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Review Article

A COMPREHENSIVE STUDY ON LITERATURE EVIDENCE, CLINICAL STUDIES AND PRACTICES OF HERBAL DRUGS FOR DIABETIC NEUROPATHY AND CARDIOMYOPATHY

ARSHIYA SHAMIM, HEFAZAT H SIDDIQUI, TARIQUE MAHMOOD*, PARAMDEEP BAGGA, RANJAN KUMAR

Department of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India. Email: ansaritariq79@yahoo.co.in

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ABSTRACT

Diabetes mellitus is a worldwide epidemic disease that eventually advances to a chronic stage and affects different vital organs by intensifying the underlying pathological factors, and through the remodeling of the tissues by the generation of reactive oxygen species leading to the development of respective organ failure. Two such complications are painful neuropathy and cardiomyopathy; both of which are common and progressive complications of diabetes. The symptoms of peripheral neuropathy include tingling, burning, lancinating pain, hyperesthesia, and allodynia. The course of the disease progression may vary from intermittent, mild symptoms to severe chronic, and daily pain; which culminates into poor quality of life. Another complication of diabetes mellitus, diabetic cardiomyopathy, is defined as a ventricular dysfunction disorder that occurs in diabetic patients. The development of the disease is characterized by a hidden subclinical period, during which cellular, structural changes and abnormalities lead to diastolic dysfunction, followed by systolic dysfunction, and terminating into heart failure. Left ventricular hypertrophy, metabolic abnormalities, extracellular matrix changes, small vessel disease, cardiac autonomic neuropathy, insulin resistance, oxidative stress, and apoptosis are the most important pathological advancements that lead to diabetic cardiomyopathy. Various pharmaceutical agents from different pharmacological categories have been proposed for the symptomatic treatment of painful diabetic neuropathy; however, it is a herculean task to select a drug due to the wide range of choices and lack of consistent guidelines for treatment. Similarly, treatment of cardiomyopathy is based on the general therapeutic rules of management of heart failure and no specifications have yet been addressed for this condition. Therefore, more studies are required to improve our knowledge of these complex syndromes. From this perspective, this review is designed to delineate a general overview of neuropathy and cardiomyopathy, referring to the conventional therapies in use and possible unconventional, natural, herbal, and safe treatments for both the above-mentioned complications of diabetes.

Keywords: Cardiomyopathy, Diabetes, Herbal treatment, Neuropathy, Neuropathic pain, Oxidative stress, Ventricular hypertrophy.

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INTRODUCTION

Statistical insight to diabetes mellitus

Diabetes mellitus is one of the most common, increasing, and serious public health problems among all the metabolic disorders worldwide both for the disease itself and for associated severe secondary complications. As per data recorded and updated to March 2013, provided by the World Health Organization and also reported by one of the Lancet journals (Diabetes –a global threat; 2011), the statistical data related to diabetes mellitus are alarming, there has been an increased incidence of diabetes cases from 1980 to 2008 when number of patients increased from 153 million to 347 million people worldwide suffering with diabetes mellitus. Moreover, it is predicted that this amount will increase to 380 million in 2025, representing 7.1% of the world's adult population [1-4]. On the basis of investigations carried by Chang *et al.* 2013; Espelt *et al.* 2013; a total of 57 million deaths occurred in the World during 2008, of which 36 million (63%) were due to non-communicable diseases, among these, diabetes alone caused 1.3 million deaths. Therefore, it is projected as a global health problem. Today, over 90% of diabetic patients are diagnosed with type 2 diabetes mellitus (T2DM), with an increased incidence in recent years probably due to an increased prevalence of its main risk factors (obesity and sedentary life). Nephropathy, retinopathy, cardiomyopathy, and peripheral neuropathy are all recognized as important complications in about 50% of diabetes mellitus patients, mostly with improper glycemic control or unsuccessful management of disease [5-10].

