



Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Review

Rye and health - Where do we stand and where do we go?

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ARTICLE INFO

Keywords:

Weight management
Blood lipid
Inflammation
Insulin
Fiber

ABSTRACT

Background: High whole grain intake has consistently been associated with lowered risk of developing a number of chronic diseases. Among cereals, rye has highest content of dietary fiber, together with a wide variety of bioactive compounds. There is accumulating evidence from intervention studies of physiological effects of rye foods with potential health benefits.

Scope and approach: This review summarizes the state of the art of rye and health and identifies future directions for research and innovation, based partly on findings presented at the international conference “The Power of Rye”, Åland, Finland, 7–8 June 2017.

Key findings and conclusions: Rye foods have well-established beneficial effects on insulin metabolism compared with wheat bread under isocaloric conditions and at standardized amounts of available carbohydrates, which may have positive implications for diabetes prevention. Recent findings suggest that alterations in blood glucose flux partly explain these effects. Moreover, several studies have shown beneficial effects of rye-based foods on satiety, which is one plausible mechanism behind recently demonstrated beneficial effects on weight management. Emerging results indicate beneficial effects of rye intake on inflammation and blood lipids. More research is needed to uncover underlying mechanisms for other demonstrated effects and the long-term implications for health. A challenge with rye-based foods is making them palatable and widely acceptable to consumers. Development of innovative and tasty rye products and targeted communication strategies is crucial in increasing awareness and consumption of rye foods. Novel results in this regard are presented in this review.

1. Background

Non-communicable diseases account for about 70 percent of deaths worldwide, the most common being cardiovascular disease, diabetes, and cancer (World-Health-Organization, 2017). Diet is one of the most important environmental factors affecting the risk of developing non-communicable diseases and premature death (Mathers, Boerma, & Ma Fat, 2008). Cereal foods constitute a major source of energy world-

wide, but are also a major source of dietary fiber. Whole grain cereals are particularly rich in dietary fiber and consumption of whole grain foods is generally higher in the Nordic countries than elsewhere. High intake of whole grain cereals has consistently been associated with lowered risk of developing type 2 diabetes, cardiovascular disease, and some cancers (Aune et al., 2016; WCRF & AICR, 2017). The underlying mechanisms explaining the health benefits of whole grain cereals are still to be elucidated, but cereal dietary fiber and associated compounds

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<https://doi.org/10.1016/j.tifs.2018.06.018>

Received 19 May 2018; Received in revised form 29 June 2018; Accepted 30 June 2018

Available online 03 July 2018

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are likely to be involved, although great diversity and interactions make it difficult to draw general conclusions. Several studies have shown beneficial effects from high whole grain consumption on gut health, satiety, blood glucose levels, and hormone secretion. In the long run, this could benefit weight management, reduce the risk of type 2 diabetes, and have beneficial impacts on other non-communicable diseases.

Among cereals, rye has the highest content of dietary fiber (Andersson, Fransson, Tietjen, & Aman, 2009) and contains a broad spectrum of bioactive compounds (Koistinen et al., 2018) that have been shown to affect physiological processes relevant to health. In several Nordic countries there is a long-standing tradition of rye consumption. In June 2017, many European researchers active in the area of rye and health gathered together with representatives from the major European cereal food industries in Åland, Finland, at the conference ‘The Power of Rye’ to disseminate recent findings, discuss the state of the art in rye and health, and identify research gaps and future priorities. This review assesses current knowledge on rye and health, based on both published data and results presented at the conference.

2. Characteristics of rye

Rye contains high amounts of dietary fiber (Andersson et al., 2009) that are distributed throughout the rye kernel (Fig. 1) and rye endosperm has a higher dietary fiber content than wheat endosperm. Rye grains also contain a wide variety of bioactive compounds that may have independent or synergistic health effects (Bach Knudsen, Norskov, Bolvig, Hedemann, & Laerke, 2017; Koistinen & Hanhineva, 2017a, 2017b).

2.1. Dietary fiber

Dietary fiber in rye consists of arabinoxylan, cellulose, β -glucan, fructans, and lignin. In this respect rye is similar to wheat, but the fiber content and the solubility of arabinoxylan are higher in rye than in wheat. Arabinoxylan is the most abundant fiber in rye (6–12% of dry grain weight) and is present in various amounts and proportions in the different tissues of the grain, i.e., the endosperm, aleurone, and pericarp/testa (Glitsø et al., 1999). Arabinoxylan has a backbone of xylose units, many of which are substituted with arabinose residues. Moreover, ferulic acid groups are esterified to some of the arabinose residues, which enable cross-linking between polysaccharides. The substitution pattern (arabinose/xylose) differs for different milling fractions and the functional characteristics of arabinoxylan differ between fractions, e.g., the water-solubility is about 70 percent in the endosperm but almost zero in the aleurone and pericarp/testa. The molecular weight of rye arabinoxylan varies depending on analytical technique and the raw material (whole grain or bran). Water-extractable arabinoxylan and soluble β -glucan are responsible for the viscous properties of soluble dietary fiber in rye (Wood, 2010), which

may contribute to the technological functionalities and the various health effects of rye. Soluble dietary fiber and fructans provide the most readily fermentable substrate for the microbiota in the large intestine, which may influence gut health and overall health in a beneficial direction (Dahl et al., 2017; Holscher, 2017; Vuholm et al., 2017). The insoluble fraction of dietary fiber in rye affects fecal bulk and intestinal transit time, which in turn may decrease the risk, and relieve symptoms, of constipation (EFSA, 2011; de Vries, Birkett, Hulshof, Verbeke, & Gibes, 2016) and may contribute to the decreased risk of colorectal cancer observed in relation to high whole grain intakes (WCRF & AICR, 2017).

