MINI-REVIEW

Research Trends in Plant-Derived Oligomers for Health Applications

Merve Deniz Kose [1], John G. Hardy [2,3], Emer Sheridan [4], Feyruz Bozoğlan [5] and Oguz Bayraktar *[,6]

[1]*Department of Chemical Engineering, Faculty of Engineering, Ege University, İzmir, Turkey;* [2]*Department of Chemistry, Lancaster University, Lancaster, UK,* [3] *Materials Science Institute, Lancaster University, Lancaster, UK,* [4]*Department of Medical and Human Sciences, University of Manchester, UK. ,*[5]*NPRO Ltd Co., İzmir, Turkey;* [6]*Department of Bioengineering, Faculty of Engineering, Ege University, İzmir, Turkey*

ARTICLE HISTORY

Received: March 26, 2020
Revised: May 09, 2020
Accepted: May 28, 2020

DOI:
10.2174/2665978601999200727103858

Abstract: ***Objective*:** Epidemiological data illustrates that there is a strong relationship between dietary intake of natural bioactive compounds and their beneficial properties against various diseases, and this stimulates academic and industrial interest in using plant-derived compounds for health and making medicines. For this reason, recent health related studies in the literature have focused on a variety of many plant-derived bioactive compounds. Even though the bioactivities of such compounds have widely been investigated, there are few studies about oligomeric species and their activities.

***Methods*:** In this review, extraction and isolation methods of the plant-derived oligomers and the use of such oligomers in health applications are summarised.

***Results*:** In the literature, many studies state that oligomeric compounds have benefits to human health. To maximize these beneficial properties, various ways to use oligomeric compounds have been examined and summarised.

***Conclusion*:** A better understanding of the specific activities of distinct components of plant-derived oligomers is expected to open new avenues for drug discovery. This review gives an overview of oligomers with health beneficial properties and their possible applications in healthcare.

Keywords: Plant-derived oligomers, oligopeptides, oligosaccharides, probiotics, prebiotics, drugs delivery systems, health applications, functional foods.

1. INTRODUCTION

The importance of functional foods, nutraceuticals, and other natural health products has generated interest in connection with disease risk reduction and the promotion of health in general [1]. Recent developments in functional foods have resulted in many studies that investigate their beneficial properties for human health [2].

There is a significant interest in using natural compounds as potential cancer therapeutics or cancer preventive agents for different cancer types [3-6]. Oligomeric compounds and their beneficial properties are important constituents of functional foods for health applications.

Oligomers are low molecular weight polymers consisting of a small number of repeated units (dimers, trimers, and tetramers are oligomers with two, three, and four monomers, respectively) whose physicochemical properties are dependent on the length of the chain [7]. Plant-derived oligomers are observed in various classes of compounds, including carbohydrates, proteins, melanins, and lipids.

Oligosaccharides are a group of carbohydrates that comprise 2–10 monosaccharides linked together in a linear or branched fashion [8]. Oligosaccharides can be produced naturally, or derived from polysaccharides after chemical, physical, or biochemical degradations; and they can be produced chemical/enzymatic synthesis [9].

The most abundant oligosaccharides are disaccharides, such as sucrose, maltose, and lactose [10]. The functional oligosaccharides are intermediate between simple sugars and polysaccharides and claimed as dietary fibers and prebiotics. These compounds, as non-absorbable food ingredients, are microbial food supplements and may benefit the host by selectively stimulating salutary bacteria in the large intestine [11]. Functional oligosaccharides are non-digestible by human microbiota, the most known of which are fructo-oligosaccharides, galacto-oligosaccharides, cyclodextrins,

*Address correspondence to this author at the Department of Bioengineering, Faculty of Engineering, Ege University, P.O. Box: 35100, İzmir, Turkey; Tel/Fax: +90-232-311-2105, +90-232-388-7776; E-mail: oguz.bayraktar@ege.edu.tr

2665-9786/20 $65.00+.00

and soy-oligosaccharides [8]. Oligosaccharides are commonly bound to lipids and amino acids via O-glycosidic and N-glycosidic bonds yielding glycolipids and glycoproteins [12]. Due to their chemical structure, the functional oligosaccharides are substrates that can only be consumed by a limited number of bacteria, thus stimulating their growth [13]. Cyclodextrins, which are a member of a family of cyclic oligosaccharides, consist of a macrocyclic ring of glucose subunits joined by α-1,4 glycosidic bonds. They are widely used in food, pharmaceutical, chemical, agricultural and environmental applications. Complexation of beta-cyclodextrin with various different food colorants or natural compounds has been shown to enhance water solubilities and improve the light stabilities of those compounds. The structure β-cyclodextrin is shown in Fig. (**1**).

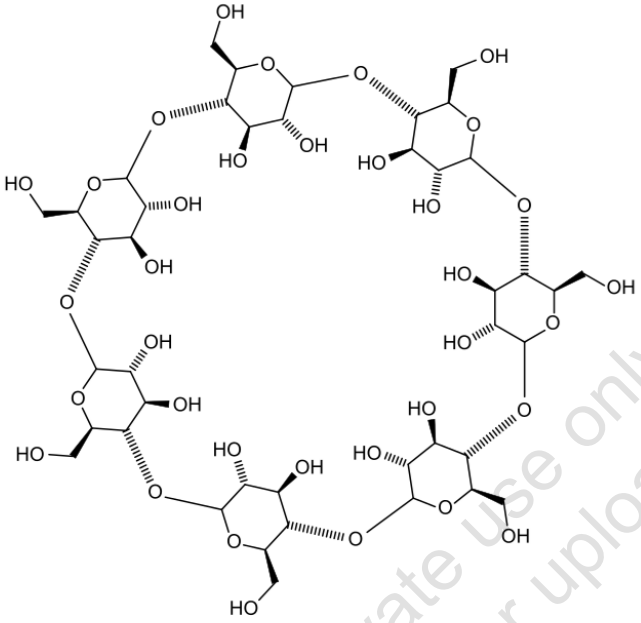

Fig. (1). Structure of β-cyclodextrin.

While carbohydrates are well known to be dietary staples, it is only recently recognized that oligosaccharides have become the subject of significant interest due to their resistance to digestion in the upper gastrointestinal tract and fermentation in the large bowel in addition to their fat replacement and sweetening ability. These properties lead to the usage of oligosaccharides for functional effects such as for a healthy gastrointestinal tract, improvement of glucose control, immune status, and modulation of the metabolism of triglycerides [14]. Interestingly, heparin oligosaccharides show anti-inflammatory, antifibrotic, and antimetastatic activities different from heparin polysaccharides [15], and fructo-oligosaccharides have been reported to increase the absorption of calcium, magnesium, and iron, and decrease the occurrence of osteoporosis [16]. Consequently, there is increasing interest in academic and industrial research and development related to the addition of oligosaccharides to processed foods for animals and humans, and as functional compounds in nutraceutical products.

Bioactive peptides underpin vital activities of living organisms. A variety of bioactive oligopeptides have been isolated from plants, animals, and microorganisms. Nutritional studies suggest that the physicochemical properties of oligopeptides play an important role in their absorption in the microbiota [17].

Essential oils found in the roots, leaves, and flowers of plants often contain lipids with oligomeric structures, consisting of terpenoids (two or more isoprene [2-methyl-1,3-butadiene] units), that possess antimicrobial and antioxidant activity [18].

For plant-derived oligomers, the peanut is a very important source for both academic and industrial teams because it contains all the oligomeric groups, thereby offering opportunities for fundamental and applied research; honey also consists of various oligomers like oligosaccharides, proteins, and polyphenols [19], however, it is important to note that some plants are rich in one oligomer group.

Van Laere and Wissing patented the use of oligosaccharides for nutritional composition with health-promoting action, in particular, having a bifidogenic effect and an anti-adhesive effect on pathogenic microorganisms to the intestinal wall [20].

The exciting potential of plant-derived oligomers has motivated fundamental studies of structure-activity relationships, and more applied studies of the structures and compositions of oligomers produced by various plant sources (variety, environmental conditions, *etc*.), and extraction and isolation methodologies with a view to generating industrially viable processes and products utilising these oligomers.

