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Regulatory mechanism of fermented wheat germ on lipid metabolism in hyperlipidemia rats via activation of AMPK pathway

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Abstract

This article study the influences of fermented wheat germ on rats in terms of the blood glucose, insulin level, serum lipid level, cholesterol metabolism, triglyceride metabolism and enzyme activity on the basis of the high-fat rat model. High fat rats were fed for modeling, and then the serum and liver were collected after sacrifice. Total cholesterol (TC), triglyceride (TG), total superoxide dismutase (SOD), Superoxide dismutase (T-SOD), glutathione peroxidase (GSH-PX), Malonic dialdehyde (MDA), lecithin cholesterol acyltransferase (lecithin cholesterol), Acyltransferase (LCAT), LDL-C, blood glucose and insulin were measured. Fermented wheat germ can significantly increase the levels of insulin and blood glucose in high-fat rats. Fermented wheat germ for 60 days did not affect the levels of serum LDL-C and TG in high-fat rats, but could significantly reduce the level of serum TC. Fermented wheat germ for 60 days did not affect the activities of serum GSH-Px, T-SOD, LCAT and T-SOD, MDA and total lipase in high-fat rats, but it could significantly reduce the activity of serum MDA and increase the activity of GSH-PX in liver. Fermented wheat germ could reduce the protein expression of CYP7A1, induced p-AMPK protein expression, but had no effect on HMGR. Fermented wheat germ can significantly reduce the level of serum cholesterol in high-fat model rats by AMPK signaling pathway, and affect some cholesterol metabolism and triglyceride metabolism related enzyme activities to a certain extent.

Keywords: fermented wheat germ; lipid metabolism; hyperlipidemia; AMPK.

Practical Application: Fermented wheat germ affect some cholesterol metabolism and triglyceride metabolism.

1 Introduction

Hyperlipidemia is a common disease of lipid metabolism disorder, and it is also the main factor inducing fatty liver and atherosclerosis (Alzahrani et al., 2022). The long-term "improper diet and excessive taste of Sorghum" is easy to form hyperlipidemia, leading to the disorder of lipid metabolism (Li et al., 2022c). Previous studies have shown that the synthesis, decomposition, metabolism and reverse transport of cholesterol are closely related to hyperlipidemia (Du et al., 2022; Li et al., 2022b). The liver is the main organ of cholesterol biosynthesis. When the liver tissue is accumulated, infiltrated and denatured by fat, it is easy to aggravate the disorder of lipid metabolism (Busnelli et al., 2022).

With the improvement of people's living standards and the change of eating habits in today's society, the balance of lipid metabolism in the human body is disturbed, the number of obese people is increasing and showing a trend of younger age (Tummala et al., 2022; Du et al., 2020). Obesity has become an important inducement of a variety of metabolic diseases (Tan et al., 2022; Han et al., 2019). According to epidemiological investigation, obesity, as a fatal factor, itself represents a variety of common chronic diseases, such as coronary atherosclerosis and type II diabetes (Zuo et al., 2022; Han et al., 2021). However, drug treatment and medical means always have more or less side effects. Therefore, the combination of drugs and non-drugs is often used for prevention and treatment. Dietary supplement and intervention have become an important part of the basic treatment of metabolic diseases (Han et al., 2019; Park et al., 2022).

At present, researchers have made a variety of attempts and studies on lipid-lowering substances in natural foods and their mechanisms (Kowluru et al., 2016; Lishianawati et al., 2022). Auricularia auricula polysaccharide, Lycium barbarum polysaccharide, hawthorn flavone, hawthorn pectin oligosaccharide and other foods have good lipid-lowering effects (Hu et al., 2021b). Food extracts such as Monascus and garlic extract can effectively control blood lipids. Ginkgo flavone can effectively increase total superoxide dismutase (T-SOD) and glutathione peroxidase (GSH-PX) in liver and reduce the activity of malonic dialdehyde (MDA); Buckwheat flour can increase liver lipoprotein lipase (LPL) and reduce liver lipase (HL) activity; Sweet potato mucin can enhance the activity of 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGR) in liver, effectively reduce cholesterol synthesis in rat liver and improve catabolic efficiency (Lishianawati et al., 2022; Amiya, 2016; Li et al., 2021a; Rosales-Cruz et al., 2018).

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The weight proportion of wheat germ in wheat is only 2%-3%, which is easily wasted in flour processing because it is used as feed (Bayat et al., 2022). However, as the part with the highest nutritional value in wheat, it is not only rich in nutrients such as protein, fat, sugar, minerals and vitamins, but also contains many bioactive substances, such as milk wheat germ lectin, octacosanol, glutathione, flavonoids and so on (El-shafey et al., 2022). Moreover, studies have shown that the content and activity of bioactive substances in the fermented product of wheat germ after fermentation are significantly increased (Ashraf et al., 2022; Emam et al., 2022).

At present, the domestic research on fermented wheat germ mostly focuses on the development of fermented wheat germ food, such as Li Yongping's wheat germ bread fermented beverage and Li Yan's mixed fermented yogurt of wheat germ and hawthorn (Hu et al., 2022; Zheng et al., 2022). Other studies have shown that glutathione, a sulfur-containing antioxidant, can be extracted from fermented wheat germ products, which plays a redox role in human cells and scavenges free radicals, so as to achieve the effects of anti-aging and anti-oxidation (Koç & Erbaş, 2022; Liu et al., 2022; Li et al., 2022d). Studies have also shown that fermented food can regulate blood lipid and lipid catabolism, so as to achieve the purpose of reducing blood lipid (Hu et al., 2022; Koç & Erbaş, 2022; Liu et al., 2022; Marzocchi et al., 2022).

