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# Management of Diabesity using Ascorbic acid and Gallic acid as Novel therapeutic candidates; a review

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**Abstract**

**Background:** Obesity is associated with chronic inflammation, which can lead to metabolic disorders such as insulin resistance, type 2 diabetes mellitus (T2DM) and cardiovascular complications. The inflammatory response leads to the formation of harmful reactive oxygen and reactive nitrogen substances, which are related to the production of oxidative stress. The fat cells of obese people have a different adipokine profile, and pro-inflammatory cytokines production increases as well as release in excess amounts, including tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). Insulin resistance and decreased insulin production are the main causes of T2DM. Reactive and toxic oxygen species can cause oxidative damage to β cells, which is the main cause of T2DM. T2DM is a progressively severe global health issue associated with the obesity epidemic. A variety of pathophysiological abnormalities that lead to impaired glucose homeostasis in T2DM are caused by environmental (including obesity, poor diet, and lack of physical activity) and genetic factors. Natural compounds, including gallic acid, a phytochemical and ascorbic acid (vitamin C), are used as antioxidants to treat obesity and T2DM. Gallic acid is basically a kind of tri-hydroxybenzoic acid, which has powerful antioxidants as well as free radical-relieving effects, and shields tissue damage from oxidative stress. Vitamin C decreases the inflammation by inhibiting C-reactive protein and TNFα mechanisms. These pathways have been found to lower lipid peroxidation, inhibit free radicals, and prevent hypoxia in adipose tissue. This review is about the antioxidant abilities of gallic acid and vitamin C in the treatment of oxidative damage diseases such as obesity and T2DM.

## Introduction:

Over 1.9 billion individuals are thought to be overweight globally, with over 600 million of them classified as obese. Congenital obesity can lead to the further development of many chronic metabolic diseases, such as type 2 diabetes mellitus, insulin resistance and heart-related complications. The exact pathway of the relationship between obesity and these metabolic diseases has not been fully explained. However, an obese body can lead to an inflammatory state, which causes oxidative stress in adipose tissue (Andersen et al., 2016). Inflammation of adipose tissue can promote the progression of obesity-induced metabolic disorders, including T2DM and insulin resistance. Due to the imbalance of diet and energy intake, adipose tissue increases due to fat production (Dludla et al., 2019). Adipocytes are involved in the secretion of a variety of hormones, including leptin, estrogen, adiponectin, and a series of cytokines. The release of chemokines depends on the intracellular levels that can regulate different signals of the cell, leading to metabolic complications. Insulin signal transduction, adipogenesis, preadipocyte proliferation, and management of energy expenditure in mitochondria by regulating lipid metabolism are some of the mechanisms regulated by different endocrine factors in obesity. This is why intracellular control of such elements has always been the main treatment goal for preventing obesity and its associated disorders like type 2 diabetes mellitus (Parida et al., 2019). Type 2 Diabetes mellitus (T2DM) is a metabolic disorder caused by elevated levels of glucose in the blood and disorders of lipid, protein and carbohydrate

absorption. Due to any abnormality of pancreatic beta cells, insulin resistance or low production of insulin by the pancreas is the main cause of T2DM. Insulin is a hormone involved in regulating glucose in the blood. Insulin is involved in inhibiting the phosphoenolpyruvate kinase, which is a gluconeogenic enzyme and stimulates the glucokinase, fructose 2,6 bisphosphatase, pyruvate kinase and phosphofructokinase which are glycolytic enzymes. Decreased insulin levels cause T2DM (Santosh and David, 2017).

Excessive intake of high-fructose diets can also lead to obesity associated with metabolic diseases, including diabetes and insulin resistance. It can cause problems related to the massive production of advanced glycation and products (AGE). Through non-enzymatic glycation, fructose can react with proteins and lead to the production of Schiff bases and the formation of advanced glycation end products. The reaction of advanced glycation end products with their receptors, RAGEs, activates transduction of signals, leading to the production of toxic oxygen species and inflammation. Fructose is a faster reducing agent than glucose and has been observed to form reactive di-carbonyl compounds and toxic radicals faster, leading to oxidative damage to cells. Oxidative stress is the main source of obesity and diabetes-related complications. Long-time incubation with fructose can cause changes in albumin, forming its structure amyloid and oxidation of protein related to many degenerative disorders such as Alzheimer's disease, atherosclerosis, rheumatoid arthritis and type 2 diabetes mellitus (Adisakwattana et al., 2017).

There are two types of free radicals based on nitrogen and oxygen because they are both very unstable and reactive in biological systems. Elevated levels of free radicals can lead to lipid peroxidation. Lipid peroxidation can be harmful for lipids present in membranes, cell proteins and nucleic acids, and damage. Acute and chronic oxidative stress can induce certain physiological and pathological effects. Recently, chronic oxidative stress has been shown to develop atherosclerotic plaques and a high possibility of metabolic disorders, obesity, type 2 diabetes mellitus, neurodegenerative diseases and cancer etc. (Gao et al., 2019). Oxidative stress reduces glucose uptake in muscles and tissues and reduces secretion of insulin from beta cells of the pancreas in diabetic patients. According to recent studies, oxidative stress can induce the accumulation of fat, the imbalance of adipocytokines, and the development of metabolic syndromes such as obesity (Furukawa et al., 2017). The increased level of oxidative stress in accumulated fat should be an important goal for researchers to discover new treatments for obesity-related metabolic disorders. According to recent studies, eating substantial amounts of fruits and vegetables can decrease the possibility of many metabolic disorders, including diabetes and obesity. Vitamins, minerals and phytochemicals in fruits and vegetables merge in a synergistic manner to increase cells' biological activity (Adisakwattana et al., 2017).

Gallic acid and its derivatives, such as lauryl gallate, octyl gallate, tetradecyl gallate, propyl gallate, and hexadecyl gallate, are phenolic compounds that serve as metabolites of plants. Gallic acid is a trihydroxybenzoic acid, with hydroxyl groups present in the 3, 4, and 5 positions of the compound. Gallic acid's derivatives and gallic acid have many uses in the pharmaceutical, food, printing, and cosmetics. In addition, gallic acid also plays a vital role in medicinal applications, such as anti-allergic, antibacterial, anti-inflammatory, and anti-oxidative stress. As a strong antioxidant, gallic acid protects cells from oxidative stress, which is why it is used as a therapeutic or dietary supplement. Because gallic acid has strong anti-oxidation and free radical scavenging properties, researchers are extremely interested in using it to treat oxidative damage disorders such as obesity and T2DM (Gao et al., 2019). Vitamins have a vital role in the healthy operation of the body's metabolic mechanisms and homeostasis. Ascorbic acid is a highly effective antioxidant that can resist the related reactive oxygen and

nitrogen species physiologically. Recent studies have revealed the advantages of ascorbic acid in combination with other antioxidants. GA is a kind of phenolic acid, present mainly in tea, grapes, different fruits, and plants. Recent studies have shown that gallic acid and vitamin C can inhibit the formation of AGEs in physiological model systems. Both can be used to treat metabolic diseases, including obesity and T2DM (Adisakwattana et al., 2017). Its antioxidant effect depends on the ability of the endogenous glutathione antioxidant system (Totan et al., 2019). Ascorbic acid is a water-soluble vitamin. It is a powerful antioxidant (Santosh and David, 2017). Oxidative stress is the main cause of T2DM and obesity. Vitamin C is an important micronutrient with antioxidant properties (Wilson et al., 2017).