2.2. Bioactive compounds

The high content of dietary fiber in rye has been regarded as the main driver of the health effects of rye foods. However, dietary fiber alone does not explain the beneficial biological effects of rye and thus other factors, such as bioactive compounds, are suggested to be part of the explanation. Phytochemicals are plant-made compounds that have functions in the plant, such as cell signaling and protection. In cereals, the majority of the phytochemicals are found in the bran, and in particular the aleurone cells (Bach Knudsen et al., 2017). Phenolic acids, lignans, benzoxazinoids, and alkylresorcinols are examples of bioactive compounds found in rye (Koistinen & Hanhineva, 2017b). However, the list of phytochemicals detected in rye is continually increasing and currently stands at almost 2000 chemical species (FoodDB, 2018). In general, the density of bioactive phytochemicals is highest in the plant parts required for reproduction, such as whole grains, berries, fruits, nuts, and seeds. Consequently, recent epidemiological studies have revealed that such food items are particularly protective against various diseases when consumed as part of the habitual diet (Schwingshackl, Schwedhelm, et al., 2017b). In humans, the role phytochemicals may have for health and the mechanisms of action that mediate effects remain to be proven. The compounds are either bound to the fiber structure or lie in close proximity, and may be released during the digestion process in the small intestine or metabolized by the gut microbiota (Bach Knudsen et al., 2017; Bolvig, Adlercreutz, Theil, Jorgensen, & Bach Knudsen, 2016; Bolvig et al., 2017; Koistinen et al., 2017).

Lignans are diphenolic compounds found in fiber-rich vegetables, whole grain, and seeds, especially flaxseed and sesame seeds (Tetens et al., 2013). In Scandinavia, rye is one of the main sources of lignans (Smeds et al., 2007; Tetens et al., 2013). After consumption by humans, lignans are converted by the gut microbiota mainly to the phytoestrogens enterodiol and enterolactone, which can be measured in blood and urine (Adlercreutz, 2007). Due to the structural similarity to estrogen, the primary research focus to date has been on hormone-related cancers, such as breast and prostate cancer. For breast cancer, high intake of lignans and high blood concentrations of enterolactone have been found to be associated with lower risk of the disease in observational

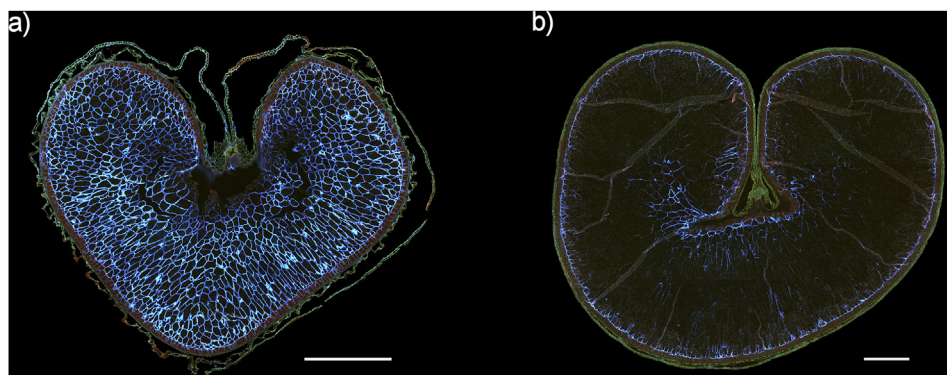


Fig. 1. Distribution of dietary fiber in the rye kernel.

Cross section of a) rye and b) wheat grains stained with Calcofluor white and Acid Fuchsin, for visualization of beta-glucan and protein, respectively. Outer grain layers appear brownish-yellow due to autofluorescence. Scale bars represent 500 μ m. Image courtesy of VTT Technological Research Centre of Finland; Ulla Holopainen-Mantila.

studies, and more clearly with improved prognosis after breast cancer (Buck, Zaineddin, Vrieling, Linseisen, & Chang-Claude, 2010; Seibold et al., 2014). For prostate cancer, enterolactone has been shown to inhibit cell proliferation in *in vitro* studies (Landberg et al., 2010). However, the evidence from human studies is less clear (Eriksen et al., 2017; Landberg et al., 2010). In addition, associations between high urinary enterolactone and lower cardiovascular mortality and all-cause mortality have been found (Reger, Zollinger, Liu, Jones, & Zhang, 2016), suggesting that enterolactone may also be of relevance in a broader health perspective. Overall, lignans may exert some health beneficial effects, especially in relation to hormone-dependent cancer, but further research is needed.

Alkylresorcinols constitute a group of phenolic lipids mainly found in wheat and rye among commonly consumed grains (Ross, 2012a; Ross et al., 2003). Minor contents are also found in barley, and even-numbered alkylresorcinols are found in quinoa (Ross, Svelander, Karlsson, & Savolainen, 2017). The content of alkylresorcinols is generally high in common whole grain wheat and rye products (200–1000 µg/g) (Menzel et al., 2012). Since they are exclusively present in the outer parts of these grains, they have been suggested and used as specific dietary biomarkers of whole grain wheat and rye intake. Alkylresorcinols are absorbed in the small intestine, transported in lipoproteins, and distributed in red blood cell membranes and adipose tissue, probably also into other body compartments. Alkylresorcinols have been suggested to interfere with micelle solubilization of cholesterol in the digestive tract, which may decrease cholesterol absorption, a mechanism that may contribute to the suggested cholesterol-lowering effect of rye (Horikawa et al., 2017). This mechanism is supported by findings in mice that alkylresorcinols increase glucose tolerance and insulin sensitivity by suppressing lipid accumulation and intestinal cholesterol absorption (Oishi et al., 2015). Alkylresorcinols have also been shown to suppress adipocyte lipolysis and hormone-sensitive lipase activity, which are important in body weight management (Andersson, Dey, Holm, & Degerman, 2011). Model experiments have demonstrated *in vitro* inhibition of colon cancer cell growth, with the strongest inhibition for shorter homologs (Zhu, Soroka, & Sang, 2012). A major obstacle in studies of bioactivity of alkylresorcinols is the fact that their solubility differs between homologs, and bioactivities may therefore be confounded by difficulties in solubilizing long-chain alkylresorcinol homologs.

