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Complementary Food to Improving HDL & LDL in Malnourished Male Wistar Strain White Rats

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Abstract. Protein-energy malnutrition (PEM) causes a decrease in amino acid synthesis, which affects the decrease in High-Density Lipoprotein (HDL) levels and an increase in Low-Density Lipoprotein (LDL) levels. Improving HDL and LDL levels in malnourished can be managed by providing Complementary Food (CF) with main ingredients such as banana flour, cassava flour, and corn flour. This study aims to describe the effect of CF supplementation on the HDL and LDL levels of malnourished male Wistar rats. The research method was experimental with a Randomized Block Design using twenty-four male rats. The experimental animals were divided into six treatment groups and carried out for 4 weeks. Data on HDL and LDL levels were obtained from rat blood serum detected by spectrophotometer and analysed by ANOVA. The results showed significant differences in HDL levels with the administration of CF ($P < 0.05$) and no significant differences in LDL levels with CF supplementation ($P > 0.05$). CF can increase HDL levels and tend to decrease LDL levels.

1 Introduction

Malnutrition is a nutritional problem resulting from inadequate nutritional intake and energy expenditure required for children's growth and development [1]. Malnutrition can occur due to several things, such as deficiencies in providing inadequate or unbalanced complementary foods and certain medical conditions that affect the digestive process of food absorption [2,3]. Malnutrition is a serious problem, especially in developing countries, one of which is Indonesia [4,5]. According to data from the Indonesian Nutrition Status Survey in 2021 and 2022, as many as 17% and 17.1% of toddlers under five years are underweight [6]. However, the research on the effect of CF supplementation on HDL and LDL levels in malnourished male Wistar rats is still underexplored.

Protein Energy Malnutrition (PEM), a prevalent form of malnutrition in children, is characterized by low energy and protein consumption [5,7]. The metabolic process of proteins results in the formation of amino acids. A decrease in amino acids in the body can lead to hormonal disorders, inflammation, and changes in metabolic function, including alterations in the lipid profile [8,9].

The lipid profile comprises triglycerides, total cholesterol, Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL) [10]. In PEM conditions, lipid metabolism

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disorders manifest as increased LDL and decreased HDL due to reduced lipoprotein synthesis [11]. This metabolic imbalance underscores the importance of our study, which aims to explore the potential of CF supplementation in restoring the lipid profile in malnourished rats.

An increase in LDL and a decrease in HDL are caused by a Very Low-Density Lipoprotein (VLDL) decrease. VLDL carries apolipoprotein, which transports triglycerides from the liver to the tissues. A reduction of amino acids disrupts the formation of VLDL apolipoprotein, resulting in fatty liver [12,13]. LDL is formed from VLDL, which is rich in triglycerides. Triglycerides will undergo cholesterol ester (CE) exchange by HDL, which is mediated by Cholesterol Ester Transfer Protein (CETP), so LDL will carry CE [14]. The more cholesterol, the LDL will undergo oxidation and make it rise in the blood vessels. The role of HDL as Reverse Cholesterol Transport (RCT) will move cholesterol esters from peripheral tissues, including artery walls, to the liver [15]. The interaction of HDL, which is rich in triglycerides and low in cholesterol, causes HDL levels to decrease [16]. Lack of apolipoprotein in HDL means that tissue cholesterol cannot be transported, causing fat to accumulate in blood vessels. Apolipoprotein also plays an important role in LDL because it binds to the LDL Receptor (LDLR). If the liver is fatty, LDLR will decrease so LDL will be retained in the blood vessels [17,18]. Accumulation of cholesterol in children can cause dyslipidemia and increase the risk of heart attack and stroke [19,20].

Handling malnutrition has been carried out by giving Ready-Use-Therapeutic Food (RUTF), which only focuses on increasing the amount of energy [21]. RUTF contains powdered milk, sugar, nuts, vegetable oil, vitamins and minerals [22]. This treatment still has limitations because it is not able to optimize the microbiota in the intestine, so additional food updates are needed. Currently, the development of additional foods to combat malnutrition focuses on increasing energy and diversity of the microbiota in the gut. The composition of the microbiota in the intestine in PEM conditions will experience dysbiosis which can cause damage to intestinal permeability and failure to absorb nutrients [23]. Complementary Food (CF) is an alternative therapeutic food that involves microbiota as a therapeutic target in the intestine. Evidence from clinical trials carried out in Malawian and Ethiopian children, CF can increase plasma proteins in neurodevelopment, inflammation, and improve gut microbiota [24]. In another study, CF showed improved health in plasma proteins of Mirpur children in Dhaka, Bangladesh [25].

