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Review article

Mechanistic insights and therapeutic potential of astilbin and apigenin in diabetic cardiomyopathy

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ABSTRACT

Diabetic cardiomyopathy (DCM) represents a critical complication of Diabetes mellitus (DM), characterized by structural and functional changes in the myocardium independent of coronary artery disease or hypertension. Emerging evidence highlights the significant roles of phytochemicals, particularly astilbin and apigenin, in modulating key molecular pathways implicated in DCM. This review synthesizes current mechanistic insights and therapeutic potential of these compounds, focusing on their interactions with AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), O-linked N-acetylglucosamine (O-GlcNAc), sodium-glucose co-transporter 2 (SGLT2), protein kinase C (PKC), nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK) pathways. Astilbin and apigenin have demonstrated the ability to improve cardiac function, mitigate oxidative stress, and reduce inflammatory responses in diabetic conditions. By activating AMPK and PPARs, these flavonoids enhance glucose uptake and fatty acid oxidation, contributing to improved metabolic homeostasis. Their inhibition of O-GlcNAcylation, SGLT2 activity, and PKC signaling further attenuates hyperglycemia-induced cellular damage. Additionally, suppression of NF-κB, MAPK, and

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JNK pathways by astilbin and apigenin results in reduced pro-inflammatory cytokine production and apoptotic cell death. Collectively, these interactions position astilbin and apigenin as promising therapeutic agents for ameliorating DCM, offering novel avenues for treatment strategies aimed at modulating multiple pathogenic pathways.

1. Introduction

Diabetes mellitus (DM) poses a serious threat to the health of people everywhere and is thus one of the most pressing issues in public health today [1]. With an estimated 700 million affected by 2040, the number of impacted individuals is expected to increase from 285 million in 2010. DMis characterised by ventricular dysfunction in patients without coronary atherosclerosis and hypertension; this was defined in 2013 by the American College of Cardiology Foundation [2], the American Heart Association, the European Society of Cardiology [3], and the European Association for the Study of Diabetes in collaboration with the European Association for the Study of Diabetes [4]. There is a hidden subclinical phase in the development of diabetic cardiomyopathy, characterised by functional and structural problems. Among these irregularities are fibrosis, aberrant cell signalling, and left ventricular (LV) hypertrophy [5]. Cardiac fibrosis, stiffness, and subclinical diastolic dysfunction are pathophysiological changes that often lead to normal ejection fraction heart failure and, later, systolic dysfunction (heart failure with reduced ejection fraction). Experimental clinical investigations have demonstrated that the prevalence of heart failure in diabetes patients ranges from 19 % to 26 % [6].

The Framingham Heart Study indicated that compared to individuals of the same age, diabetes patients had a greater incidence of heart failure. This was true for both males and females. In addition, variables like obesity, hypertension, dyslipidemia, and coronary heart disease were not determined to be independent of this connection. According to one study, after 43 months of monitoring, the relative risk of developing heart failure was 1.3 times higher in diabetic patients compared to nondiabetic patients. The incidence of heart failure was 39 percent in diabetic patients and 23 percent in nondiabetic patients. People who had experienced diabetes exhibited this characteristic. The Cardiovascular Health Study, the Strong Heart Stud, and the Multi-Ethnic Study of Atherosclerosis were population-based observational studies that found that normal individuals and diabetic patients had different left ventricular (LV) masses and wall thicknesses, and that diabetic patients had increased diastolic and systolic dysfunctions. On the other hand, those with type 1 DM had a 30 % increased risk of heart failure for every 1 % rise in glycated haemoglobin A1c [7]. However, those with type 2 DM had an 8 % increased risk for every 1 % increase in haemoglobin A1c levels.

DCM therapy options nowadays often include medication management, dietary adjustments, and increased physical exercise as part of a larger strategy for controlling diabetes. However, recent studies suggest that plant-based active components could prove useful in the fight against diabetic cardiomyopathy. Plant chemicals, including polyphenols and secondary metabolites like flavonoids, found in foods like fruits, vegetables, and teas, have antioxidant and anti-inflammatory effects. In addition to their many other useful functions, these chemicals have immunomodulatory, anticancer, antiviral, antibacterial, and anti-inflammatory effects on human health. This class of chemicals includes the flavonoid asstilbin. Astaxanthin, a dihydroflavonolrhamnoside, is present in numerous plants, including *Hypericum perforatum*, *Drimys brasiliensis, Vitis vinifera* (grapevine), *Desmos chinensis*, and *Engelhardiaroxburghiana*. It has garnered interest due to the antioxidant and anti-inflammatory qualities that it possesses [8].

As a result of the crucial roles that oxidative stress and inflammation play in the genesis and progression of diabetic cardiomyopathy, astilbin is an appealing possibility for intervention. Based on the findings of research, it has been suggested that the antioxidant properties of astilbin could potentially help reduce the harmful effects of free radicals on cardiac tissues. Furthermore, the anti-inflammatory qualities of astilbin provide a further avenue for the treatment of diabetic cardiomyopathy. In addition, Apigenin is also an another flavonoid that is found in abundance in some fruits and vegetables, such as parsley, celery, and chamomile tea. According to the findings of several studies, the antioxidant activities of apigenin have a role in the maintenance of cellular integrity in the myocardium [9,10]. Apigenin has the potential to reduce oxidative damage to heart cells by scavenging free radicals and altering redox signalling pathways. This would provide a preventive mechanism against diabetes-induced cardiomyopathy. A fresh approach to tackling the oxidative stress, inflammation, and lipid dysregulation that are characteristic of diabetes-related cardiac problems is provided by these compounds that are produced from plants. It is necessary to conduct exhaustive research in order to translate these discoveries into clinical practice, despite the fact that preclinical evidence is encouraging. It is possible that establishing the efficacy, safety, and optimal utilisation of apigenin and astilbin in the context of DCM will have the potential to expand the arsenal of therapeutic options available to people who have diabetes, thereby reducing the burden of cardiovascular complications and improving overall outcomes [11,12]. This review will critically evaluate the therapeutic application of plant-derived bioactive compounds including astilbin and apigenin in managing diabetic cardiomyopathy. Current traditional treatment strategies for DCM are centered on metabolic control, physical activity, and pharmaceutical treatment. However, oxidative stress and inflammation, unveiled in recent studies, play significant roles in the pathogenesis of this condition. Targeting pathophysiological mechanisms, thus, bioactive compounds such as astilbin and apigenin open a novel therapeutic approach. This review of the most recent evidence emerging from preclinical and clinical studies is set to expound on antioxidant, anti-inflammatory, and cardioprotective effects. The novelty of this review lies in the translation of these findings into a clinically relevant framework that brings a fresh perspective to natural compounds as adjunct therapies in diabetic cardiomyopathy. It will open new avenues for the comprehensive management of cardiac complications due to diabetes.

Search methodology:

A number of studies about the role of plant-based bioactive compounds, such as astilbin and apigenin, in the therapy of diabetic

cardiomyopathy (DCM) was identified through a review of the literature. The applied databases included PubMed, Scopus, Web of Science, and Google Scholar. Specific search terms used were combinations of the following keywords: “diabetic cardiomyopathy,” “DCM,” “astilbin,” “apigenin,” “flavonoids,” “plant-based compounds,” “oxidative stress,” “inflammation,” and “cardioprotection.” Those selected more specifically included preclinical, clinical, and mechanistic studies. There was further restriction to those written in the English language and those whose results or interpretation were clearly relevant to oxidative stress, inflammation, and cardiac remodelling in relationship to diabetes. The study lists other articles on the pharmacokinetics and bioavailability and the safety profiles of astilbin and apigenin. Relevant article references were hand-screened to look for additional sources. Studies that have provided inadequate or ambiguous data, have no relevance to the scope of the review, or are not published in peer-reviewed journals were ruled out. That is to say, quality and relevant literature will be ensured by this methodological approach toward the complete understanding of the potential roles of astilbin and apigenin in diabetic cardiomyopathy therapy.

2. Pathophysiology of diabetic cardiomyopathy

2.1. Role of ROS in diabetic cardiomyopathy

Among the many mechanisms at work here are alterations to the metabolic profile and energy generation, elevated levels of oxidative stress and inflammation, and dysfunction of the mitochondria. The presence of anomalies in the structure and turnover of extracellular matrix proteins, in conjunction with a rise in collagen deposition, leads to an increase in fibrosis symptoms. A condition known as aberrant extracellular matrix protein deposition can be brought on by an increase in the production of profibrotic factors in the diabetic heart [13]. The adult heart prefers to use free fatty acids (FFAs) as its energy substrate; but, it is possible for it to use other substrates as well, including glucose, lactate, ketone bodies, and some amino acids. The complete inability to do so is a symptom of both hyperglycemia and insulin resistance. Reduced recruitment of glucose transporter type 4 to the sarcolemma reduces the ability to use glucose as an energy source [14]. The internalization of this substrate in the cardiomyocytes is facilitated by an increase in the amount of free fatty acids (FFAs) released from adipose tissue and the movement of the FFA transporter to the sarcolemma. Loss of metabolic flexibility and increase in fatty acid oxidation lead to a decrease in efficiency between substrate utilisation and ATP generation in the heart of diabetics. With the shift in energy source comes an increase in reactive oxygen species (ROS) generation by mitochondria and a reduction in oxidative phosphorylation [15]. A decrease in cardiac energy efficiency occurs when an increase in mitochondrial uncoupling leads to an increase in mitochondrial oxygen consumption without a matching increase in ATP production. In myocardial ischemia and other hypoxic situations, the heart is more likely to sustain damage and malfunction due to its impaired capacity to switch to glucose oxidation. Because oxygen is essential for the process of glucose oxidation, this is the case. Since