Benzoxazinoids constitute a group of compounds that have recently been identified in rye and have attracted interest due to their highly bioactive structure and, hence, potential health effects (Hanhineva et al., 2011; Pedersen, Laursen, Mortensen, & Fomsgaard, 2011). Few human studies focusing in particular on the benzoxazinoids have been carried out so far, but together with findings in studies on animals and *in vitro*, the results indicate beneficial effects, including immunoregulatory, appetite- and weight-reducing, and anti-cancer effects (Adhikari et al., 2015). The benzoxazinoids are proposed to exert particularly potent effects on prostate cancer and have now been found in prostate tissue, which corroborates a role for benzoxazinoids in prostate health (Steffensen et al., 2016). Studies to evaluate the association between benzoxazinoid intake and prostate cancer are ongoing.

Overall, the role of bioactive compounds derived from rye consumption in health needs to be further investigated. Nevertheless, owing to the wide range of phytochemicals found and their bioactive chemical characteristics, it is likely that phytochemicals play a role for beneficial health effects associated with rye consumption. However, due to the co-presence of dietary fiber, it is difficult to disentangle the individual effects.

3. Metabolic effects of rye-based foods

Different study settings have been used to investigate health effects of whole grain and of rye (see Fig. 2 for the most common study designs). Many observational studies have been conducted in the area of

whole grain and health. Since 2011, eleven meta-analyses that have included and jointly evaluated all previous cohort studies have been published (Aune, Norat, Romundstad, & Vatten, 2013; Chanson-Rolle et al., 2015; Chen et al., 2016; Schwingshackl, Hoffmann, et al., 2017a; Zhang, Zhao, Guo, Bao, & Wang, 2018). All concluded that consumption of whole grain foods may be beneficial in prevention of disease, including cardiovascular disease, type 2 diabetes, and certain cancers, foremost colorectal cancer. However, the evidence on disease risk factors based on human dietary interventions is not as clear. Nevertheless, based on these meta-analyses of cohort studies, it can clearly be stated that whole grain foods are one of the most relevant dietary factors for prevention of non-communicable diseases.

The evidence from cohort studies is limited when it comes to distinguishing the beneficial effects of rye from those of other whole grains (Frolich, Aman, & Tetens, 2013). In cohort studies, the association between specific grain types and health is difficult to measure because most cohorts include populations with intakes primarily based on whole grain wheat. In addition, dietary assessment methods are typically not designed to capture in full whole grain intake, which has been suggested to be best reported in grams per day rather than products per day (Ross, Kristensen, Seal, Jacques, & McKeown, 2015). Therefore, there is a great need for new tools to measure the intake of specific whole grains, including better dietary assessment tools designed to measure whole grain intake and the use of biomarkers.

Identification of dietary biomarkers is an emerging field of research and biomarkers of whole grain wheat and rye have been identified, for example the alkylresorcinols (Landberg, Kamal-Eldin, Andersson, Vessby, & Aman, 2008). By measuring two specific alkylresorcinol molecules, it is possible to differentiate between whole grain wheat and rye intake. Alkylresorcinols in a blood sample mainly reflect short-term intake, particularly in studies of populations with low habitual whole grain intake (Ross, 2012b). However, in a recent study, measurements of alkylresorcinols in adipose tissue were shown to be useful for reflecting long-term intake of whole grain rye products (Wu, 2017). In ongoing studies, the role of whole grain wheat and rye, measured with these biomarkers, is being evaluated in relation to major chronic diseases. In addition, it is important to develop food intake questionnaires that differentiate more precisely between different types of cereal foods. An overview of potential health implications of rye consumption is provided in Fig. 3.

4. Glucose and insulin

Results from randomized controlled trials (RCTs) suggest that rye breads, in comparison with wheat-based products, reduce the demand for insulin, even when both provide equal amounts of available carbohydrates (Hartvigsen, Gregersen, et al., 2014a; Juntunen et al., 2003; Kallio et al., 2008; Lappi et al., 2014; Leinonen, Liukkonen, Poutanen, Uusitupa, & Mykkanen, 1999; Rosen et al., 2009). Insulin is the main glucose-regulating hormone and enables the cells in the body to take up and make use of glucose. The less insulin needed, the better, as a high insulin response immediately after a meal may cause blood glucose levels to decrease quickly, and even drop below fasting concentration. This induces an acute stress reaction within the body and may trigger hunger and induce inflammation. Constantly high insulin responses and large fluctuations in blood glucose levels may increase the risk of chronic disease development (Black, 2003, 2006).

4.1. Physiological effects

Comparing rye and wheat breads with similar amounts of digestible carbohydrates, the blood glucose curves appear somewhat different. On consuming rye bread, glucose concentrations peak at similar levels as on consuming wheat bread (Rosen et al., 2009). Rye bread consumption has beneficial effects on insulin metabolism, not only immediately after rye consumption, but also in the following meal (Ibrugger et al., 2014).