2. EXTRACTION AND ISOLATION METHODS

An overview of popular methods for the extraction and isolation of plant-derived oligomers is given in the following section.

2.1. Extraction Processes of Oligosaccharides from Different Sources

Various extraction methods and sources for plant-derived oligosaccharides have been reported in the literature.

Guo and coworkers investigated ultrasound-microwave synergistic extraction of prebiotic oligosaccharides from sweet potatoes (*Ipomoea batatas L*.). In the study, dried and ground sweet potatoes were mixed with distilled water at 1:15 (w/v) solid to liquid ratio, the starch was removed as explained in their earlier work with ultra-high pressure treatment [21], and the starch-depleted sample was subjected to ultrasound-microwave-assisted-extraction (UMAE). After rotary evaporation, the concentrated liquid was precipitated with three volumes of 95% ethanol (v/v) and stored overnight at 4 °C to precipitate polysaccharides and proteins. After removal of the precipitate by using a macroporous resin, the supernatant was purified via size exclusion chromatography, yielding oligosaccharides. Optimum extraction yields of prebiotic oligosaccharides from sweet potatoes (PPOS4 and PPOS5) were obtained at 100 s extraction time, 300W ultrasonic power, and 200W microwave power. Under these conditions, the experimental yields of PPOS4 and PPOS5 were 1.472, and 5.476%, respectively [22].

Liang and coworkers extracted crude oligosaccharides from pumpkins (*Cucurbita moschata* Duch). Pumpkins were pulped and mixed with distilled water at a 1:3 solid to liquid ratio and heated at 90 °C for 3 h. Isolation of the supernatant fractions after centrifugation and concentration by rotary evaporation followed by the addition of three times the volume of ethanol resulted in the precipitation of proteins and oligosaccharides. The supernatant fraction was separated by the membrane filter method yielding oligosaccharides. The pumpkin oligosaccharide recovery ratio of 81.3% was reported at optimum conditions [23].

Sanches Lopes and coworkers used *Stevia rebaudiana* (Bertoni) roots to obtain fructo-oligosaccharides to enable studies of their prebiotic activity. The roots of *S. rebaudiana* were placed in a liquid medium with 33.3% strength Murashige and Skoog (MS/3) medium that was supplemented with 30 g/L D-sucrose and 2.0 mg/L α-naphthaleneacetic acid, and the roots were then dried. The oligosaccharides were extracted from the roots with water under reflux conditions at 80 °C for 5 h followed by filtration, concentration by rotary evaporation, and mixing with ethanol at a ratio of 1:3 (v/v) to precipitate crude aqueous extract. The ethanolic supernatant was collected and lyophilized to yield the dry extract of the soluble fructan fraction (SFF). The oligosaccharides isolated from *S. rebaudiana* roots were observed to enhance the growth of both bifidobacteria and lactobacilli, with strain specificity in their fermentation ability. The FOS yield from the SFF that was obtained from *S. rebaudiana* roots was 24%, [24].

Lu and coworkers extracted oligosaccharides from lotus (*Nelumbo nucifera* Gaertn.) seeds simultaneously employing ultrasonication and microwaves to assist the extraction process. By using the response surface methodology, optimum extraction parameters were determined to be: extraction time 325 s, liquid-solid ratio 10 mL/g (L/S ratio), ultrasonic power 300 W, and microwave power 250 W. Moreover, the yield of total oligosaccharides increased by 76% compared with traditional methods like hot water extraction, ultrasonic or microwave-assisted extraction. Their findings showed that ultrasonic-microwave-assisted extraction was efficient for the extraction of oligosaccharides. The yield of lotus seed oligosaccharides achieved using traditional warm water backflow method with 82 °C for 66.05 min and liquid-solid ratio 70.00 mL/g, was 6.228 ± 0.06%. By adopting ultrasonic-assisted extraction with 320 W, liquid-solid ratio 15.00 mL/g and 65 °C for 48.32 min, the yield of lotus seed oligosaccharides was 9.362 ± 0.07%, yet by adopting the microwave-assisted extraction, ultrasonic/microwave-assisted extraction with microwave power of 320.00 W and liquid-solid ratio of 20.00 mL/g for 6.27 min, the yield was found to be 8.645 ± 0.04%. While the yield of lotus seed oligosaccharides was 11.009 ± 0.019% though ultrasonic-microwave synergy extraction for 5.42 min resulted in enhanced extraction yields with shortened extraction time compared to the independent extraction process through the traditional warm water soaking, ultrasonic-assisted, and microwave-assisted method [25].

Khuituan and coworkers extracted oligosaccharides from fresh dragon fruits. Washed fruits were separated as peel and flesh; both parts were ground and extracted using pectinase, the resultant low molecular weight fraction without prebiotic properties was removed by yeast cultivation, after which the yeast cells were removed by filtration, yielding an oligosaccharide fraction [26].

Desai and coworkers extracted oligosaccharides from green coffee beans. Hot water extraction, pressure hydrolysis, and viscozyme methods were used; the hot water infusion was carried out using distilled water at 60 °C for 2 h. The insoluble fraction in the extracts was treated with chloroform/methanol (2:1) solutions, yielding glycolipids in the chloroform fraction and oligosaccharides in the extraction solvent. The oligosaccharides extracted from green coffee were used as a carbon source for the cultivation of three probiotic LAB strains. It was observed that the oligosaccharides stimulated the growth of *Lactobacillus plantarum* (MTCC 5422), by increasing their number from 8.09×10^7 to 5.4×10^9 cells/ml within 48 h. The enzymatic (Viscozyme), thermal (roasting) and aqueous (hot water infusion) extraction yielded 19.92 ± 2.1% of Mono-oligosaccharides with mannose (6.90 ± 0.9 µg/Mg) and galactose (8.35 ± 1.0 µg/Mg) as major components. The study showed that coffee and coffee by-products can be a promising source for novel functional food rich in bioactive oligomers [27].

2.2. Extraction Processes of Oligopeptides from Different Sources

In the literature, there are various extraction methods and sources for plant-derived oligopeptides.

Marseglia and coworkers extracted oligopeptides from cocoa beans. Finely ground cocoa beans were suspended in 0.1 N HCl. With the addition of (L, L)-phenylalanylphenylalanine, the suspension was homogenized and centrifuged, then filtered and extracted 4 times with diethyl ether, and filtered again. The resulting aqueous solution was acidified with a formic acid solution (0.1%), filtered through Sartorius Vivaspin 2 filters (nominal molecular cut-off 10,000 Da) using an Amicon Micropartition system MPS-1. The filtrate was dried under nitrogen, and re-dissolved in acidified water (0.1% formic acid). Analysis by High-Pressure Liquid Chromatography (HPLC) and mass spectrometry (MS) showed 44 oligopeptides. The data obtained for roasted products showed that thermal treatments reduced the total content of peptides by almost 30% [28].

Another study using cocoa beans as a source of oligopeptides employed Dichloromethane to de-fat ground cocoa beans in a Soxhlet extraction apparatus for 18 h. The defatted powder was dried under vacuum, and then extracted using an acidified methanolic solution ($MeOH:H_2O:CH_3COOH::70:28:2$). The extraction solution was subjected to ultrasonication for 10 mins, stirred for 30 mins at room temperature, filtered, and analyzed with HPLC. Oligopeptides were extracted from the dried defatted cocoa powder with a single step process [29].

Ren and coworkers isolated two novel α-glucosidase inhibitory oligopeptides from hemp (*Cannabis sativa* L.) seed protein (HSP). The extraction process involved defatting and drying hemp seed meal, followed by sieving with a 120 mesh screen. The obtained powder was dispersed

in distilled water at a ratio of 1:20 (w/v). The pH of the extraction solution was adjusted to 8.5 with 1M NaOH. The solution was stirred for an hour at 37 °C, and after centrifugation, the supernatant was collected and the pH was adjusted to 4.5 with 1 M HCl solution. The resultant precipitate was washed and re-dispersed in distilled water. The mixture was dialyzed, homogenized, and freeze-dried prior to enzymatic hydrolysis. The hydrolysates with high α-glucosidase inhibitory activity could successfully be prepared by treatment with an Alcalase-catalysed process [30].

