BIOACTIVE COMPOUNDS AND HEALTH BENEFITS OF OATS

A Literature Review

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by

Jialing Chen

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ABSTRACT

A nutrient-balanced diet includes consuming various fruits, vegetables, and grains in a reasonable proportion. Oat is one of the whole grains preserved with a nutritional profile, playing a crucial role in the human diet. It is a nutrient-dense grain containing about 51-67.7% starch, 9-20% protein, 10.1-39% dietary fiber, 2-18% lipid, 10.8% water, vitamins, and minerals.

The health benefits associated with oats are partly attributed to the presence of distinctive bioactive compounds and nutrients. The bioactive compounds found in oats include beta-glucan, phenolic acids, flavonoids, tocols, phytosterols, and avenanthramides. High consumption of oats has been associated with reduced risk of cardiovascular diseases, obesity, type 2 diabetes, and some cancers, along with weight control, glycemic index control, and improved gastrointestinal health.

This paper aims to systematically review the current literature on the bioactive compounds of oats, nutrients, and their health benefits, and give a comprehensive insight into the unique properties and potential benefits of oats as a healthy grain food.

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BIOGRAPHICAL SKETCH

Jialing Chen is a Master of Food Science Student in the College of Agriculture and Life Science at Cornell University. A graduate of Pennsylvania State University with a Bachelor of Science in Food Science, she has a solid foundation in food product development and food nutrition. She was in Dr. Rui Hai Liu's lab, working on her MFS's thesis on the bioactive compounds and health benefits of oats. Her ongoing projects demonstrate a deep commitment to advancing food science and health.

For every moment, friend, teacher, and family member who has guided me to this point.

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TABLE OF CONTENTS

DISSERTATION

1. Introduction

A nutritious and balanced diet provides the body with the essential nutrients to maintain overall health and well-being. A balanced diet involves consuming a variety of foods to achieve and maintain overall health. Numerous research studies have implicated that consuming a wide variety of fruits, vegetables, and grains prevents chronic diseases (Boffetta et al., 2010). Recent epidemiological research has provided essential evidence that proper and nutrition-balanced diets reduce the risk of chronic diseases such as diabetes, heart disease, cancer, and Alzheimer's disease (Boffetta et al., 2010). Previous research has established that possible active constituents in fruits, vegetables, and grains are phytochemicals, including phenolic acid, flavonoids, tocols, and phytosterols that help to maintain oxidative stress and oxidant levels (Adom & Liu, 2002). Considering the evidence, researchers, consumers, and the food industries increasingly recognize the benefits of a healthy diet, leading to a greater emphasis and attention on the availability and consumption of nutrient-dense food.

Given the substantial research underscoring the health benefits of consuming a diet rich in fruits, vegetables, and grains, it becomes imperative to understand and study the role of grains within the diet. Grains are one of the crucial components of human diets. They are rich in macro/micronutrients, antioxidants, and phytochemicals and have possible health-enhancing or disease-preventing value at a particular concentration (Temple, 2022). Recently, the concept of "whole grain" has gained more attention, particularly in the United States of America, Europe, and Japan (Kim et al., 2021). Whole grain shall consist of intact, ground, cracked, flaked bran, germ, and endosperm after removing the hull and husk and preserved with the complete nutritional profile. Whole grains include whole wheat, brown rice, oats, barley, quinoa, and millet (MEZIANI et al., 2021). Whole grain consumption has grown at a remarkable rate; according to the statistical data collected by the CDC, from 2013- to 2016, the percentage of whole grain intake from 12.9% among adults aged 20-39 has increased to 19.7% for adults 60 and over (Ahluwalia et al., n.d.).
Furthermore, recent studies indicated that whole grains are associated with reducing the risk of obesity and weight gain, also contributing to reducing the risk of cardiovascular diseases (CVD), including coronary heart disease, hypertension, and stroke (Jones et al., 2010). Additionally, whole grains promote improved gut health, lower the risk of upper gut cancer, and potentially reduce the risk of colorectal cancer (Jones et al., 2010). Oats continuously hold significance as a cereal grain, and their nutritional benefits have been studied for years.

Oat (Avena sativa L.) is a unique, wildly cultivated cereal grain that belongs to the tribe Aveneae of the subfamily Pooidead in the family of Poaceae (Boczkowska et al., 2016). Compared with other grains, oats are easier to cultivate. Cultivation of oats requires fewer nutrients such as sodium, phosphorus, and potassium but more moisture (Rasane et al., 2013). Nevertheless, oat is an excellent source of carbohydrates, protein, dietary soluble fiber, vitamins, and minerals. Therefore, oat is widely used in the food industry to produce breakfast cereals, beverages, bread, infant food, and animal feed (Paudel et al., 2021). Recently, oats have gained more and more attention for their phytochemicals, nutritional profile, and health benefits. Phytochemicals are the non-nutrient bioactive compounds found in fruits, grains, vegetables, and other foods ((Liu, 2004). The phytochemicals found in oats include β -glucan, phenolic acid, tocols, sterols, avenacosides, and avenanthramides (Paudel et al., 2021). The various bioactive compounds and unique chemical structures in oats interact with the body's biological system and offer substantial health benefits, including promoting immunomodulation, reducing the risk of chronic disease, and improving gut microbiota (Paudel et al., 2021). Functional bioactive compounds in oats are studied and documented in many research studies, and several epidemiological studies provide compelling evidence that whole grains, including oats, have protective effects against several diseases (Boffetta et al., 2010). This paper aims to systematically review the current literature on the bioactive compounds of oats, nutrients, and their health benefits, and give a comprehensive insight into the unique properties and potential benefits of Oats as a healthy grain food.

2. Oats

Oat is the cereal grain of the grasses family, Poaceae, which usually refers to the two most common species of both Avena sativa, known as white oat, and Avena byzantine, known as red oat. These two species are the predominant species cultivated worldwide (Canales et al., 2021). The EU is the largest oat producer and consumer, and Canada is the second largest producer, followed by Russia, Australia, the United States, and Brazil (Zhang et al. 2021). The history of oat grain has been around for thousands of years. Evidence shows that it is one of the oldest grains cultivated in human civilization, and the earliest known oat grain can be traced back to around 2000 B.C. in the Middle East or Mediterranean. Oat is known for its adaptability to harsh growing conditions and shows greater resilience than other cereal crops (Mao et al., 2021). To understand oats' environmental adaption and optimal growth conditions, Canales et al. studied the main effects of climate and edaphic components on oat adaptation in the Mediterranean area. They found that oats are well-suited to environments characterized by cool temperatures, moderate moisture, and well-drained soil conditions (Canales et al., 2021). Adequate moisture is essential for germination, growth, and plant dry matter development. Furthermore, soil with slightly acidic to neutral pH levels of 5.5 to 7.0 is the optimal growing condition for oats (Canales et al., 2021).

Oat is one of the ancient grains widely cultivated and consumed worldwide (Paudel et al., 2021). In 2016, data from the National Institutes of Health reported that approximately 6% of the world population consumed oatmeal, with an average daily intake of 238 grams. In 2019, the consumption of oats products in the United States was about 4.9 pounds per person (Musa-Veloso et al., 2016). Oat is incorporated into the human diet as a versatile ingredient in food products, such as oat porridge, breakfast cereals, cookies, bread, muffins, energy bars, meal replacement, meat substitutes, and baby food, and was also wildly included in beverage formulations as a protein shake, and plant-based milk (Canales et al., 2021). As a food, there are multiple processing techniques, including Oat Groats, Steel-cut, Scottish Oats, Rolled Oats, and Instant Oats. (Oats | The Nutrition Source | Harvard T.H. Chan School of Public Health, n.d.). Oat Groats have the least processing: the whole oat kernels with intact germ, endosperm, and bran. The instant oat intends to have most processing steps, such as steaming before being rolled into thinner pieces, to increase its water-absorbing ability to cook within a shorter period. These processing methods highlighted the versatility of oats in modern food production and accommodating diverse dietary preferences and lifestyles. In addition to its culinary uses for flavor and texture, oats have gained recognition for their nutritional benefits and disease-prevention properties.

Oat is a complex food matrix with an outer protective hull and an inner groat comprising a thick bran layer, a germ, and a starchy endosperm. Hull mainly comprises hemicellulose and cellulose, a small amount of lignin, and phenolic compounds. The bran consists of about 13%-17% of the kernel and includes several parts, including the pericarp, seed coat, nucellus, and aleurone layer (Mao et al., 2021). The bran contains about 80% fiber and 80% phenolic in the kernel, and the primary chemical components include trace minerals such as iron, zinc, magnesium, vitamins, phytate, cellulose, arabinoxylan, and β -glucan. The starchy endosperm constitutes approximately 80-85% of the kernel, primarily consisting of protein, starch, and a small amount of fiber. The endosperm is critical for providing energy and nutritional value. Germ is also known as the embryo of the oat grain, which comprises 2-3% of the oat grain. It is a crucial part of supporting seed growth and germination and contains multiple nutrients such as B vitamins, Vitamin E, lipids, phytochemicals, and a few trace minerals (Liu, 2013). The oat grin comprises a nutritious groat with a fiber-rich bran layer, a nutrient-dense germ, and a carbohydrates-rich starchy endosperm. These specific features bring many advantages to consuming oat grain as a whole grain with intact bran, endosperm, and germ. Therefore, wholegrain oat is an excellent source of carbohydrates, protein, unsaturated fatty acids, and soluble dietary fiber. Additionally, oats are a source of various micronutrients such as vitamin E, folate, zinc, iron, selenium, copper, manganese, and other phytochemicals (Rasane et al., 2013).

