A Systematic Review on Anti-diabetic and Cardioprotective Potential of Gallic Acid: A Widespread Dietary Phytoconstituent

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ABSTRACT

Gallic acid (GA) is a bioactive phytoconstituent that has been reported to prevent a number of diseases. However, there is no systematic review to-date on its anti-diabetic and cardioprotective potential including molecular mechanisms for such activities. This review aims to summarize the anti-diabetic and cardioprotective effects of gallic acid and further propose a molecular mechanism of its anti-diabetic effects. Accumulation of associated literature was conducted through the use of databases including Google Scholar, Pubmed, Web of Science, Science Direct and Scopus databases. Articles published until December 2018 were extracted and all the retracted articles were sorted based on the inclusion and exclusion criteria and relevant articles were further consulted for necessary information. We have found substantial investigations in animals and cultured cells that supports anti-diabetic and cardioprotective effects of GA with several underlying mechanisms including antioxidant enzyme systems and non-enzymatic defense mechanisms. The reported antioxidant activity of GA as well as the modulation of some key proteins linked to diabetes could be a part of the mechanisms by which GA showed anti-diabetic effect. In summary, it is evident that GA is one of the promising dietary phytochemicals that could be beneficial for the treatment and management of diabetes and associated myocardial damage.

Key words: Gallic acid, anti-diabetic, cardioprotective, antioxidant; dietary phytoconstituents

List of abbreviation:

AGEs, Advanced glycation end products; Akt, Protein Kinase B; ALT, Alanine transaminase; AMPKα, AMP-activated protein kinase- alpha; AMPKγ, AMP-activated protein kinase-gamma; ANP, Atrial natriuretic peptide; AST, Aspartate transaminase; b.w, Body weight; CAT, Catalase; CK, Creatine kinase; CK-MB, Creatine kinase-myoglobin binding; CPK, Creatine phosphokinase; CRP, C-reactive protein; CsA, Cyclosporine A; CVDs, Cardiovascular diseases; Cx43, Gap junction protein Connexin 43; CYP, Cyclophosphamide; CTGF, Connective tissue growth factor; DM, Diabetes mellitus; D-MI, Diabetes with myocardial infraction; DOX, Doxorubicin; ECM, Extracellular matrix; ERKs, Extracellular signal–regulated kinases; GA, Gallic acid; GSIS, Glucose-stimulated insulin secretion; GLUT4, Glucose transporter protein 4; GLUT2, Glucose transporter protein 2; GR, Glutathione reductase; GSH, Reduced Glutathione reductase; GST, Glutathione-S-transferase; GATA4, Transcription factor GATA-4; HDL, High density lipoprotein; H9c2(2-1), Embryonic rat cardiomyocyte cell line; iNOS, Inducible nitric oxide synthase; ISO, Isoproterenol ; JNKs, c-Jun N-terminal kinases; L-NAME, N-nitro-L-arginine methyl ester; LDL-C, LDL-cholesterol; LDH, Lactate dehydrogenase; LDL, Low density lipoprotein; LOOH , Lipid hydroperoxides; LPO, Lipid peroxidation; LV, Left ventricular; MDA, Malondialdehyde; MHC-β, Myosin heavy chain beta; MI, Myocardial infraction; MMP, Matrix metalloproteinase; Na^+/K^+-ATPase, Sodium-potassium adenosine triphosphatase; Nox2, NADPH oxidase 2; PCO, Protein carbonyls; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI, Plasma insulin; PI3K,Phosphatidylinositol 3-kinase; PPARγ, Peroxisome proliferator-activated receptors-gamma; RAGE, Receptor for AGE; ROS, Reactive oxygen species; SC, Serum creatinine; SOD, Superoxide dismutase ; GPx, Glutathione peroxidase; SHRs, Spontaneously hypertensive rats; STZ, Steptozotocin; TBARS, Thiobarbituric acid reactive substances; TC, Total cholesterol; TG, Triglyceride; TGF-β,Transforming growth factor beta; TIMP, Tissue inhibitor of metalloproteinases; TNF-α, Tumor necrosis factor-alpha; TnI, Troponin-I; TZDs,Thiazolidinediones; UA, Uric acid ; UCP2, Uncoupling protein 2; XO, Xanthine oxidase

Introduction

Diabetes mellitus (DM) and cardiovascular diseases (CVDs) are the two most common causes of deaths that are spreading spontaneously around the world.[1, 2] Approximately 347 million people around the world are suffering from DM[3] and it is projected that about 592 million people worldwide will have DM by 2035.[4] In diabetes, glucose utilization is reduced as a results of compromised insulin secretion.[5] DM causes different ailments including neuropathy, micro and macro vascular diseases as well as nephropathy through inhibiting body's antioxidant mechanisms.[6] A number of reports confirmed that the link between DM and CVDs was the most predominant cause of morbidity and mortality in diabetic patients.[4] According to various studies, hyperglycemia is a prime cause of CVDs in DM patients.[7] Excessive blood glucose in DM patients can react with amino acid residues of proteins as well as free amino acids to form advanced glycation end products (AGEs) by non-enzymatic glycosylation reaction and this plays an important role in the pathogenesis of diabetic complications including cardiomyopathy.[8] The high levels of circulating and myocardial AGEs remains elevated [9] in DM which also contributes to heart failure.[10] Diabetes increases atherosclerotic progression and adversely contributes to the lipid profile resulting in the increased risk of myocardial infraction (MI) .[11] A number of molecules are currently exists to control DM and CVDs with varying degrees of success, but there is still no magic molecule that can control DM and its associated CVDs simultaneously.

