Review

Not peer-reviewed version

Composition of Whole Grains Dietary Fibres and Phenolic; and Its Impact on Markers of Inflammation; Role of Gut Microbiota

Jabir Khan , Palwasha Gul , Muhammad Tayyab Rashid , Qingyun Li , Kunlun Liu *

Posted Date: 29 February 2024

doi: 10.20944/preprints202402.1649.v1

Keywords: Whole grains; dietary fibres; phenolic acids; health benefits; Anti-inflammation

Review

Composition of Whole Grains Dietary Fibres and Phenolic; and Its Impact on Markers of Inflammation; Role of Gut Microbiota

Jabir Khan [1,†], Palwasha Gul [1,†], Muhammad Tayyab Rashid [1], Qingyun Li [1] and Kunlun Liu [1,2,*]

[1] College of Food Science and Engineering, Henan University of Technology, Zhengzhou, 450001, China
[2] School of Food and Strategic Reserves, Henan University of Technology, Zhengzhou 450001 China, jabirkhan@163.com (J.K), palwasha.gull68@outlook.com (P.G), trashid208@gmail.com (M.T.R), qyli2021@163.com (Q.L)
* Correspondence: Tel./Fax: +86 371 67758850. E-mail address: lkl@haut.edu.cn (K.L)
† Author has full contribution in the manuscript.

Abstract: Inflammation is an important biological response to any tissue injury. The immune system responds to any stimulus, such as irritation, damage, or infection, by releasing pro-inflammatory cytokines. Overproduction of pro-inflammatory cytokines, including TNF-α and IL-1b, can lead to several diseases eg., cardiovascular diseases, joint disorders, cancer, and allergies. Emerging science suggests that whole grains may lower the markers of inflammation. Whole grains are a significant source of dietary fibres and phenolic acids that have inverse association with the risk of inflammation. The dietary fibres and phenolic acids composition of whole grains is very distinct over different grains. Whole grains (cereals and pseudo-cereals) are rich in both dietary fibres e.g., arabinoxylan, β-glucan and phenolic acids e.g., hydroxycinnamic acids, hydroxybenzoic acids, which are predominantly present in the bran layer. Although the biological mechanisms underlying widely reported association between whole grains consumption and a lower risk diseases are not fully understood. The modulatory effects of whole grains on inflammation also likely to be influenced by several mechanisms, including the effect of dietary fibres and phenolic acids, while some of these effects are direct, others involve gut microbiota, which transform important bioactive substances into more useful metabolites that moderate inflammatory signaling pathway. Thus, the aim of this review is two folded: first is to discuss the types of dietary fibres and phenolic acids commonly found in cereals and pseudo-cereals, and their health benefits observed in animal and human studies. Second, we review existing literature on the linkage between consumption of whole grains and markers of subclinical inflammation, the role of dietary fibres, phenolic acids, and gut microbiota on the anti-inflammatory activity of whole grains intake. Altogether, scientific data on the ant-inflammatory properties of whole grains are encouraging, further researches are needed to cover the gap between the emerging sciences of whole grains dietary fibres, phenolic acids and inflammation.

Keywords: whole grains; dietary fibres; phenolic acids; health benefits; anti-inflammation

1. Introduction

According to the American Association of Cereal Chemist International (AACCI) 1999 [1], "whole grains are composed of intact, milled, cracked, or flaked grains, with endosperm, germ, and bran presenting in the same proportion as primary grains". However, the definition of whole grains was expanded by the AACCI whole grains task force working group in 2006 to include pseudo-cereals [2] (Table 1). Because pseudo-cereals are used in the same traditional way as cereals and have a macronutrient composition that is largely similar to that of cereals, they were included in the definition of whole grains, which were recognized worldwide. Consumption of whole grains in preference to refined grains is known to have numerous health benefits, with the broad range of benefits often attributed solely to the presence of dietary fibres [3]; first, by releasing indigestible

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

fibres that influence gut microbiota composition and activity; second, by giving substrates such as resistant starch, non-starch polysaccharides (β-glucan and arabinoxylans) however, other components, like phenolic acids are all likely to play a role [4] that can be metabolized into useful metabolites of microbiota. Previous observational studies have presented an inverse relationship between whole grain consumption and markers of inflammation [5–7], however the available data from randomized clinical trials is conflicting [8,9]. Additionally, regarding the relationship between consumption of refined grains and inflammation have been reported in several studies. The evidence regarding health outcomes of refined grain consumption is also inconsistent, majority studies have indicated negative or neutral effects regarding inflammation and disease outcomes [10–12]. Furthermore, refined grains have also been associated with unhealthy diet patterns that may increase the risk of developing certain diseases [13,14].

To date, many studies have been conducted on the intake of whole grains and their relationship with several diseases such as inflammation and others [4–7,15]. Whole grains have been shown to have anti-inflammatory properties that can be examined via inflammatory markers, such as C-reactive protein, (CRP), interleukin-6, (IL-6), and tumor necrosis factors (TNF), and may potentially downregulate an inflammatory response [16]. Inflammatory markers change in response to a series of internal metabolic processes, where chronic inflammation may lead to chronic disease [17]. Most observational and interventional studies have focused on the inflammation biomarkers CRP, TNF-α, TNF-α receptor-1 and receptor-2, IL-6, fibrinogen, and IL-1β because it has been developed that these biomarkers are associated with inflammation, which can result in the development of type 2 diabetes, cardiovascular disease, neurodegenerative diseases, joint disorders, cancer,T2D, and allergies. (Figure 2) [18–20]. Following IL-6, an acute-phase protein produced by the liver in response to IL-6, appears to be the most studied inflammatory biomarker in studies investigating the influence of whole grains on inflammation [21,22]. This recognition has been accompanied by researchers to investigate the effect of whole grains on the inflammatory process as a potential explanation for whole grains' ability to reduce the risk and severity of several diseases [17]. On the other hand, many anti-inflammatory drugs are generally used, which might have side effects, such as gastrointestinal disorders, water retention and renal failure, bronchospasm, and hypersensitivity reactions [23]. For these reason, slowing down the inflammation process became very important. As an alternative in inflammation treatment, whole grain dietary fibres and Phenolic acids have attracted scientific attention by being play a significant role in the reduction risk of inflammation with null side effects. Although there may never be such a single path to the prevention of inflammation diseases, it is possible that the long-term consumption of whole grains as part of an overall healthy dietary pattern may significantly reduce the development of inflammation and related diseases. Thus, the first objective of the present study was to summarize the composition of dietary fibres and phenolic acids in whole grains, as they present in common consumed grains. Second the current knowledge of the associations between whole grain intake and biomarkers of inflammation along with the underlying mechanisms. In summary, the scientific evidence that the anti-inflammatory properties is encouraging. Recent evidence suggests that the phenolic acids and dietary fibres coupled with whole grains may be beneficial to health than individual isolated components.

2. Materials and Methods

In the present study, we have summarized and reviewed the dietary fibres and phenolic acids of different targeted whole grains (Table 1). Then we examined existing literature on the association between the consumption of whole grains and the development of inflammation. All the materials for the current review were searched for in PubMed and Google Scholar, including human studies, such as observational (cross-sectional studies, case-control studies and cohort studies) and intervention studies. The major keywords used for the search of literature were whole grains, dietary fibres, phenolic acids, gut microbiota and inflammation. In the present review, pertinent data published in the English language in reputable peer-reviewed journals have been included for discussion. However, all contents available in the form of conference abstracts, books and unpublished findings were excluded.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

Table 1. Targeted cereals used for the study.

Cereal	Botanical Name
Rye	*Secalecereale L.*
Corn	*Zea mays L.*
Sorghum	*Sorghum bicolor.*
Millets	*Eleusine coracana (L.) Gaertn.*
Triticale	*Triticosecale Wittmack.*
Pseudo cereal	**Botanical name**
Quinoa	*Chenopodium quinoa Willd.*

3. Dietary Fibre and Phenolic Acids in Whole Grains and Their Health Potentials

3.1. Dietary Fibres Contents in Whole Grains

According to the definition given by the World Health Organization (WHO), dietary fibers are "carbohydrates with a degree of polymerization of 3 or more that naturally occur in foods of plant origin and that are not digested and absorbed by the small intestine" [24]. Insoluble dietary fiber (IDF) and soluble dietary fiber (SDF) are two categories of dietary fiber that may be categorized based on their water solubility [25]. IDF, which is made up mostly of cellulose, water-insoluble hemicellulose, and lignin, is found in plants as structural cell wall components [26]. SDF is made up of a range of non-cellulosic polysaccharides and oligosaccharides. Hemicellulose is a common form of DF in grains. Hemicellulose is a non-cellulosic component of cell walls composed of heterogenic polysaccharides [27]. Hemicellulose molecules are broadly classified into four types: xylans, xyloglucans, glucomannans, and mixed linkage β-glucans [28]. Hemicelluloses can be soluble or insoluble depending on their size and structure (e.g., side chain substitutions and intermolecular crosslinks) [29]. Arabinoxylan (AX) and mixed linked β-glucan make up around 70% and 20%, respectively, of the total dietary fiber composition. Thus, AX contains four structural components: non-substituted, mono and di- substituted Xyl, and O-2 or O-3 [30]. The O-5 position of arabinose residues can be used to esterify ferulic acid. These ferulic acid structures can create connections between AX chains, increasing the molecular weight of the compound while decreasing its water-extractability.

The dietary fibre content of rye is higher compared to other grains, as rye contains ranging from 14 to 21% dietary fibre (Table 2) on dry matter base [31]. In rye, the four main dietary fibre forms are AX, cellulose, fructan, and β-glucan, with AX being the predominant dietary fibre component (i.e., 45% of total dietary fibre content) contained in endosperm cell walls [32]. Although both rye and quinoa contain AX, the amount and solubility of AX in rye is greater than that of millet [27].

Rye contains the highest amount of fructan among other cereals. Fructan is a soluble dietary fibre made up of β-D-fructofuranosyl units that can have or not have a terminal glucose residue [33]. Rye fructans can be either linear or branching in structure. In rye, the degree of polymerization of fructan typically ranges from 2 to 60 [34]. The amount of dietary fibre in rye varies depending on where it is located inside the kernel. The inner endosperm has less dietary fibre (12%), but the outer endosperm and bran portion have around 22 and 38% dietary fibre, respectively [35]. The increased quantities of dietary fibre found in the outer kernel layers of rye demonstrating the benefits of consuming whole grains. The dietary fibre content of corn varies ranging to 3.7 and 19.9% on dry matter basis, of which IDF is the largest fraction (Table 2) [31,36–38]. In corn bran, cellulose and hemicellulose make up the majority of the IDF components [31,39]. The TDF of sorghum ranges from 1.5 to 12% [40], millet has a content of 13–14% [41], and triticale has a content of 14–15% on a dry matter basis g/100g [42,43].

Table 2. Content of TDF, IDF and SDF targeted grains g/100g.

Whole Grains	TDF	IDF	SDF	References
Rye (*Secalecereale L.*)	15.2-20.9	11.1-15.9	3.7-4.5	[37]
	14.7-20.9	10.8-15.9	3.4-4.6	[38]

Corn *(Zea mays L.)*	3.7-8.6	3.1-6.1	0.5-2.5	[39]
	13.1-19.6	11.6-14.0	1.5-3.6	[31]
Sorghum *(Sorghum bicolor)*	7.55–12.3	6.52–7.90	1.05–1.23	[40]
Millets *(Eleusine coracana (L.) Gaertn.)*	13.0-13.8	12.5-13.5	0.52-0.59	[41]
Triticale *(Triticosecale Wittmack)*	14.5	0.7	6.7	[42]
	14.6	12.0	-	[43]
Quinoa *(Chenopodium quinoa Willd.)*	16.2-20.6	-	-	[44]
	11.6-15.1	9.9-12.2	0.4-2.9	[45]

Quinoa is a pseudo-cereal that has a long history of use as food components and has some very interesting nutritional properties. In the past 10 years, pseudo-cereals have become increasingly popular as ingredients in gluten-free goods. Their usage significantly raises the dietary fibre content of these goods, which are typically deficient in dietary fiber [44]. Approximately quinoa contains around 7 to 21% of TDF [45,46]. The majority of the dietary fiber in these pseudo-cereals, as determined by a monosaccharide analysis of dietary fiber taken from samples of quinoa and amaranth, is made up of galacturonic acid, arabinose, xylose, glucose, and galactose. The main portions of quinoa are soluble and insoluble dietary fiber which is categorized as pectic polysaccharide [47] based on the monosaccharide composition and linkage analyses. Xyloglucans are the second most abundant dietary fibre contained in quinoa whole grains.