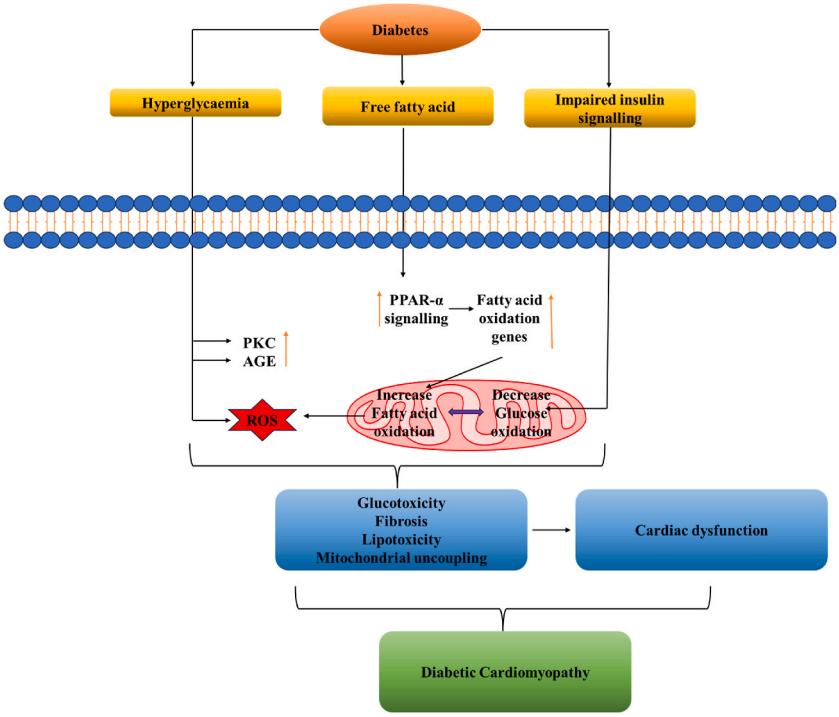

Fig. 1. The following figure depicts the molecular pathways involved in diabetic cardiomyopathy (DCM) under the conditions of diabetes. Diabetes is marked by increased levels of hyperglycemia, high free fatty acids and impaired insulin signaling. These metabolic alterations precipitate an imbalance between fatty acid and glucose oxidation within the mitochondria that enhances fatty acid oxidation as well as reduces glucose oxidation.

cardiomyocytes aren't equipped to store lipids appropriately, an excess buildup of free fatty acids (FFAs) is detrimental to them. Here we find evidence supporting the idea of lipotoxicity as a potential pathophysiology of diabetic cardiomyopathy [16]. Myocyte physiological autophagy decreases and apoptosis increases as a result of this process. Programmed cell death can also be triggered by oxidative damage and inflammation. This can also occur as a result of lipotoxicity. Biopsies taken from diabetic patients compared to non-insulin resistant individuals showed a larger number of apoptotic cardiomyocytes. Metabolic and oxidative stress make the mitochondrial permeability transition pore more sensitive to Ca^{2+} in the heart tissue of diabetic individuals [17,18]. As a result, cardiac necrosis and autophagy occur in cardiomyocytes. A maladaptive proinflammatory response is another risk factor for the progression of diabetic cardiomyopathy (Fig. 1).

2.2. Impaired AMPK activation in diabetic cardiomyopathy

The master regulator AMPK controls the homeostasis of cellular energy. When cells are under stress and the AMP/ATP ratio is high, the enzyme AMPK is activated, which causes GLUT4 to be more highly expressed and translocated, and ultimately, insulin increases glucose uptake. Glycolysis and FFA oxidation are the end outcomes of increased mitochondrial biogenesis, which in turn is caused by AMPK activation. For cardiomyocytes, activated AMPK can enhance glucose uptake, free fatty acid oxidation, and glycolysis while negatively impacting mTOR signalling, gluconeogenesis, and protein and lipid synthesis [19]. That is why it is beneficial to activate AMPK in order to slow the progression of diabetic cardiomyopathy. This has led many to believe that AMPK would be a good target for drugs that could prevent or reverse diabetic cardiomyopathy (Fig. 2) [20].

2.3. Role of altered PPARs in diabetic cardiomyopathy

The expression of α, β/δ, and γ isoforms of PPAR can be observed in the heart. When it comes to keeping energy levels stable and regulating glucose and lipid metabolism in the heart, these isoforms are major players. Additionally, it is vital to note that they have activities unrelated to metabolism, such as in inflammation and oxidative stress [21]. The rate of FFA absorption and mitochondrial FFA oxidation are directly impacted by the activation of PPAR-α, which is expressed in high amounts in the heart. In addition to regulating lipoprotein assembly and transport, PPAR-α affects both oxidant and antioxidant defences. The overexpression of PPARα receptors unique to cardiomyocytes could be the cause of a decline in Ca^{2+} absorption by the sarcoplasmic reticulum, left ventricular hypertrophy, systolic dysfunction, and an upregulation of atrial and B-type natriuretic peptide expression [22]. On the other hand, blocking the expression of fasting-induced FFA metabolic genes by deleting cardiac PPAR-α causes a shift from FFA utilisation to glucose utilisation. The expression of PPAR-α, which is linked to the development of diabetic cardiomyopathy, can be diminished by prolonged exposure to elevated FFAs [23]. It was shown using mouse cardiomyocytes that this resulted in an even more significant decrease in cardiac function by blocking FFA oxidation and causing fat to accumulate inside the cell. Human research suggests that the expression of PPAR-α in the hearts of people with type 2 DM is not significantly changed. Hence, the increased FFA oxidation and utilisation in the diabetic heart that is generated by activated PPAR-α may initially serve as a compensatory mechanism to adapt substrate oxidation to the excess of accessible substrates [24]. Moreover, as the disease advances, a diminution in PPAR-α can set off maladaptive consequences associated with the heart's metabolic processes, like glucotoxicity and functional cardiac abnormalities. Further research is needed to assess the involvement of PPAR-α in the onset of cardiac dysfunction in diabetic cardiomyopathy, as its

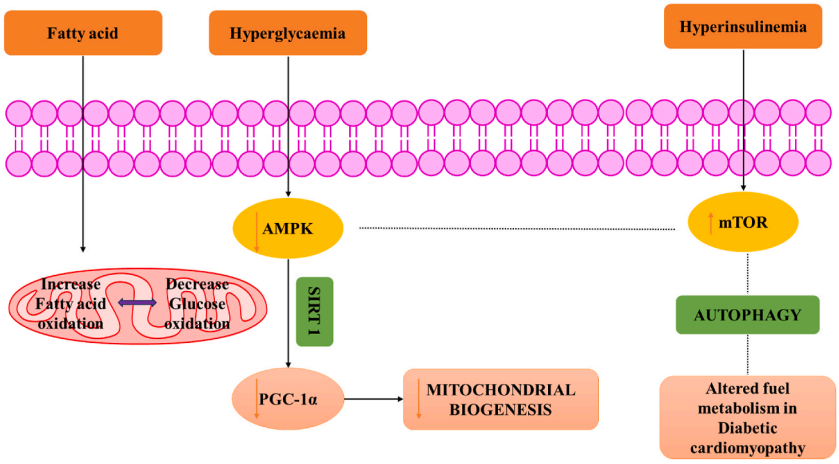

Fig. 2. This figure depicts the signalling pathways that describe the defective metabolism in diabetic cardiomyopathy. Diabetes increases the levels of fatty acids, hyperglycemia, and hyperinsulinemia due to which the balance of the oxidation of fatty acids versus oxidation of glucose within the mitochondria gets disturbed. Pathways involving AMPK and SIRT1 that regulate mitochondrial biogenesis and energy homeostasis are shown on the left. Impaired function of AMPK reduces PGC-1α recruitment, contributing to decreased mitochondrial biogenesis and impaired energy production in the diabetic cardiomyopathy.

significance has not been adequately assessed. It has been discovered that PPAR-β/δ isoforms are highly expressed in heart tissue, just as PPAR-α [25]. The transcriptional gene expression and volatile fatty acid metabolism are both affected by these isoforms. On the other hand, increased PPAR-β/δ signalling promotes the utilisation of FFA, whereas PPAR-β/δ deletion decreases FFA oxidative gene expression and FFA oxidation. PPAR-γ contributes to the heart's anti-inflammatory and anti-hypertrophic functions, which are both important roles to play [26]. Cardiomyocytes' insulin sensitivity is enhanced and their glucose absorption is enhanced by PPAR-γ agonists. In light of this, PPAR-γ might be useful for maintaining glucose and FFA metabolism and heart health. Conversely, DCM may be facilitated by factors such as an absence of PPAR-γ signalling (Fig. 3) [27].

2.4. Increased O-GlcNAc in promoting cardiac fibrosis in diabetic cardiomyopathy

An increase in O-GlcNAcylation, which modifies cardiac proteins post-translationally, is associated with hyperglycemia. The diabetic heart contains O-GlcNAc signalling, which might cause harmful effects. Among these side effects are an uptick in cardiac dysfunction and heart failure and a decrease in mitochondrial activity and energy production [28,29]. In normal conditions, the O-GlcNAc molecule is produced by a step in the fructose-6-phosphate metabolism that originates from glycolysis, and this step is driven by the hexosamine biosynthesis pathway. In many cases, cytoprotection and cell survival are enhanced by transient activation of the O-GlcNAc signalling pathway. The impairment of insulin metabolic signalling, cardiomyocyte apoptosis, myocardial excitation-contraction coupling, and cardiac relaxation caused by DM is mediated by sustained elevation of O-GlcNAc signalling in the diabetic heart, as opposed to transient upregulation [30]. The overexpression of O-GlcNAcase leads to the removal of O-GlcNAc and the restoration of normal Ca^{2+} handling and cardiac function in cardiomyocytes. This study raises the intriguing possibility that preventing and treating DCM could be as simple as focusing on hexosamine production and O-GlcNAc (Fig. 4) [31,32].

2.5. SGLT2 abnormalities and potential cardiac benefits

When present, SGLT1 (highly expressed in enterocytes' brush border membranes) is the principal component that actively transports glucose from the gut lumen into the gastrointestinal epithelium. When insulin resistance and hyperglycemia occur, the intestinal mucosa absorbs more glucose and fructose due to upregulated gene expression (SGLT1, GLUT2, and GLUT5) and enzyme activity (sucrase, maltase, lactase, and brush border disaccharidases) [32]. The expression of SGLT2 is limited to the kidney and is mostly observed in the S1 section of the proximal convoluted tubule, namely in the brush border membrane of proximal tubule epithelial cells. Researchers have discovered that SGLT2 expression is significantly upregulated in diabetic rats, db/db mice, and humans [33]. This upregulation is linked to glomerular hyperfiltration, improved glucose reabsorption, and higher plasma glucose levels. In contrast, natriuresis, osmotic diuresis, plasma volume contraction, decreased blood pressure, and arterial stiffness are all outcomes of SGLT2 inhibition [34]. All of these processes may help reduce the symptoms of DCM and heart failure. Furthermore, a change from glucose metabolism to FA oxidation can occur as a result of treatment with an SGL2 inhibitor. Thus, one of the beneficial effects of SGLT2 on the heart could be an increase in the generation of B-hydroxybutyrate, a substrate for very energy-efficient cardiac metabolism. Patients with type 2 diabetes can experience better cardiovascular outcomes and lower mortality rates by targeting SGLT2, according to many studies [35]. Research on the possible importance of these medications in the specific prevention and treatment of heart failure in diabetic individuals is now undertaken (Fig. 5) [36].