DIABETIC PERIPHERAL NEUROPATHY

The International Association for the Study of Pain defines neuropathic pain as "pain resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system. Neuropathic pain could be of many types such as paresthesias (numbness or tingling), dysesthesias (electric shock phenomenon), hyperesthesia (increased sensitivity to mild painful stimuli), hyperalgesia (increased sensitivity to normally painful stimuli), hyperpathia (pain produced by subthreshold stimuli), spontaneous pain, and allodynia (pain produced by normally non-painful stimuli. Diabetic peripheral neuropathy is characterized by symptoms such as pain, tingling, or numbness, loss of feeling in the hands, arms, feet, and legs. Painful neuropathy is common and in a few cases enfeebling complication of diabetes. The clinical trials conducted on patients suffering from type II diabetes (Davies *et al.* 2006; Ziegler *et al.* 2009) concluded that approximately one in four people with diabetes might be affected by chronic neuropathic pain. Patients often complain of symptoms such as discomfort, typically starting in the distal feet, but progressing proximally over time. Other symptoms such as numbness, tingling, burning, aching, electric shocks, or lancinating pain have also been observed, as stated in a review by Huizinga and Peltier, 2007. The body parts often affected include the legs, arms, hands, and fingers. The pain may be constant or intermittent, and there may be associated nocturnal worsening. Patients may also experience allodynia, when non-painful stimuli also become painful or hyperesthesia, when normally painful stimuli become excruciatingly painful [11-15].

CURRENT TREATMENT APPROACHES FOR DIABETIC PERIPHERAL NEUROPATHY

Although treatment of pain is critical to improvize the quality of life, it must be considered only one aspect of overall cure. Symptomatic management of neuropathy is altogether apart from treatment regimen for the disease itself, and therefore, aggressive treatment of underlying diabetes remains paramount as only then the patients can be completely

cured. Control of blood pressure, lipids, and other microvascular risk factors are necessary for effective long-term management of diabetes. There are a few medications which have been vetted in large and randomized on the basis of placebo-controlled or head-to-head clinical trials. Interpretation of the available data can be challenging because variables such as dosing, duration of treatment, and the definition of successful treatment may vary among studies. As stated in a study conducted by Gore *et al.* 2008, certain recommendations of guidelines and consensus statements available often differ, and many medications have adverse effects or interactions with medications used to treat diabetes. There are older medications, such as tricyclic antidepressants, which are commonly used to treat painful diabetic neuropathy but have not been tested in randomized clinical trials for this condition. These older medications may be excluded from recommended guidelines which use strict criteria, given their potential efficacy and utility. Hence, a report by Van *et al*.; 2009, states that due to these limitations, the actual implementation of treatment for painful diabetic neuropathy may prove daunting to clinicians and likely contributes to patients remaining untreated or undertreated [16-19].

A group of medications are suggested for use as first-, second-, and third-line treatment for painful diabetic neuropathy. These clinical suggestions are based on the criteria including evidence of efficacy, safety, tolerability, drug interactions, and cost. The list of reviewed drugs is not claimed to be an encyclopedia of all agents used to treat painful diabetic neuropathy, but have been rather compiled keeping a practical perspective of treatment in mind with substantial available evidence. First-line medications are supported by evidence from three or more randomized clinical trials in patients with painful diabetic neuropathy, while second-line medications are supported by evidence from two randomized clinical trials in patients with this condition. Third-line medications are commonly used to treat painful diabetic neuropathy and are supported by evidence from two or more randomized clinical trials in patients with this condition but also have conflicting data reported. Third-line medications offer treatment options for patients who have either not tolerated or have been unable to take first- and second-line drugs [20-22].

CLINICAL TRIALS ON DIABETIC PERIPHERAL NEUROPATHY [23-41] (TABLE 1)

Clinical case

Various clinical cases on treatment and management of diabetic neuropathy have been reported by Hovaguimian and Gibbons; 2011, one such case is mentioned below as a reference.