3. Nutrients and Bioactive compounds in oats

3.1 Nutrient composition

Table 1. Nutrient composition of oat

Nutrient Constituent	Content (%)	Reference
Starch	51- 67.7	USDA, 2022 Mao et al., 2021 Zhang et al., 2021 Rasane et al., 2015
Amylose	22.2 - 29.5	Zhang et al., 2021 Hoover, 1996 Hoover and Vasanthan, 1992
Protein	9 – 20	Zhang et al., 2021 USDA, 2022 Robert et al. 1985 Rafique et al., 2022 Paudel et al., 2021 Kim et al., 2021
Globulins	70 – 80	Rasane et al., 2015
Albuline	1 - 12	Rafique et al., 2022
Prolamins	4 – 15	Rasane et al., 2015 Rafique et al., 2022
Glutenins	<10	Rafique et al., 2022
Dietary Fiber	10.1 – 39	Banas et al., 2021 USDA, 2018 Ulmius et al., 2011
β-glucan	0.03- 8.39	Rebello et al., 2016
Water	10.84	USDA, 2018
Total lipid	2 – 18	USDA, 2018 Mao et al., 2021 Rasane et al., 2015 Banas et al., 2021 Pokhrel et al., 2022 Kim et al., 2021

Ash		1.8	Oats - Google Books, n.d.)
Vitamins	Vitamin E (mg/100 g)	1.2	Oats - Google Books, n.d.)
	Vitamin B6 (mg/100 g)	0.22	
	Niacin (mg/100 g)	0.88	
	Pantothenic acid (mg/100 g)	1.23	
	Thiamin (mg/100 g)	0.73	
	Riboflavin (mg/100 g)	0.13	
	Folic acid (ug/100 g)	49	
	Biotin (ug/100 g)	21	
	Choline (ug/100 g)	4	
Major minerals	Ca (mg/100 g)	54	Rafique et al., 2022
	Mg (mg/100 g)	145	
	K (mg/100 g)	389	
	P (mg/100 g)	459	
Trace minerals	Fe (mg/100 g)	4.3	
	Zn (mg/100 g)	3.4	
	Mn (mg/100 g)	4.1	
	Cu (mg/100 g)	0.44	

Starch was the most abundant oat grain component, accounting for 51-67.7% of the dry weight due to different plant genotypes and production environments (Zhang et al., 2021). It exhibits distinct chemical, physical, and structural properties when contrasted with starches derived from other grains (Mao et al., 2021). Amylose and amylopectin have been the most studied content in oat starch granules. The two primary carbohydrates that comprise the starch granules in oats account for approximately 98-99% of the total carbohydrate composition. The proportion of amylose within the granules varies, typically ranging from 25.2 to 29.4%. This variation is affected by several factors, including the genotype and mutant, the conditions under which the plant is cultivated, and the methodology used to measure the amylose content (Zhang et al., 2021; Punia et al., 2020). Each factor impacts the amylose and amylopectin proportion, thus affecting the functional properties of the starch, such as digestibility, texture, morphology, and pasting behavior (Zhu, 2017; Zhang et al., 2021). Amylose is a polysaccharide made of alpha-D-glucose units bounded through alpha (1,4) glycosidic bonds and a relatively low degree of polymerization of 3000. Amylopectin is a branched polysaccharide made of alpha-D-glucose units with alpha (1,4) and a high frequency of alpha (1,6) linkage side chain connecting to the main backbone (Punia et al., 2020). In terms of digestibility, starch can be categorized based on the digestion rate into three types: rapidly digestible starch (RDS) refers to a type of starch that rapidly releases glucose within the initial 20 mins of hydrolysis, slowly digestible starch (SDS) which undergoes a gradual slow breakdown in the small intestine over a period ranging from 20 to 120 mins during enzymatic hydrolysis, and resistant starch (R.S.) which is not digested in the small intestine instead was utilized by gut microbiota in colon (Zhang et al., 2021). Studies also suggested that the components of oats contribute to the glycemic index. Raw starch is composed of about 40% SDS, which may reduce the glycemic response, and 29.31% R.S. (RS2 and RS5), which contributes to lowering the glycemic index (Wang et al., 2022; Zhang et al., 2021). These characteristics made oats a promising candidate for food components in preventing diabetes.

Protein derived from oats is usually considered a low-cost plant-based protein with good nutritional value in amino acid composition. The protein content of oats is generally higher than other cereal grains such as corn, barley, wheat, and sorghum, with a range from 11%-15% (Mao et al., 2021); Zhang et al., 2021); (Mao et al., 2021; Robert et al., n.d.)). Oat also contains a higher concentration of essential amino acids such as lysine, valine, isoleucine, threonine, and histidine than other cereal grains mentioned above ((Rafique et al., 2022). The cereal protein has been categorized into four main groups based on their solubility: albumins (19-21 kDa), which dissolve in water; globulins (54-60 kDa), which are soluble in saltwater; prolamins (20-40 kDa), which can be dissolved in weak alcohol solutions; and glutelins (10-90 kDa), which are soluble in acidic or basic solutions (Rafique et al., 2022; Rasane et al., 2013). Oats have a unique protein fraction distribution compared to other grains, resulting in different gelling, emulsification, water holding, fat binding, and foaming capacity. It has been found that globulins form the predominant protein content in oats, making up 70-80%. The other protein groups, such as albumin, glutelin, and prolamins, contribute approximately 1-12%, less than 10%, and 4-15% to overall protein composition, respectively (Mao et al., 2021; Rafique et al., 2022; Rasane et al., 2013). The study by Rafique indicated that bioactive peptides, composed of 2-20 amino acids derived from oat proteins, have been recognized for their unique health-enhancing benefits. These include antidiabetic, immunomodulatory, antifatigue, antithrombotic, anti-hypoxic, antihypertensive m cholesterol-lowering, and antioxidant properties (Rafique et al., 2022). Oat proteins generally have a higher biological value than other cereals with high prolamin content. Studies have shown that naked grains have a more significant amount of essential amino acid than that of husks (Rasane et al., 2013).

Lipids in oats are usually present in the endosperm and the germ. Oats are also recognized for their unique and high lipid content, which ranges from 2 to 13% compared to other cereal grains. The lipid content in oats is primarily composed of free 7% fatty acids, 51% triacylglycerols, glycerides,3% sterol, 3% of sterile esters, 8% of glycolipids, and 20% of phospholipids (Banaś & Harasym, 2020). The primary fatty acids present in oats are oleic (18:1), linoleic (18:2), and saturated palmitic acid (16:0), and lower levels of stearic (18:0) and linoleic (18:3) (Francis Raguindin et al., 2021). Oat has the highest unsaturated fatty acid concentration among other conventional cereal grains. Phospholipids and glycolipids are content of polar lipids found in oats that exhibit considerable variation and contribute to different aggregation, emulsions, and gelling properties (Banaś & Harasym, 2020). Regarding lipid antioxidant activity, oat oil is rich in natural antioxidants, including tocopherols, alkylresorcinols, phenolic acids, and avenanthramides, which are exclusive to oats and absent in other cereal grains. Additionally, there are multiple oat phenolic acids, such as caffeine, ferulic, p-hydroxybenzoic, vanillic, sterols, and flavonoids. These compounds contribute significantly to the health benefits associated with oats, and oat lipids protect against oxidative stress and free radicals (Banaś & Harasym, 2020; Francis Raguindin et al., 2021).

Dietary fiber is nondigestible and non-absorbed in the human intestine, constituting the plant cell wall (Mao et al., 2021) The total dietary fiber in oats ranges from 10.1-12% (Banaś & Harasym, 2020; Fiber et al., 2001; Ulmius et al., 2011) Dietary fiber in oats is mainly composed of oat 2.3-

8.5% β-glucan, 0.2% resistant starch, 0.1% fructans, 0.6% cellulose, 2.1% arabinoxylan, 2.0% lignin, and 1.0% others on dry weight bases (Mao et al., 2021). Oat β-glucan was the primary and essential component found within the cell wall of the endosperm in the oat kernel, and it comprised a viscous polysaccharide constructed with a linear, branched chain of D-glucose monosaccharides. These are connected through a combination of β (1-3) and β (1,4) glycosidic bonds. B-glucan is one of the bioactive compounds in oats, and it is particularly noted for its anti-diabetic and cholesterol-lowering effects, thereby reducing the risk of CVDs (Paudel et al., 2021). Studies also indicated that β-glucan has anti-cancerous properties of colon cancer and lowers blood pressure (Rasane et al., 2013).

Besides, oats have considerable vitamins and minerals (Paudel et al., 2021). Oat bran is a good source of Vitamin B complexes such as thiamine, riboflavin, pantothenic acid, pyridoxine, niacin, vitamin B-6, folate, and choline (Butt et al., 2008; Rasane et al., 2013) Vitamin A (β-carotene), Vitamin C, and Vitamin K are also found in the oat. Studies have found that germs contain a high concentration of tocopherols, such as a and c isomers, and tocotrienols are mainly concentrated in the endosperm of the oat kernel. Rasane suggests that the total tocols in oats ranged from 19-30.3 mg/k, with primary alpha-tocopherols and alpha-tocotrienols (Francis Raguindin et al., 2021; Mao et al., 2021; Rasane et al., 2013) Vitamin E is a crucial antioxidant in oats and has free radical scavenging ability. It is commonly studied for its anti-aging, anti-inflammatory, cancer prevention, and inhibition of lipid oxidation properties(Li et al., 2022). Oat is also a good source of micro and microminerals and plays a crucial role in the immune system (Chen et al., 2021). The major minerals found in oats include calcium (0.50-0.54%), magnesium, potassium, phosphorus, sodium, and sulfur; the primary trace minerals include iron (0.042%), zinc (0.037%), copper (0.04%), and manganese (1.38%) (O. Chen et al., 2021; Ikeda et al., 2006).

Overall, oats are a nutritionally rich food with diverse components contributing to their health-enhancing properties, making them a valuable addition to a diet to prevent diabetes and cardiovascular diseases. The oat industry has gained increased attention from scientists due to its unique nutritional values and profiles.

