



Analysis of the Current Status of Research on Interventions Using Whole-Grain Foods to Regulate Key Enzyme Activities in Glycolipid Metabolism for the Management of Type 2 Diabetes

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SUMMARY: *Whole grain foods are rich in dietary fiber and phytochemicals, and they have significant potential in improving the glycolipid metabolism disorder of type 2 diabetes mellitus (T2DM). This article reviews the current research status and mechanism of action of whole grain foods in regulating T2DM by modulating key enzyme activities. The research focuses on the regulatory effects of whole grain foods on enzymes related to glucose metabolism and key enzymes of lipid metabolism. At the same time, it analyzes how dietary fiber in whole grain foods improves intestinal microecological environment, enhances insulin sensitivity, and thereby alleviates metabolic disorders. The study shows that whole grain foods mainly exert their effects through two pathways: one is directly regulating the activity of key enzymes in glycolipid metabolism, including upregulating glucose kinase and glucose-6-phosphate dehydrogenase to promote glucose utilization, while inhibiting fatty acid synthase and activating fatty acid oxidase, thereby improving hyperglycemia and hyperlipidemia; the other is reshaping the intestinal microecology through dietary fiber, and indirectly enhancing insulin sensitivity. Although studies have shown that whole grain foods have certain intervention potential for T2DM, differences in types of whole grain foods, intake amounts, and study populations may lead to heterogeneity in intervention effects. Therefore, future research needs to further reveal the mechanism of action of whole grain foods in regulating glycolipid metabolism and assess their practical application potential in clinical treatment. In summary, whole grain foods as potential auxiliary treatments for T2DM have important research value.*

Povzetek: *Based on the analysis of the abnormal characteristics of key enzymes involved in lipid metabolism in type 2 diabetes, this article systematically summarizes the research progress of whole-grain foods in regulating lipid metabolism from three aspects: the dietary fiber and phytochemical composition of whole-grain foods, the evidence from animal experiments, and multi-omics and computer modeling. The article focuses on the chain of "whole-grain - key enzymes - intestinal microecology - metabolic phenotype", summarizes the current advantages and limitations of the evidence, emphasizes that whole-grain is more suitable as an auxiliary intervention in the long-term dietary management of T2DM, and provides theoretical references for the subsequent optimization of whole-grain variety selection, processing methods, and individualized dietary strategies.*

KEYWORDS: *Whole grain foods; Type 2 diabetes; Glycolipid metabolism; Key enzyme activity; Gut microbiota; Computer modeling*

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1 Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized mainly by insulin resistance and impaired function of pancreatic β cells. Patients are chronically exposed to high glucose, high lipid, and low-level inflammation, and the disorder is characterized by disordered glycolipid metabolism throughout its entire course. Increasing evidence indicates that constructing comprehensive intervention strategies starting from glucose and lipid metabolism and their key enzymes is an important direction for delaying the disease course and reducing the risk of complications.

In terms of lifestyle and dietary intervention, Liu *et al.* found that resistant starch in potatoes can improve the inflammatory levels, glycolipid metabolism indicators, and intestinal microbial environment of T2DM patients [1]; Wu *et al.* used network Meta-analysis to compare different physical and mental exercise methods and confirmed that appropriate physical and mental exercise is conducive to overall improvement of blood sugar and lipid levels [2]. Population and lipidomics studies further revealed the importance of abnormal glycolipid metabolism: Langitan *et al.* described typical abnormal glucose and lipid profiles in T2DM patients in Indonesia [3], and Zhang *et al.* used Mendelian randomization methods to prove that specific plasma lipid composition has a causal relationship with T2DM [4]. In terms of active substances and treatment methods, Cai *et al.* reported that liposome silymarin can improve glucose and lipid metabolism in T2DM patients with non-alcoholic fatty liver disease [5], and Han *et al.* proposed to evaluate the impact of electrotherapy on T2DM patients' glycolipid metabolism indicators through a systematic review [6]. Regarding the interaction between intestinal microecology and host metabolism, Zhong *et al.* integrated randomized controlled trials and found that supplementation of *Lactobacillus plantarum* is beneficial for improving blood sugar and lipid levels in patients with type 2 diabetes and impaired glucose regulation [7]; Xiao *et al.* confirmed in animal models that oxygenated drinking water can alleviate metabolic abnormalities by regulating the intestinal microbiota and enhancing glucose metabolism in skeletal muscle [8]. Drug and genetic studies also highlight the core position of the glycolipid metabolism pathway from another perspective: Burggraaf *et al.* found that the SGLT2 inhibitor dapagliflozin can improve post-meal lipid metabolism while lowering blood sugar [9]; Li *et al.* in the Chinese population confirmed that genetic polymorphisms related to lipid metabolism are closely related to the susceptibility of T2DM [10].

In summary, different types of studies jointly point to the same fact: The occurrence and development of T2DM are closely related to the glycolipid metabolism network and its key regulatory enzymes, and inflammatory responses, intestinal microecology, and signaling pathways interact with each other in this process. Compared with studies focusing on a single component or a single therapy, whole-grain foods, such as whole wheat, have the potential to achieve more realistic dietary intervention through simultaneously influencing the activity of key enzymes in glycolipid metabolism, the intestinal microbiota, and related signaling axes. However, the existing evidence is scattered and distributed in individual animal experiments or preclinical studies, lacking systematic reviews starting from key enzymes in glycolipid metabolism, metabolic pathways, and animal models. It is necessary to build on previous work and combine computer-assisted metabolic networks and multi-omics analysis methods to review the current research status of whole-grain foods regulating the activity of key enzymes in glycolipid metabolism for type 2 diabetes and provide theoretical support for the construction of a glycolipid metabolism intervention strategy centered on whole-grain diets.

2 Overview of Glycolipid Metabolism Disorder and Key Enzyme Activity in Type 2 Diabetes Mellitus

2.1 Functions of Key Enzymes in Glucose Metabolism and Their Abnormal Manifestations in T2DM

Glucose metabolism depends on a series of rate-limiting enzymes and regulatory enzymes, which jointly determine the body's uptake, utilization, and production of glucose. The liver and skeletal muscle are the main tissues that maintain blood glucose homeostasis. Among them, hexokinase/glucokinase (HK/GK) and other key glycolytic enzymes promote glucose breakdown, glycogen synthase (GS) regulates glycogen synthesis, and glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) dominate hepatic gluconeogenesis. Glucose-6-phosphate dehydrogenase (G6PD) provides NADPH through the pentose phosphate pathway to maintain cellular antioxidant levels. These key enzymes are regulated by insulin/hormone-sensitive glucagon and nutritional status in a comprehensive manner, forming a relatively balanced glucose metabolism network [3, 4].