This is a clinical case of a 59-year-old woman suffering from type 2 diabetes with complaints of numbness and pins for the past 2 years. Over the past 4 months, the symptoms have become increasingly bothersome. She has been treated in the past with gabapentin 300 mg. Her past medical history is remarkable for liver disease secondary to alcohol use with subsequent diabetes and thrombocytopenia. She has also had both hepatic encephalopathy and hepatorenal syndrome in the past. Her paresthesias have been persistent and may also be influencing her mood; therefore, symptomatic treatment may help improve her quality of life, and hence, the only first-line drugs without a contraindication in liver disease are pregabalin and gabapentin. As both gabapentin and pregabalin have similar mechanisms of action, it is, therefore, reasonable to repeat a trial of gabapentin first. The starting dose for gabapentin is 300 mg daily, and this dose can be titrated as tolerated to symptomatic relief or to 1200 mg thrice daily [42].

Diabetic cardiomyopathy is another complication of diabetes on which earliest data was reported four decades ago, hence, substantial information on its pathogenesis and clinical features had been accumulated. The relationship between diabetes mellitus and heart failure has been known for many years and includes several underlying pathogenesis. Leyden in 1881 first claimed that diabetic cardiomyopathy is a common complication of diabetes and one worthy of attention. In 1888, Mayer reported that diabetes is a metabolic disorder that can lead to heart disease. Finally, the term "diabetic cardiomyopathy" was coined by Rubler in 1972, after conducting post-mortem studies in diabetic patients with heart failure who had no medical history of alcoholism, hypertension, coronary disease, and other structural heart diseases. Prolonged diabetes increases fatty acid metabolism, inhibits glucose oxidation and modifies intracellular signaling in the heart, leading to impairments in multiple steps of excitation-contraction coupling, inefficient energy production, and increased susceptibility to ischemia. Loss of normal blood capillaries and remodeling of the extracellular matrix are also involved in diabetic cardiomyopathy [43,44].

Oxidative stress has been long associated with the pathogenesis of diabetic cardiomyopathy. Prolonged hyperglycemia produces series of secondary transducers such as increase in reactive oxygen species (ROS), decreased nitrous oxide level, which leads to myocardial inflammation and endothelial dysfunction through PARP [poly (ADP-ribose) polymerase] inhibition. Anatomical and functional abnormalities of the vascular endothelium are commonly associated with diabetes [45].

PATHOPHYSIOLOGICAL CHANGES INVOLVED IN CARDIOMYOPATHY

Left ventricular hypertrophy (LVH)

The change in myocardial tissue due to diabetes is not an immediate pathogenesis but rather a consequence of long-term diabetes-associated changes, such as obesity. As per the findings of Eguchi *et al.* [44], there is a significant interaction between diabetes and central obesity on the risk for development of LVH. Furthermore, obesity promotes concentric LVH independently of hypertension. The recent clinical findings explain the role of cytokines, produced by the expanded adipose tissue due to obesity, in the development of LVH. For example, leptin is linked to cardiac hypertrophy in obese humans and directly induces cardiomyocyte hypertrophy *in vitro*. The mechanisms by which leptin induces LVH is not fully characterized but might involve endothelin 1- mediated ROS generation. The strong heart study conducted in Native Americans, found that both men and women with diabetes had higher LV mass and wall thickness. Furthermore, in a multi-ethnic population, the likelihood of having LV mass that exceeds the 75th percentile is greater in patients with type 2 diabetes, after adjusting for various covariates including hypertension [46-49].

Oxidative stress

There are many experimental studies which have suggested that oxidative stress may play a critical role in the development of diabetic cardiomyopathy; however, the mechanism involved in ROS generation in diabetic hearts is not well understood. Clinical and pharmacological experimental studies have implicated that increased oxidative stress is associated with lipid overload; indeed, oxidative stress is increased in hearts isolated from the db/db mice model of type 2 diabetes, which are also characterized by cardiac lipid accumulation and increased mitochondrial fatty acid oxidation. Two different experimental models were designed to study the impact of fatty acids in ROS production. One model was designed on db/db mice, whereas the other on Akita mouse. In db/db hearts, oxidative stress is exacerbated in the presence of fatty acids, which we believe leads to mitochondrial uncoupling. Whereas the Akita mouse model of Type 1 diabetes does not exhibit increased mitochondrial ROS generation or shows any evidence of mitochondrial uncoupling despite increased rates of fatty acid oxidation. An important distinction between the hearts of Akita mice versus db/db or ob/ob mice is the presence of myocardial insulin resistance in obese models with insulin resistance, whereas in Type 1 diabetes models, insulin sensitivity is preserved. Interestingly, in mice with cardiac-specific deletion of insulin receptors, hydrogen peroxide production was increased, and mitochondria were uncoupled even at stage when myocardial fatty acid oxidation was reduced. This information indicates the possibility that myocardial insulin resistance may specifically