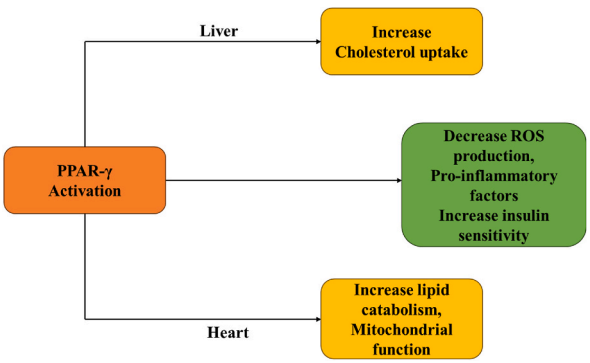

Fig. 3. This figure indicates the results of PPAR-γ activation in diabetic cardiomyopathy: it acts in the context of metabolic regulation and inflammation. This increases the uptake of cholesterol and lipid catabolism as well to support mitochondrial function in energy production and reduction of lipid accumulation in the diabetic heart. Another effect of PPAR-γ is its ability to decrease the formation of reactive oxygen species (ROS) and factors pro-inflammatory, increase insulin sensitivity, thus decrease oxidative stress and inflammation, both of which are highly involved in the pathogenesis of DCM. Essentially, activation of PPAR-γ conveys protective effects in the sense that it augments the metabolic function and decreases inflammation of DCM.

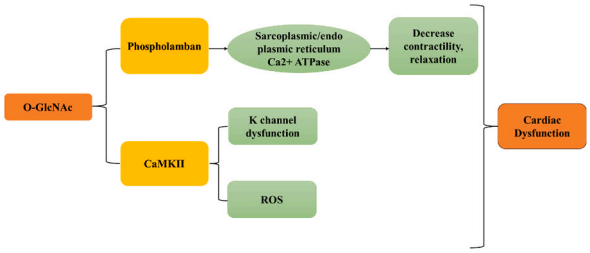

Fig. 4. This figure depicts the molecular pathways that affect functional changes in diabetic cardiomyopathy. Elevated O-GlcNAcylation activates CaMKII; activated CaMKII then disrupts the function of phospholamban and SERCA, impairs calcium handling, reduces contractility and relaxation in myocardium. Myocardial impairment is further worsened by ROS and altered potassium channel function. Collectively, these changes make significant contribution to the heart failure progression in the diabetic heart.

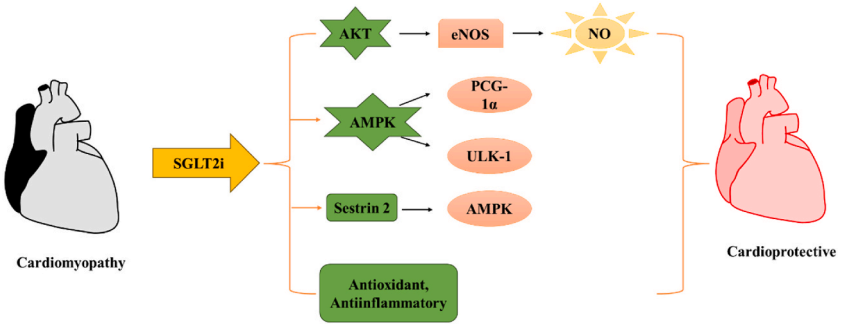

Fig. 5. This figure captures the cardiovascular effects of SGLT2i, indicating how they affect pathways in the heart and in endothelial cells. SGLT2i activate pathways of AKT and AMP-activated protein kinase (AMPK), and through this, leads to the activation of endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO). This is very important for vascular functions. Additionally, SGLT2i increases AMPK activation, promoting the expression of proteins PGC-1α and ULK-1 that contribute to mitochondrial biogenesis and autophagy, respectively. Activating Sestrin 2 with SGLT2i activates additional downstream targets with antioxidant and anti-inflammatory effects that support cardiovascular benefits.

2.6. PKC activation promotes development of diabetic cardiomyopathy

The activation of PKC signalling pathways is a consequence of diabetic cardiomyopathy, which is caused by hyperglycemia and insulin resistance. Inflammation, oxidative stress, and elevated RAAS and SNS activity are other elements that activate PKC [37,38]. About fifteen different PKC isoforms have been found in humans. These isoforms can be grouped into three subfamilies based on the second messenger signalling and activation specifics they display [39]. A theory proposes that the α, β, ε, θ, and δ isoforms of protein kinase C contribute to the progression of diabetic heart hypertrophy. As an example, research has shown that PKC β2 mediates diastolic heart failure in diabetic rats caused by hyperglycemia [40]. Modulating insulin metabolic Akt/eNOS signalling and caveolin-3 expression accomplishes this. A transgenic mouse model of DCM has demonstrated that by specifically inhibiting PKC β2, fractional shortening, reverse ventricular hypertrophy and fibrosis can be improved. The significance of this specific mechanism is further bolstered by this discovery [41]. The results that have been compiled with other data suggest that PKC activation can cause cellular and functional alterations that result in DCM and heart failure (Fig. 6) [42].

2.7. Role of NF-κB activation in the genesis of diabetic cardiomyopathy

One of the most crucial components in controlling the production of profibrotic genes, proinflammatory cytokines, and cell survival is the transcription factor NF-κB. Consequently, it contributes to the dysfunction of the heart's mitochondria and its ability to contract in diabetics. The cytoplasm contains NF-κB in cells that have not undergone activation. In response to stimulation, IκB is phosphorylated, and its p50/p65 subunits go to the nucleus to bind to κB nuclear elements on the nuclear side. Individuals with DM can directly activate NF-κB through ROS, AGEs, and an active heart tissue RAAS [43,44]. As a result, proinflammatory cytokines such as tumour necrosis factor α, interleukin-6, and interleukin-8 are released, and maladaptive immune responses are set up [45]. Research in diabetic mouse hearts has shown that the nicotinamide adenine dinucleotide phosphate oxidase (NADP+) pathway is associated with an upregulation of reactive oxygen species (ROS), peroxynitrite, and superoxide, as well as activated NF-κB [46,47]. The quantity of NO that is bioavailable is reduced as a result of these activities. One way to increase mitochondrial structural integrity and decrease oxidative stress is by using pyrrolidine dithiocarbamate, which is utilised to inhibit NF-κB. People with type 2 DM are able to regain cardiac function as a result of an increase in ATP production and NO bioavailability (Fig. 7) [48].

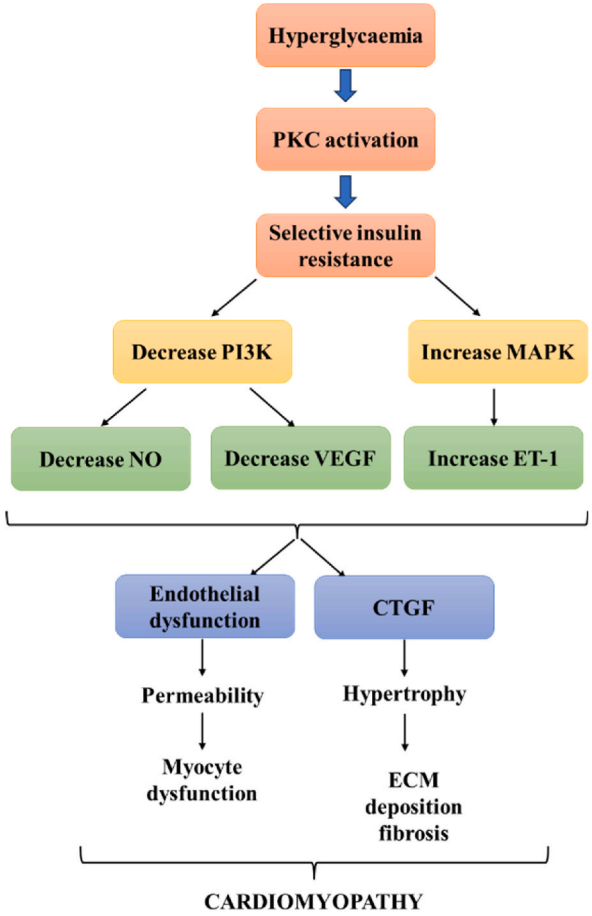

Fig. 6. The figure illustrates the process that hyperglycemia triggers to endothelial dysfunction, but more specifically earmarks PKC activation as the mediator of selective insulin resistance. Its effects have been detected to lower downstream signalling molecules such as PI3K, MAPK, NO, VEGF, ET-1, and CTGF. Hyperglycemia activates PKC, and this dramatically depresses both PI3K and NO in a way that decreases VEGF. This results in a parallel increase in activity of MAPK and an increase in the levels of ET-1. Both of these pathways can result in endothelial dysfunction and contribute to the expression of CTGF, thereby explaining the molecular interactions in complications of diabetes involving vascular health.

2.8. Role of MAPK and JNK activation in the genesis of diabetic cardiomyopathy

There is mounting evidence that MAPK activation contributes to the development of DCM and cardiac failure. The Erk1/2, p38 MAPK, and JNK subfamilies of MAPKs regulate the growth, enlargement, and remodelling of the heart. Among the several MAPK subfamilies, these three are among the most significant [49]. The activation of p38 MAPK and an increase in cardiac phosphorylation of Erk 1/2 are related with ischemia in streptozotocin-induced diabetic mice. During ischemia, all of these things happen. Heart failure due to obesity and insulin resistance is associated with elevated levels of S6 kinase 1 and Erk1/2 signalling, as demonstrated in our study and others [50]. Activation of JNK can occur in response to oxidative stress, inflammatory cytokines, or sphingolipid metabolites. Conversely, oxidative stress, endoplasmic reticulum stress, and interstitial fibrosis are all exacerbated by increased JNK signalling in diabetic hearts [51]. However, a curcumin analogue's ability to block JNK phosphorylation protects diabetic hearts against the inflammation and mortality brought on by high glucose levels. Along with these findings, it is plausible that JNK is involved in cardiomyocyte apoptosis to a considerable extent [52,53]. Consequently, it was shown that in a type 1 diabetic mouse model, activation of JNK increased the number of cardiomyocytes that died as early as days 3 and 7. When activated simultaneously, MAPK and JNK signalling seem to play a critical role in the aetiology of diabetic cardiomyopathy [54].

