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Review

The Role of Astaxanthin on Chronic Diseases

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Abstract: Natural astaxanthin exists widely in algae, fungi, shrimp and crab, and, as a strong antioxidant, has potential effects on cardiovascular diseases, cancer, liver diseases and other physical health diseases. The treatment of many diseases involves the body's signal transduction to regulate the body's antioxidant defense system and inflammation. Astaxanthin is usually used as a dietary supplement, which plays an antioxidant and anti-inflammatory role in the organism. This article reviews the structure, source of astaxanthin and how it plays an anti-inflammatory and anti-oxidant role in organisms, especially in treating diabetes.

Keywords: astaxanthin; antioxidant; anti-inflammatory; diabetes; cardiovascular diseases

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1. Introduction

Astaxanthin was discovered in terrestrial animals in the mid-20th century [1]. It is a kind of carotenoid, and the antioxidant activity of astaxanthin is 10 times stronger than other carotenoids, such as zeaxanthin, canthaxanthin. It has been reported that astaxanthin owns many functions, such as preventing cardiovascular diseases, anti-diabetics, protecting the retina, and enhancing immunity [2]. Carotenoids are the general term for a class of natural pigments, usually used as coloring agents for crustaceans, and play important roles in human health. Humans cannot synthesize this type of pigment, and can only consume it through diet or supplements, as a dietary supplement, astaxanthin can be easily absorbed and is largely incorporated into human plasma lipoproteins [3–5]. Astaxanthin has cis–trans isomers and optical isomers in nature due to its special structure, two benzene rings are attached to both ends of the polyene chain, the presence of hydroxyl and ketone groups on the benzene ring makes astaxanthin active. Its active chemical properties make it often exist in esterified form [6–8]. The polar structure of the end of astaxanthin allows astaxanthin to cross the cell membrane damaging the cell membrane, it can promote the expression of antioxidant enzymes in the cytoplasm to mediate the redox reaction and inflammatory response in the cell. In addition, astaxanthin can combine with free radicals, which can reduce the damage of free radicals to the body, and it can also activate the expression of proteins related to the antioxidant system in the body [9].

According to statistics, there are less than 500 million people with diabetes worldwide in 2019, and this number will increase by 25% by 2030 and 51% by 2045 [10]. Diabetes is a metabolic disease characterized by high blood sugar. Based on the main causes, it is divided into four categories, type 1 diabetes, type 2 diabetes, gestational diabetes mellitus (GDM) and special types of diabetes due to other causes [11]. Before developing into a diabetic patient, the patient's blood sugar level is between diabetic blood sugar and normal blood sugar, pre-diabetes is a necessary process for diabetic patients, pre-diabetes is divided into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [12,13]. Glucose metabolism is regulated by pancreatic β cells and the feedback loop of insulin. High levels of glucose in the blood may stimulate the abnormal secretion of insulin by β

cells which, in turn, decreases the peripheral sensitivity to insulin and pancreatic secretory exhaustion [14,15]. Typically, there are no symptoms in pre-diabetes. If the cells are repeatedly exposed to the environment of high blood sugar, it will cause cell dysfunction, the longer the time and no relief, the irreversible phenomenon will appear [16]. Individuals with pre-diabetes can use their diet to control the development of diabetes and some complications caused by elevated blood sugar, screening of biomarkers for pre-diabetes has become one of the ways to prevent type 2 diabetes [17].

The redox imbalance of cells will participate in the expression of β cell-related functions, leading to the development of diabetes and diabetes-related complications [18]. Oxidative stress is caused by the imbalance of the redox system in the body. ROS is the product of redox reactions and also participates in intracellular signal transduction, excessive ROS levels will lead to oxidative stress [19]. In diabetic patients, in addition to damaging cells, ROS also affects cell gene expression. Factors that regulate hyperglycemia in cells are easily activated when subjected to stress [20]. Continuously high levels of high sugar in the body can cause diabetic microvascular complications [21]. Many cancer-promoting signaling pathways are also directly or indirectly related to ROS [22].