Table 1: Criteria of trials

Safety profile **Tolerability** **Number of significant drug interactions** **Cost**				
Line of treatment and number of trials	**Type of clinical trial**	**Name of the drug**	**Study of the trial**	**References**
First-line treatment (three or more randomized clinical trials) Other first line drugs	Randomized placebo-controlled trials on different tricyclic antidepressants	Gabapentin Imipramine Amitriptyline Duloxetine	This study examined the use of gabapentin extended release which is not currently commercially available This was a randomized control trial of venlafaxine v/s imipramine in neuropathic pain and included 15 patients with painful diabetic neuropathy	[23-31]
Second line treatment (two or more randomized clinical trials)	Randomized placebo-controlled trials on different Anticonvulsant drugs (Supported by evidence from two or more randomized clinical trials in painful diabetic neuropathy.)	Venlafaxine Valproate	This study examined use of venlafaxine extended release This was a double-blind, randomized placebo-controlled trial in diabetic neuropathy which found that both valproate and a combination of valproate plus glyceryl trinitrate spray improved pain control	[32,33]
Third line treatment (two or more randomized clinical trials but with conflicting data.)	Supportive randomized controlled trials as well as conflicting randomized trials	Lamotrigine Oxcarbazepine Alpha lipoic acid	A randomized control trial was carried out comparing lamotrigine with amitriptyline and placebo for the treatment of painful diabetic neuropathy Another study with conflicting results examined lamotrigine dose up to 400 mg/day and dosing at 200 mg/day for neuropathic pain A study examined oxcarbazepine dosing at 600, 1200, and 1800 mg/day. The results were not statistically significant in respect to efficacy variable, but improvement in pain was observed in patients receiving 1200 or 1800 mg/day in comparison to placebo and 600 mg/day group Two more studies were studies were carried out which examined oxcarbazepine dosing at 1800 mg/day and 1200 mg/day the latter, however, showed conflicting results A randomized, placebo-controlled trial was conducted, and a trial with conflicting results was also carried out	[34-41]

subject cardiac mitochondria to cause free radical overproduction through mechanisms that remain to be elucidated [50-52].

Interstitial fibrosis

Regan *et al.* stated in their study that diabetic cardiomyopathy is characterized by interstitial and perivascular fibrosis. Found a significant increase in collagen deposition around intramural vessels and between myofibers in heart biopsies form diabetic patients. In addition, a significant increase in collagen Type III but not Type I or VI was found in endomyocardial biopsies obtained from patients with Type 2 diabetes, who did not have significant coronary artery disease and hypertension. Similar to humans, some animal models with Type 2 diabetes also exhibited an increase in cardiac fibrosis even before the onset of hyperglycemia which shows increased extracellular fibrosis and collagen deposition as reported in the pre-diabetic stage in OLETF rats, a genetic model of diabetes resembles human Type 2 diabetes [53-55].