In summary; whole grains cereals and pseudocereals contain a wide variety of dietary fibre types. Some examples of cereal dietary fibre types are arabinoxylan, β-glucan, xyloglucan, pectic polysaccharides and fructan. Cereal dietary fibre exists as both soluble and insoluble dietary fibre fractions. Different cereals have typically a different dietary fibre profile. Among the above studied cereals, Rye grain particularly rich in AX, while quinoa and millets are recognized for the functional properties associated with their most important dietary fibre type, i.e., β-glucan. One of the main effects of soluble dietary fibre is increasing the viscosity of the gut content. In contrast, insoluble dietary fibre absorbs more water and helps in faecal bulking. Therefore (Table 2) summarizes the content of dietary fibres in whole grains, which showed that, rye contains the highest dietary fibre levels, from 14 to 21%, while sorghum contains the lowest dietary fibre level among cereals (7–13%). The ranks become variable in the rest of the cereals. The descending order of the sum of total dietary fibre in Table 3 is Rye, quinoa, corn, triticale, millet and sorghum. In a few studies, both soluble and insoluble dietary fibre in triticale and quinoa were undetected. The consumption of whole-grain fibre has been linked to a reduced risk of chronic non-communicable diseases. Diets rich in fibres are an important role in the reduction risk of inflammation. Further experimental trials are required to confirm the contents of TDF, IDF and SDF in different whole grains.

3.2. Health Potentials

Whole grain bran is a grain's nutritious storehouse. The chemical composition of whole grain bran is highly complex, and the various health benefits of grains bran might be exploited by incorporating it in one's regular diet [48]. Besides regular nutrients like protein, vitamins, minerals, and fats, it also contains a variety of bioactive compounds like dietary fibre and phenolic acids, which have been shown to have a wide range of biological activities and other health benefits in populations eating cereal grain-based diets [49,50]. However, selecting a good source becomes complicated, due to their wide range of physicochemical properties. One of the major components found in whole grain bran is dietary fibre. The benefits of dietary fibre in human health have been supported by extensive research conducted over the last three decades [51,52]. The main focus of β-glucan in diet to decrease blood lipids, specifically serum total and LDL-cholesterol, has been the major emphasis of β-glucan in the diet, assuming that both these effects have long-term health advantages [53]. According to the author found that average cholesterol reduction was 4.4%. These data were obtained from 23 studies that had used less than 10 g dietary fiber per day. It is noteworthy that the test samples used in the meta-analysis were intact whole oats and oat bran. Furthermore whole grains β-glucan has been shown to provide a number of health advantages [54], including lowering blood cholesterol and glucose levels, Decrease glycemic index prebiotic effect and improving satiety, all of which aid

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

in the long-term management of heart disease and other chronic non communicable diseases in Table 3 [55–68].

Table 3. Dietary fibres in whole grains and their health potentials.

Grains	Dietary Fibres	Health Potentials	References
Whole grains	Arabinoxylans	Increase fecal biomass, enhance gut health, low LDL level, lipid metabolism	[55–59]
Whole grains	β-glucans	Anti-Inflammation, Decrease glycemic index; prebiotic effect, Blood cholesterol and glucose modulation, Immune function modulation	[60–63]
Whole grains	Total dietary fibres	Anti-Inflammation Lower risk of Anti-cardiovascular disease, Anti-diabetics, and certain Anti-cancers and Body weight regulation	[51,64–67]

Consumption of grains AXs has been shown to improve lipid metabolism by lowering LDL cholesterol levels in the blood, improve colonic health by lowering cancer risk, and improve glycemic management by lowering blood glucose levels [56,57]. AXs have been shown in studies to inhibit small intestinal transit, limit starch availability to digestive enzymes, and slow the rate of lumen-to-cell glucose diffusion. All of these factors can contribute to decreased glucose absorption, which reduces postprandial glycemic response [58]. The health claim that AX consumption reduces the glucose rise after a meal has been accepted by the European Food Safety Authority [59]. Significant intake of dietary fiber helps individuals to lose weight and enhances blood glucose, immunological function, and serum cholesterol concentrations. It also lowers the risk of several crippling diseases including Inflammation Lower risk of cardiovascular disease, diabetes, and certain cancers Body weight regulation [51,64–67]. Recent findings on the health implications of whole grains, precisely their bioactive fractions, have underlined the potential status of whole grains as functional foods, which can reduce the risks for several chronic diseases [65].

In Table 3 several studies has highlighted that the health potential of cereal-based food is related to their carbohydrate compounds, like β-glucan, arabinoxylan, and other dietary fibres [54–67]. Therefore, the Table 2 above summarizes the functional compounds together with their location in grain fractions. The health benefits of dietary fibres found in cereals and pseudo-cereals have been investigated extensively throughout the years. Intake of some types of dietary fibres such as β-glucan have been recommended due to approved health benefits, while many other types of dietary fibres are still studied for their unique impacts. Because these health benefits are linked to several aspects, it is difficult to obtain solid evidence of the health impacts of dietary fibres in reduction risk of chronic diseases. Furthermore dietary fibres content varies widely between grains. However, the extent to which dietary fibres in whole grains contributes in health benefits have yet to be elucidated. However, more research and communication are needed their content in different varieties of whole grains as well as the health benefits to translate the science underlying these beneficial effects into useful information.

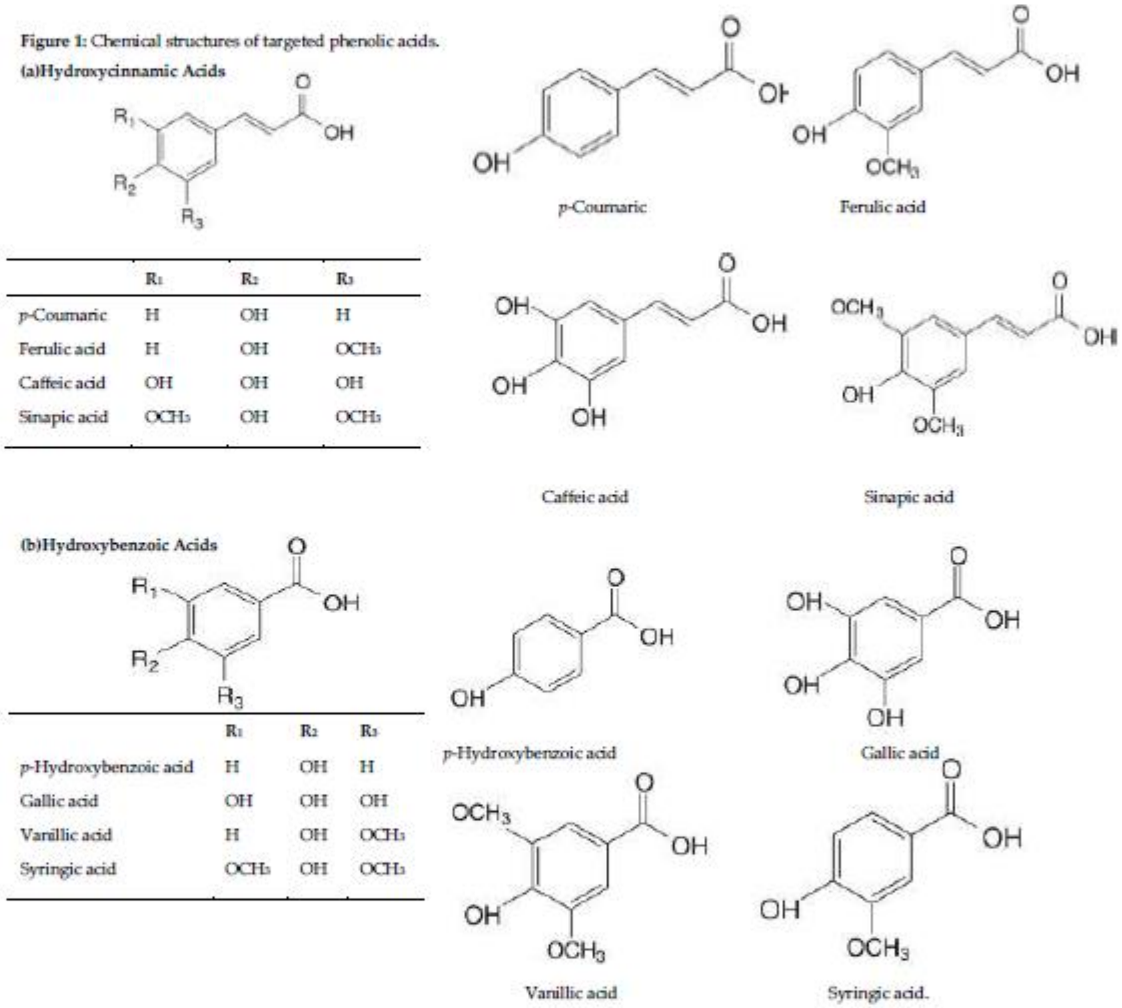
3.3. Phenolic Acids Contents in Whole Grains

Phenolic compounds are distinguished by the presence of one or more aromatic rings joined by one or more hydroxyl groups. Phenolic acids are benzoic and cinnamic acid derivatives. In general, "phenolic acids" refer to phenols with one carboxylic acid functionality. However, when defining plant metabolites, it refers to a separate category of organic acids. These naturally occurring phenolic acids have two distinct constitutive carbon frameworks: hydroxycinnamic and hydroxybenzoic. Although the fundamental structure remains the same, the numbers and positions of the hydroxyl groups on the aromatic ring create the variety.

Phenolic acids are formed in plants via shikimic acid via the phenylpropanoid pathway, as byproducts of the monolignol pathway, and as breakdown products of lignin and cell wall polymers in vascular plants [68]. Phenolic acids are found in grains in three forms: free, conjugated, and bound,

 doi:10.20944/preprints202402.1649.v1

with the binding form predominating [69,70]. They are mostly found in the bran and embryo cell walls of cereal kernels [69,71]. Hydroxycinnamic acids are aromatic carboxylic acids having a C6-C3 structure. Ferulic, *p*-coumaric, caffeic, and sinapic acids are some of the most frequent hydroxycinnamic acids found in grains (Figure 1). Hydroxybenzoic acids have a C6-C1 structure, and p-hydroxybenzoic, gallic, vanillic, and syringic acids are prevalent in grains. It should be demonstrated that hydroxycinnamic acids are more abundant in plants than hydroxybenzoic acids [72,73], and the phenolic acids present in whole grains include ferulic, vanillic, caffeic, syringic, and *p*-coumaric acids [49,72,73]. Hydroxycinnamic acids are generated in a variety of plant foods, including coffee beans, tea, maté, berries, citrus, grapes, spinach, beetroots, artichokes, potatoes, tomatoes, and cereals [74]. Cinnamic-related compounds have been shown to have anticancer, anti-tuberculosis, antimalarial, antifungal, antibacterial, antiatherogenic, and antioxidant properties. There are several cinnamic acid isoforms found in nature, with trans-CA (trans-3-phenyl-2-propenoic acid; t-CA) being the most common. Because of its low toxicity, t-CA has been widely employed as an antibacterial/antifungal component in medicine. t-CA is present in triticale, barley, oat, rye, rice, and maize [75], sorghum [76], and millet [77], with millet and quinoa having undetectable levels. The following literature will cover the composition of phenolic acids, including derivatives of benzoic and cinnamic acids in whole grains, as they are present in the most widely eaten grains. Furthermore, the significance of these phytochemicals to the health advantages of whole grain consumptions is studied.



