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Role of functional foods in the management of diabetes mellitus: a concise review

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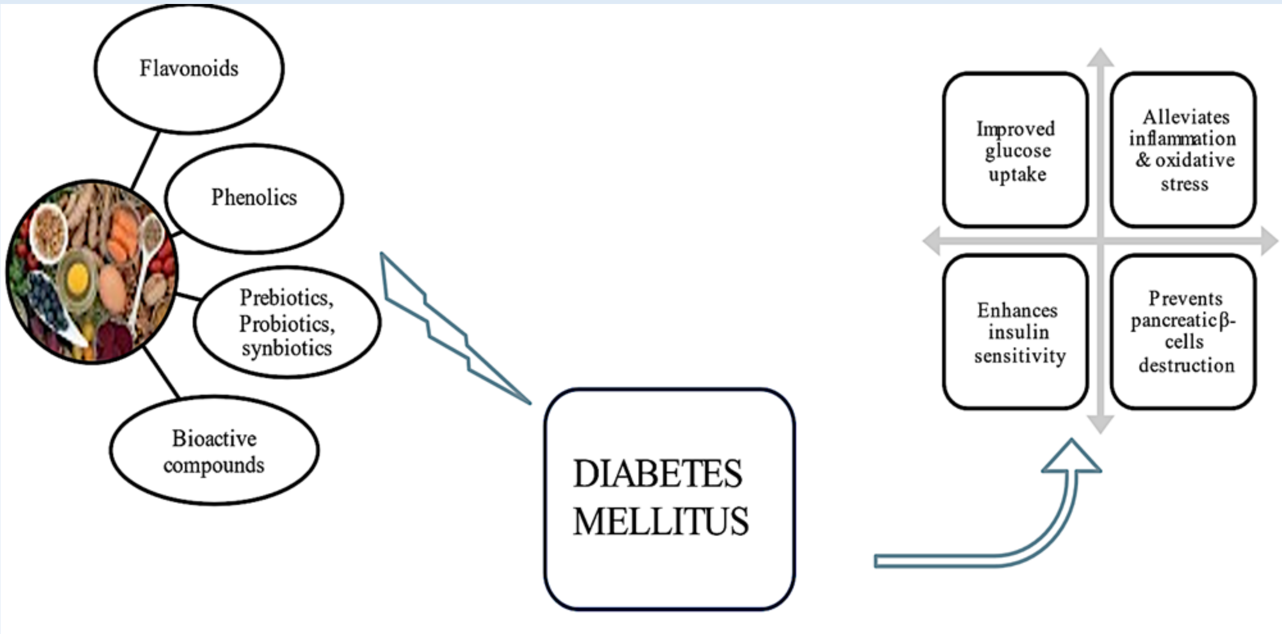
ABSTRACT

Diabetes mellitus is a group of metabolic conditions characterized by elevated levels of blood glucose and it has become a very common disease among individuals in the world at large today. The rate of incidence of diabetes, even in Nigeria, has risen drastically over the years. Different forms of treatment have been tried and used over the years, including insulin therapy and the use of various medications, although some of these medications are accompanied by side effects. Diabetes mellitus and related conditions have been stated to be treated effectively with several natural products. Functional foods are being utilized to prevent and manage diabetes mellitus because they contain antioxidant, anti-inflammatory, and insulin sensitivity potentials. Since oxidative stress, inflammation, and insulin resistance are associated with this disease, these foods can be effective in managing the disease. This review aimed to explain the modes of action of some of these functional foods in managing diabetes.

Keywords: Diabetes mellitus, management, functional foods, antioxidant, anti-inflammatory



INTRODUCTION

Diabetes Mellitus occurs as a progressive disorder of the body's metabolism and is characterized mainly by conditions ranging from chronic hyperglycemia to defects related to the secretion of insulin, its actions, or even both [1]. It is characterized by changes in lipid, protein, and carbohydrate metabolism. There are different symptoms of the disease, and the severity of the symptoms is mainly due to the diabetes type and duration. If not managed or treated properly, diabetes results in dysfunction of body organs and systems and can ultimately lead to the death of the individual. Cardiovascular complications, retinopathy, neuropathy, and nephropathy are some complications related to diabetes mellitus [2].