CLINICAL DIAGNOSIS OF DIABETIC CARDIOMYOPATHY

The structural and functional changes observed in the left ventricle (LV) of the heart, excluding other heart diseases being responsible for these changes in a diabetic patient, that occur as a result of prolonged diabetes, form the basis for the diagnosis of diabetic cardiomyopathy. There are certain specific biomarkers and their respective detection tools which serve as the diagnostic techniques of diabetic cardiomyopathy (Table 2), tissue Doppler imaging (TDI) and strain/strain rate imaging (SRI) being the most common of them. LV diastolic dysfunction, easily detected by TDI at exercise stress, may be the earliest sign of diabetes-induced LV dysfunction. Thus, normal echocardiographic studies at rest are unable detect presence of diabetic cardiomyopathy. The latest studies illustrate that diastolic dysfunction develops earlier than systolic dysfunction in diabetic hearts. However, Ernande *et al.* [56] recently reported that systolic longitudinal strain rate was abnormal in 28% of diabetic patients with normal diastolic function and in 35% of those with diastolic dysfunction. Assessment of interstitial fibrosis by integrated backscatter or Gd-enhancement of cardiac MRI is possible, but its diagnostic value has not yet been established [57-60]. A promising novel approach to diagnosis of diabetic cardiomyopathy is analysis of metabolic changes associated with the myocardium by ^{31}P-MRS and by ^{1}H-MRS (magnetic resonance spectroscopy [MRS]). A parameter for detection of energy charge, the PCr/ATP ratio, is found to be reduced in the myocardium of diabetic patients when compared with that of control subjects. The newer studies using ^{1}H-MRS have demonstrated that increase in myocardial triglyceride content (also known as; myocardial steatosis) was also found to be associated with LV diastolic dysfunction in diabetic patients. It is worthwhile to mention here that, myocardial steatosis was observed to be associated with LV longitudinal strain and with systolic/diastolic strain rates also, as determined by two-dimensional speckle tracking imaging in patients with uncomplicated diabetes mellitus. The possibility that myocardial

Table 2: Diagnostic clues of diabetic cardiomyopathy

Structural changes
LV hypertrophy assessed by 2D echocardiography or CMR
Increased integrated backscatter in the LV (septal and posterior wall)
Late Gd-enhancement of the myocardium in CMR
Functional changes
LV diastolic dysfunction assessed by pulsed Doppler echocardiography and TDI
LV systolic dysfunction demonstrated by TDI/SRI
Limited systolic and/or diastolic functional reserve assessed by exercise TDI
Metabolic changes
Reduced cardiac PCr/ATP detected by 31P-MRS
Elevated myocardial triglyceride content detected by 1H-MRS

CMR: Cardiac magnetic resonance imaging, 2D two dimensional, LV: Left ventricular, MRS: Magnetic resonance spectroscopy, SRI strain/SRI: Strain/strain rate imaging, TDI: Tissue Doppler imaging [65]

steatosis is a specific marker of the diabetic cardiomyopathy warrants further investigation [61-63]. The various clinical and pathological changes observed in diabetic cardiomyopathy can be diagnosed by different sophisticated techniques as mentioned in Table 2 [64].

CLINICAL STUDIES FOR PREVENTION AND TREATMENT OF DIABETIC CARDIOMYOPATHY

Although the high prevalence of subclinical myocardial dysfunction has been reported in the early stage of Type 1 diabetes mellitus (T1DM), clinically relevant heart failure is relatively rare in this type of diabetes. In an observational study conducted by Torffvit *et al*.; 2005, 462 T1DM patients without a previous history of heart disease were took under observation, and it was found that only 17 patients (3.7%) developed heart failure during 12-years follow-up period. The patients who developed heart failure in this cohort were older in age (35±9 years) and had been long-term diabetic, hypertensive, had albuminuria and retinopathy as compared to patients who did not have heart failure. In contrast, heart failure develops more commonly in patients with T2DM, as being associated with other predisposing factors, such as hypertension and leading to heart failure. Thus, glycemic control alone is not sufficient for the prevention of diabetic cardiomyopathy [65-67].

A number of clinical trials have been conducted to evaluate the impact of glycemic control on the prevention of cardiovascular events in T2DM. However, endpoints in the studies were atherosclerotic cardiovascular events and death, leaving non-ischemic heart failure not specifically determined. A recently published meta-analysis by Turnbull *et al*.; 2009, including a total of 27,049 subjects in the UKPDS 33 (UK Prospective Diabetes Study 33), ACCORD, ADVANCE, and VADT trials showed that mortality was not affected by intensive glycemic control, with hazard risks of 1.10 for cardiovascular death ($p<0.05$; 0.84-1.42) and 1.04 for all-cause death ($p<0.05$: 0.90-1.20) [68].