Randomized controlled trials

There are different ways to evaluate the health effects of foods. The gold standard for establishing a cause-and-effect relationship between any food or constituent and its effect is through randomized controlled trials (RCTs). In RCTs, study participants are randomized into different groups that are exposed, or not, to the food or diet of interest and compliance with the study diets is checked. However, RCTs may still run the risk of poor compliance. Another quality parameter of an RCT is that the study participants should not know whether they are exposed to the substance, food, or diet of interest, which requires 'blinding'. Blinding is often very difficult and in some cases impossible when it comes to diet interventions, such as comparisons between wholegrain rye and refined wheat breads.

Moreover, RCTs are expensive and demanding for participants and are therefore typically performed during a relatively short period (weeks or months). This makes it difficult to evaluate the effects of disease development and repression *per se*, since it usually takes years to develop a chronic disease. Instead, biomarkers such as blood lipid profile or glucose and insulin in the blood, which are correlated with the risk of developing cardiovascular disease or type 2 diabetes, respectively, are typically monitored.

Observational studies

Prospective cohort studies are observational studies that run for several years and are particularly useful for studying the role of diet for disease development. Information on dietary intake, lifestyle and medication, and biological samples, may be collected at the start, before subjects have been diagnosed with any disease. Subjects are then followed over time and information about disease and death is provided prospectively through direct measurements or links with disease and death registries. Relationships between different dietary components and disease development can then be evaluated.

However, these studies may suffer the risk of confounding, whereby intake of the food of interest may be correlated with a known or unknown factor that in turn is correlated with both the endpoint and the exposure of interest. It is therefore difficult to know whether observed associations are causal or not. In a well-designed study, known potential confounders are taken into account. However, there may also be unknown factors that could at least partly explain the associations observed. Another issue might be that the information on foods consumed is not sufficiently precise, which may lead to difficulties in formulating definitive answers to study questions. This calls for careful planning of cohort studies.

Animal studies

Animal studies may also be useful for evaluating the effects of dietary components, and particularly for identifying molecular mechanisms to explain the biological path of the beneficial or deleterious effect of a food or a substance. However, results from studies performed on animals may not be readily applicable to humans.

Fig. 2. Explanation of different studies to evaluate health effects of rye.

It has been shown that, compared with an evening meal with refined wheat bread, an evening meal with whole grain rye kernel bread or boiled rye kernels can have beneficial effects the following day. Blood glucose and insulin levels and release of free fatty acids were found to be lower after a standardized morning meal, which has been termed the 'second meal effect' (Ibrugger et al., 2014). Taken together, these results suggest that rye bread has beneficial acute to semi-acute effects on glucose and insulin metabolism. These effects have been linked to improved long-term inflammatory status in individuals with metabolic syndrome (Kallio et al., 2008), but the impact in type 2 diabetes prevention is not yet known. Differences in metabolic pattern have also been identified after a meal of whole grain rye porridge compared with refined wheat bread in healthy subjects (Shi et al., 2017), but more

studies on rye-based foods other than bread are needed to allow general conclusions to be drawn on the role of rye *per se*.

4.2. The 'rye factor'

Lower serum insulin concentrations, but similar glucose concentrations, after consumption of the same amount of carbohydrates from rye bread compared with white wheat bread have been observed repeatedly in a large number of studies, but the underlying mechanisms are unclear and a scientific explanation is lacking. This property of rye of less insulin needed has been termed the 'rye factor', and a number of possible contributing elements have been suggested. Several processes affect blood glucose concentration, including glucose uptake (rate and

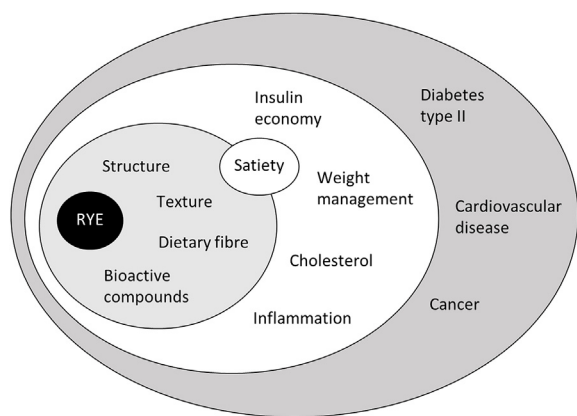


Fig. 3. Overview of rye and potential health effects.

amount), insulin production and clearance, and the sensitivity of insulin-sensitive tissues. Compounds in rye, such as dietary fiber and phytochemicals (Rosen et al., 2011), but also amino acids and fermentation products from the gut, may have different effects on these processes (Hanhineva et al., 2012; Koistinen et al., 2017). A suggested model that explains the ‘rye factor’ is shown in Fig. 4.

The rye factor appears to be particularly apparent after consumption of rye bread. However, in an acute study setting with semolina-based porridge, addition of rye kernels induced a reduction in postprandial insulin concentrations, despite similar glucose concentrations (Hartvigsen, Laerke, et al., 2014b). This effect was unrelated to the concentration of short-chain fatty acids generated (Hartvigsen, Laerke, et al., 2014b). However, it has also been shown that whole grain rye bread induces lower insulin levels, together with increased circulating short-chain fatty acid concentrations, compared with wheat bread (Lappi et al., 2014).

