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Possible treatment strategies for diabetic cardiomyopathy: A phyto-and marine-based therapeutics perspective.

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Abstract

Diabetes (DM) is a leading health concern with high morbidity and mortality. Untreated DM may lead to several complications such as macro- and micro-angiopathy, and cause heart failure (HF). The present paper attempts to review the treatment strategies of diabetic cardiomyopathy (DCM) with medicinal plants and marine-derived products. The data collected from published research articles and databases. Most diabetic patients die as a consequence of HF caused due to DM-induced coronary artery disease and cardiomyopathy. Several factors are involved in the progression of cardiac dysfunction in DM-associated coronary artery disease. No single, precise prevention or therapeutic agents identified to treat DCM; therefore, a combination of strategies required for the effective management of patients with DCM. Hence, researchers are aiming on marine and nutraceutical based natural products to revolutionize DCM management. In this context, present review focuses on the treatment approaches to DCM using natural products such as medicinal plants and marine-derived products.

Keywords: Diabetic cardiomyopathy, Marine products, Medicinal Plants, Pharmacology, bioactive compounds.

Abbreviations

DM: Diabetes mellitus, **NAD–STZ**: Nicotinamide-Streptozotocin, **DCM:** Diabetic Cardiomyopathy, **IR**: Insulin Resistance, **OS**: Oxidative stress **NP:** Natural products, **MP:** Marine products, **CVD**: Cardiovascular disease, **SOD:** Superoxide dismutase, **Nrf2:** Nuclear factor erythroid 2-related factor like-2, **GLUT:** Glucose transporter.

Introduction

Diabetes mellitus (DM) is an endocrine or pancreatic β cell disease in which insulin insufficiency or insulin resistance (IR) because insulin receptors play a decisive role in its pathogenesis (Skyler et al, 2107). DM is characterised by metabolic disturbances resulting in the malfunction of the cell's ability to transport and utilise glucose (Aronson, 2008). Type 1 DM (T_1DM), previously termed insulin-dependent DM, is triggered by the T lymphocyte-mediated destruction of pancreatic β-cells by autoimmune disease, resulting in insufficient insulin synthesis and a resultant decrease in glucose consumption (Burrack, 2017). Type 2 DM (T_2DM), previously known as adult-onset diabetes, is caused due to insulin resistance (IR), which initiates compensatory β-cell hypertrophy, resulting in hyperinsulinemia and ultimately IR. Progressive decompensatory β-cell malfunction in T_2DM decreases the quantity of produced insulin (Patel, 2016). The end result is a diminished level of serum insulin, which is inadequate to overcome the developed IR. These pathophysiological changes lead to hyperglycemia, impaired pyruvate oxidation, and cellular glycolysis (Yaribeygi et al, 2019). The constant and methodical influence of hyperlipidemia, hyperglycemia, reactive oxygen species (ROS) overproduction, activation of inflammatory cytokines, and associated metabolic changes in DM affect multi-organ systems. The end result of the multi-organ injuries is the commencement of various diabetic ailments such as damage to glomeruli, liver, heart, micro and macro vascular system, blood vessels, and eyes (Kim et al, 2019; Yu et al, 2019). A range of cardiac derangements such as atherosclerosis, congestive heart failure (CHF), microangiopathy, and cardiomyopathy occur in chronic DM because of the hyperlipidaemia and hyperglycaemia associated with IR (Parim et al, 2019; Haas et al, 2018).

Diabetic cardiomyopathy is a heart muscle disorder observed in individuals with DM, which increases the risk of HF (Murtaza, 2019). DCM is mainly characterised by metabolic disorders along with local inflammation, apoptosis, myocardial fibrosis, and oxidative stress (OS), which may lead to dilated cardiomyopathy, systolic dysfunction, and ventricular hypertrophy (VH) (Jia et al, 2018; Lee et al, 2019; Dillmann, 2019). HF is a progressive disorder that is a major global health concern. The disease may progress as several attacks that may be either severe, such as AMI (acute myocardial infarction) or constant, caused by DM comorbidities such as previous AMIs, valvular heart disease, coronary artery disease, hypertension, cardiomyopathy, congenital heart defects, chronic obstructive pulmonary disease, excessive alcohol drinking, drug abuse, and genetic factors (Unnikrishnan et al, 2016, Deshpande et al, 2008; Al-Khoury et al, 2007). DCM can also be caused due to other conditions such as anaemia, abnormal heart rhythm, nephropathy, and hyperthyroidism, resulting in either damage or loss of the functioning cardiac myocytes (Thomas, 2016; Mehdi et al, 2009. This finally leads to a decrease in the functional capability of the heart. The World Health Organization anticipates that 80% of DM deaths happen in low- and middle-income nations, and that this mortality will grow 2-fold between 2016 and 2030. According to international diabetic federation reports, T2DM will rise from 422 million currently to 438 million, whereas it will increase from 51 million in 2010 to 87 million in India by 2030. (IDF, 2016; Saeedi et al, 2019). The risk of HF in in individuals with DM having cardiovascular disease (CVD) is 4 times that in nondiabetic CVD patients. DM is a lifestyle disease or the disease of the current civilisation. Patients, especially those with T_2DM, have blood pressure (BP), which contributes to the development of CVD (Grundy et al, 1999; Glovaci et al, 2019; International Hypoglycaemia Study Group, 2019). These features have an

effect on cardiac productivity and ultimately lead to HF, which is a major reason for death in patients with DM. Extensive research has exhibited that several factors play a significant role in DCM incidence and progression, whereas various experiments have demonstrated the DCM-preventive action of innate products. Therefore, it is crucial to review the research on DCM pathophysiology to identify preventive and management strategies for DCM. Thus, we have described the effectiveness of various pharmacological substances derived from medicinal plants and marine products for the treatment of DCM to gather input at cellular and molecular levels for developing a better therapeutic strategy.

