Review Article

From Food Technology to Functional Food Development: Focus on benefits of Wholegrain Products for Diabetes

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Abstract

This review article discusses the link between food technology and functional foods development. A special focus is put on the benefits of whole grain intake in human nutrition for diabetes people. An indication for buckwheat-based products is provided with focus on the antioxidative and inhibitory activity against formation of advanced glycation end products.

Keywords: Food technology; Functional foods; Antioxidative; Nutrition; Inhibitory.

Food Technology and Functional Foods

Food technology is a discipline of food science. More appropriately it is a multidisciplinary subject including food engineering, food manufacturing, food processing, food packaging, and food preservation. The food technologists study the chemical, physical and microbiological makeup of the food. From the food technology there is an easy step towards functional food development. A functional food is a food given an additional function (often one related to health-promotion or disease prevention) by adding new ingredients or more of existing ingredients. Functional food is a natural or processed food that contains known biologically-active compounds which when in defined quantitative and qualitative amounts provides a clinically proven and documented health benefit, and thus, an important source in the prevention, management and treatment of chronic diseases of the modern age". Functional is defined as "natural or processed foods that contain known or unknown biologically-active compounds; the foods, in defined, effective, and non-toxic amounts, provided a clinically proven and documented health benefits for the prevention, management, or treatment of chronic diseases. According to the United States Department of Agriculture-Agricultural Research Service (USDA–ARS), functional foods are "designed to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions, and may be similar in appearance to conventional food and consumed as part of a regular diet".

Focus on Hyperglycaemia

Nowadays, diabetes mellitus is a disorder characterized by hyperglycaemia due to an absolute or relative deficiency of insulin and or insulin resistance. It affects 1–2% of the population worldwide. Type 2 diabetes (T2D) is currently one of the major causes of morbidity and mortality in Europe [1]. Hyperglycaemia has an important role in the

pathogenesis of long-term complications and diabetic patients with poor blood glucose control are particularly at risk. Furthermore, complications appear to affect organs where cells do not require insulin for glucose uptake, such as those of the nervous system, heart, kidneys and small blood vessels. As a consequence, these cells have high concentrations of intracellular glucose during hyperglycaemia. The precise role of hyperglycaemia in the pathogenesis of long-term complications is still unclear. However, an attractive hypothesis and one that has received considerable interest is the role of protein glycation and formation of advanced glycation end products (AGEs). Protein glycation in humans is believed to be implicated in the development of chronic degenerative diseases due to the modification of proteins with carbohydrate-and lipid-derived intermediates resulting in changes of the functional properties of proteins, lipids and DNA [2]. In long-lived tissue proteins, these chemical modifications accumulate with age and may contribute to the pathophysiology of aging and long-term complications of diabetes, atherosclerosis, renal failure and Alzheimer disease [3-5]. AGEs formation is increased in hyperglycemia and under the influence of oxidative stress [6]. Increased glycation and build-up of tissue AGEs have been implicated in diabetic complications because they can alter enzymic activity, decrease ligand binding, modify protein half-life and alter immunogenicity [4]. Glycation-derived free radicals can cause protein fragmentation and oxidation of nucleic acids and lipids. The amino groups of adenine and guanine bases in DNA are also susceptible to glycation and AGEs formation, probably by reactive intracellular sugars [7]. AGEs could also form on phospholipids and induce lipid peroxidation by a direct reaction between glucose and amino groups on phospholipids such as phosphatidylethanolamine and phosphatidylserine residues [8]. Antioxidants can protect against glycation derived free radicals and may have therapeutic potential whereas transport proteins, for example, caeruloplasmin can bind transition metals such as cupric ions, preventing them from participating in autoxidative glycation or glycoxidation reactions. However, the efficiency of these natural defences against glycation and AGEs *in vivo* is unknown. Antioxidants protect against glycation-derived free radicals and may have therapeutic potential. Vitamin E (800 mg per day) has been shown to reduce levels of glycated haemoglobin and accumulation of AGEs in the arterial walls of diabetic patients [9,10]

Diabetic Complications and Advanced Glycation End Products (AGEs)

Despite the fact that there are many concepts regarding the processes leading to development of diabetic complications, investigations still focus on the role of advanced glycation end products (AGEs) in pathogenesis of late diabetic complications. Diabetic retinopathy is the most common cause of blindness and characterized by increased proliferation of blood vessels, vascular occlusion, angiogenesis, microaneurysms, haemorrhages and infarction affecting the retina of the eye. AGEs have been detected in retinal blood vessel walls and are believed to contribute towards vascular