3.2 B-glucan

B-glucan is one of the significant components of non-starch water-soluble dietary fiber found in the endosperm cell wall and the bran of oats (Othman et al., 2011). Meanwhile, β-glucan is also wildly present in yeast, fungi, bacteria, and cereal grains (Du et al., 2019). Oat β-glucan (Fig.1) is a linear polymer that consists of glucose molecules by β glycosidic linkage (1, 4) and (1,3). Studies have indicated that β-glucan in oats consists of about 25%-30% β-1,3 and 70%-75% β-1,4 linkage, and the β-glucan in oats ranges from dry matter base (Chen et al., 2021; Francis Raguindin et al., 2021). The study reported that the β-glucan content in oats varies due to genetics, environmental conditions, and differences in analytical methods.

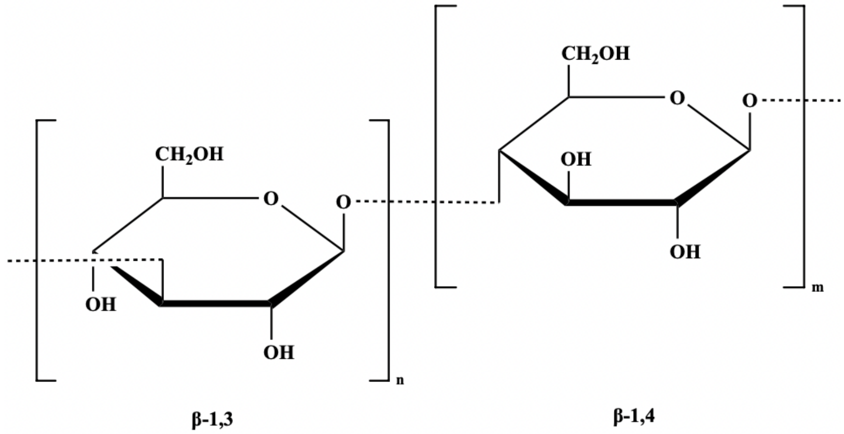


Figure 1. Molecular structure of Oat β-glucan

Moreover, aside from concentration, structure, and extraction method, various studies indicated that molecular weight impacts β-glucan's bioactivity and rheological behaviors (Li et al., 2022). The molecular and structural characteristics of β-glucan have gained more and more attention from researchers and the food industry due to its impact on the solubility, extraction, viscosity, rheological behavior, and functionality in food products (Du et al., 2019). Rebello et al. suggested that oat β-glucan has approximately 20,000 glycosidic units and a molecular weight of 3 million Daltons. Literature also reported that the molecular weight of β-glucan has an average range of 10^6 g/mol to 2* 10^6 g/mol, and the solubility of β-glucan is affected by its structures, temperature, pH of the solvent, and ionic strength (Rebello et al., 2016) Another study by Du et al. mentioned that the molecular weight of oat β-glucan was reported to be 65-3100*10^3g/mole. Meanwhile, Du further suggests that β-glucan, with a molecular weight from 1.16- 2.42*10^5 g/mole, can bind with more bile acid (Du et al., 2019). Another finding indicated that oat β-glucan, particularly its low-molecular-weight component, exhibited higher cancer cell cytotoxicity and reduced vitality of both colon and breast cancer cells; therefore, have a more effective potential for preventing cancer. Moreover, β-glucan with higher molecular weight has low solubility and processability, which limits the penetration and accessibility into the cells to perform their functions (X. Li et al., 2022).

The Food and Drug Administration has approved the health claim indicating that "soluble fiber from whole oats, as a part of a diet low in saturated fat, cholesterol, and total fat, may reduce the risk of heart disease" and "consuming 3 grams of oat β-glucan daily can reduce the risk of coronary heart disease" (Rasane et al., 2013; Ulmius et al., 2011). Due to β-glucan's unique structure as a plant polysaccharide which is resistant to digestion and absorption in the small intestine, it effectively reduces both blood cholesterol, especially low-density lipoprotein and glucose level, contributing to overall health improvement (Rasane et al., 2013; Rebello et al., 2016). It was reported that β-glucan has been linked to higher intestinal viscosity, which is connected to improving blood serum lipid levels, immune system, and gut barrier integrity (Chen et al., 2021). In animal studies, evidence demonstrated that oat β-glucan increases satiety-related hormones and reduces daily energy intake and body weight (Rebello et al., 2016). Evidence suggests that β-glucan has substantial benefits of immunomodulation, which refers to regulating the immune response to a desired level. According to Rasane et al., oat β-glucan stimulates the leukemic cell from the monocytic lineage and aids in developing dendritic cells originating from leukemic cells (Rasane et al., 2013). Paudel also suggests that the immune modulation properties of oat β-glucan were observed in a vivo study of mice, where oat β-glucan triggers the interleukin-1(IL-1) cytokines production from mice peritoneal macrophages and tumor necrosis factor-alpha cytokines from a mice microphase cell line in vitro which leading to the activation of adaptive immune responses. Research in vitro studies on human dendritic cells, as well as small intestinal and colon cell lines, further reveals oat β-glucan capacity to modulate the immune system (Paudel et al., 2021; Sahasrabudhe et al., 2016).

3.3 Phenolics compound and Phytochemical

Phenolics, characterized by their one or more aromatic rings and hydroxyl groups, are bioactive compounds typically categorized into phenolic acids, polyphenolic amides, flavonoids, stilbenes, coumarins, and tannins. Those compounds are primarily responsible for the antioxidant activity observed in cereal grain products (Francis Raguindin et al., 2021; Y. Li et al., 2022). Oat is one of the good sources of phenolic compounds, which contribute to cereal grains' functional and nutritional properties. Phenolic compounds in oats exist in two primary forms: free and conjugated. The free form is usually water soluble and can react within the oat matrix, whereas the conjugated form is attached to cellulose and hemicellulose, affecting bioavailability (X. Li et al., 2022).

In contrast, the concentration of phenolic content in oat bran was found to be higher than that in the other parts of oats, and the phenolic contents predominantly exist in the insoluble form (Adom & Liu, 2002; X. Li et al., 2022; Paudel et al., 2021). Fruits and vegetables were widely recognized as their free form phenolics, mainly available in the G.I. truck. However, the significance of the conjugated phenolics in oats and other grains cannot be underestimated. Due to the oat's unique structure, the bounded phenolic compounds cannot be digested easily by the enzymes in the small intestine of humans, which allows them to pass through the upper digestive system and eventually reach the colon. The microflora and colon microorganisms can release phenolic compounds and offer various site-specific advantages in the colon(Adom & Liu, 2002; X. Li et al., 2022).

Oats contain abundant phenolic compounds with high antioxidant activities (Adom & Liu, 2002). These phenolic compounds serve as a natural defense system against different pathogens, and their intake is associated with reducing the risk of diseases such as cancer, stroke, and chronic heart disease (Paudel et al., 2021). The phenolic content in oats also varies by cultivar and product type. In both studies by Soycan et al. and Paudel et al., ferulic acid was found to be the most predominant phenolic compound found in oat, which consists of 58-78% and followed by caffeic acid and sinapic acid (Paudel et al., 2021; Soycan et al., 2019). In the study by Adom and Liu, the total phenolic content in oat is 6.35 ± 0.91umol/g of oat. Moreover, Adom also reported that the concentration of free phenolic/ water-soluble is relatively lower than bound/conjugated phenolic compound, with a concentration of 1.77 ± 0.12 umol/g of oat and 4.76 ± 0.14 umol/g of oat, respectively (Adom & Liu, 2002). Soycan et al. determined the total phenolic content by comparing 22 different commercial oat products ranging from 394.8- 1518.6 ug/g using the HPLC analysis (Soycan et al., 2019). The findings from Meziani et al. indicated that the total polyphenol content is 0.205 ± 0.0131 mg (EAG) / g for whole oats, 0.17 ± 0.0141 mg (EAG) / g for whole black oats, 0.203 ± 0.005 mg (EAG) / g for oat bran, and 0.216 ± 0.0117 mg (EAG) / g for black oat bran (MEZIANI et al., 2021). Overall, free, conjugated, and bounded phenolic acids and their metabolites contribute to the antioxidant activity in the human body. They reduced oxidative damage to biomolecules by regulating the impact of reactive oxidants(Adom & Liu, 2002).

Phytochemical is derived from the Greek word "Phyto," which means plant chemicals (Liu, 2004). Phytochemicals are health-beneficial bioactive compounds found in fruits, vegetables, grains, and other plant-based foods that are not classified as nutrients. According to Liu, Carotenoids, Phenolics, Alkaloids, Nitrogen-containing compounds, and Organosulfur compounds fall under the phytochemical category. Estimates suggest that over 5,000 distinct phytochemicals have been discovered in fruits, vegetables, and grains. However, a significant portion of these compounds remains unidentified. Understanding the full spectrum of health benefits offered by phytochemicals in whole foods requires the identification of these unknown substances (Liu, 2004). Phytochemicals can prevent many chronic diseases caused by free radicals, such as cancer, inflammation, atherosclerosis, and aging (Liu, 2007). Studies have indicated that phytochemicals, found in both free and conjugated states within fruits and vegetables, play a significant role in enhancing their total antioxidant capacity. Furthermore, the presence of phytochemicals in various forms may also influence the bioavailability and their activity in the human body (Nayak et al., 2015; Sawicki et al., 2016).