2.9. Abnormalities of exosomes in diabetic cardiomyopathy

The release of exosomes from cells, such as cardiomyocytes, is known to have a direct connection with the process of food metabolism. Extracellular vesicles known as exosomes have a diameter that can range anywhere from 30 to 90 nm and are considered to be of great significance as mediators of communication between cells. Among the many biological components that they contain are lipids, microRNAs, proteins, and transcription factors [55,56]. These components are responsible for regulating both normal

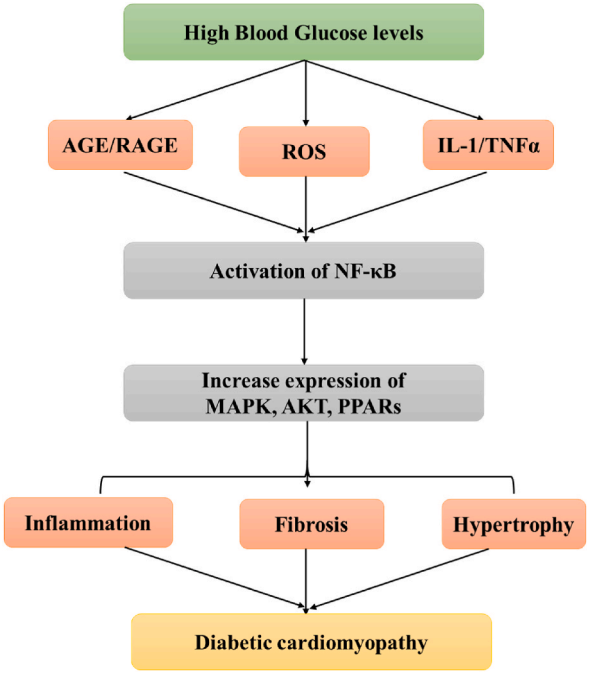

Fig. 7. This figure represents a pathway model that explains the mechanism by which elevated blood glucose levels leads to diabetic cardiomyopathy through a cascade of biochemical events. Elevated glucose levels favor increased levels of advanced glycation end-products (AGEs) along with their interaction with receptors (RAGE), generation of reactive oxygen species (ROS), and elevations in levels of inflammatory cytokines (IL-1/TNFα). These activations activate nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB, leading to the increased expression of mitogen-activated protein kinase, protein kinase B, and peroxisome proliferator-activated receptors. The enhanced signaling molecules cause inflammation, fibrosis, and hypertrophy, thus resulting in the creation of diabetic cardiomyopathy.

physiological effects and pathological symptoms. Exosomes, which are released from cardiomyocytes following glucose deprivation, are responsible for increasing glucose absorption, glycolysis, and pyruvate synthesis in endothelial cells. Together with glycolytic enzymes and glucose transporters, these exosomes carry out metabolic processes [57]. Type 2 diabetic hearts inhibit angiogenesis by reducing the amount of angiogenic factors and nitric oxide (NO) production through the release of exosomes containing high levels of miR-320 from cardiomyocytes and their subsequent transport to coronary endothelial cells. HS protein acronym However, exosomes modified with heat shock protein 20 have a positive impact on regulating the production of exosomes by cardiomyocytes and repairing cardiac dysfunction caused by hyperglycemia. This raises the intriguing prospect that exosomes not only act as markers, but that therapeutically focusing on exosomes may be a way to halt or reverse the progression of diabetic cardiomyopathy [58,59].

3. Current therapies: novel antihyperglycemic agents

Microvascular problems in the form of renal failure, retinopathy, and nerve damage can be caused by hyperglycemia and chronic persistent hyperinsulinemia. One of the most important aspects of the treatment plan for diabetes is bringing down the levels of glucose in the blood [60]. Anti-hyperglycemic medication has been administered to diabetic patients; however multiple observational studies have failed to demonstrate a reduction in the number of hospitalizations for heart failure (HF). In addition, a meta-analysis conducted in 2007 revealed that the glucose-lowering medication rosiglitazone was associated with a potentially elevated risk of myocardial infarction [61]. This finding highlights the importance of conducting a comprehensive evaluation of the drug's impact on the cardiovascular system. In order to ensure that newly developed antihyperglycemic medications are approved, the European Medicine Agency and the Federal Drug Administration now mandate that these medications undergo cardiovascular outcome trials [62,63]. Since the implementation of this new legislation, there has been a significant increase in the number of cardiovascular outcome trials, which has led to an increase in the availability of vital information regarding the impact that these medications have on cardiovascular health. Interestingly, in addition to their capacity to regulate blood sugar levels, a number of medications that are now in use have the potential to improve heart health [64]. These clinical and epidemiological investigations are the only ones that have been conducted, thus there is not a lot of information available about the processes by which these medications produce their pleiotropic effects [65].

3.1. The therapeutic approaches using compounds from natural origin

The majority of flavonoids may be broken down into six distinct subclasses, which are as follows: flavonols, flavones, flavanones, isoflavones, flavonones, and anthocyanidins. Flavonoids are found in abundance throughout the body of plant life. Flavonols have

been shown to have antioxidant, anti-inflammatory, anti-diabetic, and neuroprotective qualities, according to studies [66,67]. Flavonols may also lessen the susceptibility to developing chronic diseases. Numerous natural plants, including *Hypericum perforatum* and Smilax glabra Roxb, contain a compound known as astralbin, which is a dihydroflavonolrhamnoside [68,69]. In an effort to find healthcare solutions that are both effective and sustainable, therapeutic techniques that make use of substances originating from natural sources have emerged as a growing area of focus. An abundant supply of bioactive chemicals that may have therapeutic applications can be found in extracts and compounds derived from plants, herbs, and other natural sources. Antioxidant, anti-inflammatory, anti-microbial, and anti-cancer actions are only some of the pharmacological roles that these naturally occurring chemicals frequently play [70,71]. For the purpose of broadening the repertory of treatment techniques, particularly in the management of chronic diseases, natural substances such as apigenin and astilbin have proved fundamentally important. The reactive oxygen species (ROS) can be neutralised and the redox equilibrium can be maintained all thanks to the antioxidant characteristics of these substances [72]. Oxidative damage is a significant contributor to the development of a number of diseases, including diabetic cardiomyopathy. Astilbin and apigenin protect cells from this damage by directly scavenging free radicals. As an illustration of the promising potential of these natural agents in the field of healthcare, the role that astilbin and apigenin play in therapeutic approaches that make use of chemicals derived from natural sources stands out [73]. Among the many pathways that are influenced by it are the remodelling of extracellular matrix, the suppression of advanced glycation end product, the regulation of lipid metabolism, antioxidant activities, the activation of AMP-activated protein kinase, and the modulation of transcription factors. In addition to suppressing inflammatory responses in cardiac tissues and alleviating the inflammatory cascade that is associated with cardiac dysfunction, these substances may also limit the synthesis of cytokines that promote inflammation [74]. As part of their therapeutic functions, astilbin and apigenin simultaneously target apoptosis, also known as programmed cell death. These chemicals contribute to the maintenance of cell viability by suppressing apoptotic pathways, which in turn contributes to the prevention of the loss of heart function that is associated with diabetic cardiomyopathy [75,76]. In the treatment of a wide variety of health illnesses, including cardiovascular disorders, neurodegenerative diseases, and certain types of cancer, natural chemicals such as apigenin and astilbin are being investigated for their potential involvement in the management of these conditions [77–79].

3.1.1. *Apigenin*

The chemical name for apigenin is 4′, 5, 7,-trihydroxyflavone. In accordance with its chemical name, which is 4′, 5, 7, trihydroxyflavone, apigenin is a flavonoid derivative that has three hydroxyl substituents. Its chemical formula is C15H10O5 and its molecular weight is 270.24. It is the aglycone of several glycosides that occur in nature [80]. Apigenin, a naturally occurring flavonoid, is found abundantly in a variety of plants and vegetables such as parsley (*Petroselinum crispum*), celery (*Apium graveolens*), and chamomile (*Matricaria chamomilla*). These plant sources have shown to have antibacterial, antioxidant, anti-inflammatory, anticancer, anti-genotoxic, anti-allergic, neuroprotective, and cardioprotective qualities. It has also been demonstrated that flavones have antibacterial characteristics (Fig. 8) [81].

As a result of selective hydroxyl substitutions at positions 4′, 5, and 7 of the basic flavonoid skeleton, there are a maximum of seven potential derivatives or analogues of apigenin [82].

3.1.1.1. Pharmacological properties of apigenin. Apigenin has recently come to light as a useful and health-promoting drug due to its dramatic effects on normal cells rather than cancer cells and its low intrinsic toxicity. This is because, structurally speaking, it has close relationships to other flavonoids. Research has consistently shown that apigenin has promising therapeutic potential for a range of medical conditions. There is less evidence that apigenin, when consumed in a normal diet, causes detrimental metabolic effects in living organisms [83]. Very little study has been conducted to support this idea. But new research suggests oxidative stress could be the culprit in liver damage. Apigenin may activate many genes at higher levels in the tested Swiss mice, leading to this harm. Apigenin may have cancer-preventing effects due to its strong antioxidant and anti-inflammatory characteristics [84,85]. Evidence from both in vitro and in vivo cancer models suggests that apigenin can promote metal chelation, stimulate phase II detoxification enzymes, and scavenge free radicals. These results have been proven. Apigenin makes a big difference in cancer prevention thanks to its capacity to induce apoptosis in many different cell lines and animal models [86]. The levels of oxidative stress indicators in blood were shown to decrease

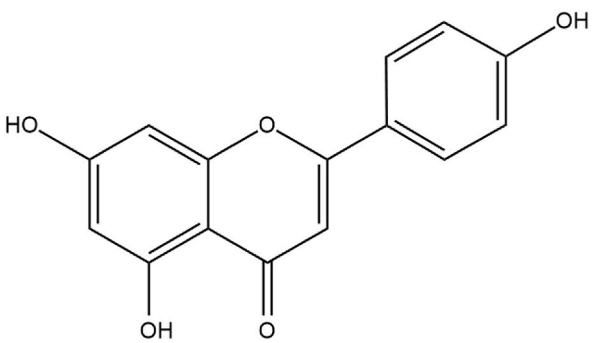

Fig. 8. Structure of apigenin.

when healthy human volunteers had flavonoid-free diets. Lymphocyte DNA damage, erythrocyte superoxide dismutase (SOD) activity, and plasma antioxidant vitamins are all indicators of heightened disease risk (Fig. 9) [87,88].