occlusion and increased permeability of retinal endothelial cells causing vascular leakage. Level of advanced glycation end products is correlated with early preclinical changes specific for diabetic nephropathy and retinopathy. Atherosclerosis is the most serious consequence of long-term diabetes and the major cause of death in these patients. It is characterized by deposition of atherosclerotic plaques on the insides of arterial walls, occlusion of blood flow and eventual myocardial infarction. Increased glycation of low-density lipoprotein (LDL) occurs in diabetes. Glycated LDL is not recognised by the LDL receptor but its uptake by macrophages is enhanced [11] and this may account, at least in part, for the hyperlipidaemia and accelerated foam cell formation observed in diabetic patients. Diabetic nephropathy is characterised by a thickening of the basement membrane, expansion of the mesangium, reduced filtration, albuminuria and ultimately renal failure. AGEs have been detected in renal tissues in amounts that correlate with the severity of diabetic nephropathy [8]. Diabetic neuropathy may present clinically as pain or numbness of limbs or as impotence in men. There is increased glycation of myelin in diabetes. The body has mechanisms to protect against glycation and AGEs such as the liver enzyme, aketogluteraldehyde dehydrogenase capable of inactivating 3-DG and preventing AGE formation [12].

A key aim of therapy in diabetic patients is to reduce hyperglycaemia and one of the important tools to achieve it is modification of the diet. There is growing interest in natural products with combined anti-glycation and antioxidant properties as they may have reduced T2D risk at higher intake. The investigation of AGEs formation inhibitors has received much attention. Indeed, a number of plant derived flavonoids (quercetin, rutin and kaempferol) with antioxidant activity have been reported to inhibit glycation, at least *in vitro* [8]. Natural inhibitors have been proven relatively safer for human consumption when compared with synthetic compounds [13]. There have been reports on the inhibitory activities of some phenolic compounds [14,15], colon derived polyphenol catabolites [16-19], extracts from microalgae [20], herbs [13,21,22], mung bean [15], aged garlic [23], wheat bran feruloyl oligosaccharides [24], coffee fractions [18], fermented byproducts [25] and buckwheat hull tea infusion [26] against AGEs formation.

The Benefits of Whole Grain intake in the Prevention of Type 2 Diabetes

Of interest in this respect is that epidemiological studies have linked products based on the whole grain (WG) intake to the prevention of T2D [27-29] [22,39,46]. Meta-analyses of prospective cohort studies during the last few years indicate substantial reduction in T2D risk at higher intake of products based on the whole grain (WG) [30]. Still, limited data are available from controlled dietary interventions. Intervention studies with WG diets have, however, reported benefits on glucose metabolism as manifested through lowered fasting glucose [31], lowered fasting insulin or lowered acute insulin

and glucose responses [32,33]. Lowered postprandial glycaemia in response to certain WG cereal products, or suppressed insulin responses in the case of rye, might also contribute to metabolic benefits of a WG diet [34-36]. Over the last few years there the postprandial glycaemia and insulinaemia to wheat and rye products were mainly investigated due to the an increasing awareness of their importance on T2D and metabolic disease risk. Indications are also available suggesting improved insulin secretion with diets included with WG rye bread compared with a control diet with refined wheat bread [37]. Furthermore, in a study where the dietary modification was made by altering the characteristics of the bread products only, it was concluded that exchanging high glycemic index (GI) low dietary fibre (DF) bread for low GI high DF bread during 4 weeks beneficially affected insulin economy in young women at risk of developing T2D [38]. Other studies have failed to show any effect on glucose metabolism [39-41]. Little information is available regarding the impact on emerging risk markers such as oxidative and carbonyl stress and low-grade inflammation. According to Katcher et al. [41] a WG diet lowered C-Reactive Protein (CRP) and Mateo Anson et al. [42] showed postprandial anti-inflammatory effects of WG wheat bread in an *ex vivo* induced inflammation; whereas in the intervention by Andersson et al. [39] and Brownlee et al. [40], inflammatory markers remained unaffected. Although the majority of intervention studies indicate benefits on risk markers of relevance for developing T2D, effects on individual risk markers in various studies are inconsistent. Differences in the metabolic characteristics of the test subjects, may of course have contributed to this. Also, the different studies have included different cereals. Most of the intervention studies have addressed wheat (or rather mixed cereals, in which wheat dominate), but in some studies WG barley, rye or rice products have been included with favorable outcome on metabolic risk markers. Although a range of potential mechanisms have been put forward related to the presence of phytochemicals, antioxidants and trace minerals, essential knowledge concerning the bioavailability of such components in products from different WG cereals is scarce.

Currently, frequent post-meal hyperglycaemic episodes are considered to promote oxidative stress and induce low-grade inflammation thereby contributing to endothelial damage and T2D [43]. This knowledge provides a possible explanation for the increased risk of CVD seen in T2D [44]. Similarly to the epidemiological evidences of a protective role of a higher WG intake, also low GI diets have been associated with lowered risk factors for T2D and CVD, as well as lowered risk of disease [45]. In consequence, low GI characteristics of WG foods are frequently mentioned as a feature contributing to the health value of WG diets. Moreover, studies with rye products have also indicated that rye favours a postprandial glycaemic profile with a low and sustained glucose increment, and that a measure of the course of glycaemia (Glycaemic Profile, GP; calculated as the duration of net increment in blood glucose/peak glucose; min/mM) better predicted the insulin response. In addition, a higher GP is associated with