Rojas and coworkers isolated low molecular weight oligopeptides from soybean hulls (which are also used as animal feed). The soybean hulls were found to be a rich source of both proteins and cellulose, and therefore also potentially an ethanol source, which is a much-needed commodity for processes and oligopeptides [31].

In 1994, Cheng and coworkers used *Aster Tataricus* as a source for oligopeptides. Three novel oligopeptides, asterinin A-C have been isolated from the roots of *A. tataricus* and their structures were elucidated by chemical, enzymatic, and spectral methods [32].

Jiang and coworkers used peanuts for the aqueous extraction of peanut oil and oligopeptides. The optimum extraction conditions were reported to be hydrolysis at 60 °C, a pH of 9.5, and the ratio of material to water 1:5 (w/w), for 90 min, followed by Alcalase enzyme treatment 1.5% (w/w) and hydrolysis for 5h, resulting in a yield of 71% (w/w) of protein hydrolysates which include %80 oligopeptides. The addition of the alkaline extraction before the enzymatic hydrolysis was observed to improve the yield of both peanut oil and oligopeptides [33, 34].

Soto-Sierra and coworkers provided an interesting review of the extraction and fractionation of protein products from microalgae [35].

2.3. Extraction Processes of Phenolic Oligomers from Different Sources

Plant-derived phenolics are produced by a variety of plants.

Jia and coworkers extracted polyphenolic oligomers from *Cinnamomum parthenoxylon* bark to investigate the hypoglycemic activity of the oligomers against streptozotocin-induced diabetes. 2 kg dried and powdered cinnamon barks were suspended in acetone/water (1:1, v/v) solution for 2 hours, filtered and the residue was subjected to the same process once again. The combined extracts were concentrated under vacuum, partitioned with ether, and a macro resin column was used to isolate the oligomers. The obtained extracts were freeze-dried. 86 g extract was obtained. The results suggested that from HPLC fingerprint data, the molecular weights of the oligomers in the extract were mostly B-type procyanidins. Results showed asignificant reduction in blood glucose levels in normal and STZ-induced rats after 2 weeks of treatment with polyphenolic oligomer-rich extract of *C. parthenoxylon* barks [36].

Sugiyama and coworkers extracted oligomeric procyanidins from apples and studied their ability to inhibit pancreatic lipase [37]. Their extraction process was adapted from a method reported by Yanagida and coworkers, where unripe apples were homogenized in 0.1% (w/w) potassium pyrosulfite solution and kept at 4 °C for 24 h. The supernatant was centrifuged and filtered, the filtrate was subjected to column chromatography to remove monomeric structures in the crude apple polyphenol isolate, after which it was freeze-dried [38]. To investigate the relationship between the degree of polymerization and the inhibitory effects on pancreatic lipase activity, the procyanidins were fractionated. The procyanidins were the main contributor to the effect of apple polyphenol extract on inhibiting triglyceride absorption [37].

Strandas and coworkers studied phenolic oligomers isolate from flaxseeds. Dried and ground flaxseeds were defatted with hexane twice, then mixed with ethanol, water, and 2 M NaOH for 16h at room temperature. The solution pH was adjusted to pH 3 with 2 M H_2SO_4. After the centrifugation, the supernatant was collected and concentrated under vacuum until it was dried. The dried extract was dissolved in 10% methanol solution and separated via silica column chromatography. The flaxseed oligomer fractions were separated according to their hydrophobicity [39].

Bors and coworkers isolated caffeic acid oligomers from *Salvia officinalis* by adaptation of the method reported by Lu and coworkers [40, 41], which enabled them to investigate the antioxidant mechanisms of the isolated caffeic acid oligomers [42].

Gonzalez Sarrias and coworkers extracted resveratrol oligomers from ground *Carex gynandra* leaves that were sequentially extracted with hexane, acetone, and methanol at room temperature. The combined extracts for each solvent were concentrated under vacuum, subjected to column chromatography, and analysed by NMR, proving that the oligomers obtained were pallidol, α -viniferin, *trans*-miyabenol C, kobophenol A and kobophenol B [43]. For example, α-viniferin, which is a trimer of resveratrol, can be isolated from various plant resources. It shows an inhibitory effect towards the enzyme acetylcholinesterase (EC 3.1.1.7), which has an important role as an anti-inflammatory agent. In Fig. (**2**), the structure of α-viniferin is shown.

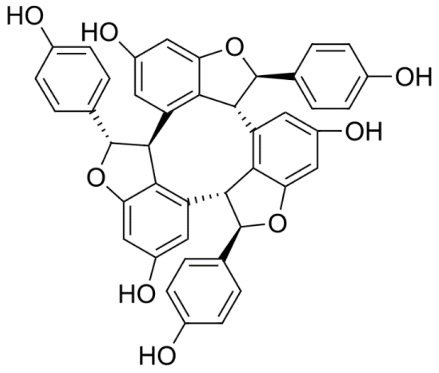

Fig. (2). Structure of α-viniferin.

Ito and coworkers isolated a new glucoside of the resveratrol trimer from the stem of *Hopea utilis*. Dried and ground stem wood of *H. utilis* was extracted with acetone and methanol followed by silica and Sephadex column

chromatography. NMR results revealed the successful isolation of a new resveratrol oligomer [44].

3. HEALTH BENEFITS AND APPLICATIONS

The potential beneficial health properties in addition to their nutritional values of plant-derived oligomers are increasingly studied.

Shankar and coworkers studied the application of amyloid- β protein (Aβ) natural oligomers to treat the effects on Alzheimer's by reducing the progressive loss of the hippocampal synapses. To treat slices with Aβ, the equivalent of 75µl pooled, and lyophilized size exclusion chromatography fractions of 7PA2 cells conditioned medium were reconstituted in slice culture medium (SCM) and applied to each insert. The study shows that physiological concentrations of naturally secreted dimers and trimers, but not monomers, are effective in reducing the loss of hippocampal synapses [45].

Phan and coworkers reported that plant-derived transient expression is an alternative platform to produce hemagglutinin-based subunit vaccines. The advantages of the subunit vaccines from plants are that they can be produced for a low price and plant production systems can be scaled up easily. They used stable trimeric H5 haemagglutinins in the endoplasmic reticulum of *Nicotiana benthamiana* leaf cells. As a result, they showed that H5 oligomers more effectively induce neutralizing antibodies in mice than H5-Strep-tag trimers [46].

A review from Ji and coworkers examined the use of functional oligopeptides as a novel strategy for drug delivery. Various studies preferred oligopeptides for their properties such as specific targeting, cell penetration, self-assembled capacity, and responsiveness to the environment. Moreover, methods to target tumor neovasculature, cells, and organelles were summarized [47].

Peanut skin is a rich source of procyanidins, which are oligomers of catechin units and their derivatives. Bansode and coworkers reviewed peanut skin oligomers and its lipid-lowering function, concluding that with peanut skin extract supplementation, a reduction in total lipid levels can be achieved [48]. In Fig. (**3**), the structure of procyanidin A2 that is one of the oligomers identified in the extract, is given.

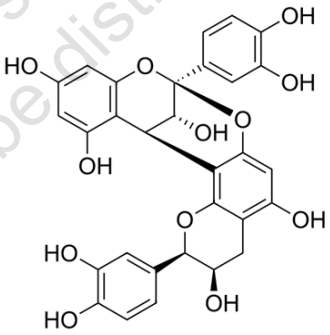

Fig. (3). Structure of procyanidin A2.

Their study revealed the bioavailability of Peanut skin extract (PSE) in rat plasma, especially procyanidin A2. The reduction in plasma lipid and fatty acid profiles of the rats, given a Western-type diet for 5 weeks, was observed. The supplementation of 300 mg/kg PSE in groups on a Western diet for five weeks also resulted in significantly lower triglyceride levels.

Yang and coworkers extracted oligosaccharides from flaxseed gum via enzymatic hydrolysis to determine their antioxidant and antitumor activities. The antioxidant activity of the extract was determined with DPPH and ABTS methods. The antitumor effect was tested against HeLa, HepG2, and MRC-5 cells. Their results showed that flaxseed gum oligosaccharides (FGOS) had better antioxidant activities than flaxseed gum (FG) on DPPH and ABTS radicals. Besides, 0.4 mg/ml FGOS displayed significant activities against HepG2 and HeLa cancer cells [49].