Diabetic cases have been described as the epidemic of the century, due to their high incidence and prevalence rates with an increased population of diabetic individuals in 1980–2014 from 108 million to 422 million respectively. In 2012, the mortality rate of 2.2 million patients was linked to increased blood sugar levels, and in 2016, diabetes mellitus caused the deaths of approximately 1.6 million people. Also in 2016, diabetes was estimated as the seventh major cause of mortality by the World Health Organization [3].

Different hypoglycemic (glucose-reducing) drugs like sulfonylureas and biguanides are utilized in diabetes treatment to restore the inadequate production of insulin and insulin resistance, although over time some of these drugs have been discovered to have side effects [4]. Alternatives such as medicinal foods, herbal plants, food supplements, and nutraceuticals that have minimal or no side effects are therefore being considered in diabetes management. Therefore, this review attempts to discover more about the modes of action of these alternatives in the management and treatment of diabetes.

Diabetes Mellitus: Type 1 diabetes, also referred to as insulin-dependent diabetes is an autoimmune disease that accounts for about 10% of diabetic cases [5]. It is caused by insufficient insulin secretion by the pancreatic beta cells leading to insulin deficiency [6]. It is due to genetic factors and is associated with endocrine and metabolic conditions [7]. T1DM also occurs in adults despite being more prevalent among juveniles [8]. Long-term complications include neuropathy, nephropathy, and coronary heart disease [9].

Type 2 diabetes mellitus (T2DM), also known as non-insulin dependent diabetes mellitus, is due to the dysfunction of the beta cell of the islet of Langerhans and reduction in insulin sensitivity of target tissues [2]. T2DM is a complex disease with lifestyle, epigenetics, and genetics playing different roles in its pathogenesis. The genetic expressions involved in the production of insulin from the β-cells and insulin sensitivity in the tissues are also affected. Oxidative stress disrupts insulin-induced glucose uptake and insulin signaling in skeletal muscle, fat tissues, and liver resulting in insulin resistance. Hepatic insulin resistance stimulates glucose production from non-carbohydrate sources, leading to excessive hyperglycemia which causes more oxidative stress-induced impairment and T2DM complications (Figure 1) [10]. Insulin resistance affects serine protein kinase B/Phosphatidylinosito-3-kinase (Akt/P13K), peroxisome proliferator-activated receptor (PPAR), AMP-related protein kinase (AMPK) which are proteins or genes involved in the insulin signaling pathway [11].