3.3.1 Phenolic acid

Phenolic acids in oats can be primarily divided into two main groups: benzoic acid derivatives such as syringic acid, benzoic acid, gallic acids, vanillic acids, protocatechuic acids, and 2,4-dihydroxybenzoic acids, and cinnamic acid derivatives including ferulic acids, caffeic acid, sinapic acids, cinnamic acid, and p-coumaric acids (Y. Li et al., 2022; Liu, 2007; Soycan et al., 2019). Ferulic acid, along with other phenolic acids, shields wheat kernels by creating physical and chemical barriers. These protections include the cross-linking of carbohydrates, antioxidant actions that neutralize damaging radicals, and an astringent taste that repels insects and animals from consuming them (Liu, 2007). Li et al. reported that the concentration of phenolic acids in oats is about 472 μg/g, with ferulic acid being the most predominant, reaching levels up to 454.56 ug/g, followed by caffeic acid, making ferulic acid the predominant phenolic acid found in oats (X. Li et al., 2022). In Soycan et al.'s study, both the bound, free, and conjugated fractions had 4-hydroxybenzoic acid, vanillic acid, caffeic acid, 4-hydroxybenzaldehyde, syringic acid, p-coumaric acid, vanillin, ferulic acid, and sinapic acid. However, only the free and conjugated fractions contained the three avenanthramides: avenanthramide A, avenanthramide B, and avenanthramide C (Soycan et al., 2019). Rasane also suggested that phenolic acids are considered potent antioxidants, and the phenolic acids found in oats have antioxidant properties in both Virto and Vivo studies (Rasane et al., 2013). According to Paudel, oat bran concentrate has a higher phenolic acid content compared to other oat products like oat bran, flaked oats, rolled oats, and oatcake because most of the phenolic compounds are found in the bran layer of oat grains. In both studies by Paudel et al. and Soycan et al., ferulic acid was the most common phenolic compound in oat products, followed by caffeic acid and sinapic acid (Paudel et al., 2021; Soycan et al., 2019). In the study by Soycan analyzing the phenolic compound in 23 oat products by HPLC assay, ferulic acid, sinapic acid, and avenanthramide B were the principal constituents across free and conjugated fractions. Among these, rolled oats contained the most ferulic acid, with a 40.8 ± 2.2 μg/g concentration. The highest level of sinapic acid was found in oat bran concentrate, measuring 36.2 µg/g, while oat bran had the greatest amount of avenanthramide B, with a concentration of 27.6 ± 4.6 µg/g (Soycan et al., 2019).

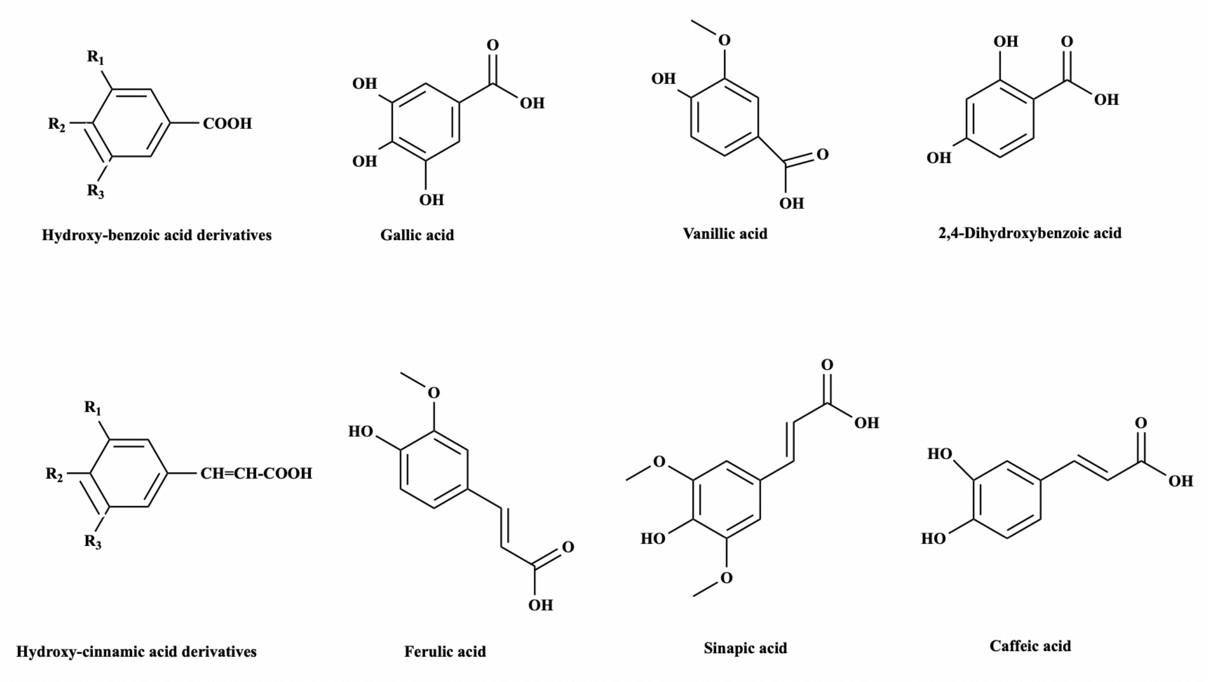


Figure 2. Molecular structures of major phenolic acids in oats

3.3.2 Flavonoids

Flavonoids are phenolic compounds known for their antioxidant properties; more than 4000 distinct flavonoids have been found in fruits, vegetables, and various plant-based foods. These compounds are associated with a decreased risk of several major chronic illnesses. Typically, flavonoids have a basic structure featuring two aromatic rings linked with a chain of three carbon atoms, often part of an oxygen-containing heterocycle (Francis Raguindin et al., 2021; Liu, 2004). Different structures at the heterocycle rings have classified flavonoids into side groups: flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids. Sixty-four flavonoids are found in oats and buckwheats (Francis Raguindin et al., 2021). Flavonoids, a diverse group of phytonutrients in many plants, predominantly exist in conjugated forms, either glycosylated or esterified. These conjugated forms of flavonoids involve attaching sugar molecules (in glycosylation) or acyl groups (in esterification) to the flavonoid backbone. This conjugation alters the flavonoids' solubility, stability, and bioavailability. Aglycones are the basic structural form of flavonoids, lacking the sugar or acyl groups, and their presence is often increased as a direct consequence of the mechanical, thermal, or chemical treatments involved in food processing (Liu, 2004).

The content of free flavonoids in grains was significantly lower than that of bound flavonoids. Adom and Liu reported that the total flavonoid content in oats is 1.16± 0.06 umol/g catechin equivalent of grain. Oat was found to have the highest concentration of free flavonoid with 0.45 (± 0.02) umole/g catechin equivalent of grain amount other gains such as corn, wheat, and rice; the concentration of bounded flavonoids is 0.71± 0.05 umol/g catechin equivalent of grain. Free flavonoids make up 39%, and bounded flavonoid contents make up 61% of total flavonoids in oats (Adom & Liu, 2002). Li et al. reported that the primary component of flavonoids found in oats is flavone, o-diacylglycerol tectorigenin, flavonol, and myricetin-3-O-xyloside, and the total concentration of flavonoids found in oat is about 45.69 ug/mL (X. Li et al., 2022). Al-Sultani et al. tested the flavonoid content of 4 different varieties of oats: Shifaa, Oat11, Al-gouda, and Carlup. The total flavonoid content of these four varieties ranged from 158 to 163.8 mg/kg quercetin equivalent, and there are significant differences observed between oat varieties ("Evaluating Oxidative Activity and Flavonoids Content of Four Varieties of Oat," n.d.). Ibrahim et al. studied the total flavonoid content from five oat cultivars (SGD81, SGD2011, PD2LV65, Avon, and S2000 and reported that the total flavonoid content varied significantly among the cultivars ($p < 0.05$), ranging from 754.16 to 1147.08 quercetin equivalent per 100 grams ((Ibrahim et al., 2020)). Thus, the variations between total flavonoid content, bound, and free fractions are significantly determined by factors such as the plant varieties, the conditions under which they are grown, how they are stored, and the methods used for extraction (Adom & Liu, 2002; Al-Sultani et al., 2023).

Rutin, Catechin, Myricetin, Apigenin, Quercetin, and Kaempferol are major flavonoids found in oat, with content varying from 32.19 to 35.25, 13.15 to 14.38,1.28 to 13.23, 9.76 to 12.08, 22.72 to 25.14, and 17.15 to19.98 quercetin equivalent mg/kg dry weight in oat samples, respectively (Al-Sultani et al., 2023). Quercetin was reported as the predominant flavonoid compound in oats. The samples of husked oats displayed the greatest concentration, reaching levels as high as 8.9 mg per 100 grams of rutin equivalent (Francis Raguindin et al., 2021).

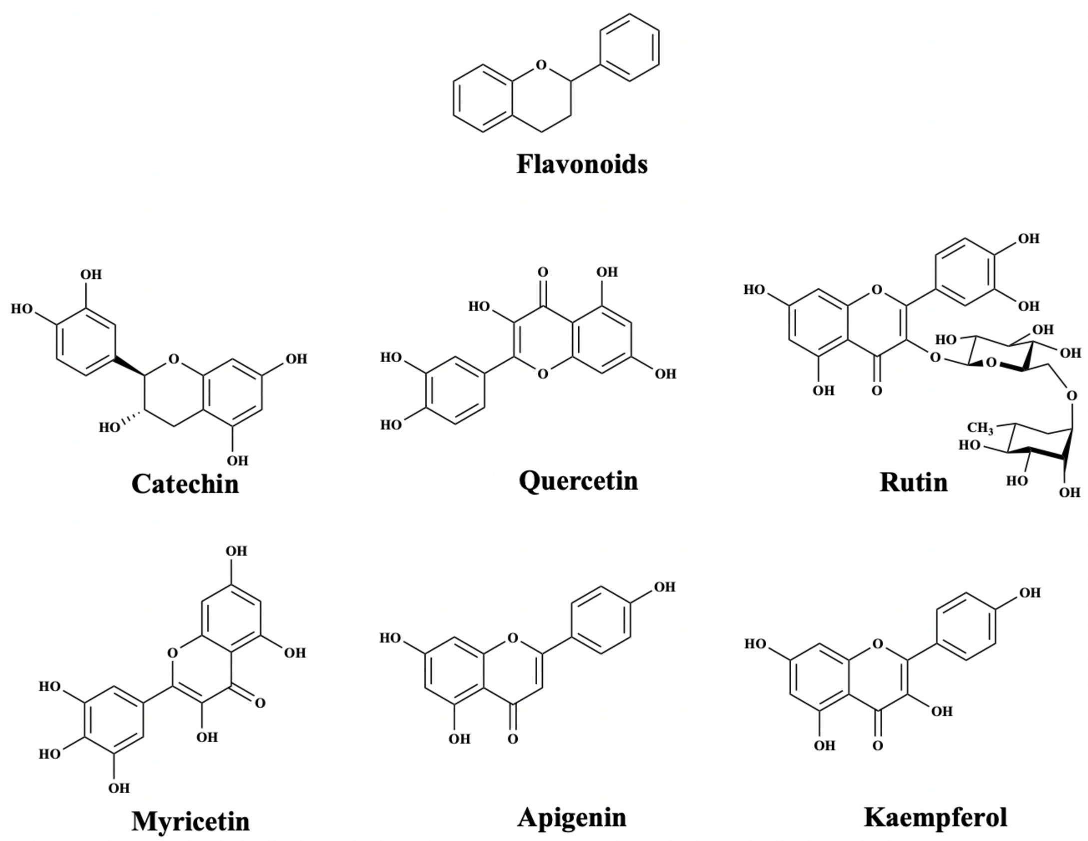


Figure 3. Generic structure of flavonoids and molecular structures of major flavonoids in oats

Table 2. Concentration of total, free, conjugated phenolic acids and flavonoids.

