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REVIEW

Ancient wheats: beneficial effects on insulin resistance

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ABSTRACT

Non-alcoholic fatty liver disease and type 2 diabetes mellitus are two conditions that commonly co-exist in the context of metabolic syndrome. Several scientific advances in understanding this association have identified insulin resistance as the key point in the pathogenesis of both diseases. The first line treatment suggested in the management of these diseases is represented by lifestyle changes, and in particular, the modification of alimentary regimen, with the transition to a healthy diet. In this context, several studies have focused their attention on the identification of food products with beneficial actions, like ancient wheat (AW). AW is defined as the early cereals that were domesticated in their places of origin in the "Fertile Crescent" of the Middle East, and played a central role as a main source of food for the early civilizations in that region. The present narrative review aims at providing a systematic overview of the state of the art on the effects of AW on insulin resistance.

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Insulin resistance is clinically defined as a condition in which the body becomes less sensitive to insulin, and subsequently, higher levels of this hormone are required to maintain the metabolic equilibrium.[1] Insulin resistance is increasingly recognized as an important pathogenetic step in pathways leading to the development of the main non-communicable diseases, and in particular heart disease, stroke, cancer and diabetes.[2, 3] Also, the global increase in prevalence of metabolic syndrome emphasizes the need for the development and definition of healthy alimentary regimens. Additionally, non-alcoholic fat liver disease (NAFLD) is directly related to metabolic changes, and up to now there is no definite treatment for this disease.[4] Although the pathogenesis of NAFLD has not been yet fully understood, insulin resistance is identified as crucial for NAFLD progression and 70-80% of obese and diabetic individuals receive a diagnosis of NAFLD. Moreover, hyperinsulinemia and dyslipidemia are more pronounced when type 2 diabetes mellitus (T2DM) is associated with NAFLD.[5]

The first step of treatment for both insulin resistance and NAFLD is the introduction of favorable nutritional and lifestyle habits. Therefore, recently, research interests have focused on the identification of food products with beneficial actions on insulin resistance and its associated diseases, like ancient wheat (AW). AW is defined as the early cereals that were domesticated in the "Fertile Crescent" of the Middle East, and played a central role as a main source of food for the early civilizations in that region. However, since then, human dietary habits have undergone significant changes, especially during the last century.

With the increase in the number of patients with celiac disease and non-celiac gluten sensitivity, the assumption that AW possesses better nutritional properties in comparison to modern wheat has provoked scientists to investigate their potential as functional food.[6] Although AW has attracted growing attention in recent years, the vast majority of studies that investigated the role of AW in insulin resistance and NAFLD were conducted in animals rather than humans.

The present narrative review aims at providing an overview of the state of the art on the effects of AW on insulin resistance.

Botany of AW

Poaceae Barnhart (Order Poales) is one of the biggest botanical families in the world with approximately 11,506 species belonging to 768 genera.[7, 8] This family includes spontaneous and domesticated plants, also commonly known as "grasses." Among all, cereal grasses or simply "cereals" are the cultivated grasses whose seeds are used as food, due to their high content in carbohydrates and proteins.[9] Wheat is one of the three most representative cereal crops of the world.[7, 10]

Wheats are several taxonomical entities belonging to the genus *Triticum* L., whose taxonomy is very controverted and has been studied by many authors.[11, 12] This genus belongs to the tribe Triticeae Dumort subfamily Pooideae Benth., and includes 18 different species that follow a C3 photosynthetic pathway.[8] Over time, several domestic varieties among wheat species have been selected, beginning with genus *Aegilops* L., and it was possible thanks to their ability of self-pollination.[13, 14]

Bordoni *et al.* defined "ancient wheat" the medley of wheat used by ancient civilizations.[15] On the contrary, modern wheat is made up of homogeneous strains, which are the result of intensive breeding programs usually started after World War II.[15] The AW are: *Triticum monococcum* L. (einkorn), *Triticum turgidum* L. subsp. *dicoccum* (Schrank ex Schübl.) Thell. (emmer) and *Triticum aestivum* L. subsp. *spelta* (L.) Thell. (spelt). Table I briefly summarizes the scientific names, in accordance with Global Biodiversity Information Facility (GBIF) and Plants of the World Online (POWO),[16-18] alongside chromosome number and systematic order.[19-22] The varietal diversity is particularly high in the south of Italy,[23] and several studies have increased our knowledge on AW in this geographical area.[24, 25] It is also possible to find several ethnobotanical uses of these wheats in Southern Italy.[26]