Unfermented rye crispbread has been shown to exert stronger insulin-lowering effects than yeast-fermented rye crispbread (Johansson, Lee, Riserus, Langton, & Landberg, 2015). This suggests that the rye factor is linked to the texture and structure of rye products, which are proposed to slow down release of glucose to the bloodstream (Juntunen et al., 2003; Leinonen et al., 1999; Rosen et al., 2009, 2011). To evaluate the rate of appearance of glucose in the blood, consumption of rye breads containing labeled glucose has been studied. In a recent human study, slower influx of glucose to the blood and slower efflux of glucose

from the blood into cells were shown for rye bread compared with refined wheat bread (Moazzami et al., unpublished results). These results support the suggestion that differences in uptake rate due to differences in digestion and/or absorption are one important explanation for the rye factor in humans. However, in pigs, which have a similar digestive system to humans, no difference in glucose flux has been observed after feeding rye or refined wheat bread (Theil, Jorgensen, Serena, Hendrickson, & Bach Knudsen, 2011), but significant differences have been detected in the net portal flux of insulin (Ingerslev, Theil, Hedemann, Laerke, & Knudsen, 2015). This suggests that several underlying processes may contribute to the rye factor.

5. Satiety and weight management

It is well established that whole grain rye-based porridge, soft bread, and crispbread increase satiety, lower hunger, and lower the desire to eat, compared with corresponding calorie intake in the form of refined wheat bread (Isaksson, Fredriksson, Andersson, Olsson, & Aman, 2009; Isaksson, Sundberg, Aman, Fredriksson, & Olsson, 2008; Isaksson et al., 2012, 2011; Johansson et al., 2015; Lee et al., 2016). The increased satiety may be related to nutrient availability and digestion kinetics, as affected by both the content and composition of dietary fiber in rye foods, which determine physiochemical properties such as viscosity and degree of encapsulation (Johansson, Gutierrez, Landberg, Alminger, & Langton, 2017). It has also been proposed that serotonin-like substances in rye bread may increase satiety (Bondia-Pons et al., 2011; Lankinen et al., 2011). Furthermore, short-chain fatty acids, in particular butyrate, which is formed during fermentation of some of the dietary fiber in rye (Tolhurst et al., 2012), have been correlated with increased satiety in one study (Sandberg, Bjorck, & Nilsson, 2017), but not others (Lee et al., 2016; Sandberg, Bjorck, & Nilsson, 2016). In studies comparing non-fermented rye crispbread and yeast-fermented rye crispbread with refined wheat crispbread, non-fermented crispbread had the strongest effect on satiety, but the two types of rye crispbread did not differ in their effect on appetite (Johansson et al., 2015).

In the long run, increased satiety may be beneficial for weight management. According to a systematic review and meta-analysis of RCTs on apparently healthy subjects, there is a small beneficial effect on body fat after consumption of whole grain compared with non-whole grain foods, but no significant difference in body weight (Pol et al., 2013). This lack of difference in body weight may be explained by the relative small sample size of the studies included in that review and their short duration. In a recent study, effects on body weight and fat

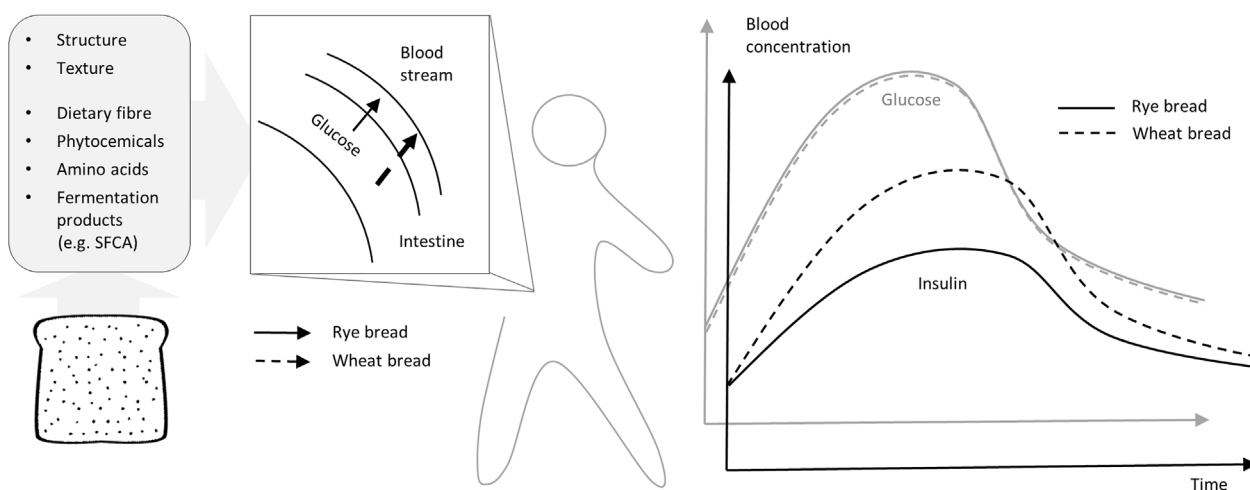


Fig. 4. Suggested model for the ‘rye factor’.

Lower serum insulin concentrations after intake of rye bread compared with wheat bread, despite similar serum glucose concentrations, is suggested to be explained by slower intestinal glucose absorption from rye than wheat bread. Absorption, in turn, may depend on a variety of factors, such as differences in the type and amount of dietary fiber, phytochemicals, amino acids, and fermentation products, particularly short-chain fatty acids (SCFAs) from the gut, food texture, and structure.

mass were evaluated after six weeks of intake of whole grain rye, whole grain wheat, and refined wheat in 60 subjects at risk of developing metabolic syndrome (Suhr, Vuholm, Iversen, Landberg, & Kristensen, 2017). The results showed that participants who consumed whole grain rye had greater weight loss than those who consumed whole grain or refined wheat, primarily explained by a reduction in energy intake. There was also a tendency for lower fat mass. A larger study is currently being undertaken to confirm these findings and to elucidate the potential role of gut microbiota in weight loss.

