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Lanosteryl triterpenes from *Protorhus longifolia* as a cardioprotective agent: a mini review

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Abstract
The epidemic of cardiovascular diseases is a global phenomenon that is exaggerated by the growing prevalence of diabetes mellitus. Coronary artery disease and diabetic cardiomyopathy are the major cardiovascular complications responsible for exacerbated myocardial infarction in diabetic individuals. Increasing research has identified hyperglycemia and hyperlipidemia as key factors driving the augmentation of oxidative stress and a pro-inflammatory response that usually results in increased fibrosis and reduced cardiac efficiency. While current antidiabetic agents remain active in attenuating diabetes-associated complications, overtime, their efficacy proves limited in protecting the hearts of diabetic individuals. This has led to a considerable increase in the number of natural products that are screened for their antidiabetic and cardioprotective properties. These natural products may present essential ameliorative properties relevant to their use as a monotherapy or as an adjunct to current drug agents in combating diabetes and its associated cardiovascular complications. Recent findings have suggested that triterpenes isolated from *Protorhus longifolia* (Benrh.) Engl., a plant species endemic to Southern Africa, display strong antioxidant and antidiabetic properties that may potentially protect against diabetes-induced cardiovascular complications. Thus, in addition to discussing the pathophysiology associated with diabetes-induced cardiovascular injury, available evidence pertaining to the cardiovascular protective potential of lanosteryl triterpenes from *Protorhus longifolia* will be discussed.

Keywords Cardiovascular diseases · Diabetic cardiomyopathy · Diabetes · *Protorhus longifolia* · Triterpenes

Introduction

The medicinal usage of herbal derivatives as pharmaceutical products has been the major focus of an increasing number of investigations, with the aim of reducing the burden of non-communicable diseases through prophylactic and therapeutic interventions. For thousands of years, our ancestors have relied on herbal medicine, also known as phytomedicine, to treat diseases such as diabetes mellitus (DM). Plants such as *Allium sativum*, *Gymnema sylvestre*, and *Pterocarpus marsupium*, to name a few, have been traditionally consumed and scientifically investigated for their therapeutic effects against diabetes and associated complications [1–3]. *Galega officinalis*, a rich source of guanidine from which biguanides are derived, is one of the few herbal plants that were previously used in traditional medicine to treat type II diabetes mellitus (TIIDM) but were later found to be cytotoxic with a reduced efficacy [4, 5]. From this, several other biguanides were investigated which led to the discovery of dimethylbiguanide, an antidiabetic agent now commonly known as metformin. To date, metformin is a widely prescribed first-line antidiabetic drug with known cardioprotective properties [6, 7]. However, the effectiveness of metformin to alleviate diabetes and protect the diabetic heart is known to decrease over time [8, 9]. Furthermore, scientific data clearly demonstrates the evidence gap in the lack of specific drugs to treat diabetes-induced

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cardiac injury [10, 11]. Evidently, in the last decade, there has been a rapid rise in the prevalence of diabetes-associated cardiovascular diseases, classified under "other heart diseases" [12], and therefore, the search of alternative treatment regimens warrants intensive investigation [13].

Generally, there has been renewed interest in the use of herbal medicine, containing triterpenes and polyphenols, as an alternative or adjunctive therapy to the current synthetic antidiabetic drugs. The diverse flora kingdom of Southern Africa is a rich source of polyphenols with known phytochemical properties [14]. Such examples are *Aspalathus linearis* and *Protorhus longifolia*. *Aspalathus linearis,* commonly known as rooibos, is a leguminous shrub native to the Cederberg mountain region of South Africa. The regular consumption of rooibos has been linked with the reduction of serum triglycerides and cholesterol in human subjects [15]. In addition, the use of compounds specific to rooibos, such as aspalathin and phenylpyruvic acid-2-*O*-β-D-glucoside, have been shown to display an enhanced effect in reducing hyperglycemia, dyslipidemia, and cardiovascular complications [16–18]. Similarly, the use of triterpenes to alleviate prolonged blood glucose levels and myocardial functional derangements has been investigated adequately [19, 20]. Various studies have shown that triterpenes possess antidiabetic properties and exert their hypoglycemic effect by regulating enzymes involved in glucose metabolism, so as to reduce hyperglycemia and associated cardiovascular complications [21–23].