AMPK is an energy sensor discovered in recent years (Lin et al., 2021). It is considered to be a key enzyme protein that regulates cell metabolism, regulates fat content and affects the balance of lipid metabolism (Pu et al., 2020; Li et al., 2022a). Activating AMPK phosphorylation, if activating downstream molecular pathway signals, can not only increase energy catabolism (such as fatty acid oxidative catabolism) but also close anabolism (such as de novo lipid synthesis pathway) (Lin et al., 2021). It is two important pathways of lipid metabolism (Shen et al., 2019).

In this experiment, rats were fed with high-fat diet to establish a high-fat model. The effects of fermented wheat germ on key enzymes in the process of lipid metabolism were studied by measuring the activities of lipid metabolism related enzymes in serum and liver tissue.

2 Materials and methods

2.1 Grouping and modeling of rats

Male SD rat (5-6 weeks) were randomly divided: control, model, High-Liguid, Med-Liguid, Low-Liguid, High-Drug residue, Med-Drug residue, Low-Drug residue group. Body weight was measured twice a week at a fixed time to adjust the gavage dose. The feeding design of each test group is shown in Table 1. The duration of the test was 60 days. After fasting for 14-16 h on 30 days, the orbital venous blood was taken to measure the serum total cholesterol (TC) and triglyceride (TG). The analytical model was established.

2.2 Enzyme-Linked Immunosorbent Assay (ELISA)

TC, TG, LDL-C, HDL-C, SOD, MDA, LCAT, SOD, CYP7A1 and HMGCoAR levels were measured using ELISA kit (Beyotime) according to the manufacturer's protocol.

2.3 Western blot assay

Proteins were extracted from tissues or cells samples in protein lysis buffer. Protein content was quantified with the BCA reagent kit. Protein lysates were separated on 10% SDS-PAGE and transferred to polyvinylidene difluoride (PVDF) membranes (Millipore Corp. Billerica, MA, USA). The PVDF was incubated by AMPK, p-AMPK and β-actin at 4 °C over-night. PVDF was incubated with horseradish peroxidase-conjugated secondary antibody (Beyotime, 1:5000) for 2 h. The signal was tested with the chemiluminescence system (Amersham Pharmacia).

2.4 Data and statistical analysis

Statistical analyses were performed using SPSS 16.0 statistical software (SPSS, Inc., Chicago, IL, USA) and reported as the mean ± SD. The experiments have been repeated at least three times. The unpaired Student's t-test was used to analyze differences between the two groups. One-way ANOVA was employed for the comparison of data between groups. $p < 0.05$ was considered to indicate a statistically significant difference.

3 Results

3.1 Model building

From the point of view of serum TC index and body weight of rats adapted to culture for 7 days, there is little individual difference, and it is easy to achieve the goal of grouping (Figure 1A, 1B).

According to the measurement results of serum TC and TG in the test group for 30 days, the serum TC in the model group was significantly higher than that in the blank control group, showing a very significant difference ($P < 0.01$). Therefore, it is considered that the hyperlipidemia model was successfully

Table 1. Feeding operation of rats.

Group	Feed	Drinking water	Gavage
Control	Normal	Normal	Water
Model	High-fat	Normal	Water
High-Liguid	High-fat	Normal	221 mg/kg/d supernatant lyophilized powder
Med-Liguid	High-fat	Normal	442 mg/kg/d supernatant lyophilized powder
Low-Liguid	High-fat	Normal	884 mg/kg/d supernatant lyophilized powder
High-Drug residue	High-fat	Normal	221 mg/kg/d precipitate lyophilized powder
Med-Drug residue	High-fat	Normal	442 mg/kg/d precipitate lyophilized powder
Low-Drug residue	High-fat	Normal	884 mg/kg/d precipitate lyophilized powder

constructed. Among the test groups, only the serum TC of low liquid group and high slag group decreased to a certain extent compared with the model group, but the difference was not significant (Figure 1C, 1D).

3.2 Effects of fermented wheat germ on blood glucose and insulin levels in rats

The results are shown in Figure 2. The mid-term measurement results showed that the blood glucose concentration in the model group began to rise during the test, but the difference was not significant (P > 0.05). The insulin content in the model group also began to increase, which was significantly different from that in the blank control group (P < 0.05). At the end of the test, the blood glucose concentration in the model group was significantly higher than that in the blank control group (P < 0.01). The insulin content in the model group also increased continuously and reached a significant difference (P < 0.05). It shows that under the high-fat diet, the increase of insulin content can-not reduce the blood glucose concentration.