6. Blood lipids

Beneficial effects on bowel movement and stool transit are well known for rye foods, but effects on blood lipids are less well established. Oats and barley contain viscous beta-glucan, which to a large extent explains the cholesterol-reducing effects of these cereals when consumed in sufficient amounts. Rye contains only small amounts of beta-glucan but is rich in arabinoxylan, which increases the viscosity, but to a lesser extent than beta-glucan due to lower molecular weight (Ajithkumar, Andersson, & Åman, 2005; Bengtsson, Andersson, Westerlund, & Åman, 1992; Cyran, Courtin, & Delcour, 2003). More than 80 percent of the variation in viscosity in rye has been attributed to soluble arabinoxylan (Bengtsson et al., 1992), because its structure is less affected by processing than beta-glucan. To date, two health claims have been authorized by the European Commission for use with food products containing beta-glucan, stating an effect of lowered levels and maintenance of normal levels of blood cholesterol. However, the cholesterol-lowering properties of whole grain rye-based foods have not been established and the effects of rye-based foods on cholesterol levels in humans have only been examined in a few published studies. In one study, rye bread intake resulted in significantly lower total and low-density lipid (LDL) cholesterol levels in men, but not in women, compared with refined wheat bread intake (Leinonen, Poutanen, & Mykkanen, 2000). In a recent, as yet unpublished, study, whole grain rye foods with added fermented rye bran lowered LDL cholesterol by 6 percent after 12 weeks compared with refined wheat in a dietary intervention conducted in 190 healthy Chinese men and women (Landberg et al., unpublished results). This effect is of similar magnitude to the cholesterol-lowering effects of oats, and in line with findings in a study performed on a Finnish population (Leinonen et al., 2000). In another recent study in 40 men with metabolic syndrome, a beneficial effect on cholesterol levels was found after four weeks on a rye diet, although the effect disappeared after eight weeks (Eriksen et al., unpublished). The reduced effect could be due to a drop in compliance with the study diet, but this remains to be confirmed. Moreover, beneficial effects of rye foods on cholesterol levels have been found in pigs. In a study testing a diet rich in cholesterol, saturated fat, and either rye or wheat with the same amount of fiber, significantly lower LDL cholesterol levels and LDL:high density lipid cholesterol ratio were found with the rye diet compared with the wheat diet (Lærke et al., 2008). In summary, research results suggest a cholesterol-lowering effect of high-fiber rye products, but more studies are required to elucidate the specific amount and type needed.

7. Inflammation

Beneficial effects of whole grain or high-fiber cereal foods on chronic, low-grade inflammation are reported in an increasing number of studies showing lower adipose tissue inflammation, circulating inflammatory markers, and inflammation-related lipid profile (Kallio et al., 2008; Roager et al., 2017). However, only a few studies with whole grain rye foods have been undertaken so far (Kallio et al., 2008, 2007; Sandberg et al., 2017). In a small study on men with prostate cancer, the inflammatory marker C-reactive protein was found to be significantly lower after consumption of high-fiber rye foods compared with refined wheat (Landberg et al., 2010). Moreover, in a 12-week

study of Chinese subjects, C-reactive protein was significantly lower after consumption of a diet including whole grain rye with fortified bran at 25 percent of total energy intake, compared with refined wheat (Landberg et al., unpublished results). Beneficial blood glucose levels related to lower insulin response and lower later-phase response of free fatty acids after a meal of whole grain rye, compared with refined wheat products, may contribute to lower inflammation (Sandberg et al., 2017). Lowered gastrointestinal permeability after a rye-based diet may also contribute to a lower degree of pro-inflammatory bacterial residues entering the bloodstream, stimulating inflammatory responses. More research is needed before any firm conclusions can be drawn and the underlying mechanisms need to be identified.

8. Metabolic effects related to food processing

Rye is often pre-processed before being used in actual products (i.e., bread and breakfast products). Relevant pre-processing methods include sourdough fermentation, germination, milling combined with chemical treatment, and hydrothermal treatment with oxidation. Pre-processing can induce profound changes in the chemical composition, structural features, and functional capabilities of cereal fibers that may affect physiological responses. For example, fermentation is a good method for pre-treating flour or fiber fractions to achieve changes in both the structural and chemical composition of raw materials. Sourdough fermentation is one of the most common bioprocessing techniques used to produce tasty and well-preserved rye breads. The sourdough process induces enzymatic activity and formation of bioactive components in the dough and bread, with subsequent changes in nutritional, structural, and sensory quality. Sourdough fermentation is important in modifying rye proteins and cell wall polysaccharides in the bread baking process. Unlike wheat gluten, rye proteins do not form a continuous gluten network in bread. Instead, arabinoxylan plays an important role in binding water in the dough and contributes to formation of structure (Katina, Hartikainen, & Poutanen, 2014; Poutanen, Katina, & Heiniö, 2014). Sourdough fermentation may also influence many other properties, such as content of vitamins, forms and bioaccessibility of phytochemicals, and lowered pH. Such alterations may have implications for metabolic responses (Johansson et al., 2017, 2015; Liljeberg, Lonner, & Bjorck, 1995; Zamaratskaia et al., 2017). Type and amount of sourdough and compositional properties of the bread may yield different results and may have different effects on the bread and, in turn, on metabolic parameters (Johansson et al., 2017, 2015; Poutanen, Flander, & Katina, 2009).