Pathophysiology of DCM

DCM has a multifactorial pathophysiology. Numerous theories such as metabolic derangement, abnormalities in Ca^{2+} homeostasis, autonomic dysfunction, interstitial fibrosis, and alteration in structural proteins have been proposed (Fig. 1) (Borghetti et al, 2018). The number of proposed mechanisms for DCM pathogenesis represents the intricate nature of this disease. The metabolic milieu, categorised by hyperinsulinemia (Jia et al, 2016), hyperlipidemia (Abbate et al, 1990), and hyperglycemia (Joubert et al, 2019), in which the heart of a patient with DM functions, trigger a significant quantity of structural, functional, and cellular changes in the DM myocardial phenotype (Horowitz et al, 2010).

Conventional therapy for DCM

A specific therapy does not presently exist for DCM, but may be discovered in the future. Daily life modifications, together with exercise and diet, can decrease the occurrence of T_2DM and lead to better cardiovascular health. Moreover, drugs assisting in glycemic control such as antidiabetic drug metformin, which activates 5' AMP-activated protein kinase, offer cardiovascular assistance. AMPK plays a vital role in heart-regulating energy and metabolism equilibrium. Incretin pathway modulators such as GLP-1 agonist are cardioprotective, but they may lengthen the treatment of DCM (Sanchez-Rangel et al, 2017; Bailey, 2017). Modulators of free fatty acid metabolism (amiodarone, ranolazine, trimetazidine, and perhexiline), initially identified as antianginal drugs, may be of benefit and may reduce lipotoxicity (Horowitz et al, 2010). Ofstad et al studied HF outcomes in 38,600 patients with T_2DM associated with HF therapy and modern trials of precise glucose-lowering drugs such as angiotensin receptor-neprilysin inhibitor, angiotensin receptor blockers, β-blockers, digoxin, mineralocorticoid receptor antagonists, and ACE inhibitors in 74,351 patients (Ofstad et al, 2018). The support base for DCM management in the T_2DM patients stems mainly from subgroup analyses in HF trials and indicates the parallel enormity of favourable effect on symptoms and death as in non-diabetic populace. On the other hand, unconditional threat and event rates in patients with heart stroke and T_2DM are elevated than in nondiabetic, signalling room for momentous improvements in the management of patients with HF and T_2DM (Kokil et al, 2015).

In spite of the escalating incidence of CVD and DCM, no sufficiently effective and safe medication is currently available in the market, and they have considerable side effects (Fang et al, 2004; Marwick et al, 2018). Some of these medications have been withdrawn from the market due to their adverse effects. In spite of the numerous pharmacological agents available to practitioners, they are doubtful of the fundamental aetiology of DM, particularly, IR and the decrease of pancreatic β-cell function. The death rates of the disease are worrying, with DM and its associated DCM causing twelve death every minute. Although the number and

class of oral antidiabetic agents endorsed for human use in T_2DM have grown considerably over the past twenty years, these drugs, which are mostly used to realise and maintain euglycaemic levels, have been unable to achieve the required clinical quality levels. This is exacerbated by their partial effectiveness, which translates to lowering glycaemic control exposing the patients to a broad range of micro- or macro-vascular complications, eventually leading to early death. Because of severe associated side effects, there is a rising shift to plant-and marine product-based drugs. Nutraceutical interventions and nature-based remedies belonging to the native systems of medicine are more attractive for treating DM and DCM, which are the major causes for HF. As medicinal plants and marine products appear to be the alternative medications and formulations, researchers are trying to isolate bioactive active compounds to develop a superior strategy for the prevention and treatment of Diabetic cardiomyopathy (Tian et al, 2017; Salehi et al, 2019).

Treatment of DCM with medicinal plants

The medicine obtained from thyme and its formulations are usually considered to be free from side effects and less toxic. Antidiabetic plants exploited in conventional medication can be a useful source of novel oral hypoglycaemic compounds, which may be evaluated as simple nutritional adjuvants to existing strategies. Such studies facilitate the development of natural antidiabetic drugs in the future. Ethnopharmacologically, more than 1000 taxa of organisms have been used to experimentally replicate the symptoms of DM. This list phylogenetically extends from oceanic fungi and algae to higher plants. The large number of taxa reportedly used experimentally or conventionally for the treatment of DM may be coincidental (Shukia et al, 2007; Salehi et al, 2019).

Sesbania grandiflora

Ghanshyam et al. demonstrated the antihyperglycemic potential of *S. grandiflora* (Fabaceae) leaves (400 mg/kg BW) in glucose-induced hyperglycemic rats. Nandi et al. observed the hypoglycaemic activity in its fruit (400 mg/kg BW) extract, which significantly reduced the levels of blood glucose, triglyceride, cholesterol, low-density lipoprotein (LDL), lipid peroxidation, and catalase, and noticeably improved the levels of superoxide dismutase (Mund et al, 2017). Sangeetha et al. demonstrated the antidiabetic activity of *S. grandiflora* leaves (300 mg/kg BW) in streptozotocin (STZ)-induced DM rats, which restored all the biochemical parameters such as glucose, blood urea nitrogen, glycated haemoglobin, creatinine, uric acid, aspartate, alkaline phosphatase, alanine transaminase, and glycogen content. Hence, *S. grandiflora* has noteworthy antilipidemic, antioxidant, and hypoglycaemic efficiency that might alleviate DCM (Sangeetha et al, 2014; Prasanna et al, 2018).