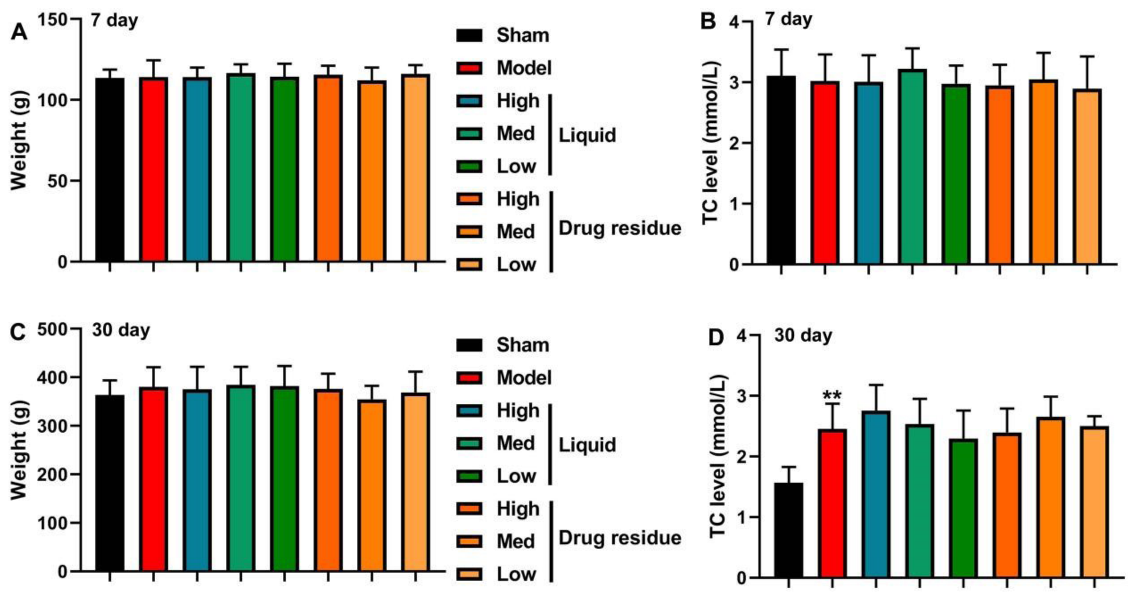

Figure 1. Model building. Weight at 7 day (A), TC level at 7 day (B), weight at 30 day (C), TC level at 30 day (D). **Compared with the control group, the difference was very significant (P < 0.01).

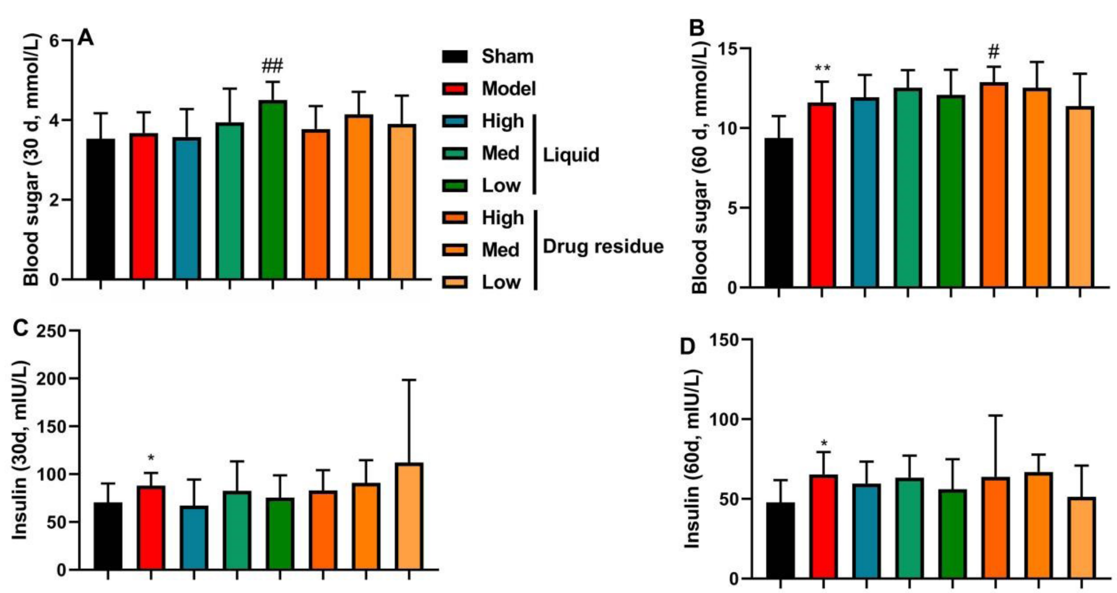

Figure 2. Effects of fermented wheat germ on blood glucose and insulin levels in rats. Blood sugar at 30 day (A), blood sugar at 60 day (B), insulin at 30 day (C), insulin at 60 day (D). *Compared with the control group, the difference was very significant (P < 0.05). **Compared with the control group, the difference was very significant (P < 0.01). #Compared with the model group, the difference is extremely significant (P < 0.05). ##Compared with the model group, the difference is extremely significant (P < 0.01).

In the mid-term measurement results, the blood glucose concentration of each test group was higher than that of the blank control group, and the difference between the low liquid group and the model group was very significant ($P < 0.01$, Figure 2). The insulin content of each test group was higher than that of the blank control group except the high liquid group, but there was no significant difference compared with the model group (Figure 2). At the end of the test, the blood glucose concentration of each test group continued to rise, which was higher than that of the model group, but only the slag high group showed significant difference compared with the model group ($P < 0.05$, Figure 2). Although the insulin content of each test group continued to increase, there was no significant difference compared with the model group (Figure 2). It is speculated that fermented wheat germ can not eliminate the abnormal regulation of blood glucose caused by insulin resistance.