A recent factorial experiment in humans suggests that the content of rye may be of higher relevance than the amount of sourdough added to a bread product for appetite and for the postprandial insulin response (the 'rye factor') (Nöhr Iversen et al., submitted). In comparison with unfermented rye crispbread, sourdough rye crispbread has been found to increase the desire to eat and also to cause higher insulin response compared with unfermented breads, most likely due to degradation of viscous fiber and faster bolus disintegration of the sourdough crispbread (Johansson et al., 2015; Zamaratskaia et al., 2017). Previous studies have suggested beneficial metabolic effects related to intake of sourdough fermented breads due to high concentrations of organic acids that may alter gastric emptying, and subsequent digestion and absorption kinetics of carbohydrates (Liljeberg & Bjorck, 1996, 1998; Ostman, Granfeldt, Persson, & Bjorck, 2005). However, recent studies show that the amount of sourdough normally used in commercially available breads may be insufficient to obtain positive metabolic effects, as previously suggested based on model experiments with high contents of organic acids and low pH (Johansson et al., 2015; Zamaratskaia et al., 2017). Since most studies conducted on rye breads have used sourdough fermented rye breads, and comparisons with unfermented rye breads are lacking, disentangling the effect of sourdough fermentation *per se* is difficult. More research is needed to distinguish the role of the fermentation process and the role of different

sourdoughs on food structure and chemical composition of relevance for metabolic effects. Based on such knowledge, tailored sourdough fermented breads could be developed for optimal health and taste.

In addition to the effect of sourdough, the effects of structure and texture on the satiating properties of rye products have also been studied. For example, one study showed that the structure of rye-based food has an impact on satiety (Pentikäinen et al., 2017). During the first hour after a snack consisting of rye bread or rye puffs in that study, the feeling of satiety was more intense than after eating rye flakes or a rye smoothie. An important parameter in the physiological responses of rye products is believed to be the mastication step. Results of one study indicate that the digestion process of rye breads differs from that of wheat bread even in its earliest phases (Pentikäinen et al., 2014). This may be one reason behind the unique postprandial responses reported for rye breads. However, more studies are needed to fully understand the impact of the mastication process and rye product micro- and macrostructure on the responses in the human body.

When assessing different metabolic responses, such as the postprandial glucose response, the release of glucose during digestion of foods is generally determined by several factors, which may vary in their importance depending on product-specific properties. Such properties include starch gelatinization and fiber degradation induced by food processing, such as fermentation of bread, extrusion, or cooking, i.e., in porridge (Johansson et al., 2017). Flour particle size may also have a substantial effect (Mandalari et al., 2016). This makes it difficult to draw conclusions on general effects attributable to individual factors when comparing differently processed foods, since the observed effects may be the net result of several mechanisms and their interactions.

9. Communication of health messages

Communication of health messages may be of interest to different commercial companies, institutes, organizations, and authorities in general. Health messages should be science-based but, to stay in the mind of people, they also need to be short, positive, consistent, easily understood, and easily memorable. Examples of communication of science-based dietary guidelines are food-based dietary guidelines and different symbols. Food-based dietary guidelines include dietary recommendations, such as those of national food agencies. In the Nordic countries, the Nordic Nutrition Recommendations are converted by the national food agencies into recommendations in terms of foods and food groups. The 'keyhole symbol' in Sweden, Norway, and Denmark, and the 'heart symbol' in Finland, are ways to communicate a healthier choice of a type of food in a simple way. These symbols may only be displayed on a product when certain nutrient criteria are fulfilled. Content of whole grain and content of dietary fiber are examples of nutrients that are regulated using the keyhole and heart symbols. In Denmark, there is also a whole grain logo that is permitted on products containing a sufficient amount of whole grain and fiber. High rye content is an excellent way to meet these criteria for cereal-based foods.

Another way to communicate health messages on commercial food products is to use specific nutrient or health claims authorized by the European Commission. These nutrient claims describe what the product contains. When present in sufficient amounts, certain components considered healthy may be declared using a nutrient claim. Products with a high rye content are likely to be permitted to bear the claim 'rich in dietary fiber'. Depending on the type of product and the accompanying ingredients, other nutrient claims, such as 'low in saturated fats' or 'low in sodium', may be used. When it comes to specific health claims, they are authorized based on a scientific assessment of the highest possible standard conducted by the European Food Safety Authority (EFSA). To date, there is only one authorized health claim for rye: 'Rye fibre contributes to normal bowel function' (EFSA, 2011). There is a need, and high potential, for additional research on rye foods and its constituents, in order to pave the way for additional authorized

health claims.

10. Consumer perception

Regardless of how healthy rye may be, rye foods must be available, chosen, and eaten to have a beneficial effect in reality. Therefore, consumption patterns, health-related and sensory qualities, and consumer perceptions of commercial rye breads in Sweden have been evaluated in recent studies (Sandvik, 2017; Sandvik, Kihlberg, Lindroos, Marklinder, & Nydahl, 2014). The results showed that a liking for rye breads was frequently associated by subjects with bread types consumed in childhood. Perceived characteristics of healthy breads in that study were coarseness and presence of whole grain, fiber, sourdough, and rye. These types of breads were considered good for the stomach and bowel, and to have properties beneficial for satiety and blood glucose levels. An estimation of bread properties beneficial for blood glucose levels was made by *in vitro* measurements of fluidity. These properties were associated with a chewy, dry texture and sour flavor, although they varied widely among the rye breads. A higher preference for breads with less whole grain and rye was found in younger consumers (18–44 years), those with children, and groups with lower education levels, while a higher preference for breads with more whole grain and rye was found mainly for whole grain consumers (Sandvik et al., 2014). The perception of healthy breads generally corresponded to what is actually healthy, although the healthiest breads were not always preferred by consumers (Sandvik et al., 2014). Efforts need to be made to develop a wide range of healthy breads that appeal to diverse groups of consumers, aided by more research on what consumers actually prefer and tend to choose.