Terminalia chebula

The desiccated ripe fruit of *T. chebula* Retz (Combretaceae) is used comprehensively in Ayurveda and is found extensively all over India, Burma, and Sri Lanka. An herbal combination enclosing *T. chebula* under the name Triphala is an extremely well known conventional drug in the management of DM comorbidities. The chloroform extract of *T. chebula* seeds exhibits dose-dependent (100, 200, and 300 mg/kg BW) decrease in the blood glucose of rats with DM similar to that of the control drug, glibenclamide, in a pilot study (Nalamolu et al, 2006). It also exhibited a considerable decrease in blood glucose in an enduring study. The study shows long-lasting decrease in blood glucose by *T. chebula* and is perhaps arbitrated through improved emission of insulin from the β-cells or through extrapancreatic mechanism (Nalamolu et al, 2006; Sasidharan et al, 2012). Chebulagic acid extracted from *T. chebula* considerably condensed the postprandial blood glucose altitude in maltose-loaded SD rats. It may also help in restraining gluttonous hyperglycemia as a powerful antidiabetic mediator (Huang et al, 2012).

Brucea javanica

B. javanica (Simaroubaceae) originates in tropical Asia and Africa and is most frequently grown in the Malaya Peninsula (Liu et al, 2009). Its seeds exhibit a hypoglycaemic effect in both nondiabetic and STZ-provoked DM rats at lesser dose (1 mg/kg BW) during a 0–8 h screening (NoorShahida et al, 2009). Ablat et al reported the antioxidant and antidiabetic effects of the ethyl acetate portion of *B. javanica* seeds (25 and 50 mg/kg/day BW) on rats with nicotinamide (NAD)–STZ-induced T_2DM and its chemical composition associated with its pharmacological activities (Ablat et al, 2017). Chromatographic isolation of the *B. javanica* seeds of the ethyl acetate fraction demonstrated the presence of gallic acid, parahydroxybenzoic acid, bruceine D and E, vanillic acid, luteolin, and protocatechuic acid. These compounds demonstrate its prospective therapeutic property in the treatment of T_2DM acting as α-glucosidase and GP-α inhibitors by recovering carbohydrate metabolism and hepatic glucose, reducing OS, and warding off of inflammation in T_2DM rats.

Momordica charantia

Momordica charantia (Cucurbitaceae) is grown in humid countries in Asia and Africa. Its juice exerts a variable hypoglycaemic effect in experimental T_1DM and human T_2DM. Ahmed et al exhibit the therapeutic effect of its juice (10 mL/kg body weight) in the management of DM (Ahmed et al, 2004). The juice can reduce blood glucose level, repair and regenerate the islets of Langerhans, increase the glucose intake into brush border membrane vesicles, excite glucose uptake into cells of skeletal muscle, and prevent the reduction of myelinated fibre size in experimental DM. Assuming that these animal studies can be extended to humans, *M. charantia* administration may be used as an adjunct therapy to condense the dosage of insulin or oral hypoglycaemic agents in the management of DM and its complications. Mahmoud et al. demonstrated the antihyperlipidaemic effect of *M. charantia* by escalating insulin discharge, which inhibited lipoprotein lipase and averted lipolysis, suggesting that this functional food has high antioxidant activity and a defensive function in reducing OS accompanied by DM and its complications (Mahmoud et al, 2017; Malekshahi et al, 2019; Peter et al, 2019).

Withania somnifera

W. somnifera Dunal (Solanaceae) is one of the most valuable plants in conventional Indian Ayurvedic system. It is utilised in more than 100 formulations in Ayurveda, Siddha, and Unani, and therapeutically corresponds to ginseng (Tripathi et al, 2018; Lim et al, 2018). Udayakumar et al. investigated the hypolipidaemic and hypoglycaemic effects of its leaf and root extracts on alloxan-induced DM in rats by orally supplementing them to DM rats every day for 45 days. The levels of blood glucose, urine sugar, glycated haemoglobin, glucose-6-phosphate, aspartate aminotransferase, alanine aminotransferase, serum lipids with the exclusion of high density lipoprotein (HDL-C), and lipids in tissues such as kidney, heart, and liver, were considerably increased, whereas haemoglobin, albumin, albumin:globulin ratio, total protein, glycogen, and tissue protein were notably decreased in rats with alloxan-induced DM. *W. somnifera* extracts restored the parameters to their regular levels after 45 days of supplementation in rats with DM, signifying that *W. somnifera* leaf and root extracts have hypolipidaemic and hypoglycaemic effects in rats with alloxan-induced DM (Udayakumar et al, 2009).

Mohanty et al. assessed the cardioprotective mechanisms of *W. somnifera* in ischaemia and reperfusion injury. Pretreatment with *W. somnifera* constructively restored the myocardial antioxidant equilibrium, exerted marked antiapoptotic effects, and reduced myocardial damage, as confirmed by histopathological assessment (Mohanty et al, 2008). Therefore, *W. somnifera* has cardioprotective antiapoptotic and antioxidant properties. *W. somnifera* extract and a viable polyherbal formulated product including atenolol (CardiPro®) capsules offer cardioprotection against doxorubicin-linked cardiotoxicity, as evidenced by lower mortality, increased hypolipidemic, and antioxidant action (Mohan et al, 2006; Visavadiya et al, 2007). Additionally, *W. somnifera* has profound hypocholesteremic, hypolipidemic, and antiatherogenic activities. Mary et al. established the antiatherogenic activity of CapsHT2, a botanical medicine consisting of numerous plants together with *W. somnifera* against atherogenesis and vascular intimal damage, which leads to various types of CVDs. This formulation altered the atherogenic index, reduced the body weight of rats, and increased the HDL-C levels in hyperlipidemic rats (Mary et al, 2003).