higher satiety in the late postprandial phase, and a lower voluntary food intake at a subsequent meal [35,36]. Up till now, there is some only a scare evidences on the effect of wheat and barley diets on insulin sensitivity and metabolic variables in patients with T2D (Frid et al., unpublished results). Fifty-eight patients with diabetes type 2, divided into 4 groups, participated in the intervention dietary studies. They received: (1) refined wheat bread (High GI, low WG); (2) whole meal wheat bread (High GI, high WG); (3) Kernel based WG wheat bread (Low GI, high WG) and (4) kernel based barley bread (Low GI, high WG).The patients were treated with life-style intervention, and did not receive pharmacological treatment. Primary end-point was insulin first-phase response and insulin sensitivity, measured using the Glucagon Insulin Tolerance Test (GITT) [46]. Secondary end-points were HbA1c, fasting plasma glucose, HDL, LDL, TG, ApoA, ApoB, PAI-1 and high sensitivity (hsCRP). All measures were performed at the beginning and end of each diet period. No differences were seen in any of the above parameters over the diets with refined wheat bread, whole meal wheat bread or kernel based wheat bread, suggesting that the increase in wheat fibre and or lowering of GI in the case of the kernel based wheat product was not capable of affecting metabolic control in these patients. In contrast, dietary enclosure of the low GI, WG kernel based barley bread significantly improved insulin sensitivity as measured with the GITT. No significant effects were seen on other risk markers analysed. The absence of effects on GITT in the case of the diet enclosed with the corresponding low GI kernel based wheat bread, may indicate that the specific combination of dietary fibre and RS in the barley kernel bread promote benefits on insulin sensitivity through a mechanism involving colonic fermentation. Evidence for such a mechanism has been reported in semiacute experiments in healthy subjects fed this type of kernel based barley bread, whereas a kernel based wheat bread was devoid of benefits [47].

Results with WG barley kernel products indicate benefits on glucose tolerance mediated through colonic fermentation of indigestible carbohydrates. Whole grain product constituents may be metabolized by the gut microbiota, which need to be considered when evaluating mechanisms for potential effects of WG on metabolic risk markers of T2D. Major colonic substrates are cereal fibre, but also resistant starch (RS). Studies in humans have also linked enhanced SCFA production, and butyrate in particular, to improved insulin sensitivity and glucose homeostasis [47-49]. Additionally, also other grain components such as e.g. phenolics may enter the large bowel, and be subjected to microbial metabolism [50]. Only part of phytochemicals ingested with food is absorbed. Phytochemicals which were not absorbed in the upper part of the gastrointestinal tract and these which underwent detoxification process in liver and were returned to the small intestine with bile reach the large intestine where they are modified by microbiota [50]. Therefore, profile, number of, and activity of microbiota in the gastrointestinal tract has a huge impact on human metabolomic profile which may in part have an impact on the health status of humans. Food ingredients which were undigested and unabsorbed in the upper sections of digestive tract reach the

colon, there are transformed, providing a source of carbon and energy for bacteria, but they may also exhibit stimulatory or inhibitory effect on bacteria. The colonic microbiota shows diverse deglycosylation activities, thus releasing aglycones that are rapidly degraded to produce simpler phenolic [51,52]. Degradation of flavonoid aglycones involves C-ring cleavage and reactions affecting functional groups, such as dehydroxylation, demethylation or decarboxylation [52]. The metabolic activity of the gut microflora on polyphenols is often responsible for the modulation of the biological activity of these dietary compounds and their potential health effects [19]. Some studies have been published regarding the activity of conjugated metabolites of quercetin [53,54]. Metabolites of bacteria influence on other bacteria, stimulating or inhibiting their growth as well as on host intestinal epithelial cells affecting the permeability of the gut and immune system. Food components reaching the colon are one of the main factors directly influencing microbiota of this part of digestive. A well-balanced and varied diet ensures that the dynamic equilibrium of the intestinal microbiota is "resistant" to the long-term disorder. Proper development and functioning of the digestive system and the host organism is provided by a properly shaped and stable microbiota. Further study require the processes occurring in the "healthy" intestine, in which constituents of a diet, including phytochemicals, may undergo changes under the influence of gut microbiota, and then be absorbed into a host organism, where they can possess specific biological functions. The area associated with changes of phytochemicals in large intestine, including buckwheat phytochemical originating from the diet, requires in-depth research. The complexity of interactions between bacteria as well as the host organism and microbiota with taking into account the impact of dietary components, makes the study of dietary components transformation occurring in the gut with the involvement of bacteria, it becomes crucial to the full understanding of the micro system functioning of large intestine. Up till now, the colonic availability of ferulic acid and its specific colonic metabolites derived from whole wheat grain products ingestion remains to be elucidated [55].