Gallic acid (GA), chemically known as 3,4,5-trihydroxybenzoic acid, is a naturally occurring aromatic polyphenolic acid mostly found in different fruits and other plants.[12] GA mainly occurs in plants in the form of free acids or as esters in catechin derivatives and hydrolysable tannins (Fig. 1). Different fruits and foodstuffs contain different amounts of GA

including strawberries, bananas, grapes[13, 14], teas[15], cloves[16], and vinegars[17]. GA has been reported to occur in a number of terrestrial plants such as *Cynomorium coccineum, Garcinia densivenia, Bridelia micrantha, Diospyros cinnabarina, Terminalia bellerica*[18, 19], as well as in aquatic plant *Myriophyllum spicatum*, and the blue-green algae *Microcystis aeruginosa*.[20] Various oak species[21], stem bark of *Boswellia dalzielii*[22], and *Caesalpinia mimosoides*[23], also contain GA. GA has been reported to be used as a dietary herbal supplement[24] and about thirty ayurvedic formulations containing considerable amount of GA are used for different diseases in India.[25] GA is a strong natural antioxidant and has the ability to combat different reactive oxygen species (ROS).[26] GA is reported to affect multiple pharmacological and biochemical pathways through which it exerts a number of biological activities including anti-inflammatory, anti-diabetic, cardioprotective, anti-cancer and hepatoprotective activity (Table 1). However, there is no systematic review to-date covering its anti-diabetic and cardioprotective effects. The aim of this review is to summarize the anti-diabetic and cardioprotective effects of GA with focus on underlying mechanisms of action that is available in published literature using afore-mentioned databases.

Search strategy

A comprehensive literature search was conducted by using several databases including PubMed, Google Scholar, Web of Science, Science Direct and Scopus with the term ‘gallic acid’ with ‘anti-diabetic’, ‘diabetes’, ‘cardioprotective’, ‘cardiovascular disease’ ‘myocardial damage’ and ‘cardiotoxicity’. Reports that are only in English were selected due to the language barrier, time efficiency and non-feasible costs of translation.

Selection of studies for inclusion in the systematic review

To prepare this review, a number of criteria have been structured to include articles in this review. The following types of reports were included in this review: a) *in vivo* animal studies, b) *in vitro* studies, c) studies that include the effects of GA on diabetes and cardiovascular diseases, e) studies that indicate the concentrations or doses employed and the form of administration and f) studies that pointed out the mechanisms of action of GA.

Data extraction

All the searched literature were assessed for the information according to surname of first author, year of publication, GA, test system, observation, result, concentrations tested and suggested molecular mechanism involved. The general steps of the data search, the exclusion-inclusion data and other relevant information are presented in Fig. 2.

Literature review

A total number of 2217 reports were revealed under anti-diabetic and cardioprotective effects of GA using different databases including PubMed, Google Scholar, Web of Science, Science Direct and Scopus in which 35 studies met the inclusion criteria. The exclusion of 2182 documents was because of duplication of information, absence of any title and non-relevance of the study.

Anti-diabetic effect of GA

DM is a chronic metabolic disorder characterized by hyperglycemia as a results of reduction of secretion and action of insulin.[26] A number of complications are directly linked with DM including neuropathy, cardiovascular (micro and macro vascular) diseases and nephropathy through affecting body's antioxidant mechanisms.[6] A number of reports confirmed that the excessive production of ROS and oxidative stress plays an essential role in the progression of

diabetes and its complications through alteration of lipid peroxide production, antioxidant enzyme levels, auto-oxidation of glucose, glutathione metabolism, formation of AGEs as well as alteration of several signaling pathways in different tissues.[27, 28] A number of phytomedicines and herbal preparations have long been evaluated to develop natural product based new anti-diabetic drug. GA is a natural dietary triphenolic antioxidant that has diverse bioactivity including radical scavenging activity, inhibition of lipid peroxidation (LPO), metal ion chelation, maintenance of endogenous defence system and interfering cell signaling pathways.[29] Literature study demonstrated that GA has the ability to decrease the harmful consequences in diabetic rats via altering biochemical and histopathological biomarkers of oxidative stress as well as affecting a number of cellular signaling pathways. It also showed protection of pancreatic β-cell, increased cellular glucose uptake as well as increase plasma insulin secretion and insulin sensitivity (Table 2). Table 2 and 4 summarized the anti-diabetic effect of GA in both *in-vivo* and *in-vitro* test models. A number of possible mechanisms for anti-diabetic effect of GA is shown in Fig. 3**.**

In vivo experiments of GA revealed that GA has the ability to alter different biochemical parameters in diabetic animals. A number of reports demonstrated that treatment of GA at a dose of 10-20 mg/kg b.w. in steptozotocin (STZ) induced diabetic rats can reduce blood glucose level, total cholesterol (TC), triglyceride (TG), uric acid (UA) and serum creatinine (SC), while increasing plasma insulin (PI), C-peptide and glucose tolerance level.[30, 31] In 2014, Kade, *et al*., showed that GA mitigates pancreatic dysfunction by its anti-oxidative effect (increased vit C, glutathione, Fe^{2+} chelation and Fe^{3+} reduction ability of pancreas) and enhances glucose uptake in STZ-induced oxidative stressed rat.[32] Another report by Ramkumar, *et al*., (2014) showed protective effect of GA on alloxan-induced oxidative stressed diabetic rats via scavenging of ROS, upregulation of antioxidant enzymes (catalase (CAT), suproxide dismutase (SOD),

glutathione peroxides (GPx)) and increased insulin secretion.[33] Other report by Al-Salih et al.(2010) showed synergistic effect of GA with tannic acid that decreased blood glucose level and serum malondialdehyde (MDA) level in alloxan induced female diabetic rabbits and *in-vitro* rat pancreas homogenate.[34, 35] It is reported that MDA is the accumulated ROS induced oxidative breakdown product of phospholipid which has key role in modifying low density lipoprotein (LDL), non-enzymatic and auto-oxidative glycosylation as well as act as a surrogate marker of oxidative stress in diabetics.[36]