Allium sativum (Garlic) and Aged Garlic

A. sativum (Amaryllidaceae) is a variety of onion species and is endemic to Central Asia. It has long been a recurrent seasoning worldwide, with it being used for human utilisation and as a food ingredient since centuries (Thomson et al, 2003). Consumption of *A. sativum* and its constituents has been known to have numerous benefits together with antilipidemic and antidiabetic properties (Choudhary et al, 2018). The antihyperglycaemic activity of garlic is well known in assorted animal models of DM. The effectiveness of crude garlic in lowering hyperglycemia and in treating cardiac complications in T_2DM is well known. Garlic supplementation improves the myocardial Nrf2 and amplified myocardial Mn-superoxide dismutase expression, and enhances the myocardial glutathione peroxidase, superoxide dismutase, catalase activity, and glutathione levels. Effects of garlic on Nrf2, keap1, and endogenous antioxidants after garlic supplementation in fructose-fed rats may account for the reduction in OS and cardiac hypertrophy. Supplementation of raw

garlic homogenate in rats with T_2DM stimulated myocardial Nrf2 through H_2S and PI3K/AKT pathway, thus preventing DCM (Padiya et al, 2013; Sun et al, 2009).

Among several obtainable garlic preparations, aged garlic extract has a distinctive mechanism to concentrate the enhanced water soluble cysteinyl moieties and has no toxic side effects. Sun et al. reported that aged garlic extract develops the expression of both the glutamate–cysteine ligase modifier and the heme oxygenase-1 (HO-1) gene in human umbilical vein endothelial cells. Allicin and diallyl sulfide, the active constituents of raw garlic, activate Nrf2 and increase HO-1 and NQO1expression through the ERK/p38 pathway. Aged garlic extract contains water soluble sulfur-containing compounds, such as S-allyl mercaptocysteine and S-allycysteine. Garlic and its preparations are widely known as advantageous dietary agents in the treatment of DCM (Khatua et al, 2013; Sathibabu Uddandrao, V. V. et al, 2018).

Syzygium cumini

S. cumini (Myrtaceae) is a renowned Indian therapeutic plant with several curative properties and is utilised in treating DM (Helmstädter, 2008; Chhikara et al, 2018). Atale et al. studied the cardioprotective activities of the methanolic seed extract of *S. cumini* (1 mg/mL) in diabetic *in vitro* conditions (Atale et al, 2013). Its ROS scavenging activity was examined in glucose-stressed H9C2 cardiac myoblasts after optimising the harmless dose of glucose and *S. cumini* by 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide. 20,70-dichlorfluorescein diacetate staining and fluorescence-activated cell sorting analysis established the inhibition of ROS production by *S. cumini* in glucose-induced cells. The present study confirmed the dual protective role of *S. cumini* seeds, which exert a cardioprotective action by reducing ROS production, and prevent increase in extracellular matrix components and cell size in hyperglycaemic condition. A model can therefore be proposed that a raise in OS due to ROS consequences in myocardial remodelling and increase in overall collagen content in DCM. *S. cumini* has the capability to considerably reduce ROS-mediated events, minimising glucose-mediated cardiac stress. Neha et al. have demonstrated that *S. cumini* and silver nanoparticles (20 μg/mL) have synergistic antioxidant properties that can protect the cardiac cells against glucose stress in glucose-stressed H9C2 cardiac cells on the basis of their capability to hunt free radicals, restrain lipid peroxide formation, and preserve nuclear and cellular reliability against glucose stress (Atale et al, 2016).

Trigonella foenum-graecum

T. foenum-graecum (Fabaceae), generally known as fenugreek, the leaf and seed extracts of which are a widely used plant sources of antidiabetic compounds. Basic animal experiments and human trials demonstrate the potential antihyperlipidaemic and hypoglycaemic properties of fenugreek seed powder taken orally (Zameer et al, 2018). In humans, its seeds exhibited a hypoglycaemic effect by stimulating glucose-dependent insulin secretion from pancreatic β-cells and inhibiting sucrose and α-amylase activities. Fenugreek seeds also lower total serum cholesterol, triglycerides, and LDL cholesterol. These effects may be due to sapogenins, which increase biliary cholesterol emission in liver, leading to poorer serum cholesterol levels (Hamden et al, 2010; Mohammad et al, 2006).

Siddiqui et al. confirmed that Glut-4 protein considerably reduced the total membrane fractions of cardiac muscle of rats with alloxan-induced DM. As glucose transport in cardiac muscle occurs mostly through Glut-4, the decrease in Glut-4 level results in decreased uptake of glucose and consequently contributes to raised

blood glucose levels in DM conditions. Similar results were also attained from brain and skeletal muscle (Siddiqui et al, 2006). Puri et al isolated a bioactive compound from fenugreek with hypoglycaemic properties. They demonstrated considerable attenuation of the glucose tolerance curve and improvement in glucose-induced insulin response in rabbits with DM, suggesting that the hypoglycaemic effect intercedes through stimulating insulin-producing β-cells of the Islets of Langerhans (Puri et al, 2002).

Nigella sativa

N. sativa (Ranunculaceae) and propolis are among the innate sources to have beneficial effects such as anti-inflammatory, cardiovascular, antidiabetic, and antihypertensive effects (Hamdan et al, 2019). Kanter et al proved the hypoglycaemic effect of *N. sativa* extracts. *N. sativa*-fixed oil is rich in unsaturated fatty acids, eicosenoic acid, and linoleic acids, which have antioxidant and lipid-lowering activity (Kanter et al, 2003). It is a reservoir of large quantitites of α-tocopherol, β-tocopherol, polyphenols, selenium, γ-tocopherol, and phytosterols such as 5-avenasterol, 7-avenasterol, and β-sitosterol, and minute quantities of campesterol and stigmasterol, which account for its antidiabetic activity (Zuchi et al, 2010). Meral et al observed the hypoglycaemic effect of *N. sativa,* in which the blood glucose was significantly reduced in rats with DM supplemented with its extract as compared with the control (Meral et al, 2001). Idris-Khodja and Schini-Kerth et al, have demonstrated that thymoquinone extracted from *N. sativa* enhanced endothelial function through normalisation of the angiotensin system and inhibition of the OS (Idris-Khodja et al, 2012).