Many in vitro and in vivo studies involving different mammalian systems have demonstrated the diverse biological effects of apigenin. Reasons for these effects include its role in free radical scavenging, its antioxidant and antigenotoxic characteristics, and so on. Murine peritoneal macrophages laden with oxidised low density lipoprotein (OxLDL) facilitate apoptosis, which allows apigenin to exercise its anti-atherogenic effects [89]. Some have speculated that apigenin's pro-apoptotic effects stem from its ability to suppress the phosphorylation of AKT at Ser473, which in turn down-regulates plasminogen activator inhibitor-2 (PAI-2). More so, research has shown that it can reduce inflammation in IPEC-J2 non-transformed intestinal epithelial cells generated by LPS by lowering the production of COX-2, IL-8, and TNF-α. Apigenin inhibits bone resorption in ovariectomized mice and, according to Goto and colleagues' hypothesis, slows down osteoblastogenesis and osteoclastogenesis as well [90]. Evidence suggests that apigenin and its derivatives have a wide range of medicinal uses beyond just reducing inflammation and cancer. An apigenin derivative called apigenin-7-glycoside can reduce oxidative enzyme production and decrease MAPK activation, therefore protecting the lungs from acute lipopolysaccharide (LPS) harm. A priori, it was shown that apigenin stimulates autophagia, a cellular dormant period [91]. This simultaneously induces resistance against chemotherapy and may explain apigenin's chemopreventive properties. Sapigenin is an effective competitive inhibitor of the enzyme CYP2C9, which is involved in the metabolism of numerous medicinal drugs in the body. Apigenin may be able to counteract the harmful effects of cyclosporine, according to certain studies. To study how apigenin reverses cyclosporine damage, researchers used immuno-histochemistry to evaluate bcl-2 and estimate apoptosis in histological sections [92].

3.1.1.2. Role of apigenin in diabetes mellitus. Apigenin is considered to be an anti-diabetic medication due to its ability to inhibit the activity of α-glucosidase, increase insulin secretion, and manage reactive oxygen species, all of which are essential in managing diabetic problems or complications related to diabetes. Apigenin has the ability to transport nitric oxide to endothelial cells, and as a result, it can prevent or prevent damage to endothelial cells that is caused by an increase in the amount of glucose in the blood circulation [93]. Apigenin is believed to have cardioprotective effects because it improves cardiac disorder and fibrosis, as well as increases in 4-hydroxynonenal. This was achieved by downregulating B-cell lymphoma 2, glutathione peroxidase, and superoxide dismutase, upregulating L-malondialdehyde, cleaved caspase3 antibodies, and the Bax gene, which is a proapoptotic protein, and as a result, NF-kappaB was translocated in mice [94]. The administration of a little amount of Apigenin has the ability to treat renal issues, oxidative stress, and fibrosis in rats. An increased level of sorbitol in diabetics can lead to a variety of complications, including cataracts, retinopathy, and neuropathy. Apigenin extract can be used to control the aldose reductase enzyme, which is the primary enzyme involved in the polyol pathway [86]. Apigenin also prevents the diffusion of sorbitol out of the cell membranes. Additionally, the potential of this molecule to preserve the architecture of the Langerhans islets was demonstrated through histopathology of pancreatic tissue that had been treated with celery apigenin. Additionally, immunohistochemistry analysis demonstrated that pancreatic cells secrete insulin. As an example, flavonoids like apigenin have the ability to control free radicals that are produced as a consequence of diabetes and to prevent damage to the pancreas [95]. Not only may flavonoids like apigenin enhance glucose levels in skeletal muscle cells, but they can also regulate the absorption of glucose and carbohydrates, as well as influence the pathways that are activated by AMP-activated protein kinase. In patients with neuro-diabetes, apigenin and luteolin both have the ability to block sodium-glucose cotransporter-2. A patient with type II diabetes can be managed with the help of flavonoids like apigenin, which up-regulate the expression of glucose transporter-1. The effect of apigenin-6-C-(2″-O-α-L-rhamnopyranosyl)- β-L-fucopyranoside, a compound derived from Averrhoa carambola L. leaves, on the absorption of 14C-glucose was examined in a study by Cazarolli and colleagues. Acute effects on lowering blood glucose levels and enhanced glucose-induced insulin production were noted in diabetic rats following oral administration of this compound to hyperglycemic rats [96]. In addition to increasing glucose absorption, phenolics can also increase the expression of glucose yransporter-4. Therefore, apigenin is considered to be an anti-hyperglycemic drug [97–99].

3.1.1.3. Role of apigenin in treating diabetic cardiomyopathy. The risk of developing cardiovascular disease is significantly increased in individuals who have diabetes mellitus. One of the most significant complications of DM is known as diabetic cardiomyopathy, which

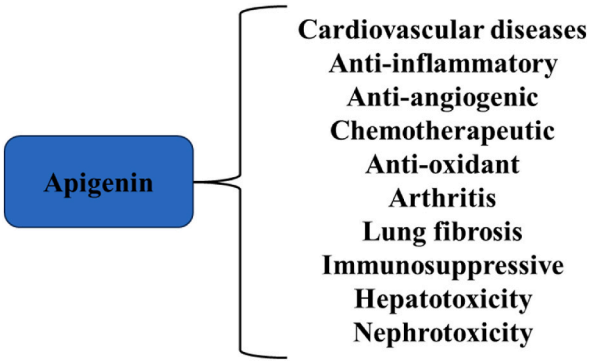

Fig. 9. Pharmacological properties of Apigenin.

also plays a role in the higher death rate associated with the disease. Vein enlargement, myocardial fibrosis, steatosis, and apoptosis are the hallmarks of diabetic cardiomyopathy, which is a condition that affects the heart [100,101].

Apigenin, when administered orally at a dose of 100 mg/kg, reduced streptozotocin (STZ)-induced hyperglycemia, reduced ventricular hypertrophy, and improved cardiac function in a DCM mouse model [102]. Apigenin increased the activity of inhibitory enzymes in heart tissue upon treatment. Apigenin decreased the production of IL-1β, IL-6, and TNF-α via inhibiting the nuclear translocation of NF-κB. Results from in vitro studies using cardiac tissue and H9c2 cardiomyocytes were also consistent with the ones mentioned before. The following are some of the ways in which apigenin's cardioprotective effects are observed in a study: improved cardiac and left ventricular function, preserved endogenous antioxidants, myofibrils salvaged histologically, reduced apoptosis, and reduced lipid peroxidation in myocardial tissues [103,104].

In a DCM mouse model, apigenin treatment improved heart function and reduced ventricular hypertrophy and interstitial fibrosis. This was achieved by enhancing the activities of glutathione peroxidase (GPX), catalase, and SOD, and by decreasing cardiac oxidative stress [105]. In transgenic mice, where miRNA103 is overexpressed, apigenin ameliorates glucose intolerance. In obese mice, apigenin enhances glucose and lipid homeostasis via increasing NAD + levels through decreasing cluster of differentiation 38 (CD38). Obesity, metabolic syndrome, and type 2 diabetes can be averted by elevating tissue intracellular NAD + levels. Notably, evidence suggests that addressing metabolic disorders may be possible through focusing on the NAD + pathway [106].

In vivo treatment with apigenin could reverse the pathologic changes seen in diabetic cardiomyopathy-induced mice. These changes included increased cardiac dysfunction, fibrosis, and overaccumulation of 4-hydroxynonenal. Then, there was down-regulation of Bcl2, GPx, and SOD, and upregulation of MDA, cleaved caspase3, and pro-apoptotic protein Bax. Apigenin also contributed to the translocation of NF-kappaB. The purpose of this would be to prove that apigenin protects the heart [107]. After receiving apigenin at a dosage of 20 mg/kg (which reduced transforming growth factor-beta1, fibronectin, and type IV collagen), male albino Wistar rats showed improvements in renal failure, oxidative stress, and fibrosis [108].

Another study indicated that apigenin treatment stabilised redox state in vivo, restored left ventricular function, and reduced hemodynamic fluctuations. Rats were protected from heart injury due to a decrease in myonecrosis, edoema, cell death, and oxidative stress [109].

Apigenin has been shown in several studies to potentially reduce the symptoms of cardiovascular diseases (CVDs) through influencing a number of related pathways. One of the targets that apigenin can activate is the peroxisome proliferator-activated receptor-γ (PPAR-γ). This activation maintains a balanced redox condition in the myocardium of diabetic rats, restores left ventricular function, and prevents hemodynamic disturbances. Consequently, it prevents myocardial infarction by lowering oxidative stress, edoema, myonecrosis, and cell death [110–112].

Similarly, Liu et al. showed that apigenin improved cardiac function, decreased interstitial fibrosis, inhibited cardiac remodelling, prevented cardiocyte apoptosis, and suppressed cardiac oxidative stress, thus alleviating diabetic cardiomyopathy. The following inflammation and suppression of NF κB/p65 translocation were the causes of all these effects [113].

The main ways that dietary apigenin shows its immune-regulatory properties, according to Cardenas and colleagues, are by reducing NF-κB pathway activity, stopping leukocyte infiltration, and restoring normal metabolic function [114]. Moreover, there is a belief that reducing activity in the NF-κB pathway can help prevent abdominal aortic aneurysms, a complex vascular disease caused by elastin degradation, chronic inflammation, and alterations in the phenotypic control of vascular smooth muscle cells. Aortic pathological expansion reduction, elastic fibre preservation, and vascular inflammation reduction all contribute to this end [115].

To determine the beneficial benefits of apigenin on Dox-induced cardiomyopathy, it was administered to Dox-treated mice three

Table 1
Summary of the effects of Apigenin in Diabetic cardiomyopathy.