Many studies have shown that there is a causal relationship between chronic inflammation and insulin resistance [23]. Inflammation is a common pathological process in clinics: when the body undergoes tissue damage and infection, the body will repair the tissue and resist the infection through an inflammatory response [24]. For patients with type 2 diabetes, studies have reported that the use of anti-inflammatory drugs can reduce blood sugar levels in patients, so type 2 diabetes is considered an auto-inflammatory disease [25]. People can usually intervene in their own inflammatory response through external factors such as lifestyle. The antioxidant and anti-inflammatory functions of astaxanthin have been reported in many aspects [26,27], as a strong antioxidant and anti-inflammatory natural compound. The role of astaxanthin in the organism, especially its influence on diabetes and complications, will be shown below.

2. The Structure of Astaxanthin

The basic structure of carotenoids consists of a polyolefin chain and the terminal groups at the two ends through the process or methods of hydrogenation, dehydrogenation, cyclization and oxidation. When the arrangement of elements is in its native arrangement, the C–C and C=C in the polyene chain are hindered and undergo steric rotation, resulting in stereoisomerism of the compound, which becomes a cis–trans isomerism of the compound. Different carotenoids have different terminal groups, which makes their properties and intermolecular forces different [28]. In nature, astaxanthin mostly exists as all trans-astaxanthin. All trans-astaxanthin will isomerize with light exposure and when dissolved in organic solvents, among several cis structures, the most studied ones are 9-cis and 13-cis [29]. The hydroxyl group on the terminal benzene ring of all-trans astaxanthin have optical rotation, and there are two chiral centers on C-3 and C-3′, so all-trans astaxanthin has three structures: levorotatory, dextrorotatory and meso (also known as 3S, 3′S, 3R, 3′R and 3S, 3′R) [30], The structure of astaxanthin is shown in Figure 1. The presence of the ketone group and the hydroxyl group at the end of the benzene ring of astaxanthin gives astaxanthin an active chemical property, which can be combined with protein or esterified with fatty acids to stabilize the molecule. In addition, the esterification of astaxanthin is also a way of accumulation in the organism [8,31]. The esterification of astaxanthin mainly depends on the hydroxyl groups (–OH) at both ends of the molecules.

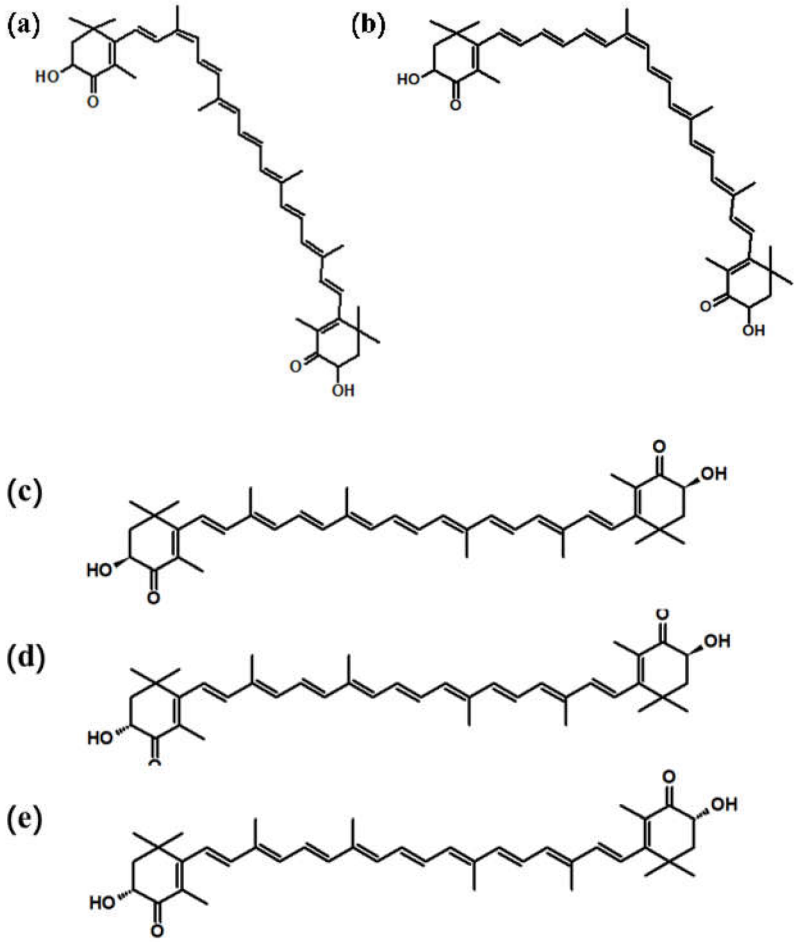

Figure 1. (**a**) 9-cis astaxanthin; (**b**) 13-cis astaxanthin; (**c**) 3S, 3′S astaxanthin;(**d**) 3R, 3′S astaxanthin; (**e**) 3R, 3′R astaxanthin.