In the state of type 2 diabetes, this network is systematically disrupted. In the liver, G6Pase and PEPCK are upregulated, while HK and other glycolytic enzymes are downregulated, resulting in enhanced hepatic gluconeogenesis, even under hyperglycemic conditions, and continuous glucose output to the blood, which is an important source of fasting hyperglycemia. Insulin resistance in skeletal muscle is accompanied by a decrease in GS activity, and the ability of peripheral tissues to take up glucose and synthesize glycogen is weakened, with blood glucose maintained at a high level after meals. At the same time, multiple studies suggest that the activity of G6PD is reduced in T2DM patients or model animals, with insufficient NADPH supply, and increased oxidative stress levels, further damaging pancreatic β -cells and the insulin signaling pathway, forming a "high glucose - oxidative stress - insulin resistance" vicious cycle. Overall, the abnormality of key enzymes in glucose metabolism synergistically promotes hyperglycemia and metabolic imbalance, providing potential intervention targets for regulating these target enzymes from dietary factors [32].

2.2 Function of Key Lipid Metabolism Enzymes and Their Relationship with Insulin Resistance

Key lipid metabolism enzymes mainly participate in fatty acid synthesis, oxidation, and the synthesis and breakdown of triglycerides, being an important hub for maintaining lipid levels and fat distribution patterns. Among them, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) dominate the "new fatty acid synthesis" from acetyl-CoA to long-chain fatty acids; carnitine palmitoyltransferase-1 (CPT-1) controls the entry of fatty acids into mitochondria for β -oxidation; diacylglycerol acyltransferase (DGAT) catalyzes the final formation of triglycerides; hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) mediate the breakdown of triglycerides in adipose tissue. These enzyme systems are maintained in a balance of "synthesis - decomposition" and "storage - mobilization" under the regulation of insulin, glucagon, and nuclear receptors (such as PPAR α , SREBP-1c) [10].

In the state of type 2 diabetes and its pre-disease state, high-sugar and high-fat diets and chronic inflammation cause an imbalance in lipid metabolism key enzymes. ACC, FAS, and DGAT, etc., enzymes related to fatty acid and triglyceride synthesis are often in a high-expression or high-activity state, while the activity of CPT-1 decreases, resulting in the accumulation of triglycerides and diacylglycerol in the liver and skeletal muscle. Excessive lipids are deposited in non-fat tissues, which is one of the key links in inducing insulin

resistance: lipid intermediates such as diacylglycerol and ceramides can activate protein kinase C (PKC) family, inhibit insulin receptor substrate (IRS) and AKT phosphorylation, weaken the ability of insulin to promote glucose transport and inhibit hepatic gluconeogenesis; at the same time, abnormal activity of HSL and ATGL can exacerbate fat mobilization, causing continuous increase in free fatty acids, and further promoting hepatic steatosis and impaired insulin signaling. The changes in the activity of key enzymes involved in lipid metabolism and the HOMA-IR stratification are shown in Figure 1. Taking data from animal models or population studies as an example, the trend of FAS and CPT-1 activities changing with the stratification of the insulin resistance index (such as HOMA-IR) is visualized: As the HOMA-IR increases from 1.5 to 4.5, the FAS activity can increase by approximately 30% to 40% relative to the baseline, while the CPT-1 activity decreases by about 20% to 30%. The two lines show opposite trends, directly reflecting the positive correlation between "synthesis enhancement, oxidation inhibition" and the degree of insulin resistance.

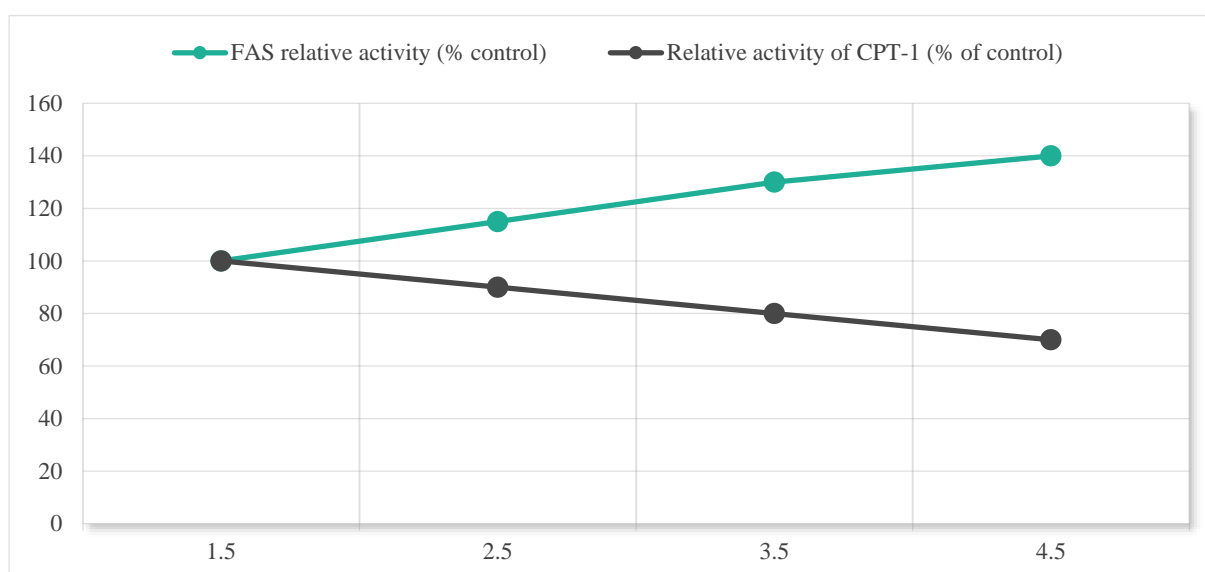


Figure 1: Line chart showing the changing trends of the activities of key enzymes in lipid metabolism and HOMA-IR stratification.

The trend shown in Figure 1 can further emphasize that the abnormality of key enzymes in lipid metabolism not only leads to hypertriglyceridemia and fatty liver, but also plays a core role in the formation and maintenance of insulin resistance in T2DM through lipid toxicity and interference of signaling pathways, providing an important pathological basis for subsequent regulation of these target enzymes at the level of dietary factors such as whole grains.

2.3 Changes in the activities of key enzymes in glycolipid metabolism and association with the course and complications of T2DM

The abnormality of key enzymes in glycolipid metabolism is not static but progresses gradually with the prolongation of the course of T2DM and the accumulation of complications. In the early stage, the body can maintain a relatively stable metabolic state through insulin secretion compensation and regulation of partial enzyme activities, such as a slight decrease in liver glucokinase (GK), a slight increase in glucose-6-phosphatase (G6Pase), limited changes in fatty acid synthase (FAS) and carnitine palmitoyltransferase-1 (CPT-1), and mostly presenting a "high-risk metabolic phenotype" rather than obvious organ damage.