Study Design	Source of Apigenin	Treatment Duration	Dosage	Effect on Diabetic Cardiomyopathy	Reference
Mouse model of STZ-induced diabetic cardiomyopathy	Synthetic apigenin	8 weeks	100 mg/kg orally	Reduced hyperglycemia, ventricular hypertrophy, and improved cardiac function. Decreased IL-1β, IL-6, TNF-α levels via NF-κB inhibition	[102]
In vivo (DCM mouse model) and in vitro (H9c2 cardiomyocytes) studies	Synthetic apigenin	6 weeks	100 mg/kg orally	Enhanced GPX, catalase, and SOD activities; reduced oxidative stress, ventricular hypertrophy, and fibrosis	[103, 104]
Mouse model (miRNA103 overexpression)	Synthetic apigenin	12 weeks	50 mg/kg orally	Improved glucose intolerance, enhanced glucose and lipid homeostasis via increased NAD + levels and CD38 inhibition	[106]
Male Wistar rats with induced renal failure	Synthetic apigenin	8 weeks	20 mg/kg orally	Reduced fibrosis, oxidative stress, and renal failure	[120, 121]
Rat model of DCM	Apigenin derived from Averrhoa carambola L. leaves	2 weeks	Not specified	Lowered blood glucose levels, enhanced glucose-induced insulin secretion	[96]
Mouse model of Dox-induced cardiomyopathy	Synthetic apigenin	3 days before Dox injection	20 mg/kg intraperitoneally	Reduced cardiac dysfunction, fibrosis, inflammation, neutrophil infiltration, and oxidative stress	[116, 117]
Rat model of aortic expansion and aneurysm	Synthetic apigenin	Not specified	Not specified	Reduced NF-κB pathway activity, preserved elastic fibres, reduced vascular inflammation	[115]

days before histological and molecular tests. The initial step in determining the extent of cardiac injury was to evaluate the serum TnT, BNP, and CK-MB levels using ELISA [116]. The results showed that after Dox treatment, the concentrations of all three markers were much greater than in the control group of mice fed PBS. Serum TnT, BNP, and CK-MB levels were significantly reduced in mice treated with apigenin. Sirius Red staining was utilised to find out whether the apigenin treatment alleviated the histological alterations brought on by Dox in the heart tissue [117]. Pretreatment with apigenin alleviated these structural defects, in line with the earlier reported results. Injection of Dox caused myofibrillar fibrosis and edoema in the mice. As shown by GR-1 immunofluorescence, animals treated with Dox had a significantly higher concentration of neutrophils in the heart regions compared to PBS-treated mice. However, neutrophil concentration was shown to decrease following apigenin injection, suggesting a diminished inflammatory mechanism. In addition, RT-PCR findings showed that, in contrast to control mice, mice given Dox had elevated transcription of proinflammatory genes (IL-6 and MMP9) in their hearts [118]. However, when apigenin was given, the changes stated earlier were greatly undone. These results demonstrate that apigenin considerably reduced the severity of myocardial damage in mice induced by Dox (Tables 1 and 2) (Fig. 10) [119].

3.1.2. Astilbin

Astilbin, which has been shown to contribute significantly to the sweet flavour of dry wines, is found in large concentrations in wines, which is an interesting fact. Astilbin has been demonstrated to possess a variety of pharmacological properties, including anti-inflammatory, immunosuppressive, antioxidant, anti-diabetic, and cardiovascular protective qualities, according to contemporary pharmacological research [122]. Astilbin was found to be a promising molecule and a "star material" for the development of new health food products, according to the overall observations and data that were discovered.

A large number of plants and plant-based foods, including *Engelhardtiaroxburghiana, Smilax glabra Rhizoma* (SGR), grapes, and wine, contain the dihydroflavonolasstilbin, which is made of (2R,3R)-3,3′,4′,5,7-pentahydroxyflavanon-3-α-l-rhamnopyranoside. Neoastilbin (2S, 3S), astilbin (2R, 3R), neoisoastilbin (2S, 3R), and isoastilbin are the four stereoisomers of astilbin [123]. The structure

Table 2
Patent on apigenin.

Sr. No.	Patent No.	Title	Description
1.	CN 107865859 A	Application of orientin to preparation of drugs capable of lowering blood sugar	The application of orientin to the manufacturing of pharmaceuticals that are capable of decreasing blood sugar levels is disclosed in the following invention. There is evidence that demonstrates that the administration of orientin has a significant anti-diabetic impact. Orientin is a compound that has a specific chemical structure and is of a brand new skeleton type; orientin has good activity in the prevention and treatment of diabetes; the application of apigenin has outstanding substantial distinguishing features; and significant progress is being made towards the treatment of rheumatoid diabetes as a result of the application of apigenin.
2.	WO 2000/ 059522 A1	Compositions and Methods for Treatment of Diabetes	Products that have been extracted from Brickellia californica and flavonoids that have been separated from the plant are beneficial for the treatment of diabetes. These flavonoids include apigenin, luteolin, quercetin, and dihydroxykaemferol. Due to the fact that these materials lead to a large reduction in blood sugar levels, the items that have been extracted and the flavonoids that have been purified can be utilised in an alternative manner for the treatment of diabetes that is either insulin dependent or non-insulin dependent.
3.	US 2002/ 0068704 A1	Compositions and methods for treatment of diabetes	In the treatment of diabetes mellitus, flavonoids, particularly luteolin, have been demonstrated to be beneficial against both insulin-dependent (Type I) and insulin-independent (Type II) forms. The fact that luteolin is effective in mammals has been proven by the process of binding to and blocking the K 1.3 potassium channel found in T-cells and Beta cells. By evaluating the capacity of drugs to bind to and inhibit the K 1.3 channel, it is possible to choose compounds that have the ability to treat diabetes and autoimmune diseases.
4.	US 2005/ 0181076 A1		
5.	CN 109125315 A	Composition for lowering blood sugar, blood fat and blood pressure and application	Specifically, the invention pertains to a composition that can reduce blood sugar, blood fat, and blood pressure, as well as the application of said composition. Apigenin and ginsenoside Rh4 are both components of the composition, which has the potential to act as effective components of medication or health-care food for the simultaneous prevention or treatment of diabetes, hyperlipidemia, high blood pressure, and problems associated with these conditions. It is possible for the composition to fully play the activity of the ginsenoside Rh4 in the blood fat lowering and blood sugar lowering aspects, as well as the activity of the apigenin in the blood pressure lowering aspect. In the meantime, it is possible to achieve synergistic interaction between the ginsenoside Rh4 and the apigenin, which results in the pharmaceutical effects being significantly improved, and a single medicine having multiple effects.
6.	CN 109381455 A		
7.	US 10232005 B2	Compositions and methods for controlling carbohydrate and fat metabolism	Any compound that contains at least a mixture of molecules produced from Chrysanthellum indicum, Cynara scolymus, and Vaccinium myrtillus, and wherein the mixture of molecules also contains piperine is considered to be a composition. The composition is especially helpful as a nutritional product or health product for the purpose of preventing and/or treating problems of carbohydrate and/or fat metabolism in both humans and animals.

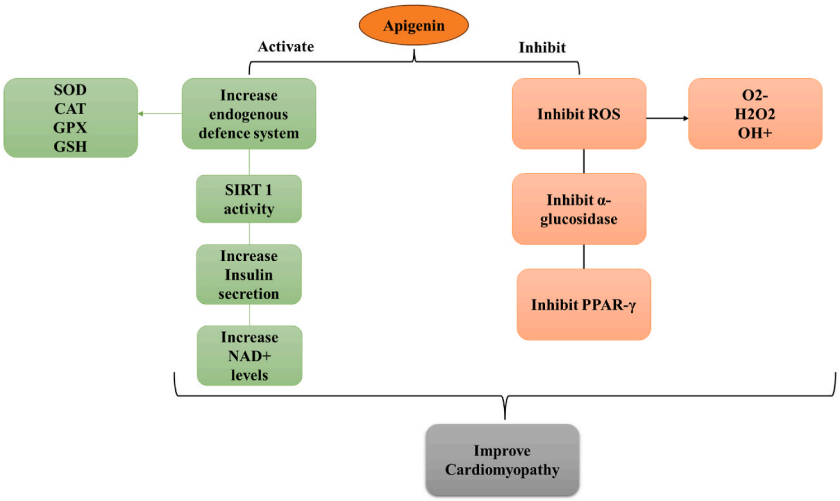

Fig. 10. The diagram depicts cardioprotective effects of Apigenin with a variety of biochemical pathways. Through activation of SOD, CAT, GPX, and GSH to the body's endogenous defense mechanism, Apigenin triggers subsequent increase in SIRT 1 activity that, in turn further stimulates insulin secretion and enhances NAD + levels. The other end is the inhibition of the formation of ROS molecules that include O2-, H2O2, and OH+, in addition to a downregulating activity that affects the activities of α-glucosidase and peroxisome proliferator-activated receptor gamma (PPAR-γ). These accumulate to result in improved outcomes for cardiomyopathy.

of astilbin reveals the presence of two asymmetric carbon atoms at positions C-2 and C-3, denoted as 2R and 3S, respectively. These four stereoisomers typically coexist in plants without any problems. To get astilbin that is really pure, you can use separation and purification techniques like high-performance centrifugal chromatography or high-speed counter-current chromatography. Still, out of the three, astilbin usually comes out on top. Due to its antioxidant, hypoglycemic, and selective immunosuppressive effects, among other biological pathways, it has been the focus of extensive investigation. Regardless, the other three plant stereoisomers are extremely uncommon, therefore there is a dearth of relevant research on them [124]. Isomerization of substances can significantly alter their bioactivity and/or physical properties, and the pharmacological effects of some drugs are very different between their two enantiomers. For instance, astilbin lacks a distinctive flavour, whereas neoastilbin has a sweet flavour. Wheat grains naturally contain the mycotoxin deoxynivalenol, or DON for short. It has devastating effects on all forms of life. The original chemical was quite dangerous, but its stereoisomer, 3-epi-DON, is much safer. The S-isomers of cefpodoxime proxetil have a reduced rate of degradation in the gastrointestinal area and a higher resistance to enzyme metabolism, which results in significant bioavailability benefits compared

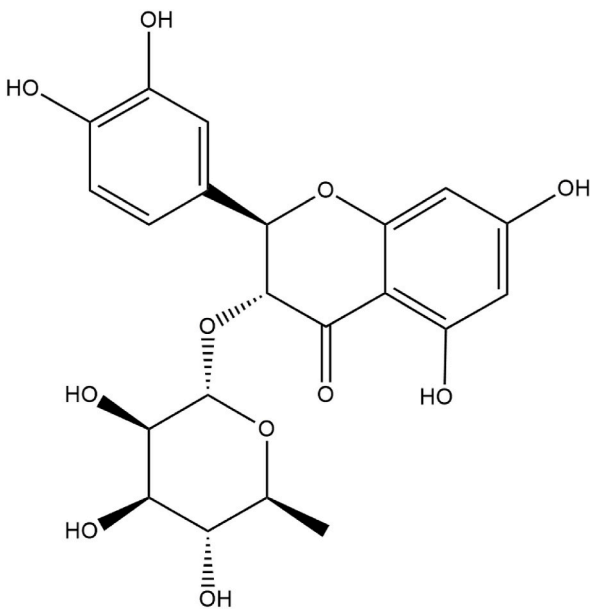

Fig. 11. Structure of astilbin.

to the R-isomers (Fig. 11) [63,125,126].