Components of AW

In the last decade, there has been growing interest in the consumption of AW, which often derives from the belief that they contain superior antioxidant and anti-inflammatory properties than modern wheats. Because they provide more vitamins, minerals and bioactive compounds. Although several studies investigated

Table I.—*Scientific names, synonyms, English names, native ranges (according to Global Biodiversity Information Facility [GBIF] and Plants of the World Online [POWO], and chromosome number of ancient wheats.*

	Triticum mococcum L.	*Triticum turgidum* L. subsp. *dicoccum* (Schrank ex Schübl.) Thell.	*Triticum aestivum* L. subsp. *spelta* (L.) Thell.
Synonyms	*Crithodium monococcum* (L.) Á. Löve, *Nivieria monococca* (L.) Ser.	*T. dicoccum* Schrank *ex* Schübl., *T. dicoccon* Schrank	*T. spelta* L.
English name	Einkorn	Emmer	Spelt
Native range	SE Europe to Afghanistan	SE Turkey	W Transcaucasus
Chromosome number	Diploid wheat (2n=2x=14)	Tetraploid wheat (2n=4x=28)	Hexaploid wheat (2n=6x=42)

the contents and the composition of AW species, especially spelt, definitive comparisons of these species with modern wheats are rare in the literature.[27, 28] This is because AW species are usually grown in organic or traditional low input farming systems, while modern wheat species are usually bred with high input intensive systems. Moreover, it is necessary to analyze sufficient numbers of cultivars grown on multiple sites to be able to distinguish the independent contribution of genotype, environment, or their interactions on wheat composition.[29] AW species mostly contain carbohydrates, proteins, lipids and minerals. In addition to these compounds, they are an important source of other health-related ingredients, above all phytochemicals, vitamins and antioxidants, especially if consumed as a whole-grain.[30]

From a technological point of view, it is possible to divide wheat proteins into two groups: gluten proteins (gliadins and glutenins, 80-85%) and non-gluten (albumins and globulins, 15-20%) fractions. Glutenins can provide strength and elasticity to dough, whereas gliadins are proteins responsible for dough viscosity.[31] When subjected to gastrointestinal digestion, each component of wheat grain protein breaks down into a vast variety of peptides with variable lengths. Comparisons of ancient and common wheats revealed that grain protein content of AW is commonly superior to those of the modern wheats. This fact can be explained by the bigger and heavier grain of modern wheats that yields a larger starchy endosperm, which, in turn, lessens its protein content.[19]

Carbohydrates account for the most abundant fraction (about 65% to 75%) of the wheat, with starch as the main storage constituent. Starch is composed of amylose and amylopectin which are α-D-glucose polymers of different structures intertwined to form a starch granule. Amylose is easily hydrolyzed by amylase enzymes to maltose, while amylopectin is degraded to maltose (approximately 60%) and dextrins (approximately 40%). Total starch can be divided into rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS). Starch provides an excellent source of energy and influences the level of glycaemia.[32]

Antioxidants in AW

Some researchers showed differences between ancient and modern wheats, arguing that the former is better from a functional point of view. Others, however, claimed that genetic has improved modern grains both from a technological and functional point of view.[33-37] Finally, the analysis of functional components of the grains of both ancient and modern hard wheat, showed that the values of 70 phenolic compounds, including coumarins, phenolic acids, anthocyanins, flavones, isoflavones, proanthocyanidins, stilbenes, and lignans are, two times or more, higher in ancient than in modern wheats. Thus, AW offers unique nutraceutical values that are absent in modern wheats.[38] Some authors tried to analyze the profiles and the distribution of lignans in the whole grain of soft wheat, as they are compounds with beneficial effects on human health. Lignans such as arctigenin, hinokinin and syringaresinol were present only in AW.[39] The same research group investigated the health properties of various ancient and modern soft wheats and confirmed that the grains of ancient varieties generally contain considerably more phenols, flavonoids, coumarin, stilbene, proanthocyanidin and lignans than the modern ones.[40]