Indonesia is rich in local food diversity that can be used in making CF, for example bananas, cassava, and corn. These three ingredients have a high complex carbohydrate content which is known to be good for the body [26-28]. Complex carbohydrates consisting of fiber and starch are difficult to digest, thus encouraging the growth of bacteria in the large intestine to ferment fiber and protein [29]. The results of this fermentation will become short-chain fatty acids (SCFA), then absorbed by blood vessels to be used for metabolism such as increasing fatty acid oxidation and inhibiting fat synthesis [30]. In addition, it maintains immunity and intestinal homeostasis and provides additional calories to the body [31]. Thus, CF can improve the body's metabolism, especially lipids, through intestinal microbial fermentation.

Banana is an export fruit that contains high levels of complex carbohydrates and consists mostly of starch. Generally, the resistant starch content in banana flour is 70-80% and the fiber is 17.5% [32]. Banana flour intervention can reduce LDL levels in dyslipidemic mice for 4 weeks [33]. Resistant starch can be fermented by microflora bacteria in the large intestine to reduce cholesterol [34]. The fiber and starch in banana flour are also effective in reducing triglycerides and LDL cholesterol levels and increasing HDL cholesterol [35]. Cassava is a plant that has been exported to various countries because it is rich in nutritional components. Tapioca flour is flour derived from cassava starch with a nutritional content of 0.59% protein, 3.39% fat, 73.3%-84.9% starch, and 2.5% fiber [36,37]. Corn is a food resource with nutritional value in quite large quantities compared to other grains [38]. Corn contains carbohydrates consisting of 72-73% starch and 8.56-9.36% crude fiber [39,40]. The complex carbohydrates contained in these three ingredients can bind bile acids and prevent reabsorption in the liver so that they can inhibit cholesterol synthesis [41]. This study aims to analyze the effect of giving CF on LDL and HDL in white mice (*Rattus novergicus* L.) malnourished male Wistar strain.

2 Methods

The research was carried out from May to December 2023 in the Green House Department of Biology, Faculty of Mathematics and Natural Sciences, State University of Malang, and Clinical Pathology Laboratory, Faculty of Medicine, Brawijaya University. This research has passed the test of ethical approval with the Reg code. No. 802/KEPK-POLKESMA/2023. The research used an experimental method with a Randomized Group Design (RAK). The experimental animals used were male Wistar strain rats with a body weight range of 80 ± 10 g and 5 weeks of age. Twenty-four mice were divided into 6 treatment groups and 4 replications. The first group was a group of mice on a normal diet without PEM, only given standard milk pellets A (P1). The second group was malnourished mice that were given standard food in the form of milk pellets A (P2). The third group was malnourished mice that were fed malnutrition food (P3). The fourth group was malnourished mice given CF bananas (P4). The fifth group was malnourished mice given CF cassava (P5). The sixth group was malnourished mice that were given CF corn (P6).

2.1 Research Flow

2.1.1 Creating Conditions of Malnutrition

Mice were acclimatized for 7 days and placed in plastic cages with 30 g of standard feed (milk A pellets) and drinking mineral water regularly. Mice were recorded and weighed initially, then separated individually. On day 8, mice were given a Protein Energy Malnutrition (PEM) diet for treatment groups P2, P3, P4, P5, and P6. Group P1 was still given standard feed. Body weight was measured every week to determine changes in body weight in the malnutrition model.

2.1.2 Making Malnutrition Feed

Malnutrition feed is made with several ingredients, namely, 5 g corn oil, 10g tapioca flour, 20 g corn flakes, and vitamins mineral mix 0.015 g and adding a little water. The feed mixture was formed into balls and given to mice at 30 g per day.

2.1.3 Making CF Feed

CF feed is given for 4 weeks as much as 30 g. The main flour consists of banana, cassava, and corn. Each flour weighed 9.375 g with the addition of 3.75 g tempeh flour, 3.75 g chickpea flour, 3.75 g peanut flour, 3.75 g corn oil, 5.625 g sucrose, and vitamins-mineral mix 0.015 g. Each main flour is mixed with additional flour and a little water.