**Relationship between Obesity and Inflammation**

The increase in body adiposity (weight gain) is called obesity. It can be identified with the help of body mass index (BMI). Body mass index is calculated by height and weight. For men and women, BMI uses the cut-off point between BMI C 25 to 30, considered overweight and obesity BMI C 30. According to the new instructions for the Asia-Pacific population, people with a BMI of more than 23 are considered overweight, and those with a BMI of more than 25 are considered obese (Ellulu, 2017). The increase in body adiposity (weight gain) is called obesity. It can be identified with the help of body mass index (BMI). Body mass index is calculated by height and weight. Obesity can cause many other metabolic diseases, including T2DM, non-alcoholic fatty liver, steatohepatitis, asthma, cancer, heart diseases and neurodegenerative disorders. Obesity is closely related to inflammation, which may further lead to severe insulin resistance and type 2 diabetes. Chronic inflammation includes three stages, including stress, adaptive and maladaptive. In the case of obesity, the initial trigger may be the steady-state stress caused by the excessive anabolic state in the fat cells. The adaptive inflammatory response is an acute type triggered by chemokines, which can lead to the expansion of fat cells. The maladaptive phase is a long-term complex phase in which homeostasis re-establishes new set points for body weight, certain hormones and blood levels (Reilly & Salti, 2017).

Too much abdominal adipose tissue will accelerate the formation of pro-inflammatory cytotoxins, leading to metabolic dysfunction. Adipose tissue is very vascularized and growing. In adipose tissue, the effective regulation of the vascular system and angiogenesis has been considered as an applicable mechanism against obesity and related complications. Abnormal expansion of adipose tissue in obesity can also lead to lipid metabolism dysfunction, such as excessive lipolysis (Figure 1), which may lead to the formation and release of free fatty acids (FFA) (Dludla et al., 2019). Inflammation of adipocytes alters their adipokine profile and can transform into a pro-inflammatory phenotype, leading to the secretion of pro-inflammatory cytotoxins, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α) and inflammation of other mediators. TNF-α is the most advanced pro-inflammatory cytokine, and its excessively elevated levels are related to obesity, insulin resistance and T2DM (Dludla et al., 2019).

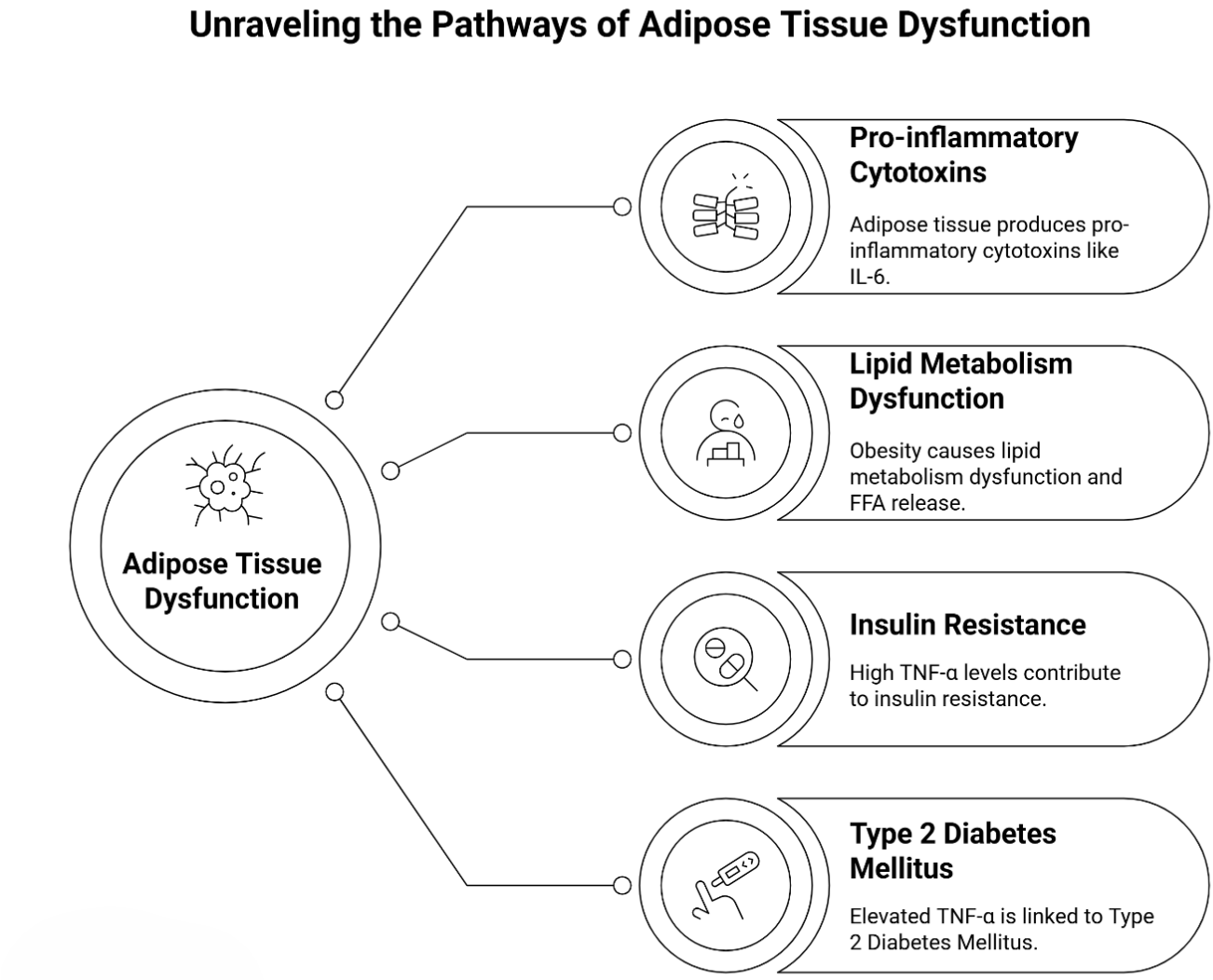


**Figure 1:** Mechanism linking obesity to the development of inflammation in the body and insulin resistance, adapted and modified from Dludla et al. (2019).

The condition of obesity is associated with dysfunction in lipid metabolism, characterized by heightened lipolysis, which subsequently leads to an increase in the secretion and production of free fatty acids (FFA). Elevated levels of FFA can lead to abnormal pro-inflammatory reactions and lead to the progression of insulin resistance. The reduction of the intracellular antioxidant system in adipose tissue results from elevated production of reactive oxygen species (ROS), potentially causing oxidative stress and contributing to the onset of insulin resistance. NADPH stands for nicotinamide adenine dinucleotide phosphate (Dludla et al., 2019).