3. Source of Astaxanthin

Most astaxanthin is found in aquatic animals and plants, it can act as a coloring agent of those species. The astaxanthin separated from Haematococcus pluvialis has optically pure (3S, 3′S) chirality if it is free astaxanthin or esterified astaxanthin [32,33]. The conformation of astaxanthin extracted from different organisms is not the same. The optical rotation of astaxanthin isolated from Antarctic krill is mainly 3R, 3′R [34]. Moreover, astaxanthin can form cis-astaxanthin under certain conditions, and some studies have confirmed that cis-astaxanthin is a superior antioxidant than all-trans astaxanthin, but the preparation of cis-astaxanthin is not easy. Direct extraction from microalgae is one of the ways to obtain cis-astaxanthin [35]. Synthetic astaxanthin is more economical than natural astaxanthin, but it is not suitable for human supplements. Synthetic astaxanthin is synthesized from petrochemical products, which toxicity makes the biosafety of synthetic astaxanthin becomes a problem, besides, the antioxidant activity of synthetic astaxanthin is 20–30 times lower than natural astaxanthin [36,37].

4. The Function of Astaxanthin

The biological safety and unique properties of astaxanthin determine that astaxanthin has a great role in biologically-related fields, and provides photo-protection for cells by mediating the antioxidant system of skin cells [38]. The benefits of astaxanthin to the human body have been studied, and in cardiovascular systems, it can inhibit the oxidation of low-density lipoproteins and prevent atherosclerosis [39]. As an extracellular factor, it can promote the proliferation and differentiation of neural stem cells as well as neuroprotection [40,41]. In a randomized trial, participants (average age 21.8 years old) took

astaxanthin for 8 weeks, astaxanthin showed anti-inflammatory effects in the volunteers after taking astaxanthin for 4 weeks (2 mg/day), and the concentration of astaxanthin in the plasma reached the maximum [42]. Chemotherapy drugs (doxorubicin) can cause liver damage in the human body through cytotoxicity. Using AST-corn (astaxanthin dissolved in corn oil) to treat the liver injury mouse, the dose is 100 mg per kg BW, experimental results showed that astaxanthin treatment can increase catalase and reduce the concentration of ROS, protect liver cell damage and reduce the degree of apoptosis [43]. Vascular calcification is a common pathological change common in atherosclerosis and diabetic vascular disease. The in vitro vascular calcification model shows that astaxanthin can up-regulate the expression of antioxidant enzymes during the process of vascular calcification, and 1M astaxanthin has the best therapeutic effect on calcification [44]. Over the years, research on astaxanthin and the role of astaxanthin are briefly described in Table 1, and the research of astaxanthin in the human body is shown in Table 2.

Table 1. Current research of astaxanthin in the field of biomedicine.

Species	Organ	Method	Dose	Function	Researcher
mice	Hippocampus	oral	60 mg/kg/day	PI3K/AKT/Nrf-2↑	Yuan Lu et al. [45]
rat	Brain	oral	60 mg/three times a week	COX-2↓, BDNF levels↑	Wanqiang Wu et al. [46]
mice	Testis	oral	60 mg/kg/day	RIPK1-RIPK3-MLKL↓	Yuan Lu et al. [47]
rat	joint	injection	50 mg/kg/day	COX-2/IL-6↓	Yi-Jen Peng et al. [48]
rat	pancreas	oral	40 mg/kg/day	ROS↓, GSH↑	Dilek Özbeyli et al. [49]
mice	Lung, thymus	injection	50 mg/kg/day	ROS↓, Nrf-2↑	Xiaolei Xue et al. [50]
mice	Liver	injection	60 mg/kg/day	TNF-α /JNK↓	Jingyao Zhang et al. [51]
mice	Bone	oral	4 μM/mL	Improve mitochondrial function of MC3T3-E1 cells	Hiroko Hoshi et al. [52]
mice	Eye	oral	50 mg/kg/day 5 μM/mL	Reduced apoptosis of retinal ganglion cells TNF-α/IL-1β↓	LingYan Dong et al. [53] Hui Li et al. [54]
rat	kidney	oral	20 mg/kg/day 20 mg/kg/day	SOD/CAT/GPX/GSH↑	Zohra Ghlissi et al. [55] Assaâd Sila et al. [56]

Table 2. Research on Astaxanthin in Human Body.