	R1	R2	R3
p-Coumaric	H	OH	H
Ferulic acid	H	OH	OCH3
Caffeic acid	OH	OH	OH
Sinapic acid	OCH3	OH	OCH3

	R1	R2	R3
p-Hydroxybenzoic acid	H	OH	H
Gallic acid	OH	OH	OH
Vanillic acid	H	OH	OCH3
Syringic acid	OCH3	OH	OCH3

Figure 1. Chemical structures of targeted phenolic acids.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

In (Table 4) we have reviewed 8 phenolic acids in targeted cereal grains, which demonstrate that Ferulic acid (4-hydroxy-3-methoxycinnamic acid; FA) is prevalent in plants and is the product of phenylalanine and tyrosine metabolism. FA is one of the

most abundant phenolic acids in cereals, found primarily in the cell walls of rye, triticale [75], corn [78], sorghum [79], millet [80–82], and quinoa [83,84]. The average FA content of these grains ranges from 46.2 to 827.2 g/g dry weight, with rye and millet having the highest levels and triticale having the lowest. *p*-Coumaric acid (3-(4-hydroxyphenyl)-2-propenoic acid; *p*-CA) has been found in rye, [75], corn and triticale [85], millet [81], sorghum [80], and quinoa [84]. The range of average *p*-CA concentration in grains is from 43.6 g/g dry weight in sorghum up to 340.5 g/g in corn. Caffeic acid (3,4-dihydroxycinnamic acid) is found mostly in foods as an ester with quinic acid to create chlorogenic acid. Caffeic acid can be found in rye, corn and triticale [75], millet and sorghum [80], and quinoa [84]. Sorghum has an average value of 4.6 g/g dry weight, while sorghum has a content of 32.1 g/g. Sinapic acid (4-hydroxy-3, 5-dimethoxy cinnamic acid; SA) is prevalent in several plants, including rye [75,86], corn and triticale, [73,75,87], sorghum [79], and millet [80]. In cereals, the average concentration varies from undetected in quinoa to 94.2 g/g in millet.

Table 4. Review of four hydroxycinnamic acids four hydroxybenzoic acids in targeted cereals µg/g of Dry Weight.

Hydroxycinnamic Acids in Targeted Cereal Grains µg/g of Dry Weight					
Whole grains	**Ferulic acid**	***p*-Coumaric**	**Caffeic acid**	**Sinapic acid**	**References**
Rye (*Secalecereale L.*)	827.2 (218.7–1170.0)	49.0 (29.9–70.0)	16.2 (12.3–20.0)	94.2 (51.7–140.0)	[75,86]
Corn (*Zea mays L.*)	94.2 (51.7–140.0)	340.5 (97.0–584.0)	15.0 (5.7–24.4)	66.1 (52.9–79.3)	[73,75,78,84,85]
Sorghum (*Sorghum bicolor*)	66.1 (52.9–79.3)	43.6 (3.8–83.4)	32.1 (1.9–62.4)	8.2	[79]
Millets (*Eleusine coracana (L.) Gaertn.*)	233.4 (20.0–571.3)	46.0 (18.0–118.3)	4.6 (1.1–8.2)	46.7 (21.3–72.1)	[80–82]
Triticale (*Triticosecale Wittmack*)	46.7 (21.3–72.1)	139.8 (21.2–258.5)	9.9 (6.0–13.9)	83.0 (50.0–140.0)	[75,85]
Quinoa (*Chenopodium quinoa Willd.*)	87.7 (23.7–150.0)	48.6 (17.1–80.0)	7.0	-	[83,84]
Hydroxybenzoic acids in targeted cereal grains µg/g of Dry Weight					
	p-Hydroxybenzoic acid	**Gallic acid**	**Vanillic acid**	**Syringic acid**	
Rye (*Secalecereale L.*)	14.1 (8.1–20.0)	7.7	18.0 (15.9–20.0)	6.3	[75]
Corn (*Zea mays L.*)	8.2 (4.9–11.6)	55.4 (0.5–116.5)	10.3 (5.4–15.4)	45.3 (4.3–108.4)	[75,85]
Sorghum (*Sorghum bicolor*)	36.2 (6.1–148.0)	28.0 (13.2–46.0)	23.2 (8.3–50.7)	16.9 (15.6–19.7)	[78,88]
Millets (*Eleusine coracana (L.) Gaertn.*)	3.0	68.6 (38.7–109.0)	22.2 (11.0–33.3)	13.1 (2.1–24.0)	[73,80,81]
Triticale (*Triticosecale Wittmack*)	7.1 (6.9–7.4)	333.7 (123.4–544.0)	446.0 (154.0–738.0)	173.2 (5.3–341.0)	[75,85]
Quinoa (*Chenopodium quinoa Willd.*)	21.7 (13.8–29.0)	-	30.4 (11.7–110.0)	-	[84]

Hydroxybenzoic acids are phytochemicals found in various diets. It should be emphasized that circulating hydroxybenzoic acids in humans can be the absorbed products of bacterially mediated polyphenol metabolism in the lower intestine [89,90]. This chapter discusses widely discovered hydroxybenzoic acids in grains, namely *p*-hydroxybenzoic (p-OHBA), gallic (GA), vanillic (VA), and syringic (SyA) acids. p-OHBA is present in rye, corn, and triticale [75], sorghum [88], millet [72], and quinoa [84]. The average p-OHBA ranges from 3.0 g/g in millet to 36.2 g/g in sorghum. GA is found in rye, corn triticale, [75], sorghum [79], millet [80,81], and quinoa [84]. Its presence has not been reported in quinoa, and the greatest amount among grains was found in triticale, at 333.7 g/g. VA has been detected in rye, corn, and triticale [75], sorghum [73], millet [87], and quinoa [84]. The average concentration varies from 10.3 g/g in corn to 446.0 g/g in triticale. SyA has been found in rye [75], corn and triticale [85], sorghum [79], millet [72]. It was content was highest in triticale (173.2 g/g) and undetected in quinoa.

In summary of 8 reviewed phenolic acids (Table 4), FA is the most abundant in all grains except corn and triticale. In corn, FA is ranked is ranked second and *p*-Coumaric acid being on the top, while in triticale, FA is ranked 5th, with Vanillic acid, gallic acid, syrengic acid and *p*-Coumaric acid, and Vanillic acid being the top in triticale, respectively. In buckwheat, vanillic acid and gallic acid are predominant in descending order. The ranking becomes variable in the rest of the phenolic acids within grains. The descending order of the sum of the 8 reviewed phenolic acids is triticale, rye, corn, millet, sorghum and quinoa, of five hydroxycinnamic acids is rye, corn, millet, triticale, sorghum and qunioa, and of five hydroxybenzoic acids is triticale, corn, millet, sorghum, quinoa, and rye. Interestingly, the ratio of the sum of hydroxycinnamic acids to hydroxybenzoic acids is larger than 1 in all grains except triticale. These comparisons suggest that each grain prefers one phenolic acid synthesis pathway to the others, leading to a unique phenolic acid profile. Phenolic acid content in quinoa appears much lower than in other grains, probably due to low synthesis. However, more studies are warranted to confirm their contents.

Health Potentials

Epidemiological evidence suggests that phenolic acids have remarkable health-promoting impacts on chronic disorders, including anti-carcinogenic, anti-inflammatory, and antioxidant activity (**Table 1**). The anti-carcinogenic capacity of phenolics is a major disease-preventive effect; they inhibit the development and progression of malignancies by limiting normal cell transformation, tumor growth, angiogenesis, and metastasis. Furthermore, phenolics stimulate the expression of tumor-suppressing proteins such as p53, phosphatase, and the tensin homolog PTEN [91]. Several investigations have demonstrated that *p*-coumaric acids have antibacterial, anti-inflammatory and anti-carcer [92,93] properties. For example, Janicke et al. [94] discovered that *p*-coumaric acid protects against colon cancer formation by decreasing the cell cycle progression of Caco-2 colon cancer cells. Feruloyl-L-arabinose reduced lung cancer cell penetration, motility, and the formation of reactive oxygen species. Other phenolic acids, such as ferulic, feruloyl-L-arabinose, and *p*-coumaric, have also been examined in various cell lines for their anti, inflammation, anti-carcinogenic, antihypertensive, and antidiabetic potential [95–98]. Ferulic acid possesses anticancer characteristics, according to Fahrioğlu et al. [96], via influencing the cell cycle, invasion, and apoptotic behavior of MIA PaCa-2 (human pancreatic cells). Eitsuka et al. [99] investigated the synergistic anticancer potential of ferulic acid against cancer cell proliferation and discovered that this combination inhibits the proliferation of DU-145 (prostate cancer), MCF-7 (breast cancer), and PANC-1 (pancreatic cancer) cells better than their individual use. Moreover, numerous studies have shown that consuming whole grains rich in phenolic acids protects against a number of cardiovascular and blood circulation-related diseases, including caffeic acid, while also improving insulin resistance, plasma triglyceride levels, and platelet function, anti-carcinogenic and anti-mutagenic properties [100].

Furthermore, no comprehensive investigation on the biological activities of sinapic acid was found. A literature search revealed the existence of both free and ester forms of sinapic acid, with some examples of esters being sinapoyl esters, sinapine (sinapoylcholine), and sinapoyl malate [101]. Spices, citrus and berry fruits, vegetables, cereals, oilseed crops, and vegetables are among the edible plants that contain the phytochemical sinapic acid [102,103]. Sinapic acid has been investigated and documented in relation to a number of clinical disorders, including infections, oxidative stress [104], inflammation [105], cancer [106], diabetes [107], neurodegeneration [108], and anxiety [109]. Studies have also been conducted on the acetylcholinesterase inhibition [110,111], antimutagenicity [112], and antioxidant activity [113] of a few sinapic acid derivatives, including sinapine, 4-vinylsyringol, and syringaldehyde. In regards to *p*-hydroxybenzoic acid, we looked at the antithrombogenic, anticoagulation, and inhibitory effects of protocatechuic acid, isovanillic acid, and 4-hydroxybenzoic acid, which all function as antithrombotic and anticoagulant agents [114,115]. However, there are no studies on how these substances affect blood cell viability or their inhibitory effects on fibrin clot formation, plasma recalcification, or the enzymatic activities of procoagulant proteases or fibrinoligases. DU-145 human prostate carcinoma cells and human leukemia (HL)-60 cancer cells are two examples of the cancer cells that gallic acid has been shown to have a strong anticancer impact on in a number of studies [116,117]. Furthermore, human epidermoid carcinoma (A431) skin cancer cells are not able to proliferate when methyl gallate is present [96,118]. In addition, it has been demonstrated that phenolic acids are considered excellent antioxidants that are capable of neutralizing excessive damage to the body produced by free radicals and chronic disorders. The antioxidant capacity of hydroxybenzoic acids is centered on phenolic hydroxyl. Other than that's, methoxy and carboxy groups have a significant impact on phenolic acid antioxidant capability. Which have an important role in the prevention of Alzheimer's and Parkinson's diseases, both of which are neurological illnesses, including vascular dementia and cerebrovascular insufficiency syndromes [119–121], as well as antidiabetic, anticancer, cardio-protective, and anti-inflammation agents [122] Table 5.

Table 5. Phenolic acids and their health potentials.

Phenolic Acids	Health Potentials	References
p-Coumaric	Anti-microbial, Anti-inflammatory, Anti-cancer,	[92,2]
Ferulic acid	Anti-cancer, Anti-hypertension, Anti-diabetes, Anti-inflammation	[95–98]
Caffeic acid	Anti-mutagenic, Andti-arcinogenic activity	[100]
Sinapic acid	Anti-oxidative , Anti-inflammation, Anti-cancer, Anti-diabetes, Anti-neurodegeneration, Anti-anxiety	[104–109]
p-Hydroxybenzoic acid	Anti-thrombotic and Anti-coagulant	[114,115]
Gallic acid	Anti-cancer HCV inhibition Anti-bacterial	[116–118]
Vanillic acid	Alzheimer's disease and Parkinson's Disease. Neurological disorders, Vascular dementia, Anti-inflammatory and Cerebrovascular insufficiency states.	[119–121]
Syringic acid	Antidiabetic, Anticancer, Cardioprotective, Anti-inflimation	[122]

Table 5 summarizes the grains phenolic acids and health potentials, with regard to *p*-Hydroxybenzoic acid intake, there is a large body of epidemiological evidence on its protective effects against a variety of chronic ailments such as cancer, inflammatory diseases, and bacterial disorders, as well as lowering diabetes, cardiovascular, and neurodegenerative diseases. Several studies have been conducted to investigate the anti-platelet aggregation and antithrombotic activities of protocatechuic acid, isovanillic acid, and 4-hydroxybenzoic acid, which act as antithrombotic and anticoagulant, but no studies have been conducted on the effect of these compounds on blood cell viability and their inhibitory effects on fibrin clot formation, enzymatic activities of procoagulant proteases or fibrinoligases, and plasma recalcification. Furthermore, there is no extensive research on the biological properties of sinapic acid in the literature. These studies have been outlined in this brief review article so that the scientific community can pay more attention to sinapic acid's biological characteristics. Furthermore, cereal grains phenolics have been shown to inhibit Parkinson's and Alzheimer's illnesses, as well as have anti-analgesic, anti-allergic, cardio-protective, and anti-diabetic properties. As a result, phenolic compounds are considered to be beneficial natural bioactive and nutraceutical agents for preventing/inhibiting of inflammation and other several chronic non-communicable diseases.