Gynostemma pentaphyllum

G. pentaphyllum is an herbaceous, dioecious climbing vine of the genus Gynostemma belonging to the family Cucurbitaceae (Li et al, 2019). Gao et al. evaluated the antidiabetic activity of its saponins, providing substantiation in *G. pentaphyllum* saponin (200 and 400 mg/kg body weight) application to regulate hypolipidaemia and hypoglycaemia. The antioxidant effect of *G. pentaphyllum* saponins was established by the stimulation of the Nrf2 antioxidant pathway to raise the enzyme activities of superoxide dismutase (SOD) and GPx, decrease malondialdehyde (MDA) content, and encourage insulin secretion, thus eliminating ROS. Consequently,

G. pentaphyllum saponins might be applied as an efficient antioxidative compound and provide prospective novel restorative approaches for DM and its associated complications (Gao et al, 2016).

Houttuynia cordata

H. cordata (Saururaceae) is often used as a therapeutic plant in Asian countries. Kumar et al.exhibited that ethanol extract prepared from the whole plant of *H. cordata* (1% or 2%) had a hypoglycaemic effect in mice with DM through the elevation of glucose transporters and antioxidant activity (Kumar et al, 2014). Hsu et al. evaluated the antioxidative and antiglycative effects of the aqueous extract of *H. cordata* leaves in the heart of the mice with DM, confirming that *H. cordata* intake preserved plasma insulin and lowered glucose levels. *H. cordata* concentrated ROS, N^{ε}-(carboxymethyl)-lysine, IL-6, TNF-α, protein carbonyl, fructose and pentosidine levels, and standoffish glutathione content in the heart. DM improved aldose reductase activity and protein expression in the heart. *H. cordata* intake decreased renal aldose reductase activity and protein expression. DM increased protein expression of p47phox, gp91phox, RAGE, NF-κB p50, NF-κB p65, and MAPK, whereas *H. cordata* intake downregulated the expression of NF-κB p65, p-p38, and p47phox in the

heart. This study accomplished that *H. cordata* leaves extract ingestion attenuated oxidative, glycative, and inflammatory stress in the heart of mice with DM through mediating RAGE, aldose reductase, NADPH oxidase, MAPK, and NF-κB. These results recommend that the extract of *H. cordata* may alleviate DCM (Hsu et al, 2017).

Carica papaya

C. papaya (Caricaceae) is extensively cultivated for its edible fruit, and its leaf methanol extract has displayed antioxidant and vasodilating properties, both associated with CVD management (Jarisarapurin et al, 2019). Runnie et al. assessed the antihyperglycaemic effect of the aqueous extract of *C. papaya* leaves (0.75, 1.5, and 3 g/100 mL) in rats with DM and observed a notable decrease in the blood glucose, triacylglycerol, cholesterol, and aminotransferase levels in the blood (Runnie et al, 2004). Low plasma insulin levels did not change after treatment in rats with DM; however, they increased considerably in nondiabetic animals. Pancreatic islet cells were normal in nondiabetic treated animals, whereas in rats with DM, *C. papaya* helped in islet regeneration manifested as cell size conservation. In the liver of treated rats with DM, *C. papaya* prevented hepatocyte distraction and lipids and glycogen accumulation, and exhibited an antioxidant effect in rats with DM. The findings of this study concluded that the aqueous extract of *C. papaya* could restore the metabolic disturbance caused by DM (Juárez-Rojop et al, 2012).

Terminalia arjuna

T. arjuna (Combretaceae) is a therapeutic plant extensively used to treat several diseases. Its bark is widely used in the management of hypercholesterolemia (Amalraj et al, 2016). Arjunolic acid offers considerable cardiac protection in myocardial necrosis and chronic HF in rats (Praveen et al, 2011). Khaliq et al. examined the benefits of *T. arjuna* bark extract (500 mg/kg BW) in improving the cardiovascular autonomic neuropathy in STZ-induced DM in rats. After 8 weeks of STZ administration, the responses of reflex tachycardia and bradycardia to hypotension and hypertension, respectively, were impaired in the DM group. The impulse bradycardia resolved considerably after treatment with *T. arjuna* for 30 days, whereas the reflex tachycardia did not improve. Further, it extensively reduced inflammatory cytokine levels and OS in rats with DM. Therefore, the study confirmed that oral supplementation of the *T. arjuna* bark extract enhanced the cardiovascular autonomic neuropathy in rats having unrestrained DM probably by decreasing cytokine levels and maintaining endogenous antioxidant enzyme activities (Khaliq et al, 2013).

Piper longum

P. longum belongs to Piperaceae family (Salehi et al, 2019). Nabi et al. evaluated the hypoglycaemic and hypolipidaemic effects of its root aqueous extract in STZ-provoked DM rats. The extract was established to have noteworthy antihyperglycaemic action at a quantity of 200 mg/kg BW subsequent to 6 h of administration in this short-term study. The administration of *P. longum* at the same dose for one month in rats with STZ-induced DM resulted in a higher reduction in fasting blood glucose levels and DM-induced dyslipidaemia compared with untreated rats with DM. There was a greater reduction in the activities of renal and liver functional markers in treated rats with DM compared with untreated ones, indicating the protective role of *P. longum* against kidney and liver damage and its nontoxic property. Thus, *P. longum* extract is capable of managing DM and its complications, presenting as a possible source for novel oral hypoglycaemic agents.