3.3 Regulation of cholesterol level by fermented wheat germ

The results showed that the content of TC in the model group was significantly higher than that in the blank control group (Figure 3). Among the test groups, the liquid low group was significantly lower than the model group (Figure 3); The slag group was significantly lower than the model group (Figure 3); The other test groups were lower than the model group to some extent, but the difference was not significant (Figure 3). It can be seen that fermented wheat germ has a certain cholesterol lowering effect on hyperlipidemia rats, and its effect is related to the tested dose and duration of the test.

The liver TC in the model group was significantly higher than that in the blank control group (Figure 3). However, there was no significant difference between the other test groups and the model group (Figure 3). Therefore, it is speculated that the body preferentially regulates and maintains the homeostasis of serum TC. When serum TC exceeds a certain level, it will choose to transport serum TC to the liver for reprocessing and redistribution. For this reason, the content of serum and liver TC in the model group and the test substance group fed with high-fat diet increased significantly, while the level of liver TC in each test group was higher than that in the model group, but the level of serum TC was lower than that in the model group. It is speculated that fermented wheat germ may have the potential to promote the transport of serum TC to the liver (Figure 3).

The results of mid-term determination showed that the content of serum low density lipoprotein cholesterol (LDL-C) in the model group was significantly higher than that in the blank control group (Figure 4). There was no significant difference among the test groups ($P > 0.05$). At the end of the experiment, the measurement results of the model group were still significantly higher than those of the blank control group (Figure 4). Although the LDL-C content of high liquid group, low liquid group and low slag group decreased to some extent, the difference was not significant (Figure 4). Therefore, it is speculated that fermented wheat germ can not reduce blood lipid by reducing the content of LDL-C. By increasing the content of high density lipoprotein (HDL-C), it may promote HDL-C to send cholesterol back to the liver for metabolism and reduce the risk of atherosclerosis.

3.4 Regulation of triglyceride level by fermented wheat germ

Serum cholesterol acyl transferase (LCAT) catalyzes the esterification of free cholesterol to form cholesterol esters into HDL core, and finally form a new HDL ball for reverse transport. Serum of each group (Figure 5).

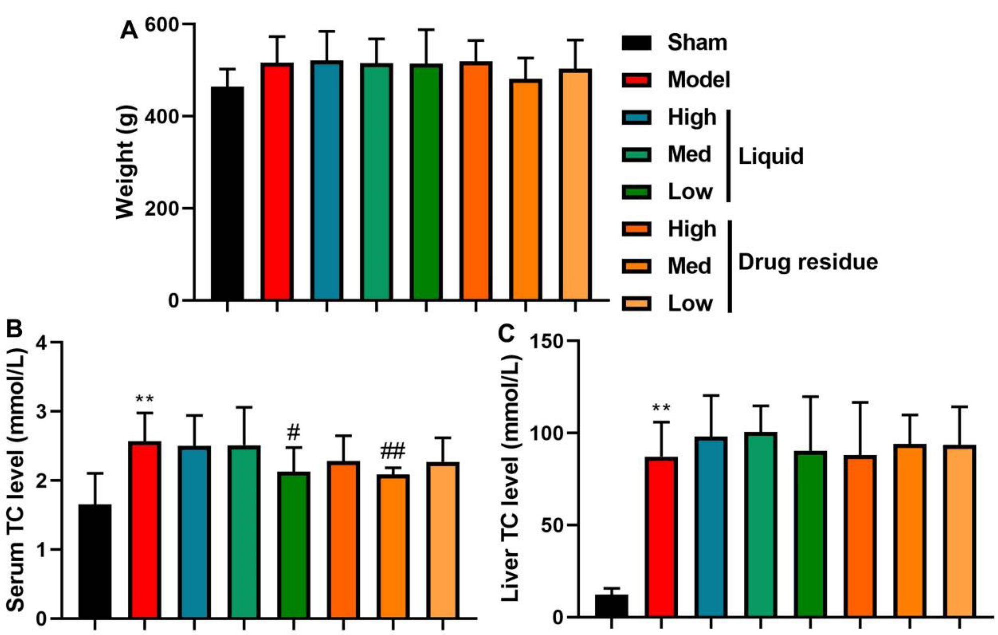

Figure 3. Regulation of TC level by fermented wheat germ. Weight (A), serum TC level (B), liver TC level (C). **Compared with the control group, the difference was very significant ($P < 0.01$). #Compared with the model group, the difference is extremely significant ($P < 0.05$). ##Compared with the model group, the difference is extremely significant ($P < 0.01$).

LCAT enzyme activity did not show a clear change law, and the standard deviation between individuals was very large, suggesting that the esterification of free cholesterol in blood was not simply affected by feed and gavage, but more by the regulation of cholesterol homeostasis itself (Figure 5).

At the end of the experiment, the content of TG in the liver of the model group was significantly higher than that of the blank control group, indicating that high-fat diet will promote the accumulation of fat in the liver, so high-fat diet may be the dietary pathogenesis condition of fatty liver (Figure 5).