**Impact of Obesity on Oxidative Stress**

Obesity is a condition of increased severe oxidative stress. It further causes severe metabolic disorders such as dyslipidemia and insulin resistance, which eventually lead to atherosclerosis and endothelial dysfunction. A high-fat diet leads to the production of ROS as well as oxidative stress (OS), especially in the liver and adipose tissue (Atabay et al., 2017). During obesity, the expansion of fat tissue causes an increase in the formation of toxic free radical species, which further leads to the production of oxidative stress (Figure 2). Reactive oxygen species (ROS) identified as second

messenger in signaling of cell and are also involved in cell homeostasis. ROS are free radical species, such as superoxide ($O_2^-$), hydroxyl ($^{\bullet}OH$), and hydrogen peroxide ($H_2O_2$). The imbalance between the production and removal of ROS can lead to oxidative stress. However, chronic oxidative stress can be associated with cell damage caused by the oxidation of cellular elements, including DNA, protein, and lipids. Obesity can cause oxidative stress in adipose tissue through the catalytic ability of NADPH oxidase (NOX) enzyme (McMurray et al., 2016).

Oxidative damage can also be caused by dysfunctional mitochondrial oxidative phosphorylation. NOX is the main way to produce ROS in adipose tissue. This enzyme binds to the plasma membrane by transferring electrons from nicotinamide adenine dinucleotide phosphate to oxygen and participates in the formation of ROS. As a result, $O_2^-$is produced and converted to $H_2O_2$ with the help of superoxide dismutase (Dludla et al., 2019). NOX has seven different isomers, which are expressed in large numbers in different tissues. The production of ROS and oxidative stress due to NOX has a major part in the expansion of insulin resistance in adipose tissue. The increase in FFA and glucose levels in obesity leads to NOX activation and ROS production (Figure 2). The electron transport chain (ETC) of mitochondria is the major place where different mammalian cells produce ROS, which mainly occurs in the process of oxidative phosphorylation. According to recent studies, it is determined that mitochondrial-derived reactive oxygen species formation is related to late obesity, while NOX-derived reactive oxygen species formation is related to early obesity (Dludla et al., 2019).

In the case of obesity, adipose tissue uses FFA obtained from triglyceride storage through excessive lipolysis to produce energy (figure 2) (McMurray et al., 2016). Excessive FFA will cause the electrons in the ETC to move during the oxidative phosphorylation process, leading to the outflow and generation of $O_2^-$, thereby producing other ROS molecules. By activating NF-κB, increasing the production of mitochondrial-derived ROS can lead to the expansion of insulin resistance in adipose tissue] (Dludla et al., 2019). ROS functions in many ways, including post-translational changes of specific proteins (such as UCP) and activation of important transcription processes. Hypoxia-inducible factor (HIF) is the main transcriptional regulator of cell response to different cellular stressors (including hypoxia) and is known to be activated by ROS. HIF is a heterodimer composed of strictly regulated HIFa subunits and constitutively produced HIFb subunits (McMurray et al., 2016).

The activation of HIF in hypoxia and other non-hypoxic stimuli is caused by the generation of mitochondrial ROS, most likely in ETC complex III. HIF is just one of several wonderful ways that ROS activates transcription factors. Increased mitochondrial dysfunction and ROS signaling are thought to be related to the oversupply of obesity-related energy substrates, which may explain insulin resistance. Both obesity and obesity-induced insulin resistance are related to c-Jun N-terminal kinase (JNK) and NF-jB, both of which are regulated by ROS (McMurray et al., 2016). This pro-inflammatory response and oxidative stress in obesity can result in the progression of other metabolic diseases, such as T2DM, several types of cancer, and cardiovascular disease. Researchers focus on producing therapeutics that prevent inflammation and oxidative stress, and can also treat these diseases (Dludla et al., 2019).

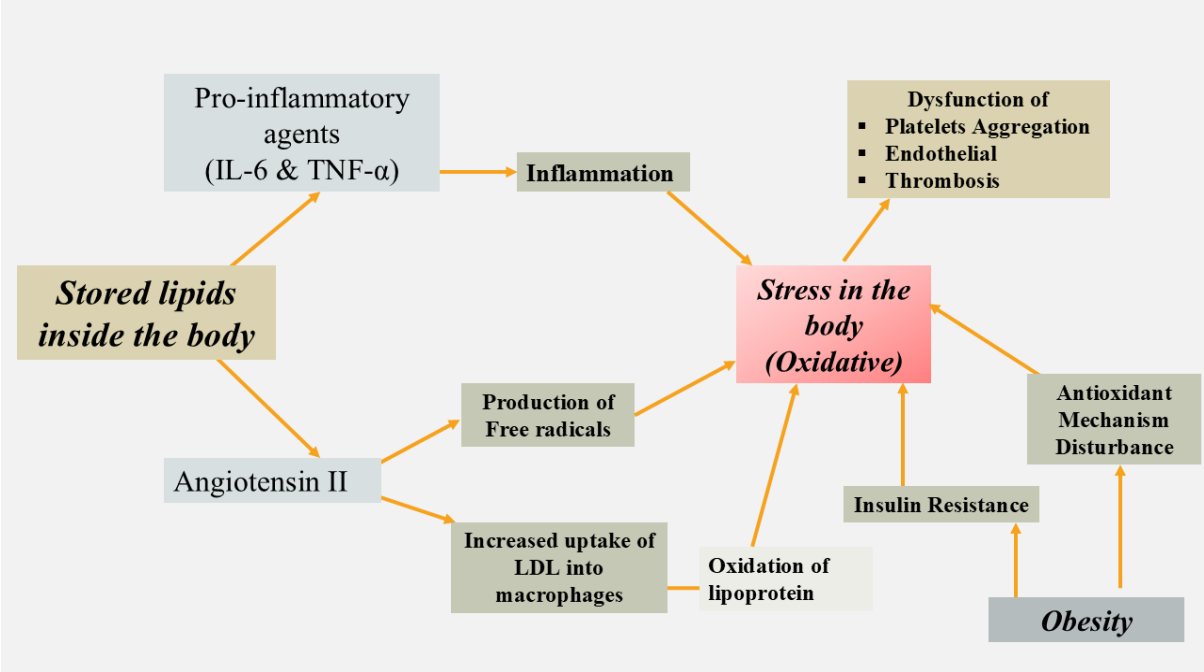


**Figure 2:** Association of obesity and storage of lipids with Oxidative stress, inflammation, endothelial dysfunction and thrombosis modified and adopted from Ellulu, (2017).

**DNA Damage associated with Inflammation and Reactive Oxygen Species (ROS)**

In obesity, oxidative stress and inflammation can cause DNA damage and prohibit DNA repair pathways, which result in high mutation frequency and could change expression of gene. This DNA damage can further cause the development of cancer through cancer cell proliferation and anti-apoptosis. During the period of hyperglycemia in obese condition, the increase in the amount of glucose in cells promotes glycolysis and Krebs cycle, produces excessive NADH and $FADH_2$, which leads to the termination of oxidative phosphorylation and the generation of superoxide (Di Domenico et al., 2019).