Keeping in mind that oxidative stress affects not only insulin sensitivity but also β-cell mass, natural polyphenols could prevent disease and help in health maintenance primary *via* free radical scavenging.[41] Based on recent scientific data, the highest level of phenolic compounds is measured in the bran of different wheat grains.[42] The antioxidative activity of AW mostly depends on the content of free and bound flavonoids, as well as the flavonoids/polyphenols ratio.[27] Regarding carotenoids, it has been suggested that lutein is present in several times higher concentration in AW species, especially einkorn.[6] This is of great importance considering the anti-inflammatory and antioxidant properties of this compound. Lutein supplementation could improve insulin sensitivity and may have positive effects on NAFLD through the decreased hepatic lipid accumulation.[43] Among the glycoflavonoid pigments present in wheat, vicenin-2 and iso-orientin are identified as promising agents.[44] It has been suggested that vicenin-2 has antidiabetic properties via the short- and long-term promotion of glucose-stimulated insulin secretion. This effect is absent at low glucose concentration.[45] Also, the administration of iso-orientin appeared to significantly reduce oxidative stress and glucose level in the blood of a rat model.[46] Still there is no study that investigated the association between the content of the above-mentioned substances in different wheat species and insulin resistance.

A study comparing the effect of the cultivation environment, the genotype of wheat and their interactions on the phytochemical composition of the grain of different soft wheats has shown that, in general, the environment has a greater influence on the beneficial effects of the bran components with respect to genotype and genotype-environment interaction. The environment has a greater impact on the content of α-tocopherol, δ-tocopherol, total tocopherols, total phenols, ferulic acid and antioxidant capacity.[47]

A more recent study on soft AW, wanted to ascertain the optimal balance between the presence of secondary metabolites having beneficial effects both on health and technological characteristics. The results confirmed the significant effect of the environment on the various parameters considered. Some AW (*i.e.* Verna and Gentil Rosso varieties) showed the best values for the antioxidant properties of polyphenols, as well as the protein and gluten content compared to the modern commercial ones (*i.e.* Palesio variety). Therefore, there are AW good for both health and industry.[34]

Insulin resistance

Reduced insulin sensitivity in peripheral tissues leads to hyper-insulinemia in order to maintain glucose homeostasis. Over time, elevated glucose levels in blood can hinder β-cell function and worsen insulin resistance. The progression of both states causes the aggravation of T2DM.[48, 49]

Chronic hyperglycemia induces both oxidative stress and inflammation (Figure 1) and may disrupt the regulation of gene expression. β-cells exposed to chronic hyperglycemia eventually fail at producing insulin and β-cell mass is lost to apoptosis.[50] At a molecular level, elevated glucose concentrations in blood cause overpro-

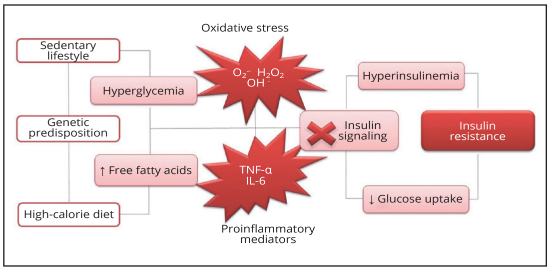

Figure 1.—The role of oxidative stress and inflammation in insulin resistance onset.

duction of endogenous reactive oxygen species (ROS) as superoxide, hydrogen peroxide, and hydroxyl radical ions in the mitochondria and peroxisomes, therefore fostering oxidative stress. ROS are generated mainly at complex I (NADH CoQ reductase) and complex III (bc1 complex). ROS act as signaling and damaging agents and are involved in pathogenesis of insulin resistance.[49, 51] Overproduction of ROS leads to the damage of proteins, DNA, membrane lipids and causes mitochondrial dysfunction, in a self-sustained vicious cycle. Indeed, insulin resistance is associated with mitochondrial abnormality in number and morphology as well as decreased ATP synthesis and oxidative enzymes levels.[51]

In physiologic conditions, when insulin is attached to the insulin receptor, glucose transporter 4 is activated and glucose is transported into the cell. Insulin resistance is linked to the impairment of insulin signaling, which causes less sensitivity of skeletal muscle, liver and white adipose tissue to insulin. The impairment of intra-cellular components of the insulin signal transduction pathway, such as IRS-2, PKB, FOXO proteins and PI-3 kinase (p85 subunit), has been observed *in vivo*.[52] However, abnormalities in lipid metabolism also occur. Increased levels of free fatty acids in blood trigger the accumulation of lipids in skeletal muscle, liver, heart, and β-cells and reduces glucose uptake stimulated by insulin. Inappropriate synthesis of lipids from the liver may also be promoted due to the less pronounced antilipolytic insulin effect. Therefore, insulin resistance is strongly associated with NAFLD.[51, 52]