2.1.4 CF Treatment

CF was administered to mice in groups P4, P5, and P6. The feed is shaped like a circle. The CF treatment was carried out for 4 weeks in the amount of 30 g and given by drink optional. The remaining feed is weighed every day and the body weight is monitored every week.

2.1.5 Data Collection

After being given treatment for 4 weeks, the mice were anesthetized by intramuscular injection with xylazine and ketamine, as well as surgery. Blood is taken from the heart as much as 1.5 ml using a syringe of 3 ml. Blood was put into a microtube and incubated at 37 °C for 15 minutes. Next, the blood was centrifuged at 3000 rpm for 15 minutes. The resulting blood serum is taken using a micropipette to be inserted into the new microtube. All blood was stored at −20 °C. Blood serum samples were analyzed by the method directly using a spectrophotometer.

2.2 Data Analysis

The results of LDL and HDL levels were analyzed by normality distribution tests, homogeneity tests, and Analysis of Variance (ANOVA) to determine the effect of CF. Furthermore, if there is a significant difference, then continue with Duncan's Multiple Range Test (DMRT) with a significance level of 5% to compare results and see the average differences in each treatment. Data were analyzed using SPSS 25 and presented in diagram form.

3 Results and Discussion

During malnutrition, mice show physical changes such as weight loss, hair loss, stiffness, and less active behaviour compared to normal mice [42]. Rats that were given CF food showed an improvement in body weight and behaviour that began to become active again.
The data obtained in this study were data on LDL and HDL levels in malnourished Wistar strain white mice. The data will be analyzed statistically. Data on HDL and LDL levels are presented in Fig. 1. and Fig. 2. This data was processed using the Shapiro-Wilk test and it was concluded that all data had a normal distribution ($p > 0.05$).

3.1 HDL Levels

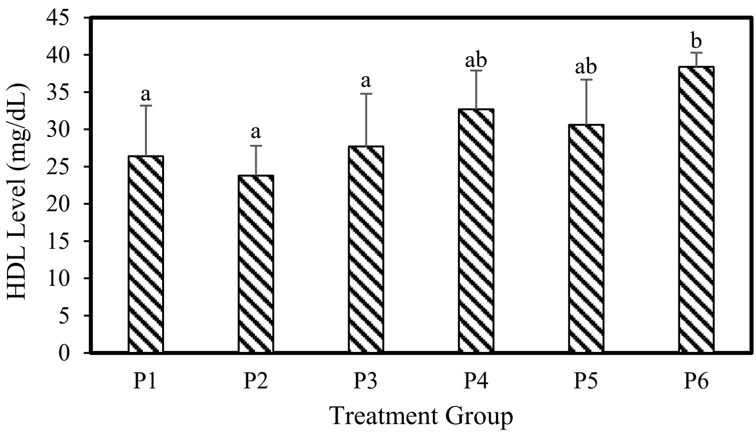
The analysis results in Figure 1 show that when giving CF, there was a significant difference in HDL levels between each treatment. HDL levels at P1 were 26.45 ± 6.89 mg/dL, at P2 were 23.80 ± 4.01 mg/dL, at P3 were 27.72 ± 7.08 mg/dL, at P4 were 32 .75±5.21 mg/dL, at P5 it was 30.67±6.08 mg/dL, and at P6 it was 38.47±1.89 mg/dL. The analysis of HDL levels in Figure 1 shows that treatment P6 has the highest HDL levels and is significantly different from treatments P1, P2, and P3 and not significantly different from P4 and P5. These results indicate that giving CF affects HDL levels of malnourished male Wistar strain white rats.

The P1 treatment group was a group that was given a normal diet without PEM, so the blood plasma HDL level value in this group was a normal HDL level value. Blood plasma HDL levels in normal mice are between 35 – 85 mg/dL [43] (Indra & Panunggal, 2015). Malnourished mice fed standard feed (P2) had a mean below the normal treatment group (P1), which was thought to be due to physiological changes in increased triglyceride (TG) levels. Increased triglyceride levels are caused by liver X receptor (LXR) increases; thus, the activity of Lipoprotein Lipase (LPL) decreases. An increase in triglycerides is followed by a decrease in HDL levels [44].