	Concentration
Total Phenolic Acid	6.35 ± 0.91 umol gallic acid equivalent/ gram of oat
Free Phenolic Acid	1.77 ±0.12 umol gallic acid equivalent/ gram of oat
Conjugated/bound Phenolic Acid	4.76 ±0.14 umol gallic acid equivalent/ gram of oat
Total Flavonoids	1.16± 0.06 umol catechin equivalent/ gram of oat
Conjugated/bound Flavonoids (61%)	0.71± 0.05 umol catechin equivalent/ gram of oat
Free Flavonoids (39%)	0.45 (± 0.02) umol catechin equivalent/ gram of oat

3.4 Tocols

Tocopherols and tocotrienols are known as tocols, or vitamin E. Vitamin E is the generic term for eight compounds: α-, β-, γ-, δ-tocopherols and α-, β-, γ-, δ-tocotrienol. They are lipid-soluble compounds and primary natural sources of tocopherols, and tocotrienols are the oil-rich fractions of nuts and seeds. The synthesis of these compounds is exclusive to photosynthetic organisms, including plants, algae, and cyanobacteria (Liu, 2007; Szewczyk et al., 2021). The non-photosynthetic organisms include fungi, corals, sponges, and tunicates (Szewczyk et al., 2021). Both tocopherol and tocotrienol have fundamental structures consisting of a 6-hydroxychroman group and a phytyl side chain composed of isoprenoid units. Moreover, tocopherol and tocotrienol share similar chemical structures, with the difference being that tocopherols have saturated phytol side chains. In contrast, tocotrienols feature three carbon-carbon double bonds in their phytol side chain (Liu, 2007). Their unique chemical structure determines their bioavailability and antioxidant potency (Francis Raguindin et al., 2021; Kim et al., 2021). Vitamin E is commonly known for its antioxidant activity. The antioxidant activity of vitamin E is attributed to the free hydroxyl group on the aromatic ring, which can donate a hydrogen atom to free radicals, leading to the formation of a resonance-stabilized vitamin E radical (Liu, 2007). Both Liu and Szewczyk suggest that tocols are incorporated into the amphipathic phospholipid bilayer of cell membranes to maintain membrane integrity and protect organs and organs of photosynthesis in plants from oxidative stress (Liu, 2007; Szewczyk et al., 2021).

Studies have indicated that α-Tocopherol is predominantly found in the germ, while α-tocotrienol is primarily located in the endosperm but absent in the germ (Rasane et al., 2013; van den Broeck et al., 2015). Many studies have indicated that the total concentration of tocols varies from 19.0 to 30.3mg/kg in oat (Mao et al., 2021; Peterson, 2001; Rasane et al., 2013). Raguindin et al. reported that the tocol concentration in oats ranged from 5.0-36.1mg/kg (Francis Raguindin et al., 2021). α -Tocopherol and a-tocotrienol are the dominating tocols which account for 86-91% combined in oats, and the levels of β-tocopherol and β-tocotrienol were approximately ten times lower than those of the corresponding α-compounds (Rasane et al., 2013; Redaelli et al., 2015) The primary tocols in oat, a-tocotrienol, has been reported to have the most potent antioxidant activity, with an average concentration of 56 mg/kg D.M and 8–69 mg/kg D.M. (Redaelli et al., 2015; Liu, 2007). Meanwhile, a-tocopherol content has been reported to range from 6–65 mg/kg D.M. (Redaelli et al., 2015). Besides genotype, cultivation conditions, and the measure methodology, the total tocols content in oats was also impacted by temperature and air exposure (Peterson, 2001; van den Broeck et al., 2015).

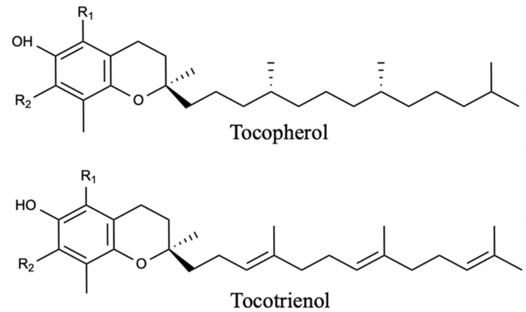


Figure 4. Molecular structure of tocopherol and tocotrienol in oats

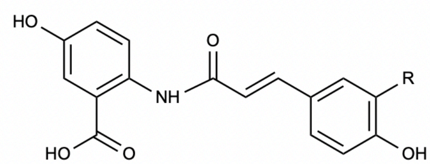
3.5 Phytosterols

Phytosterols, bioactive compounds found in plant-based foods, can be categorized into plant sterols and their saturated derivatives, plant stanols (Cabral & Klein, 2017). Phytosterols have a similar chemical structure to cholesterol. However, with different side chain groups, the sterol is characterized by a double bond in the sterol ring. In contrast, plant stanols, the hydrogenated forms of corresponding sterols, do not contain a double bond in the sterol ring (Liu, 2007). Over 250 phytosterols have been identified in plants, and the esterified forms of plant sterols and stanols are predominantly utilized in human clinical trials and for the fortification of foods (Cabral & Klein, 2017; Liu, 2007).

The primary food sources of phytosterols include vegetable oils (corn, sunflower, soybean, and olive), cereal grains (wheat, barley, highland barley, and oat), nuts, legume grains, and other fruits and vegetables (cauliflower, orange, and passion fruits) (Cabral & Klein, 2017; Y. Li et al., 2022; Liu, 2007). Sitosterol, campesterol, delta5-avenasterol, and delta7-Avenasterol are the major sterols found in oats. Määttä et al. quantified the sterols content from 7 different oats cultivars with 21 samples. They reported that sitosterol was found most predominant with a range from 237 -321 ug/g, followed by campesterol ranging from 32-46 ug/g, delta5-avenasterol 15-47 ug/g, and delta7-Avenasterol 11-21ug/g. Statistical analysis suggested significant differences in sterols content between the seven cultivars (Määttä et al., 1999). According to Piironen et al., the total sterol content is 0.447mg/g, and the total stanol content was detected in a very low amount in oats (Piironen et al., 2002).

Avenanthramides (AVAs) are the unique low-molecular-weight, soluble phenolic alkaloids found exclusively among other cereal grains (Chen et al., 2021; Sang & Chu, 2017). These substances act as phytoalexins, compounds that plants produce in response to being exposed to pathogens like fungi, serving as antipathogenic agents (Meydani, 2009; Redaelli et al., 2015). Ava was first purified from oat groats. They are a group of phenolic acid derivatives N-cinnamoylanthranilate. Avenanthramides consist of conjugates formed between a phenylpropanoid and anthranilic acid or 5-hydroxy anthranilic acid, and the biosynthesis of AVAs involves the acylation of anthranilic acid and its derivatives with the CoA thioester of cinnamic acid (Meydani, 2009; Sang & Chu, 2017). To date, more than 20 different forms of AVAs have been identified, with the esters of 5-hydroxyanthranilic acid with primary forms AVA-A (p-coumaric), AVA-B (caffeic), 2C, 2P, and 2F, which 2C, 2F, and 2P have been reported as the most abundant AVAs in oat, and AVA 2C have the highest total antioxidant capacity (Francis Raguindin et al., 2021; Paudel et al., 2021; Redaelli et al., 2015). Soycan et al. also suggested that 2c, 2p, and 2f are the most prevalent in the grains, and 2p and 2f are especially abundant in the leaves (Soycan et al., 2019). The highest concentrations of AVAs were found in the oat bran, with levels decreasing towards the endosperm. The oats' genotype and the harvest timing were identified as the most significant factors affecting AVA content (Francis Raguindin et al., 2021).

AVAs are only present in the soluble form in oats. Current studies and literature reviews indicate that the total concentration of AVAs in oats varies wildly. Soycan et al. reported that the total AVAs in oat ranged from 0.05 mg to 7.185 mg/kg (Soycan et al., 2019). Chen et al. reported that the AVA content in commercial oat products is 1-2 mg per 40g serving (C. Chen et al., 2018). Multiple studies indicated that Avenanthramides offer a broad range of health advantages, complemented by well-established health benefits associated with oat consumption (Meydani, 2009; Redaelli et al., 2015; Soycan et al., 2019).