3.5 Effects of fermented wheat germ on serum related enzyme activity and MDA concentration

The activity of serum superoxide dismutase (SOD) in model group and test group fluctuated slightly compared with the blank control group. Comparing the amount of lipid peroxidation product malondialdehyde (MDA), the model group was slightly higher than the blank control group, but the difference was not significant (Figure 6). However, each test group was lower than the model group and lower than the blank control group, and the difference was significant in the liquid high group (Figure 6). It is suggested that fermented wheat germ can prevent the lipid peroxidation damage of blood cell membrane to a certain extent, and has a certain protective effect.

Serum cholesterol acyl transferase (LCAT) catalyzes the esterification of free cholesterol to form cholesterol esters into HDL core, and finally form a new HDL ball for reverse transport. Serum of each group (Figure 6).

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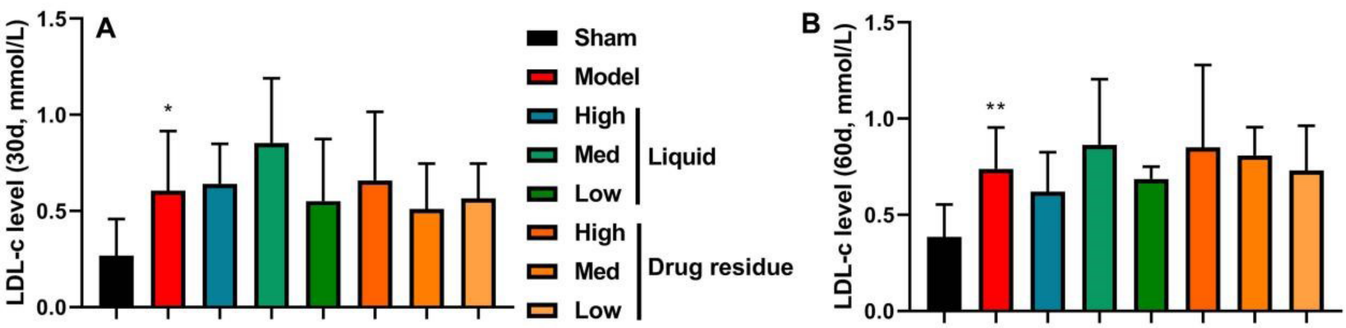

Figure 4. Regulation of LDL-c level by fermented wheat germ. LDL-c level at 30 day (A), LDL-c level at 60 day (B). *Compared with the control group, the difference was very significant (P < 0.01). **Compared with the control group, the difference was very significant (P < 0.01).

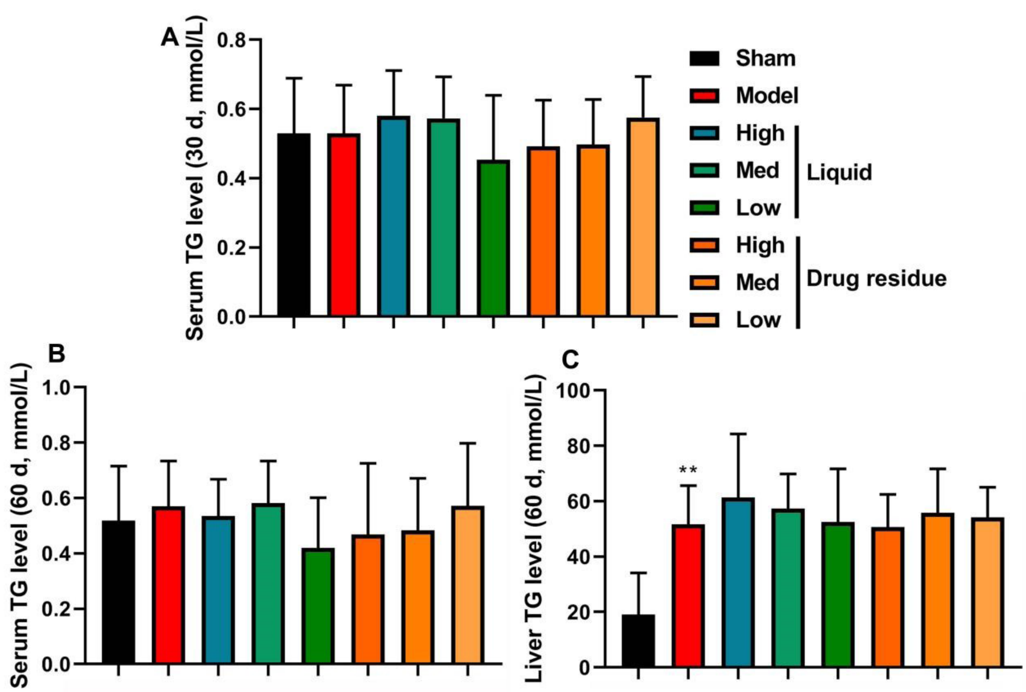

Figure 5. Regulation of triglyceride level by fermented wheat germ. Serum TG level at 30 day (A), serum TG level at 60 day (B), liver TG level at 60 day (C). **Compared with the control group, the difference was very significant (P < 0.01).

suggesting that the esterification of free cholesterol in blood was not simply affected by feed and gavage, but more by the regulation of cholesterol homeostasis itself (Figure 6).