4. Effect of Consuming Whole Grains on Inflammation Active Components

4.1. Evidences from Epidemiological Studies

Epidemiological studies significantly support the findings that whole grain intake is associated with a lower risk of inflammation as well as several other diseases like coronary heart disease, cardiovascular disease, type 2 diabetes and cancer [18–20,47,123]. Research indicates that consuming whole grains may reduce the incidence of inflammation [4–7,15,21–23]. Although the mechanisms underlying this beneficial impact remain unclear, the significance of subclinical inflammation as a common denominator in most disease processes is gradually attracting attention in the literature [124,125].

In this regard, Xu et al. [126] conducted a meta-analysis of data collected from different randomised controlled trial studies to investigate the relationship between whole grain intake and circulating inflammation markers. This meta-analysis contained data on 838 individuals from nine RCTs. The findings of these analyses revealed that alterations in the inflammatory markers CRP, IL-6, TNF-α, and IL-1β were negatively correlated with higher whole grain intake (standardized mean

 doi:10.20944/preprints202402.1649.v1

difference, 0.16; 95% confidence interval, 0.02–0.30). Furthermore, whole grain consumption was found to be inversely associated with a significant decrease in the levels of IL-6 (standardised mean difference, 0.19; 95%CI, 0.03-0.36) and CRP (standardised mean difference, 0.29; 95%CI, 0.08-0.50). Similar in another meta-analysis of 13 studies including 466 participants indicated that consuming whole grains significantly increased blood concentrations of hs-CRP and IL-6, but had no significant influence on TNF-α levels [127].

Furthermore, in another intervention trail study, Zamaratskaia et al. [128] investigated the impact of a whole grain diet on low-grade inflammatory biomarkers in individuals with prostate cancer. Seventeen men with untreated, low-grade prostate cancer were given 485 g/d of whole grain rye and rye bran products, or refined wheat products with added cellulose. In males with prostate cancer, consumption of whole grains rye and rye bran decreased the inflammatory biomarkers TNF receptor-2, E-selectin, and endo-statin compared to diets including refined wheat products. A beneficial impact of whole grains consumption on subclinical inflammation was reported by [129], when 50 obese participants (body mass index > 30 kg/m2) consumed whole grains-rich meals for a period of 12 weeks. The author discovered that CRP concentrations in the whole grains group had significantly decreased, by 38%, at the end of the intervention, while refined-grain concentrations remained unchanged [129].

Many systematic reviews and meta-analyses have been published summarizing these benefits, which have now been collected into so-called "umbrella reviews" [130–132] that validate these findings. Whole grains have been shown in studies to enhance glucose kinetics, reduce peripheral insulin resistance, and lower inflammation [6,7,126,133]. However, consuming whole grains may not be the only reason for the observed improved health outcomes because people who eat whole grains tend to live a healthier lifestyle in general, including smoking less, drinking less alcohol, and being more physically active [134,135].

4.2. Dietary Fibres

Whole grains are high in soluble dietary fiber, particularly β-glucan, which has numerous physiological and nutritional benefits. However, β-glucan is considered to be a major active component of whole grains that alters and stimulates the gut bacteria (Figure 2). Increased dietary fiber consumption has been shown to provide a number of health benefits, including anti-inflammatory properties. There are additional indications of a direct link between carbohydrate-rich and dietary fiber-deficient diets in the development of inflammation, providing support to the essential role of dietary fibers in inflammation [136]. Qi et al. [137] investigated the effect of whole grains dietary fiber on inflammatory markers and revealed an inverse correlation between the highest and lowest quintile of cereal fiber consumption and lower levels of CRP and TNF receptor-2 concentrations (18% and 8%, respectively). The impact of β-glucan from whole grains products on ulcerative colitis has also been studied. Ulcerative colitis is a severe inflammatory bowel disease characterized by inflammation in the gastrointestinal tract and caused by persistent or recurrent immune system activity. Upregulation of pro-inflammation markers, such IL-1β, has been observed in both colitis patients [65] and animal models [66]. Most research on colitis focus on the pro-inflammation biomarker IL-1β, which is primarily generated by lamina propria monocytes, including macrophages that infiltrate the colitis mucosa [67]. In a similar study, diets which includes 2 whole grains barley cultivars, SW and Hadm, varying in dietary fiber and β-glucans content, as well as the solubility of dietary fiber, were provided to male Wistar rats, and their anti-inflammatory activities were investigated [60]. The author found that consumption of barley can reduce the risk of inflammation, as evidenced by observed lower levels of plasma LPS-binding protein and monocyte chemoattractant protein-1.

Liu et al [61] examined the protective effect of oat β-glucan against colitis induced by dextran sodium sulfate in 80 mice. The results of this study revealed a decrease in aberrant mRNA expression of the inflammation biomarkers in intervention diet, TNF-α, IL-6, and IL-1β after consuming of oat β-glucan (500 mg/kg and 1000 mg/kg). In contrast, Wilczak et al [138] studied the impact of two types of β-glucan (high molecular weight oat β-glucan and low molecular weight oat β-glucan) on 72 male

 doi:10.20944/preprints202402.1649.v1

Sprague-Dawley rats with LPS-induced enteritis. This study found that β-glucan, particularly low molecular weight oat β-glucan, has strong anti-inflammatory properties, as evidenced by pro-inflammatory (IL-12, TNF-*α*) data, anti-inflammatory markers, and the profiles of both lymphocyte populations (intraepithelial and lamina propria) residing in colon tissue.

Given the likely effects of dietary fiber on colonic microbiota diversity and Short chain fatty acid (SCFAs) production outlined above, as well as the known effects of butyrate in the mediation of inflammatory pathways, it is entirely plausible, if not likely, that dietary fiber has an influence on inflammatory status both within the colon and systemically. Future research should focus on the mechanisms implicated. Given the numerous potential beneficial effects of dietary fibre discussed in this section, as well as the complexity of the implicated mechanisms (including the involvement of the colonic microflora), identifying the actual mechanisms that mediate dietary fibre's anti-inflammatory effects will be difficult and will require a variety of approaches, including prospectively designed Randomized Controlled Trials (RCTs) and rodent-based mechanistic studies.

4.3. Phenolic Acids

Inflammation is an important biological response to any tissue injury. The immune system responds to any stimulus, such as irritation, damage, or infection, by releasing pro-inflammatory cytokines [139]. Overproduction of pro-inflammatory cytokines, including TNF-*α* and IL-1b, can lead to serious adult disorders like CVDs, joint disorders, cancer, and allergies. Thus, suppressing the overproduction of these pro-inflammatory cytokines is critical for controlling and preventing these diseases. Phenolic compounds have been used to treat inflammation and related disorders since prehistoric era. In order to better understand the impact of whole grains on inflammation, several bioactive components of whole grains and their metabolites were investigated for their potential impact on inflammation indicators [17,140]. Although previous research has primarily focused on the presence of fiber in whole grains for their anti-inflammatory properties, current research suggests that anti-inflammatory agents in whole grains extend beyond fiber [141,142]. Other bioactive compounds found in whole grains, such as phenolic compounds, tocols, folates, and phytosterols, have also been linked to their anti-inflammatory properties. In this regard [143] investigated the anti-inflammatory properties of *p*-coumaric acid by measuring TNF-*α* level in arthritic rats' synovial tissue. *P*-coumaric acid has strong anti-inflammatory activity, reducing TNF-*α* expression. In addition [95] reported that ellagic and caffeic acid have anti-inflammatory properties. Both caffeic acids and ellagic acids were fed to mice by mixing it into their usual diet in the ratio of 2.5 and 5.0%. The expression of inflammatory mediators was decreased upon inculcation of these phenolic acids. Furthermore, caffeic acid also had anti-inflammatory, anti-hyperglycaemic, and anti-hyperlipidemia effects in a high fructose diet-mediated metabolic alteration model by reducing pro-inflammatory cytokines like serum IL-6, IL-8, and TNF-*α* [18]. Interestingly, Ibitoye et al., found [144] that by increasing the bioavailability of NO, caffeic acid positively regulates blood pressure in rats with cyclosporine-induced hypertension.

Whole grains contain avenantramides (AVAs), which are secondary metabolites. These polyphenolic compounds, which are found in the bran portion of oat grains and are crucial components of oat groats, have also been investigated for their potential to promote health, particularly in relation to inflammation. The three most prevalent AVAs in oat are, Esters of 5-hydroxyanthranilic acid with *p*-coumaric acid (2p or AVA-A), ferulic acid (2f or AVA-B), or caffeic acid (2c or AVA-C). Oat's phenolic compound, AVAs, has also been shown to have anti-inflammatory and antioxidant properties. AVAs have demonstrated antioxidant and anti-inflammatory properties in both in vitro and in vivo studies, has been found to significantly reduce the systemic pro-inflammatory response in exercise-induced inflammation in both younger and older women [145]. This study observed that AVA treatment decreased neutrophil respiratory burst, CRP, IL-1β, IL-6 levels, and NFκB activation. Liu et al. [146] studied the anti-inflammatory and anti-atherogenic properties of oat AVAs in a human aortic endothelial cell culture system. Pretreatment of human aortic endothelial cells with AVAs for 24 hours significantly reduced IL-1β-induced inflammation. Additionally, Sur et al. [147] also investigated the anti-inflammatory effects of AVA on human keratinocytes. Results of this study found that AVA treatment significantly lowered NF-κB-dependent luciferase activity and a subsequent reduction in the release α-IL-8 release in TNF-α-treated keratinocytes.

Phenolic acids and their circulating metabolites have been shown to have anti-inflammatory effects ex vivo. In this regard, Mateo Anson et al. [34] investigated the effects of phenolic acids and their metabolites on inflammation biomarkers. In this study, 8 healthy men followed a low-phenolic-acid diet for 3 days and then fasted overnight before consuming either 300g of whole wheat bioprocessed bread with high phenolic acid concentrations or normal wheat bread with low phenolic acid concentrations. Blood samples were drawn and incubated with LPS after consuming bread for 0, 1.25, 6, and 12 hours, respectively. A comparison of different blood samples revealed a significantly lower pro-inflammatory to anti-inflammatory cytokine ratio in LPS-stimulated blood obtained after consuming bioprocessed wheat bread with high phenolic acid content versus bread with low phenolic acid content.

In summary, studies on the effect of whole grains on inflammation have been inconclusive, most likely due to differences in study approaches and designs. For example, while some studies completely controlled the diet, maintained weight, and kept the dietary components under investigation constant, others were not as controlled. Furthermore, some study designs did not include biomarkers of adherence, which may have influenced the observed effect of whole grains on inflammatory markers. Furthermore, while some studies were conducted on healthy individuals who were unlikely to be immune compromised or have a high inflammatory status, it is possible that more pronounced changes would have been observed in participants preselected for having a high inflammatory status or chronic disease. Hence, further studies and clinical trials are greatly needed to fully establish the therapeutic efficacy of phenolic acids as well as to determine their safety for human consumption.

4.4. Proposed Mechanism of Anti-Inflammatory Properties of Whole Grains Dietary Fibres and Phenolic Acids; and Involvement of Gut Microbiota

The ability of whole grains to modulate inflammation has also been attributed to SCFAs, which are byproducts of the microbial degradation of whole grains dietary fiber (Figure 2). The anti-inflammatory properties of whole grains may be partially attributed to the bioactive properties of SCFAs. Furthermore highlighting the significance of SCFAs in reducing inflammation, it has been reported that WG consumption increases the concentration of *Lachnospira*, a producer of SCFAs, and stool SCFA concentration when compared to refined-grain consumption [148]. Through controlling leukocyte functions and cytokine production, SCFAs (butyrate, propionate, and acetate) in the blood and gastrointestinal tract can reduce inflammation. Cytokines are intercellular messengers and soluble regulatory signals that initiate and constrain inflammatory responses via signaling pathways, including NF-κB and mitogen-activated protein kinase. Cytokines migrate to the sites of inflammation and destroy microbial pathogens [149]. While cytokines are important in coordinating the development of innate and adaptive immune responses to inflammation, they can be life-threatening in excess. In addition, SCFAs can have an effect on histone deacetylase function. Histone deacetylase inhibitors have been shown to reduce cytokine levels in plasma as well as ex vivo responses to pro-inflammatory stimuli [150,151]. Several studies have recently been published that describe SCFAs' ability to activate immune cells, which helps in the destruction of inflammation-triggering pathogens while also controlling the production of cytokines and chemokines when in excess.