These elucidations appear to contradict the notion, which tight glycemic control is beneficial for prevention of diabetic cardiomyopathy. However, these results do not eliminate the possibility that intensive glycemic control commenced at an earlier stage of diabetes together with control of other risk factors can prevent heart failure in diabetic patients. This speculation is supported by a few evidence. First, clinical studies using TDI showed that glycemic control improved LV diastolic function in T2DM [69,70].

Second, the Steno-2 trial showed that simultaneous control of glycemia, hypertension, and dyslipidemia significantly reduced cardiovascular events and mortality in T2DM patients. Third, a recent meta-analysis of clinical trials on hypertension indicates that diabetes increases the incidence of heart failure by more than fourfold in hypertensive patients. Whether incidence and/or outcome of heart failure differ depending on the type of hypoglycemic agent selected for hyperglycemia control remains unclear. This issue has not been addressed by a prospective randomized clinical trial. Eurich *et al*.; 2007 conducted observational cohort studies and retrospective analyses of registered patients, and reported that use of metformin is associated with low incidence of heart failure compared with other glycemia control regimens. Furthermore, clinical outcomes in diabetic patients with heart failure were better in groups treated with metformin as reported in a trial conducted by Aguilar *et al.* on metformin-treated and metformin-untreated groups of diabetic patients with heart failure and showed that mortality was lower in the metformin-treated group. In contrast with metformin, thiazolidinedione (TZD) has been shown to increase the incidence of "heart failure" in diabetes compared with sulfonylurea. Unfortunately, it is not clear whether the increase in "heart failure" by TZD is due to worsening of LV function or just retention of fluids [71-78].

In fact, recent studies carried out by Horio *et al*.; 2005 and van der Meer *et al*.; 2009 have suggested a favorable effect of TZD on cardiac function. Pioglitazone was used for a 6 month treatment regimen followed by which diastolic function was improved as assessed using Doppler echocardiography in hypertensive patients in proportion to the amelioration of insulin resistance. The same duration of treatment with pioglitazone was also reported to improve diastolic function and LV compliance assessed using MRI in uncomplicated T2DM patients. It is critical; however, that improvement in the function could not be proven by treatment-related myocardial metabolic change diagnosed by positron emission tomography and MRS alone. Therefore, prospective clinical trials are necessary to clarify efficacies and explain the pharmacological role of hypoglycemic drugs in the prevention of diabetic cardiomyopathy [79-80].

CURRENT TREATMENT APPROACH FOR DIABETIC CARDIOMYOPATHY

The approach for the treatment of diabetic cardiomyopathy is based on four fundamentals: Lifestyle changes, maintenance of blood glucose level, modification of risk factors for cardiovascular disease, and the treatment of heart failure. However, all the above-mentioned criteria revolve around the management of cardiomyopathy to provide symptomatic relief to the patient rather than aiming to cure the root problem. Hence, we need to research other unconventional approaches to treat this complication of diabetes. Herbal drugs offer a good thrust area for this purpose as they are free from unwanted side effects and hold the extreme unexplored potential to cure diabetes and its related complications. Thus, the latter part of this review focuses on the herbal treatment approach for diabetic cardiomyopathy which demands illustrative research to find its place in the current clinical scenario.

Lifestyle modification

Smoking cessation, healthy eating habits, reduction in body weight and aerobic exercise are the cornerstones in terms of lifestyle change. It has been shown in people with diabetes mellitus type 2 that, following reduction of their body weight and increased aerobic activity, the incidence of diabetic cardiomyopathy decreased significantly [81-83].

MANAGEMENT OF HYPERGLYCAEMIA AND OTHER RISK FACTORS

The modern therapeutic arsenal has several effective medications to treat diabetes, such as metformin, sulfonylureas, glitazones, insulin, and some modern drugs, such as GLP1 agonists and antagonists of DPP4. Although these drugs appear effective in treating diabetes in people without concomitant heart failure, in patients with heart failure there are some limitations.

The classic example is metformin, which has been previously contraindicated in heart failure because of the risk of lactic acidosis. However, in clinical practice and use, it turns out that the risk of lactic acidosis associated with metformin in people with diabetes and heart failure is not so great. In addition, metformin can upregulate cardiomyocyte autophagy, which plays an important role in the prevention of diabetic cardiomyopathy in animal models. Metformin

has also been reported to reduce mortality rates and lower all-cause hospital admissions [84-88].