3.6 Effect of fermented wheat germ on the activities of various enzymes in liver

For 60 days, high-fat diet could reduce the activities of antioxidant enzymes glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD) in the liver of model group, and the difference between GSH-PX and blank group was significant (Figure 7). GSH-PX in each group was higher than that in the model group, and the difference was significant in the low liquid group (Figure 7); Sod increased and decreased in each group, with great individual differences; It is speculated that fermented wheat germ can resist oxidative damage and protect hepatocyte function through GSH-px.

The changes of total lipase showed that high-fat diet could increase the activity of total lipase in liver. There was a significant difference between the model group and the blank group (Figure 7), but there was no significant difference between the test groups and the model group (Figure 7). It shows that high-fat feed can promote the accumulation and degradation of fat in the liver, but fermented wheat germ cannot significantly promote its degradation, and total lipase may not be its target.

Model group cholesterol 7 α- The activity of hydroxylase (CYP7A1) was significantly higher than that of the blank group ($P < 0.05$), the liquid low group and slag low group were slightly higher than that of the model group, and the liquid high, liquid medium, slag high and slag medium groups were slightly lower than that of the model group, but there was no significant difference ($P > 0.05$).

There was no significant difference between the test groups. It shows that high-fat diet will affect the body's cholesterol metabolism. Its important metabolic direction is to convert it into bile acids and discharge them into the intestine under the action of CYP7A1 (Figure 7). The feedback effect of bile acids in CYP7A1 receptor in the test group is higher and lower than that in the model group; At the same time, due to the interaction and influence of body status, gene loci and environmental factors on the homeostasis of cholesterol level, it is the result of multi-channel synergy (Figure 7). Therefore, the amount of CYP7A1 varies greatly among individuals in the group, and it is difficult to have significant differences between groups.

HMGCoA reductase (HMGCoAR) has great individual differences in the test groups, and the change lacks certain rules (Figure 7). It may not be the stress target of the test object in this experiment.

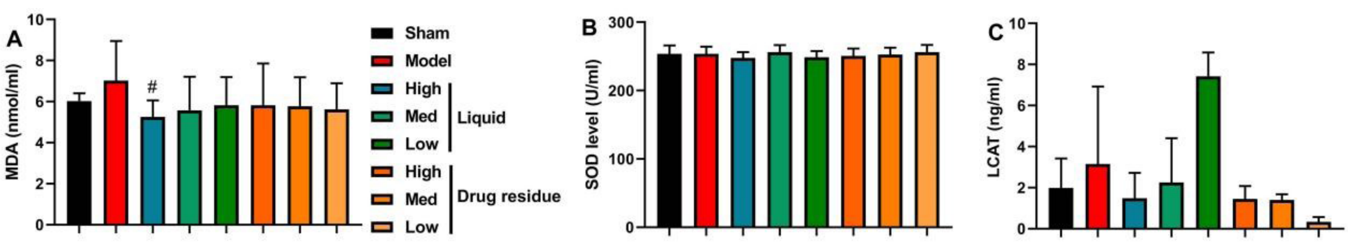

Figure 6. Effects of fermented wheat germ on serum related enzyme activity and MDA concentration. MDA (A), SOD (B), LCAT (C). #Compared with the model group, the difference is extremely significant ($P < 0.05$).

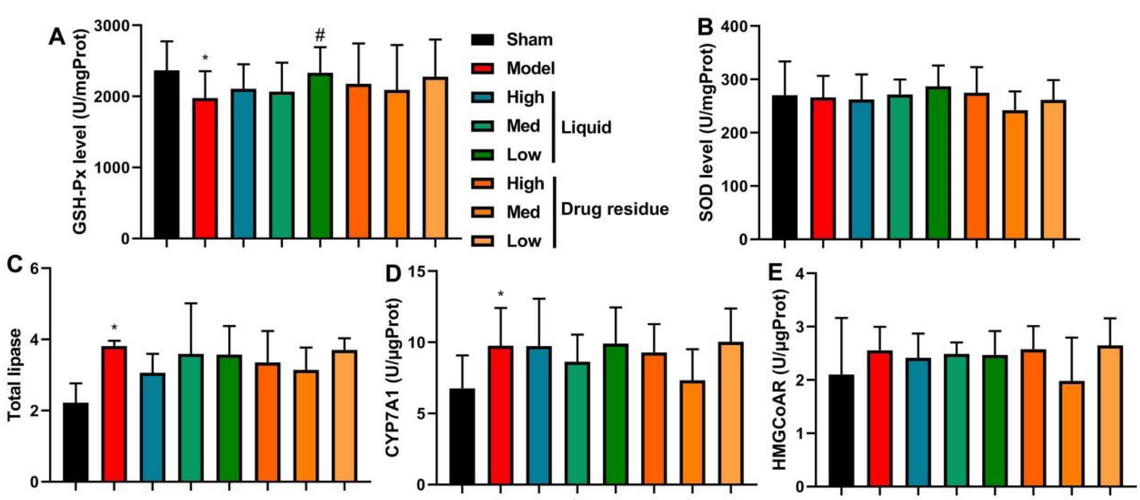

Figure 7. Effect of fermented wheat germ on the activities of various enzymes in liver. GSH-PX (A), SOD (B), total lipase (C), CYP7A1(D), HMGCoAR (E). *Compared with the control group, the difference was very significant ($P < 0.05$); #Compared with the model group, the difference is extremely significant ($P < 0.01$).