The phenolic acid has also been shown to have antioxidant and anti-inflammatory properties. In vitro and in vivo studies have shown that phenolic acids have antioxidant and anti-inflammatory properties (**Figure 2**). Supplementation with phenolic acids was found to significantly reduce the systemic pro-inflammatory response to exercise-induced inflammation [145]. The study found that treatment with phenolic acids reduced neutrophil respiratory burst, CRP, IL-1β, IL-6 levels, and NFκB activation. Furthermore, Liu et al [146] investigated the anti-inflammatory and anti-atherogenic effects of whole grain phenolic acids in a human aortic endothelial cell culture. The

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

author discovered that pretreatment of human aortic endothelial cells with phenolic acids for 24 hours significantly reduced IL-1β-induced inflammation. Sur et al. [147] investigated the potential anti-inflammatory effects of phenolic acids in human keratinocytes. This study found that phenolic acids significantly inhibited NF-κB-dependent luciferase activity and reduced IL-8 release in TNF-α-treated keratinocytes.

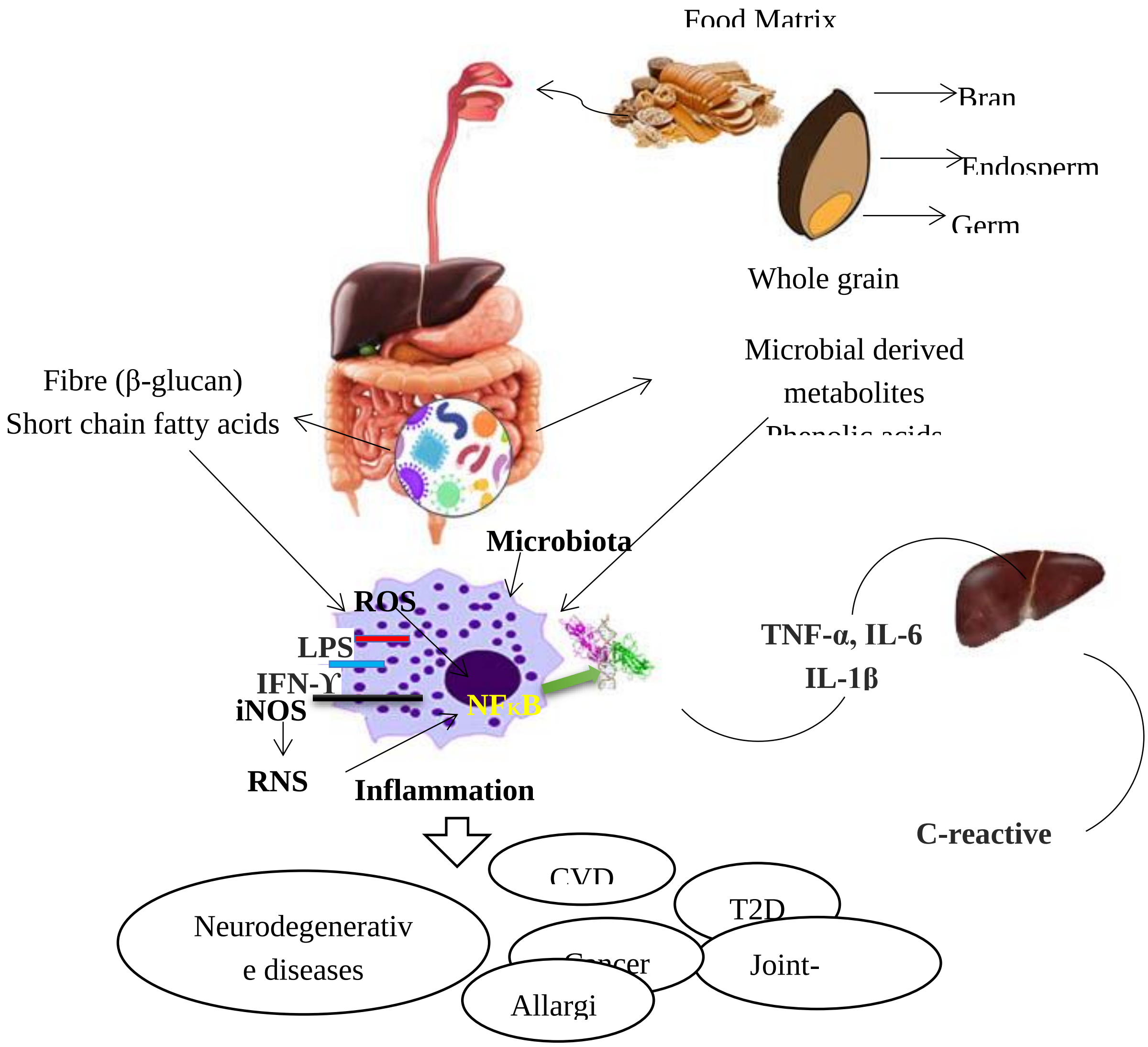


Figure 2. Overview of the anti-inflammatory properties of whole grains dietary fibres and phenolic acids, involvement of gut microbiota and diseases outcomes. IFN-ϒ, interferon gamma; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; CVD, cardiovascular diseases; T2D, type 2 diabetes.

The ability of whole grains to affect both host metabolism and gut microbial ecology suggests that some of their benefits are mediated by their effects on the gut microbiome (Figure 2). As a result, some nutritional studies have investigated the effect of whole grains on inflammation, as well as the role of the gut microbiome in this intervention. Lee et al [152] discovered that whole grains had a modulatory effect on inflammation markers, as well as changes in the population of useful microbiota such as *Lactobacillus* and *Bifidobacterium*, as well as a lower abundance of the *Bacteroides fragilis* bacteria group in the cecum. Furthermore, Vitaglione et al. [33] found a correlation between an increase in Lactobacillus and Bacteroides spp. abundance and a noteworthy decrease in the inflammatory marker TNF-α. Furthermore, Martínez and colleagues [153] investigated if the impact

 doi:10.20944/preprints202402.1649.v1

of whole grains on markers of inflammation was linked to the gut microbiota. Results of this investigation indicated a decrease in plasma IL-6 levels and a tendency toward a decrease in plasma hs-CRP levels. These findings may have stimulated anti-inflammatory effects, which could be associated to a reduction in LPS translocation and an enhancement of the gut barrier function. It seems that a number of mechanisms affect how whole grains modulate inflammation. The effects of fiber, phenolic acids and their metabolites, and microbial metabolites SCFAs (associated with fiber) may be among these actions. While some of these effects are direct, others are due to the prebiotic effects on gut microbiota that change significant bioactive compounds into more beneficial metabolites, which then influence biomarkers associated with inflammation.

5. Conclusions

This article presents a comprehensive review of the composition and biological activity of whole grain dietary fibres and phenolic acids. As reviewed above, whole grains contain a variety of dietary fibres and phenolic acids; however, different grains have typically had a distinct dietary fibre and phenolic acid profile. The benefits of dietary fibres and phenolic acids from whole grains (cereals and pseudo-cereals) have been extensively studied throughout the years. The majority of components associated with health are concentrated in the bran and germ, which are removed during the grains-refining process. Emerging evidences suggest that consumption of whole grains provide benefits beyond basic nutrition, a fact sustained by epidemiological studies demonstrating, a protective effect of a whole grains and inflammation. The anti-inflammatory activity may involve the impact of dietary fibres, microbial metabolites SCFAs and phenolic acids. While some of these effects are direct, others involve the prebiotic on gut microbiota that transform essential bioactive compounds to more beneficial metabolites, which, in turn, affect inflammatory biomarkers. Challenges appear in diverse areas, therefore it is critical to determine which of these components may have the greatest protective action. Future research may investigate whether the whole grain's bran and germ are directly associated with reducing the risk of inflammatory markers, or whether the associations are primarily driven by dietary fibres, specific phenolic acids, or another aspect of the diet, and could significantly contribute to the next generation of healthy cereal-based products.

In general, whole grains contain both dietary fibers and phenolic acids. The modulatory effects of whole grains on inflammation appear to be influenced via several mechanisms. Consumption of whole grains on risk of inflammation includes not only the beneficial effects of dietary fibres, but also the direct anti-inflammatory and antioxidant effects of phenolic acids. Moreover, gut microbiota also contributes a significant role in the anti-inflammatory properties of whole grains. Therefore, it will be interesting to determine the independent effects of bran and germ while investigating the relationship between consumption of whole grain dietary fibres and phenolic acids; and the influence on inflammatory markers. In order to validate the action and strength of the relationship, the gut microbiota should be considered when interpreting the data and making conclusions in future studies.

Author Contributions: Conceptualisation, J.K. and P.G.; writing—original draft preparation, editing, and technical review, M.T.R, Q.L, K.L.; visualisation, K.L.; supervision, K.L. All authors have read and agreed to the published version of the manuscript. All authors listed above have made a substantial and intellectual contribution to the work and approved for publication.

Funding: This study was supported by the National Natural Science Foundation of China (32172259), Key Research and Development Project of Henan Province (231111111800), the Program for the Top Young Talents of Henan Associate for Science and Technology (2021), and the Innovative Funds Plan of Henan University of Technology (2021ZKCJ03).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All the data are already provided in the main manuscript.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in study design, the decision to publish and the preparation of the manuscript.

 doi:10.20944/preprints202402.1649.v1

References

1. AACCI. Definition of Whole Grain. 1999. Available online: http://www.aaccnet.org/definitions/wholegrain.asp (accessed on 15 February 2024).
2. AACCI. 2006. Available online: http://www.aaccnet.org/definitions/pdfs/AACCIntlWholeGrainComments.pdf (accessed on 17 February 2024).
3. Saleh, A. S.; Wang, P.; Wang, N.; Yang, S.; & Xiao, Z. Technologies for enhancement of bioactive components and potential health benefits of cereal and cereal-based foods: Research advances and application challenges. *Crit. Rev. Food Sci. Nutr.*, **2019**, *59*(2), 207-227.
4. Calabriso, N.; Massaro, M.; Scoditti, E.; Pasqualone, A.; Laddomada, B.; & Carluccio, M. A. Phenolic extracts from whole wheat biofortified bread dampen overwhelming inflammatory response in human endothelial cells and monocytes: Major role of VCAM-1 and CXCL-10.*Eur. J. Nutr.* **2020**, *59*, 2603-2615.
5. Milesi, G.; Rangan, A.; & Grafenauer, S. Whole Grain Consumption and Inflammatory Markers: A Systematic Literature Review of Randomized Control Trials. Nutr. **2022**, 14, 374, 7.
6. Sang, S.; Idehen, E.; Zhao, Y.; & Chu, Y. Emerging science on whole grain intake and inflammation. *Nutr. Rev.*, **2020**, *78*(1), 21-28.
7. *Rahmani, S.; Sadeghi, O.; Sadeghian, M.*; Sadeghi, N.; Larijani, B.; Esmaillzadeh, A. The effect of whole-grain intake on biomarkers of subclinical inflammation: A comprehensive meta-analysis of randomized controlled trials. Adv. Nutr. **2020**, 11, 52–65.
8. Andersson, A.; Tengblad, S.; Karlstrom, B.; Kamal-Eldin, A.; Landberg, R., Basu, S. et al. Whole-grain foods do not affect insulin sensitivity or markers of lipid peroxidation and inflammation in healthy, moderately overweight subjects. *The J. Nutr.*, **2007**, *137*(6), 1401-1407.
9. Roager, H. M.; Vogt, J. K.; Kristensen, M.; Hansen, L. B. S.; Ibrügger, S.; Mærkedahl, R. B et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut*, **2019**, *68*(1), 83-93.
10. Vanegas, S. M.; Meydani, M.; Barnett, J. B.; Goldin, B.; Kane, A.; Rasmussen, H.; et al. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. *Am. J. Clin.* **2017**, *105*(3), 635-650.
11. Taskinen, R. E.; Hantunen, S.; Tuomainen, T. P.; & Virtanen, J. K. The associations between whole grain and refined grain intakes and serum C-reactive protein.Eur. *J. Clin. Nutr*, **2022**, *76*(4), 544-550.
12. Aune, D.; Norat, T.; Romundstad, P.; & Vatten, L. J. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis of cohort studies. *Eur. J. Epid.*, **2013**, *28*, 845-858.
13. Jones, J. M.; García, C. G.; & Braun, H. J. Perspective: Whole and refined grains and health—Evidence supporting "make half your grains whole". *Adv Nutr.* **2020**, *11*(3), 492-506.
14. Sanders, L. M.; Zhu, Y.; Wilcox, M. L.; Koecher, K.; & Maki, K. C. Whole grain intake, compared to refined grain, improves postprandial glycemia and insulinemia: a systematic review and meta-analysis of randomized controlled trials. *Crt. Rev.Food Sci. Nutr.* **2023**, *63*(21), 5339-5357.
15. Arabzadegan, N.; Daneshzad, E.; Fatahi, S.; Moosavian, S. P.; Surkan, P. J.; & Azadbakht, L. Effects of dietary whole grain, fruit, and vegetables on weight and inflammatory biomarkers in overweight and obese women. *Eat. Wei. Dis. Stud. Anor. Bul. Obes.*, **2020**, *25*, 1243-1251.
16. Browning, L. M.; Krebs, J. D.; & Jebb, S. A. Discrimination ratio analysis of inflammatory markers: implications for the study of inflammation in chronic disease. *Meta.* **2004**, *53*(7), 899-903.
17. Wang, W. Y.; Tan, M. S.; Yu, J. T.; & Tan, L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann. Transl. Med.* **2015**, *3*(10).
18. Agunloye, O. M.; Oboh, G.; Ademiluyi, A. O.; Ademosun, A. O.; Akindahunsi, A. A.; Oyagbemi, A. A. et al. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: Mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Bio. Phar.*, **2019**, *109*, 450-458.
19. Lee, Y. M.; Han, S. I.; Song, B. C.; & Yeum, K. J. Bioactives in commonly consumed cereal grains: implications for oxidative stress and inflammation. *J. Med. Food*, **2015**, *18*(11), 1179-1186.
20. Del Giudice, M.; & Gangestad, S. W. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, Beh. Imm*, **2018**, *70*, 61-75.
21. Fink-Neuboeck, N.; Lindenmann, J.; Bajric, S.; Maier, A.; Riedl, R.; Weinberg, A. M.; & Smolle-Juettner, F. M. Clinical impact of interleukin 6 as a predictive biomarker in the early diagnosis of postoperative systemic inflammatory response syndrome after major thoracic surgery: a prospective clinical trial. *Surg*, **2016**, *160*(2), 443-453.
22. Chen, W. W.; Zhang, X. I. A.; & Huang, W. J. Role of neuroinflammation in neurodegenerative diseases. *Mol. Med Rep*, **2016**, *13*(4), 3391-3396.
23. Hawkey, C. J.; & Langman, M. J. S. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. *Gut*, **2003**, *52*(4), 600.