Project	Dose	Time	Function	Researcher
Male	12 mg/day	4 week	Maintain the body's antioxidant capacity after high-intensity exercise	Wu L. et al. [57]
2 diabetes mellitus	8 mg/day	8 week	MDA/IL-6↓	Shokri M. N. et al. [58]
Random	12 mg/day	8 week	Improve sleep quality of depressed people	Masahiro H. et al. [59]
Male/Female	12 mg/day	8 week	Reduce average heart rate at submaximal endurance intensities	Shawn M. T. et al. [60]
Overweight	12 mg/day	12 week	LDL/MDA/ApoA1↓	Choi H. D. et al. [61]
Smokers	5/20/40 mg /day	3 week	MDA↓, SOD↑	Kim J. H. et al. [62]

5. Diabetes and Cardiovascular Disease

Among various complications of diabetes, American Diabetes Association (ADA) and the American Heart Association (AHA) consider diabetes to be a high-risk disease of cardiovascular disease [63]. Some people think that pre-diabetes can predict macrovascular

disease [64]. The formation of diabetes complications is inseparable from oxidative stress, the process of glucose self-oxidation and protein glycosylation will produce ROS. Excessive ROS causes the body's antioxidant defense system to decline, and continuous oxidative stress will induce cellular apoptosis and the expression of inflammatory factors eventually form a vicious circle [65]. Diabetes can cause many complications, and every patient with type 2 diabetes has at least one complication [66]. Microvascular disease caused by high blood sugar can cause capillary occlusion, and then capillary occlusion again causes retinal ischemia, which is the cause of the proliferation stage of diabetic retinopathy [67]. Similarly, the high blood sugar environment of the brain can also cause abnormal capillaries, this increases the probability of a cognitive decline in the elderly with brain atrophy [68].

Research suggested that diabetes plays an important role in cardiovascular disease [69–71]. Whether in vitro or in vivo, studies have shown that exposure of endothelial cells to high concentrations of glucose can cause endothelial dysfunction [72,73]. The nitric oxide, endothelin-1, tissue plasminogen activator and plasminogen activator inhibitor-1 released by the EC were inhabited by the high glucose level, demonstrating that glucose is the key determinant of endothelial function. [74].

The media layer of blood vessels is mainly composed of smooth muscle cells, which mainly regulate the blood flow and blood pressure of the body. Pathological vascular smooth muscle migration is also one of the main causes of cardiovascular disease [75]. ROS could be produced by hyperglycemia in a variety of ways, and the proliferation promoting the proliferation of pathological vascular smooth muscle cells, and finally, lead to a series of cardiovascular diseases such as atherosclerosis [76]. Studies have shown that smooth muscle cells derived from patients with type 2 diabetes have a larger cell proliferation area and cytoskeletal disorders compared with those derived from non-diabetic patients [77]. The gene expression involved in the synthetic phenotype of contractile smooth muscle cells and the secreted protein of synthetic smooth muscle has a great influence on macrovascular disease [78].

Excessive ROS will lead to the proliferation of neutrophils and the increase of pro-inflammatory factors secreted by proteases, when the human body's hyperglycemia is controlled, complications and inflammation will still occur, this phenomenon is called metabolic memory [79]. When hyperglycemia affects the expression of oxidation and antioxidant signals, it also affects the expression of inflammatory factors in the body. Jan A, Ehses et al. [80] found that exposure of mouse pancreatic islets to the environment of type 2 diabetes stimulates the secretion of pancreatic islet-derived inflammatory factors and increases the number of pancreatic islet-related macrophages. The increase of macrophages is an important feature of inflammatory diseases. Macrophages have anti-inflammatory and pro-inflammatory phenotypes. Rita E. Mirza et al. [81] found that the macrophages in the wounds of diabetic mice showed persistent pro-inflammatory phenotypes.

When the blood vessel continues to undergo oxidative stress, the endothelial function becomes impaired. The low-density lipoprotein (LDL) in the endothelial cells is oxidized to form oxidized low-density lipoprotein. The oxidized low-density (ox-LDL) lipoprotein further destroys the endothelial cells, and part of the ox-LDL passes through Endothelial cells enter the inner membrane and accumulate, while monocytes enter the inner membrane and differentiate into macrophages to phagocytize ox-LDL. Macrophages accumulate too much in the body to form foam cells [82,83]. Whether it is an endothelial dysfunction or pathological smooth muscle migration and the increase in the number of macrophages, they have a great relationship with cardiovascular disease. The effect of high glucose on vascular diseases is shown in Figure 2.