As the disease course exceeds 5-10 years, especially under continuous high sugar, high fat

and low-grade inflammatory stimulation, the disorder of key enzyme activities gradually becomes fixed and amplified. Clinical and animal studies suggest that in T2DM patients with non-alcoholic fatty liver disease (NAFLD), the activities of FAS and G6Pase are significantly increased, while GK and CPT-1 are continuously decreased, promoting lipid deposition in the liver and hyperactivity of hepatic gluconeogenesis; when combined with cardiovascular diseases, the abnormality of lipid synthesis-related enzymes is more likely to be intensified with the formation of atherosclerotic plaques; in the stage of diabetic nephropathy, the levels of oxidative stress and inflammatory factors increase, the upregulation of G6Pase and FAS further increases, the inhibition of CPT-1 and other fatty acid oxidation enzymes becomes more obvious, presenting a "high sugar, high fat, low oxidation" malignant combination [9, 33].

This imbalance of enzyme activity that worsens with the progression of the disease course and the expansion of the complication spectrum can be regarded as the molecular manifestation of the "metabolic memory" in T2DM. The changing trends of the activities of several representative key enzymes in glycolipid metabolism under different disease courses and complication states are shown in Table 1, which is helpful for understanding the characteristics of enzyme spectrum remodeling in the natural course of T2DM from a longitudinal perspective and provides a reference for evaluating the targeted value of whole-grain and other dietary interventions at different stages.

Table 1: Changing trends of the activities of key enzymes in glycolipid metabolism and T2DM disease course and complication status.

Disease course and complication status	GK activity	G6Pase activity	FAS activity	CPT-1 activity
Newly diagnosed T2DM, no obvious complications	Lightly decreased	Lightly increased	Lightly increased	Lightly decreased
Disease course ≥ 5 years, combined with NAFLD	Moderately decreased	Moderately to significantly increased	Significantly increased	
Disease course ≥ 5 years, combined with cardiovascular diseases	Moderately decreased	Lightly increased	Lightly increased	Lightly decreased
Disease course ≥ 10 years, combined with diabetic nephropathy	Significantly decreased	Significantly increased	Moderately to significantly increased	Significantly decreased

3 Mechanism of the effect of whole-grain foods on the activities of key enzymes in glycolipid metabolism

3.1 Composition characteristics of dietary fibers and phytochemicals in whole grains

Whole grain foods retain the bran, endosperm and germ of wheat grains, and are more rich in dietary fibers and various phytochemicals than refined products. Prospective cohort and randomized controlled studies have shown that the intake of whole grains is closely related to a reduced risk of type 2 diabetes and improved blood glucose control [11-13], with wheat being one of the most common sources of whole grains in the dietary structure. Nutritional studies suggest that dietary fibers in whole grains and the accompanying polyphenols, phenolic acids, lignans, etc., are important substances for regulating glycolipid metabolism [18]. From the

perspective of dietary fiber composition, the non-starch polysaccharides in whole wheat mainly consist of arabinogalactan and β -glucan, and contain a certain proportion of resistant starch. Arabinogalactan is mainly distributed in the bran layer and can delay starch digestion in the small intestine, reducing post-meal blood glucose generation. In the colon, it is fermented by intestinal bacteria to produce short-chain fatty acids, providing signaling molecules for subsequent effects on insulin sensitivity and expression of metabolic-related enzymes [18]. β -glucan and resistant starch indirectly buffer the peak glucose load faced by key enzymes by increasing the viscosity of chyme, delaying gastric emptying and glucose absorption, and reducing the pressure on the liver and peripheral tissues caused by long-term high sugar environment.

In terms of phytochemicals, whole wheat bran and germ are rich in phenolic acids (such as ferulic acid), flavonoids, polyphenols, and small amounts of tocopherol and phytosterols. These components have antioxidant, anti-inflammatory and certain lipid-regulating effects. Studies have shown that wheat-derived arabinogalactan preparations and associated polyphenols can improve impaired glucose homeostasis and reduce fasting blood glucose and insulin levels [18], providing clues at the component level for their role in regulating the activity of key enzymes such as glucose anabolism and lipid synthesis.

In specific studies, the dietary fiber and phytochemical contents of different whole grains such as whole wheat, whole oats, and whole barley are often compared to explain the differences in the improvement of blood glucose and lipid levels in intervention trials. Figure 2 presents the relative contents of several typical whole grains in total dietary fiber, arabinogalactan, β -glucan, polyphenols, and resistant starch in a radar chart form, visually reflecting the characteristics of the component combinations of different whole wheat foods and providing a background for understanding the differences in the activity and metabolic phenotype of key enzymes and metabolic profiles described later.

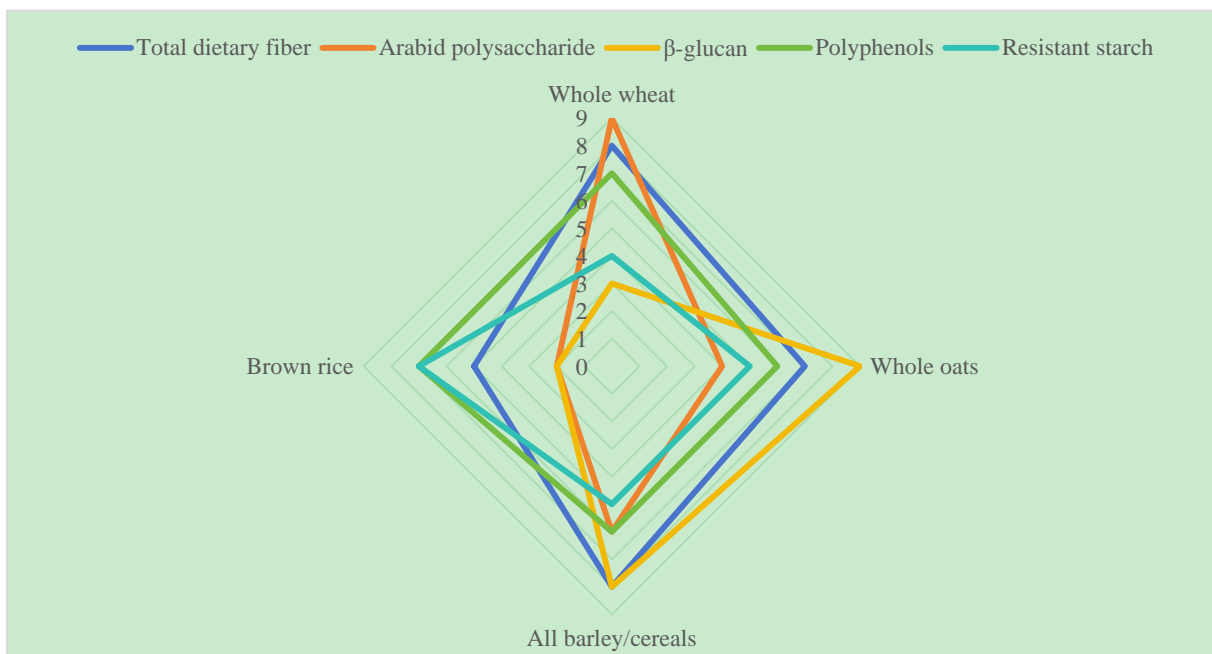


Figure 2: Schematic diagram showing the relative content of different typical whole grains/whole wheat raw materials in terms of major dietary fibers and phytochemicals.

