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Combine Therapy of Gallic Acid and Allicin in Management of Diabetes

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ABSTRACT

Type 2 diabetes, also known (DM) is a metabolic disorder with a high mortality and disability incidence. The development and activation of oxidative stress (OS) are crucial to the pathogenic development of DM. Pathophysiological evidence suggests that OS contributes to the onset and progression of DM through its association with hyperglycemia, resistance to insulin, and inflammation. It's worth noting that more and more studies are investigating the benefits of natural antioxidants for managing DM. Many different types of culinary and herbal plants contain the antioxidant and anti-inflammatory compounds gallic acid (GA) and allicin, respectively. The synthesis of advanced glycation end products (AGEs) is inhibited, fat is stored less, blood sugar and weight are improved, and the body produces fewer AGEs, according to the study's authors. Inhibition of RAGEs and prevention of AGE activity following treatment with GA and allicin resulted in reduced oxidative stress and enhanced insulin secretion. The goals of this article are to (1) provide evidence that GA and allicin may be effective antihyperglycemic treatments for DM and its complications and (2) provide a comprehensive review of the current state of knowledge regarding studies examining the role of oleic acid in this disease.

Keywords- Diabetes, Chemical Constituents, Treatment, Chronic Disease, Oxidative stress.

I. INTRODUCTION

Type 2 diabetes is differentiated by anomalies in insulin synthesis, insulin action, or both, and is characterised by chronic hyperglycemia and changes in the metabolism of carbohydrates, lipids, and proteins. Damage, malfunction, and eventual collapse of various organs are long-term effects of diabetes mellitus[1]. Type 1, type 2, and type 3 diabetes are the three most common forms of the disease [2]. In people with type 1 diabetes, the pancreas either stops generating insulin altogether or produces very little insulin due to an autoimmune response. Regular doses of insulin are essential to the survival of people with type 1 diabetes. Prevalence is highest among children and young adults. More than 90% of adult DM cases are of type 2, often known as insulin-dependent DM[3]. When the pancreas generates the proper amount of insulin but the body is unable to use it properly due to insulin resistance, a diagnosis of diabetes is made[4]. Gestational diabetes mellitus (GDM) is a form of glucose intolerance that develops or is first diagnosed in the second or third trimester of pregnancy in certain women. Gestational diabetes can develop for a number of reasons, including an insulin deficit or a lack of the pregnancy hormone. Pregnancy-related GDM is a classic example of a metabolic disease. The cardiovascular system, blood vessels, eyes, kidneys, nervous system, and nerves are all negatively impacted by hyperglycemia [5]. Figure 1 shows that by 2030, the estimated number of persons

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with diabetes is projected to increase from 463 million in 2019.[6], as reported by the International Diabetes Federation's (IDF) ninth edition 2019 Diabetes Atlas. More people die each year from diabetes mellitus than from AIDS (1.5 million), tuberculosis (1.5 million), or malaria (0.6 million) [7,8].

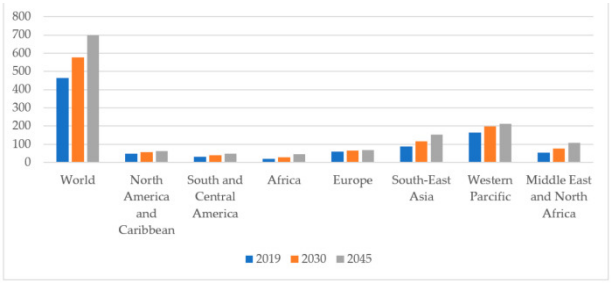

Figure 1: Number of People with Diabetes worldwide & International as per IDF report