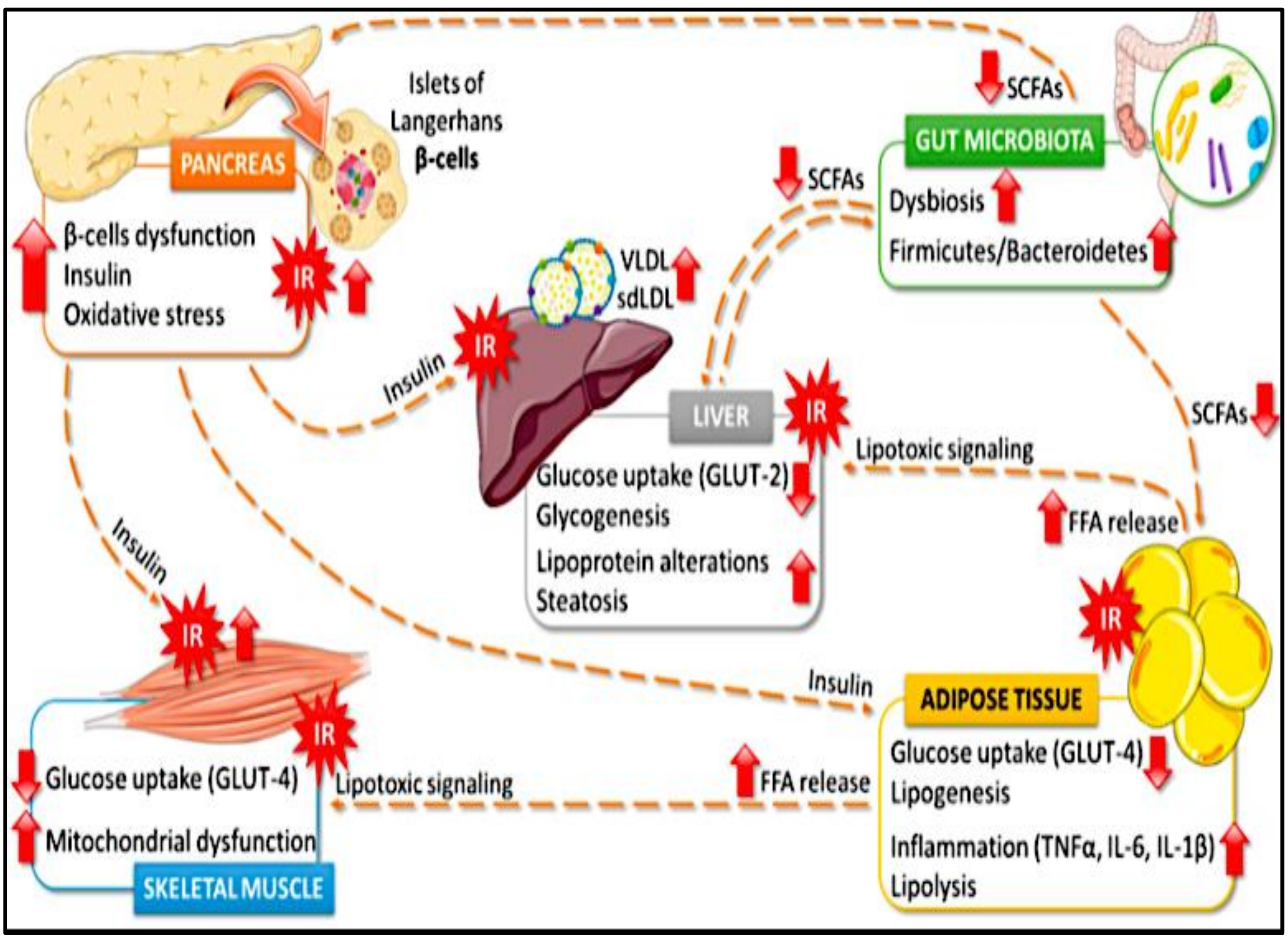


Figure 1: Etiology of Type 2 Diabetes Mellitus [12].

Functional Foods: According to the Functional Food Center (FFC), "functional foods are defined as natural or processed foods containing known or unknown biologically active compounds, which when consumed in defined, effective non-toxic quantities provide a clinically established and recognized health benefit for the prevention, management or treatment of chronic diseases" [13]. Functional foods can either be natural (fruits, vegetables, nuts, legumes, vitamins, minerals, and seafood) [14] or processed (fortified food products) [15]. They can either be of a plant (rice, soy, rice, flaxseed, garlic) or animal origin (fish, dairy products) [16] or value-added foods [17]. Bioactive compounds are the main effective constituents of functional foods. Some of these bioactive compounds include prebiotics, probiotics, synbiotics, polyunsaturated fatty acids, vitamins, essential fatty acids, dietary minerals, phytochemicals, antioxidants, and phytosterols [18-19]. Asides from their nutritional values, they may lower the risks of cardiovascular-related diseases, dyslipidemia, T2DM, and cancer [20-21]. Consistent consumption of functional foods has been reported to improve oxidative stress, cholesterol levels, and inflammation, and reduce insulin resistance while improving insulin sensitivity which is integral in preventing, managing, and treating T2DM [22]. Bioactive peptides from functional foods have been discovered to inhibit enzymes involved in digesting carbohydrates (α-glucosidase and α-amylase), reduce glucose absorption in the small intestine and improve insulin secretion [23].

MECHANISMS OF ACTION OF FUNCTIONAL FOODS IN DIABETES MANAGEMENT

Phytochemicals: Phenolic compounds in blackberries stimulate glucose uptake by HepG2 cells and increase cellular glycogen content [24]. Adequate maintenance of mitochondrial membrane potential is necessary for normal cell functioning because mitochondria are crucial for controlling cellular ROS [25]. The pathogenesis of insulin resistance and diabetes-related complications may be influenced by mitochondrial dysfunction [26]. Blackberries therefore cause increased levels of cellular glutathione and improve mitochondrial membrane potential, indicating that these compounds perform their antidiabetic activity via the antioxidant properties they possess [24].