Peroxisome proliferator-activated receptors- alpha, beta, gamma (PPAR-α, β, γ) are nuclear receptor proteins that play an essential role in the regulation of glucose and fat metabolism.[37] A number of anti-diabetic drugs such as thiazolidinediones (TZDs) exert their action (increased insulin sensitivity) via interacting with PPAR-γ.[38] PGC1α is another protein that interact with PPAR-γ to control a number of transcription factors which helps to regulate mitochondrial biogenesis, oxidative metabolism as well as inhibits pro-inflammatory cytokine production.[39-42] AMP-activated protein kinase (AMPK) has a key role in cellular glucose and fatty acid uptake via translocation of GLUT4 in the plasma membrane[41, 43, 44] and inducing mitochondrial biogenesis by regulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α).[45] AMPK also facilitate cellular fatty acid oxidation via upregulation and activation of PPAR-α, PGC1α and UCP.[46, 47] Mitochondrial uncoupling proteins (UCP2) help to control of mitochondria-derived ROS production.[48-50] Studies have shown that one of the mechanisms of AMPK action in maintaining intracellular redox regulation is to up-regulate the expression of mitochondrial UCP2 and SOD.[51, 52] Therefore, these proteins play a crucial role in glucose and fat metabolism as well as reducing cellular oxidative stress. Any molecules that interact with these key proteins could be important in the prevention and management of DM. Interestingly, a

number of reports studied and found that GA has the ability to alter a number of such cellular signaling pathways to exhibit its anti-diabetic action. A number of *in vivo* experiments demonstrated anti-diabetic effect of GA through the increase in glucose uptake, insulin sensitivity, adipocytokines as well as reduction in adipocyte hypertrophy caused by the upregulation of cellular PPAR-γ expression and translocation of GLUT4 in Akt signaling pathway in high fat diet induced hyperglycemic mice and rat.[53-55] Another interesting report showed that GA plays an important role in glucose and insulin homeostasis as well as thermogenesis through the activation of AMPK and by regulating mitochondrial function via the activation of PGC1α as well as elevation of UCP2 together with other genes related to energy expenditure in the brown adipose tissue.[56] Several *in vitro* experimental studies done in cultured cell lines and pancreatic cell homogenate (3T3-L1, RINm5F, isolated rat pancreas) showed that GA has the ability to induce GLUT4 translocation and glucose uptake activity, inhibit α-amylase and α-glucosidase, increases insulin secretion and prevent insulin amyloid fibril formation in the cultured cell lines which were further supported by *in vivo* studies reported elsewhere.[35, 57-59]

From the above literature study, it is clear that GA exerts anti-diabetic effects not only by its antioxidant mechanism but also by inducing PPARγ and PGC1α expression, activating AMPK and Akt signaling pathway as well as enhancing glucose uptake through translocation and activation of GLUT4. GA further prevents mitochondrial dysfunction through upregulation of UCP proteins which leads to improve oxidative stress along with improved glucose metabolism and insulin resistance and ultimately showing anti-diabetic effect (Fig. 3).

Cardioprotective effect of GA

CVDs such as coronary artery disease, hypertensive heart diseases, and stroke are attributed for most of the mortalities around the world.[60] It is well established that DM increases

the incidence of CVDs and a major risk factor for the development of CVDs.[61-63] Clinical studies showed that patients with type II DM possesses a number of risk factors for the development of CVDs including hyperglycemia, abnormalities of inflammatory mediators, lipid profiles and thrombolytic parameters, as well as other abnormalities associated with insulin resistance.[61] A significant number of studies over the last few decades confirmed that oxidative stress-related factor such as ROS, play an important role in the pathophysiology of CVDs and DM.[60, 64] Clinical studies also demonstrated that antioxidant balance is a key indicator for diabetes induced myocardial damage and patients with diabetes and myocardial infraction (D-MI) exhibit high level of total cholesterol (TC), triglyerides (TG), low-densitylipoprotein (LDL), cardiac markers such as creatine phosphokinase (CPK), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), C-reactive protein (CRP), lactate dehydrogenase (LDH), troponin-I (TnI) as well as low level of oxidative stress marker such as high-density lipoprotein (HDL), superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA), catalase (CAT) in comparison to non-myocardial infraction (N-MI) patients.[65, 66] Therefore, antioxidant based interventions are an important tool to treat diabetes and associated CVDs. Natural polyphenols are one of the prominent antioxidants that has been reported to manage efficiently CVDs and DM.[67, 68]

GA is a bioactive natural polyphenolic acid and possesses strong antioxidant activity. Over the last decade, a number of significant studies have been conducted on the health beneficial effects of GA including its cardioprotective and anti-diabetic activities. Table 3 and 4 summarizes the cardioprotective effects of GA done in *in-vivo* or *in-vitro* test models. Elevation of lipid peroxidation in experimental myocardial infarction is an established phenomenon caused by oxidative modification of lipids by ROS as a results of cell damage and alterations in the