3.1.3. Structure of astilbin

3.1.3.1. Pharmacological properties of astilbin. It was discovered that Astilbin is the primary active component of many herbs and plants that have long been employed in traditional medicine systems, particularly in China (e.g., the Erhuang formula). Astilbin has the potential to be a highly effective immunosuppressive medication with little side effects because of its natural origins; these investigations showed that it has a wide-ranging influence on the immune system by working on a number of immunomodulators and inflammatory modulators [127]. This is in addition to the numerous other claimed properties of astilbin, such as its ability to reduce inflammation, fight against bacteria, protect the liver, and neutralise free radicals. Many areas of study remain open for astilbin, including its possible anticancer effects, protective effects against a range of diabetes problems, and many more [128]. As oxidative stress is a key contributor to many diseases, several research have investigated astilbin's antioxidant capabilities. In these studies, astilbin's in vitro antioxidant activity was evaluated using a battery of tests, including its protective action on mesenchymal stem cells (MSCs) subjected to oxidative stress caused by the Fenton reaction, total phenolic content, DPPH radical scavenging activity, ABTS radical cation scavenging activity, reducing power assay, scavenging activity on superoxide anion radical, and antioxidant activity in the linoleic acid system. The goal of this study was to compare the results of three commonly used antioxidants: Trolox, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA). The results of these investigations demonstrated that astilbin had potent antioxidant properties [129,130]. Astilbin reduced depressive behaviours in a dose-dependent manner after 21 days of intraperitoneal administration of doses of 10, 20, and 40 mg/kg. This effect was observed in a number of models, including the Tail suspension test, the sucrose preference test, and the forced swim test, but had no effect on locomotor activity. When tested in mouse models of depression, astilbin showed promising antidepressant effects [131,132].

3.1.3.2. Beneficial impacts of astilbin in the management of diabetes. Researchers conducted in vitro studies to examine how the root extract of Smilax aristolochiifolia affected the α-glucosidase enzyme. The amount of astilbin in the final product was rather high. The α-glucosidase enzyme's role in carbohydrate metabolism in the gut and, by extension, the absorption of glucose from food has the potential to make it an important tool in the fight against type-2 diabetes mellitus [133,134]. The pNPG (ρnitrophenyl-α-D-glucopyranoside) approach was used to determine the influence of the astilbin-rich fraction and thereby assess the α-glucosidase enzyme activity. The amount of ρ-nitrophenol released from the pNPG substrate after the enzyme had done its job was one indicator of the enzyme's activity. The absorbance of the sample was calculated at a wavelength of 405 nm using a microplate reader, which allowed us to determine the percentage of enzyme inhibition [135]. The enzyme was observed to be non-competitively inhibited by the astilbin rich fraction, with an IC50 value of 12.30 μg/mL. Being a well-known α-glucosidase used to treat type-2 diabetes mellitus, acarbose had much weaker inhibitory efficacy compared to the astilbin rich fraction. In this work, molecular docking was used to bolster the findings that were already achieved in vitro. According to this investigation, the α-amylase enzyme did not identify the astilbin rich fraction as active. The findings lend credence to the idea that the herb's long-standing hypoglycemic use may have a contemporary, mechanical basis [136,137].

3.1.3.3. Astilbin in the prevention of diabetic cardiomyopathy. DM is one of the main causes of many heart conditions. In vivo and in vitro studies were conducted on diabetic rats with myocardial ischemia and reperfusion injury to determine the effects of astilbin. After surgically ligating the left coronary artery with silk thread, we created myocardial ischemia and reperfusion injury in streptozotocin-induced diabetic rats. During reperfusion, we released the ligature [138]. The in vitro investigation utilised myocardiac H9c2 cells. As a means of simulating the ischemia circumstances, the cells were cultured in an environment with low oxygen levels. The study compared the effects of astilbin on H9c2 cells with those of glycyrrhizin (an inhibitor of HMGB1) and Pyrrolidinedithiocarbamic acid (an inhibitor of NF-κB) [139]. The cell viability was assessed using the Microculture Tetrazolium assay (MTT), and TNF-α was used to stimulate the examination of NF-κB activation and HMGB1 expression using western blotting. The rats' myocardial injury and recovery were evaluated by measuring the infarct diameters, histological assessment, serum levels of TNF-a, Tn-T, and IL-6, left ventricular systolic pressure (LVSP), and ± dp/dtmax. By reducing HMGB1 expression and NF-κB activation, it was determined that astilbin significantly enhanced the cell viability of H9c2 cells. Not only that, but astilbin reduced infarct dimensions relative to the control group. Additionally, there was a decrease in the serum levels of TNF-α, Tn-T, and IL-6. Improved as well were LVSP and ± dp/dtmax. This proved conclusively that astulbin prevented cardiac damage in diabetic patients [140].

During the process of extracellular matrix remodelling, astilbin has the potential to affect the activity of matrix metalloproteinase (MMP), which might potentially reduce excessive extracellular matrix breakdown and fibrosis [141]. As a result of its activities against oxidative stress and inflammation, astilbin has the potential to suppress AGEs, which are considered to be a contributor to DCM. The ability of astilbin to reduce circulating free fatty acids, so reducing the stress that is caused by lipids on the heart, is a treatment for dysregulated lipid metabolism, which is a characteristic of DCM [142].

The modulation of peroxisome proliferator-activated receptors (PPARs) by astilbin has an effect on the metabolism of lipids and glucose, which contributes to the prevention of metabolic abnormalities in diabetic retinopathy (DCM). astilbin has the potential to influence abnormalities in the function of sodium-glucose co-transporter 2 (SGLT2), which are common in diabetes. These abnormalities have the potential to effect glucose reabsorption in the kidneys and to assist in the regulation of blood glucose levels [143].

Because it inhibits the activation of protein kinase C (PKC), astilbin lowers the contribution that PKC makes to the inflammatory and fibrotic processes that occur in the diabetic heart. The anti-inflammatory and anti-apoptotic effects of the substance entail the

potential modification of mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways, which contribute to the protection of the heart. NF-κB activation, a crucial component in the process of inflammation, is inhibited by astilbin, hence reducing the impact it has on the heart of a diabetic patient (Tables 3 and 4) (Fig. 12) [144].

4. Directions for the treatment of DM in the future

Although many investigations have made improvements to our comprehension of how DM impacts CVD risk, additional research needs to be done in order to more precisely determine and assess CV risk in patients with DM. Another subject that requires additional research is how controlling blood sugar links to CVD [145]. There is some evidence that individuals who have diabetes who exhibit better control over their glucose levels actually have better CV outcomes. According to one study, HbA1c in non-diabetic patients is even a reliable indicator of the degree of coronary artery disease, suggesting that glycemic control is a prerequisite for controlling CV health across the entire spectrum. Large randomized control, Examinations have demonstrated that the detrimental impact of stringent glucose management on subsequent CVD is minimal and mostly related to coexisting conventional risk variables, despite the fact that the current evidence suggests an independent connection between blood sugar levels and CVD [146,147].

For it to be possible to monitor and control classic cardiovascular disease risk factors in people with diabetes, such as dyslipidemia, obesity, and blood pressure, additional investigation is additionally required. As an example, in contrast to the current advice, which mostly emphasizes statin mono-treatment, a combination of medications might be the best strategy to manage dyslipidemia [148,149]. Additional study is needed to determine whether pharmacological medications developed that improve HDL can have a beneficial medicinal effect in diabetic individuals due to the intricate nature of HDL's function on CV health. It's not entirely obvious as to what amount of loss of weight must occur in those with diabetes to improve CV results in a way that is clinically relevant [150–152]. A height and weight decrease of 5 % might not be sufficient for those with diabetes with additional CV risk variables and various underlying medical problems. Additional study is needed to find the most effective weight loss method and the amount of bodyweight loss necessary for achieving a CV benefit. The recently introduced blood pressure standards will have to be proactively followed up on moving ahead, particularly for individuals' older individuals who suddenly come within the more elevated systolic blood pressure benchmark [153].

5. Conclusion

It is logical to assume that as the incidence of diabetes increases, so will the likelihood of related cardiovascular disease, taking into account both typical CV risk variables and the direct effect of diabetes on CVD. As a result, effective DM management and therapy as well as proactive treatment of associated CV risk factors are needed to limit the incidence and development of DM and CVD, both of which are on the rise. Despite reduced rates of CVD among individuals having both kinds of diabetes as well as in the general

Table 3
Summary of the effects of Astilbin in Diabetic cardiomyopathy.

Parameter	Study Design	Source of Astilbin	Treatment Duration	Dosage	Effect on Diabetic Cardiomyopathy	Reference
In vivo (Animal)	Diabetic rats (Streptozotocin-induced) with myocardial ischemia-reperfusion injury created by ligation and reperfusion	Natural plant compound	Not specified	Not specified	- Reduced infarct dimensions - Lower serum TNF-α, Tn-T, and IL-6 - Improved LVSP and ± dp/dtmax - Enhanced myocardial injury recovery	[138, 140]
In vitro (Cellular)	Myocardiac H9c2 cells cultured in low oxygen environment to simulate ischemia conditions	Natural plant compound	Not specified	Not specified	- Increased cell viability - Reduced NF-κB activation and HMGB1 expression	[139]
Oxidative Stress and Inflammation	Mechanistic analysis (potential inhibition of AGEs)	Natural plant compound	Not specified	Not specified	- Reduced oxidative stress and inflammation - Suppressed AGEs	[141, 142]
Extracellular Matrix Remodelling	Mechanistic analysis (inhibition of MMP activity and fibrosis reduction)	Natural plant compound	Not specified	Not specified	- Reduced excessive extracellular matrix breakdown - Decreased fibrosis	[141]
Dysregulated Lipid Metabolism	Mechanistic analysis (effect on free fatty acids and lipid metabolism)	Natural plant compound	Not specified	Not specified	- Reduced circulating free fatty acids - Mitigated lipid stress in the heart	[142]
Metabolic Abnormalities in DCM	Mechanistic analysis (modulation of PPARs, SGLT2 function, and lipid/glucose metabolism)	Natural plant compound	Not specified	Not specified	- Prevention of metabolic abnormalities - Improvement in glucose reabsorption and regulation	[143]
Inflammatory and Fibrotic Processes	Mechanistic analysis (PKC, MAPK, JNK, and NF-κB pathways inhibition)	Natural plant compound	Not specified	Not specified	- Inhibited PKC activation - Suppressed inflammation and fibrosis through MAPK, JNK, and NF-κB pathways	[144]

Table 4
Patents on astilbin.