Avenanthramide

Avenanthramide-a R=H
Avenanthramide-b R=OCH3
Avenanthramide-c R=OH

Figure 5. Molecular Structure of Avenanthramides

4. Health Benefits of Oats

4.1 Oat in the Prevention of CVD

Cardiovascular diseases (CVDs) are the primary leading cause of death worldwide, causing around 17.9 million deaths each year, and around 47% of deaths in females and 39% in males (Y. Li *et al.*, 2022; World Health Organization (WHO), n.d.). These conditions encompass a variety of heart and blood vessel disorders, including coronary heart disease, cerebrovascular disease, peripheral artery disease, and aortic atherosclerosis, among others (World Health Organization (WHO), n.d.). Coronary artery disease (CAD), also referred to as coronary heart disease which is results from decreased blood flow to the heart muscle, including angina, heart attacks, and heart failure; Cerebrovascular (CVD) includes stroke and transient ischemic attack; Peripheral artery disease (PAD) is the arterial disease exclusively involved in the limbs; and Aortic atherosclerosis encompasses both thoracic and abdominal aneurysmsril (Wehrli et al., 2021)According to the World Health Organization, over 80% of CVD fatalities result from heart attacks and strokes, with one-third of such deaths happening prematurely in individuals below the age of 70 (World Health Organization (WHO), n.d.). Many cases of cardiovascular diseases are related to unhealthy diets (Mathews et al., 2020). According to data from the National Health Interview Survey, the global prevalence of cardiovascular disease affected 485.6 million individuals in 2017, marking a 28.5% increase over a decade (World Health Organization (WHO), n.d.).

Moreover, oxidative stress, high LDL levels, and inflammation are also recognized as key contributors to the development of atherosclerosis, which is considered one of the major cardiovascular diseases (Y. Li et al., 2022; Liu, 2013). Multiple epidemiological studies and meta-analysis reviews have indicated that the consumption of oats, oat extracts, and oat supplements is associated with a decrease in the risk of chronic diseases such as heart disease, cancer, diabetes, and Alzheimer's disease (Adom & Liu, 2002; Liu, 2013; Mao et al., 2021). Oats' phytochemicals have been extensively studied for their potential role in reducing cardiovascular disease risk. These compounds exhibit antioxidant, anti-inflammatory, and anti-atherogenic properties, crucial for cardiovascular health (Cui & Liu, 2013; Liu, 2007).

B-glucan, the primary dietary fiber found in oats, has been approved by the FDA as an effective dietary supplement for reducing cholesterol levels, with a recommended dose of 3 grams of β-glucan daily. This highlights the significant role that β-glucan can play in managing cholesterol, contributing to a healthier cardiovascular profile as part of a daily dietary regimen (U.S. Food and Drug Administration, n.d.). Elevated serum cholesterol and low-density lipoproteins (LDL) have been linked to an increased risk of cardiovascular diseases (CVD) (Paudel et al., 2021). Research has indicated that consuming oats can lower both total and LDL cholesterol levels, thus reducing the risk of CVD, and β-glucan has been shown to lower LDL cholesterol levels, thus reducing the risk of CVD (Cui & Liu, 2013). Wolever et al. conducted a study on the effect of oat β-glucan on LDL cholesterol levels of varying molecular weights. They found that a diet high in β-glucan with a greater molecular weight was more effective in reducing LDL cholesterol than an equivalent amount of β-glucan with a lower molecular weight (MS Wolever et al., 2021). The finding of the study suggested that intake of high M.W. β-glucans can enhance the gut populations of Bacteroides and Prevotella, which leads to a reduction in blood pressure, triglyceride levels, and other cardiovascular disease risk factors (Y. Li et al., 2022). Ho et al. reviewed 58 clinical trials and reported that there is a significant LDL-cholesterol reduction observed with a dose of 3.5 grams per day in 6 weeks (MD= −0·19 mmol/l; 95 % CI −0·23, −0·14; P<0·00001), non-HDL-cholesterol (−0·20; 95 % CI −0·26, −0·15 mmol/l, *P*<0·00001) (Ho et al., 2016). Whitehead et al. had a meta-analysis performed on 28 RCTs incorporating at least 3 grams of oat β-glucan per day into the diet to decrease LDL cholesterol and total cholesterol by 0.25 mmol/L and 0.30 mol/L, respectively, while not affecting HDL and triglyceride level (Whitehead et al., 2014). Wolever et al. reported that from a clinical trial, taking 1 gram of high-molecular-weight oat β-glucan (OBG) beverage three times daily for four weeks led to a significant decrease in LDL cholesterol by approximately 6% and reduced cardiovascular disease (CVD) risk by about 8% in healthy adults whose LDL cholesterol levels were between 3 and 5 mmol/L (MS Wolever et al., 2021). According to Yu et al., a meta-analysis incorporated 30 trials with 927 participants. They found that supplementation with oat β-glucan led to a significant reduction in total cholesterol levels (pooled difference (WMD) = -0.24 mmol/L; 95% confidence interval: -0.28 to -0.20 mmol/L) and LDL cholesterol (LDL-c) levels (WMD = -0.27 mmol/L; 95% CI: -0.35 to -0.20 mmol/L) (Yu et al., 2022). Onning et al. reported that consuming oat milk for five weeks significantly reduced serum total cholesterol and LDL cholesterol (-6%, p =0.005; -6% p=0.0036) within 52/66 males with moderate hypercholesterolemia (Önning et al., 1999). In an 80-participant double-blind, placebo-controlled randomized trial with oat β-glucan fortified biscuit, the total and LDL cholesterol were significantly reduced by (-5.7% and -8.6%; p< 0.001) (Virani et al., 2020). One of the most recognized theories is that β-glucan worked as soluble fibers to decrease the absorption of cholesterol and bile acid in the intestine, resulting in reduced cholesterol uptake (Y. Li et al., 2022).

Oats are also a good source of protein, with total protein content varying from 7-20% (table 1) in oat groats. Unlike other cereals, oat proteins are predominantly made up of albumins (1-12%) and globulins (70-80%), with a lower proportion of prolamins (4-15%), which leads to oats having a higher bioavailability than other cereal grain with a high concentration of prolamins. Due to their favorable amino acid composition, specifically the low Lysine/Arginine and Methionine/Glycine ratios, oat proteins may contribute to reducing total and LDL cholesterol levels in the serum (Paudel et al., 2021). Guo et al. also reported that oat proteins reduce serum total cholesterol and LDL (low-density lipoprotein) cholesterol levels thanks to their low Lysine/Arginine and Methionine/Glycine ratios. In addition to oat proteins, oat lipids have also been implicated in the cholesterol-reducing impact of oat products. Multiple studies have indicated that diets rich in monosaturated and polyunsaturated fatty acids reduce serum total cholesterol and LDL cholesterol levels (Guo et al., 2014).

Moreover, oat lipids contain abundant phytochemicals such as vitamin E and phytosterols. Oleic acid, linoleic acid, vitamin E, and plant sterols in oat lipids enhance their cholesterol-lowering properties (Paudel et al., 2021). Studies have indicated that vitamin E (Tocols) supplementation reduced plasma levels of LDL cholesterol and oxidized LDL while preventing LDL cholesterol oxidation and atherosclerosis (Guo et al., 2014; Vardi et al., 2013). Tocols are recognized for their antioxidant activity. Campesterol, stigmasterol, and β-sitosterol are the most abundant phytosterols found in oats (Määttä et al., 1999). Studies reported that phytosterol has a cholesterol-lowering effect by blocking cholesterol absorption in the intestine. This effect is achieved as plant sterols displace cholesterol from bile salt micelles, a critical step in the digestive process that inhibits cholesterol absorption (Guo et al., 2014). Cui and Liu reported that, among the ten studies that satisfied the inclusion standards, oat intake was observed to lower blood total cholesterol by 0.13 mmol/L, with a 95% confidence interval ranging from 0.017 to 0.19 mmol/L (Cui & Liu, 2013).

Oats are rich in various phenolic compounds, the predominant phytochemicals believed to play a role in antioxidant activities and enhancing cardiovascular health benefits. Oat phenolic compounds serve as potent antioxidants with strong free radical scavenging capacity, which can donate an H group to neutralize reactive oxygen and nitrogen species (Alemayehu et al., 2023). Additionally, phenolics possess the capability to chelate or bind with transition metals. Transition metals can catalyze the formation of free radicals; thus, their chelation by phenolics further reduces the potential for oxidative damage (Cui & Liu, 2013). Spencer et al. reported that consuming oats high in phenolic content resulted in a notable enhancement in 24-hour systolic blood pressure (SBP) by -1.16 mm Hg, nighttime SBP by -5.1 mm Hg, and nighttime diastolic blood pressure (DBP) by -2.3 mm Hg, with statistical significance achieved at $P < 0.05$, $P < 0.01$, and $P < 0.05$, respectively; and the result suggesting that the phenolic. Compounds found in oats have a beneficial contribution to cardiovascular protection (Spencer et al., 2020). Vazquez-Ruiz et al. also suggested that phenolic compounds have an antioxidant effect by counteracting senescence and protecting the mitochondrial function in vascular and endothelial smooth muscle cells through the modulation of signal transduction pathways (Vázquez-Ruiz et al., 2022). Flavonoids, including flavonols, flavanols, flavanones, and flavones, as well as stilbenes, are oxidized by free radicals, resulting in a less reactive and more stable ROS and causing less oxidation to the LDL cholesterol. Additionally, phenolic compounds exhibit antioxidant activities by enhancing cellular antioxidant defense activating transcription factors for antioxidants, and cytoprotective enzymes (Alemayehu et al., 2023; Liu, 2007). From 59 RCTs, the subjects receiving oat supplementation interventions compared to control groups have a reduction in the total cholesterol level by 0.42 mmol/l (95% CI, -0.61; -0.22) and a reduction in LDL cholesterol of 0.29 mmol/L (-0.37; -0.20) (Llanaj et al., 2022). Wehril et al. examined 8 RCT studies comparing oat and non-consumers. The relative risks for combined CVD incidence were 0.73 (95% CI, 0.5-1.07) (Wehrli et al., 2021).