ROS produces a lipid peroxidation process, which leads to the generation of DNA reactive damage. Toxic free radicals, such as superoxide and hydroxyl radicals, are more hazardous within reactive oxygen species. Superoxide (O2-) is generated during aerobic respiration, while hydrogen peroxide (H2O2) is formed through the dismutation of superoxide, facilitated by superoxide dismutase. Various oxidases may also produce hydrogen peroxide. Hydroxyl radicals ($HO^{\bullet}$) can be produced by Fenton reaction and Weber-Weiss reaction. Macrophages and neutrophils that cause inflammation produce oxidants, such as peroxynitrite ($ONOO^-$) and nitrosoperoxycarbonate ($ONOOCO2^-$), nitrosating agents ($N_2O_3$) and hypohalous acid (HOCl), HOBr). ROS is also involved in lipid peroxidation and produces some by-products, including etheno-, propano-, malondialdehyde. The interaction of these products with DNA leads to the production of DNA Adducts and damages the structure of DNA. Reactive oxygen species strike causes base damage, such as oxidation, methylation, nitration, deamination, alkylation, and 1 or 2-stranded DNA smash, or cross-links in the DNA structure. Such DNA damages are 8-hydroxyguanine, Fapy Ade, thymine glycol, 7,8-dihydro-8-oxoguanine (commonly termed 8-oxoguanine: 8-OHdG) and Fapy Gua. These DNA damages can cause mutations in the process of replication of DNA, result in mutagenesis and initiation of cancer (Włodarczyk & Nowicka, 2019).

**Relationship in Type 2 Diabetes mellitus and inflammation**

The concept that T2DM is an inflammatory disorder is considered a key component in understanding the variables that lead to the progression of T2DM. Observing the presence of inflammatory mediators can predict the occurrence of T2DM in humans in the future. A study showed that elevated plasma levels of sialic acid, interleukin 6 and C-reactive protein, and elevated inflammatory biomarkers can predict the progression of insulin resistance and T2DM (Oguntibeju, 2019)

Patients with T2DM have an initial state of insulin resistance, which can be compensated by excessive secretion of insulin in β cells. However, as the disease progresses, this pancreatic functional reserve becomes unable to process the required insulin production, and β cells become unable to produce enough insulin when diabetes is diagnosed. Although the proportional contributions of β-cell dysfunction and insulin resistance in T2DM patients may be different, it is observed that impaired insulin sensitivity may occur 15 years before the clinical diagnosis of diabetes (Tsalamandris et al., 2019). According to more and more data, inflammation is now closely related to insulin resistance. Obese people with insulin resistance have a lot of adipose tissue inflammation, but obese people with insulin sensitivity do not have this kind of tissue (Reilly and Saltiel, 2017).

JNK, NFB kinase subunit inhibitor (IKK-), extracellular signal-regulated kinase (ERK), ribosomal protein S6 kinase (S6K), mammalian target of rapamycin (mTOR), PKC and glycogen synthase kinase 3 are all pro-inflammatory chemicals. These enzymes inhibit insulin activity by phosphorylation of serine residues rather than tyrosine residues in the insulin signaling pathways. Insulin resistance is related to two main transcription element signaling pathways: JNK and IKK/NF-B are two proteins involved in the production of a protein called JNK. These two pathways are activated by many pro-inflammatory stimuli, many of which include NF-B activators and up regulators. Pattern recognition receptors, including TLR and RAGE receptors, are also involved in activating these pathways. An increase in FFA levels leads to excess in diglycerides (DAG), which activates the PKC isoform and simultaneously activates the JNK and NF-B mechanisms. The formation of ROS, endoplasmic reticulum stress and changes in obesity are other triggers (Hameed et al., 2015).

JNK and IKK have different pathways in the development of inflammation-induced insulin resistance. Unlike JNK, which phosphorylates the serine residue of IRS-1, IKKB induces insulin resistance by activating the transcription factor NF-B. The physiological substrate of IKK is an inhibitor of NF-B protein called IB protein. Phosphorylation of IKKβ increases the breakdown of IκBα proteosome, translocates NF-κB to the nucleus and triggers the expression of many target genes. Insulin resistance is caused by the outcomes of such NF-κB target genes. The synthesis of inflammatory chemicals further stimulates the JNK and NF-κB pathways, leading to a feedforward cycle of insulin resistance (Hameed et al.,2015).

Insulin resistance is related to higher levels of inflammation biomarkers. This connection may be due to the effects of the pro-inflammatory cytokine TNF and leptin on insulin sensitivity and secretion. Tumor necrosis factor may cause insulin resistance by reducing insulin receptor autophosphorylation, converting insulin receptor substrate-1 into an insulin receptor tyrosine kinase activity inhibitor, reducing GLUT transporter activity in muscle cells, and increasing circulating free fatty acids. These mechanisms improve or promote the progression of T2DM, prove the link between insulin resistance and inflammation, and explain how resistance and inflammation cause the development of T2DM. This information and understanding should force scientists to devise a method to suppress inflammation as a preventive measure for diabetes management (Oguntibeju, 2019).

**Relationship in Type 2 Diabetes mellitus and oxidative stress**

Free radicals are chemical entities that are reactive and have one or more unpaired electrons. They are short-lived species. They can also be regarded as necessary evils that signal the process of routine differentiation and migration. By transferring unpaired electrons between cells, free radicals can cause the oxidation of cell components and molecules, which can damage the cells. They are notoriously unreliable and highly reactive (Asmat et al., 2016). ROS and RNS in the body can cause oxidative stress. Superoxide anion ($O_2^{\cdot-}$), hydroxyl (OH), hydrogen peroxide ($H_2O_2$) and hypochlorous acid (HOCl) are examples of ROS, while nitric oxide (NO) and nitrogen dioxide ($NO_2^{\cdot-}$) And peroxynitrite ($OONO^-$) are examples of RNS. However, increasing levels of free radicals leads to harmful reactions, which can destroy the cell structure due to oxidative stress (Phaniendra et al., 2015).

By the evaluation of oxidative stress indicators in diabetic patients and animals, some experimental evidence shows that there is a clear connection with oxidative stress and diabetes. Hyperglycemia can cause excess level of oxidative stress-induced DNA damage markers, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-OHdG); outcomes of lipid peroxidation, such as thiobarbituric acid reactive substances (TBARS); and oxidation of protein products, including nitrotyrosine and carbonyl levels, as well as reduce the antioxidant enzymes activity. Insulin resistance caused by chronic hyperglycemia is also observed to be related to oxidative stress. According to experimental and clinical studies, oxidative stress is believed to take part mostly in the etiology and pathophysiology of diabetes (Oguntibeju, 2019).

This is because it is known that chronic hyperglycemia exposure in human and animal cells and tissues promote non-enzymatic glycation of proteins, leading to the formation of ROS in the form of Schiff bases and Amadori products. The inactivation of proteins or enzymes, including SOD, GPX, CAT, and reduced glutathione, is the result of oxidative stress, and the reduction of these proteins promotes oxidative stress (Singh et al., 2018). The act of oxidative stress in diabetes is based on whether they have been diagnosed by an oral glucose tolerance test (OGTT) and/or are taking anti-hyperglycemic drugs to select individuals with diabetes. People in the control group did not have diabetes, cardiovascular disease, kidney disease, or respiratory disease, and all participants were similar in age, gender, smoking, drinking, and physical activity. According to scientists, diabetics experience oxidative stress, which can lead to further complications (Oguntibeju, 2019).