II. MANAGEMENT OF DIABETIC MELLITUS

According to the recently published WHO study on the categorization of diabetes mellitus, there are other "other specific types" of diabetes, such as monogenic diabetes and what was formerly known as "secondary diabetes[9]. Unlike type 1 and type 2 diabetes, which are both affected by multiple genes and environmental variables, monogenic diabetes is caused by a mutation in a single gene. Although only 1-2% of diabetics have the condition for no apparent reason, this estimate may be low because type 1 and type 2 diabetes are often misdiagnosed as monogenic diabetes[10]. Neonatal diabetes mellitus (sometimes called "monogenic diabetes of infancy") and maturity-onset diabetes of the young (MODY) are two forms of hereditary diabetes. Despite their rarity, they can serve as "human knockout models" for research into the causes of diabetes. It is helpful to identify the specific genetic defect responsible for monogenic diabetes in the clinic, as this allows for more targeted treatment[11]. A more accurate clinical prognosis and treatment differentiation of MODY's 14 subgroups is now possible. The accumulation of genome-wide association studies has led to the identification of an increasing number of monogenic types of diabetes in recent years[12][13][14]. As a result, it's possible that these figures don't fully capture the true prevalence of these forms. The start of diabetes is caused by a combination of environmental and genetic factors[15]. Conflicting definitions of type 2 diabetes could make it difficult to compare studies. World Health Organisation and International Association of Diabetes and Pregnancy Study Groups-preferred diagnostic criteria have been implemented. The prevalence of GDM has increased due in part to these factors[16].The plasma glucose concentration is measured before and after 75 grammes of glucose is eaten, as well as at two additional time points. People whose insulin secretion is inadequate to counteract the diminished effect of insulin (insulin resistance) brought on by placental hormone secretion are also at risk for developing GDM, just like pregnant women who experience early hyperglycemia[17]. Age, obesity, prior GDM, rapid weight gain during pregnancy, a family history of diabetes, polycystic ovary syndrome, chronic cigarette smoking, and a history of stillbirth or delivering a child with a congenital defect all increase the likelihood of developing GDM. Some racial and ethnic groups have a higher prevalence of GDM than others. In most cases, GDM is a temporary ailment that manifests itself only during pregnancy and resolves itself after the delivery of the baby. Hyperglycemia during pregnancy increases a woman's risk of gestational diabetes in future pregnancies. The relative risk is highest between three and six years following GDM, and type 2 diabetes can develop as early as age 40. After that point, danger remains high[19]. Due to the significant risk of early onset type 2 diabetes and the fact that prior GDM raises the risk of cardiovascular disease (CVD), with or without type 2 diabetes, any lifestyle intervention for the prevention of diabetes should begin no later than three years after the pregnancy.[20][21]. Adult type 2 diabetes and obesity are more common in children born to moms with GDM. A normal birth may be difficult or even dangerous for the baby if the mother has hyperglycemia throughout pregnancy and other risk factors are present, such as high blood pressure (including pre-eclampsia) or a large baby for gestational age (known as "macrosomia"). These dangers can be mitigated by keeping an eye out for hyperglycemia throughout pregnancy and maintaining close track of blood sugar levels for the entire nine months[23]. A woman of childbearing age who has diabetes should have preconception counselling, a review of her pharmaceutical regimen (which may involve a higher folic acid dose), intense diabetic treatment, and a carefully crafted conception plan before attempting to conceive[24]. Women with HIP, whether from GDM, undiagnosed DIP, or known diabetes, need the best prenatal care and postpartum support available[25]. A good diet, weight loss, moderate activity, and regular monitoring of blood glucose levels may help a pregnant woman with hyperglycemia bring her condition under control. Regular check-ins with their healthcare experts can aid with self-management as they can also help assess whether any medical (such as the prescription of insulin and/or oral medications) or obstetrical intervention is necessary[26][27].