Avenanthramides, unique to oats, are particularly notable for their antioxidant properties, helping to prevent the oxidation of LDL cholesterol, a critical factor in the development of atherosclerosis. In agreement with the previous studies, the study by Ji et al. showed that ANAs increase the superoxide dismutase activity, which increases antioxidant activity in a rat model (Li Ji et al., 2003). When the rats (n=48) were fed a diet supplemented with 100 mg/kg of AVN-enriched oat extracts (equivalent to about 20 mg/kg AVNs), there was an increase in superoxide dismutase activity in their skeletal muscle, liver, and kidneys. Additionally, glutathione peroxidase activity was boosted in the heart and skeletal muscles (Li Ji et al., 2003). AVNs also have good antioxidant capacity. An extensive study conducted by Yang et al. reported that the antioxidant capacity of AVA was found to be 10 to 30 times greater than that of common cereal grain antioxidants, including ferulic acid, gentisic acid, p-hydroxybenzoic acid, protocatechuic acid, syringic acid, vanillic acid, and vanillin (Alemayehu et al., 2023). AVNs are attributed to their ability to prevent monocyte adhesion to human aortic endothelial cells and their potential to inhibit the release of pro-inflammatory compounds from macrophages. Moreover, AVNs regulate blood pressure by producing nitric oxide, which causes blood vessels to dilate (Rasane et al., 2013).

Overall, oats' phytochemicals and soluble fiber content contribute to a reduction in risk factors for cardiovascular disease, including lowering high cholesterol levels, improving blood vessel health, and reducing inflammation.

4.2 Improve Gastrointestinal Health and Weight Control

Oats also play a crucial role in improving gastrointestinal health. Several studies have indicated that phenolic compounds and β-glucan are the phytochemicals mainly contributing to gut and gastrointestinal health (O. Chen et al., 2021; Valido et al., 2021; Y. Zhang et al., 2023). Oat is a rich source of soluble and insoluble oat dietary fibers that impact the gastrointestinal system in distinct ways: soluble fiber affects it primarily through its high-swelling and water-binding capacity and serving as a substrate for colon fermentations. In contrast, insoluble fiber influences it by creating a bulking effect. (Daou & Zhang, 2012)**.** The soluble dietary fiber β-glucan has been reported to have multiple health benefits, including the human immune system, gut microbes' health, and the production of short-chain fatty acids (O. Chen et al., 2021). B-glucan has been recognized as prebiotics, which are the nondigestible food components that are fermented by the intestinal microflora and have the potential to selectively promote the growth of health-beneficial microorganisms in the colon, such as Bifidobacterium and Lactobacillus (Valido et al., 2021).

The effect of β-glucan on the gut microbiota is supported by the increase in Bacteroides and reduction in Enterobacteriaceae families found in a vitro human fecal fermentation experiment (O. Chen et al., 2021). The gut microbiota enhances barrier functionality, boosts intestinal permeability, and maintains mucous layer integrity (Fabiano et al., 2023). Fabiano et al. and Valido et al. suggested that β-glucan is fermented by human gut microbiota, which potentially influences the composition of the microbiota and results in the production of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate (Fabiano et al., 2023; Valido et al., 2021). Bifidobacterium can produce acetate, thereby contributing to the SCFAs in the gut. Bifidobacterium also facilitates the coinhibition of butyrate-producing bacteria. Thus, the concentration of butyrate is significantly enriched in the colon. Research also demonstrated that Bifidobacterium has been shown to improve disease prevention abilities, such as colorectal cancer, diarrhea, necrotizing enterocolitis, and inflammatory bowel disease, by effectively inhibiting pathogens from attaching to epithelial cell sites through competitive inhibition. At the same time, Lactobacillus protects intestinal permeability caused by inflammation, chemicals, and stress. It also acts as a lactate course, which is metabolized to short-chain fatty acids (Valido et al., 2021). According to Xu et al., Enterobacteriaceae, Roseburia, and Faecalibacterium prausnitzii showed a positive association with the concentrations of plasma butyric acid and valeric acid while displaying a negative association with isobutyric acid levels (Xu et al., 2021).

Recent studies have reported that oats' phenolic compounds have shown prebiotic effects on gut microbiota. A small proportion of oat's phenolic compounds were absorbed in the small intestine. In contrast, the majority (90%) of the phenolic compounds remain in the colon and are utilized by gut microbiota (Y. Zhang et al., 2023). Chen et al. also indicated that polyphenolics are not well absorbed in the small intestine and remain intact in the colon (O. Chen et al., 2021). The study reported that oat phenolic compounds associated with the proliferation of gut microbiota, Lactobacillus spp., Enterococcus spp., Bifidobacterium spp., Bacteroides spp., and

Clostridium/histolyticum group during fermentation. Three phenolic fractions (bund- n-butanol fraction, free-ethyl acetate fraction, and bound-ethyl acetate fraction) could significantly ($p < 0.05$) promote the proliferation of Bifidobacterium spp. And Lactobacillus/Enterococcus spp.at 6hrs, 12hrs, and 18hrs (Y. Zhang et al., 2023).

Obesity, recognized as a leading risk factor of global mortality, is strongly associated with several chronic conditions, including type 2 diabetes, hypertension, cardiovascular disease, and cancer. The latest report from the World Health Organization revealed that these conditions affect around 60% of adults in Europe. Overweight and obesity are recognized as critical risk factors for the onset of numerous non-communicable diseases, such as cardiovascular diseases (CVD) and certain types of cancer. In individuals with obesity, the adipose tissue releases pro-inflammatory cytokines that play a role in inducing insulin resistance, leading to type 2 diabetes (Y. Li *et al.*, 2022; World Health Organization (WHO), n.d.). Furthermore, an excessive amount of body weight plays a crucial role in the emergence of metabolic syndrome, a condition defined by the WHO that encompasses a cluster of cardiovascular risk factors, including abdominal obesity, elevated blood lipid levels, insulin resistance, and high blood pressure (García-Cordero *et al.*, 2023; World Health Organization (WHO), n.d.). Numerous clinical trials suggested that oat phytochemicals could control body weight, lower fasting blood glucose, and improve blood lipid profiles. WHO also indicated that an increase in whole grains intake in the diet could lower the risk of obesity development (World Health Organization (WHO), n.d.). Oats and their phytochemicals, such as β-glucan and phenolic compounds, have shown anti-obesity and anti-diabetes effects in both in vitro and in vivo studies.

Chang et al. investigated participants with a BMI of 27 or higher, aged between 18 and 65, with the control group (18 participants) or an oat-treated group (16 participants) in 12 weeks. The results have shown that both body weight and BMI were significantly decreased by 2.08 ±2.05 kg and 0.81 ±0.80 kg/m^2, respectively. In the oat-treated group, a slight increase in BMI and weight was observed in the control/placebo group. Throughout the trial, a reduction in body fat and waist-to-hip ratio was observed in over 60% of the subjects treated with oats, although the data are not displayed. In the oat-treated group, there was a notable average reduction of 0.93±1.73% in body fat and 0.01±0.02 in waist-to-hip ratio (Chang et al., 2013). Charlton et al. conducted 328 participants RCT with 197 males and 131 females within 1.5g/d oat β-glucan intake (OL) and 3.2g/d β-glucan intake (OH), and all groups were observed with weight loss. After three weeks, the average weight loss across all groups was 1.0 kg (with a standard deviation of 1.32 kg). In the following three-week period, the two intervention groups reported approximately 50% greater weight loss, at 0.64 kg (SD 0.78) and 0.62 kg (SD 0.78), respectively. Additionally, a decrease in body fat percentage was noted across all groups, recording 20.45% (SD 2.30), 21.28% (SD 1.84), and 20.57% (SD 1.32) in the O.H., O.L., and control groups, respectively; however, this change was not statistically significant ($P=0.263$), according to the linear mixed model analysis (Charlton et al., 2011).

Overall, integrating oats into the diet presents a promising approach for improving gastrointestinal health and preventing obesity and related non-communicable diseases. Clinical evidence suggests that oat intake can significantly reduce body weight, BMI, and possibly body fat and waist-to-hip ratios, potentially combating obesity and metabolic syndrome.

4.3 Glycemic Control and Prevention of Obesity and Diabetics

Numerous scientific studies have demonstrated that oats contribute to health benefits such as lowering glycemic responses, reducing cholesterol levels, balancing gut microbiota, and regulating blood pressure. Moreover, some mate-analysis has indicated explicitly that high consumption of oats is also associated with improved glycemic control (Wang et al., 2022; K. Zhang et al., 2021). The Glycemic Index (G.I.) measures the impact of consuming a specific food on blood glucose levels compared to that induced by pure glucose. It measures how carbohydrate-containing food raises blood sugar. Food was sometimes classified based on the G.I. value; those with values under 55 are considered low G.I., values ranging from 56 to 69 are considered medium G.I., and values over 70 are high G.I. G.I. is a rating tool for the glycemic rising capacity and offers a method to select food beneficial for managing Type 2 diabetes (K. Zhang et al., 2021). As in oats, starch is the main component, making up about 51-67.7% of the kernel and playing the most significant determinant of the G.I. level. Resistant starch (R.S.) influences blood glucose levels and modulates the G.I. value. R.S. constituted about 29.31% of the starch content in the raw granules of oat starch (K. Zhang et al., 2021). The R.S., specifically in raw oat starch, is named RS2 starch, which digests slowly primarily due to the compaction of the starch granules that hinder enzyme access. Furthermore, the presence of an amylose-lipid complex in oats, which is resistant to enzymatic breakdown, coupled with oats' high lipid content (3–7%), also contributes to a higher level of R.S. (Wang et al., 2022; K. Zhang et al., 2021).

Several studies have suggested the correlation between β-glucan and glycemic index. The most compelling theory proposes that the high viscosity of β-glucan solutions slows down gastric emptying, delays the digestion of food matrices, and therefore decreases the glucose-releasing rate. As the digestion progresses into the intestine, the high viscosity of β-glucans may impede the transfer of glucose to the enterocytes, resulting in a more stable glycemic response (K. Zhang et al., 2021). The Glycemic index value of food tends to decrease with an increase in the dosage of oat β-glucan. Wolever et al. investigated the impact of the dosage of oat β-glucan sourced from oat bran. They found that each gram of oat β-glucans decreased the incremental area under the blood glucose response curve by 7% and reduced the peak-rise response by 15% (Wolever et al., 2018).