Thus, the therapeutic efficacies of *P. longum* are particularly useful in the management of DM and hepatic, renal, and cardiovascular diseases (Nabi et al, 2013).

Otostegia integrifolia

O. integrifolia, belonging to the Lamiaceae family is a globally widespread innate antioxidant that can be utilised as a health-promoting mediator for different disorders such as DM (Chekol et al, 2018). Shewamene et al. demonstrated its noteworthy antidiabetic, hypoglycaemic, and oral glucose tolerance-enhancing effects in rodents when treated with the dosages of 100, 200, and 400 mg/kg body weight (Shewamene et al, 2015).

Psidium guajava

P. guajava L., commonly known as Guava, belongs to the Myristaceae family. Sowmya et al. investigated the antiglycative and antioxidant prospective of the ethyl acetate fraction of *P. guajava* leaves (25, 50, 100 mg/kg BW) (Soman et al, 2010). Oral supplementation of the *P. guajava* extract in various doses demonstrated a considerable reduction in blood glucose level and an enhanced antioxidant property as supported by reduced lipid peroxidation and a considerable increase in the activities of various antioxidant enzymes such as SOD, GPx, glutathione, and catalase. Indicators of glycation such as HbA1 and fructosamine were also reduced considerably in *P. guajava*-administered groups when compared with the DM control group. Therefore, this study concluded that *P. guajava* leaves held powerful antiglycative and antioxidant properties against rats with DM in a dose-dependent way, which supports the utilisation of *P. guajava* both as a food source and for the management of DM and its associated complications (Díaz-de-Cerio et al, 2017).

Marine products

Because of its exceptional variety, the marine world is a source of several biologically active compounds such as proteins, sterols, polysaccharides, pigments, polyunsaturated fatty acids, and antioxidants. Several marine organisms live in habitats open to harsh circumstances generate an extensive range of biologically active metabolites to adapt to these surroundings. Furthermore, considering the great taxonomic diversity, fresh bioactive compounds from aquatic habitats are researched for applications in numerous fields. Marine-based bioactive products can be obtained from sources such as marine microorganisms, sponges, and plants, all of which hold their own unique set of biomolecules. Naturally occurring bioactive substances have a distinct health advantages in dietary research (Sharifuddin et al, 2015; Lordan et al, 2011).

Macrocystis angustifolia

Macrocystis species belong to Laminariaceae and are kelps that form widespread beds with large floating canopies below low intertidal regions. Rengasamy et al. explored the restrictive effects of a crude 80% methanol extract, solvent fractions, and isolated compounds from the kelp *M. angustifolia* against enzymes involved in T_2DM (Rengasamy et al, 2014). The crude extract from *M. angustifolia* had two phenol derivatives as its bioactive constituents from the ethyl acetate soluble fraction. The isolated compounds, such as 4-(2-hydroxyethyl) phenol (tyrosol) and 4-(1,2-dihydroxyethyl) phenol were reported for the first time in marine algae. The crude methanol extract, three solvent fractions, and its isolated compounds were tested for their enzyme inhibitory effect against α-glucosidase and acetylcholinesterase. Ethyl acetate and butanol fractions exhibited potent activity against α-glucosidase and acetylcholinesterase inhibitory

activities, respectively. The inhibitory activities of the isolated compounds were lower than those of the therapeutic drugs acarbose (IC_{50} = 122.9 μM) for α-glucosidase and galanthamine (IC_{50} = 0.33 μM) for acetylcholinesterase. However, the data indicated the potential of these compounds as inhibitors of α-glucosidase and acetylcholinesterase enzymes. The experimental results were further confirmed by bioactivity screening of the prediction of activity spectra of substances. These two compounds have a higher oral bioavailability than the oral hypoglycaemic drug, acarbose, in accordance with the Lipinski's Rule of Five without any toxicity risks. Thus, *M. angustifolia* as a dietary supplement could be a safe addition to traditional remedies to prevent and treat DM and its associated complications.

Chitin and Chitosan

Crustacean shells and shell fish wastes constitute byproducts released during the processing of seafood. Chitin is one of the chief structural components of these byproducts and has been studied in detail for its diverse physiological and biological activities. Crustacean shells are major sources of chitin and an impending source for chitosan and other oligomers, which are hydrolysed derivatives of chitin (Muanprasat et al, 2017). Liu et al. investigated the potential mechanisms of the antihyperglycaemic activity of chitosan in rats with STZ-induced DM, demonstrating that both high- and low-molecular weight chitosan noticeably lowered the fructosamine and blood glucose levels, and the liver weight in rats with STZ-provoked T_1DM. Both types of chitosans could also successfully activate AMP-activated kinase phosphorylation, increase glycogen content, overturn the increase in DM liver phosphor enolpyruvate carboxykinase and phospho-p38 protein expressions, and reverse the decrease in diabetic skeletal muscle Glut-4 translocation and AKT protein phosphorylation. These findings suggest that chitosan possesses a potential to cure T_1DM by decreasing liver gluconeogenesis and increase skeletal muscle glucose utilisation (Liu et al, 2010).

Sinularia firma* and *Sinularia erecta

Soft corals of the genus *Sinularia* belong to the Coelenterata phylum and are usually found in India. They are a rich source of organically active and structurally distinctive secondary metabolites. The methanolic extracts of *S. firma* and *S. erecta* (250 mg/kg BW) demonstrated antihyperglycaemic activities against rats with STZ-induced DM. Their antidiabetic effect may be due to the occurrence of more than one hypoglycaemic principle and their interactive properties (Tamrakar et al, 2007).