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Table 1: Estimated total number of adults (20–79 years) with diabetes in 2021, 2030 and 2045

At a glance	2021	2030	2045
Total world population	7.9 billion	8.6 billion	9.5 billion
Adult population (20–79 years)	5.1 billion	5.7 billion	6.4 billion
Diabetes (20–79 years)			
Prevalence[i]	10.5%	11.3%	12.2%
Number of people with diabetes	536.6 million	642.7 million	783.2 million
Number of deaths due to diabetes	6.7 million	–	–
Total health expenditure due to diabetes[ii] (2021 USD)	USD 966 billion	USD 1,028 billion	USD 1,054 billion
Hyperglycaemia in pregnancy (20–49 years)			
Proportion of live births affected[iii]	16.7%	–	–
Number of live births affected	21.1 million	–	–
Impaired glucose tolerance (20–79 years)			
Prevalence[i]	10.6%	11.0%	11.4%
Number of people with impaired glucose tolerance	541.0 million	622.7 million	730.3 million
Impaired fasting glucose (20–79 years)			
Prevalence[i]	6.2%	6.5%	6.9%
Number of people with impaired glucose tolerance	319.0 million	369.7 million	440.8 million
Type 1 diabetes (0–19 years)			
Number of children and adolescents with type 1 diabetes	1.2 million	–	–
Number of newly diagnosed cases each year	184,100	–	–

III. BIOACTIVE COMPOUNDS FROM PLANTS EXTRACT HAVING TYPES 2 ANTI-DIABETIC PROPERTIES

Hyperglycemia may be treated with any one of the many available anti-diabetic drugs. Glucose tolerance, insulin secretion, and absorption are all increased and improved by these medications. However, the efficacy of metformin and sulfonylurea type antidiabetic medications is diminished by a number of unfavourable side effects, including diarrhoea and lactic acidosis (shown by metformin) and hepatic failure, weight gain, tachycardia, and hypothyroidism[28]. One of the most reliable sources of the therapeutic benefits of synthetic drugs is plant life. Recent research (Figure 2) suggests that the usage of plants and plant derivatives may be useful in the treatment of diabetes[29].

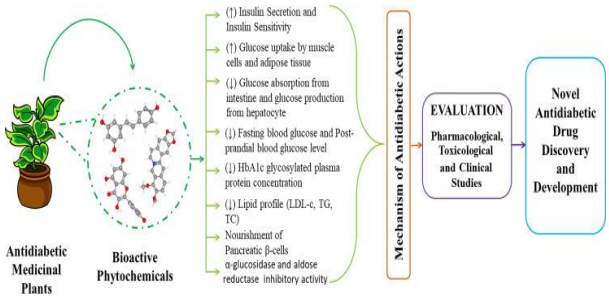

Figure 2: Plant-based anti-diabetic phytochemicals for the development of new medications

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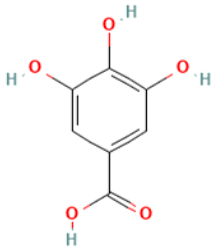
IV. BIOACTIVE COMPOUND ACT AS INSULIN