The P3 treatment group had higher HDL levels than the normal treatment group (P1) and the P2 treatment group. The results of this study are not in line with previous research, which showed that HDL levels decreased compared to normal treatment [13]. The malnutrition treatment group (P3) showed increased cholesterol mobilisation from the tissues to the liver. The increase in HDL levels is thought to be due to the biosynthesis of Apolipoprotein A1 (ApoA1) in the liver in response to oxidative stress [45]. ApoA1 is the main Apoprotein that binds lipids, cholesterol, and triglycerides to form HDL. The increase in ApoA1 in malnutrition is a form of compensatory response to protect against free radicals. In other cases of malnutrition, it revealed an increase in ApoA1 in the liver to treat inflammatory disorders because it has antioxidant and anti-inflammatory [46].

Malnourished mice given CF banana (P4), CF cassava (P5), and CF corn (P6) had higher HDL levels than the P1 group. Increased HDL levels indicate improvements in blood vessels that occur in conditions of malnutrition. The P4 group of mice was given the main ingredient, banana flour. Banana flour contains 70-80% resistant starch, 0% fat, 3.04% protein, and 17,5% fiber [32]. The P5 group of mice was given the main ingredient, tapioca flour. Tapioca flour is flour derived from cassava starch. This flour has a nutritional content of protein 0.59%, fat 3.39%, water 12.9%, and carbohydrates 6.99% with starch 73.3%-84.9% [36]. Starch is a glucose polymer carbohydrate consisting of amylose and amylopectin. Tapioca flour comprises 17% amylose and 83% amylopectin [47]. The P6 group of mice was given corn flour as the main ingredient with carbohydrates consisting of 72-73% starch and 8.56-9.36% crude fiber [39,40].

The three main ingredients in the CF variant contain quite highly complex carbohydrates. Complex carbohydrates consist of fiber and starch. Fiber and starch cannot be digested by digestive enzymes and the small intestine but can be hydrolyzed by bacteria in the large intestine. Fiber and starch can also reduce fat absorption in the small intestine and fermentation of these two materials by several specific bacteria will produce metabolites in the form of SCFA [48]. The presence of SCFA plays an important role in oxidative stress, inflammation, and improving lipid metabolism. After being digested and fermented, the fiber will turn into SCFA and then enter the liver via the hepatic portal vein. SCFA will play a role in inhibiting lipogenic enzymes in the liver, namely glycerol-3-phosphate acyltransferase. This enzyme has a role in lipid synthesis in the body [49].



Description: P1: normal feed; P2: standard feed; P3: malnutrition; P4: CF banana; P5: CF cassava; P6: CF corn

Fig. 1. HDL levels in mice after treatment

The prior research in mice shows that SCFA can improve animal-induced dyslipidemia and atherosclerosis by inhibiting intestinal cholesterol. Inhibited cholesterol can reduce LDL levels and increase HDL [50]. This is in line with research that proves that fiber and starch interventions can increase the activity of lecithin cholesterol acyltransferase (LCAT) and hepatic lipase (HL) in hyperlipidemia experimental mice. Increased LCAT activity can convert free cholesterol into cholesterol esters, one of the ingredients for the formation of new HDL in the body so that the amount increases. Increased HL activity results in a decrease in triglycerides, cholesterol, VLDL levels, and HDL levels due to increased lipolytic activity in the liver [51].

Due to the low protein content of the three main ingredients, it is necessary to add protein sources such as nuts to increase protein and energy [52]. An increase in protein can cause increased apolipoprotein synthesis. The presence of additional protein can also increase the catabolic rate of ApoA1 in HDL particles [53]. Sufficient apolipoprotein can increase the synthesis of HDL levels which were previously disturbed. The addition of vegetable protein content consisting of tempeh flour, chickpea flour, and peanut flour increases blood plasma HDL levels.