3.7 Effects of fermented wheat germ on histopathology of liver and aortic arch

The score of lipid droplet accumulation in the model group was significantly higher than that in the blank group (Figure 8), and the test groups were lower than that in the model group, and the difference was very significant in the liquid group (Figure 8). It can be seen that fermented wheat germ will change the lipid droplet accumulation, concentrate on a few cells as much as possible and preserve other cell metabolic functions. Other types of cytopathy mainly include cytoplasmic condensation, watery degeneration, balloon degeneration and steatosis. There is no obvious degeneration law between the groups, and its physiological significance needs to be further discussed.

3.8 Fermented wheat germ induced AMPK activation

This experiment found that high or med of Liquid group significantly induced p-AMPK protein expression in liver tissue of hyperlipidemia rats (Figure 9). However, drug residue cannot affected p-AMPK protein expression in liver tissue of hyperlipidemia rats (Figure 9).

4 Discussion

Lipids are the main substances for energy storage and supply, and they are also important components of biofilm (Lumpuy-Castillo et al., 2022). Lipid metabolism refers to the multi-step and complex biochemical reactions of lipids in organisms under the action of various metabolic enzymes, including a series of physiological processes such as digestion, absorption, synthesis, decomposition and transport (Miah et al., 2022). It is of great significance to maintain the normal life activities of the body (McDonald et al., 2022). This study showed that Fermented wheat germ can significantly increase the levels of insulin and blood glucose in high-fat rats. Boros et al. showed that Wheat germ extract decreases glucose uptake and increases fatty acid synthesis in pancreatic adenocarcinoma cells (Boros et al., 2001). Taken together, Fermented wheat germ may be novel treatment for lipid metabolism in Hyperlipidemia, a possibility that is currently under active investigation.

AMPK activator can phosphorylate and regulate the activities of various metabolic enzymes, such as ACC, fatty acid synthase (FAS) and other key enzymes, regulate lipid metabolism signal transduction pathway, turn on catabolism and turn off anabolic pathway, and supplement ATP supply (Han et al., 2019). Recent studies have found that spermidine, a new AMPK activator, also regulates lipid metabolism (Bruckbauer et al., 2017; Li et al., 2011). Spermidine can inhibit the expression of srebp1c and Fas by activating AMPK and effectively regulate lipid metabolism (Li et al., 2021b). AMPK inhibits lipid synthesis, promotes lipid decomposition and oxidation, and plays a key role in energy and lipid metabolism. In addition, AMPK also plays an important role in glucose and protein metabolism (Bordoloi et al., 2019). In this study, This experiment found that high or med of Liquid group significantly induced p-AMPK protein expression in

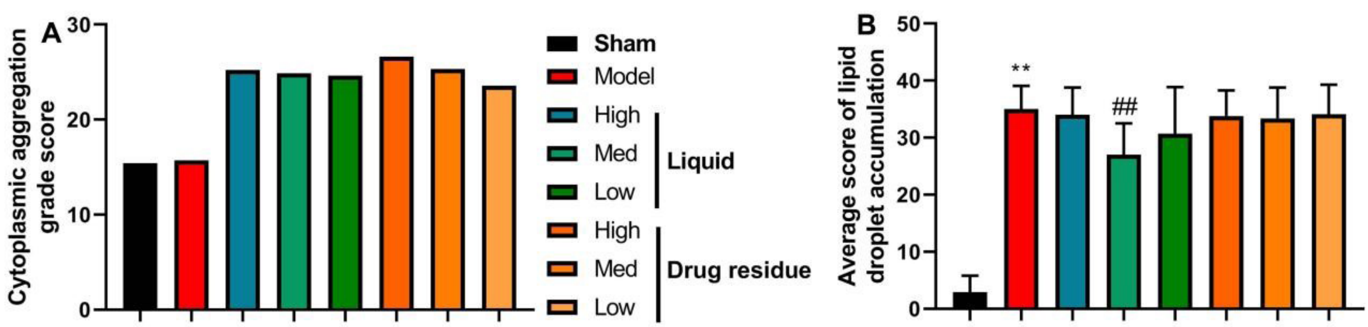

Figure 8. Effects of fermented wheat germ on histopathology of liver and aortic arch. Cytoplasmic aggregation grade score (A), average score of lipid droplet accumulation (B). **Compared with the control group, the difference was very significant (P < 0.01); ##Compared with the model group, the difference is extremely significant (P < 0.01).