Treatment of heart failure

According to the 2013 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases, three neurohormonal antagonists—an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), a beta-blocker, and a mineralocorticoid receptor antagonist (MRA)—are the most important pharmacological agents for the treatment of all patients with heart failure and reduced LV ejection fraction, including those with diabetes mellitus. They are usually combined with a diuretic for relieving congestion and may also be supplemented by ivabradine.

ACE-I and ARB

An ACE-I is indicated in diabetes mellitus type 2 and heart failure, since it improves symptoms and reduces mortality [89-92]. The beneficial effects of ARBs are equivalent to those of ACE-I, according to subgroup analyses of clinical trials, and therefore, an ARB can be used as an alternative in ACE intolerant patients. When ACE-I and ARBs are used in patients with diabetes mellitus, monitoring of kidney function and potassium is mandatory, since nephropathy is a frequent occurrence [93].

Beta-blockers

Beta-blockers are the standard drugs for patients with systolic heart failure [94,95]. As reported by Deedwania *et al.*; 2005, a subgroup analysis of the MERIT-HF trial, showed that beta-blockers reduce mortality and hospital admissions and improve symptoms, significantly in both, diabetes mellitus type 2 and non-diabetic patients. Beta-blockers recommended in heart failure and diabetes mellitus type 2 are metoprolol succinate in the slow release form (MERIT-HF), bisoprolol (Cardiac Insufficiency Bisoprolol Study II), and carvedilol (carvedilol prospective randomized cumulative survival and carvedilol or metoprolol European Trial) [96-99]. Adverse effects of beta-blockers in patients with diabetes mellitus type 2 and heart failure include hypoglycemia, especially with non-cardioselective regimens, and negative metabolic effects (hypoglycemia, dyslipidemia and decreased insulin sensitivity) [100,102].

MRA

An MRA is recommended for all patients with persisting symptoms (New York Heart Association Class II-IV) and an LV ejection fraction =35%, despite treatment with an ACE-I (or, if not tolerated, an ARB) and a beta-blocker, to reduce the risk of heart failure hospitalization and premature death (Class IA). The benefit of spironolactone and eplerenone on mortality did not differ between patients with or without diabetes mellitus type 2 and heart failure. Monitoring of kidney function and potassium is mandatory, due to the increased risk of nephropathy in patients with diabetes mellitus [64,103].

Diuretics

These drugs are useful for the relief of dyspnea and edema in heart failure with fluid retention, irrespective of the ejection fraction, although there is no evidence of a reduction in mortality or morbidity. Loop diuretics are recommended, rather than thiazides, because of their better glycemic profile [104].

Ivabradine

The SHIFT trial, involving 6558 patients with heart failure, in sinus rhythm and with heart rate =70 bpm (3241 on ivabradine; 30% with diabetes mellitus type 2), demonstrated that ivabradine significantly reduced cardiovascular deaths and hospital admissions for worsening heart failure. The beneficial difference was similar in a pre-specified subgroup analysis of patients with and without diabetes mellitus. Finally, the presence of diabetes mellitus is not a contraindication for cardiac resynchronization therapy and/or cardiac transplantation in patients with advanced systolic heart failure. Heart failure with preserved LV ejection fraction is a primary phenotype in diabetes, and therapy to improve the prognosis of this type of heart failure is in general still under intensive investigation [105].

SELECTED HERBAL DRUGS AND NATURAL COMPOUNDS FOR DIABETIC NEUROPATHY AND CARDIOMYOPATHY

Treatment of diabetic cardiomyopathy and neuropathy is based on the general therapeutic rules of heart failure and pain respectively; therefore, further investigation studies are required for prevention and treatment of these two complex conditions. With increased significance of the two aforesaid conditions, this review has summarized the associated structural, functional and metabolic changes to provide a novel and more targeted therapies free of side effects. With this view, some lesser known, potentially strong herbal therapies for diabetic cardiomyopathy and neuropathy are illustrated. These have huge potential to improve the quality of life of patients. As the mechanisms responsible for diabetic cardiomyopathy and neuropathy continue to be elucidated, it is hoped that these insights will provide the impetus for novel therapies that reduce the risk of heart failure and debilitating pain in individuals with diabetes mellitus and are free of the hazardous side effects which currently in use medications pose to diabetic patients [106].