4.1 Gallic Acid



Our research centred on GA, a polyphenol found in high concentrations in a wide variety of plants. Because of its high concentration of phytochemicals [30-32], GA has been shown to alleviate metabolic disorders such as obesity and dyslipidemia. It is still unclear how exactly GA causes its beneficial effects on metabolism. Using a diet-induced obesity mouse model and the HepG2 cell line, we analysed the metabolic effects of GA and the underlying molecular pathways involved[33]. Our data suggest that GA stimulates this pathway, leading to elevated PGC1 activity (a key inducer of mitochondrial biogenesis) and the subsequent induction of autophagy. Consistent GA administration strongly activated this pathway in the tissues of the mice. These findings suggest that the beneficial metabolic benefits of GA originate from autophagy, mitochondrial activity, and the stimulation of the AMPK/Sirt1/PGC1 pathway. It has been hypothesised that sirt1 activation increases glucose production[34]. via activating gluconeogenic genes such PEPCK and G6Pase. Consequently, GA therapy may lead to elevated PEPCK and G6Pase levels by activating Sirt1. PEPCK and G6Pase expression was downregulated, however, after GA treatment[35]. The pleiotropic effects of activated AMPK could account for some of the variance. Therefore, GA treatment-induced AMPK activation may be responsible for the downregulation of insulin receptor substrate-1 Ser636/639, which suppresses gluconeogenesis[36], the upregulation of the SHP gene, which inhibits PEPCK and P6Pase[37], and the facilitation of transducer of regulated cAMP response element-binding protein-2, which inhibits PEPCK and G6Pase gene expression [38]. Indeed, we found that administering GA to mouse liver and hepatocytes led to an upregulation of Akt signalling[40]. Liver Akt activity is associated with maintaining normal blood sugar levels[41]. GA's capacity to activate hepatic Akt may have assisted the beneficial effects on glucose and insulin metabolism by downregulating gluconeogenic genes such PEPCK and G6Pase. Consistent with the studies showing GA improves insulin sensitivity before impacting body weight, the findings show GA reduces glucose levels before there is a change in weight. Acute phosphorylation of metabolic enzymes like ACC can also induce the positive metabolic regulation brought on by AMPK activation, as can chronic phosphorylation of transcriptional proteins or coactivators like PGC1.[42]. GA's suppressive effect on oleic acid-induced TG generation may be connected to its inhibitory influence on ACC via activation of AMPK, as ACC is the rate-limiting enzyme for fatty acid synthesis. By reducing TG storage in lipid droplets,[42] autophagy elicited by GA treatment appears to aid in regulating lipid metabolism. When AMPK is turned on, it stimulates the production of PGC1 and other genes involved in regulating mitochondrial biogenesis and oxidative metabolism. Sirt1 regulates PGC1 through posttranslational modification[43-44]. There are two ways in which AMPK activates Sirt1: by regulating NAMPT, the rate-limiting enzyme in nicotinamide adenine dinucleotide production, or by regulating the ratio of NAD+ to nicotinamide adenine dinucleotide hydroxide. Therefore, we postulated that GA might engage Sirt1, and consequently, promote PGC1[45]. PGC1 regulates the expression of mitochondrial genes, and sirt1-specific knockdown reduced both the deacetylated form of PGC1 and the expression of its target genes. The role of AMPK in the activation of the Sirt1/PGC1 axis in response to GA treatment was investigated, but other pathways that might contribute to this activation were not. More research is needed to determine whether or not Sirt1/PGC1 axis activation in response to GA also involves other pathways. For instance, this may be done by inhibiting AMPK's activity with a small interfering RNA. In order to activate AMPK,[46]. Sirt1 may first deacetylate the upstream kinase LKB1, which phosphorylates AMPK. However, it is still unclear whether or not GA has the ability to stimulate LKB1. Since Sirt1 activation is known to regulate longevity and improve life expectancy,[47]. investigating if GA has similar effects may be beneficial.Furthermore, GA treatment inhibited HFD-induced weight gain without affecting food intake, as demonstrated by our findings[48]. Weight gain suppression was connected to reduced white adipose tissue (WAT) size and increased expression of thermogenic-related proteins and genes in iBAT. Thermogenic pathways appear to be activated by GA's regulation of iBAT activity, suggesting that GA may have positive effects on body weight, glucose homeostasis, insulin sensitivity, and lipid metabolism[49]. It will be interesting to learn if and how GA affects the thermogenic gene iBAT's regulation. Uncoupling proteins (UCPs), a class of mitochondrial

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proteins, are thought to contribute to heat dissipation in iBATs. Some studies have shown that catechin-rich green tea extracts can stimulate thermogenesis in iBAT through the sympathetic nervous system (50, 51).

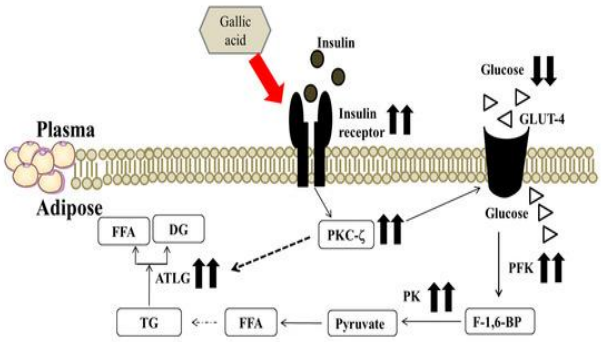


Figure 3: In high fructose diet-induced diabetic rats, the potential mechanism by which GA controls glucose and lipid metabolism in perirenal adipocytes involves the restoration of insulin signalling and the increase of glycolysis and lipolysis pathways. Fats include triglycerides (TG), diglycerides (DG), adipose triglyceride lipase (ATGL), and gallic acid (GA). Fructose-1,6-biphosphate, pyruvate kinase, glucose transporter 4, phosphofructokinase, and protein kinase C-zeta are all abbreviations for the compound fructose-1,6-biphosphate.