3.2 Direct Regulation of Key Enzyme Activities in Glucose Metabolism by Whole-Grain Foods

When whole-grain foods improve glucose metabolism in T2DM, they do not merely stop at the level of "changing staple foods and lowering blood sugar". Instead, they affect the activity of a group of key enzymes in the liver and skeletal muscles, thereby altering the balance between glucose production and utilization. Current research suggests that whole grains and their dietary fibers are expected to upregulate enzymes that promote glucose utilization, such as glucose kinase (GK) and glucose-6-phosphate dehydrogenase (G6PD), and inhibit enzymes that induce gluconeogenesis, such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), resulting in a decrease in endogenous glucose output in the liver and an enhancement of glucose uptake and glycogen synthesis in peripheral tissues.

In T2DM rats, replacing part of refined staple foods with whole-grain noodles can significantly lower fasting blood glucose, improve oral glucose tolerance, and alleviate insulin resistance [14]. Although the enzyme activities were not individually detected in the experiments, the phenotypes of reduced hepatic gluconeogenesis activity and increased hepatic glycogen content are usually accompanied by upregulated GK expression and downregulated activities of G6Pase and PEPCK, providing indirect evidence for the "whole grains promoting glucose utilization and inhibiting abnormal gluconeogenesis" enzymatic changes [14]. When wheat dietary fibers intervene in db/db mice, blood glucose and HOMA-IR improve significantly, liver inflammatory factors decrease, and the TLRs/NF- κ B/TNF pathway is inhibited [16]. The alleviation of chronic inflammation is conducive to repairing the insulin signaling pathway, thereby restoring the expression of enzymes regulated by insulin, such as GK, G6PD, etc., and inhibiting the abnormal upregulation of key enzymes for gluconeogenesis, such as G6Pase and PEPCK [16].

In population studies, the intervention trials of wheat-derived arabinogalactan concentrates in individuals with impaired glucose homeostasis show a decrease in fasting blood glucose and peak postprandial blood glucose levels, and an improvement in insulin sensitivity [18]. Combined with the results of animal experiments, it can be speculated that whole-grain wheat foods rich in arabinogalactan, by slowing down starch digestion and glucose absorption, alleviating inflammation, and improving insulin signaling, form a comprehensive regulatory effect on key enzymes in lipid metabolism [14, 16, 18]. At present, direct determination of specific enzyme activities and transcriptional levels is still limited. In future standardized animal models, introducing systematic enzymology detection and pathway analysis will help further refine the mechanism by which whole grains regulate key enzymes in glucose metabolism.

3.3 Direct Regulation of Key Enzyme Activities in Lipid Metabolism by Whole-Grain Foods

In T2DM and related metabolic syndromes, the imbalance of key enzymes in lipid metabolism, such as fatty acid synthase, diacylglycerol acyltransferase, and carnitine palmitoyltransferase-1, is an important biochemical basis for abnormal lipid droplet deposition in the liver and skeletal muscles and the aggravation of insulin resistance. Existing studies have shown that whole grains and other whole grains intervention not only help improve blood glucose control but also simultaneously improve lipid profiles and liver fat deposition, suggesting that they have a certain remodeling effect on key enzymes in lipid metabolism and related pathways.

In T2DM rats, replacing part of refined staple foods with whole-grain noodles can reduce serum triglycerides and total cholesterol and alleviate liver steatosis [14]; in mice on a high-fat diet, intake of whole-grain barley slows weight gain, reduces liver fat content and lipid levels

[15]. These phenotypes are often accompanied by decreased activity of the fatty acid synthesis pathway and relatively enhanced fatty acid oxidation pathway. Wheat dietary fibers intervention in db/db mice shows a decrease in lipid indicators and a reduction in inflammatory factor levels, with inhibition of the TLRs/NF- κ B/TNF pathway [16], indirectly supporting the possible transformation of key enzymes in lipid metabolism from a "synthesis tendency" to an "oxidation tendency" from the perspective of inflammatory regulation. Based on this, the directional information regarding the effects of whole wheat and whole grain interventions on lipid metabolism and key enzymes/paths as reported in the literature is presented in Table 2.

Table 2: Effects of whole wheat and whole grain interventions on lipid metabolism and related key enzymes/paths as reported in the literature.

Literature number	Model and intervention	Principal changes in lipid metabolism	Clues on changes in related key enzymes/paths (directional inference)
[14]	T2DM rats, whole wheat noodle diet	Decreased serum TG and TC, reduced liver steatosis	Activity of enzymes related to fatty acid synthesis may decrease, the fatty acid oxidation pathway may be relatively enhanced
[15]	HFD mice, whole grain barley	Slower weight gain, reduced liver fat content, improved lipid profile	Reconfiguration of lipid metabolism-related gene expression, promoting fatty acid breakdown and cholesterol metabolism
[16]	db/db mice, wheat dietary fiber	Improved lipid indicators, accompanied by decreased inflammatory factors	TLRs/NF- κ B/TNF pathway is inhibited, indirectly beneficial to the recovery of fatty acid oxidation enzyme system

3.4 Whole wheat dietary fiber - Gut microbiota - Insulin sensitivity regulation pathway

Whole wheat dietary fiber is difficult to be completely digested in the small intestine and can be utilized by specific bacteria in the colon, forming a continuous regulatory chain of "dietary fiber - gut microbiota - short-chain fatty acids - insulin sensitivity". When whole grain barley is used to intervene in high-fat diet mice, the α diversity of the intestinal microbiota increases, the abundance of beneficial bacteria rises, accompanied by an increase in the production of short-chain fatty acids and alleviation of obesity and liver fat deposition [15]. The application of wheat dietary fiber in db/db mice shows a decrease in inflammatory factors and inhibition of TLRs/NF- κ B/TNF pathways [16], suggesting that the microbiota and its metabolites may indirectly improve insulin signaling through the inflammatory pathway.