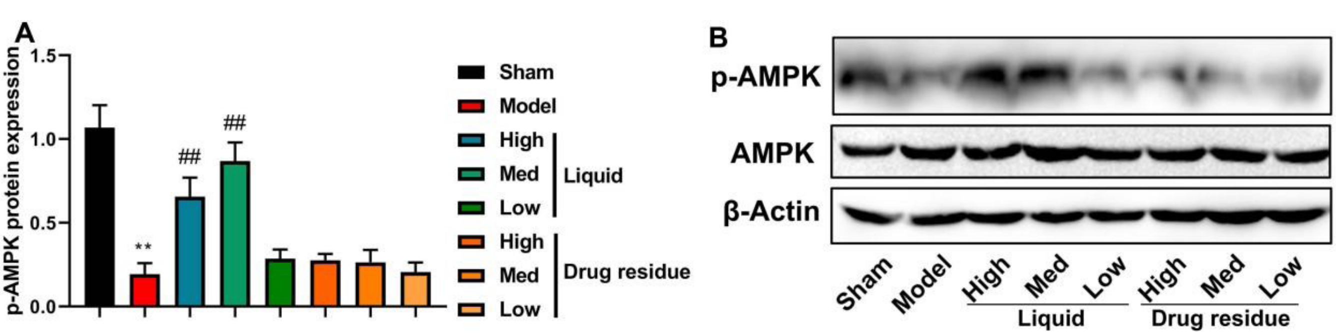

Figure 9. Fermented wheat germ induced AMPK activation. p-AMPK protein expression (statistics, A), p-AMPK protein expression (Western blot, B). **Compared with the control group, the difference was very significant (P < 0.01); ##Compared with the model group, the difference is extremely significant (P < 0.01).

liver tissue of hyperlipidemia rats. Taken together, these results indicate that Fermented wheat germ induced AMPK signaling pathway to regulate lipid metabolism in hyperlipidemia.

Hyperlipidemia (HLP) is a disease caused by abnormal blood lipid metabolism (Busnelli et al., 2022). It is often manifested as the decrease of serum high density lipoprotein cholesterol (HDL-C) or the increase of total cholesterol (TC), triglyceride (TG) and low density lipoprotein cholesterol (LDL-C) (Li et al., 2022b). Hyperlipidemia is not only a pathogenic factor of obesity and type 2 diabetes, but also closely related to metabolic diseases such as hypertension, fatty liver and atherosclerosis (McDonald et al., 2022). At present, the treatment drugs for hyperlipidemia are mainly western drugs simvastatin, pravastatin, fenofibrate, clofibrate, etc (Xenoulis & Steiner, 2010). These drugs have clear effects, but the target is single. Long term use is often accompanied by side effects, such as gastrointestinal adverse reactions, liver and kidney function damage, and the rebound probability is high after drug withdrawal (McDonald et al., 2022). Therefore, the research of plant-derived drugs has become a hot spot. Relevant studies have found that flavonoids, saponins and other chemical components in many natural products can regulate the liver lipid metabolism system, so as to achieve the purpose of reducing blood lipid (Hu et al., 2021a). We found that Fermented wheat germ for 60 days did not affect the levels of serum LDL-C and TG in high-fat rats, but could significantly reduce the level of serum TC. Fermented wheat germ for 60 days did not affect the activities of serum GSH-Px, T-SOD, LCAT and T-SOD, MDA and total lipase in high-fat rats, but it could significantly reduce the activity of serum MDA and increase the activity of GSH-PX in liver. Fermented wheat germ could reduce the protein expression of CYP7A1, but had no effect on HMGR. Mackei et al. determined that Fermented wheat germ extract reduced Oxidative Stress in Primary Cultured Rat Hepatocytes (Mackei et al., 2020). Pontonio et al. demonstrated Food Wastes met nutritional and sensory requests of modern consumers through antioxidant activity and Lactic Acid Bacteria Fermentation (Mackei et al., 2020). Li et al. found that fermented wheat bran decreases trimethylamine by gut microflora and AMPK pathways of the host (Li et al., 2017). These data together demonstrated that Fermented wheat germ is efficiently drug for lipid metabolism and oxidative stress through AMPK pathways in hyperlipidemia (Figure 10).

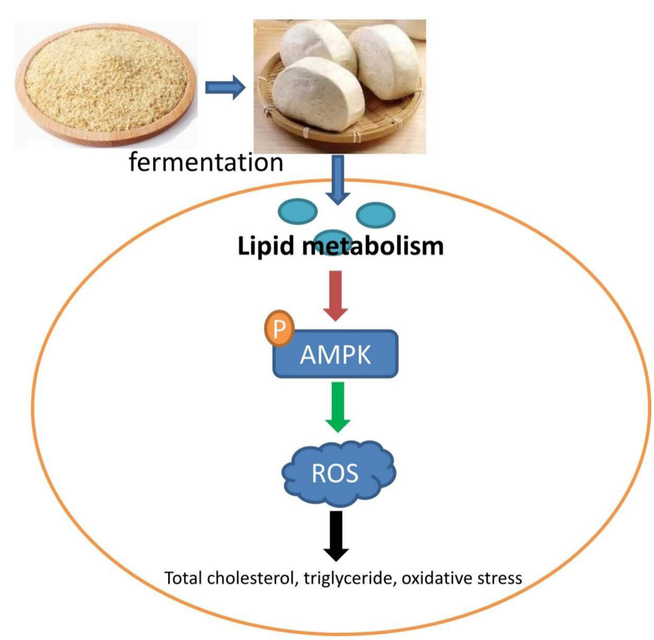

Figure 10. Regulatory mechanism of fermented wheat germ on lipid metabolism in hyperlipidemia rats via activation of AMPK pathway.

5 Conclusion

Our study showed that Fermented wheat germ can significantly reduce the level of serum cholesterol in high-fat model rats, and affect some cholesterol metabolism and triglyceride metabolism related enzyme activities to a certain extent by AMPK signaling pathway. Fermented wheat germ might be a clinical treatment for treatment of hyperlipidemia.

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