In recent years, there has been an increased interest in lanosteryl triterpenes extracted from the stem barks of *Protorhus longifolia* (Benrh.) Engl. (Anacardiaceae), a plant commonly known as red beech native to Southern Africa, which possesses compounds such as methyl-3β-hydroxylanosta-9,24-dien-21-oate (RA3) and 3β-hydroxylanosta-9,24-dien-21-oic acid (RA5). The medicinal benefits of these triterpenes stems from their antimicrobial, antidiabetic, and cardioprotective properties, which have been increasingly demonstrated in studies conducted by Mosa and colleagues [19, 20, 24–27]. While these triterpenes are gaining popularity as antidiabetic agents, there is currently limited scientific evidence accentuating the mechanism by which *P. longifolia* and its lanosteryl triterpenes exert their pharmaceutical effects against diabetes and accompanying cardiovascular complications. Thus, this review will provide a concise summary of the current knowledge available on the antidiabetic and cardioprotective properties of lanosteryl triterpenes from *P. longifolia*. A brief overview of the pathophysiological mechanisms implicated in the development of diabetes and linked myocardial diseases such as coronary artery disease (CAD) and diabetic cardiomyopathy (DCM) is provided to accentuate the cardioprotective potential of these triterpenes. To achieve this, various major databases, including PubMed, EMBASE, African Journals OnLine, and Google Scholar, were searched for available studies reporting on the antidiabetic and cardioprotective properties of lanosteryl triterpenes from *P. longifolia*. The search was conducted without any language restrictions, while unpublished and ongoing studies in addition to review articles were screened for primary findings.

An overview of the prevalence of diabetes and associated cardiovascular diseases

Diabetes mellitus is a complex metabolic disease that is characterized by chronic hyperglycemia, hyperlipidemia, and insulin resistance. The International Diabetes Federation reports that, globally, over 425 million people currently have diabetes, and this number will escalate to over 629 million by the year 2045 [13]. In Africa, approximately 16 million individuals have diabetes of which 10.7 million are undiagnosed and it is predicted that the prevalence of this condition in this region will reach 41 million by 2045 [13]. Alarmingly, this estimated increase supersedes Western Pacific, which currently has the highest prevalence of diagnosed diabetic individuals for 2017 [28]. The rapid rise in the prevalence of diabetes in developing countries such as those in Southern Africa has been attributed to factors such as urbanization and unhealthy lifestyle [28]. In South Africa, diabetes is among the top 10 leading causes of mortality and is responsible for approximately 460,236 deaths as recorded in 2015 [29] with cardiovascular disease (CVD) being the most prevalent cause of mortality and morbidity in this region [12, 28].

Globally, CVDs remain the leading cause of reduced life expectancy in individuals with and without diabetes [28]. As such, a projected 17.7 million deaths in 2015 were attributed to CVDs, representing 31% of all global mortalities [28]. In South Africa, CVDs are the fourth leading cause of mortality, with more than five people dying of myocardial infarction every hour [29]. Ischemic heart disease, or rather CAD, remains the major type of CVD that is responsible for over 41% of the 17.7 million CVD deaths, worldwide [28]. However, in the diabetic individual, increased incidence of heart failure exists even in the absence of CAD or hypertension, a condition termed diabetic cardiomyopathy. Though there is currently limited epidemiology-based data reporting on the global prevalence of DCM, available estimates show that the prevalence of DCM is between 15 and 65% depending on the population under study [30, 31]. Diabetic cardiomyopathy is a common, but underestimated form of heart failure in the diabetic population that manifests differently compared to CAD. Nonetheless, the pathophysiology of both diseases is not fully defined but they share similar disease characteristics at a late stage. The shared characteristics include abnormally raised lipid levels, as well as thickened left ventricular wall with concomitant reduced cardiac efficiency [31–34].