Özdemir and coworkers aimed to use ε-viniferin with cisplatin for its apoptotic effects in Glioma cell lines (C6). Cisplatin is a chemotherapy medication used to treat various cancer types. However, the major problem faced with treating glioblastoma is the inability of drugs to pass through the blood-brain barrier. With a combination of natural bioactive compounds and chemotherapy, agents can improve the sensitivity and cytotoxicity of the drugs. Their study showed a strong apoptotic effect with a combination of cisplatin and ε-viniferin. The combined 13.25 µM/cisplatin and 95 µM ε-viniferin treatment caused maximum caspase-3 activation in C6 cells (15.5%) at the end of the 72 h incubation. Their conclusion was the combined use of CDDP and e-VNF in C6 cells has the potential to treat glioblastoma [50].

Pai and coworkers used oligosaccharides to increase the binding properties of the nanostructured lipid carriers (NLC) to ocular mucins. In comparison with commercially available chitosan itself, chitosan oligosaccharides (COs) are more suitable for drug delivery applications due to lower molecular weight. Moreover, COs have better solubility in aqueous media at neutral pH, where it carries a net positive charge. These properties allow the nanocarriers to have a higher availability at the eye surface. In the study, the surface coating of the prepared NLC was done with the dripping method. The mucoadhesive behavior of COS-coated NLC changed drastically when compared to the uncoated NLC, resulting in higher amounts available at the ocular surface [51].

Chi and coworkers studied the effect of fructo-oligosaccharides (FOS) from *Morinda officinal* on mild to moderate depression. To investigate microbiota-gut-brain used in the study, FOS was introduced via intragastric gavage to rats subjected to mild stress conditions. The anti-depressive effects were investigated through behavioral tests, intestinal morphology, and corticosterone levels. The results showed that FOS eased depression-like behaviors and repaired intestinal epithelial damages. In addition to that, FOS treatment decreased the corticosterone levels in the plasma and urine of the model rats. They concluded that the antidepression efficacy of the FOS depends on the modulation of the gut microbiota [52].

The importance of gut microbiota has recently become a priority for biomedicine, with studies showing that both the immune system and metabolism are affected by gut microbiota.

Gong and coworkers studied the effects of wheat bran feruloylated oligosaccharides (FOs) on the gut microbiota.

The study was performed by *in vitro* fermentation with healthy human feces. They stated that FOs affect the overall community of the gut microbiota, and increased beneficial microorganisms such as *Bifidobacterium* and *Faecalibacterium* inhibit the growth of disease-related bacteria such as *Alistipes*, *Bilophila, Dorea, Enterobacteriaceae*, and *Oscillopira* [53].

Li and coworkers examined the impact of oligosaccharides on the growth of four probiotic bacteria (*Lactobacillus plantarum, Leuconostoc mesenteroides, Lactobacillus casei,* and *Lactobacillus rhamnosus*). In the study, mulberry oligosaccharides were obtained from mulberry polysaccharides with three methods: physical hydrolysis, chemical hydrolysis, and enzymatic hydrolysis. Their findings were first showed that the oligosaccharides produced with enzymatic hydrolysis had the greatest effect on the growth of *L. rhamnosus*. sSecondly, enzymatically prepared oligosaccharides were superior to the untreated mulberry polysaccharide and commercially available prebiotics [54].

An investigation of the effect of cellulose-derived oligomers on damage-associated molecular patterns and their responses was reported by de Azevedo Souza and coworkers. They showed that *Arabidopsis thaliana* could detect cellulose degradation products like cellobiose and respond by activation of a signalling cascade leading to the increased expression of defense-related genes, with substantial overlap in Arabidopsis seedlings, an immune response that resulted in less cell damage following *P. syringae* infection [55].

Segun and coworkers used resveratrol derivatives from *Commiphora Africana* to investigate cytotoxicity against several human cancer cell lines. Cytotoxicity testing was carried out using the MTT assay on the breast (MCF7), liver (HepG2), lung (A549), and prostate (PC3) cancer cells. The obtained data validated the traditional use of *C. africana* in the treatment of cancer. They report the antiproliferative properties of the extracts and isolated compounds of *C. africana* on four human carcinoma cells [56].

Bose and coworkers used alginate oligosaccharides (AOs) to preserve fruit quality and increase storage life for strawberries. The ripening of the non-climacteric fruits mostly depends on the abscisic acid (ABA) amount. The use of AOs delayed the accumulation of ABA, which resulted in the prolonged storage life of strawberry. Strawberries were immersed into AOs solution for 60 seconds. The control group was immersed in distilled water. Then both treated and untreated fruits were kept at room temperature. With AOs treatment, the storage quality of the strawberry increased drastically. In AOs treated fruits, level of hardness, titratable acidity, pH, total soluble solids, vitamin C, anthocyanin, total phenol, and flavonoids increased and decay percentage found to decrease. Moreover, AOs treatment delayed the degradation of cell wall components and repressed the expression of cell wall degradation related genes [57].

Chen and coworkers used oligopeptide liposomes to deliver paclitaxel and anti-survivin siRNA for the synergistic treatment of breast cancer and metastasis. One of the problems faced during paclitaxel treatment is the drug resistance in cancer cells. Recent studies show that proteins like survivin cause the upregulation of the paclitaxel resistance. To downregulate the survivin expression has become the priority of the novel cancer treatments. For this purpose, Chen and coworkers preferred co-delivery of the paclitaxel and anti-survivin siRNA. Their results showed that the nano-carrier could successfully deliver two drugs into breast cancer cells. With the release of the anti-survivin siRNA, the survivin proteins were successfully blocked, allowing paclitaxel to work. They reported that the combination of paclitaxel and anti-survivin siRNA is a promising strategy to inhibit breast tumor growth and metastasis by using oligopeptide liposomes [58].

Noor and coworkers used stearic acid-chitosan oligomer coated nanostructured lipid carriers for topical delivery of dutasteride. Dutasteride promotes hair growth. To ease the delivery to the hair follicles, dutasteride-loaded nano lipid structures coated with chitosan oligomer-stearic acid were prepared. Dutasteride-loaded lipid particles prepared with the melt-dispersion ultrasonication method. Then, the prepared particles were dripped into chitosan oligomer-stearic acid solution. The characterization of the particles was done with NMR and FTIR analysis. They successfully prepared stearic acid-chitosan conjugates. The permeability studies revealed that with coating, the amount of dutasteride found in the skin was increased [59].

Ohara and coworkers investigated the beneficial properties of resveratrol dimer ε -viniferin against diet-induced obesity in mice. In the study to determine the anti-obesity effects of grape shoot extract (GSE) *in vivo*, mice were fed a high-fat diet with or without GSE for 4 weeks. Results showed that ε -viniferin exerted higher anti-adipogenesis activity in 3T3-L1 cells than t-resveratrol [60]. The obtained data suggested that GSE could be used to develop beverages or foods with health benefits against obesity.

Ose and coworkers investigated the ability of human intestinal anaerobes to metabolize different oligosaccharides. In the study, the metabolic properties of six oligosaccharides in 31 key gut anaerobes were investigated. The fermentation profiles indicated specific links between the microbial end-products and specific gut microbes. For instance, *bifidobacteria* readily metabolized fructooligosaccharide (FOSs) with a degree of polymerization (DP) 3, *i.e.* 1-kestose, but several strains used did not actively metabolize FOSs with DP4 and DP5, *i.e*. nystose and fructosylnystose. They stated that with the obtained data, it was possible to predict the impact of oligosaccharides in human intervention and gut microbiota modulation [61].

Zheng and coworkers reported that compressed food with added functional oligopeptides (CFMO) improved performance during military endurance training. When both the groups were compared, the recovery heart rates were significantly lower with the CFMO diet. CFMO led to better heart rate recovery, improved and maintained blood glucose, and increased removal of blood lactate. CFMO accelerated the removal of blood lactate during recovery, maintained oxygen supply, and increased fluid retention [62].