The role of inflammation in insulin resistance is complex. Mainly c-Jun N-terminal kinase (JNK) and IKKβ nuclear factor-κB signaling pathways are involved in the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and IL-1β[53]. Activation of these pathways leads to the phosphorylation of insulin receptor substrates at their inhibitory sites and results in insulin resistance. Adipocytes, macrophages and dendritic cells in adipose tissue are responsible for releasing cytokines and play a major role in linking insulin resistance and inflammation. Beside these mechanisms, insulin resistance may be induced by reduced glycogen synthesis, resulting from the stimulus of IL-6. Finally, mitochondrial impairment triggered by ROS production may activate NLRP3 inflammasome pathway, responsible for the production of pro-inflammatory cytokines IL-β and IL-18.[53, 54]

AW and NAFLD

Non-alcoholic fatty liver disease (NAFLD) is a complex pathology characterized by an unclarified etiopathogenesis. Nonetheless, it has been shown that obesity, the imbalance of lipid metabolism and insulin resistance, plays a fundamental role in the development of NAFLD.[55] Furthermore, oxidative stress and inflammation are responsible for the progression of NAFLD. Currently, change of lifestyle and diet represent the therapeutic gold standard.[56] Hence, the need to identify food products with therapeutic actions emerges clearly. In this regard, AW has shown promising activities.

The main part of *in-vivo* and *in-vitro* studies available in literature were focused on antioxidative potential of AW, and in particular Kamut®. Usually called khorasan wheat, it is a registered trademark of Kamut International Ltd. The cultivation of Kamut® apparently started in the Middle East and subsequently expanded to the Mediterranean area. The exact taxonomy identification is still debated, nevertheless, Kamut® is considered an ancient relative of durum subspecies, and in particular a form of *T. turgidum*. Experimental investigations performed in cultured liver cells treated with *in-vitro* digested cookies supported the hypothesis about antioxidative and anti-inflammatory properties of Khorasan wheat in comparison to modern wheats.[57]

The first attempt to compare the impact of ancient and modern wheat, cultivated under the same conditions, on human liver HepG2 cells was made by Valli *et al.*[58] HepG2 cells were treated with ultra-filtered digesta after *in-vitro* digestion. Both total antioxidative capacity (TAC) and total phenolic content were increased in digesta of all analyzed breads except the one made of modern wheat (Redwin), for which a significant decrease of TAC was recorded. Although differences in nutritional profiles and selenium content between wheat species were not observed, cell viability was increased in cells supplemented with AW in basal condition (Kamut® khorasan bread and spelt bread). Supplementation with AW as well as with some heritage wheat (Turkey red) decreased the intracellular concentration of ROS. Pretreatment with modern wheats was able to increase the intracellular concentration of ROS and IL-8 production, where as only supplementation with Kamut® Khorasan bread reduced IL-8 produced by HepG2 cells. IL-8 is a pro-inflammatory agent that induces cytotoxicity. Also, IL-8 serum levels are significantly higher in non-alcoholic steatohepatitis and NAFLD patients.[59, 60] Therefore, the findings of Vali *et al.* suggest the protecting role of AW in NAFLD.[58]

In particular, a significant decrease in total cholesterol, LDL and IL-8 was observed in a study involving 20 healthy volunteers of both genders after 10 weeks of *Triticum aestivum* Verna bread diet.[61] In another randomized, double-blinded crossover trial that was done on 45 healthy volunteers of both genders, the significant decrease in total cholesterol, LDL and blood glucose was also obtained after the consumption of AW (Verna, Gentil Rosso and Autonomia B heritage varieties) in comparison to modern wheat.[35] Consistent with this, similar results were obtained in a study involving 20 healthy individuals assigned to a 10 weeks dietary regimen with pasta obtained from ancient Italian wheats like *Senatore Cappelli*.[62] The above reported clinical trials performed on healthy volunteers imply that the intake of AW products may result in the improvement of antioxidative and pro-inflammatory parameters as well as lipid profile in NAFLD.