function of membrane proteins including ion channels, enzymes and receptors as well as produced pro-antherogenic and pro-inflammatory mediated toxic products.[69, 70] Clinically, CK, CK-MB, LDH, AST and ALT are found in the cardiac tissues that played different functions and act as a biomarker for damage of cardiac tissues by ROS and LPO such as in myocardial infarction whereas CRP and MDA are the products of inflammation and lipid peroxidation which act as a marker of oxidative stress.[71-73] SOD, GPx, CAT are the first line defence antioxidants that play an indispensable role in the protective effect of cells against ROS and lipid peroxidation.[74] Literature study revealed that GA showed cardioprotective effect through improving antioxidant defence mechanisms *via* upregulation of enzymatic (CAT, SOD, GPx, glutathione reductase (GR) and glutathione-S-transferase (GST)) and non-enzymatic (GSH, Vit. C and E) antioxidants, reduction of LPO i.e. attenuates levels of TG, TC, LDL, very low density lipoprotein (VLDL) and MDA as well as downregulation of the activity of cardiac biomarkers (CK, CK-MB, AST, alanine transaminase (ALT), LDH, CRP and TnI) either in isoproterenol (ISO), STZ, doxorubicin (DOX), alumina (Al_2O_3), AGEs, cobalt chloride ($CoCl_2$), diazinon, sodium fluoride (NaF), isoprenaline or cyclophosphamide (CYP)-induced cardiotoxicity in rat model.[75-85] DM increases the incident of CVDs development and interestingly GA showed cardioprotective effect through inhibition of LPO and boosting antioxidant defence mechanisms in STZ or alloxan-induced diabetic rat model.[76, 86] GA showed cardioprotective effect when given orally in different doses (15-120 mg/kg/daily b.w for 1-4 weeks) to experimentally induced myocardial infarcted rats.[75-85] Badavi, M., *et al*. (2014) and Ramezani-Aliakbari, *et al.* (2017) also found the attenuation of antioxidant defence mechanisms by different doses of GA in ischemic reperfusion in isolated rat heart tissue.[86, 87]

Lysosomal enzymes such as β-glucuronidase, β-*N*-acetylglucosaminidase, β-galactosidase, also play important roles in the normal turnover of tissue proteins and other macromolecules. These enzymes are also responsible for alterations in the rate of degradation of many tissue components such as abnormal release and activation of lysosomal enzymes during ischemia.[88] Along with improving antioxidant defence mechanisms and reduction of LPO, GA has been reported to improve myocardial infraction via downregulation of liposomal enzymes in ISO-treated myocardial infarcted rats.[89] It is reported that the gap junction protein Connexin 43 (Cx43) can express in connective tissues, inflammatory cells and vascular elements that help to reduces ventricular tachycardia (VT) incidence following myocardial infraction.[90] Na^+/K^+ ATPase (Sodium-potassium adenosine triphosphatase) is another enzyme found in all cell membrane that helps to maintain resting potential, transport, cell volume as well as signal transduction to regulate mitogen-activated protein kinases (MAPKs) and ROS pathway.[91] In myocardial tissues, there is a correlation between decrease in heart function and decreased concentration of Na^+/K^+ ATPase.[92] El-Hussainy *et al*., (2016) and Padma *et al*., (2012) showed that GA has the ability to protect myocardial injury via upregulation of Cx43 and Na^+/K^+ ATPase in alumina or lindane induced myocardial injury in rats.[78, 93] Furthermore, cellular MAPKs signaling pathway is responsible to control a vast array of physiological processes. MAP kinase family such as c-Jun N-terminal kinases (JNKs), extracellular signal–regulated kinases (ERKs), p38 play key role to regulated MAPKs pathway by activating one another and help to control cell division (by ERKs) or transcription (by JNKs).[94] Inflammatory cytokines, growth factors, oxidative stress by ROS, protein synthesis inhibitors, and other stress stimuli can activate MAPKs family.[95] Activation of MAPKs system through oxidative stress (excess ROS) has key role for the formation of AGEs that takes part in pathogenesis of myocardial toxicity and

accelerate atherosclerosis in DM.[96-98] AGEs also induce myocardial fibrosis through activation of extracellular matrix protein (ECR) such as collagen.[99] Smads (or SMADs) are another protein family that are the main signal transducers for receptors of transforming growth factor beta (TGF-β) and downregulation of TGF-β/Smads can induce accumulation of extracellular matrix (ECM) proteins such as collagen and promote cellular fibrosis.[100] Interestingly, literature study demonstrated that GA can prevent ISO-induced cardiac hypertrophy and fibrosis by improved oxidative stress and inhibition of collagen deposition via down regulation of JNK2, ERK signaling pathway and Smad3 binding activity in GA treated mice.[101] Later, Jin et al., (2017) confirmed that GA can attenuate cardiac remodeling and fibrosis in *N*-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive mice through downregulation of ECM such as collagen type I, collagen type III, and connective tissue growth factor (CTGF).[102] However, Akinrinde, *et al.*, (2016) reproted that the protective effects of GA against $CoCl_2$ -induced cardiorenal dysfunction via suppression of oxidative stress and activation of the ERK signaling pathway.[80] Recent study by Jin, *et al*. (2017) reported that GA attenuates hypertension and cardiac hypertrophy in both *in-vitro* and *in vivo* test models.[102, 103] *In vitro* cardioprotective studies of GA were mainly conducted (10-100 µM) in cultured rat neonatal cardiomyocytes H9c2(2-1) cells treated by different agents such as AGE, L-NAME, ISO and renin-angiotensin II (Table 4). *In vitro* data also demonstrated that GA has the ability to reduce cardiotoxicity through inhibition of cell proliferation, elevation of cellular antioxidant mechanisms, inhibition of LPO and downregulation of JNK, Samds and GATA4-induced NADPH oxidase (Nox) signaling pathway following reduction of AGE-induced cytokines (tumor necrosis factor-alpha (TNF-α), TGF-β, inducible nitric oxide synthase (iNOS)) and matrix proteins, receptor for AGE (RAGE), tissue inhibitor metalloproteinase (TIMPs), matrix metalloproteinase (MMP)) of cultured

cells.[101-105] The *in vitro* results also support the *in vivo* cardioprotective data as mentioned in proposed mechanism of action of GA in fig. 3.