Buckwheat-based products in the prevention of type 2 diabetes

There are limited publications which have indicated the potential use of buckwheat as a source of natural products with combined anti-glycation and antioxidant properties [56,57]. In Europe and North America, buckwheat (*Fagopyrum esculentum* Moench) is considered as a high nutritional value pseudo-cereal due to its balanced amino acid composition and high contents of vitamin B_1 and B_2, lysine, flavonoids, phenolic acids, tocopherols, phytosterols, soluble carbohydrates, D-*chiro*-inositol, fagopyritols, thiamin-binding proteins and flavone *C*-glucosides [56,58-60]. Compared to most fruits, vegetables and grain crops, buckwheat contains more rutin (quercetin 3–rutinoside), a highly potent flavonol glucoside with antioxidant, anti-inflammmatory, anticarcinogenic [61] and antiglycative properties [8,15-17,62]. Orientin and homoorientin, a pair of isomeric compounds, and their 4'-deoxy analoques, namely

vitexin and isovitexin are the main flavone *C*-glucosides present in buckwheat grain [63]. Various biological and pharmacological activities have been attributed to these compounds, such as hypotensive, anti-inflammatory, antispasmodic [64], antioxidant/free radical scavenging [65,66], radioprotective effects [67] and anti-glycation activities [68-70]. Recently, vitexin and isovitexin in the bovine serum albumin (BSA) - glucose system showed strong inhibitory effects on the formation of fluorescent advanced glycation endproducts (AGEs), comparable to that of rutin, one of the most potent natural AGE inhibitors suggesting that their anti-glycation activities may mainly be due to their radical scavenging capacity [15]. D-*Chiro*-inositol is an inositol isomer that occurs in relatively high levels in buckwheat seeds [71]. Chemically synthesized D-*chiro*-inositol has lowered elevated plasma glucose in insulin-resistant monkeys, streptozotocin-treated hyperglycaemic rats, and normal rats after administration intravenously or orally [72,73]. Administering doses of 10 and 20 mg of D-*chiro*-inositol in the form of natural buckwheat concentrate decreased serum glucose concentrations by 12-19% in streptozotocin-diabetic rats, however, further studies of the effect of D-*chiro*-inositol on humans are needed [74]. Recently it has been reported that D-*chiro*-inositol enriched tartary buckwheat bran extract lowered the blood glucose level in mice, confirming the beneficial effect of this compound by improving glucose tolerance and insulin response to glucose metabolism without affecting body weight [75]. Having all these evidences, buckwheat based-products were found to display various biological activities, including increasing number of lactic acid bacteria in rat intestine, lowering effect on serum glucose concentration in diabetic rats, treatment of allergic inflammation, suppressing cholesterol level, inhibiting protease and scavenging free radicals [74,76,77] [57,34,33]. Among buckwheat based products, extremely interesting seems to be buckwheat enriched dark wheat breads as it is based on whole meal wheat flour and buckwheat flour from milled groats. Because the inhibitory activities of wheat bran feruloyl oligosaccharides have been found to inhibit the formation of AGEs, and their inhibition of free radical generation in the glycation process has been considered as the major mechanism of their anti-glycation activities mediation [24]. Moreover, the recent evidences have indicated that the consumption of buckwheat enhanced wheat bread caused a positive increase of serum antioxidant capacity in humans [78]. These finding, supported by quality and antioxidant property of buckwheat enhanced wheat bread provided by Lin [79], makes buckwheat enhanced wheat bread an attractive product for long term dietary interventions in 'at risk' subjects and in subjects with T2D. The role of diet in shaping metabolomic profile is not fully elucidated. It is clear that diet have both an acute and chronic effect. Understanding the chronic effects of diet is the most relevant in the terms of nutrition research, and in the terms of the interpretation of food metabolomics data, and the effect on the human body. Previous research on food metabolomics showed, that in addition to exogenous compounds discriminating diet rich and poor in the test product or group of products in biological fluids of volunteers, is changed the level of endogenous substances. It was observed an increase level of creatinine, creatine, trimethylamine N-oxide, taurine, and

1 - and 3-methylhystidine in the urine of persons who were on a diet with a higher content of meat, and increase the level of p-hydroxyphenylacetate derivatives in subjects with a diet without meat but a high amount of fruit and vegetables [80]. Similarly, the study of Walsh [81] showed that a diet with low phytochemicals concentration resulted in elevated levels of creatinine and metylohistydyny in urine of volunteers while the diet with high content of phytochemicals resulted in increased levels of hippuric acid derivatives. Very often compounds resulting from the activities of the colon microbiota are markers of consumption of plant origin products. Llorach [82] study showed that after ingestion of almonds in the urine of volunteers are present metabolic products of gastrointestinal microbiota, derivatives of hydroxyphenylacetic, hydroxyphenylpropionic, and hydroxyphenylvaleric acid. In other studies, after cocoa consumption in the urine of volunteers' derivatives of dihydrophenylvalerolactone was detected [82]. All of these issues point to the necessity of conducting research related to the food metabolomics including research on the effects of regular consumption of buckwheat products on the human metabolome, the formation of biomarkers intake and plasma antioxidant capacity of consumers.

Conclusion

In conclusion, we suggest that regular consumption of whole grain products with the participation of buckwheat can lead to significant changes in the metabolome of consumers which may be relevant in the context of the prevention of diabetes type 2 as well as its chronic complications.