Various indicators, such as DNA destruction biomarkers and lipid peroxidation products, have been used in experiments to show the relation among diabetes and oxidative stress. Due to their ability to destroy lipids, proteins and DNA, reactive toxic radicals are observed to play a key role in the occurrence and development of advanced diabetes problems. Oxidative stress can cause many clinical diseases, including rheumatoid arthritis, diabetes, and cancer. Coronary artery disorders, neural disorders, kidney related disorders, retinopathy, and stroke are all consequences of DM caused by toxic radicals and oxidative damage. In vivo research supports the theory that high blood sugar causes oxidative stress, which leads to vascular endothelial dysfunction in diabetic patients. Elevated glucose and insulin levels and dyslipidemia can induce macrovascular disease, leading to oxidative stress and atherosclerosis in diabetic patients (Asmat et al., 2016).

**Gallic Acid and its characteristics**

Gallic acid is basically a 3,4,5-trihydroxybenzoic acid with a molecular formula of C7 H6 O5 (MW 170.12 g/mol), which is present in large amount in gallic, tea, oak bark, sumac, witch hazel and other plants. Gallic acid is a group of phenolic acids, a group of naturally occurring compounds, usually formed by the hydrolysis of tannic acid. In

all compounds belonging to this category, there is a phenol ring with almost one carboxylic acid functional group. Phenolic acids are further subdivided into benzoic acid (C6-C1) with seven carbon atoms and cinnamic acid (C6-C3) with nine carbon atoms. Gallic acid exists in the form of hydroxybenzoic acid. Gallic acid exists in a variety of ester and salt forms, such as gallocatechin gallate, epigallocatechin gallate, ethyl gallate, methyl gallate, theaflavin-3-gallate, gallate Ester propionic acid, etc (Rajan & Muraleedharan, 2017).

Gallic acid is a colorless or light-yellow crystalline compound that has many uses in the food and pharmaceutical industries. Gallic acid can also be obtained from many plant species including Quercus. And Punica spp., through different chromatographic methods; from an industrial point of view, gallic acid is obtained by industrially using glycoprotein esterase (such as tannase) through tannin hydrolysis. There are various scientific reports on the medicine related and biological activities of these phytochemicals, including antioxidants, anti-inflammatory, gastric protection, anti-cancer, cardio-protection, antibacterial and neuroprotective effects (Kahkeshani et al., 2019).

The health-related benefits of phenolic compounds (such as gallic acid) may be affected by different elements, such as poor stability and reduced bioavailability and absorption. According to experimental research, the effectiveness of gallic acid will be interfered with by rapid metabolism and elimination. According to oral administration, it has been identified that about 70% of gallic acid is absorbed by the human body and then excreted in the urine in the form of 4-O-methylgallic acid. Researchers are working hard to find ways to enhance the gallic acid bioavailability in blood circulation and tissues. This involves repeated administration and applications of gallic acid-derived compounds that can increase plasma levels of this phenolic acid. Gallic acid has been used to treat metabolic complications for many years (Dludla et al., 2019).

**Anti-Obesity Properties of Gallic Acid**

In the early 1800s, it was observed that gallic acid could treat complications such as hemoptysis, and further studies reported its anti-obesity properties about 30 years ago. A search on the subject of "gallic acid and metabolic diseases" revealed about 246 articles; from which 60 studies were related to gallic acid and its ameliorating effects on obesity-related problems (Dludla et al., 2019). Current studies have identified that gallic acid has benefits to reduce the weight of obese people. Gallic acid can directly inhibit the production of liver lipid droplets or fat tissue and can also reduce serum triglycerides and low-density lipoprotein levels. The regulation of lipids and glucose intermediates may be related to the role of gallic acid in enhancing glucose uptake, improving insulin sensitivity and increasing energy expenditure. Different additional natural elements, including Celastrol and resveratrol, have been determined to improve metabolism of glucose and lipid and treat obesity-related issues such as inflammation and oxidative stress with the help of regulatory pathways including PI3K/Akt and AMPK (Tanaka et al., 2020).

Gallic acid has a strong ability to resist oxidation and scavenging free radicals and can restore abnormal metabolism to a normal state. This is why it may be used as an effective drug for the treatment of metabolic diseases such as obesity and T2DM. Gallic acid has the capacity to reduce the level of C-reactive protein, maintain the stability of genetic material, and reduce the level of low-density lipoprotein that resists oxidative damage in individuals with diabetic mellitus, as indicated by clinical trials. Gallic acid treatment can effectively reduce the level of ROS and lipid peroxidation in the diabetic rats' liver, and increase the activities of antioxidant enzymes such as SOD, CAT, Δ-aminolevulinic acid dehydratase and GST. It also reduces serum TGA (antithyroglobulin), cholesterol, insulin, phospholipids and leptin levels. Gallic acid is

a protective compound that can withstand endogenous and exogenous toxic substances and free radical-mediated damage, as evidenced by the presence of excessive glutathione and associated enzymes (e.g., glutathione transferase, glutathione peroxidase, and glutathione reductase) (Choubey et al., 2018).

Different research have determined the benefits of gallic acid on reducing blood glucose levels, glycoprotein components, lipid peroxidation products and enhancing antioxidant enzyme activity in STZ-induced diabetic animals. Gallic acid also showed great protection in various obesity experimental models. According to reports, gallic acid can decrease the insulin level, triglycerides and glucose in plasma, and can also reduce the oxidative damage of DNA bases in different organs of animals with obesity. Intake of gallic acid can increase serum parameters (phospholipids, total cholesterol, tumor-associated glycoprotein (TAG), low-density lipoprotein cholesterol, leptin and insulin) and reduce oxidative stress glutathione (GSSG) reduction and improvement of GSH, glutathione reductase (GRd), GPx and GST) in obese mice. Gallic acid can not only reduce blood sugar rise and excessive lipid storage but also enhance the expression of related cytotoxins and enzymes, such as SOD, CAT, GST, GSH, GPx and GRd (Gao et al., 2019).

Improving the intracellular activities of antioxidants including glutathione and inhibiting the lipid peroxidation products are associated with reducing oxidative stress (Dludla et al., 2019). GA affects liver fat accumulation, apoptosis and inflammation induced by hepatocyte-macrophage interaction. In experimental studies, it was found that gallic acid inhibits palmitic acid (PA)-caused fat formation in HepG2 cells by activating AMP-activated protein kinase (AMPK). Gallic acid also improves cell viability as well as reduces the expression of apoptosis-related genes and caspase 3/7 activity caused by palmitic acid and $H_2O_2$. In the co-culture of lipid-rich Hepa 1-6 hepatocytes and RAW 264 macrophages, gallic acid inhibits the expression of inflammatory cytokines and enhancing the expression of antioxidant enzymes. GA reduces the expression of inflammatory cytokines while enhancing the expression of antioxidant enzymes. These findings identified that gallic acid reduces liver fat accumulation, apoptosis and inflammation induced by the relation of liver cells and macrophages (Tanaka et al., 2020). The available evidence will certainly arouse great interest in the clinical community or researchers in the therapeutic effects of gallic acid to treat metabolic disorders such as obesity and type 2 diabetes mellitus (Gao et al.,2019).