Dinu *et al.* conducted an interesting clinical study in order to evaluate the effects of Khorasan wheat on NAFLD patients.[63] The study was carried out on 40 volunteers, who had mild steatosis in 70% of cases and moderate steatosis in the remainder. Participants followed different food regimens either Khorasan wheat-based food products or control wheat products (pasta, bread, crackers, biscuits). The results of the study showed that patients who consumed a diet enriched with Khorasan wheat had a significant reduction in liver enzymes. In particular, a reduction of transaminases level has been observed. On the contrary, the volunteers belonging to the control group presented a significant increase in liver enzymes. Furthermore, a reduction in levels of TNF-α was reported in the Khorasan wheat arm of the study. This finding is of particular relevance since TNF-α is a cytokine associated with the onset of insulin resistance. Among the observed secondary factors, a reduction in IL-1Rα levels was noticed. This is very important because IL-1Rα is correlated with the development of obesity, a factor tightly related to the development of NAFLD and insulin resistance. These findings are in agreement with the previous clinical trials.[64, 65]

Beside the antioxidative status improvement and the significant decrease in glucose, insulin, total cholesterol and LDL, clinical trials revealed that a diet with Kamut® products also resulted in the significant reduction of pro-inflammatory parameters in serum of volunteers (IL-6, IL-12, TNF-α and vascular endothelial growth factor-VEGF). These results are important for the implementation of AW in diet, considering the role of IL-6, TNF-α and VEGF in both insulin resistance and NAFLD pathogenesis. Also, the promising results of Khorasan wheat diet were recently confirmed in a randomized, single-blinded cross-over trial performed on 20 young male athletes. A significant reduction in monocyte chemoattractant protein-1 (MCP-1) level was observed in the blood of participants after 4 weeks of Khorasan wheat diet.[66] MCP-1 has an important role in hepatic inflammation and fibrosis progression, and elevated levels of MCP1 have been recorded in NAFLD patients and are correlated with obesity and glucose homeostasis.[67]

These studies gave promising results about AW induced anti-inflammatory and antioxidative properties, and suggested that consumption of AW in human diet may prevent NAFLD progression, probably via the modulation of insulin resistance. Further clinical trials performed on a larger number of volunteers with diagnosed NAFLD associated with insulin resistance are needed in order to confirm the obtained results.

AW and insulin resistance

Besides polyphenols, one of the most interesting compounds of AW is gliadin, an oligopeptide characterized by the concatenation of different amino acids which can be found in four different forms α, β, γ, and ω.[68] It has been a subject of particular interest because of its promising effect in type 1 diabetes mellitus (T1DM). T1DM is a particularly insidious chronic autoimmune disease, characterized by the destruction of β-pancreatic cells by the components of immune system.[69] Besides insulinopenia, insulin resistance is also pronounced in T1DM. In addition to insulin therapy, insulin resistance should also be treated in T1DM in order to decrease the insulin dose requirement.[70] Unfortunately, despite the increase in knowledge regarding this pathology, a definitive therapeutic solution seems to be still far away.

The quest for new therapeutic options brought researchers to evidences that treatment with 50 μg of gliadin for one month in non-obese diabetic mice reduces the incidence of disease by 56% compared to mice treated with gluten and ovalbumin.[71] Zucker diabetic fatty rats and non-obese diabetic mice were used as model to compare effects caused by AW and modern wheat varieties.[72, 73] In the study performed on non-obese diabetic mice, lower incidence of T1DM was observed for AW varieties (*T. aestivum*, *T. turgidum* subsp. *dicoccoides*, *T. turgidum* subsp. *dicoccum*) and a reduction in cholesterol, glucose and IFN-γ was noticed for all AW species together with the increase in insulin and IL-10 levels. All of that imply that AW may reduce the incidence and related complication of T1DM.[27, 73] The impact of AW diet, in particular spelt, emmer and einkorn, on glycaemia, lipid profile and expression levels of hepatic genes involved in glucose and lipids metabolism were evaluated in Zucker diabetic fatty rats. Refined wheat flour was used as negative and whole grain rye flour was applied as positive control. After 9 weeks of diet, PPARα, GLUT2, and SREBP-1c hepatic genes were down regulated in the emmer group of rats while SREBP-2 expression was reduced in emmer, einkorn, and even rye group compared with the negative control group. These genes are important for metabolism of glucose and lipids. Both groups fed with spelt and rye exhibited lower acute glycemic response while increased HDL and total cholesterol were observed in the group fed with refined wheat.[72]