The term "radical oxygen species" (ROS) refers to free radicals that contain oxygen, such as superoxide, peroxide, and hydroxyl radicals. The formation of hydroxyl radicals and hydroxide ions is inhibited by hydrogen peroxide (H2O2), which is generated during the dismutation of superoxide. Damage to DNA, lipids, and proteins results from the oxidative stress brought on by the generation of these free radicals [50].Mitochondrial respiration and other common biological processes generate ROS. The mitochondria are crucially important as both a source of ROS and a sink for these free radicals. Toxins, chemotherapeutic medicines, insecticides, and toxicants are just some of the environmental variables that might generate reactive oxygen species (ROS) [51]. Mice given GA were the same size as their wild-type counterparts, but their blood sugar and insulin levels were more stable. Serum triglyceride (TG), phospholipid, total cholesterol, low-density lipoprotein cholesterol, hepatic TG, and cholesterol[52] and glucose[53]. homeostasis are all enhanced by GA consumption. Therefore, GA's possible protective effects against HFD-induced obesity may be attributable to these advantages. In certain pathophysiological settings, GA and its derivatives can modulate oxidative stress, apoptosis, and inflammation by acting as powerful antioxidants and free radical scavengers. It has been suggested that GA's antioxidant and anti-inflammatory actions contribute to its antihyperglycemic potential [54].

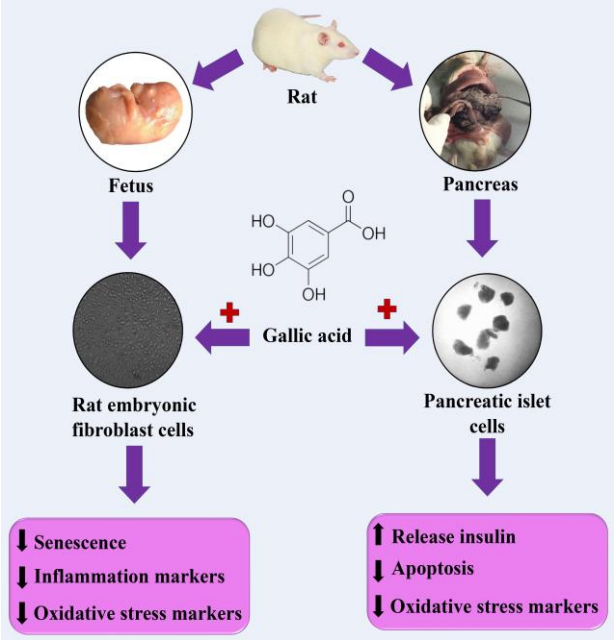
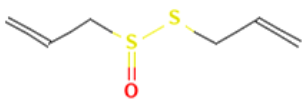


Figure 4: Therapeutic Effects of Gallic Acid in Oxidative Stress marker & Diabetes

The activation of PPAR may be critical in preserving insulin homeostasis, as GA from Punica granatum flower extract is a powerful inducer for PPAR and its downstream target lipoprotein lipase[55]. When injected intraperitoneally (ip), GA improves glucose tolerance and lipid metabolism, as shown by Bak et al.[56]. Accelerated glucose transporter-4 membrane translocation is associated with pAKT activation by GA, which in turn leads to insulin action. Therefore, it is possible that GA's additive effects on insulin sensitivity, such as the inhibition of gluconeogenesis via the activation of AKT and the improvement of insulin sensitivity via the activation of PPAR and lipoprotein lipase, or the inhibition of ACC, are responsible for the observed increase in insulin sensitivity following GA administration. The term "radical oxygen species" (ROS) refers to free radicals that contain oxygen, such as superoxide, peroxide, and hydroxyl radicals. The formation of hydroxyl radicals and hydroxide ions is inhibited by hydrogen peroxide (H2O2), which is generated during the dismutation of superoxide. Damage to DNA, lipids, and proteins results from the oxidative stress brought on by the generation of these free radicals [57].