**Anti-Diabetic Properties Of Gallic Acid**

Diabetes mellitus is a chronic metabolic disorder described by high blood glucose caused by insufficient secretion of insulin or insulin action. T2DM disrupts the metabolism of carbohydrates, lipids, and proteins, leading to significant secondary effects, such as higher blood glucose and glycosylated hemoglobin levels, lower plasma insulin levels, and lower body weight and total hemoglobin (Rehman & Akash, 2017). Gallic acid can reduce total cholesterol, low-density lipoprotein cholesterol, urea, uric acid and creatinine levels, while rising plasma insulin, C-peptide and glucose tolerance. Using gallic acid, total protein, albumin and body weight also returned to near normal levels. It can also regenerate islet cells and normalize all biochemical variables associated with the pathology and biochemistry of T2DM. Diabetes mellitus also leads to increased liver and brain lipid peroxidation products, glycoprotein components, lipids and HMG-CoA activity, as well as decreased liver and brain antioxidant activity (Huang et al., 2018).

The anti-lipid peroxidation effect of gallic acid helps restore normal levels of peroxidation. Gallic acid has been shown to have a significant impact on the negative consequences of hyperglycemia, and its capacity to attenuate changes in gene

expression caused by hyperglycemia. TNF, IL-6, NADPH oxidase, and TXNIP mRNA expression increased in cells having increased level of glucose, but this increased expression decreased in the existence of gallic acid. It can also promote insulin secretion in cells by up-regulating PDX-1 and insulin mRNA (Choubey etal., 2018). There are several evidence that adipocytokines and PPAR play a vital role in diabetes. The regulatory benefits of gallic acid and coumaric acid on the adipocytokines secretion and the expression of PPAR mRNA in T2DM mice were tested in experimental studies, (Figure 3).

Diabetic rats were given 20 mg/kg body weight of gallic acid and 40 mg/kg body weight of p-coumaric acid for 6 weeks after being induced by type 2 diabetes (Abdel-Moneim et al., 2018). Comparison with the normal group, the levels of glucose and glycosylated hemoglobin in diabetic rats significantly decreased, but the insulin levels and body weight increased significantly. As shown in Figure 3, gallic acid and p-coumaric acid significantly reduced TNF-α, and significantly increased PPAR mRNA and adiponectin levels. Gallic acid and p-coumaric acid have a strong anti-diabetic effect, which may be due to the changes in the secretion of tumor necrosis factor alpha and adipo-cytokines, and the increased expression of PPAR mRNA (Abdel-Moneim et al., 2018).

**Ascorbic acid and its Characteristics**

Vitamin C, also called ascorbic acid, is a water-soluble vitamin having powerful antioxidant effect. It was first separated in 1928 by a biochemist and Nobel Prize winner Szant-GyorGyi. Due to the complete lack of L-gulonic acid lactone oxidase in the liver, body of an adult is thoroughly relied on the external sources of ascorbic acid. Important dietary sources of ascorbic acid are citrus fruits, tomatoes and green peppers. It is also present in lesser amounts in dairy products. The biological activity of ascorbic acid will decrease with time. Vitamin C absorption begins from the oral mucosa through passive diffusion. In the gastrointestinal and renal system, reabsorption occurs through energy usage and carrier-mediated transport mechanisms (Devaki & Raveendran, 2017).

It is recommended to get ascorbic acid in small doses because it will reach the saturation point very quickly. About 70% of ascorbic acid is most absorbed in the gastrointestinal tract. If the orally uptake of vitamin C is 90-150 mg/day, the highest content of vitamin C in plasma can reach 68-86 moles/liter. The quantity of ascorbic acid present in the body is consumed within 2 hours, and the amount of ascorbic acid excreted in the blood is about 3-4 hours. Lymphocytes are rich in vitamin C, but their levels decrease during injury and inflammation. Ascorbic acid exists in two isomeric forms, including L-xylose ascorbic acid and D-xylose ascorbic acid. The L-form is oxidized and converted to L-dehydroascorbic acid, the active form of vitamin C. After oxidation, L-dehydroascorbic acid is further converted into 2-3 diketoxyluronic acid (Santosh and David, 2017).

Vitamin C has many biological functions, such as tyrosine, folate and tryptophan metabolism, catecholamine and carnitine synthesis. These amino acids help iron absorption and histamine breakdown; non-heme forms present in plants and drinking water The iron is called here as iron. Ascorbic acid helps produce serotonin and norepinephrine from dopamine, as well as the development and regulation of collagen. Ascorbic acid increases the amount of procollagen messenger RNA in the body. Proline and lysine are converted to hydroxyproline and hydroxylysine with the help of vitamin C as a coenzyme (Totan et al.; 2019). Ascorbic acid helps osteoblasts grow, mature and maintain their structure, thereby preventing osteoporosis. By neutralizing hydroxyl and superoxide free radicals, ascorbic acid protects the body from free radical damage. Vitamin C can prevent the oxidation of vitamin E into tocopherol free radicals, thereby helping vitamin E to stay young. By doing so, it protects the throat of the protein from oxidation. Ascorbic acid provide protection to sperm from oxidative stress and helps

the body detoxify from toxic pollution elements such as hydrocarbons. Vitamin C improves lymphocyte function while reducing bacterial activity (Totan et al; 2019).

**Anti-Obesity properties of vitamin C**

According to recent studies, it has been observed that people with a BMI higher than 27kg/m2, regardless of whether they smoke or not, have incredibly low serum vitamin C levels in their bodies. Another study of 850 Indian men found that lack of vitamin C is associated with abdominal obesity and body fat. It is found that obese people consume 51% less vitamin C than normal people, and their serum level of ascorbic acid are 38% lower. However, studies have shown that a high-antioxidant diet has a profound impact on weight loss. In an experiment with 71 children aged 7-15, after a 10-week diet plan (1500-2000 kcal), it was observed that a diet high in antioxidants (vitamin C, folic acid, vegetable and fruit intake) had an effect. Diet. The weight contributes a lot. Lose (Totan et al., 2019) In another experimental study, 38 patients were classified into 2 groups. The group who took 3 grams of vitamin C supplements for six weeks lost more weight than the other group. Through all these studies, it is believed that vitamin C can be used to treat obesity through several methods provided by its antioxidant activity (Totan et al.,2019).

**The Effect of Vitamin C on Oxidative Stress**

One of the main reasons for obesity is oxidative stress. In obesity, the rise in the level of ROS is because of the lack of balance between reactive oxygen species and the antioxidant defense system. The increase of reactive oxygen species leads to DNA, lipids and proteins oxidation and stimulates cell damage, necrosis, and apoptosis. Overnutrition includes high fat and carbohydrate diets, NADPH oxidase formation of superoxide, protein kinase C (PKC) activity, oxidative phosphorylation, glyceraldehyde oxidation, increase expenditure of saturated fatty acids and trans fats, and polyol 6 amines, etc (Totan et al., 2019).