Flavonoids found in diverse fruits, nuts, grains, chocolate, and plants possess anti-diabetic potentials. They regulate insulin secretion, glucose uptake, and blood glucose levels [27]. Flavonoids in hibiscus petals reduced high glucose levels by promoting insulin release from the pancreatic β-cells. It also down-regulated inflammatory cytokines expressions by reducing NF-κB nuclear translocation and up-regulated foxO-1, MafA, and Ucn-3 expressions in the β-cell [28]. Flavonoids in the citrus genus increased GPx, SOD, and CAT levels; expressions of Akt, PPARγ, and P13K while reducing PTP1B expression. Modulation in IL-6, IL-2, NF-KB, IL-1β, and TNF-α expressions were also observed. All these improved glucose absorption in the peripheral cells by reducing the levels of inflammatory biomarkers linked with the pathogenesis and development of diabetes-related complications [29].

Quercetin, a flavonoid derived from berries, onions, apples, seeds, flowers, and leaves has antihyperglycemic activity [30]. Quercetin regulated the mitogen-activated protein kinase (MAPK) insulin-dependent pathway, thus enhancing the uptake of glucose [31]. It increased the level of glutathione peroxidase, regulated NF-κB signaling, and prevented pancreatic β-cells death [32]. In diabetic rats, quercetin reduced malondialdehyde (MDA) and increased liver GPx activity [33]. Quercetin from F.racemosa stem bark reduced glucose levels, and increased CAT, SOD, and GSH levels [34].

Prebiotics, Probiotics, and Synbiotics: Prebiotics are food supplements with non-digestible fibers that selectively enhance the actions and growth of gut bacteria. They include inulin, oligofructose, and galacto-oligosaccharides. *Bifidobacterium and Lactobacillus* which are commonly utilized probiotics incorporated in dietary supplements and functional foods [35]. Probiotic food products can be infant formula, ice cream, cheese, and fruit juices. Synbiotics are food supplements with both prebiotics and probiotics having synergistic roles which improve probiotics' survival, and balance the gut microbiota by increasing lactobacilli and bifidobacteria levels [35-38].

There is a link between gut microbiota and diabetes; prebiotics and probiotics which control gut microbiota can therefore be employed in diabetes management due to their mechanisms of action which include: responses to inflammation and oxidative stress and modifying intestinal microbiota [39-40]. Probiotics had a possible effect on glycemic index and significantly decreased blood glucose in diabetic individuals [41] but no significant effect on lipid profile. Zhang *et al* [42] reported a significant decrease in FBG, OGTT, HbA1c, LDL, HOMA-IR, and TC levels in diabetic rats. Positive effects of probiotics supplements on fasting blood glucose, HbA1c, and insulin were observed in individuals with T2DM [43] while Akbari & Hendijani [44] reported a significant decrease in fasting blood glucose and Hb1Ac with no effect on insulin levels and insulin resistance. The antioxidant and anti-inflammatory roles of probiotics are still controversial. However, Zhang *et al* [42] discovered that *Bifidobacterium animalis* had a significant impact on GSH, CAT, SOD, and GSH-Px levels but reduced MDA levels in diabetic rats; there was also increased production of IL-10. Co-administration of probiotics and synbiotics significantly reduced TNF-α, MDA, and CRP levels while increasing NO, GSH, and TAC levels in diabetic individuals but no effect on IL-6 [39,45]. Supplements of *Bifidobacteria,* a significant probiotic in the human intestine greatly improved insulin sensitivity with studies on *B. animalis ssp. lactis 420, Bifidobacterium lactis HY8101, Bifidobacterium adolescentis,* and *Bifidobacterium breve* confirm this effect [42]. Probiotics stimulated cholecystokinin (CCK), gastric inhibitory proteins (GIP), peptide YY and GLP-1 production, enhancing insulin secretion and uptake of glucose especially in the muscle [46-47].

Studies have shown that synbiotics and probiotics lowered the levels of inflammatory mediators and hyperglycemia [48-49] Treatment with probiotics improved the binding potential of insulin in T2DM and prevented β-cells destruction in diabetic mice [50]. It also promoted the transcription of glucose transporter thereby increasing the sensitivity of insulin in tissues [51].