Li and coworkers regulated the lipid homeostasis with oligomer procyanidins from lotus seedpod. Regulating the lipid in the human body is crucial. Chronic accumulation of lipids can cause obesity, diabetes, and insulin resistance [63].

Table 1. Sources of oligomers and their application areas.

Oligomer Source	Application Area	Ref
Adzuki Beans	Anti-cancer activity	[69]
Rice Straw	Antibacterial activity	[66]
Grape shoot	Diet-induced obesity	[60]
Lotus seedpod	Lipid homeostasis	[64]
Lotus seedpod	Emulsifiers and antioxidants	[68]
Commiphora Africana	Anticancer activity	[56]
Dragon fruit	Gut motility	[26]
Morinda officinal	Depression	[52]
Flaxseed	Antitumor activity	[49]
Cocoa Beans	Antidiabetic activity	[70]
Carex Species	Against Colon Tumorigenic Cells	[43]
Salvia officinalis	Antioxidant properties	[42]
Peanut Skin	Lipid-lowering activity	[48]
Cyphostemma crotalarioides	Antifungal properties	[71]

Oligomers were extracted with ethyl acetate to obtain lotus seedpod oligomeric procyanidin (LSOPC). LSOPC loaded emulsions were prepared with spontaneous emulsification method. *In vivo* studies showed that lotus seedpod oligomeric procyanidin (LSOPC) decreased total serum triglyceride and total cholesterol and elevated the high-density lipoprotein level in the hyperlipidemic rat model. They reported that the LSOPC-enriched emulsion showed increased antioxidant properties and suppressed fat hydrolysis in stimulated gastrointestinal medium through inhibition of lipase, which may contribute to the hypolipidemic effect. These results concluded that LSOPC could serve as a promising dietary supplement [64].

Shi and coworkers studied condensed tannin from rice straw and its inhibitory effect on *Staphylococcus aureus.* Rice straw is an agricultural waste, which can be used to utilize value-added products. In the study, rice straw was used as a source for tannins. For the extraction process, rice straw was treated as decribed in the literature [65]. Then. the treated rice straw was extracted with 70% ethanol solution at 60 °C for 2 hours. Then the inhibitory effect of extracted tannins was investigated. The tannins exhibited strong inhibitory effects on the growth of *S. aureus*. The fraction with 0.31g tannins/kg straw concentration showed the highest impact. In addition to that, the tannins inhibited biofilm formation by accelerating planktonic cell aggregation, and reduced the ability of cells to adhere to the surface [66].

Chen and coworkers used lotus seedpod proanthocyanidin (LSPC)-whey protein (WPI) complexes to enhance the physical and chemical stability of β-carotene-nanoemulsions. Lotus seedpod has been used for the extraction of proanthocyanidin in various studies [64, 67]. The results showed that LSPC-WPI complexes could be used as effective emulsifiers and antioxidants in nutraceutical-loaded nanoemulsions. The only drawback for the complexes was to obtain nanoemulsions stable in the pH above or below the isoelectric point of whey protein as pH 6.5 [68].

Another study used oligomeric proanthocyanidins to investigate its anti-cancer activity. Kawahara and coworkers extracted oligomeric proanthocyanidins from adzuki beans (*Vigna angularis*). Adzuki beans were soaked in water for 15 h. Then five fractions were obtained using Amberlite XAD-1180N, Toyopearl HW40F, and Sepacore C-18 reverse-phase flash column chromatography. Each fraction was characterized as (epi)catechin hexamer, heptamer, and octamer, epigallocatechin-(epi)catechin pentamer, and epigallocatechin-(epi)catechin hexamer using Mass Spectrometry. The anti-cancer activity was investigated against the human PC-3 prostate cancer cell line. The obtained data showed that each fraction showed significant anti-cancer activity. They also reported that fractions significantly suppressed the expression of the fatty acid-binding protein 5 gene, which plays critical roles in cell growth and metastasis in prostate cancer [69].

In Table **1**, various oligomer sources and their application areas are summarized.

CONCLUSION

In this review, we aimed to provide an overview of plant-derived oligomeric structures, their sources, and extraction methods, which are interesting in current research in both academic and industrial settings. Early studies about oligomers focused on their extraction and characterization, which led to studies of their potentially beneficial properties to health. The interesting functional properties, bioavailability, and bioactivity of oligomers motivate further study (*e.g.* for their potential to act as drugs or drug delivery systems).

From an economic point of view, the growing use of plant-derived materials will have environmental benefits, including waste reduction, lower greenhouse gas emissions, rewilding, and others. By utilizing the waste products of the agricultural and food industries it may be possible to obtain value-added products, promote rural investment, reduce the volume of harmful chemicals/pollutants, conserve ecosystems and biodiversity, and this will help transition to the circular economy; all of which support the United Nations Sustainable Development Goals (SDGs), specifically SDG 1, 2, 3, 8, 9, 12, 13 and 15. We believe that the findings and promising results of these studies reviewed here will be of interest to a broad readership and hopefully inspire collaborative research involving parties from both academic and industrial settings.

ACKNOWLEDGEMENTS

Authors acknowledge the support from the European Cooperation in Science and Technology (COST) Action CA16112/NutRedOx.

CONFLICT OF INTEREST

Authors declare no conflict of interest, financial or otherwise.

CONSENT FOR PUBLICATION

Not applicable

FUNDING:

None.

ABBREVIATIONS

ABA	=	Abscisic Acid (ABA) Amount.
ABTS	=	2, 2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)
AOs	=	Alginate Oligosaccharides
Aβ	=	Amyloid β protein
CDDP	=	Cisplatin, Platinol
CFMO	=	Compressed Food with Added Functional Oligopeptides
CH_3COOH	=	Acetic Acid
COs	=	Chitosan Oligosaccharides
DPPH	=	2,2-diphenyl-1-picrylhydrazyl
DPs	=	Degree of Polymerization
e-VNF	=	ε-viniferin
FG	=	Flaxseed Gum
FGOS	=	Flaxseed Gum Oligosacchasrides
FOs	=	Feruloylated Oligosaccharides
FOS	=	Fructo-Oligosaccharides
GSE	=	Grape Shoot Extract
H_2SO_4	=	Sulfuric Acid
HCl	=	Hydrochloric Acid
HPLC	=	High-Pressure Liquid Chromatography
HSP	=	Hemp Seed Protein
LSOPC	=	Lotus Seedpod Oligomeric Procyanidin
MeOH	=	Methanol
MS	=	Mass Spectrometry
NaOH	=	Sodium Hydroxide
NLC	=	Nanostructured Lipid Carriers
NMR	=	Nuclear Magnetic Resonance
PSE	=	Peanut Skin Extract
SCM	=	Slice Culture Medium
SFF	=	Soluble Fructan Fraction
STZ	=	Streptozotocin
UMAE	=	Ultrasound-Microwave-Assisted-Extraction
WPI	=	Whey Protein Complexes

REFERENCES

[1] Hailu, G.; Boecker, A.; Henson, S.; Cranfield, J. Consumer valuation of functional foods and nutraceuticals in Canada. A conjoint study using probiotics. *Appetite,* **2009**, *52*(2), 257-265. http://dx.doi.org/10.1016/j.appet.2008.10.002 PMID: 19007828

[2] Shahidi, F. Nutraceuticals and functional foods: Whole versus processed foods. *Trends Food Sci. Technol.,* **2009**, *20*(9), 376-387. http://dx.doi.org/10.1016/j.tifs.2008.08.004

[3] Arts, I.C.W.; Hollman, P.C.H. Polyphenols and disease risk in epidemiologic studies. *Am. J. Clin. Nutr.,* **2005**, *81*(1)(Suppl.), 317S-325S. http://dx.doi.org/10.1093/ajcn/81.1.317S PMID: 15640497

[4] Yahia, E.M.; De Jesus Ornelas-Paz, J.; Gonzalez-Aguilar, G.A. Nutritional and health-promoting properties of tropical and subtropical fruits.*Postharvest Biology and Technology of Tropical and Subtropical Fruits*; Elsevier Ltd., **2011**, pp. 21-78. http://dx.doi.org/10.1533/9780857093622.21