The review studies further indicate that various fermentable dietary fibers can act on receptors such as GPR41/43 by regulating the structure of the intestinal microbiota and the spectrum of short-chain fatty acids, reducing the level of low-grade inflammation and improving the responsiveness of the liver and skeletal muscles to insulin [17]. Under this framework, whole wheat dietary fiber is regarded as indirectly influencing the expression and activity of key enzymes related to gluconeogenesis and lipid synthesis by changing the microbiota and metabolite environment. Table 3 summarizes the key links of "whole wheat or dietary fiber intervention - microbiota and metabolite changes - improvement of insulin sensitivity" in several representative studies, providing a basis for the subsequent construction of the "whole wheat - microecology - key enzymes" integrated pathway.

Table 3: Summary of the effects of whole wheat and dietary fiber interventions on gut microbiota and insulin sensitivity.

Literature number	Intervention type	Main changes in the microbiota/metabolites	Changes in insulin sensitivity and metabolic phenotypes
[15]	Whole grain barley, high-fat diet mice	The α diversity increases, beneficial bacteria rise, and the production of SCFA increases.	Body mass increase slows down, liver fat and blood lipid levels decrease, and glucose metabolism improves.
[16]	Wheat dietary fiber, db/db mice	Reduced activity of inflammation-related microbiota and pathways	Fasting blood glucose and HOMA-IR decreased, and the TLRs/NF- κ B/TNF pathway was inhibited.
[17]	Various dietary fibers, review on T2DM-related topics	Fibers promote the growth of acid-producing bacteria and the formation of short-chain fatty acids (SCFAs), while reducing inflammatory factors.	The insulin sensitivity of the liver and skeletal muscles has increased, and the disorder of sugar and lipid metabolism has been alleviated.

3.5 Based on computer, key enzymes - metabolic network modeling and mechanism analysis

In the studies of whole wheat and whole grain interventions, more and more work simultaneously collects multi-dimensional data such as blood glucose and lipid levels, inflammatory factors, composition of gut microbiota, and metabolite spectra [14–17]. Rather than interpreting a single indicator in isolation, it is better to utilize computer modeling and metabolic network analysis to integrate "whole-grain components - key enzymes in sugar and lipid metabolism - signaling pathways - metabolic phenotypes" into the same framework. On the one hand, this allows for the systematic organization and standardization of existing evidence regarding recurring key enzyme nodes, and on the other hand, it provides more targeted hypotheses for subsequent animal experiments and mechanism verification.

In terms of the methodological approach, one can first systematically organize and standardize the enzyme activities, gene expressions, metabolites, and clinical indicators from different studies, and complete the annotation of metabolic pathways by combining databases such as KEGG. Then, the components of whole-grain dietary fiber and arabinogalactan, key enzymes in sugar and lipid metabolism, representative metabolites, and phenotypic indicators can be constructed as directed or undirected networks [15–17]. On this basis, through topological analyses such as node degree, betweenness centrality, and module division, key enzyme nodes with high connectivity or located at the intersection of pathways can be selected. Correlation analysis or regression models can also be superimposed to evaluate the strength and direction of the association between different enzyme nodes and outcomes such as blood glucose, blood lipids, and insulin sensitivity.

Further, scenarios of different whole-grain types, intake doses, or combined dietary patterns can be set up on the network to simulate and predict changes in key enzyme activities and pathway flows, providing theoretical basis for designing more optimized whole-grain intervention combinations. The key enzyme-metabolic network modeling process based on computer is shown in Figure 3, providing a way to integrate scattered whole-grain intervention evidence into an calculable mechanism map.

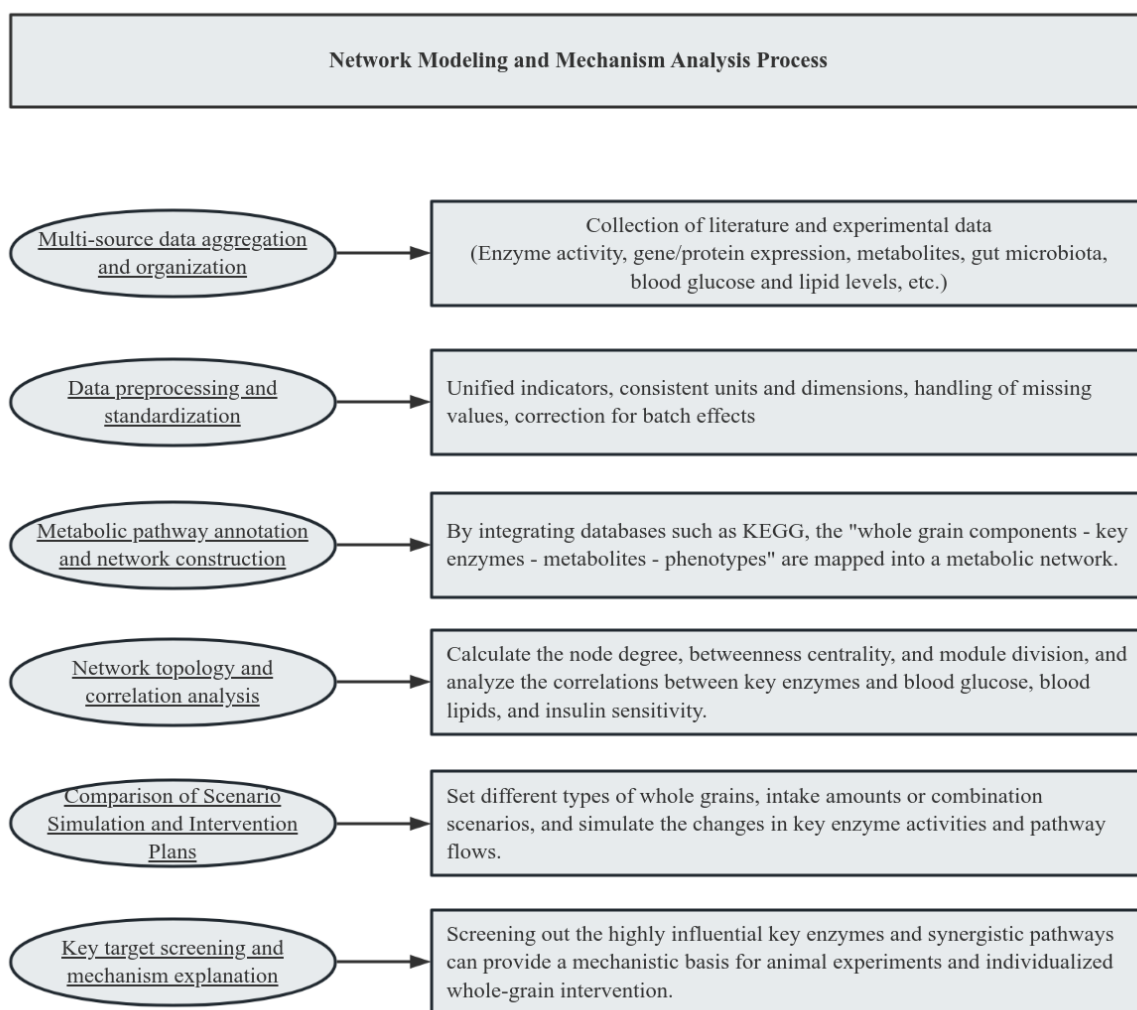


Figure 3: Flowchart of computer-based "Whole Wheat Components - Key Enzymes for Sugar and Lipid Metabolism - Metabolites - Phenotype" Network Modeling and Mechanism Analysis Process