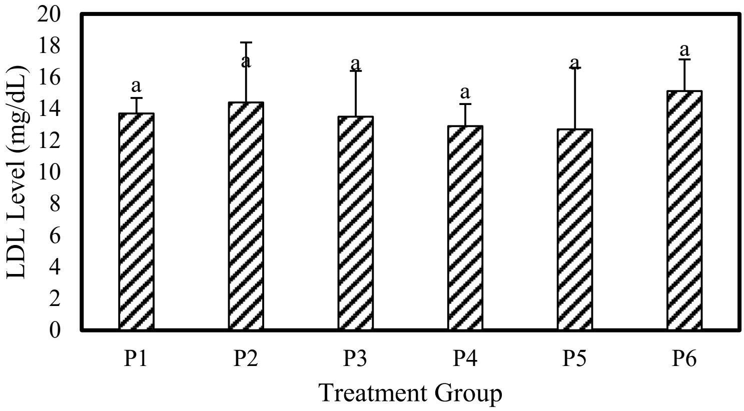
Peanuts are rich in protein content. About 30% of peanut protein consists of essential amino acids such as lysine, isoleucine, leucine, methionine, tryptophan, phenylalanine, arginine, histidine, and valine [54]. These essential amino acids are needed to support the growth of rumen microbes, so they positively affect the fermentation ability and digestibility of feed [55]. Tempe flour contains around 51.73% protein, complete essential and non-essential amino acids, high isoflavones, high fiber, and is easy to digest [56]. The amino acids contained in tempeh flour include arginine, alanine, and glycine. Chickpea flour or chickpeas have quite high nutritional content. Chickpeas contain many healthy basic ingredients such as protein, starch, fiber, minerals, vitamins, fatty acids, and phenolic compounds, namely phenolic acids and flavonoids, especially isoflavonoids. Isoflavonoids are the main bioactive components in chickpeas [57].

The isoflavone content in tempeh, chickpea, and peanut flour is important in reducing hydroxyl free radicals, superoxide free radicals, and lipid peroxyl free radicals. Isoflavones, which have antioxidant properties, can help prevent oxidation of LDL cholesterol in the arteries, thereby reducing cholesterol levels. In line with previous research, giving tempeh flour to rats on a malnourished diet can increase HDL levels [13]. The isoflavone content in nuts can increase the secretion of ApoA-1 from liver cells. Apolipoprotein A-1 is the main precursor for the formation of HDL cholesterol. It is known that an increase in apolipoprotein A-1 will stimulate HDL synthesis. Apolipoprotein A-1 will bind LCAT which plays a role in converting free cholesterol into cholesterol esters, so that HDL levels are formed [58].

3.2 LDL Levels

Rate check results LDL in malnourished Wistar strain mice that have been given CF are shown in Figure 2. The results of examining LDL levels in malnourished Wistar strain mice that had been given CF showed no significant differences between each treatment regarding LDL levels (Figure 2). LDL levels at P1 were 13.75 ± 0.99 mg/dL, at P2 were 14.47 ± 3.82 mg/dL, at P3 were 13.45 ± 2.95 mg/dL, at P4 were 12, 95±1.42 mg/dL, at P5 it was 12.77±3.99 mg/dL, and at P6 it was 15.12±2.04 mg/dL. The analysis of LDL levels in Figure 2 shows that treatments P1, P2, P3, P4, P5, and P6 are not significantly different. These results indicate that administration of CF does not affect HDL levels of malnourished male Wistar strain white rats.

The normal treatment group (P1) is a normal diet group without PEM, so the blood plasma LDL level value in this group is the normal LDL level value. The normal threshold for LDL in mice is 7-27.2 mg/dL [43]. Malnourished mice fed standard feed (P2) had a higher mean than the normal treatment group (P1), which was thought to be due to physiological changes in triglyceride (TG) levels. The increase in triglyceride levels is caused by increased LXR so that Lipoprotein Lipase (LPL) activity decreases. This situation also affects the increase in cholesterol synthesis because there is a failure to inhibit the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (3HMG-CoA). Therefore, more cholesterol is synthesized, thus influencing an increase in LDL levels [44].



Description: P1: normal feed; P2: standard feed; P3: malnutrition; P4: CF banana; P5: CF cassava; P6: CF corn

Fig. 2. LDL levels in mice after treatment

The malnutrition treatment group (P3) had lower LDL levels than the normal treatment group (P1) and the P2 treatment group. The results of this research are not in line with research conducted by previous researchers [13]. The malnutrition treatment group (P3) showed a decrease in cholesterol synthesis in blood plasma, which caused LDL levels to decrease. The reduction in LDL levels compared to normal treatment in malnourished mice also aligns with previous research [59]. The decrease in LDL levels in malnutrition is thought to be due to interference with CETP. Disruption of CETP causes CE-rich HDL levels to increase ApoA1 and LDL and ApoB levels to decrease [60].