Acknowledgments

Conflict of Interest

The authors confirm that there is no conflicts of interest regarding this manuscript.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

References

1. No authors. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352(9131): 837–851.

2. Ames JM. Dietary Maillard Reaction Products: Implications for Human Health and Disease. *Czech J Food Sci*. 2009; 27: S66-S69.

3. Makita Z, Bucala R, Rayfield EJ, et al. Reactive glycosylation end products in diabetic uremia and treatment of renal failure. *Lancet*. 1994; 343(8912): 1519-1522. doi: 10.1016/S0140-6736(94)92935-1

4. Vlassara H, Palace MR. Diabetes and advanced glycation end products. *J Intern Med*. 2002; 251(2): 87-101. doi: 10.1046/j.1365-2796.2002.00932.x

5. Lapolla A, Traldi P, Fedele D. Importance of measuring products of non-enzymatic glycation of proteins. *Clin Biochem*, 2005; 38(2): 103-115. doi: 10.1016/j.clinbiochem.2004.09.007

6. Fu MX, Wells-Knecht KJ, Blackledge JA, Lyons TJ, Thorpe SR, Baynes JW. Glycation, glycoxidation, and cross-linking of collagen by glucose. Kinetics, mechanisms, and inhibition of late stages of the Maillard reaction. *Diabetes*. 1994; 43(5): 676-683. doi: 10.2337/diab.43.5.676

7. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes*. 1991; 40(4): 405-412. doi: 10.2337/diab.40.4.405

8. Ahmed N. Advanced glycation endproducts – role in pathology of diabetic complications. *Diabetes Res Clin Pract*. 2005; 67(1): 3-21. doi: 10.1016/j.diabres.2004.09.004

9. Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G, Lefebvre PJ. Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications? *Diabetes Care*. 1991; 14(1): 68–72. doi: 10.2337/diacare.14.1.68

10. Giardino I, Edelstein D, Horiuchi S, Araki N, Brownlee M. Vitamin E prevents diabetes-induced formation of arterial wall intracellular advanced glycation endproducts. *Diabetes*, 1995; 44: 73A.

11. Lopes-Virella MF, Klein RL, Lyons TJ, Stevenson HC, Witztum JL. Glycosylation of LDL enhances cholesteryl ester synthesis in human monocyte-derived macrophages. *Diabetes*. 1988; 37(5): 550–557. doi: 10.2337/diab.37.5.550

12. Hata F, Igaki N, Nakamichi T, Masuda S, Nishimoto S, Oimomi M, et al. Suppressive effect of a-ketogluteraldehyde dehydrogenase on the advanced process of the Maillard reaction. *Diabetes Res Clin Pract*. 1988; 5: 5413-5417.

13. Lunceford N, Gugliucci A. Ilex paraguariensis extracts inhibit AGE formation more efficiently than green tea. *Fitoterapia*. 2005; 76(5): 419-427. doi: 10.1016/j.fitote.2005.03.021

14. Wu CH, Yen GC. Inhibitory effect of naturally occuring flavonoids on the formation of advanced glycation end products. *J Agric Food Chem*. 2005; 53(8): 3167-3173. doi: 10.1021/jf048550u

15. Peng X, Zheng Z, Cheng KW, et al. Inhibitory effect of mung bean extract and its constituents vitexin and isovitexin on the formation of advanced glycation endproducts. *Food Chem*. 2008; 106(2): 475-481. doi: 10.1016/j.foodchem.2007.06.016

16. Cervantes-Laurean D1, Schramm DD, Jacobson EL, Halaweish I, Bruckner GG, Boissonneault GA. Inhibition of advanced glycation end product formation on collagen by rutin and its metabolites. *J Nutr Biochem*. 2006; 17(8): 531-540. doi: 10.1016/j.jnutbio.2005.10.002

17. Pashikanti S, de Alba DR, Boissonneault GA, Cervantes-Laurean D. Rutin metabolites: Novel inhibitors of nonoxidative advanced glycation end products. *Free Radic Biol Med*. 2010; 48(5): 656-663. doi: 10.1016/j.freeradbiomed.2009.11.019

18. Verzelloni E, Pellacani C, Tagliazucchi D, et al. Antiglycative and neuroprotective activity of colon-derived polyphenol catabolites. *Mol Nutr Food Res*. 2011; 55: S35-S43. doi: 10.1002/mnfr.201000525

19. Serra A, Macia A, Romero MP, Reguant J, Ortega N, Motilva MJ. Metabolic pathways of the colonic metabolism of flavonoids (flavonols, flavones and flavanones) and phenolic acids. *Food Chem*. 2012; 130(2): 383-393. doi: 10.1016/j.foodchem.2011.07.055

20. Sun Z, Peng X, Liu J, Fan KW, Wang M, Chen F. Inhibitory effects of microalgal extracts on the formation of advanced glycation endproducts (AGEs). *Food Chem*. 2010; 120: 261-267. doi: 10.1016/j.foodchem.2009.10.018