24. Tomas-Barberan, F. A.; & Andres-Lacueva, C. Polyphenols and health: current state and progress. *J. Agr. Food Chem*, **2012**, *60*(36), 8773-8775.
25. Zeng, Z.; Liu, C.; Luo, S.; Chen, J., & Gong, E. The profile and bioaccessibility of phenolic compounds in cereals influenced by improved extrusion cooking treatment. *PloS one*, **2016**, *11*(8), e0161086.
26. Tian, M.; Pak, S.; Ma, C.; Ma, L.; Rengasamy, K. R.; Xiao, J. et al. Chemical features and biological functions of water-insoluble dietary fiber in plant-based foods. *Crit. Rev. Food Sci. Nutr.*, **2022**, 1-15.
27. Ciudad-Mulero, M.; Fernández-Ruiz, V.; Matallana-González, M. C.; & Morales, P. Dietary fiber sources and human benefits: The case study of cereal and pseudocereals. Adv. *Food Nutr, Res.*, **2019**, (90), 83-134. Academic Press.
28. Zhang, X.; Li, L.; & Xu, F. Chemical characteristics of wood cell wall with an emphasis on ultrastructure: A mini-review. *Forests*, **2022**, *13*(3), 439.
29. Van der Kamp, J. W.; Poutanen, K.; Seal, C. J.; & Richardson, D. P. The HEALTHGRAIN definition of 'whole grain'. *Food Nutr. Res.*, **2014**, *58*(1), 22100.
30. Singh, A.; & Eligar, S. M. Feruloylated oligosaccharides-emerging natural oligosaccharides for human health: Production, structural characterization, bioactive potential, and functional food applications. *Res. Tech. Adv. Food Sci*, **2022**, 141-173.
31. Whole Grain Poster. Available online: https://nutritioneducationstore.com/products/go-for-thewhole-grain-_poster (accessed on 18 February **2024**).
32. Laddomada, B.; Durante, M.; Minervini, F.; Garbetta, A.; Cardinali, A.; D'Antuono, I. et al. Phytochemical composition and anti-inflammatory activity of extracts from the whole-meal flour of Italian durum wheat cultivars. *Int. J. Mol. Sci*, **2015**, *16*(2), 3512-3527.
33. Vitaglione, P.; Mennella, I.; Ferracane, R.; Rivellese, A. A.; Giacco, R.; Ercolini, D. et al. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. *Amer. J. Clin. Nutr.*, **2015**, *101*(2), 251-261.
34. Mateo Anson, N.; Aura, A. M.; Selinheimo, E.; Mattila, I.; Poutanen, K.; Van Den Berg, R. et al. Bioprocessing of wheat bran in whole wheat bread increases the bioavailability of phenolic acids in men and exerts antiinflammatory effects ex vivo. *J. Nutr.*, **2011**, *141*(1), 137-143.
35. Sánchez-Maldonado, A. F.; Schieber, A.; & Gänzle, M. G. Structure–function relationships of the antibacterial activity of phenolic acids and their metabolism by lactic acid bacteria. *J. App. Mic.*, **2011**, *111*(5), 1176-1184.
36. Ozcan, T.; Akpinar-Bayizit, A.; Yilmaz-Ersan, L.; & Delikanli, B. Phenolics in human health. *Int. J. Chem. Emg. Appl.*, **2014**, *5*(5), 393-396.
37. Anson, N. M.; Hemery, Y. M.; Bast, A.; & Haenen, G. R. Optimizing the bioactive potential of wheat bran by processing. *Food Func*, **2012**, *3*(4), 362-375.
38. Li, L.; Shewry, P. R.; & Ward, J. L. Phenolic acids in wheat varieties in the HEALTHGRAIN diversity screen. *J. Agri. Food Chem.*, **2008**, *56*(21), 9732-9739.
39. Rawat, N.; Laddomada, B.; & Gill, B. S. Genomics of cereal-based functional foods. *Cereal Gen. II*, **2013**, 247-274.
40. Verma, B.; Hucl, P.; & Chibbar, R. N. Phenolic content and antioxidant properties of bran in 51 wheat cultivars. *Cereal Chem*, **2008**, *85*(4), 544-549.
41. Juurlink, B. H.; Azouz, H. J.; Aldalati, A. M.; AlTinawi, B. M.; & Ganguly, P. Hydroxybenzoic acid isomers and the cardiovascular system. *Nutr. J.*, **2014**, *13*, 1-10.
42. Rakha, A.; Åman, P.; & Andersson, R. Dietary fiber in triticale grain: Variation in content, composition, and molecular weight distribution of extractable components. *J.Cereal Sci.*, **2011**, *54*(3), 324-331.
43. Biel, W.; Kazimierska, K.; & Bashutska, U. Nutritional value of wheat, triticale, barley and oat grains. Acta. Sci. Pol. Zootech., **2020**, *19*(2), 19-28.
44. Fernandez-Orozco, R.; Li, L.; Harflett, C.; Shewry, P. R.; & Ward, J. L. Effects of environment and genotype on phenolic acids in wheat in the HEALTHGRAIN diversity screen. *J. Agr. Food Chem.*, **2010**, *58*(17), 9341-9352.
45. Laddomada, B.; Durante, M.; Mangini, G.; D'Amico, L.; Lenucci, M. S.; Simeone, R. et al. Genetic variation for phenolic acids concentration and composition in a tetraploid wheat (Triticum turgidum L.) collection. *Genet Resour Crop Evol Title*, **2017**, *64*, 587-597.
46. Pang, Y.; Ahmed, S.; Xu, Y.; Beta, T.; Zhu, Z.; Shao, Y.; & Bao, J. Bound phenolic compounds and antioxidant properties of whole grain and bran of white, red and black rice. *Food Chem.*, **2018**, *240*, 212-221.
47. Aune, D.; Keum, N.; Giovannucci, E.; Fadnes, L. T.; Boffetta, P.; Greenwood, D. C. et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *bmj*, **2016**, *353*.
48. Saini, P.; Islam, M.; Das, R.; Shekhar, S.; Sinha, A. S. K.; & Prasad, K. Wheat bran as potential source of dietary fiber: Prospects and challenges. *J. Food Comp. Anal.*, **2023**, *116*, 105030.

49. Chauhan, M.; Mahanty, J.; Kumar, S.; Singh, H.,; & Sharma, A. An Insight into the Functional Benefit of Phenolic Acids from Whole Grains: An Update. *Cur. Nutr. Food Sci.*, **2023**, *19*(9), 906-921.
50. Khan, J.; Khan, M. Z.; Ma, Y.; Meng, Y.; Mushtaq, A.; Shen, Q.; & Xue, Y. Overview of the composition of whole grains' phenolic acids and dietary fibre and their effect on chronic non-communicable diseases. *Int. J. Env. Res. and Pub. Heal.*, **2022**, *19*(5), 3042.
51. Waddell, I. S.; & Orfila, C. Dietary fiber in the prevention of obesity and obesity-related chronic diseases: From epidemiological evidence to potential molecular mechanisms. *Crit. Rev. Food Sci. Nutr.*, **2023**, *63*(27), 8752-8767.
52. Snauwaert, E.; Paglialonga, F.; Vande Walle, J.; Wan, M.; Desloovere, A.; Polderman, N. et al. The benefits of dietary fiber: the gastrointestinal tract and beyond. *Pediatric Nephrology*, **2023**, *38*(9), 2929-2938.
53. Wood, P. J. Cereal β-glucans in diet and health. *J. Cereal Sci.*, **2007**, *46*(3), 230-238.
54. Mathews, R.; Shete, V.; & Chu Y. The effect of cereal B-glucan on body weight and adiposity: a review of efficacy and mechanism of action. *Crit. Rev. Food Sci. Nut.*, **2023**, *63*(19), 3838-3850.
55. Neyrinck, A. M.; Possemiers, S.; Druart, C.; Van de Wiele, T.; De Backer, F.; Cani, P. D. et al. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. *PloS one*, **2011**, *6*(6), e20944.
56. Rosicka-Kaczmarek, J.; Komisarczyk, A.; Nebesny, E.; & Makowski, B. The influence of arabinoxylans on the quality of grain industry products. *Eur. J.* Food Res. Nutr., **2016**, *242*, 295-303.
57. Kellow, N. J.; & Walker, K. Z. Authorised EU health claim for arabinoxylan. *In Foods, nutrients and food ingredients with authorised eu health claims,* **2018**, 201-218.
58. Chen, Z.; Li, S.; Fu, Y. Li, C.; Chen, D.; & Chen, H. Arabinoxylan structural characteristics, interaction with gut microbiota and potential health functions. *J. Func. Food*, **2019**, *54*, 536-551.
59. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of health claims related to arabinoxylan produced from wheat endosperm and reduction of post-prandial glycaemic responses (ID 830) pursuant to Article 13 (1) of Regulation (EC) No 1924/2006. *EFSA Journal*, **2011**, *9*(6), 2205.
60. Zhong, Y.; Marungruang, N.; Fåk, F.; & Nyman, M. Effects of two whole-grain barley varieties on caecal SCFA, gut microbiota and plasma inflammatory markers in rats consuming low-and high-fat diets. *Brit. J. Nutr*, **2015**, *113*(10), 1558-1570.
61. Liu Bo, L. B.; Lin QinLu, L. Q.; Yang Tao, Y. T.; Zeng LinNa, Z. L.; Shi LiMin, S. L.; Chen Yaya, C. Y.; & Luo FeiJun, L. F. Oat β-glucan ameliorates dextran sulfate sodium (DSS)-induced ulcerative colitis in mice. *Food Func.* **2015** 3454-3463
62. Keegstra, K.; & Walton, J. β-Glucans--brewer's bane, dietician's delight. *Science*, **2006**, *311*(5769), 1872-1873.
63. Slavin, J. L.; Tucker, M.; Harriman, C.; & Jonnalagadda, S. S. Whole grains: Definition, dietary recommendations, and health benefits. *Cereal Foods Wor.* **2013**, *58*(4), 191-198.
64. Hu, J.; Wang, J.; Li, Y.; Xue, K.; & Kan, J. Use of Dietary Fibers in Reducing the Risk of Several Cancer Types: An Umbrella Review. *Nutr.*, **2023**, *15*(11), 2545.
65. Mao, L.; Kitani, A.; Strober, W.; & Fuss, I. J. The role of NLRP3 and IL-1β in the pathogenesis of inflammatory bowel disease. *Front. Immunol.*, **2018**, *9*, 2566.
66. Zhang, H.; Gong, C.; Qu, L.; Ding, X.; Cao, W.; Chen, H.; ... & Zhou, G. Therapeutic effects of triptolide via the inhibition of IL-1β expression in a mouse model of ulcerative colitis. *Exp Ther Med* , **2016**, *12*(3), 1279-1286.
67. Shmuel-Galia, L.; Aychek, T.; Fink, A.; Porat, Z.; Zarmi, B.; Bernshtein, B.; ... & Shai, Y. Neutralization of pro-inflammatory monocytes by targeting TLR2 dimerization ameliorates colitis. *The EMBO J.* **2016**, *35*(6), 685-698.
68. Zagoskina, N. V.; Zubova, M. Y.; Nechaeva, T. L.; Kazantseva, V. V.; Goncharuk, E. A.; Katanskaya, V. M.; ... & Aksenova, M. A. Polyphenols in plants: structure, biosynthesis, abiotic stress regulation, and practical applications. *Int. J. Mol. Sci.* **2023**, *24*(18), 13874.
69. Sahu, R.; Mandal, S.; Das, P.; Ashraf, G. J.; Dua, T. K.; Paul, P.; ... & Khanra, R. The bioavailability, health advantages, extraction method, and distribution of free and bound phenolics of rice, wheat, and maize: A review. *Food Chem. Adv.*, **2023**, 100484.
70. Perez-Jimenez, J.; Neveu, V.; Vos, F.; & Scalbert, A. Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the phenol-explorer database. *J. Agri. Food Chem.*, **2010**, *58*(8), 4959-4969.
71. Ragaee, S.; Seetharaman, K.; & Abdel-Aal, E. S. M. The impact of milling and thermal processing on phenolic compounds in cereal grains. *Crit. Rev. Food. Sci. Nutr*, **2014**, *54*(7), 837-849.
72. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; & Jiménez, L. Polyphenols: food sources and bioavailability. *Am. J. Clin. Nutr.* **2004**, *79*(5), 727-747.
73. Obayiuwana, O. A. Phenolic acid content and fibre in Nigerian wholegrains; their metabolism, and potential cardiovascular benefits (Doctoral dissertation, University of Roehampton London). **2023**