Sr. No.	Patent No.	Title	Description
1.	CN 116585259 A	Hydrogel loaded with nano lignin/astilbin composite material as well as preparation method and application of hydrogel	It is specifically disclosed that the invention includes a hydrogel that is loaded with a nano lignin/astilbin composite material, as well as a method for preparing the hydrogel and an application for the hydrogel. The following aforementioned steps are included in the preparation method: dissolving astilbin in deionized water to prepare an astilbin solution, and dissolving alkali lignin in tetrahydrofuran to prepare an alkali lignin solution; dropwise adding the alkali lignin solution into the vortex astilbin solution until a nano lignin/astilbin solution with the water content of 75 percent is obtained, magnetically stirring, and centrifugally drying to obtain a nano lignin/astilbin composite material; and dissolving the nano lignin/astilbin composite material in a hydrogel solution to gelatinize the nano lignin/astilbin composite material to obtain the hydrogel loaded with the nano lignin/astilbincomposite material. The hydrogel that is loaded with the nano lignin/astilbin composite material has a good slow release performance, and it is able to release astilbin that is capable of promoting revascularization for an extended period of time. As a result, the hydrogel has a good effect of treating ischemic diseases of the lower limbs, and it is also biologically safe.
2.	CN 109762038 A	Astilbin amino acid derivative targeting prodrug and preparation method and application thereof	One of the products of this innovation is a prodrug-targeting astilbin amino acid derivative. It is demonstrated in formula I that the prodrug has a structure. After modifying astilbin through a chemical semi-synthesis process, the astilbin amino acid derivative prodrug that is capable of targeting the inflammation part is obtained. This allows for the targeted therapy effect to be achieved, the bioavailability of the prodrug to be improved, the anti-inflammation effect to be significantly superior to that of astilbin, and the effective development and utilisation of astilbin to be accomplished.
3.	KR 101846368 B1	Method for Preparing Astilbin from Taxifolin Using Microorganism Mutants	Specifically, the present invention pertains to a method for producing astilbin, and more specifically, to a microorganism mutant that contains a metabolic pathway that is capable of producing astilbin from taxifolin, as well as to a method for producing astilbin from taxifolin using the same metabolic pathway. The method of the present invention allows for the mass production of astilbin, which is a significant substance that possesses physiological activities such as antibacterial, antioxidant, and anti-inflammatory properties.
4.	CN 105566415 A	Astilbin derivatives and preparation method thereof	In particular, the invention pertains to astilbin derivatives and a technique of preparation for said derivatives. The invention falls under the category of medical knowledge. It is possible to create acylated astilbin derivatives by performing a selective acylation procedure on the phenolic hydroxyl groups that are present on astilbin. In particular, tri-acetylated astilbin and tetra-acetylated astilbin have a better bioavailability in animal bodies.
5.	US 2007/ 0003510 A1	Preparations containing an extract of eperua falcata and/or constituents of the latter	A preparation that is used in the cosmetic, pharmaceutical, or dermatological industries that contains extract of the plant Eperua falcata, active principles of the plant Eperua falcata, astilbin, or engeletin. For the treatment of skin and hair conditions such as sensitive skin, acne, scalp itch, and neurogenous inflammation, the preparation is helpful because it inhibits the production of pro-inflammatory mediators and neuropeptides, such as CGRP and SP.
6.	CN 103768082 A	Application of astilbin to preparation of medicament for treating or preventing diabetes accompanied with stroke	The invention presents a novel medicinal application of astilbin, and it is specifically related to the application of astilbin to the formulation of a medication for the treatment or prevention of diabetes that is accompanied by a stroke. According to the application, the oral dosage range for astilbin is between 25 mg and 1000 mg, with the ideal range being between 50 mg and 500 mg. As an additional benefit, the invention offers a pharmaceutical composition that contains astilbin as an active component.
7.	CN 116059247 A	Application of astilbin to stimulation of mesenchymal stem cells in preparation of medicine for treating diabetic nephropathy	Astilbin is specifically applied to the stimulation of mesenchymal stem cells in the creation of a drug for the treatment of diabetic nephropathy, which is the subject of the invention, which pertains to the technical field of nephropathy therapy. While the

(*continued on next page*)

Table 4 (*continued*)

Sr. No.	Patent No.	Title	Description
			mesenchymal stem cells are being subcultured, 5–20 [mu] g/ml of astilbin is being added to a cell culture solution. This is done in accordance with the application of the mesenchymal stem cells in the creation of the drug for the treatment of nephropathy. According to the invention, the traditional Chinese medicine monomer astilbin, which is pretreated in advance, has differentiation capacity and has potential for treating diabetes mellitus, is found for the first time, so that the treatment effect of the bone marrow mesenchymal stem cells on diabetic nephropathy is greatly enhanced; animal models also prove that in a diabetic nephropathy mouse model, the urine protein level can be obviously reduced, the renal function can be improved, the pathological score of kidney tissue is also obviously reduced, the kidney injury is obviously relieved, and a remarkable curative effect is achieved.
8.	CN 111437302 A	Application of extract obtained after macroporous resin treatment after water extraction of Engelhardiaroxburghiana Wall leaves in preparation of diabetes drugs and analysis method of engelhardiaroxburghiana wall leaves	The flavonoid glycoside composition and an application of extract obtained after macroporous resin treatment after water extraction of Engelhardiaroxburghiana Wall leaves containing the flavonoid glycoside composition are both provided by the invention. The drugs that are used to treat diabetes are also included in the invention. Neoastilbin, astilbin, isoastilbin, neoisoastilbin, neoengelitin, engelitin, isoengelitin, neoisoengelitin, kaempferol-3-O-rhamnoside, taxifolin-3-O-(3″-O-p-(E)-galloyl)-alpha-L-rhamnoside, and stereoisomers of these compounds are found in the leaves of the Engelhardiaroxburghiana Wall and its leaves. A flavonoid glycoside composition, preparation, application, and product are the specific topics that are covered by this invention, which falls under the purview of the pharmacy, foods, health-care foods, and pharmaceutical preparations fields.

population as a result of rising rates of both types of diabetes, the worldwide incidence of cardiometabolic diseases continue to increase around the world. This will counteract the improvements made in many nations in the prevention and treatment of CVD and might lead an upsurge in life expectancy to come to a halt. The association between type 2 diabetes and rising obesity rates is clear, and data from a variety of sources suggests that type 2 diabetes with early onset is especially detrimental in terms of a combination of microvascular complications and macrovascular consequences. The source of an upsurge in type 1 diabetes incidence is less apparent and likely complex, even though the broad range in incidence and the greater number of cases in high-income nations suggest that rising obesity rates may be a factor. It will require an integrated, worldwide approach to prevent hyperglycemia and its associated issues. These attempts, particularly with regard to glycaemic management, have to start early and include determining and addressing CVD risk factors, as advised by numerous regulations. More research is required for improved comprehension of the physiological mechanism and its effects on cardiovascular health in order to improve medical care and CV outcomes for patients with diabetes.

CRediT authorship contribution statement

Sachin Dhiman: Writing – review & editing, Writing – original draft, Visualization, Resources, Formal analysis, Data curation, Conceptualization. **Sanchit Dhankhar:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Anjali Garg:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Manni Rohilla:** Writing – original draft, Validation, Software, Investigation, Formal analysis. **Monika Saini:** Writing – original draft, Visualization, Supervision, Methodology, Formal analysis. **Thakur Gurjeet Singh:** Writing – original draft, Visualization, Project administration, Formal analysis, Conceptualization. **Samrat Chauhan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis, Data curation, Conceptualization. **Samy Selim:** Writing – review & editing, Validation, Funding acquisition. **Soad K. Al Jaouni:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis. **Sabina Yasmin:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Naseem Begum:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis. **Aziza Alshahrani:** Writing – review & editing, Supervision, Funding acquisition. **Mohammad Yousuf Ansari:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis.

Data availability statement

All data generated or analyzed during this study are included in this article.

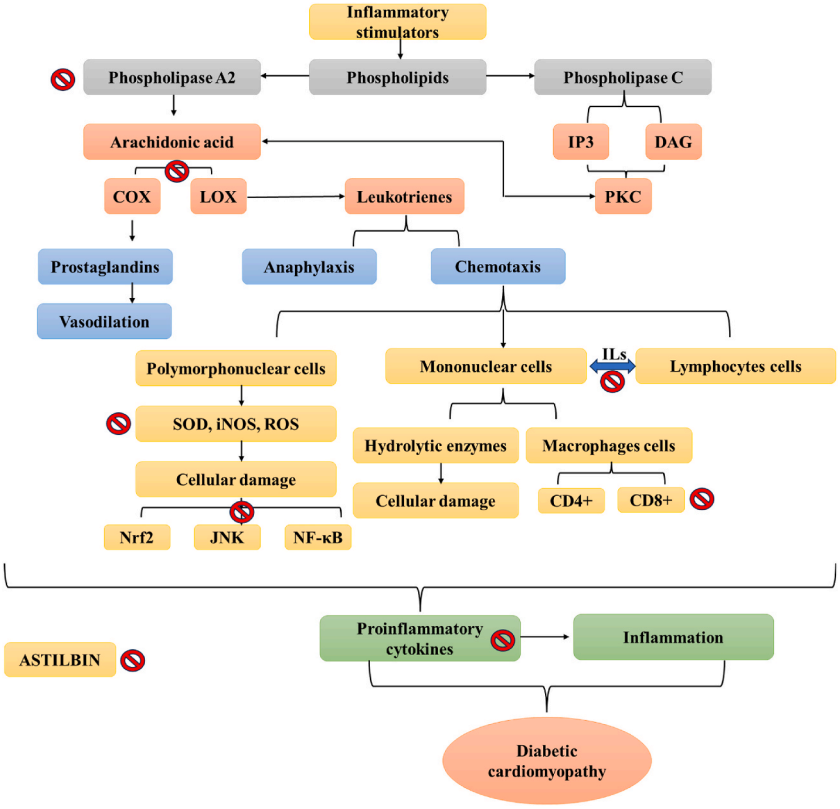

Fig. 12. A mechanistic pathway of inflammatory stimulation and its relationship with diabetic cardiomyopathy can be described on a diagram focusing on Astilbin as an inhibitor. Inflammatory stimulators including phospholipase A2 and phospholipase C are engaged into arachidonic acid release, which ends in prostaglandins synthesis through COX, in association with leukotriene synthesis due to LOX, causing anaphylaxis, vasodilation, and chemotaxis. These processes activate polymorphonuclear cells, mononuclear cells, and lymphocytes and release inflammatory mediators such as SOD, iNOS, ROS, and hydrolytic enzymes to deal with injury. Activation of the key transcription factors Nrf2, JNK, and NF-κB and proinflammatory cytokines also contribute to inflammation and tissue damage. Astilbin acts on several steps in this cascade, such as phospholipase A2, COX, and the function of immunocompetent cells like $CD4^{+}$ and $CD8^{+}$, and it reduced the emission of proinflammatory cytokines and inflammation thus, alleviating diabetic cardiomyopathy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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