Exacerbated oxidative stress, as a result of the overproduction of intracellular reactive oxygen species (ROS), and inflammation, associated with enhanced pro-inflammatory markers, are the major molecular mechanisms implicated in the development of diabetes-induced cardiac injury [35–37]. Thus, in addition to providing insights into the association between diabetes and the development of CAD or DCM (Fig. 1), the following sections will briefly elaborate the pathophysiological mechanisms implicating oxidative stress and inflammation in accelerated cardiac injury in a diabetic state.

The association between diabetes and the development of CAD and DCM

At present, several risk factors have been implicated in the etiology of CAD with plaque buildup in the arterial walls (atherosclerosis) being the major contributing factor associated with the development and progression of CAD [32]. Furthermore, dyslipidemia, which is among the major characteristics of TIIDM in obese individuals, has been linked to enhanced lipid deposits in the arterial walls, thereby aggravating the development of atherosclerosis [38]. In a cross-sectional study performed by Garg and colleagues [39], they demonstrated that a cohort of both male and female diabesity individuals displayed increased levels of total cholesterol, triglycerides, and low-density lipoproteins when compared to control subjects, showing an enhanced risk of the development of CAD. Furthermore, these effects were associated with abnormal weight circumference, systolic blood pressure, and diastolic blood pressure and atherosclerotic plaques. The imbalance between food intake and energy expenditure has been described as the major contributing factor for the observed increase in obesity-induced dyslipidemic complications, leading to CAD [39, 40]. While CAD contributes to the increased prevalence of morbidity and mortality associated with diabetes, it is worth noting that DCM, an asymptomatic clinical entity, could be the primary cause of death in these individuals.

Cardiomyopathies are a group of diseases that affect the myocardium independent of atherosclerotic compilations. They are among the leading cause of death in Africa [41], with the prominent symptoms associated with these myopathies being dyspnea, lethargy, and irregular heart beat [42]. In the case of DCM, although known to be among the leading causes of mortality in diabetic patients [31], limited data exists on the precise mechanisms implicated in the onset and development of this condition. Diabetic cardiomyopathy is distinctly characterized by a disproportionately enlarged left ventricular mass and diastolic dysfunction that is associated with reduced cardiac efficiency and ejection fraction [43, 44]. Consequently, the ability of the heart to pump blood into the circulatory system is impaired which restricts blood flow thus, leading to myocardial infarction [45]. The latter has been associated with impaired substrate metabolism during the early developmental stages of DCM (Fig. 2), with the heart becoming almost completely reliant on free fatty acids (FFAs) as an energy source [33, 46]. This consequence was initially described by Randle and colleagues, where they showed that increased flux of FFAs into the myocardium inhibits the uptake and oxidation of glucose [47]. Similarly, in a study performed by our group, we reported on the shift in substrate preference in a high-glucose embryonic rat heart-derived H9c2 cell model [48]. In this study, elevated lipid accumulation with the resultant decrease in glucose uptake was observed in the cardiac cells [48]. Physiologically, while glucose utilization is relatively low and produces only 30% of energy in the non-diabetic heart when compared to the 70% generated from the oxidation of FFAs, glucose provides better energy efficiency due to its reduced use of oxygen per ATP molecule produced [33, 49]. This phenomenon has been confirmed in in vitro and in vivo studies performed on H9c2 cardiomyocytes exposed to high glucose and in type II diabetic animal models as well as in human subjects [38, 50]. Asymptomatic diabetic patients without cardiac ischemia usually present altered myocardial substrate metabolism accompanied with impaired left ventricular diastolic function when