Marine Peptides

Peptides isolated from different seafood hydrolysates are rich in biological properties such as antioxidative, antithrombotic, immunomodulatory, and antihypertensive activities. New studies are adding additional value to the utilisation of seafood waste for bioactive peptide isolation. A number of fish protein hydrolysates have glucose uptake-stimulating properties, which provide a different perspective to DM treatment (Gogineni et al, 2018). Zhu et al. also reported that fish collagen-derived peptides improved insulin sensitivity and consequently, glucose metabolism in T_2DM patients. The oral supplementation of these peptides is strongly connected to serum-level changes in three DM-related hormones; adiponectin, leptin, and resistin. Correspondingly, ACE inhibitor peptides in sardine protein hydrolysates restrain rising blood glucose levels with enhanced glucose metabolism (Zhu et al, 2010).

Marine Cryptides

Autelitano et al. defined cryptic peptides as bioactive peptides concealed within the chain of a parent protein. The release of these peptides is common in proteins associated with endocrine signalling and ECM (Autelitano et al, 2006; Giri et al, 2012). A number of marine cryptides have previously been isolated by the hydrolysis of fish protein from skin, frame, and muscle. Crustaceans and shellfish contain crypteins, proteins capable of releasing cryptides, which demonstrate antiplatelet and anticoagulant properties *in vitro*, signifying potential interactions with coagulation factors. Persuasive antioxidant activities have also been identified in addition to immunostimulatory effects. Marine cryptides also have antihypertensive activity, inhibiting the action of ACE sometimes to a greater extent than other natural peptides from earthly sources. These cryptides lower BP in humans and hypertensive rats (Kim et al, 2010). Peptides derived from marine sources may control BP through mechanisms other than the well-known ACE inhibition. The release of vasodilatory substances such as nitric oxide, carbonic oxide, and prostaglandin I2 can also contribute to the BP-lowering effects of various ACE-inhibitory peptides (Najafian et al, 2012; Erdmann et al, 2008).

Marine mollusc, waste, and crustacean protein hydrolysates enclose antioxidant peptides that may deter oxidation-related damages. Other peptides possess hypoglycaemic properties exerted through glucose uptake modulation and insulin sensitivity. Further studies exhibited that the cellular mechanisms of the nutritional cod protein restored insulin-induced activation of phosphatidylinositol 3-kinase/AKT and Glut-4 translocation to T-tubules in the skeletal muscle of high-fat diet-induced obese rats. The favourable aspects of salmon skins were assessed using a rat model of T_2DM. Zhu et al. studied the β-cell dysfunctions, which are a vital characteristic of T_2DM (Zhu et al, 2010). Oligopeptides from marine salmon skin considerably decrease fasting blood glucose levels and the frequency of β-cell apoptosis in the pancreatic islet. Furthermore, the effect may be arbitrated by the downregulation of T_2DM-related inflammation and OS. A treatment based on marine peptides from wild fish meat hydrolysed by pancreatic lipase, trypsin, chymotrypsin, and pepsin was administered to Chinese patients with T_2DM. On the other hand, marine fish hydrolysate treatment enhanced lipid and glucose metabolism in DM and in patients with DM and hypertension (Zhu et al, 2010)

Lamellodysidea herbacea

Yamazaki et al. evaluated the outcome of ethanol extort of an Indonesian marine sponge, *L. herbacea* (Dysideidae), and found it inhibiting the protein tyrosine phosphatase 1B (PTP1B), a central objective enzyme in the management of T_2DM. This study proved that bromodiphenyl ether is a powerful inhibitor of PTP1B and that the methoxy derivative is more helpful than the original phenol and ester derivatives. The compound methoxy derivative will be a novel lead compound for PTP1B inhibitors (Yamazaki et al, 2013).

Marine oil

Marine oils are major seafood derivatives extracted from waste fish internal organs, muscle, and shellfish remnants using numerous techniques, varying from steam stripping to solvent extraction to release lipids; these lipids are unbalanced and need low-temperature methods to preserve them. Marine oils are primarily formed by docosahexaenoic acid and eicosapentaenoic acid, which are normally classified as omega-3 fatty acids of polyunsaturated fatty acids. Studies demonstrate that the beneficial effects of seafood are predominantly due

to its polyunsaturated fatty acids. As a dietary constituent, polyunsaturated fatty acids have some cardiac benefits to patients with T_2DM and obese patients (Djoussé et al, 2011).

Brown algae-derived phlorotannins

Marine algae are plentiful and well-liked food ingredients mostly in Asia and are also acknowledged for their medicinal benefits due to the presence of biologically active compounds such as phlorotannins and marine polyphenols. Among marine algae, brown algae have been widely examined for their prospective antidiabetic properties. Research on brown algae-derived phlorotannins exhibit assorted antidiabetic mechanisms such as α-amylase and α-glucosidase restrictive effect, glucose intake effect in skeletal muscle, PTP1B enzyme inhibition, enhancement of insulin sensitivity, and defence mechanism against DM complication (Lee et al, 2013).

Marine algal polyphenol, dieckol

Dieckol is one of the chief compounds among the polyphenols (Phlorofucofuroeckol-A, phloroglucinol, 6, 6-bieckol, 7-Phloroekol, dieckol) of *Ecklonia cava* (Wijesinghe et al, 2011; Gunathilaka et al, 2020). Eun et al reported the antidiabetic activity of dieckol in zebra fish model. In this study, the administration of dieckol in the liver tissues and augmented phosporylation of protein kinase B in the muscle tissue of zebra fish exhibited suppressed blood glucose levels and reduced glucose-6-phosphate and phosphoenolpyruvate carboxykinase. Protein kinase B activation is related with arbitrating the effect of dieckol on insulin sensitivity and glucose transport activation. These data suggest that dieckol exerts a potential antidiabetic efficacy by ensuring hepatic glucose metabolic and blood glucose regulation, and protein kinase B upregulation in alloxan-induced DM in zebra fish (Eun et al, 2016).