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 February 2024 doi:10.20944/preprints202402.1649.v1

74. Liu, R. H. Health Benefits of Dietary Phytochemicals in Whole Foods. In *Nutritional Health: Strategies for Disease Prevention*, **2023**, 177-190.
75. Irakli, M. N.; Samanidou, V. F.; Biliaderis, C. G.; & Papadoyannis, I. N. Development and validation of an HPLC-method for determination of free and bound phenolic acids in cereals after solid-phase extraction. *Food Chem*, **2012**, *134*(3), 1624-1632.
76. Hassan, S. M. Nutritional, Functional and Bioactive Properties of Sorghum (Sorghum Bicolor I. Moench) with its Future Outlooks: A Review. **2023**
77. Chandrasekara, A.; & Shahidi, F. Determination of antioxidant activity in free and hydrolyzed fractions of millet grains and characterization of their phenolic profiles by HPLC-DAD-ESI-MSn. *J. Func. Food*, **2011b**, *3*(3), 144-158.
78. Zilić, S.; Serpen, A.; Akıllıoğlu, G.; Gökmen, V.; & Vančetović, J. Phenolic compounds, carotenoids, anthocyanins, and antioxidant capacity of colored maize (Zea mays L.) kernels. *J. Agr. Food Chem.*, **2012**, *60*(5), 1224-1231.
79. Hithamani, G.; & Srinivasan, K. Bioaccessibility of polyphenols from wheat (Triticum aestivum), sorghum (Sorghum bicolor), green gram (Vigna radiata), and chickpea (Cicer arietinum) as influenced by domestic food processing. *J. Agr. Food Chem*. **2014**, *62*(46), 11170-11179.
80. N'Dri, D.; Mazzeo, T.; Zaupa, M.; Ferracane, R.; Fogliano, V.; & Pellegrini, N. Effect of cooking on the total antioxidant capacity and phenolic profile of some whole-meal African cereals. *J. Sci. Food Agri.*, **2013**, *93*(1), 29-36.
81. Viswanath, V.; Urooj, A.; & Malleshi, N. G. Evaluation of antioxidant and antimicrobial properties of finger millet polyphenols (Eleusine coracana). *Food Chem.*, **2009**, *114*(1), 340-346.
82. Chandrasekara, A.; & Shahidi, F. Bioactivities and antiradical properties of millet grains and hulls. *Journal of Agricultural and Food Chem.* **2011a**, *59*(17), 9563-9571.
83. Gómez-Caravaca, A. M.; Iafelice, G.; Verardo, V.; Marconi, E.; & Caboni, M. F. Influence of pearling process on phenolic and saponin content in quinoa (Chenopodium quinoa Willd). *Food Chem.* **2014**, *157*, 174-178.
84. Repo-Carrasco-Valencia, R.; Hellström, J. K.; Pihlava, J. M.; & Mattila, P. H. Flavonoids and other phenolic compounds in Andean indigenous grains: Quinoa (Chenopodium quinoa), kañiwa (Chenopodium pallidicaule) and kiwicha (Amaranthus caudatus). *Food Chem.* **2010**, *120*(1), 128-133.
85. Kandil, A.; Li, J.; Vasanthan, T.; & Bressler, D. C. Phenolic acids in some cereal grains and their inhibitory effect on starch liquefaction and saccharification. *J. Agri. Food Chem.* **2012**, *60*(34), 8444-8449.
86. Van Hung, P. Phenolic compounds of cereals and their antioxidant capacity. *Crit. Rev. Food Sci. Nutr*, **2016**, *56*(1), 25-35.
87. Shao, Y.; & Bao, J. Polyphenols in whole rice grain: Genetic diversity and health benefits. *Food Chem*, **2015**, *180*, 86-97.
88. Sène, M.; Gallet, C.; & Doré, T. Phenolic compounds in a Sahelian sorghum (Sorghum bicolor) genotype (CE145–66) and associated soils. *J. Chem. Ecol*, **2001**, *27*, 81-92.
89. Gade, A.; & Kumar, M. S. Gut microbial metabolites of dietary polyphenols and their potential role in human health and diseases. *J. Physiol. Biochem*., **2023**, *79*(4), 695-718.
90. Bié, J.; Sepodes, B.; Fernandes, P. C.; & Ribeiro, M. H. Polyphenols in health and disease: Gut microbiota, bioaccessibility, and bioavailability. *Compounds*, **2023**, *3*(1), 40-72.
91. Anantharaju, P. G.; Gowda, P. C.; Vimalambike, M. G.; & Madhunapantula, S. V. An overview on the role of dietary phenolics for the treatment of cancers. *Nutr. J.* **2016**, *15*(1), 1-16.
92. Grande, T.; Souid, A.; Ciardi, M.; Della Croce, C. M.; Frassinetti, S;, Bramanti, E.; ... & Pozzo, L. Evaluation of antioxidant and antimicrobial activities of whole flours obtained from different species of Triticum genus. *Eur. Food Res. Technol*., **2023**, *249*(6), 1575-1587.
93. Abdel-Wahab, M. H.; El-Mahdy, M. A.; Abd-Ellah, M. F.; Helal, G. K.; Khalifa, F.; & Hamada, F. M. A. Influence of p-coumaric acid on doxorubicin-induced oxidative stress in rat's heart. *Pharmacol. Res.*, **2003**, *48*(5), 461-465.
94. Janicke, B.; Hegardt, C.; Krogh, M.; Önning, G.; Åkesson, B.; Cirenajwis, H. M.; & Oredsson, S. M. The antiproliferative effect of dietary fiber phenolic compounds ferulic acid and p-coumaric acid on the cell cycle of Caco-2 cells. *Nutr. Canc.*, **2011**, *63*(4), 611-622.
95. Chao, C. Y.; Mong, M. C.; Chan, K. C.; & Yin, M. C. Anti-glycative and anti-inflammatory effects of caffeic acid and ellagic acid in kidney of diabetic mice. *Mol. Nut. Food Res.*, **2010**, *54*(3), 388-395.
96. Fahrioğlu, U.; Dodurga, Y.; Elmas, L.; & Seçme, M. Ferulic acid decreases cell viability and colony formation while inhibiting migration of MIA PaCa-2 human pancreatic cancer cells in vitro. *Gene*, **2016**, *576*(1), 476-482.
97. Hou, Y. Z.; Zhao, G. R.; Yang, J.; Yuan, Y. J.; Zhu, G. G.; & Hiltunen, R. Protective effect of Ligusticum chuanxiong and Angelica sinensis on endothelial cell damage induced by hydrogen peroxide. *Life Sci.* **2004**, *75*(14), 1775-1786.
98. Narasimhan, A.; Chinnaiyan, M.; & Karundevi, B. Ferulic acid regulates hepatic GLUT2 gene expression in high fat and fructose-induced type-2 diabetic adult male rat. *Eur. J. Pharmacol.*, **2015**, *761*, 391-397.