Conclusion

GA is a very common dietary plant constituent possessing strong antioxidant proprieties and used in several herbal formulations to treat different diseases. In this review, we have summarized the anti-diabetic and cardioprotective reports of GA published to-date. Studies done in *in vivo* and *in vitro* test models clearly demonstrated anti-diabetic and cardioprotective potential of GA. Such activities of GA were exerted through improving cellular antioxidant defence mechanisms, inhibiting lipid peroxidation as well as regulation of different key proteins related to DM and CVDs. A number of interesting studies were also found where GA showed significant protection against diabetes and diabetes induced myocardial damage. To conclude, the antioxidants based interventions as well as upregulation of key proteins was the major pathway for anti-diabetic activity of GA. Therefore, it is evident that GA can be considered as promising dietary lead molecule for the prevention of diabetes. The anti-diabetic studies on GA conducted over the last few years were mainly *in vivo* or *in vitro* models and data-related preclinical or clinical trials for such activities still remains absent. Thus, more clinical and pharmacokinetic investigation on GA is important to conclude on the anti-diabetic and cardioprotective potential of GA.

Author Contribution

The paper was designed by SJU and written by SJU, MF and SMNKZ. MSR, SA, INK and SMSAR did the molecular mechanism discussion. RR, MTI, JAS, LN, ET and SDS provided valuable guidance, revision, correction and other insight into the work.

Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Table 1: Chemical name, molecular formula, chemical group and reported pharmacological activity of GA

IUPAC Name	Molecular formula	Chemical Group	Reported Pharmacological activity	References
3,4,5-trihydroxybenzoic acid	$C_6H_2(OH)_3COOH$	Polyphenol	Antioxidant Anti-inflammatory Anti-diabetic Anti-mutagenic Cardioprotective Hepatoprotective Nephroprotective Anti-cancer Gastroprotective	[12, 30, 34, 75, 89, 106-113]

Table 2: *In vivo* anti-diabetic activity of GA with its test model, dose used, route of administration and possible mechanism of action.

Test model	Dose/b.w	Route of administration	Mechanism of action	Reference
STZ-induced diabetic rat	20 mg/kg for 28 days	Orally	Reduction of serum TC, TG, LDL-C, urea, UA, creatinine and increased plasma insulin, C-peptide and glucose tolerance level.	[30]
STZ-induced diabetic rat	10 and 20 for 21 days	Orally	Reduction of blood glucose and increased plasma insulin.	[31]
Alloxan-induced diabetic female rabbit	100 mg/kg for 21 days	Intravenously	Reduction of blood glucose and serum MDA levels.	[34]
STZ-induced oxidative stress in diabetic rat	25 mg/kg for 35 days	Orally	Significant increase ofpancreatic vitamin C and glutathione level and improvedROS scavenging, Fe2+ chelation and Fe^{3+} reduction property of the pancreas	[32]
Alloxan-induced oxidative stress in diabetic rat	5, 10, and 20 mg/kg for 45 days	Orally	Reduction of blood glucose, increase insulin level, and upregulation of antioxidant enzymes (CAT, SOD, and GPx)	[33]
High fat diet-induced obesity mice	10 mg/kg for 14 days	Intraperitoneally	Reduction of blood glucose, TG, adipocyte size and upregulation of PPARγ expression and activation of Akt signaling pathway	[54]
High-fat diet fed-STZ-induced insulin resistance rat	20 mg/kg for 30 days	Orally	Enhancing glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway	[53]
STZ-induced diabetic rat	20 mg/kg for 42 days	Orally	Reduction of TNF-α level and enhance upregulation of PPARγ mRNA and adiponectin	[55]
High fat diet-induced obesity mice	10 mg/kg for 28 days	Intraperitoneally	Activation of AMPK and regulates mitochondrial function via the activation of PGC1α	[56]

Table 3: *In vivo* cardioprotective activity of GA with its test model, dose used, route of administration and possible mechanism of action

Test model	Dose/b.w	Route of administration	Mechanism of action	Reference
ISO-induced myocardial infarction in male Wistar rats	15 mg/kg for 10 days	Orally	Reduction of LPO and myocardial infraction biomarker (↓CK, CK-MB, AST, alanine transaminase (ALT), LDH and troponin-T) as well as upregulation of enzymatic (↑SOD, CAT, GPx, GR and GST) and non-enzymic antioxidants (↑GSH, vitamin C and E) in plasma and heart	[75]
STZ-induced diabetic rat	100, 50, and 25 mg/kg for 8 weeks	Orally	Reduction of serum glucose and LPO (↓TG, TC, LDL-C, VLDL-C) as well as increased dose dependently antioxidant parameters in heart	[76]
DOX- induced cardiotoxicity in rat	15 mg and 30 mg/kg	Orally	Reduction of LPO (↓CK-MB, MDA, TG, TC, LDL in serum) as well as increased non-enzymic antioxidant (GSH) and antioxidant enzymes (↑CAT and SOD) in the heart	[77]
Alumina -induced myocardial injury in rat	100 mg/kg for 14 days	Orally	Reduction of LPO (↓CPK, CK-MB, TG, TC, LDL and LDH in serum)and increased antioxidant enzymes (↑GR, CAT and SOD) as well as upregulation of gap junction protein connexin 43 (Cx43) in heart	[78]
ISO- treated myocardial infarcted rats	15 mg/kg for 10 days	Orally	Reduction of LPO (↓CK-MB, LDH, thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH)) and reduction of activity of lysosomal enzymes (↓β-glucuronidase, β-N-acetylglucosaminidase, β-galactosidase, cathepsin-B and D) as well as increased non-enzymic antioxidant (GSH) in the serum and heart of myocardial infracted rat	[89]
Lindane- induced cardiotoxicity in rat	15 mg/kg for 30	Orally	Reduction of serum cardiac marker enzymes, LPO, and membrane-bound Ca^{2+} ATPase, with a concomitant increased of non-enzymic antioxidant	[93]