Octaphlorethol-A

Octaphlorethol-A is a type of phlorotannin and one of the most active compounds in *Ishige foliacea.* It has been investigated as a possible antidiabetic agent because it manipulated glucose uptake in skeletal muscle cells (Lee et al, 2012). Another study demonstrated that it cured postprandial hyperglycemia in mice with STZ-induced DM (Lee et al, 2014). On the other hand, Lee et al. exposed that octaphlorethol-A has the ability to improve T_2DM. Octaphlorethol-A exhibited therapeutic effects on DM by treating hyperinsulinemia and altered glucose acceptance in T_2DM *db/db* mice. The mechanism of octaphlorethol-A involves rise in Glut-4-mediated glucose utilisation through activation of 5' AMPK in the muscle. Additionally, octaphlorethol-A attenuated hepatic gluconeogenesis in T_2DM *db/db* mice by inhibiting glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity. Thus, this study shows that octaphlorethol-A is a potential antidiabetic agent capable of treating DM and its associated complications (Lee et al, 2016).

Fucoidan-A

Fucoidans are intricate and assorted sulphated polysaccharides habitually available in brown seaweed. Vinoth et al. observed an excellent α-d-glucosidase restrictive effect in fucoidan isolated from *Sargassum wightii* collected from India, probably offering a mechanism to control the postprandial hyperglycaemia in diabetic patients. Fucoidan maintains the assimilation of nutritional carbohydrates in the intestine and controls blood glucose level after food. Therefore, the fucoidan from *S. wightii* may be made as a therapeutic agent for DM and its complications (Vinoth Kumar et al, 2015).

Ishige okamurae

The brown algae *I. okamurae* (Ishigeaceae) is found in temperate coastal zone areas such as the Korean peninsula. It is well-liked in both Japan and Korea as a food element and folk medicine. Several researchers have suggested the numerous biological advantages of its extract, together with antioxidant effects in free radical-mediated oxidative systems (Zou et al, 2008). Min et al. examined the effect of the *I. okamurae* extract on blood glucose level and IR in C57BL/-KsJ-db/db mice. The fasting blood glucose level and IR were improved, and the HbA1 levels were lowered in the *I. okamurae*-treated group as compared with those in the DM control group. Furthermore, *I. okamurae* extract administration improved glucokinase activity; conversely, the phosphoenolpyruvate carboxykinase and glucose-6-phosphatase activities were considerably lower in the *I. okamurae* extract-treated group of mice than in the DM control. These findings suggest that the *I. okamurae* extract addition in the food may lower the blood glucose level and improve IR. Thus, *I. okamurae* extract supplement has benefits in T_2DM, signifying that it can be used as an antidiabetic supplement (Min et al, 2011).

Capsosiphon fulvescens

C. fulvescens (Ulotrichaceae) is a green alga commonly found in the coastal areas of Korea, Europe, and North America (Synytsya et al, 2015). Islam et al. studied the aldose reductase inhibitory effects of *C. fulvescens* (50µg/mL) using rat lens aldose reductase (RLAR) inhibitory assay. *C. fulvescens* and its different solvent-soluble fractions demonstrated prospective AGE formation and RLAR restrictive activities. The chalinasterol, capsofulvesin A, and capsofulvesin B compounds extracted from *C. fulvescens* exhibited a strong RLAR inhibitory activity. This study clearly demonstrated the prospective therapeutic and prophylactic effects of *C. fulvescens* on DM complications. However, further broad biological experiments must be carried out to completely appraise its benefits as a novel antidiabetic mediator and study the mode of action of the active compounds (Islam et al 2014).

Conclusions

The present review proves that DCM is a multifaceted complication and an assortment of mechanisms account for the progression of HF in chronic DM. Epidemiologic studies suggest that the natural history of DCM starts with hyperglycaemia and probably takes years to reach overt diastolic or systolic dysfunction. DM patients are at a significant risk of HF, whether from DM alone or from a mixture of some cardiovascular risks is unknown. Thus, cardiometabolic preclusion, concentrating on hypertension, dysglycaemia, and dyslipidaemia should form the foundation in the management of such high-risk patients. Further study of the mechanisms underlying the structural and functional complications in the DM heart will indisputably aid the development of more accurate medicines for DCM management. Therefore, a combination treatment with diverse interventions might be helpful for the treatment of HF in DCM. There is a scanty of clinical intervention trials, particularly in DCM patients; hence, no evidence-based interventions can be suggested to treat it.

However, medicinal plants with associated benefits could be studied as adjunctive or substitute herbal formulations/compounds for the prevention or treatment of DM and DCM. The effects of natural products on DM must also be studied in more detail to attain scientific evidence on the pharmacological and biological effects of these products. There are a scanty of reports are available antidiabetic effects of medicinal plants and

marine-derived products at preclinical and clinical level on to prevent and manage DM and DCM. Natural products have immense potential as therapeutic agents to be feasible functional foods or nutraceuticals for alternative and complementary DM therapy. The data available on the antidiabetic effect of plants and marine-derived products discussed here can be used for further research or to conduct clinical trials to ensure beneficial effect, bioavailability, absorption, toxicity, dose, and their mode of action for the proper treatment of DM and its associated DCM without any adverse effects.

Declaration of competing interest

There is no potential conflict of interest from the authors.

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Figure legend

Fig 1: Multifactorial hypotheses of pathophysiologic mechanisms of DCM.