Although preclinical studies have revealed AW health benefits, the number of clinical trials related to AW role in insulin resistance is still limited. Bakhøj *et al.* compared the effects of AW einkorn and modern wheat (*Triticum aestivum*) on the modulation of post prandial insulin and glucose levels via affecting the gastrointestinal response of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1).[74] This study was performed on a small number of patients (11, males), and no significant differences were observed in GLP-1, insulin and glucose response. However, the bread made of einkorn appeared to significantly decrease the postprandial release of GIP. It is necessary to point out that the obtained results need to be taken with caution. The differences in fiber content between refined and non-refined flours as well as the fact that reliable indexes of insulin resistance, such as the homeostatic model assessment (HOMA) index, have not been measured. More recently, a clinical trial performed on healthy volunteers suggested that the intake of AW product may result in the improvement of glycaemia and lipid profile.[35]

Hence, Yenagi *et al.* compared the effects of bread made of *T. dicoccum* (emmer) with bread from *T. aestivum*, during a 6 weeks parallel clinical trial performed on 22 diabetic patients of both genders (6 under insulin therapy).[75] A statistically significant decrease in total lipids, triglycerides and LDL was observed in individuals assigned to the emmer diet. According to these studies, it is plausible that AW have the potential to reduce cardiovascular risk factors related to T2DM. A recently published randomized parallel arm study performed on 30 healthy volunteers has demonstrated diabetes-preventive properties for AW.[76] Kamut®, a genotype of Khorasan wheat (*T. turgidum* subsp. *turanicum*), was compared to modern wheat. Volunteers assigned to Khorasan wheat products manifested a reduction in fat mass and insulin, while a significant increase of the docosaesaenoic acid (DHA) was measured.[76] Although this study was carried out on a small number of patients, the obtained results support the hypothesis by Whittaker *et al.* that the consumption of AW is associated with a reduction of fat mass and risk factors related to T2DM.[77, 78] In a randomized, double-blinded crossover trial, performed on 21 T2DM patients of both genders, for 8 weeks, bread, pasta, crackers and biscuits made of semi-whole flour composed of AW (the Khorasan group) or modern wheats (the control group). A reduction in LDL and total cholesterol as well as insulin, glucose, ROS, VEGF and IL-1ra was observed, while a significant increase in total antioxidant capacity occurred in individuals on AW diet.[77] Therefore, the AW diet appeared able to reduce some markers related to the development of insulin resistance and T2DM compared to modern wheats, but more studies are needed to confirm these findings. These data suggest that the possible AW role in improving insulin sensitivity might be mediated by the reduction of oxidative stress and attenuation of inflammation.

Research limitations

Overall, the described studies supply the evidence of a general beneficial effect of AW on diabetes and related comorbidities, but several limitations have emerged during the review process. First, the number of *in-vitro* and *in-vivo* studies comparing different types of AW (einkorn, emmer and spelt) with modern ones is limited. Furthermore, the control wheat in most clinical trials was grown in different conditions and the interactions between genotype and environment were not considered. Most of the studies have been performed on animal models and featured the use of extracts or lysates instead of finished products, consequently, the influence of digestion was omitted. In addition to this, results from animal models cannot be immediately extrapolated to humans. The few clinical trials performed involved small numbers of patients and tested different wheat varieties. Most of the studies were focused on Kamut® (khorasan wheat) which is related to "the tetraploid Italian wheat Graziella Ra®." However, Colomba *et al.* comparative analysis has revealed that they are similar but their genome is distinctive.[79, 80]

Conclusions

The influence of the diet in the onset of insulin resistance has been thoroughly reported. Nowadays, the cornerstone in its clinical management includes two easy concepts that are dietary modification associated with improvement of physical activity, also defined as lifestyle changes. In the era of evidence-based medicine, it is possible to underline the role of a healthy alimentary regimen in a medical approach focused on preventing a spectrum of chronic diseases, including metabolic disorders.

Based on the results obtained from animal and clinical trials, the role of AW in the management of insulin resistance is mostly related to the antioxidative and anti-inflammatory properties of wheat components, particularly polyphenols. Despite this acknowledgement, a large body of evidence is still needed in order to state that AW diet is superior to modern varieties. Further extensive comparative studies, performed on large numbers of individuals, investigating the differences between ancient and modern grains, taking into account the differences in content of fiber, polyphenols, and the environmental conditions are necessary.

The present review addresses several aspects that could propel researchers to expand knowledge about AW in order to better understand the exact metabolic mechanisms involved and to clarify their antioxidant and anti-inflammatory properties.

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