	days		(GSH) and enzymic antioxidants (↑SOD, CAT, GPx, and GST) as well as membrane-bound Na^+/K^+ ATPase in heart tissue	
Ischemia reperfusion in isolated rat heart tissue	7.5,15,30 mg/kg for 10 days	Orally	Reduction of LPO (↓ MDA, LDH)and increased antioxidant enzymes (↑CAT, SOD, GPx) in heart tissue.	[87]
Ischemia reperfusion in isolated rat hearts with alloxan-induced DM	25mg/kg for 8 weeks	Orally	Reduction of LPO (↓ CK-MB, troponin I, LDH)and increased antioxidant enzymes (↑ CAT, SOD, GPx) in diabetic heart tissue. It also improved both left ventricular dysfunction and hypertrophy through antioxidant mechanism	[86]
AGEs- induced oxidative stress rat	25 mg/kg for 30 days	Orally	Reduction of LPO (↓CK, LDH) and protein carbonyls (PCO)in plasmaand increased non-enzymic antioxidant (GSH) and enzymatic antioxidants (↑ SOD, CAT) in heart tissue	[79]
ISO-induced cardiac hypertrophy in mice	100 mg/kg for 3 weeks	Intraperitoneally	Downregulation of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and beta-myosin heavy chain (MHC-β) as well as prevention of interstitial collagen deposition and expression of fibrosis-associated genes in cardiac tissues. Overall, prevention of cardiac hypertrophy and fibrosis through regulating the JNK2 and Smad3 signaling pathway	[101]
$CoCl_2$-induced cardiorenal damage in rats	120 mg/kg for 14 days	Orally	Reduction of oxidative stress (↓ serum CK-MB, LDH, AST, xanthine oxidase (XO), urea, MDA, creatinine, H_2O_2, NO, and ↑ SOD, CAT, GST) and activation of ERK	[80]
Diazinon-induced cardiovascular dysfunction in rat	60 mg/kg and 120 mg/kg for 21 days	Orally	Reverses the oxidative stress markers (↓ MDA, H_2O_2, NO, and ↑ GSH, SOD, CAT, GST) and increased antioxidant defense system as well as and reduces deleterious effects on hematological parameters	[85]
NaF-induced oxidative stress in rat's heart	10 and 20 mg/kg for 7 days	Intraperitoneally	Reduction of LPO (↓TBARS, MDA) and increased non-enzymic antioxidant (GSH) and enzymatic antioxidants (↑ SOD,	[81]

			CAT) activity in heart tissue	
Isoprenaline-induced myocardium infraction in rats	15 mg/kg for 10 days	Orally	Reduction of cardiac marker enzymes activity (AST, ALT, CK and LDH), LPO (MDA) and elevated antioxidant parameters (↓SOD, GSH)	[83]
CYP-induced cardiorenal dysfunction in rat	60 and 120 mg/kg for 7 days	Intraperitoneally	Reduction of LPO (↓MDA, H_2O_2) and restores the enzymic (↑SOD, GPx, CAT, GST) and non-enzymic (↑GSH) antioxidants and also attenuates cardiotoxicity through free radical scavenging activity	[82]
DOX- induced cardiac dysfunction in rat	60 and 120 mg/kg for 7 days	Orally	Improving antioxidant defense system (↑CAT, GST, GPx and GSH) and reduction of cardiac tissue LPO (↓MDA, LDH, CK-MB)	[84]
L-NAME-induced hypertensive mice	50 and 100 mg/kg during 3-6 weeks	Intraperitoneally	Reduces left ventricular (LV) posterior wall thickness and interventricular septum thickness. Anti-fibrosis effect through downregulation of ECM proteins (collagen type I, collagen type III, and CTGF)	[102]
Spontaneously hypertensive rats (SHRs) rat	320 mg/rat for 16 weeks	Orally	Reduced BP through components of the renin-angiotensin II system as well as reduction of cardiac hypertrophy via down regulation of cardiac-specific GATA4-induced Nox2	[103]

Table 4: *In vitro* cardioprotective activity of GA with test model, concentration used, proposed mechanism of action

Reported activity	Test model	Concentration	Mechanism	Reference
Anti-diabetic	Cultured 3T3-L1 cells	10 μM	Stimulation of glucose uptake through translocation and activation of GLUT4 in Akt signaling pathway	[57]
	Cultured rat pancreas homogenates	20 μM	Reduction of MDA contents, improved ROS scavenging, Fe^{2+} chelation and Fe^{3+} reduction property of the cultured cells and inhibition of α-amylase and α-glucosidase	[35]
	Culturd RINm5F β-cell	0.3–10 μM	Significant increase insulin secretion and upregulation of mRNA of PDX-1 in cultured cells	[58]
	In vitro insulin fibril formation	0-17 mM	Prevention of insulin amyloid fibril formation.	[59]
Cardioprotective	AGE-induced oxidative stressed in cultured (H9c2(2-1)) cells	10 μM	Elevation of antioxidant defense mechanism (SOD, CAT, GSH) and scavenging ROS as well as reduction of LPO	[104]
	AGE-treated in cultured H9c2(2-1) cell	10 μM	Attenuates upregulation of AGE-induced cytokines (TNF-α, TGF-β, iNOS and matrix proteins, RAGE, TIMPs, MMP)	[105]
	L-NAME treatedcultured H9c2(2-1) cells	100 μM	Attenuation of cardiac fibrosis and reduced the expression of histone deacetylase 1 and 2	[102]
	ISO treated cultured H9c2(2-1) cells	100 μM	Downregulation of ANP, BNP, and MHC-β as well as downregulation of JNK2 and Smad3 signaling pathway	[101]
	Renin-angiotensin II treated cultured H9c2(2-1) cell	100 μM	Downregulation of GATA4-induced Nox activity in angiotensin II-treated H9c2(2-1) cells	[103]