4 Current Status of Animal Experiment Research on the Intervention of Whole Wheat Food on T2DM

4.1 Common T2DM Animal Models and Their Characteristics of Sugar and Lipid Metabolism Phenotypes

Type 2 diabetes animal models provide a relatively stable metabolic disorder basis for the intervention study of whole wheat food. Common models include db/db mice, mice induced by high-fat diet, and the combined model of high-fat diet and streptozotocin (STZ). db/db mice, due to the mutation of the leptin receptor gene, are accompanied by obesity, high blood sugar, and insulin resistance, and are suitable for evaluating the effects of wheat bran dietary fiber and other interventions on sugar and lipid metabolism and inflammatory pathways [19]. C57BL/6J mice fed with a high-fat diet exhibit mild to moderate hyperglycemia, abnormal lipid profile, and hepatic fat deposition, and are often used to observe the effects of whole wheat staple foods and flour layer products [24]. The high-fat + STZ combined model, on the basis of insulin

resistance, adds β -cell damage, and can simultaneously reproduce hyperglycemia and hyperlipidemia, providing a platform for analyzing the regulation of whole wheat and its active components on key enzymes and pathways of sugar and lipid metabolism [25, 29, 32]. Different models have their own characteristics in disease progression, fat distribution, and complication spectrum, and reasonable selection is helpful for more precisely evaluating the targets and mechanisms of whole wheat food intervention in subsequent studies. Common T2DM animal models and their sugar and lipid metabolism phenotypes and applicability are shown in Table 4.

Table 4: Common T2DM Animal Models, Their Sugar and Lipid Metabolism Phenotypes, and Applicability

Model type	Modeling method	Main sugar metabolism phenotype	Main lipid metabolism phenotype	The application characteristics in the whole-grain intervention study	Relevant literature
DB/DB mice	Leptin receptor gene mutation	Fasting hyperglycemia and significant impairment of glucose tolerance	Increased triglycerides and total cholesterol	The phenotype is stable, making it suitable for evaluating the effects of wheat bran dietary fiber on sugar and lipid metabolism enzymes and inflammatory pathways.	[19],[27],[32]
High-fat diet-fed C57BL/6J mice	Long-term feeding with high-fat diet	Mild to moderate hyperglycemia and delayed recovery of post-meal blood sugar levels	Abnormal lipid profile and hepatic fat deposition	More in line with the common "energy surplus" scenario, it is often used to examine the effect of replacing refined grains with whole grain foods.	[20],[24],[28]
High-fat + STZ combined model	High-fat diet combined with low-dose STZ injection	Obvious fasting hyperglycemia, with partial impairment of pancreatic function	High levels of cholesterol	It simultaneously reflects insulin resistance and secretion defects, and is suitable for comprehensive assessment of the regulation of key enzymes and pathways by the active components of whole grains.	[19],[25],[29]
Other examples of whole grain fiber models	HFD or db/db combined with barley bran, buckwheat bran, etc.	Depending on the specific condition, it is more often manifested as high blood sugar or impaired glucose tolerance.	Hyperlipidemia, hepatic steatosis	The results can be compared with the whole wheat model and are used to extract the common mechanism of action of "grain dietary fiber".	[25],[29],[32]

4.2 Summary of the Animal Experiment Results on the Effects of Whole Wheat Intervention on the Activity of Key Enzymes and Metabolic Indicators of Glucose and Lipid Metabolism

Current animal experiments generally indicate that dietary intervention based on whole wheat and cereal bran can simultaneously improve the glucose and lipid metabolism phenotypes of T2DM and high-fat diet models. The carboxymethylated wheat bran dietary fiber significantly reduced fasting blood glucose, the area under the OGTT curve, and HOMA-IR in high-fat + STZ mice, while down-regulating multiple inflammatory factors, providing a basis for its action by remodeling key enzymes and signaling pathways [19]. Wheat germ and its protein in high-fat diet rats can reduce serum TG, TC, and LDL-C, enhance antioxidant enzyme activity, and alleviate hepatic steatosis; wheat bran protein intervention observed a decrease in liver HMG-CoA reductase content and inhibition of the lipid synthesis pathway. Long-term feeding of high-fat mice with whole wheat or flour layer-enhanced Chinese steamed buns also showed comprehensive improvements in fasting blood glucose, insulin sensitivity, and hepatic lipid deposition, accompanied by the coordinated remodeling of intestinal flora and liver metabolic pathways [24].

Apart from wheat, related studies have also reported similar key enzyme regulation effects in whole-grain models such as barley: high-fat/high-sugar mice consuming active components rich in proanthocyanidins and p-coumaric acid from whole-grain barley showed a decrease in liver gluconeogenesis-related enzyme expression and improved glucose tolerance [25, 27]; in high-fat hyperlipidemia or type 2 diabetes models, the PPAR α -mediated lipid oxidation pathway was activated, and lipid levels and hepatic steatosis were significantly alleviated [26, 28]. These results collectively indicate that whole grains and their active components, represented by whole wheat, can improve glucose and lipid metabolism disorders at the animal level by influencing the activity of key enzymes such as those involved in liver glucose production, lipid synthesis, and oxidation, providing experimental evidence for subsequent mechanism analysis focusing on "whole wheat - key enzymes - metabolic network".

4.3 Comparative Analysis of the Differences in Intervention Effects among Different Whole Wheat Varieties, Processing Methods, and Intake Doses

The animal experiment results suggest that the metabolic benefits of whole wheat intervention are not a single pattern, and there are significant differences among different grain varieties, processing methods, and intake doses. Taking wheat as an example, long-term intake of wheat germ or germ protein by high-fat diet rats can significantly reduce serum TG, TC, and LDL-C at similar energy levels and enhance antioxidant enzyme activity [21]; while with wheat bran protein as the main intervention component, the decrease in liver HMG-CoA reductase content is more prominent, suggesting a direct impact on the cholesterol synthesis pathway [22]. In terms of the form of staple food, whole wheat or flour layer-enhanced Chinese steamed buns, when compared with refined controls, are more conducive to controlling fasting blood glucose, improving insulin sensitivity, and reducing hepatic lipid deposition in high-fat diet mice [24], indicating that the increase in whole wheat proportion can bring considerable metabolic differences under processing conditions close to the real dietary structure.