11. New trends and technologies

In order to lessen the ecological burden of global food consumption, the global population is being urged to consume a more plant-based diet, which provides an opportunity for rye to enter new product categories. Although bread is a staple food category, the industry should examine wider usage of rye in food products, to give it a more significant role in a balanced daily diet. Several food companies are already working on the challenge of increasing consumption of healthy rye foods. It is critical to understand consumer preferences and combine these preferences with new processing tools and crop breeding. In addition to new product categories, new concepts such as fresh-packed and bake-off products should be used, as well as innovative approaches to combine rye with other ingredients and the use of innovative techniques in product development.

Since snacking and on-the-go eating are increasing, traditional bakery and cereal products have great potential for use in healthy snack options for consumers. For example, extrusion technology can be applied to produce rye-based snacks. Particle size reduction of rye bran (440 → 28 μm) is reported to improve the expansion of extruded rye bran snacks (Alam et al., 2014), which may improve the taste and the mouth feel. In addition to extruded products, baked sweet and savory snacks and chips made of rye flour have been appearing in the Nordic market, presumably with a good response from consumers.

While rye breads are a popular food category in the Nordic countries, especially in Finland, not all people tolerate rye breads well. For the Finnish population, rye breads constitute one of the most important fiber sources, but 10 percent of that population suffer from irritable bowel syndrome, with symptoms that may be relieved by a diet low in fermentable oligo-, di-, monosaccharides and polyols (FODMAPs). FODMAPs are a collective name for carbohydrates that pass through the upper intestinal tract fairly intact and instead reach the colon, where they are rapidly fermented by the gut microbiota. Because of its high content of fructans, rye bread is a major source of FODMAPs. Hence, a low FODMAP diet generally means a diet low in fiber and rye products. To overcome this problem, there is now a low-FODMAP bread available

on the Finnish market, the first of its kind in the world (Laatikainen et al., 2016). To produce this bread, a unique sourdough culture is used that consumes FODMAPs extremely efficiently, resulting in bread with a very low FODMAP content. In two clinical trials, low-FODMAP bread has been found to be better tolerated than regular rye breads (Laatikainen et al., 2016; Pirkola et al., 2018).

Overall, the food industry has an important role to play in translating research into products that reach consumers, and there is room for new kinds of palatable rye products that attract new consumers. Good continuous dialog between researchers, the food industry, and consumers is needed to enable the health properties of rye to benefit more people.

12. Rye for the future

Although consumption of rye specifically and its health effects have not been studied as extensively in cohort studies as consumption of whole grain foods, clinical trials show promising results. Effects of rye foods on satiety have been reported quite consistently. The beneficial effects of rye consumption on insulin metabolism are already well established, but more research is needed to fill gaps in knowledge regarding the underlying mechanisms and the long-term implications for health, such as the risk of developing type 2 diabetes and cardiovascular disease. Furthermore, use of emerging state-of-the-art analytical methods, including OMICs techniques, is highly important and expected to provide major breakthroughs. Emerging research results suggest that, because of their content of soluble dietary fiber, rye foods have cholesterol-lowering properties. This area is currently rather unexplored, but seems promising for future findings of beneficial effects on blood lipids and application of health claims. Larger studies are needed to demonstrate whether rye foods are beneficial for blood lipid profile and weight management, and to provide a scientific basis for health claims authorized by the European Commission. Rye foods may also be promising in terms of new products providing an environmentally sustainable source of protein.

Regardless of the many health benefits rye foods may have, these foods will not be of benefit unless they are consumed. Development of many new, innovative and tasty rye products, associated health claims, good marketing, and efficient communication are crucial in order to increase awareness and consumption of rye foods among consumers.

Funding sources

This work was supported financially by the Nordic Rye Forum, a pre-competitive platform for rye and health research by academia, institutes, and food industries in the Nordic countries funded through membership fees from companies in the food industry: Fazer, Lantmännen, Leksandsbröd, Pågen, and Wasa/Barilla. The Nordic Rye Forum is also supported by NKJ. None of the companies had any role or impact on the planning, execution, or interpretation in this review.

Declaration of interest

Karin Jonsson: None.
 R. Andersson: None.
 K.E. Bach Knudsen: None.
 G. Hallmans: Has worked as an advisor for Barilla.
 K. Hanhineva: Principal investigator in a research project funded by Lantmännen.
 K. Katina: Principal investigator in research projects funded by Lantmännen.
 M. Kolehmainen: None.
 C. Kyrø: None.
 M. Langton: None.
 E. Nordlund: None.
 H. Nygaard Lærke: None.

A. Olsen: None.
 K. Poutanen: Board member of the company Leipurin.
 A. Tjønneland: None.
 R. Landberg: Project leader and budget administrator for the Nordic Rye Forum, for which funding is provided by industrial partners and NKJ. Principal investigator in research projects funded by Lantmännen and Barilla. No remuneration, salary, or any other financial recompense from the food industry.

Acknowledgements

This review was produced jointly by researchers from the Nordic Rye Forum (www.nordicryeforum.info), a platform initiated by Nordic researchers that involves academics and industries with a joint interest in rye and health. The review was based on results presented at the conference ‘The Power of Rye’ organized by the Nordic Rye Forum in Åland, Finland, in June 2017. We thank all presenters for their informative presentations, and industries participating in the Nordic Rye Forum (Fazer, Lantmännen, Leksandsbröd, Pågen, and Wasa/Barilla) for financial support. The Nordic Joint Committee for Agricultural and Food Research (NKJ) is also acknowledged for financial support of the Nordic Rye Forum. We also gratefully thank Mary McAfee, ScanText (Wiltshire, England), for skillful and efficient proofreading of the paper.

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