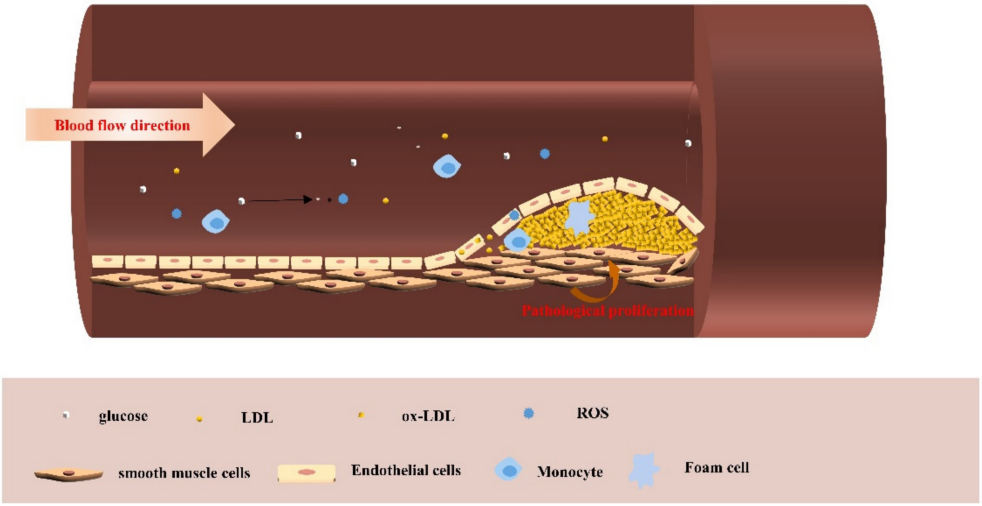

Figure 2. The effect of ROS on the cardiovascular system caused by hyperglycemia. Oxidative stress caused by glucose auto-oxidation leads to endothelial dysfunction and pathological proliferation of smooth muscle cells, which ultimately leads to the formation of vascular atherosclerosis.

5.1. Astaxanthin and Diabetes

Astaxanthin as an antioxidant is a potential drug for the treatment of diabetes and has been reported in many studies [84,85]. Although pre-diabetes can keep the body's blood sugar at a normal level through diet and other methods, the oxidative stress and inflammation caused by high blood sugar still have potential risks for cardiovascular disease. Therefore, we can know that certain drugs can be given in the case of pre-diabetes treatment. Oxidative stress caused by hyperglycemia can damage various tissues and cells of the body [86]. Li et al. [87] established a mouse model of hyperglycemia and administered astaxanthin powder (2% astaxanthin content) to mice. The results confirmed that astaxanthin successfully lowered the body's blood sugar. However, the mechanism by which astaxanthin lowers blood sugar is not clear. Chen et al. [88] administered astaxanthin to mice with gestational diabetes and found that astaxanthin activated the Nrf2/HO-1 antioxidant signal in the mice, Nrf2 is an important transcription factor that regulates cellular oxidative stress response, Kelch-like ECH-associated protein 1 (Keap1) is a binding protein of Nrf2. Nrf2 will enter the nucleus to activate the transcription of antioxidant enzymes when Keap1 is activated by oxidation [89]. For pre-glucose insulin resistance, astaxanthin can reduce insulin resistance by improving insulin sensitivity and glucose intake [90–92].

Inflammation is one of the mechanisms of the pathogenesis of type 2 diabetes, after supplementing astaxanthin in patients with type 2 diabetes, it was found that astaxanthin can reduce the level of IL-6 in patients over time [58]. At present, the correction of pre-diabetes is still a huge unexplored opportunity to prevent diabetes and thereby reduce the burden of cardiovascular disease [93].