Peroxidase is present in mitochondria. It catalyzes the reduction of two glutathione (GSH) molecules to glutathione disulfide, thereby degrading $H_2O_2$ (GSSG). There are other non-enzymatic antioxidant processes that help convert GSSG to GSH. Vitamins A, C, E, and α-lipoic acid are examples of antioxidant vitamins (Figure 3). However, all such anti-oxidant defenses, especially vitamin C, work collectively to remove $H_2O_2$ from cells (and therefore superoxide), $H_2O_2$ may be converted to $^{\bullet}OH$ through the Fenton reaction in a small portion of oxygen, one A highly active ROS used for aerobic activities will be converted into superoxide anions, which must be removed or transformed into fewer reactive (and potentially dangerous) molecules. SOD, GSH-Px and catalase are the key enzymes that control this process, (Figure 3). When the activity of these enzymes is not sufficient due to overproduction of ROS or chronic hyperglycemia, more ROS and RNS are produced, activating the oxidative stress pathway. SOD is considered to be the first line of defense against ROS. This enzyme converts $^{\cdot}O_2^-$ into $H_2O_2$, which is present in almost all cells. Mitochondrial GSH has reduced transition metals (Cu, Fe) (Fernández-Mejía, 2013).

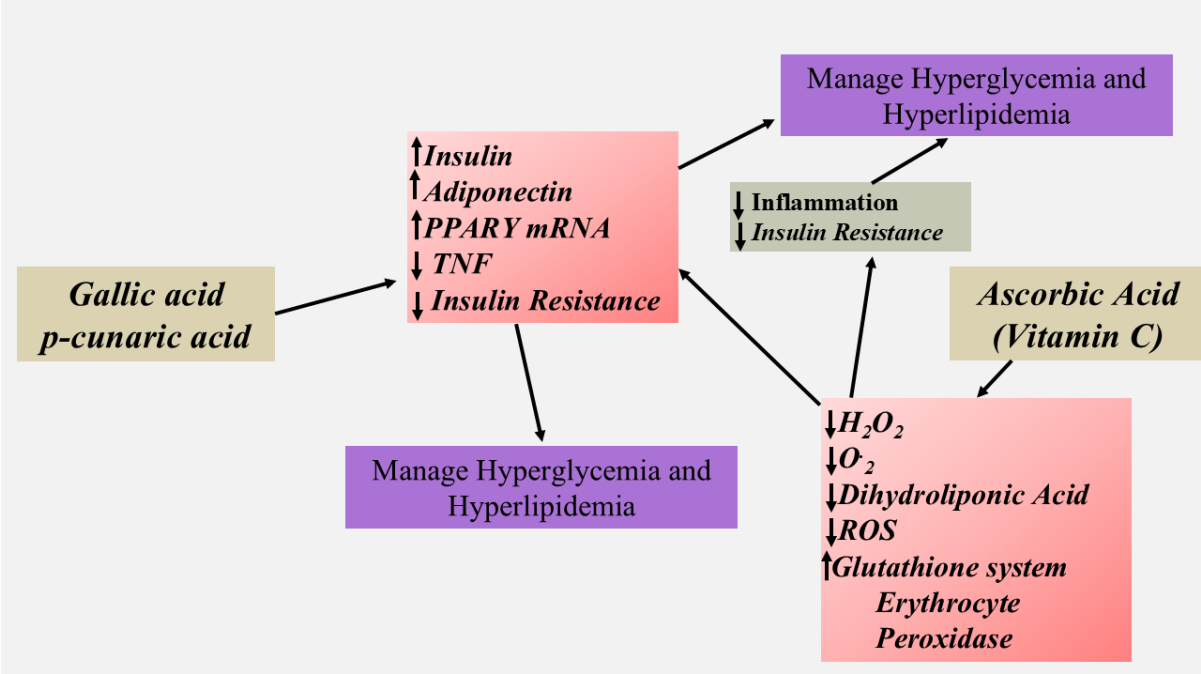


**Figure 3:** Role of gallic acid and Vitamin C in the management of diabetes, obesity and oxidative stress (Abdel-Moneim et al., 2018; Fernández-Mejía, 2013).

Vitamin C can be used as a strong reducing agent and antioxidant, because it has the property of providing one or more electrons, so it plays a vital role in metabolic diseases. As an antioxidant, it can neutralize toxic radicals and control stress by releasing 1 or 2 electrons. Ascorbic acid helps protect different tissues from oxidative stress in body cells and fluids and helps treat metabolic diseases. Its structure is similar to glucose. It can be used as a substitute for glucose in many chemical reactions and has a significant effect on preventing non-enzymatic glycosylation of protein (Ellulu, 2017).

**Effect of vitamin C on Systemic Inflammation**

Due to the increase in white adipose tissue in obesity, endogenous products are produced and released, making these tissues have pro-inflammatory properties. This is why fat tissue is not only a storage organ for triglycerides but also participates in the production of some biologically active substances called adipokines. Adipokines contain inflammatory markers, such as IL-6, TNF-α, and monocyte chemoattractant protein 1. Adipokines like this play a role in the formation of ROS, OS and systemic inflammation. Increased fat accumulation can cause cell damage, leading to the production of increased number of cytokines in fat tissue. Cytokines play a role in tissue lipid peroxidation and the formation of ROS. It was identified that when the body fat level drops, the antioxidant activity rises, and the oxidation index disappears (Carrillo et al., 2018).

It has been found that ascorbic acid can inhibit the interleukin 1, CRP and TNF-α mechanisms. In vitro, it has also been shown to block the activity of IkB kinase a and b, as well as the nf-kb transcriptional activity induced by TNFα. These two enzymes are related to immunity and inflammation and participate in the nf-KB signaling pathway. Lipid peroxidation is also reduced. The anti-inflammatory effect of vitamin C is related to the reduction of interleukin and tumor factor liver mRNA expression and the regulation of NF-KB DNA binding activity. It was found that TNFα IL6 cytokines were significantly reduced in a diet containing 200 mg/kg ascorbic acid, as did liver m-RNA regulation. When taking fruit juice rich in ascorbic acid to relieve postprandial stress caused by excess fat meals, the levels of TNFα and interleukin 6 are reduced (Totan et al., 2019).

**Other obesity related functions of vitamin C**

Vitamin C is necessary for the post-translational modification of procollagen polypeptides to form elasticity, that is, cross-linked collagen molecules. Abnormal collagen synthesis is one of the common symptoms of scurvy, because scurvy can cause fatigue, reduce the willingness to exercise, and then lead to the regeneration of obesity. The oxidation of long-chain fatty acids through the mitochondrial membrane and fat oxidation requires the production of carnitine. Vitamin C is required for this process. Studies have shown that people who are deficient in vitamin C have difficulty losing weight. Insufficient eating habits may be the main reason for the lack of vitamin C in obese people. Because vitamin C may be found in different fresh fruits and vegetables (Wilson et al., 2018). Because of its antioxidant properties, it is included in many processed foods. According to recent studies, among 926 women between 40 and 60 years of age, fruit consumption is associated with higher central obesity. Obese people have increased ascorbic acid concentration and low vitamin C intake. An in vitro study showed that vitamin C has the ability to limit glucose uptake and lactic acid production, reduce glycerol release, and reduce leptin secretion in a dose-dependent manner (Carr & Rowe, 2020).