[5] Tomé-Carneiro, J.; Larrosa, M.; González-Sarrías, A.; Tomás-Barberán, F.A.; García-Conesa, M.T.; Espín, J.C. Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. *Curr. Pharm. Des.,* **2013**, *19*(34), 6064-6093. http://dx.doi.org/10.2174/13816128113199990407 PMID: 23448440

[6] Kose, M.D.; Bayraktar, O. Encapsulated Plant- Derived Polyphenols as Potential Cancer Treatment Agents.*Herbal Medicine : Back to the Future Cancer Therapy*; Murad, F.; Rahman, A.; Bian, K., Eds.; Bentham Science, **2019**, pp. 91-122. http://dx.doi.org/10.2174/9789811411205119030005

[7] Jenkins, A.D.; Stepto, R.F.T.; Kratochvíl, P.; Suter, U.W. Glossary of basic terms in polymer science (IUPAC Recommendations 1996). *Pure Appl. Chem.,* **1996**, *68*(12), 2287-2311. http://dx.doi.org/10.1351/pac199668122287

[8] Ibrahim, O.O. Functional Oligo-saccharides: Chemicals Structure, Manufacturing, Health Benefits, Applications and Regulations. *J Food Chem Nanotechnol,* **2018**, *4*(4), 65-76. http://dx.doi.org/10.17756/jfcn.2018-060

[9] Courtois, J. Oligosaccharides from land plants and algae: production and applications in therapeutics and biotechnology. *Curr. Opin. Microbiol.,* **2009**, *12*(3), 261-273. http://dx.doi.org/10.1016/j.mib.2009.04.007 PMID: 19467920

[10] Ouellette, RJ; Rawn, JD *Organic Chemistry [Internet]*; Academic Press, **2018**, pp. 29.Jan;889-928.

[11] Kunz, C.; Rudloff, S. Health promoting aspects of milk oligosaccharides. *Int. Dairy J.,* **2006**, *16*(11), 1341-1346.

http://dx.doi.org/10.1016/j.idairyj.2006.06.020
[12] Dilworth, L.L.; Riley, C.K.; Stennett, D.K. Plant Constituents: Carbohydrates, Oils, Resins, Balsams, and Plant Hormones.*Pharmacognosy: Fundamentals, Applications and Strategy*; Elsevier Inc., **2017**, Vol. 1, pp. 61-80..
[13] Qiang, X. YongLie C, QianBing W. Health benefit application of functional oligosaccharides. *Carbohydr. Polym.,* **2009**, *77*(3), 435-441.
http://dx.doi.org/10.1016/j.carbpol.2009.03.016
[14] Roberfroid, M.; Slavin, J. Nondigestible oligosaccharides. *Crit. Rev. Food Sci. Nutr.,* **2000**, *40*(6), 461-480.
http://dx.doi.org/10.1080/10408690091189239 PMID: 11186236
[15] Yan, Y.; Ji, Y.; Su, N.; Mei, X.; Wang, Y.; Du, S.; Zhu, W.; Zhang, C.; Lu, Y.; Xing, X.H. Non-anticoagulant effects of low molecular weight heparins in inflammatory disorders: A review.*Carbohydrate Polymers*; Elsevier Ltd, **2017**, pp. 71-81..
http://dx.doi.org/10.1016/j.carbpol.2016.12.037
[16] Ohta, A. [Prevention of osteoporosis by foods and dietary supplements. The effect of fructooligosaccharides (FOS) on the calcium absorption and bone]. *Clin. Calcium,* **2006**, *16*(10), 1639-1645.
PMID: 17012821
[17] Liao, S.F.; Nyachoti, M. *Using probiotics to improve swine gut health and nutrient utilization*; Animal Nutrition. KeAi Communications Co., **2017**, Vol. 3, pp. 331-343.
[18] Aly, S.E.; Sabry, B.A.; Shaheen, M.S.; Hathout, A.S. Assessment of antimycotoxigenic and antioxidant activity of star anise (Illicium verum) in vitro. *J. Saudi Soc. Agric. Sci.,* **2016**, *15*(1), 20-27.
http://dx.doi.org/10.1016/j.jssas.2014.05.003
[19] Luchese, R.H.; Prudencio, E.R.; Guerra, A.F. Honey as a Functional Food.*Honey Analysis*; InTech, **2017**.
http://dx.doi.org/10.5772/67020
[20] Van Laere, KMJ; Wissing, E Nutritional composition with health promoting action containing oligosaccharides. *US 8,227,448 B2,* **2012**, *Vol. 2*.
[21] Guo, Z.; Zeng, S.; Zhang, Y.; Lu, X.; Tian, Y.; Zheng, B. The effects of ultra-high pressure on the structural, rheological and retrogradation properties of lotus seed starch. *Food Hydrocoll.,* **2015**, *44*, 285-291.
http://dx.doi.org/10.1016/j.foodhyd.2014.09.014
[22] Guo, Z.; Zhao, B.; Li, H.; Miao, S.; Zheng, B. Optimization of ultrasound-microwave synergistic extraction of prebiotic oligosaccharides from sweet potatoes (Ipomoea batatas L.). *Innov. Food Sci. Emerg. Technol.,* **2019**, *54*, 51-63.
http://dx.doi.org/10.1016/j.ifset.2019.03.009
[23] Liang, L.; Liu, G.; Yu, G.; Song, Y.; Li, Q. Simultaneous decoloration and purification of crude oligosaccharides from pumpkin (Cucurbita moschata Duch) by macroporous adsorbent resin. *Food Chem.,* **2019**, *277*, 744-752.
http://dx.doi.org/10.1016/j.foodchem.2018.10.138 PMID: 30502211
[24] Sanches Lopes, S.M.; Francisco, M.G.; Higashi, B.; de Almeida, R.T.R.; Krausová, G.; Pilau, E.J.; Gonçalves, J.E.; Gonçalves, R.A.C.; Oliveira, A.J.B. Chemical characterization and prebiotic activity of fructo-oligosaccharides from Stevia rebaudiana (Bertoni) roots and in vitro adventitious root cultures. *Carbohydr. Polym.,* **2016**, *152*, 718-725.
http://dx.doi.org/10.1016/j.carbpol.2016.07.043 PMID: 27516323
[25] Lu, X.; Zheng, Z.; Li, H.; Cao, R.; Zheng, Y.; Yu, H.; Xiao, J.; Miao, S.; Zheng, B. Optimization of ultrasonic-microwave assisted extraction of oligosaccharides from lotus (Nelumbo nucifera Gaertn.) seeds. *Ind. Crops Prod.,* **2017**, *107*, 546-557.
http://dx.doi.org/10.1016/j.indcrop.2017.05.060
[26] Khuituan, P.; K-da, S.; Bannob, K.; Hayeeawaema, F.; Peerakietkhajorn, S.; Tipbunjong, C.; Wichienchot, S.; Charoenphandhu, N. Prebiotic oligosaccharides from dragon fruits alter gut motility in mice. *Biomed. Pharmacother.,* **2019**, *114*108821
http://dx.doi.org/10.1016/j.biopha.2019.108821 PMID: 30951951
[27] Desai, NM; Martha, GS; Harohally, N V.; Murthy, PS. Non-digestible oligosaccharides of green coffee spent and their prebiotic efficiency. *LWT.,* 2020 1Jan;, 118..
http://dx.doi.org/10.1016/j.lwt.2019.108784
[28] Marseglia, A.; Sforza, S.; Faccini, A.; Bencivenni, M.; Palla, G.; Caligiani, A. Extraction, identification and semi-quantification of oligopeptides in cocoa beans. *Food Res. Int.,* **2014**, *63*, 382-389.
http://dx.doi.org/10.1016/j.foodres.2014.03.046
[29] D'Souza, R.N.; Grimbs, A.; Grimbs, S.; Behrends, B.; Corno, M.; Ullrich, M.S.; Kuhnert, N. Degradation of cocoa proteins into oligopeptides during spontaneous fermentation of cocoa beans. *Food Res. Int.,* **2018**, *109*, 506-516.
http://dx.doi.org/10.1016/j.foodres.2018.04.068 PMID: 29803477
[30] Ren, Y.; Liang, K.; Jin, Y.; Zhang, M.; Chen, Y.; Wu, H.; Lai, F. Identification and characterization of two novel α -glucosidase inhibitory oligopeptides from hemp (Cannabis sativa L.) seed protein. *J. Funct. Foods,* **2016**, *26*, 439-450.
http://dx.doi.org/10.1016/j.jff.2016.07.024
[31] Rojas, M.J.; Siqueira, P.F.; Miranda, L.C.; Tardioli, P.W.; Giordano, R.L.C. Sequential proteolysis and cellulolytic hydrolysis of soybean hulls for oligopeptides and ethanol production. *Ind. Crops Prod.,* **2014**, *61*, 202-210.
http://dx.doi.org/10.1016/j.indcrop.2014.07.002
[32] Cheng, D.; Shao, Y.; Hartman, R.; Roder, E.; Zhao, K. Oligopeptides from Aster tataricus. *Phytochemistry,* **1994**, *36*(4), 945-948.
http://dx.doi.org/10.1016/S0031-9422(00)90468-0 PMID: 7765211
[33] Jiang, L.; Hua, D.; Wang, Z.; Xu, S. Aqueous enzymatic extraction of peanut oil and protein hydrolysates. *Food Bioprod. Process.,* **2010**, *88*(2–3), 233-238.
http://dx.doi.org/10.1016/j.fbp.2009.08.002
[34] Prabal, K.G.; Digvir, S.J.; Yogesh, C.A. Enzymatic Hydrolysis of Oilseeds for Enhanced Oil Extraction: Current Status. *In: 2007 Minneapolis, Minnesota,* June 17-20, 2007.St. Joseph, MI**2007**,
[35] Soto-Sierra, L.; Stoykova, P.; Nikolov, Z.L. *Extraction and fractionation of microalgae-based protein products*; Algal Research. Elsevier B.V., **2018**, Vol. 36, pp. 175-192.
[36] Jia, Q.; Liu, X.; Wu, X.; Wang, R.; Hu, X.; Li, Y.; Huang, C. Hypoglycemic activity of a polyphenolic oligomer-rich extract of Cinnamomum parthenoxylon bark in normal and streptozotocin-induced diabetic rats. *Phytomedicine,* **2009**, *16*(8), 744-750.
http://dx.doi.org/10.1016/j.phymed.2008.12.012 PMID: 19464860
[37] Sugiyama, H.; Akazome, Y.; Shoji, T.; Yamaguchi, A.; Yasue, M.; Kanda, T.; Ohtake, Y. Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J. Agric. Food Chem.,* **2007**, *55*(11), 4604-4609.
http://dx.doi.org/10.1021/jf070569k PMID: 17458979
[38] Yanagida, A.; Kanda, T.; Shoji, T.; OhnishiKameyama, M.; Nagata, T. Fractionation of apple procyanidins by size-exclusion chromatography. *J. Chromatogr. A,* **1999**, *855*(1), 181-190.
http://dx.doi.org/10.1016/S0021-9673(99)00684-6 PMID: 10514983
[39] Strandås, C.; Kamal-Eldin, A.; Andersson, R.; Åman, P. Composition and properties of flaxseed phenolic oligomers. *Food Chem.,* **2008**, *110*(1), 106-112.
http://dx.doi.org/10.1016/j.foodchem.2008.01.064 PMID: 26050172
[40] Lu, Y.; Foo, L.Y.; Wong, H. Sagecoumarin, a novel caffeic acid trimer from Salvia officinalis. *Phytochemistry,* **1999**, *52*(6), 1149-1152.
http://dx.doi.org/10.1016/S0031-9422(99)00368-4
[41] Lu, Y.; Yeap Foo, L. Antioxidant activities of polyphenols from sage (Salvia officinalis). *Food Chem.,* **2001**, *75*(2), 197-202.
http://dx.doi.org/10.1016/S0308-8146(01)00198-4
[42] Bors, W.; Michel, C.; Stettmaier, K.; Lu, Y.; Foo, L.Y. Antioxidant mechanisms of polyphenolic caffeic acid oligomers, constituents of Salvia officinalis. *Biol. Res.,* **2004**, *37*(2), 301-311.
http://dx.doi.org/10.4067/S0716-97602004000200017 PMID: 15455660
[43] González-Sarrías, A.; Gromek, S.; Niesen, D.; Seeram, N.P.; Henry, G.E. Resveratrol oligomers isolated from Carex species inhibit growth of human colon tumorigenic cells mediated by cell cycle arrest. *J. Agric. Food Chem.,* **2011**, *59*(16), 8632-8638.
http://dx.doi.org/10.1021/jf201561e PMID: 21761862
[44] Ito, T.; Hoshino, R.; Iinuma, M. Absolute Configuration of Resveratrol Oligomers Isolated from Hopea utilis. *Helv. Chim. Acta,* **2015**, *98*(1), 32-46.