21. Tsuji-Naito K, Saeki H, Hamano M. Inhibitory effects of *Chrysanthemum* species extracts on formation of advanced glycation end products. *Food Chem*. 2009; 116(4): 854-859. doi: 10.1016/j.foodchem.2009.03.042

22. Zhang LS, Wang X, Dong LL. Antioxidation and antiglycation of polysaccharides from *Misgurnus anguillicaudatus*. *Food Chem*. 2011; 124(1): 183-187. doi: 10.1016/j.foodchem.2010.06.006

23. Ahmad MS, Ahmed N. Antiglycation properties of aged garlic extract: possible role in prevention of diabetic complications. *J Nutr*. 2006; 136: S796-S799. doi: 10.1093/jn/136.3.796S

24. Wang J, Sun B, Cao Y, Tian Y. Protein glycation inhibitory activity of wheat bran feruloyl oligosaccharides. *Food Chem*. 2009; 112(5): 350-353. doi: 10.1016/j.foodchem.2008.05.072

25. Ye XJ, Ng TB, Nagai R. Inhibitory effect of fermentation byproducts on formation of advanced glycation end-products. *Food Chem*. 2010; 121(4): 1039-1045. doi:10.1016/j.foodchem.2010.01.045

26. Zielińska D, Szawara-Nowak D, Zieliński H. Antioxidative and anti-glycation activity of buck wheat hull tea infusion. *Int J Food Prop*. 2013; 16(1): 228-239. doi: 10.1080/10942912.2010.551308

27. Fung TT, Hu FB, Pereira MA, et al. Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr*. 2002; 76(3): 535-540.

28. Liu S, Manson J E, Stampfer MJ, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health*. 2000; 90: 1409-1415.

29. Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fibre, and incident type 2 diabetes in older women. *Am J Clin Nutr*. 2000; 71(4): 921-930. doi: 10.1093/ajcn/71.4.921

30. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Med.* 2007; 4(8): e261. doi : 10.1371/journal.pmed.0040261

31. Jang Y, Lee JH, Kim OY, Park HY, Lee SY. Consumption of whole grain and legume powder reduces insulin demand, lipid peroxidation, and plasma homocysteine concentrations in patients with coronary artery disease: randomized controlled clinical trial. *Arterioscler Thromb Vasc Biol*. 2001; 21(12): 2065-2071. doi: 10.1161/hq1201.100258

32. Pereira MA, Jacobs DR Jr, Pins JJ, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr*. 2002; 75(5): 848-855. doi: 10.1093/ajcn/75.5.848

33. Rave K, Roggen K, Dellweg S, Heise T, tom Dieck H. Improvement of insulin resistance after diet with a whole-grain based dietary product: results of a randomized, controlled cross-over study in obese subjects with elevated fasting blood glucose. *Br J Nutr*. 2007; 98(5): 929-936. doi: 10.1017/S0007114507749267

34. Kallio P, Kolehmainen M, Laaksonen DE, et al. Inflammation markers are modulated by responses to diets differing in postprandial insulin responses in individuals with the metabolic syndrome. *Am J Clin Nutr*. 2008; 87(5): 1497-1503.

35. Rosén LA, Silva LO, Andersson UK, Holm C, Östman EM, Björck IM. Endosperm and whole grain rye breads are characterized by low post-prandial insulin response and a beneficial blood glucose profile. *Nutr J*. 2009; 8: 42-49. doi: 10.1186/1475-2891-8-42

36. Rosén LA, Östman EM, Shewry PR, et al. Postprandial glycemia, insulinemia, and satiety responses in healthy subjects after whole grain rye bread made from different rye varieties. 1. *J Agric Food Chem*. 2011; 59(22): 12139-12148. doi: 10.1021/jf2019825

37. Juntunen KS, Niskanen LK, Liukkonen KH, Poutanen KS, Holst JJ, Mykkänen HM. Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. *Am J Clin Nutr*. 2002; 75: 254-262. doi: 10.1093/ajcn/75.2.254

38. Östman EM, Frid AH, Groop LC, Björck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. *Eur J Clin Nutr*. 2006; 60: 334-341. doi: 10.1038/sj.ejcn.1602319

39. Andersson A, Tengblad S, Karlstrom B, et al. Whole-grain foods do not affect insulin sensitivity or markers of lipid peroxidation and inflammation in healthy, moderately overweight subjects. *J Nutr*. 2007; 137(6): 1401-1407. doi: 10.1093/jn/137.6.1401

40. Brownlee IA, Moore C, Chatfield M, et al. 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: 125-134. doi: 10.1017/S0007114510000644

41. Katcher HI, Legro RS, Kunselman AR, et al. The effects of a whole grain enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr*. 2008; 87(1): 79-90. doi: 10.1093/ajcn/87.1.79

42. Anson NM, Havenaar R, Vaes W, et al. Effect of bioprocessing of wheat bran in wholemeal wheat breads on the colonic SCFA production *in vitro* and postprandial plasma concentrations in men. *Food Chem*. 2011; 128(2): 404-409. doi:10.1016/j.foodchem.2011.03.043

43. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes.* 2008; 57(5): 1349-1354. doi: 10.2337/db08-0063

44. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation.* 2002; 106: 2067-2072. doi: 10.1161/01.cir.0000034509.14906.ae

45. Barclay AW, Petocz P, McMillan-Price J, et al. Glycemic index, glycemic load, and chronic disease risk e a meta-analysis of observational studies. *Am J Clin Nutr*. 2008; 87(3): 627-637. doi: 10.1093/ajcn/87.3.627

46. Dorkhan M, Tripathy D, Malm G, Asgharian H, Tuomi T, Groop L. Independent measures of insulin secretion and insulin sensitivity during the same test: the glucagon-insulin tolerance test. *J Intern Med*. 2008; 264(1): 62-71. doi: 10.1111/j.1365-2796.2008.01921.x

47. Nilsson AC, Ostman EM, Granfeldt Y, Bjorck IM. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008; 87: 645-654

48. Denise Robertson M. Metabolic cross talk between the colon and the periphery: implications for insulin sensitivity. *Proc Nutr Soc*. 2007; 66(3): 351-361. doi: 10.1017/S0029665107005617

49. Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. *Am J Clin Nutr*. 2005; 82(3): 559-567. doi: 10.1093/ajcn.82.3.559

50. Rechner AR, Smith MA, Kuhnle G, et al. Colonic metabolism of dietary polyphenols: influence of structure on microbial fermentation products. *Free Radic Biol Med*. 2004; 36(2): 212-225.

51. Aura AM, O'Leary KA, Williamson G, et al. Quercetin derivatives are deconjugated and converted to hydroxyphenylacetic acids but not methylated by human fecal flora *in vitro*. *J Agric Food Chem*. 2002; 50(6): 1725-1730. doi: 10.1021/jf0108056

52. Aura AM. Microbial metabolism of dietary phenolic compounds in the colon. *Phytochem Rev*. 2008; 7: 407-429. doi: 10.1007/s11101-008-9095-3

53. Duenas M, González-Manzano S, González-Paramás A, Santos-Buelga C. Antioxidant evaluation of O-methylated metabolites of catechin, epicatechin and quercetin. *J Pharm Biomed Anal.* 2010; 51(2): 443–449. doi: 10.1016/j.jpba.2009.04.007

54. Justino GC, Santos MR, Canario S, Borges C, Florencio MH, Mira L. Plasma quercetin metabolites: Structure-antioxidant activity relationships. *Arch Biochem Biophys*. 2004; 432(1): 109–121. doi: 10.1016/j.abb.2004.09.007

55. Mateo Anson N, van den Berg R, Havenaar R, Bast A, Haenen GRMM. Bioavailability of ferulic acid is determined by its bioaccessibility. *J Cereal Sci*. 2009; 49(2): 296-300. doi: 10.1016/j.jcs.2008.12.001

56. Li SQ, Zhang QH. Advances in the development of functional foods from buckwheat. *Crit Rev Food Sci Nutr*. 2001; 41(6): 451-464. doi: 10.1080/20014091091887

57. Szawara-Nowak D, Koutsidis G, Wiczkowski W, Zieliński H. Evaluation of the *in vitro* inhibitory effects of buckwheat enhanced wheat bread extracts on the formation of advanced glycation end-products (AGEs). *LWT-Food Science and Technology*. 2014; 58(2): 327-334. doi: 10.1016/j.lwt.2013.03.005

58. Campbell C. Buckwheat crop improvement. *Fagopyrum*. 2003; 20: 1-6.

59. Zielińska D, Zieliński H. Low molecular weight antioxidants and other biologically active components of buckwheat seeds. *Eur J Plant Sci Biotech*. 2009; 3: S29-S38.

60. Zieliński H, Michalska A, Piskuła MK, Kozłowska H. Antioxidants in thermally treated buckwheat groats. *Mol Nutr Food Res*. 2006; 50(9): 824-832. doi: 10.1002/mnfr.200500258

61. Oomah DB, Mazza G. Flavonoids and antioxidative activities in buckwheat. *J Agric Food Chem*. 1996; 44(7): 1746-1750. doi: 10.1021/jf9508357

62. Duenas M, Surco-Laos F, González-Manzano S, Gonzalez-Paramas AM, Santos-Buelga C. Antioxidant properties of major metabolites of quercetin. *Eur Food Res Technol*. 2011; 232(1): 103-111. doi: 10.1007/s00217-010-1363-y.

63. Zielińska D, Szawara-Nowak D, Zieliński H. Comparison of spectrophotometric and electrochemical methods for the evaluation of antioxidant capacity of buckwheat products after hydrothermal treatment. *J Agric Food Chem*. 2007; 55(15): 6124-6131. doi: 10.1021/jf071046f

64. Prabhakar MC, Bamo H, Kumar I, Shamsi MA, Khan SY. Pharmacological investigations on vitexin. *Planta Med*. 1981; 43(4): 396-403.