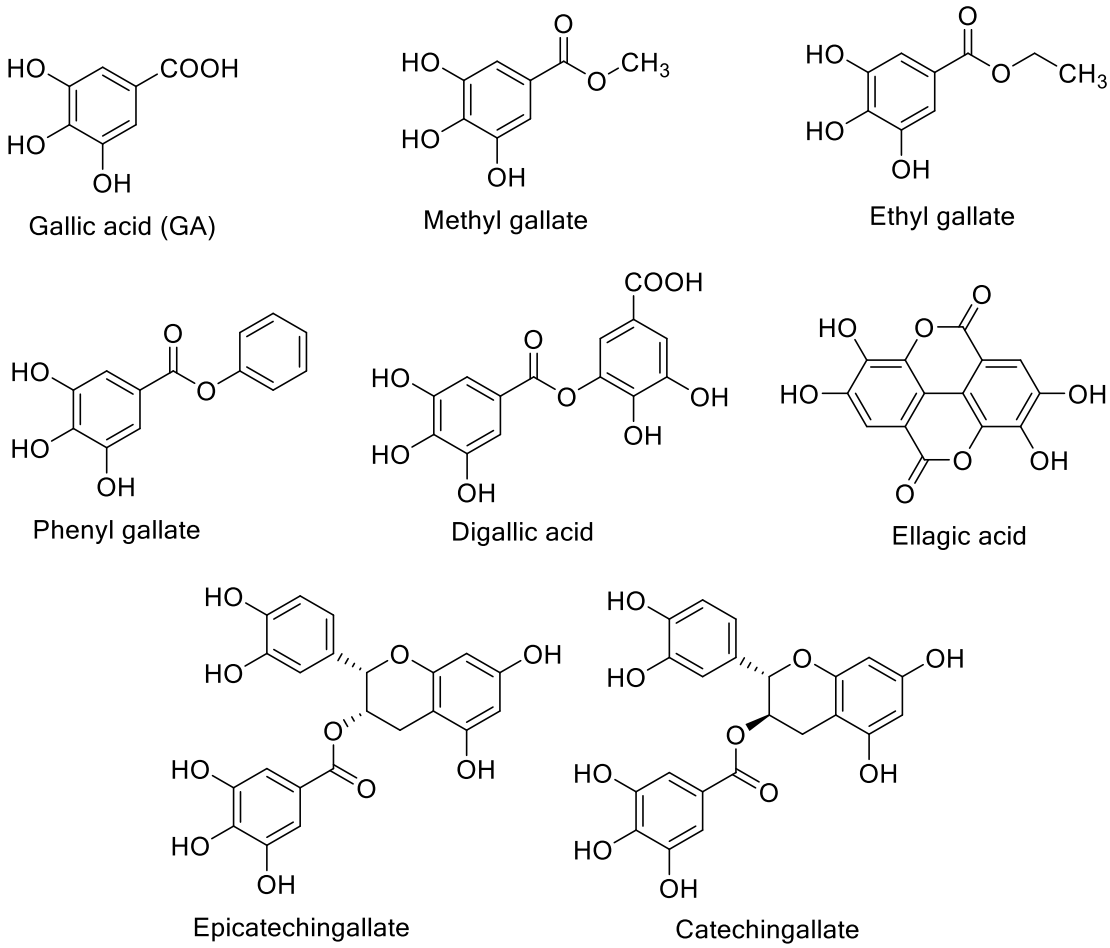

Figure 1. Structure of Gallic acid and its derivatives

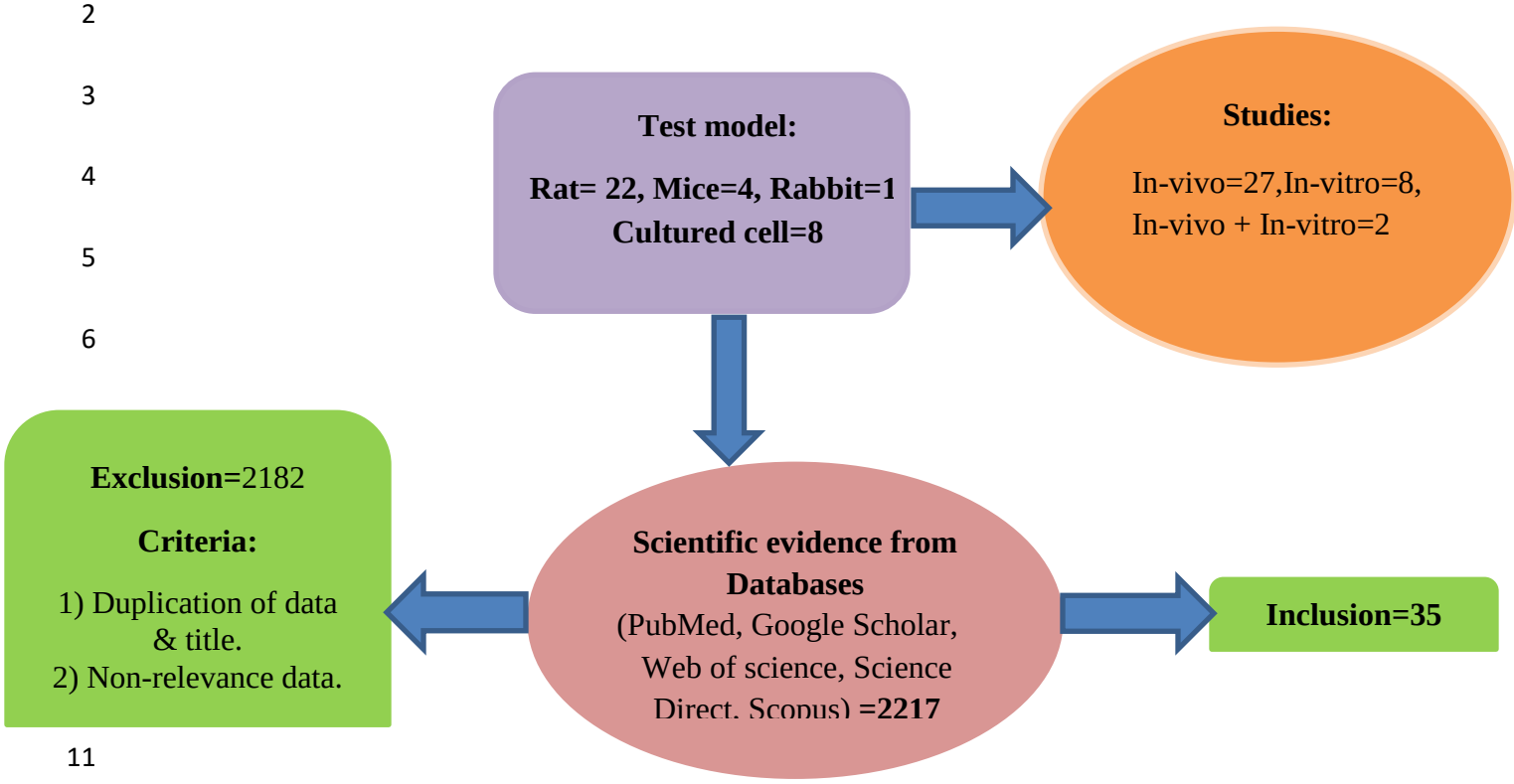

Figure 2. Workflow of database searches