Studies on other whole-grain varieties such as barley emphasize the importance of phytochemicals and processing modifications. The combination of proanthocyanidins, p-coumaric acid, epicatechin, and β -glucan from whole-grain kernels shows a synergistic effect on glucose tolerance improvement and activation of the PPAR α -mediated lipid oxidation

pathway in different T2DM or high-fat models [25–27]; physically modified barley shows more significant relief of liver lipid deposition and inflammatory responses in high-fat/high-cholesterol diet mice [28]. These results indicate that under the same energy supply, the gradient design of grain varieties, structural parts (germ, bran, flour layer), processing techniques, and whole wheat proportion will affect the response intensity of key enzymes and related pathways involved in glucose and lipid metabolism through changes in dietary fiber types and phytochemical spectra. Table 5 summarizes the differential results related to "variety - processing - dose" in the main animal studies.

Table 5: Comparative Overview of the Effects of Different Whole Wheat Varieties, Processing Methods, and Intake Doses on Glycolipid Metabolism in T2DM Animal Models.

Document Number	Grain/variety and structural part	Processing form and intake level	Animal model	Main effects of sugar and lipid metabolism (directionality)
[21]	Wheat germ, germ protein	Added to the high-fat diet and administered at a moderate dose for a long term	Rats on a high-fat diet	Serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) decreased, while antioxidant enzyme activity increased, and liver steatosis was alleviated.
[22]	Wheat gluten protein	Some alternative protein sources in high-fat feed	Rats on a high-fat diet	Blood lipid levels decreased, the content of HMG-CoA reductase in the liver decreased, and the cholesterol synthesis pathway was inhibited.
[24]	Whole wheat flour, gluten layer fortified wheat flour	Whole wheat/fibrous layer fortified steamed buns account for a relatively high proportion of the main food in the diet.	Mice on a high-fat diet	Improved fasting blood glucose and insulin sensitivity, reduced liver lipid deposition, and remodeling of the microbiota and metabolome
[25]	Whole-grain barley active ingredients	High-dose supplementation of extracts such as proanthocyanidins and p-coumaric acid	HFD+STZ mice, etc.	Glucose tolerance improves, expression of enzymes related to gluconeogenesis is downregulated, and the liver glucose metabolism pathway is optimized.
[26–28]	Whole grain/modified barley (containing β -glucan and other components)	Different processing modifications and dose gradient combinations for intervention	High-fat or T2DM mouse models	Blood lipid levels decreased, liver steatosis improved, activation of lipid oxidation pathways such as PPAR α occurred, and inflammatory responses were alleviated.

4.4 Computer-assisted analysis and key target screening under multi-omics and high-throughput data

In recent years, studies on the intervention of whole wheat and related grains on T2DM in animals have gradually shifted from single-index observation to multi-omics combined

analysis. In experiments with high-fat diet mice intervened by whole wheat or bran layer fortified steamed bread, researchers simultaneously obtained 16S rRNA sequencing data of intestinal flora and non-targeted metabolomics data of the liver, and found that whole wheat intervention could reshape the intestinal flora structure and short-chain fatty acid-related metabolic pathways, and corresponded to the improvement of blood glucose, lipid levels and liver lipid deposition [24]. In high-altitude barley and other whole-grain models, active components such as proanthocyanidins, epicatechin and β -glucan were also revealed to have extensive regulation of glucose and lipid metabolism-related pathways through LC-MS metabolomics [25–28], suggesting a multi-level linkage between "whole-grain components - metabolic network - phenotype".

Systematic reviews on dietary fiber and cereal bran show that different sources of fermentable dietary fibers can affect the host's glycolipid metabolism pathways and inflammatory state by regulating the composition and metabolite spectrum of the intestinal flora [19, 20, 29, 30]; animal and population studies further support the potential of cereal dietary fibers in improving T2DM outcomes [31]. From a more macroscopic perspective, the association mechanism between the gut flora and T2DM and the bidirectional causal relationship with metabolic syndrome have been demonstrated in multiple reviews and Mendelian randomization studies [32, 33], providing a methodological basis for introducing multi-omics integration and causal inference in whole-grain intervention studies.

Under this framework, key target screening for T2DM animal experiments intervened by whole wheat can be carried out through a computer-assisted multi-omics integration process: On the one hand, with blood glucose, lipid levels, insulin sensitivity and key enzyme activities as phenotypic targets, combined with high-throughput data of flora, metabolomics, lipidomics, etc., methods such as principal component analysis, weighted correlation network analysis and random forest are used to screen for bacterial groups, metabolites and pathway modules highly related to the phenotypes [24–28, 29]; On the other hand, by mapping the differential features to pathways such as gluconeogenesis, fatty acid synthesis and oxidation, AMPK/PPAR signaling, etc., a network structure of "whole grain components - key enzymes for sugar and lipid metabolism - metabolites - microbiota - phenotype" was constructed. Through network centrality analysis and multivariate regression, a few key enzymes and their upstream regulatory nodes were identified [25–28, 30, 32, 33]. This technology route based on multi-omics and computer analysis is expected to provide quantitative target basis for the subsequent refinement of whole grain active components, dose optimization, and individualized dietary intervention strategies.

5 Conclusions and Research Prospects

5.1 Comprehensive Evaluation of Whole Grain Food as an Auxiliary Intervention Measure for T2DM

Based on the existing animal experiments and epidemiological evidence, it can be concluded that whole grain foods are more suitable to be positioned as a long-term, mild, and easily integrated into the daily dietary structure as an auxiliary intervention measure in the prevention and control of type 2 diabetes. Compared with refined grains, whole grains retain the bran, germ, and aleurone layer, and are rich in active components such as dietary fiber, polyphenols, and phenolic acids. By regulating the activities of key enzymes in glucose and lipid metabolism and improving the intestinal microecology and inflammatory state, they produce a cumulative effect on multiple metabolic pathways, helping to alleviate high blood sugar, high blood lipids, and insulin resistance.

From the perspective of intervention intensity and safety, whole grain foods are difficult to replace the hypoglycemic effect of drug treatment in a short period of time. They are more suitable as part of the basic diet and lifestyle management, combined with drugs, exercise, and body weight control, to jointly slow down the progression of the disease. Compared with some functional preparations, whole grains have a wide source, lower cost, and diverse forms of consumption, which can be achieved through the substitution of staple foods for long-term adherence, and are more in line with the actual needs of T2DM patients for "intervention through eating".

It should be noted that the benefits of whole grains vary significantly among individuals and varieties. The differences in dietary fiber types, plant chemical spectra among different wheat varieties, structural parts, and processing methods may lead to different intensities of regulation on key enzyme activities and metabolic networks; for some patients with gastrointestinal diseases or severe complications, a significant increase in crude fiber intake also requires careful assessment. Overall, whole grain foods, when used in reasonable doses and under a scientific dietary pattern, have a good safety margin and practical feasibility, and can be a recommended dietary intervention option in the comprehensive management of T2DM. Their true value depends on the continuous deepening of subsequent mechanism research and evidence-based application.