Malnourished mice were given CF banana (P4) and CF cassava (P5), and their LDL levels decreased compared to those of the normal treatment group (P1). Decreased LDL levels indicate improvements in blood vessels that occur in conditions of malnutrition. In malnourished mice given CF banana (P4), did not differ significantly from those given CF cassava (P5); it is suspected that this was due to disruption of CETP so that ApoB and LDL levels decreased [60]. CF corn (P6) had higher LDL levels than P1, allegedly because triglyceride levels increased, increasing LDL levels. The increase in LDL levels at P6 is still considered normal [43]. The increase in LDL levels in the P6 group is also thought to be due to fatty liver caused by previous malnutrition treatment, so LDLR is unable to capture LDL levels that go to the liver [18].

The CF banana malnourished rat group (P4) was given the main ingredient banana flour. Banana flour contains 70-80% resistant starch, 17,5% fiber, 0% fat, and 3,04% protein [32]. Banana flour has several advantages, including a high resistant starch content and functional properties, namely as a prebiotic, which is good for intestinal health because it contains fiber. Additionally, banana flour contains pectin. Pectin is often referred to as anti-cholesterol because it can bind bile acids resulting from cholesterol metabolism. The more bile acids that bind to pectin, the more cholesterol is excreted from the body so that the amount of LDL levels in blood plasma decreases. Pectin is a dietary fiber that can reduce cholesterol absorption. Pectin binds and increases the excretion of bile acids, which are then excreted in the feces. A decrease in bile acid level causes the liver to use cholesterol in the blood as bile acid. Increasing bile acids impacts reducing plasma cholesterol and LDL levels and increasing turnover cholesterol in experimental animals.

Flavonoids in bananas are also rich in antioxidants, which act as oxidation inhibitor compounds by neutralizing free radicals and reducing oxidative stress [61]. The liver is the site of endogenous cholesterol biosynthesis into the bloodstream and received exogenously as VLDL. VLDL will produce LDL which is responsible for carrying cholesterol to all tissues that need it. This excess cholesterol will be returned to the liver to be broken down through the HDL mechanism [62]. Therefore, reducing cholesterol can reduce LDL.

Tapioca flour has a nutritional content of protein 0.59%, fat 3.39%, water 12.9%, and carbohydrates 6.99%, with starch 73.3%- 84.9% [36]. High starch content causes a decrease in LDL levels. This shows that there is a mechanism for reducing cholesterol, which is thought to involve bile acid secretion. Previous research revealed that giving tapioca flour to mice caused lower LDL levels than normal treatment, which involved increased bile acid secretion [63].

Corn flour has a content of carbohydrates consisting of 72-73% starch and 8.56-9.36% crude fiber [39,40]. Fiber cannot be digested by digestive enzymes and the small intestine but can be hydrolyzed by bacteria in the large intestine. Bile acids will then be excreted into the intestines to be reabsorbed in the liver. Some bile acids will be converted into secondary bile acids by bacteria. The ability of fiber to bind bile fluid in the intestine will signal the liver to absorb cholesterol from the blood continuously and sustainably for metabolism and excretion in the gallbladder. As a result, cholesterol in the blood is reduced so that LDL levels decrease [64].

Preliminary evidence suggests that adding nuts to the regular diet reduces blood levels of apolipoprotein B and improves HDL function. There is also evidence that nuts dose-dependently increase lipids and lipoproteins. Previous research stated that the body that received nuts intake could reduce triglycerides, total cholesterol, and LDL levels [65].

4 Conclusion

Giving the CF variant increased HDL levels and reduced LDL levels compared to normal and malnourished mice. The treatment of malnourished mice given CF showed a significant difference in HDL levels, with the administration of CF banana, CF cassava, and CF corn improving serum HDL levels. The treatment of malnourished mice given CF showed no real difference in LDL levels, but giving CF banana and CF cassava could reduce serum LDL levels.

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