http://dx.doi.org/10.1002/hlca.201400146

[45] Shankar, G.M.; Bloodgood, B.L.; Townsend, M.; Walsh, D.M.; Selkoe, D.J.; Sabatini, B.L. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J. Neurosci.*, **2007**, *27*(11), 2866-2875. http://dx.doi.org/10.1523/JNEUROSCI.4970-06.2007 PMID: 17360908

[46] Phan, H.T.; Gresch, U.; Conrad, U. In vitro-formulated oligomers of strep-tagged avian influenza haemagglutinin produced in plants cause neutralizing immune responses. *Front. Bioeng. Biotechnol.*, **2018**, *6*(AUG), 115. http://dx.doi.org/10.3389/fbioe.2018.00115 PMID: 30177967

[47] Ji, Y.; Qiao, H.; He, J.; Li, W.; Chen, R.; Wang, J.; Wu, L.; Hu, R.; Duan, J.; Chen, Z. Functional oligopeptide as a novel strategy for drug delivery. *J. Drug Target.*, **2017**, *25*(7), 597-607. http://dx.doi.org/10.1080/1061186X.2017.1309044 PMID: 28338354

[48] Bansode, R.R.; Randolph, P.; Ahmedna, M.; Hurley, S.; Hanner, T.; Baxter, S.A.S.; Johnston, T.A.; Su, M.; Holmes, B.M.; Yu, J.; Williams, L.L. Bioavailability of polyphenols from peanut skin extract associated with plasma lipid lowering function. *Food Chem.*, **2014**, *148*, 24-29. http://dx.doi.org/10.1016/j.foodchem.2013.09.129 PMID: 24262521

[49] Yang, C.; Hu, C.; Zhang, H.; Chen, W.; Deng, Q.; Tang, H.; Huang, F. Optimation for preparation of oligosaccharides from flaxseed gum and evaluation of antioxidant and antitumor activities in vitro. *Int. J. Biol. Macromol.*, **2020**, *153*, 1107-1116. http://dx.doi.org/10.1016/j.ijbiomac.2019.10.241 PMID: 31756466

[50] Özdemir, F.; Apaydın, E.; Önder, N.İ.; Şen, M.; Ayrım, A.; Öğünç, Y.; İncesu, Z. Apoptotic effects of ε-viniferin in combination with cis-platin in C6 cells. *Cytotechnology,* **2018**, *70*(3), 1061-1073. http://dx.doi.org/10.1007/s10616-018-0197-5 PMID: 29476302

[51] Pai, R.V.; Vavia, P.R. Chitosan oligosaccharide enhances binding of nanostructured lipid carriers to ocular mucins: Effect on ocular disposition. *Int. J. Pharm.*, **2020**, *577*119095 http://dx.doi.org/10.1016/j.ijpharm.2020.119095 PMID: 32004680

[52] Chi, L.; Khan, I.; Lin, Z.; Zhang, J.; Lee, M.Y.S.; Leong, W.; Hsiao, W.L.W.; Zheng, Y. Fructo-oligosaccharides from Morinda officinalis remodeled gut microbiota and alleviated depression features in a stress rat model. *Phytomedicine,* **2020**, *67*153157 http://dx.doi.org/10.1016/j.phymed.2019.153157 PMID: 31896054