Type 2 diabetes is also a significant health problem worldwide. Epidemiological research indicates that a majority of individuals with Type 2 Diabetes Mellitus (T2DM) are either overweight or obese. Similarly, a considerable proportion of obese people are found to have diabetes (Y. Li et al., 2022). Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) due to defects in insulin-secretory response or resistance to insulin action. Hyperglycemia can induce non-enzymatic glycosylation of macromolecules and subsequent accumulation of advanced glycation end-products (AGEs). AGEs cause cellular and tissue damage by impairing protein function and clearance and lead to the development of diabetic complications (Spínola et al., 2019). Numerous studies on oat β-glucan have confirmed its effectiveness in managing type 2 diabetes mellitus (Shen et al., 2016). Li et al. conducted a clinical trial with 445 individuals and a subgroup of 298 overweight subjects for a 30-day intervention with 50g/d and 100g/d oat composition. Significant differences were observed in the following parameters which are associated with diabetes: Fasting Plasma Glucose (FPG), 2-H Postprandial Plasma Glucose (PPG), Glycosylated Hemoglobin (HbA1c), Fasting Plasma Insulin, 2-Hour Postprandial Plasma Insulin, Total Triglycerides (T.G.), Total Cholesterol (T.C.), Low-Density Lipoprotein Cholesterol (LDL-c), and High-Density Lipoprotein Cholesterol (HDL-c). Compared with the control group, the 50g/d oat group has a larger reduction in PPG) and showed a mean difference of -1.04 mmol/L, with a 95% CI ranging from -2.03 to -0.05. Meanwhile, the group consuming 100 grams of oats experienced a more significant decrease in PPG with a mean difference of -1.48 mmol/L and a 95% CI of -2.57 to -0.39. Additionally, there was a significant reduction in the HOMA-IR, with an MD of -1.77 mmol/L^2 and a 95% CI of -3.49 to -0.05 (X. Li et al., 2016). Guo et al. also reported that oatmeal consumption significantly reduced the acute postprandial glucose and insulin responses in diabetic patients. In his meta-analysis with 14 RCTs and two uncontrolled observational studies, that oat intake significantly reduced the glycosylated hemoglobin A1c (HbA1c) concentration (M.D., −0.42%; 95% CI, −0.61% to −0.23%), FPG (MD, −0.39 mmol/L; 95% CI, −0.58 to −0.19 mmol/L) (Hou et al., 2015). Shen et al. also have similar findings on four RCTs dealing with 350 type-2 diabetes mullites that intake oat β-glucan from 2.5-3.5 g/day for 3 to 8 weeks. The concentration of FPG and hbA1c was significantly decreased by −0.52 (95% CI: −0.94, −0.10) mmol/L ($p = 0.01$) and −0.21% (95% CI: −0.40, −0.02) ($p = 0.03$), respectively (Shen et al., 2016).

In summary, the unique oat phytochemicals contributed to glycemic control and prevention of obesity and diabetes. The β-glucans are particularly noteworthy for their ability to slow gastric emptying and decrease the transfer rate of glucose to the enterocytes, resulting in a more stable glycemic response and the ability to manage T2DM affecting fasting plasma glucose and postprandial glucose. Clinical trials have shown significant improvements in these parameters with the consumption of oats, suggesting that regular oat intake could be a strategic part of a dietary approach to manage and prevent T2DM and its associated risks.

4.4 Cancer Prevention

Cancer remains a significant chronic health issue worldwide, characterized by high morbidity and mortality rates. It is also the leading cause of death among individuals under 70 years old in most countries. In 2020, it was estimated that there were 19.3 million new cancer cases and about 10 million cancer-related deaths across 185 countries, involving 36 different types of cancers. Aging is a significant factor that contributes to cancer incidents with the ongoing global increase in elderly populations. Aging is also expected to increase cancer cases further in the future, especially in the age group of 80 years or above. The study showed that around 2.3 million new cancer cases were estimated in 2018, and in 2050, the number of new cases will reach 6.9 million (K. Zhang et al., 2021). Recent research has underscored the significant impact of dietary factors on cancer development, prevention, and adjunctive treatment (K. Zhang et al., 2021). The potential mechanisms of cancer prevention of oat phytochemicals include activating apoptosis, inhibiting cell proliferation, deterring the conversion of epithelial cells to mesenchymal cells and the spread of cancer, facilitating the repair of damaged DNA, and modifying the profile of miRNA (X. Li et al., 2022), in recent years. Studies indicate a close relationship between whole grain consumption and cancer prevention. The health benefits of whole grains have been attributed to their phytochemical composition, especially β-glucan, phenolic acid, flavonoids, AVNs, ferulic acid, and phytosterols. These health-beneficial phytochemicals within whole grains are found in various forms: free, soluble-conjugated, and bounded. Numerous research has suggested that whole grains and their phytochemicals have a consistent protective effect, including lowering the risk of colorectal cancer, breast cancer, and coronary heart disease and reducing total mortality (Adom & Liu, 2002). As a well-known whole grain, oats' unique phytochemical composition and anti-cancer properties have gathered much attention and have been studied in detail.

Numerous studies have highlighted the positive association between bioactive compounds in oats and a decrease in cancer risk. Notably, the antitumor properties and cancer-preventive effects of oat β-glucan have been observed in various cancer cases, including skin, epithelial lung, and colon cancer (Paudel et al., 2021). Due to oats' unique chemical structure, most of the phytochemicals are in the insoluble/ conjugate form and bound to the cell wall. Most bound phytochemicals were not digested in the stomach or small intestines and reached the colon. The resilience might explain the mechanism of oat consumption, particularly in preventing colon cancer and other cancers in the digestive system, in multiple epidemiological research (Adom & Liu, 2002; Paudel et al., 2021). Li et al. mentioned that β-glucan is transported into cells via the glucose transporter -1(GLUT1) protein, which clarified the mechanism of how β-glucan gets transported into the cell and its potential for cancer prevention (Li et al., 2022). Many studies have recognized Oat β-glucan as a potent anti-cancer and antitumor compound. The effects of β-glucan not only promote macrophages that attack and eliminate tumor cells but also modulate lymphocyte, neutrophil, and N.K. cell activity and other elements of the innate immune system (Daou & Zhang, 2012). Oat β-glucan has shown cytotoxic effects and induced oxidative stress in lung cancer cells more than in normal cells (Paudel et al., 2021). Li et al. also reported that oat β-glucan exhibits enhanced cytotoxic effects on lung cancer A549 and H69AR cells and colon cancer HCT-116 cells by increasing antioxidant activities (Y. Li et al., 2022). In mice, in vivo studies demonstrated that both soluble and insoluble forms of β-glucan can lower fecal bile acid levels, generate short-chain fatty acids, and promote ketosis in cells adjacent to cancer, significantly contributing to the prevention of colon carcinoma. Shen et al. reported that in mice treated with β-glucan, bile acid content was significantly reduced ($p< 0.05$), and apoptosis in tumor cells was significantly promoted ($P<0.05$) (Shen et al., 2016). B-glucan also increases the viscosity of food clumps. Thus shortening the time of irritation and carcinogens' interaction in the gut and promoting the proliferation of beneficial gut microbes and the production of active metabolites. Li et al. indicated that consuming oat β-glucan significantly increases SCFAs in the colon and triggers cancer cell apoptosis. Therefore, it prevents DMH-induced colon cancer (Y. Li et al., 2022). Han et al. investigated the impact of high M.W. (67kDa), and their research revealed that administering high M.W. polysaccharide extract at doses of 80 mg/Kg and 160 mg/Kg effectively stimulated the proliferation of natural killer cells (Han et al., 2019). Protein from oats also plays a crucial role in cancer prevention. The protein content comprises about 9-20% of the oat grain, and the oat protein and peptide have contributed to human health. Research has shown that oats' proteins, hydrolyzed peptides, and amino acids exhibit biological activities, including antioxidant, antihypertensive, and cancer-preventive effects, by regulating apoptosis and angiogenesis (Li et al., 2022). The meta-analysis conducted by Aune et al. has shown that the relative risk per 90g/day increases in whole grain intake and mortality for total cancer was 0.85 (0.80 to 0.91; Ci (2)=37%, n=6)(Aune et al., 2016).

Studies have illustrated oats' anti-carcinogenic and anti-cancer effects and potential immunomodulatory activity. The mechanisms involved in the anti-cancer capacity of oats are associated with the anti-proliferation and anti-oxidation properties of the bioactive compounds such as phenolic acid, β-glucan, and Avenanthramides. Oats, with their unique profile of bioactive compounds such as β-glucan, have been linked to a reduction in cancer risk, especially in digestive system cancers like colorectal, due to their ability to bypass digestion in the stomach and small intestine and directly impact the colon where they can exert their effects. The vitro and in vivo findings indicated the potential of oats and oats' bioactive compounds in cancer prevention; further human studies are crucial to fully establish the therapeutic efficacy and mechanistic pathways of oats' phytochemicals in cancer.

5. Conclusion and Future Perspectives

Oats, the nutrients, bioactive compound-dense cereal grain have become increasingly recognized for their multitude of health benefits and with a broad spectrum of bioactive compounds including β-glucan, phenolic acids, flavonoids, tocols, phytosterols, and avenanthramides. These components have shown promising roles in preventing chronic diseases, such as cardiovascular diseases, obesity, diabetes, and certain cancers, and aiding in weight control and gastrointestinal health. Studies have shown that the bioactive compounds in oats can modulate blood lipid profiles, enhance glycemic control, exert anti-inflammatory and antioxidant effects, and potentially contribute to cancer prevention. Other health benefits include the modulation of gut microbiota, reduced serum cholesterol levels, improved insulin sensitivity, and the antioxidative capacity associated with oat-derived phenolic compounds.

For future perspectives, the bioavailability and synergistic effects of these bioactive compounds in humans require further investigation to understand how these beneficial effects can be optimized in the diet. Besides oat beta-glucan and phenolic compounds, more human clinical trials are needed for other bioactive compounds such as phytosterols, tocols, and avenanthramides. Exploring the long-term effects of oat consumption on chronic disease prevention and management is also needed for future studies. With these research directions, oats could play a significant role in the future of public health nutrition, disease prevention, and sustainable food systems.

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