99. Eitsuka, T.; Tatewaki, N.; Nishida, H.; Kurata, T.; Nakagawa, K.; & Miyazawa, T. Synergistic inhibition of cancer cell proliferation with a combination of δ-tocotrienol and ferulic acid. *Biochem. Biophys. Res. Commun*, **2014**, *453*(3), 606-611.
100. Ji, L.; Deng, H.; Xue, H.; Wang, J.; Hong, K.; Gao, Y.; ... & You, Y. Research progress regarding the effect and mechanism of dietary phenolic acids for improving nonalcoholic fatty liver disease via gut microbiota. *Compr. Rev. Food Sci. Food Saf.*., **2023**, *22*(2), 1128-1147.
101. Roney, M.; Dubey, A.; Zamri, N. B.; & Aluwi, M. F. F. M. Inhibitory effect of Sinapic acid derivatives targeting structural and non-structural proteins of dengue virus serotype 2: An in-silico assessment. *Mol Aspects Med*, **2023**, *2*, 100028.
102. DMoreno, D. A.; Pérez-Balibrea, S.; Ferreres, F.; Gil-Izquierdo, Á.; & García-Viguera, C. Acylated anthocyanins in broccoli sprouts. *Food Chem*, **2010**, *123*(2), 358-363.
103. Maddox, C. E.; Laur, L. M.; & Tian, L. Antibacterial activity of phenolic compounds against the phytopathogen Xylella fastidiosa. *Curr. Microbiol*, **2010**, *60*, 53-58.
104. Tuncer, S. Ç.; Akarsu, S. A.; Küçükler, S.; Gür, C.; & Kandemir, F. M. Effects of sinapic acid on lead acetate-induced oxidative stress, apoptosis and inflammation in testicular tissue. *Environ. Toxicol.*, **2023**, *38*(11), 2656-2667.
105. Yun, K. J.; Koh, D. J.; Kim, S. H.; Park, S. J.; Ryu, J. H.; Kim, D. G.; ... & Lee, K. T. Anti-inflammatory effects of sinapic acid through the suppression of inducible nitric oxide synthase, cyclooxygase-2, and proinflammatory cytokines expressions via nuclear factor-κB inactivation. *J. Agric. Food Chem*, **2008**, *56*(21), 10265-10272.
106. Taştemur, Ş.; Hacısüleyman, L.; Karataş, Ö.; Yulak, F.; & Ataseven, H. Anticancer activity of sinapic acid by inducing apoptosis in HT-29 human colon cancer cell line. *Canadian Journal of Physiology and Pharmacology*. **2023**.
107. Kanchana, G.; Shyni, W. J.; Rajadurai, M.; & Periasamy, R. Evaluation of antihyperglycemic effect of sinapic acid in normal and streptozotocin-induced diabetes in albino rats. *World J. Pharmacol.*, **2011**, *5*(1), 33-39.
108. Sun XiuLan, S. X.; Ito, H.; Masuoka, T.; Kamei, C.; & Hatano, T. Effect of Polygala tenuifolia root extract on scopolamine-induced impairment of rat spatial cognition in an eight-arm radial maze task. *Biol. Pharm. Bull. Biological* **2008** 1727-1731.
109. Yoon, B. H.; Jung, J. W.; Lee, J. J.; Cho, Y. W.; Jang, C. G.; Jin, C. B.; ... & Ryu, J. H. Anxiolytic-Like effects of sinapic acid in mice. *Pharm. Sci*, **2008**, *35*(1), 67-67.
110. He, L.; Li, H. T.; Guo, S. W.; Liu, L. F.; Qiu, J. B.; Li, F.; & Cai, B. C. Inhibitory effects of sinapine on activity of acetylcholinesterase in cerebral homogenate and blood serum of rats. *China Journal of Chinese Materia Medica*, **2008**, 813-815.
111. Ferreres, F.; Fernandes, F.; Sousa, C.; Valentao, P.; Pereira, J. A.; & Andrade, P. B. Metabolic and bioactivity insights into Brassica oleracea var. acephala. *J. Agric. Food Chem.*, **2009**, *57*(19), 8884-8892.
112. Wakamatsu, D.; Morimura, S.; Sawa, T.; Kida, K.; Nakai, C.; & Maeda, H. Isolation, identification, and structure of a potent alkyl-peroxyl radical scavenger in crude canola oil, canolol. *Biosci. Biotechnol. Biochem.*, **2005**, *69*(8), 1568-1574.
113. Kuwahara, H.; Kanazawa, A.; Wakamatu, D.; Morimura, S.; Kida, K.; Akaike, T.; & Maeda, H. Antioxidative and antimutagenic activities of 4-vinyl-2, 6-dimethoxyphenol (canolol) isolated from canola oil. *J. Agric. Food Chem.*, **2004**, *52*(14), 4380-4387.
114. Park, J.; Lee, B.; Choi, H.; Kim, W.; Kim, H. J.; & Cheong, H. Antithrombosis activity of protocatechuic and shikimic acids from functional plant Pinus densiflora Sieb. et Zucc needles. *J. Nat. Med.***2016**, *70*, 492-501.
115. Choi, J. H.; & Kim, S. In vitro antithrombotic, hematological toxicity, and inhibitor studies of protocatechuic, isovanillic, and p-hydroxybenzoic acids from Maclura tricuspidata (Carr.) Bur. *Molecules*, **2022**, *27*(11), 3496.
116. Yeh, R. D.; Chen, J. C.; Lai, T. Y.; Yang, J. S.; Yu, C. S.; Chiang, J. H.; ... & Chung, J. G. Gallic acid induces G0/G1 phase arrest and apoptosis in human leukemia HL-60 cells through inhibiting cyclin D and E, and activating mitochondria-dependent pathway. *Anticancer Res.*, **2011**, *31*(9), 2821-2832.
117. Veluri, R.; Singh, R. P.; Liu, Z.; Thompson, J. A.; Agarwal, R.; & Agarwal, C. Fractionation of grape seed extract and identification of gallic acid as one of the major active constituents causing growth inhibition and apoptotic death of DU145 human prostate carcinoma cells. *Carcinog.* **2006**, *27*(7), 1445-1453.
118. Kamatham, S.; Kumar, N.; & Gudipalli, P. Isolation and characterization of gallic acid and methyl gallate from the seed coats of Givotia rottleriformis Griff. and their anti-proliferative effect on human epidermoid carcinoma A431 cells. *Toxicol. Rep.***2015**, *2*, 520-529.
119. Kumar, R.; Khurana, N.; & Kaur, B. Effect of INM 176 on ischemia reperfusion injury using rat heart model. **2017**.
120. Kumar, R.; Kumar, R.; Anand, A.; Mahajan, R.; Khatik, GL.; Duggal, N.; Mehta, M.; Satija, S.; Sharma, N.; Khurana, N. Potential of Prediction of Activity Spectra of Substances Software to Justify 3Rs Ethics for In Vivo Anti-Alzheimer's Studies of Phytochemicals. *Int. J. Green Pharm*. **2018**, 66-72.

121. Sharma, N.; Tiwari, N.; Vyas, M.; Khurana, N.; Muthuraman, A.; & Utreja, P. An overview of therapeutic effects of vanillic acid. *Plant Arch*, **2020**, *20*(2), 3053-3059.
122. Srinivasulu, C.; Ramgopal, M.; Ramanjaneyulu, G.; Anuradha, C. M.; & Kumar, C. S. Syringic acid (SA)–a review of its occurrence, biosynthesis, pharmacological and industrial importance. *Biomedicine & Pharmacotherapy*, **2018**, *108*, 547-557.
123. Della Pepa, G.; Vetrani, C.; Vitale, M.; & Riccardi, G. Wholegrain intake and risk of type 2 diabetes: evidence from epidemiological and intervention studies. *Nutr.* **2018**, *10*(9), 1288.
124. Sang, S.; & Chu, Y. Whole grain oats, more than just a fiber: Role of unique phytochemicals. *Mol. Nutr. Food Res.*, **2017**, *61*(7), 1600715.
125. Sang, S.; & Landberg, R. The chemistry behind health effects of whole grains. *Mol. Nutr. Food Res.*, **2017**, *61*(7), 1770074.
126. Xu, Y.; Wan, Q.; Feng, J.; Du, L.; Li, K.; & Zhou, Y. Whole grain diet reduces systemic inflammation: A meta-analysis of 9 randomized trials. *Med.* **2018**, *97*(43).
127. Hajihashemi, P.; & Haghighatdoost, F. Effects of whole-grain consumption on selected biomarkers of systematic inflammation: a systematic review and meta-analysis of randomized controlled trials. *J. Am. Coll. Nutr.* **2019**, *38*(3), 275-285.
128. Zamaratskaia, G.; Omar, N. A. M.; Brunius, C.; Hallmans, G.; Johansson, J. E.; Andersson, S. O.; ... & Landberg, R. Consumption of whole grain/bran rye instead of refined wheat decrease concentrations of TNF-R2, e-selectin, and endostatin in an exploratory study in men with prostate cancer. *Clin. Nutr.* **2020**, *39*(1), 159-165.
129. Brownlee, I. A.; Moore, C.; Chatfield, M.; Richardson, D. P.; Ashby, P.; Kuznesof, S. A.; ... & Seal, C. J. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. *Br. J. Nutr*. **2010**, *104*(1), 125-134.
130. Kwok, C. S.; Gulati, M.; Michos, E. D.; Potts, J.; Wu, P.; Watson, L.; ... & Mamas, M. A. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur. J. Prev. Cardiol.*, **2019**, *26*(13), 1415-1429.
131. Neuenschwander, M.; Ballon, A.; Weber, K. S.; Norat, T.; Aune, D.; Schwingshackl, L.; & Schlesinger, S. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. *bmj*, **2019**, *366*.
132. Tieri, M.; Ghelfi, F.; Vitale, M.; Vetrani, C.; Marventano, S.; Lafranconi, A.; ... & Grosso, G. Whole grain consumption and human health: an umbrella review of observational studies. *Int. J. Food Sci. Nutr.* **2020**, *71*(6), 668-677.
133. Ampatzoglou, A.; Atwal, K. K.; Maidens, C. M.; Williams, C. L.; Ross, A. B.; Thielecke, F.; ... & Yaqoob, P. Increased whole grain consumption does not affect blood biochemistry, body composition, or gut microbiology in healthy, low-habitual whole grain consumers. *J. Nutr*, **2015**, *145*(2), 215-221.
134. Andersen, J. L. M.; Halkjær, J.; Rostgaard-Hansen, A. L.; Martinussen, N.; Lund, A. S. Q.; Kyrø, C.; ... & Olsen, A. Intake of whole grain and associations with lifestyle and demographics: a cross-sectional study based on the Danish Diet, Cancer and Health—Next Generations cohort. *Eur. J. Nutr.* **2021**, *60*, 883-895.
135. Egeberg, R.; Frederiksen, K.; Olsen, A.; Johnsen, N. F.; Loft, S.; Overvad, K.; & Tjønneland, A. Intake of wholegrain products is associated with dietary, lifestyle, anthropometric and socio-economic factors in Denmark. *Public Health Nutr*. **2009**, *12*(9), 1519-1530.
136. Mazidi, M.; Kengne, A. P.; Mikhailidis, D. P.; Cicero, A. F.; & Banach, M. Effects of selected dietary constituents on high-sensitivity C-reactive protein levels in US adults. *Ann. Med.*, **2018**, *50*(1), 1-6.
137. Qi, L.; Van Dam, R. M.; Liu, S.; Franz, M.; Mantzoros, C.; & Hu, F. B. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Car.*, **2006**, *29*(2), 207-211.
138. Wilczak, J.; Błaszczyk, K.; Kamola, D.; Gajewska, M.; Harasym, J. P.; Jałosińska, M.; ... & Gromadzka-Ostrowska, J. The effect of low or high molecular weight oat beta-glucans on the inflammatory and oxidative stress status in the colon of rats with LPS-induced enteritis. *Food Fun.* **2015**, *6*(2), 590-603.
139. Shahidi, F.; & Peng, H. Bioaccessibility and bioavailability of phenolic compounds. *Journal of Food Bioactives*, **2018**, *4*, 11-68.
140. Esmaillzadeh, A., Kimiagar, M.; Mehrabi, Y.; Azadbakht, L.; Hu, F. B.; & Willett, W. C. Dietary patterns and markers of systemic inflammation among Iranian women. *J. Nutr*, **2007**, *137*(4), 992-998.
141. McRorie Jr, J. W. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 1: what to look for and how to recommend an effective fiber therapy. *Nutr. Today*, **2015**, *50*(2), 82.
142. Jacobs Jr, D. R. The whole cereal grain is more informative than cereal fibre. *Nat. Rev. Endocrinol.*, **2015**, *11*(7), 389-390.
143. Pragasam, S. J.; Venkatesan, V.; & Rasool, M. Immunomodulatory and anti-inflammatory effect of p-coumaric acid, a common dietary polyphenol on experimental inflammation in rats. *Inf.* **2013**, *36*, 169-176.
144. Ibitoye, O. B.; & Ajiboye, T. O. Dietary phenolic acids reverse insulin resistance, hyperglycaemia, dyslipidaemia, inflammation and oxidative stress in high-fructose diet-induced metabolic syndrome rats. *Arch. Physiol. Biochem.* **2018**, *124*(5), 410-417.

145. Koenig, R.; Dickman, J. R.; Kang, C.; Zhang, T.; Chu, Y. F.; & Ji, L. L. Avenanthramide supplementation attenuates exercise-induced inflammation in postmenopausal women. *Nutr. J.* **2014**, *13*(1), 1-11.
146. Liu, L.; Zubik, L.; Collins, F. W.; Marko, M.; & Meydani, M. The antiatherogenic potential of oat phenolic compounds. *Atherosclerosis*, **2004**, *175*(1), 39-49.
147. Sur, R.; Nigam Sur, A.; Grote, D.; Liebel, F.; & Southall, M. D. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. *Arch. Dermatol.* **2008**, *300*(10), 569-574.
148. Tetens, I. Substituting whole grain for refined grain: what is needed to strengthen the scientific evidence for health outcomes? *Am. J. Clin.* **2017**, *105*(3), 545-546.
149. Vinolo, M. A.; Rodrigues, H. G.; Nachbar, R. T.; & Curi, R. Regulation of inflammation by short chain fatty acids. *Nutr.* **2011**, *3*(10), 858-876
150. Fischer, N.; Sechet, E.; Friedman, R.; Amiot, A.; Sobhani, I.; Nigro, G. et al. Deacetylase inhibition enhances antimicrobial peptide but not inflammatory cytokine expression upon bacterial challenge. *Proc. Natl. Acad. Sci.* **2016**, *113*(21), 2993-3001.
151. Felice, C.; Lewis, A.; Armuzzi, A.; Lindsay, J. O.; & Silver, A. Selective histone deacetylase isoforms as potential therapeutic targets in inflammatory bowel diseases. *Aliment. Pharmacol. Ther*. **2015**, *41*(1), 26-38.
152. Lee, J. C. Y.; AlGhawas, D. S.; Poutanen, K.; Leung, K. S.; Oger, C.; Galano, J. M. et al. Dietary oat bran increases some proinflammatory polyunsaturated fatty-acid oxidation products and reduces anti-inflammatory products in apolipoprotein E−/− mice. *Lipids*, 2018, *53*(8), 785-796.
153. Martínez, I.; Lattimer, J. M.; Hubach, K. L.; Case, J. A.; Yang, J.; Weber, C. G et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. *ISME J.* **2013**, *7*(2), 269-280.