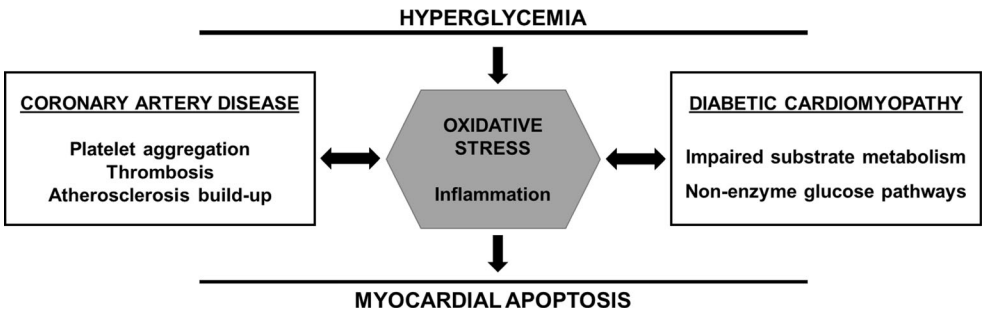


Fig. 1 The interlinking pathophysiology of diabetic cardiomyopathy (DCM) and coronary artery disease (CAD). Diabetic cardiomyopathy and CAD remain the leading cardiovascular complications implicated in accelerated myocardial infarction within a diabetic state. The mechanism explaining the pathophysiology leading to myocardial infarction, especially distinguishing between the development of CAD and DCM, in a diabetic state is still to be fully elucidated. Although inflammation and non-enzymatic glucose pathways are identified in the development of both CAD and DCM, atherosclerosis buildup is absent in DCM

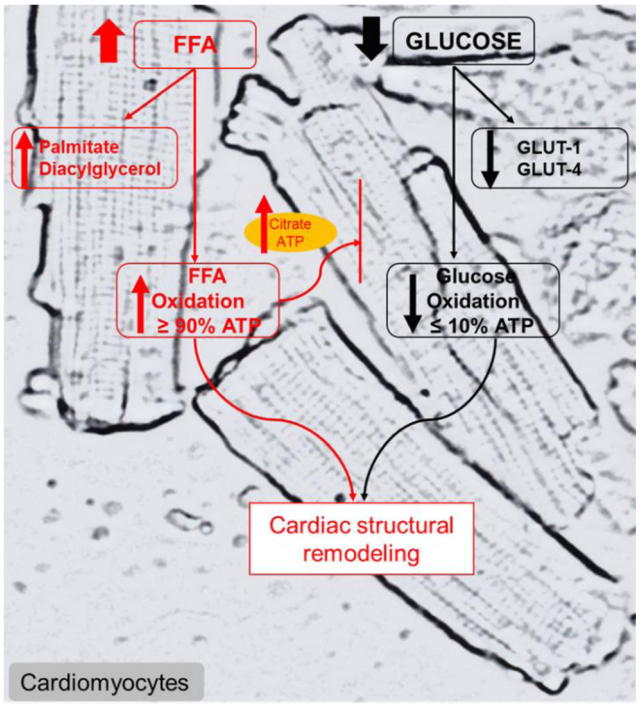


Fig. 2 Free fatty acid oxidation and glucose uptake in the diabetic heart. Cardiac structural remodeling as a consequence of impaired cardiac substrate metabolism is associated with enhanced fatty acid uptake and oxidation (up to 90%) and repressed glucose uptake and oxidation (to less than 10%). GLUT-1 and GLUT-4 are the main glucose transporters compromised in the diabetic heart, while palmitate and DAG are the main intermediates indicative of enhanced intramyocardial lipid accumulation. ATP adenosine triphosphate, FFA free fatty acid, GLUT-1 glucose transporter 1, GLUT-4 glucose transporter 4

compared to nondiabetic control subjects [51, 52]. Cumulative literature has elaborated on the role that impaired myocardial substrate preference can contribute to left ventricular diastolic dysfunction through the activation of oxidative stress and pro-inflammatory processes that eventually lead to accelerated myocardial apoptosis [33, 37, 53]. Hereunder, the impact of oxidative stress and inflammation in the induction of cardiac injury within a diabetic state is further accentuated.