[53] Gong, L.; Wang, H.; Wang, T.; Liu, Y.; Wang, J.; Sun, B. Feruloylated oligosaccharides modulate the gut microbiota in vitro via the combined actions of oligosaccharides and ferulic acid. *J. Funct. Foods,* **2019**, *60*103453 http://dx.doi.org/10.1016/j.jff.2019.103453

[54] Li, E.; Yang, H.; Zou, Y.; Wang, H.; Hu, T.; Li, Q.; Liao, S. In-vitro digestion by simulated gastrointestinal juices of Lactobacillus rhamnosus cultured with mulberry oligosaccharides and subsequent fermentation with human fecal inocula. *LWT,* **2019**, *101*, 61-68. http://dx.doi.org/10.1016/j.lwt.2018.11.029

[55] Souza, C.A.; Li, S.; Lin, A.Z.; Boutrot, F.; Grossmann, G.; Zipfel, C.; Somerville, S.C. Cellulose-derived oligomers act as damage-associated molecular patterns and trigger defense-like responses. *Plant Physiol.*, **2017**, *173*(4), 2383-2398. http://dx.doi.org/10.1104/pp.16.01680 PMID: 28242654

[56] Segun, P.A.; Ogbole, O.O.; Ismail, F.M.D.; Nahar, L.; Evans, A.R.; Ajaiyeoba, E.O.; Sarker, S.D. Resveratrol derivatives from Commiphora africana (A. Rich.) Endl. display cytotoxicity and selectivity against several human cancer cell lines. *Phytother. Res.*, **2019**, *33*(1), 159-166. http://dx.doi.org/10.1002/ptr.6209 PMID: 30346066

[57] Bose, S.K.; Howlader, P.; Jia, X.; Wang, W.; Yin, H. Alginate oligosaccharide postharvest treatment preserve fruit quality and increase storage life via Abscisic acid signaling in strawberry. *Food Chem.*, **2019**, *283*, 665-674. http://dx.doi.org/10.1016/j.foodchem.2019.01.060 PMID: 30722925

[58] Chen, X.; Zhang, Y.; Tang, C.; Tian, C.; Sun, Q.; Su, Z.; Xue, L.; Yin, Y.; Ju, C.; Zhang, C. Co-delivery of paclitaxel and anti-survivin siRNA via redox-sensitive oligopeptide liposomes for the synergistic treatment of breast cancer and metastasis. *Int. J. Pharm.*, **2017**, *529*(1-2), 102-115. http://dx.doi.org/10.1016/j.ijpharm.2017.06.071 PMID: 28642204

[59] Noor, N.M.; Sheikh, K.; Somavarapu, S.; Taylor, K.M.G. Preparation and characterization of dutasteride-loaded nanostructured lipid carriers coated with stearic acid-chitosan oligomer for topical delivery. *Eur. J. Pharm. Biopharm.*, **2017**, *117*, 372-384. http://dx.doi.org/10.1016/j.ejpb.2017.04.012 PMID: 28412472

[60] Ohara, K.; Kusano, K.; Kitao, S.; Yanai, T.; Takata, R.; Kanauchi, O. ε-Viniferin, a resveratrol dimer, prevents diet-induced obesity in mice. *Biochem. Biophys. Res. Commun.*, **2015**, *468*(4), 877-882. http://dx.doi.org/10.1016/j.bbrc.2015.11.047 PMID: 26596701

[61] Ose, R.; Hirano, K.; Maeno, S.; Nakagawa, J.; Salminen, S.; Tochio, T.; Endo, A. The ability of human intestinal anaerobes to metabolize different oligosaccharides: Novel means for microbiota modulation? *Anaerobe,* **2018**, *51*, 110-119. http://dx.doi.org/10.1016/j.anaerobe.2018.04.018 PMID: 29734011

[62] Zheng, Z-Q.; Geng, Z-H.; Liu, J-X.; Guo, S-T. Compressed food with added functional oligopeptides improves performance during military endurance training. *Asia Pac. J. Clin. Nutr.*, **2017**, *26*(6), 1066-1075. PMID: 28917232

[63] Buckley, M.L.; Ramji, D.P. The influence of dysfunctional signaling and lipid homeostasis in mediating the inflammatory responses during atherosclerosis.*Biochimica et Biophysica Acta - Molecular Basis of Disease*; Elsevier, **2015**, pp. 1498-1510.. http://dx.doi.org/10.1016/j.bbadis.2015.04.011

[64] Li, X.; Chen, Y.; Li, S.; Chen, M.; Xiao, J.; Xie, B.; Sun, Z. Oligomer Procyanidins from Lotus Seedpod Regulate Lipid Homeostasis Partially by Modifying Fat Emulsification and Digestion. *J. Agric. Food Chem.*, **2019**, *67*(16), 4524-4534. http://dx.doi.org/10.1021/acs.jafc.9b01469 PMID: 30945544

[65] Wang, X.; Tsang, Y.F.; Li, Y.; Ma, X.; Cui, S.; Zhang, T.A.; Hu, J.; Gao, M.T. Inhibitory effects of phenolic compounds of rice straw formed by saccharification during ethanol fermentation by Pichia stipitis. *Bioresour. Technol.*, **2017**, *244*(Pt 1), 1059-1067. http://dx.doi.org/10.1016/j.biortech.2017.08.096 PMID: 28851161

[66] Shi, J.; Wang, Y.; Wei, H.; Hu, J.; Gao, M.T. Structure analysis of condensed tannin from rice straw and its inhibitory effect on Staphylococcus aureus. *Ind. Crops Prod.*, **2020**, *145*112130 http://dx.doi.org/10.1016/j.indcrop.2020.112130

[67] Xiao, J.; Li, S.; Sui, Y.; Li, X.; Wu, Q.; Zhang, R.; Zhang, M.; Xie, B.; Sun, Z. In vitro antioxidant activities of proanthocyanidins extracted from the lotus seedpod and ameliorative effects on learning and memory impairment in scopolamine-induced amnesia mice. *Food Sci. Biotechnol.*, **2015**, *24*(4), 1487-1494. http://dx.doi.org/10.1007/s10068-015-0192-y

[68] Chen, Y.; Zhang, R.; Xie, B.; Sun, Z.; McClements, D.J. Lotus seedpod proanthocyanidin-whey protein complexes: Impact on physical and chemical stability of β-carotene-nanoemulsions. *Food Res. Int.*, **2020**, *127*108738 http://dx.doi.org/10.1016/j.foodres.2019.108738 PMID: 31882082

[69] Kawahara, S.I.; Ishihara, C.; Matsumoto, K.; Senga, S.; Kawaguchi, K.; Yamamoto, A.; Suwannachot, J.; Hamauzu, Y.; Makabe, H.; Fujii, H. Identification and characterization of oligomeric proanthocyanidins with significant anti-cancer activity in adzuki beans (*Vigna angularis*). *Heliyon,* **2019**, *5*(10)e02610 http://dx.doi.org/10.1016/j.heliyon.2019.e02610 PMID: 31687492

[70] Castro, M.C.; Villagarcía, H.; Nazar, A.; Arbeláez, L.G.; Massa, M.L.; Del Zotto, H.; Ríos, J.L.; Schinella, G.R.; Francini, F. Cacao extract enriched in polyphenols prevents endocrine-metabolic disturbances in a rat model of prediabetes triggered by a sucrose rich diet. *J. Ethnopharmacol.*, **2020**, *247*112263 http://dx.doi.org/10.1016/j.jep.2019.112263 PMID: 31580944

[71] Bala, A.E.A.; Kollmann, A.; Ducrot, P-H.; Majira, A.; Kerhoas, L.; Leroux, P.; Delorme, R.; Einhorn, J. Cise-viniferin: A New Antifungal Resveratrol Dehydrodimer from Cyphostemma crotalarioides Roots. *J. Phytopathol.*, **2000**, *148*(1), 29-32. http://dx.doi.org/10.1046/j.1439-0434.2000.00071.x

DISCLAIMER: The above article has been published in Epub (ahead of print) on the basis of the materials provided by the author. The Editorial Department reserves the right to make minor modifications for further improvement of the manuscript.