Flavonoids form a class of benzo-gamma pyrone derivatives that are pharmacologically very potent. Quercetin, for instance, found most abundantly among dietary flavonols, is a potent antioxidant due to its all the right structural features for free radical scavenging activity. It is evident that the flavonoids play an important role in the various types of metabolic activities of life. They have also been suggested to play a protective role in liver diseases, cataracts, and cardiovascular diseases [107].

Curcumin is known to have shown a neuroprotective effect in multiple animal models and has great potential for the prevention or treatment of age-related neuropathy arising from chronic diabetes. Curcumin, being pharmacologically safe and effective, is a potential compound for treatment and prevention of a wide spectrum of human diseases. Curcumin has been known to have a potential role in reducing serum glucose level, sciatic neuronal proteins, neuronal protein carbonyls, nociceptive, motor coordination, nerve conduction velocity, Aldose reductase COX, PG peroxidase and Na^+ K^+ ATPase activity [108].

Acacia arabica: **(Babhul)**

It is a wild growing plant, found all over India. The plant extract has an antidiabetic effect, behaving as a secretagouge stimulating the insulin release. It induces hypoglycemia in control rats but not in alloxan-treated animals. Powdered seeds of *A. arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells [109].

Aegle marmelos: **(Bengal Quince, Bel or Bilva)**

The aqueous extract of leaves of *A. marmelos* when administered to alloxanized rats, improved digestion and reduced blood sugar level, urea, and serum cholesterol, as compared to control. Along with exhibiting antidiabetic activity, this extract also prevented peak rise in blood sugar at 1h in oral glucose tolerance test [110].

Azadirachta indica: **(Neem)**

A. indica, commonly known as Neem, Nimtree, and Indian Lilac is a tree of family Meliaceae. The genus *Azadirachta* is known to have two species of which *A. indica* is native to India. The hydroalcoholic extracts of this plant showed antihyperglycemic activity in streptozotocin-induced diabetic rats, and this effect was observed due to increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm [109,110]. Apart from having anti-diabetic activity, this plant has also been reported to possess antibacterial, antimalarial, antifertility, hepatoprotective, and antioxidant properties [112].

Eugenia jambolana: **(Indian gooseberry, jamun)**

E. jambolana is used as household remedy for diabetes in India, specifically the decoction of its kernels. Hence, it forms a major constituent of

many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows hypoglycemic activity. This varies with the different level of diabetes. As found in a study by Chattopadhyay *et al.*, in mild diabetes (plasma sugar >180 mg/dl) it shows 73.51%reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) it is reduced to 55.62% and 17.72%, respectively. The extract of jamun pulp showed the hypoglycemic activity in streptozotocin-induced diabetic mice within 30 min of administration, whereas the seed of the same fruit required 24 hrs. The oral administration of the extract resulted in increased serum insulin level in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney [113].

Tinospora cordifolia: **(Guduchi)**

It is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. It is commonly known as Guduchi or Giloe. *T. cordifolia* is widely used in Indian Ayurvedic medicine for treating diabetes mellitus. Although the aqueous extract at a dose of 400 mg/kg could show a significant antihyperglycemic effect in different animal models, its effect was equivalent to only one unit/kg of insulin. It is reported that the daily administration of either alcoholic or aqueous extract of *T. cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents.

CONCLUSION

Medicinal plants are being scientifically explored once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes. *G. officinalis* is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available. However, experiment with guanidine and biguanides lead to the development of metformin. Till date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received a scientific and medical evaluation to assess their efficacy. The World Health Organization Expert Committee on Diabetes has recommended that traditional medicinal herbs be further investigated. The major hindrance in the amalgamation of herbal medicine in modern medical practices is a lack of scientific and clinical data proving their efficacy and safety. There is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation. It is also important to extract the active components from these plant extracts.

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