In practical promotion, such dietary recommendations need to be detailed to specific dietary contexts. For example, in regions where rice and pasta are the main staples, the proportion of whole wheat steamed buns, whole wheat noodles, or some whole wheat mixed flour products can be gradually increased instead of completely replacing the existing staple foods to reduce the threshold of compliance. Medical and nutrition teams should also dynamically assess the tolerance and blood sugar fluctuations of patients during follow-up, guide patients to form a rational expectation of the boundaries of the effects of whole grains, and view them as a sustainable adjustment, monitorable, and optimized dietary tool, rather than a simple "single magical food".

5.2 Main Factors Affecting Intervention Effect Differences and Current Research Limitations

The existing evidence shows that the intervention effect of whole grain food on T2DM varies significantly. Firstly, it comes from the raw materials themselves: different wheat varieties, purple or common wheat, as well as the structural parts such as bran, germ, and aleurone layer, have significant differences in dietary fiber types, amylose content, and the content of polyphenols and phenolic acids, resulting in inconsistent intensities of effects on key enzymes for sugar and lipid metabolism and intestinal microecology. Secondly, it lies in the processing and consumption methods. The fineness of whole grain flour, cooking or baking techniques, and whether it is combined with other grains or protein and fat, will change the digestion speed of starch and the accessibility of active components, thereby affecting the shape of the blood glucose curve and subsequent enzymatic reactions. Thirdly, it is related to individual factors, including the baseline blood glucose control level, combined obesity or fatty liver, intestinal microbiota structure, and drug treatment plans, which will largely determine the intervention effect.

From the perspective of the research itself, there are still several limitations at present: most studies focus on a few animal models, with small samples and short cycles, which are difficult to reflect the impact of long-term dietary intervention on the disease course and complication spectrum; the definitions and characterizations of "whole grain" in different experiments are not unified, and the reports of raw material components, doses, and energy ratios are not detailed enough, making it difficult to compare results laterally; The direct activity assays for

key enzymes such as glucokinase and fatty acid synthase are still limited. The multi-omics and computer modeling mostly remain at the level of correlation. Truly achieving research from "correlation" to "causality" and "predictability" is still insufficient. In the future, it is necessary to continuously strengthen efforts in standardized intervention plans, refined component characterization, and cross-model comprehensive analysis.

5.3 The Application Prospects of Computer Technology in the Integration of Evidence and the Construction of Individualized Whole-Grain Intervention Strategies

In the field of research on whole-grain food intervention for type 2 diabetes, the value of computer technology is shifting from "auxiliary statistics" to "core hub". On one hand, a large amount of data from animal experiments, multi-omics detection, and epidemiological follow-up, which need to be integrated through methods such as machine learning, network analysis, and Bayesian models, in order to identify truly stable key enzyme nodes, metabolic pathways, and gut microbiota-metabolite axes from the complex results. Through a unified database and standardized data structure, incorporating blood glucose and lipid indicators, enzyme activity changes, microbiota characteristics, and metabolic spectrum information from different studies into the same analytical framework, it is expected to form an updatable "whole-grain-sugar-lipid metabolism-T2DM" evidence map, providing more quantitative basis for subsequent reviews and guideline development.

On the other hand, computer technology also provides the possibility for the construction of individualized whole-grain intervention strategies. By leveraging clinical electronic medical records, dietary questionnaires, and basal metabolic assessment, a multi-dimensional feature library containing blood glucose control levels, comorbidities, gut microbiota types, and lifestyle characteristics can be established. On this basis, using cluster analysis and prediction models, different metabolic phenotypes of T2DM populations can be classified, and more suitable whole-grain varieties, structural parts, and intake patterns can be matched. In the future, if the key enzymes and pathways information obtained from animal experiments can be mapped to real population data and presented through a visual decision support system with information such as "recommended whole-grain proportion" and "synergistic space with current medications", it is expected to gradually transform the currently overly macroscopic dietary recommendations into individualized dietary intervention plans that are interpretable, calculable, and effect-tracked.

It should be noted that the application of such technologies also relies on several prerequisite conditions, including whether the collection of basic data is standardized, whether the detection platforms of different studies and hospitals can be calibrated, and whether the model outputs are sufficiently transparent and easy for clinical personnel to understand and question. If the data itself has high noise or systematic biases, even the most complex algorithms will be difficult to be transformed into reliable decision-making basis. Therefore, in the future, on the one hand, it is necessary for information science, nutrition, and clinical teams to jointly formulate data standards and modeling processes applicable to whole-grain intervention research; on the other hand, under the premise of privacy protection and patient informed consent, adopt a gradual path from research scenarios to clinical pilot and then to large-scale promotion, allowing computer-assisted decision-making to continuously iterate and verify within a controllable range.

5.4 Future Research Focus and Practice Transformation Directions Based on Model-Mechanism Integration

From the perspective of research paths, subsequent work needs to establish a clearer correspondence among "model", "component", and "mechanism". Animal experiments should not merely remain at a single species or model level. A hierarchical design can be formed among db/db mice, high-fat diet models, and high-fat + STZ composite models: one focusing on "obesity with insulin resistance", one highlighting "lipid disorder and fatty liver", and one considering pancreatic function impairment. Each type of model should be accompanied by clear descriptions of whole-grain raw materials, such as wheat varieties, bran/germ ratio, dietary fiber content and phytochemical spectrum, to lay the foundation for subsequent horizontal comparisons.

At the mechanism level, future research should integrate the determination of key enzyme activities, multi-omics analysis, and computer network modeling from beginning to end, rather than separating them. In the same batch of animal samples, the activities and expressions of key enzymes such as glucose kinase, glucose-6-phosphate enzyme, fatty acid synthase, and carnitine palmitoyltransferase can be simultaneously detected, and the data of intestinal microbiota, metabolome, and lipidome can be included in the integrated analysis. Through a unified metabolic pathway framework, "high-weight" nodes and synergistic pathways can be identified, and then guide the refinement of components and the optimization of intervention strategies in reverse.

In the practice transformation direction, on the one hand, based on this, functionalized staple foods and meal plans based on specific whole-grain parts or composite formulas can be developed, providing differentiated recommendations for T2DM patients with different metabolic phenotypes. On the other hand, the key enzymes and pathways obtained from animal experiments and computer simulations can be integrated into the nutrition management system and decision support tools, forming a visual "whole-grain intervention-metabolic response" map, providing easy-to-access references for clinical nutritionists and grassroots medical staff. With the deepening collaboration among different disciplines, the role of whole-grain foods in type 2 diabetes management is expected to shift from empirical recommendations to precise dietary intervention paths based on mechanism evidence and data support.

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