Dietary Polysaccharides: Dietary polysaccharides are derived from fruits, vegetables, and herbs and they are naturally edible [52]. They possess anti-diabetic, antimicrobial, anti-cancer, anti-inflammatory, and antioxidant [53]. Polysaccharides from *Acacia tortilis* gum reduced glycated hemoglobin (HbA1c), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), total cholesterol, fasting blood glucose, very low-density lipoprotein (VLDL), liver enzymes like AST, ALT and significantly increased high-density lipoprotein (HDL) [54]. Polysaccharides in *Morus alba* L. fruit improved blood insulin levels by increasing the expressions of glucose transporter 4 (GLUT4), insulin receptor (InsR), serine/threonine-specific protein kinase (Akt), and insulin receptor substrate 2 (IRS-2) in rats induced with T2DM [55]. Polysaccharides from mulberry leaf increased the production of insulin by upregulating insulin promoter factor 1 (PDX-1) and prevented apoptosis of the pancreatic β-cell by increasing B-cell lymphoma 2 (Bcl-2) and reducing BCL2 associated X protein (Bax) expressions in STZ-diabetic rats [56]. Mulberry fruit-derived polysaccharides reduced MDA and blood glucose; increased CAT, GSH-Px, and SOD levels, and improved pancreas and liver damage significantly [57]. Polysaccharides derived from G.frondosa, a mushroom also lowered the levels of NO synthase, and MDA while increasing CAT, GSH-Px, and SOD levels in STZ-diabetic rats [58]. Polysaccharides from other mushrooms like *Hericium erinaceus*, *Ganoderma lucidum*, and *Agaricus bisporus*, have been discovered to regulate GLUT, glycogen synthase (GS), and glycogen synthase kinase (GSK-3 ß) expressions in the muscle and liver thereby regulating blood glucose and glycogen levels [59]. They also decreased the actions of α-amylase, and α-glucosidase, and enhanced P13K/AKT pathways [60]. ß-D-glucan, a constituent of mushrooms decreased NF-kB activity inhibiting inflammatory cytokines activation. It also prevented apoptosis of β-cell in the pancreas [61]. In STZ and high fat-induced diabetic mice, polysaccharides of *I. obliquus* enhanced GLUT4 translocation and activated P13/Akt pathways thereby reducing blood glucose [62].

Polysaccharides from *Vigna radiate* L. ameliorated damage to the pancreas by reducing nuclear factor kappa B (NF-κB), IL-6, IL-8, and TNF-α levels [63-64]. Polysaccharides improved glucose uptake by stimulating P13K/Akt and MAPK/JNK/ERK pathways which enhance insulin sensitivity [65-66].

Polyunsaturated Fatty Acids (PUFAs): Sources of PUFAs include fish, cereals, fish oil, and oilseeds [67]. They are beneficial in their protective effects against inflammation, and it has been discovered that in T2DM, PUFAs reduced the levels of inflammatory biomarkers like TNF-α, IL-6, and CRP [68]. Omega-3 fats are found in fish such as salmon, tuna, and a few plant oils while omega-6 fats are found in many plants' oils [69-70]. In children, omega-3 fatty acids (ω-3 FA) reduced the risk of beta cell islet autoimmunity at greater possibility of developing T1DM because of its anti-inflammatory activities. Omega-3-fatty acids also improved mononeuropathy in T1DM patients. ω-3 FA regulated carbohydrate metabolism by upregulating the PPAR signaling pathway in the skeletal muscle thereby reducing gluconeogenesis and increasing glycolysis [71].

Bioactive Compounds*:* Bioactive compound are chemical constituents present in minimal quantities in food or plant products that have impacts on the body, supporting good health [72].

Lycopene, a bioactive compound in tomatoes, increased insulin secretion in STZ-induced rats, lowering blood glucose levels [73].

Kaempferol exhibited antidiabetic properties by reducing lipid peroxidation, activity of α-glucosidase, increasing insulin sensitivity, and antioxidant activity [74-75]. It also inhibited the NF-κB pathway by degrading I-kappa B kinase (IKK) thereby improving inflammation and insulin signalling [76].