In primary cultured rat fat cells, vitamin C can improve glucose and fat metabolism. Vitamin C supplementation can reduce the C-reactive protein content in 75% of obese people. In this case, vitamin C can exacerbate endothelial dysfunction caused by oxidative stress. Vitamin C supplementation improved the impaired vasodilation of acetylcholine in obese people (24 men and 13 women) and may protect them from endothelial damage. Obesity and antioxidant deficiency are largely related. Increasing vitamin C concentration is essential to improve obesity treatment and confirm the potential benefits of supplements for obese people (Thomas-Valdés et al., 2017).

**Anti- diabetic properties of vitamin C**

The role of ascorbic acid in DM2 can be described by the antagonism of sugar ascorbic acid. Both sugar and ascorbic acid require insulin to pass through the cell membrane through a special pump. Ascorbic acid and sugar enhance the insulin-mediated passage through the cell membrane into the cell. Due to high glucose levels, vitamin C cannot enter cells. WBC has more insulin pumps than other parts of the body. This describes why ascorbic acid and sugar are hostile to each other. Ascorbic acid prevents end-organ destruction in diabetes through three mechanisms: 1. Vitamin C is a powerful antioxidant. 2. Ascorbic acid reduce the sorbitol accumulation in cells. Vitamin C inhibits glycosylation of protein. Because ascorbic acid is structurally similar to glucose, it may compete with sugar to move into cells. In the case of high blood glucose, the absorption of ascorbic acid into the cells seems to decrease (Santosh and David 2017). Vitamin C has drug-level antioxidant activity, which explains its role in sepsis. Delta-6- and adelta-5-desaturases convert dietary essential fatty acids (EFA), linoleic acid (LA) and α-linolenic acid (ALA) into their respective long-chain metabolites, γ-linolenic acid (GLA), Dihomo-γ-linolenic acid (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA). Elongase is responsible for converting GLA into DGLA. DHA can be converted back to EPA, and DHA can be converted back to EPA. GLA, DGLA, AA, EPA and DHA all help vascular endothelial cells produce more eNO. Folic acid, vitamins B6, B12, and C are cofactors for proper desaturase activity and the conversion of DGLA to PGE1. Both PGI2 and LXA4 are precursors of AA. GLA, DGLA, AA, EPA and DHA, as well as PGE1, PGI2 and LXA4 have anti-inflammatory properties, inhibit the production of IL-6 and TNF-α, while rise in the formation of anti-inflammatory chemicals (Das, 2019).

In case of healthy physiological conditions, balance exists between pro-inflammatory and anti-inflammatory cytokines. However, substantial amounts of ROS can inactivate eNO, resulting in the increased vascular tone and hypertension. EPA and DHA are the precursors of decomposins, protectins, and hippocampus, all of which have anti-inflammatory properties, similar to the way LXA4 is formed from AA. B6, B12, folic acid and vitamin C are expected to promote the production of decomposing factors, protective factors and maresins from EPA and DHA. Excess doses of ascorbic acid can rise the production of ROS in tumor cells and lead to their apoptosis. Surprisingly, when people with sepsis take vitamin C in drug doses, oxidative stress is reduced. Therefore, the effect of vitamin C depends on the dose, the time of administration (ranging from some hours to a few days and weeks) as well as the environment. Ascorbic acid has antioxidant and pro-oxidant properties (Wilson et al., 2018). T2DM and hypertension are low-grade inflammatory diseases characterized by elevated plasma IL-6 and TNF-α levels, elevated lipid peroxides, and AA and LXA4 deficiency. It is known that EFA deficiency is induced by IL-6 and TNF-α. Therefore, it is a promising idea to supplement vitamin C with additional cofactors (folate, B6, B12) and polyunsaturated fatty acids. For best results, polyunsaturated fatty acids, vitamin B6, vitamin B12, folic acid and vitamin C should be taken at the same time for all inflammatory diseases (Das, 2019).

When vitamin C was added to the diet, the malondialdehyde levels of mice on a high-fat diet improved. Prevent the formation and cell growth of mature adipocytes. In animal studies, pre-adipocytes are transformed into mature adipocytes, because glycerol phosphate dehydrogenase (GPDH) rise its activity in fat tissue and promotes lipid metabolism build up. Vitamin C inhibits this transition by reducing the activity of the GPDH enzyme. When mature adipocytes are processed by intracellular vitamin C, triglyceride concentration, GPDH activity, and mRNA suppression are all reduced. Continuous phosphate ascorbic acid (a form of ascorbic acid with increase bioavailability) inhibits fat cell development. The 3t3-l1 (resistin synthesis) pre-adipocyte pathway was found to be spontaneously stimulated by vitamin C. All these findings may indicate a link among losing weight and the antioxidant properties of vitamin C (Totan et al., 2019).

It was found that ascorbic acid competed with sugar in the transport of the GLUT 1-3-4 carrier. In a mouse study, it was found to have benefits on insulin sensitivity in fat tissue. The modification of the IRS-1/JNK cell pathway produced results. It has been found to inhibit the release of leptin. In obese diabetic animals, hyperglycemia and its effect of reducing glycosylation have been improved. It has also been found that moderate obesity and ascorbic acid supplementation have beneficial effects on lipid and carbohydrate absorption in diabetic individuals (Totan et al., 2019). Attempts have been made to use different supplementation of ascorbic acid in diabetic patients to lower blood sugar levels. Fasting blood glucose (FBG), postprandial blood glucose (PPBG) and glycosylated hemoglobin are the main results of all these studies (HbA1c). After oral vitamin C treatment, FBG and PPBG were significantly reduced. Vitamin C intake and time have an effect on the reduction of FBG and PPBG (Santosh and David 2017).

## Conclusion

This review emphasized the role of gallic acid and ascorbic acid in the treatment of obesity and type 2 diabetes mellitus. Oxidative stress leads to cause the obesity and T2DM. Toxic oxygen free radicals and nitrogen radicals are associated with lipid peroxidation, non-enzymatic protein glycation and glucose oxidation, all of them linked to T2DM and obesity development. Vitamin C is a strong antioxidant that is abundant in food and can compete with glucose to enter cell membranes. Insulin helps this process. Therefore, in addition to food consumption, vitamin C should also be provided

comprehensively to improve diabetes management. Antioxidant therapies for obesity and T2DM may be beneficial in treating systemic oxidative stress. Antioxidant supplements can help to decrease the production of toxic radicals, elevated ROS, and nitric oxide by regulating enzyme activity. In addition to obesity by nutrition and medication, supplementation of antioxidant nutrients such as C, E and A vitamins is believed to treat obesity and T2DM through treating pathological problems associated with oxidative stress. Ascorbic acid has anti-inflammatory properties and can reduce the improper production of cytokines by fat cells with antioxidant activity, thereby solving the problem of abnormal fat formation by reducing the free radicals and lipid peroxidation.

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