4.2 Allicin



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Advanced glycation end-products (AGEs) are a class of hazardous compounds that contribute to the development of diabetes and its consequences [58]. AGEs are directly responsible for the death of pancreatic cells.[59]. Diabetic problems can be better managed by preventing the production of AGEs. The antibiotic component allicin, which is naturally present in garlic, was used in the experiment. Allicin has multiple pharmacological activities, one of which is antibacterial characteristics [59,60]. They have effects including lowering cholesterol and inflammation as well as fighting cancer. While most of the focus has been on allicin's antioxidant and anti-inflammatory effects, recent studies [61,62] have shown that it may also help mitigate the negative effects of diabetes.[63]. Allicin decreased insulin resistance in diabetics, as measured by the insulin tolerance test (ITT). Our results are consistent with those of earlier studies [64,65] that found that allicin reduced AGEs and blood glucose levels in diabetics, and also helped alleviate insulin resistance.

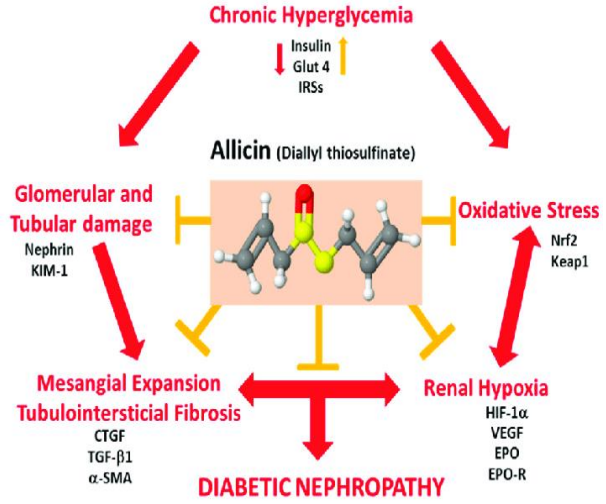

Figure 5: Effects of Allicin on Pathophysiological Mechanisms during the Progression of Nephropathy Associated to Diabetes

Advanced glycation end products (AGEs) are largely formed from lipid peroxidation products [66], and hyperlipidemia is a major consequence of diabetes. Precursor molecules of AGEs, such as reactive dicarbonyl compounds, cross-link with proteins during lipid peroxidation, resulting in stable AGE. Allicin has been demonstrated to have hypolipidemic effects in the past [67]. The diabetic rat model group also had higher levels of triglyceride (TG) and low-density lipoprotein (LDL-C). The levels of aminotransferases and high-density lipoprotein changed, albeit only little. The biggest effects of allicin therapy were seen on triglyceride and low-density lipoprotein cholesterol levels, whereas there was a notable reduction in blood glucose levels. The liver is the primary site for fatty acid oxidation and ketone body production [68]. It is necessary for lipid transport and lipoprotein production. Lipid peroxidation can cause an increase in advanced glycation end products (AGEs), which can disrupt liver metabolism [69]. H&E staining revealed a remarkable reduction in the amount of large, dense fatty particles in the liver after allicin administration in the model group of rats. A statistically insignificant increase in liver AGE was observed in the model group compared to the NC group, however the increase was not large enough to be considered clinically relevant. Hepatic AGE levels were significantly reduced after treatment with allicin. Allicin's hypolipidemic activity and suppression of lipid peroxidation, which produce AGE active intermediates, may account for the reduction in AGE levels found in vivo, as suggested by data from serum indices and serum AGE levels[70].

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