with literature inclusion and exclusion criteria.

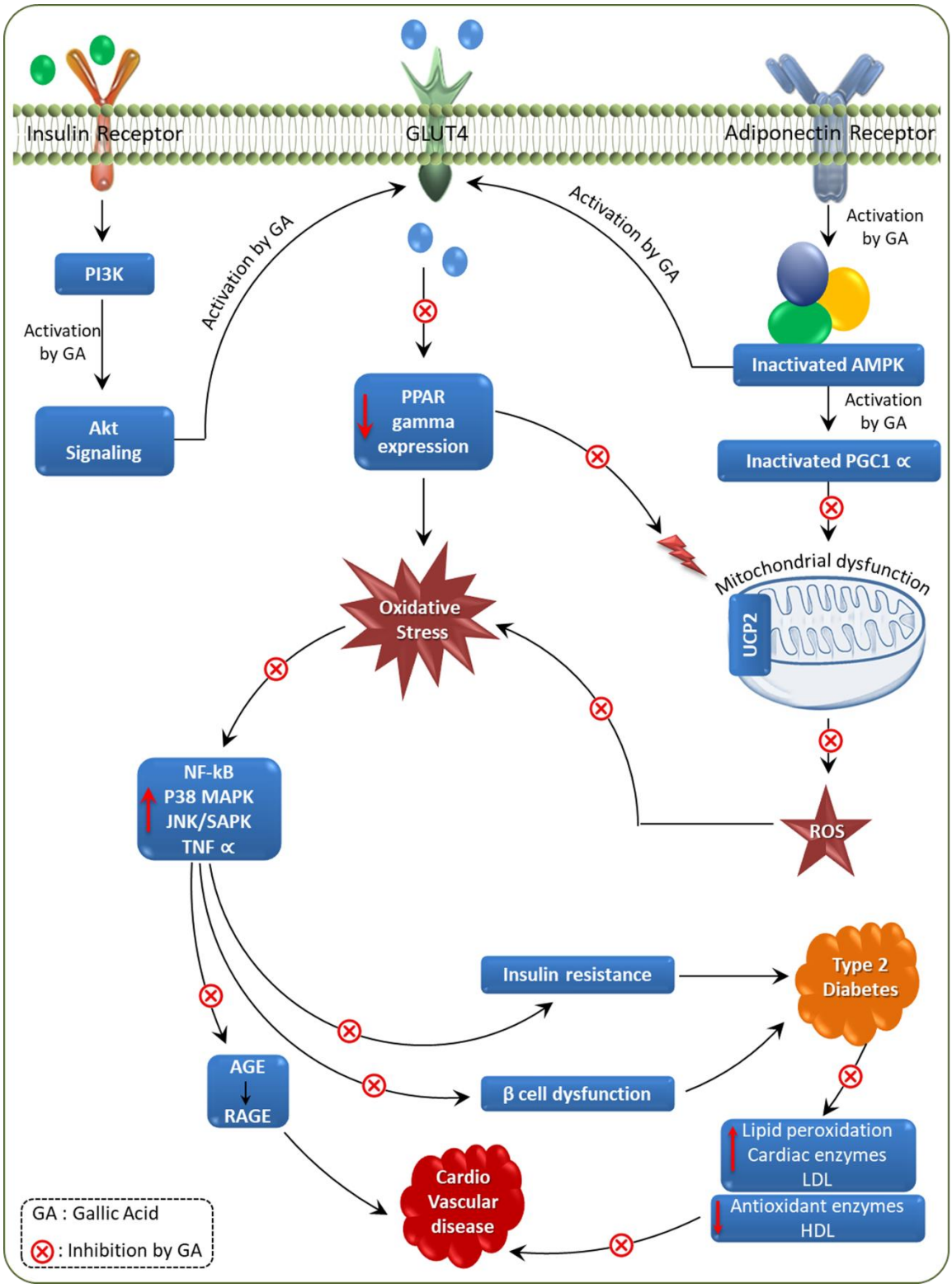

Figure 3. Proposed anti-diabetic and cardioprotective mechanism of action of GA