for the determination of the Se content. More common and routinary techniques include FT-IR spectroscopy, for which diagnostic

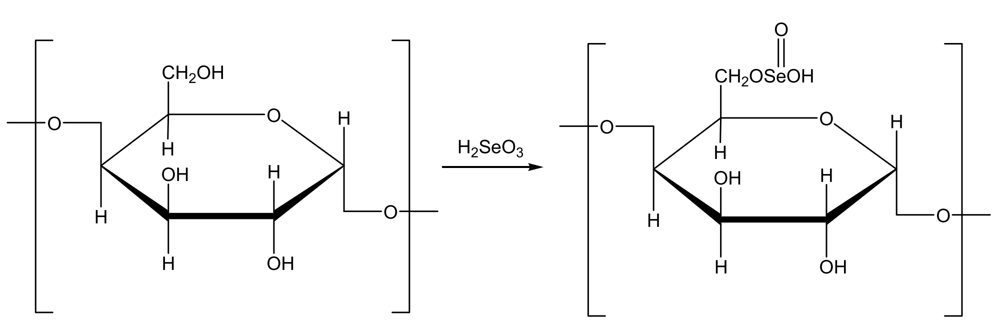

Fig. 1. Selenylation mechanism of naturally occurring polysaccharides.