Oxidative stress and pro-inflammatory-induced cardiac injury in a diabetic state

Impaired myocardial substrate metabolism corresponds to the enhanced generation of ROS, which triggers aggravated cellular apoptosis, thereby making the diabetic heart susceptible to cardiomyopathy [33, 37]. In addition to the actions of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, ROS production can be elevated in the cardiomyocytes as a result of impaired mitochondrial membrane potential, as reported in several hyperglycemic studies [17]. The mitochondria are the fundamental basis of ATP synthesis in cells; however, energy production can be diverted through the expression of catecholamine-regulated uncoupling proteins (UCPs). The presence of UCPs on the inner mitochondrial membrane alters its proton conductivity and may therefore influence mitochondrial membrane potential (MMP). The importance of maintaining the MMP is fundamental for the proper functioning and survival of cells that have high-energy requirements, such as cardiomyocytes [53]. In the diabetic state, changes in MMP have been linked with increased oxidative and nitrative stress, which may trigger the activation of stress signaling pathways facilitating mitochondrial membrane depolarization within the cardiomyocytes [33, 54, 55]. In cardiomyocytes exposed to hyperglycemic conditions, increased expression of UCP1 and UCP2 has been correlated with improved MMP and reduced oxidative stress [56, 57]. Activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), an important antioxidant response transcriptional factor, has played an essential role in the modulation of UCPs and other antioxidant genes, including glutathione, that are crucial for the reduction of oxidative stress-induced cardiac injury [58]. In agreement, a recent review by Satta and colleagues provided compelling evidence that "targeted activation of Nrf2, or downstream genes may prove to be a useful avenue in developing therapeutics to reduce the impact of cardiovascular disease" [59].

Depolarized mitochondria are key regulators of apoptotic stimuli as they release proapoptotic and apoptosis-inducing factors from the intermembrane space to the cytosol, and have been shown to be involved in both acute and chronic losses of cardiomyocytes in the hearts of diabetic individuals [53]. Apoptosis is a unique process that encompasses morphological and biochemical alterations, such as nuclear condensation and DNA fragmentation [53, 60]. Numerous studies have illustrated an increase in apoptosis in the early and late stages of cardiac injury, suggesting that cell death might play a role in cardiac remodeling and in the subsequent development of DCM [61–64]. B cell lymphoma 2 (Bcl-2) is an anti-apoptotic protein that plays a crucial role in mitochondrial homeostasis [63]. It is well established that chronic hyperglycemia decreases the expression of Bcl-2 (Fig. 3), which consequently increases the depolarization of the mitochondria, while subsequently releasing cytochrome C [60]. This release of cytochrome C, and subsquent activation of caspases, as demonstrated in Fig. 3, can lead to the nuclear translocation of caspases. Once in the nucleus, caspases can cleave poly(ADP-ribose) polymerase (PARP) and the inhibitor of caspase-activated DNase (ICAD) [60, 63], a process known to induce nuclear DNA fragmentation, leading to exacerbated apoptosis and necrosis.

Increased oxidative stress-induced cell death within a diabetic state has also been linked to an increased proinflammatory response [65, 66]. Obesity- or diabetes-induced chronic inflammation and the subsequent activation of cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which, together with increased ROS, can cause