65. Bramami L, Aquilano F, Pietta P. Unfermented rooibos tea: quantitative characterization of flavonoids by HPLC-UV and determination of the total antioxidant activity. *J Agric Food Chem*. 2003; 51(25): 7472-7474. doi: 10.1021/jf0347721

66. Picerno P, Mencherini T, Lauro MR, Barbato F, Aquino R. Phenolic constituents and antioxidant properties of *Xanthosoma violaceum* leaves. *J Agric Food Chem*. 2003; 51(22): 6423-6428. doi: 10.1021/jf030284h

67. Hien TV, Huong NB, Hung PM, Duc NB. Radioprotective effects of vitexin for breast cancer patients undergoing radioteraphy with cobalt-60. *Integr Cancer Ther*. 2002; 1(1): 38-34. doi: 10.1177/153473540200100103

68. Yamaguchi F, Ariga T, Yoshimura Y, Nakazawa H. Antioxidative and anti-glycation activity of garcinol from *Garcinia indica* fruit rind. *J Agric Food Chem*. 2000; 48(2): 180-185. doi: 10.1021/jf990845y

69. Gugliucci A Menini T. The botanical extracts of *Achyrocline satureoides* and *Ilex paraquariensis* prevent methylglyoxal-induced inhibition of plasminogen and antithrombin III. *Life Sci*. 2002; 72(3): 279-292. doi: 10.1016/s0024-3205(02)02242-7

70. Lee GY, Jang DS, Lee YM, Kim JM, Kim JS. Naphthopyrone glucosides from the seeds of *Cassia tora* with inhibitory activity on advanced glycation end products (AGEs) formation. *Arch Pharm Res*. 2006; 29(7): 587-590. doi: 10.1007/BF02969270

71. Horbowicz M, Obendorf RL. Fagopyritol accumulation and germination of buckwheat seeds matured at 15, 22, 30°C. *Crop Sci*. 2005; 45(4): 1264-1270. doi: 10.2135/cropsci2004.0431

72. Ortmeyer HK, Huang IC, Zhang I, Hansen BC, Larner J. Chiroinositol deficiency and insulin resistance. II. Acute effects of D-chiro-inositol administration in streptozotocin-diabetic rats, normal rats given a glucose load, and spontaneously insulin-resistant rhesus monkey. *Endocrinology*. 1993; 132(2): 646-651. doi: 10.1210/endo.132.2.8425484

73. Ortmeyer HK, Larner J, Hansen BC. Effects of D-chiroinositol added to a meal on plasma glucose and insulin in hyperinsulinemic rhesus monkeys. *Obes Res*. 1995; 3: 605S-608S. doi: 10.1002/j.1550-8528.1995.tb00232.x

74. Kawa JM, Taylor CG, Przybylski R. Buckwheat concentrate reduces serum glucose in streptozotocin-diabetic rats. *J Agric Food Chem*. 2003; 51(25): 7287-7291. doi**:** 10.1021/jf0302153

75. Yao Y, Shan F, Bian J, Chen F, Wang M, Ren G. D-chiro-inositol-enriched tartary buckwheat bran extracts lowers the blood glucose level in KK-Ay mice. *J Agric Food Chem*. 2008; 56(21): 10027-10031. doi: 10.1021/jf801879m

76. Prestamo G, Pedrazuela A, Penas E, Lasuncion MA, Arroyo G. Role of buckwheat diet on rats as prebiotic and healthy food. *Nutr Res*. 2003; 23(6): 803-814. doi: 10.1016/S0271-5317(03)00074-5

77. Kim SL, Kim SK, Park CH. Introduction and nutritional evaluation of buckwheat sprouts as a new vegetable. *Food Res Int*. 2004; 37: 319-327. doi: 10.1016/j.foodres.2003.12.008

78. Bojňanská T, Frančaková H, Chlebo P, Vollmannová A. Rutin content in buckwheat enriched bread and influence of its consumption on plasma total antioxidant status. *Czech J Food Sci*. 2009; 27: 236-240.

79. Lin LY, Liu HM, Lin SD, Mau JL. Quality and antioxidant property of buckwheat enhanced wheat bread. *Food Chem*. 2009; 112(4): 987-991. doi: 10.1016/j.foodchem.2008.07.022

80. Stella C, Beckwith-Hall B, Cloarec O, et al. Susceptibility of human metabolic phenotypes to dietary modulation. *J Proteome Res*. 2006; 5(10): 2780-2788. doi: 10.1021/pr060265y

81. Walsh MC, Brennan L, Pujos-Guillot E, et al. Influence of acute phytochemical intake on human urinary metabolomic profiles. *Am J Clin Nutr*. 2007; 86(6): 1687-1693. doi: 10.1093/ajcn/86.5.1687

82. Llorach R, Garrido I, Monagas M, et al. Metabolomics study of human urinary metabolome modifications after intake of almond (Prunus dulcis (Mill.) D.A. Webb) skin polyphenols. *J Proteome Res*. 2010; 9(11): 5859-5867. doi: 10.1021/pr100639v