P-coumaric acid reduced blood glucose levels by stimulating GLUT-2 in the pancreas, regulating lipid metabolism, and lowering levels of inflammatory biomarkers [77].

Cinnamic acid in berry, kiwi, pear, and plum exerted its antidiabetic actions by increasing glucose uptake, secretion of insulin and adiponectin, improving pancreatic β-cells functioning, and reducing actions of protein tyrosine phosphatase 1B, pancreatic α-amylase, α-glucosidase, and dipeptidyl peptidase-4 [78].

Catechin increased nitric oxide production by stimulating endothelial phosphoinositide (P13K) and nitric oxide synthase (eNOS) thereby reducing lipid peroxidation and oxidative stress [79]. Bioactive compounds in garlic downregulated inducible NO synthase (iNOS) and cyclooxygenase-2 (COX2) expressions and decreased the levels of NO, TNF-α, NF-κB, and IL-1β [80].

Curcumin, a purified compound from *Curcuma longa* L improved insulin signaling by upregulating the expressions of P13K, Akt, IRS-2, and (IGF)-1R and downregulating IRS-1 and IR [81]. A significant reduction in glucose levels, IL-6, and C-reactive protein and an improvement in insulin levels were observed in diabetic rats after curcumin administration [82]. The expression of cyclic nucleotide phosphodiesterases was downregulated by curcumin thereby increasing pancreatic secretion of insulin [83]. In STZ-induced rats, there was a decrease in iNOS, vascular endothelial growth factor (VEGF), and intercellular adhesion molecule-1 (ICAM-1) levels [84]. Curcumin extract greatly improved HbA1c level and HOMA-IR index [85]. In diabetic women with polycystic ovarian syndrome, curcumin increased HDL-C, insulin sensitivity, expressions of low-density lipoprotein receptor and peroxisome proliferator-activated receptor gamma (PPAR-γ) but decreased fasting glucose, insulin, HDL-C, and total cholesterol levels after 12 weeks of daily intake [86-87].

Curcuminoids, phenolic compounds from *Curcuma longa* roots have hypoglycemic activity and improve insulin resistance in the skeletal muscle by upregulating GLUT4 actions and the level of insulin receptor substrate 1 (IRS-1) thereby enhancing glucose absorption in high-fructose fed Wistar rats [88].

Resveratrol, a polyphenol found in peanuts, grapes, and berries exerts anti-inflammatory properties by suppressing the activities of cytokines, and pro-inflammatory kinases, increasing the expression of sirtuin (SIRT1), and inhibiting nuclear factor-κB. Resveratrol also has antioxidant capacities. In cellular and animal studies, resveratrol possesses glucose-reducing effects and enhances insulin production from the β-cells in T2DM [85]. It prevented dysfunctions of the pancreatic β-cells and suppressed phosphodiesterase activity thereby increasing β-cells function [89].

Ferulic acid, abundant in grapes, cereal, spinach, whole grains, barley has been discovered to possess cardioprotective potentials by significantly reducing blood glucose, HbA1c, cardiac hypertrophic index, cardiac CK-MB, LDH while significantly increasing SOD, CAT, GPx, GRd and GSH in the cardiac tissue in STZ-induced diabetic rats [90

CONCLUSION

Diabetes prevalence is rapidly rising at an alarming rate. Prevention and management of the disease have become of optimum concern amongst health workers and researchers. Several studies have uncovered the usefulness and effectiveness of functional foods in the management of diabetes. Some of these functional foods improve insulin resistance, reduce oxidative stress, and lower blood glucose and inflammation which are associated with diabetes. Therefore, their use can be encouraged in the management of diabetes.

List of Abbreviations: T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, PPAR: peroxisome proliferator-activated receptor, AMPK: AMP related protein kinase, ROS: Reactive oxygen species, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, FBG: Fasting blood glucose, OGTT: Oral glucose tolerance test, LDL: Low-density lipoprotein, TC: Total cholesterol, GLUT: Glucose transporter, NO: Nitric oxide, HDL: High-density lipoprotein, IR: Insulin resistance, IRS: Insulin receptor substrate, AST: Aspartate transaminase, ALT: Alanine transaminase, MDA: Malondialdehyde.

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