5.2. Astaxanthin and Cardiovascular Disease

The onset of atherosclerosis-related cardiovascular disease is dependent on oxidative stress and inflammation [94,95]. There are also reports on the research of astaxanthin in cardiovascular aspects. Inhibiting endothelial cell apoptosis and aging can inhibit cardiovascular disease to a certain extent, vascular endothelial dysfunction and smooth muscle pathological migration are mainly related to oxidative stress. Human umbilical vein endothelial cells (HUVEC) will stop growing and age when exposed to 200 μM H_2O_2 for 8 to 24 h [96], the senescent endothelial cells usually accumulate in the arteries and eventually form atherosclerotic plaques [97]. When vascular smooth muscle cells (VSMC)

respond to oxidative stress, the secreted proteins will not only promote the apoptosis of endothelial cells, but also cause the proliferation of macrophages and VSMC [98].

The increase of ROS has an important influence on cell proliferation and apoptosis. The oxidation of deoxynucleotides affects the transcription and replication of genes, the oxidation of lipids potentially damages cell membranes, and the oxidation of proteins can cause loss of activity [99]. Cui et al. [100] have confirmed astaxanthin can protect the heart by against oxidative stress. However, the mechanism by which astaxanthin works is not yet clear. The signaling of Nrf2/HO-1 was related to cardiomyocyte apoptosis and cardiac insufficiency induced by coronary microembolization (CME). In order to study whether astaxanthin is helpful for HO-I signal activation, researchers set up two groups of mice in the experimental group (Feeding astaxanthin) and the control group. The results show that astaxanthin can protect the heart by activating Nrf2/HO-1 signal [101]. The inflammatory factors secreted by macrophages are the manifestation of inflammatory response in the body. Macrophages are a therapeutic target of atherosclerosis. Astaxanthin can effectively regulate the related reactions of macrophages in the formation of atherosclerosis [102].

To investigate the effect of astaxanthin on the aortic endothelial cells of hyperglycemia, Lin et al. [103] selected 18 male rats to construct a diabetes model, and divided the blank group and the diabetes group into 2 groups, the blank group (diabetes group) and the blank group (diabetes group) + high-dose astaxanthin group, the results proved astaxanthin inhibited the expression of ox-LDL and its receptor, and up-regulated the expression of eNOS, alleviating the vascular endothelial dysfunction in diabetic rats. The denaturation of glycosylated protein is one of the reasons for the complications of diabetes. The cultured endothelial cells are stimulated with 50 mM 1 mL Glycated fetal bovine serum (GFBS). Under this condition, the antioxidant capacity of endothelial cells decreases. After treatment with astaxanthin, GFBS stimulates endothelial cells, and the results show that astaxanthin can inhibit the production of ROS and improve the antioxidant capacity of endothelial cells [104]. In patients with type 2 diabetes, the level of LDL in the plasma of patients supplemented with astaxanthin, and the release of pro-inflammatory factors TNF-α and IL-6 are also inhibited, overproduction of TNF-α and IL-6 can cause inflammation and endothelial dysfunction, which can lead to aggravation of diabetes [105].

6. Conclusions

The strong antioxidant properties and biological safety of astaxanthin have been proved in many aspects and have applications in many aspects. Astaxanthin can cross the cell membrane and has no side effects on cells. Astaxanthin is used as a targeted drug to scavenge free radicals at specific locations through a carrier; as a strong antioxidant to protect cells damaged by oxidation, etc. Based on these advantages, Astaxanthin has potential application value in the treatment of diabetes and its complications. At present, astaxanthin is usually in the form of oral medicine or direct injection in vitro research. As a coating material, it has not been reported to affecting the target site directly. This can provide a new direction for future astaxanthin research.

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Abbreviations

GDM	Gestational diabetes mellitus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
ADA	American Diabetes Association
AHA	American Heart Association
LDL	Low-density lipoprotein
ox-LDL	oxidized low-density
HO-1	Heme oxygenase-1
Nrf2	Nuclear factor erythroid-2-related factor 2
IL-6	Interleukin 6
HUVEC	Human umbilical vein endothelial cells
VSMC	Vascular smooth muscle cells
eNOS	Endothelial nitric oxide synthase
GFBS	Glycated fetal bovine serum
TNF-α	Tumor necrosis factor alpha
PI3K	Phosphatidylinositol 3-kinase
AKT	Protein kinase B
COX-2	Cyclooxygenase-2
BDNF	Brain-derived neurotrophic factor
RIPK1	Receptor-interacting protein kinase 1
RIPK3	Receptor-interacting kinase-3
ROS	Reactive oxygen species
GSH	Glutathione
SOD	Superoxide dismutase
JNK	C-Jun N-terminal kinase

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