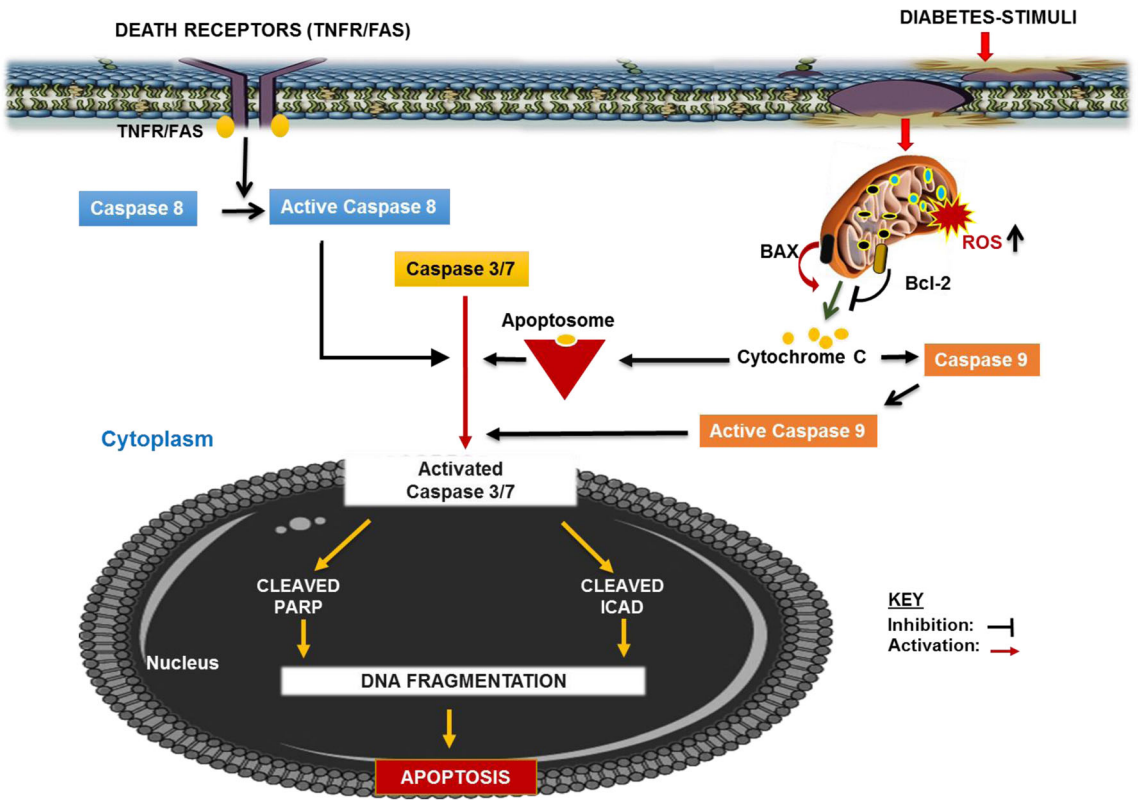


Fig. 3 Schematic diagram of mitochondrial depolarization, DNA fragmentation, and apoptotic signaling. Changes in mitochondrial membrane potential have been linked with increased oxidative stress, a key regulator of apoptosis driven by the pro-apoptotic Bcl-2-associated X (BAX) protein. The depolarization of the mitochondrial membrane releases cytochrome C which results in the activation of caspase-3/7, resulting in its nuclear translocation. Once in the nucleus, caspase-3/7 cleaves poly(ADP-ribose) polymerase (PARP) and inhibitor of caspase-activated DNase (ICAD) which induces nuclear DNA fragmentation, a hallmark of apoptosis. Image modified from https://smart.servier.com/smart_image/cell-1

thickening of the left ventricular wall in the cardiac muscle, a well-established morphological hallmark of DCM [43, 67]. Mitogen-activated protein kinases such as c-Jun N-terminal kinases (JNKs) have been revealed to play a major role in the regulation of diabetes-induced inflammation. Increased ROS is linked with the activation of JNKs via double phosphorylation of threonine and tyrosine residues, leading to the elevation of NF-κB and TNF-α levels and the subsequent increase in cell apoptosis [51, 68].

It is of interest that some natural products can protect the cardiomyocytes against hyperglycemia-induced damage through the modulation of oxidative stress and inflammation [69–72]. Such effects have also been evident when treating high glucose-exposed cardiomyocytes with aspalathin as reviewed by Johnson and colleagues [16]. This compound prevented diabetes-induced myocardial injury through the modulation of key genes involved in insulin resistance, oxidative stress, and inflammation such as insulin growth factor 1, Akt serine/threonine kinase 1, superoxide dismutase, UCP1, IL-3, IL-6, TNF-13, and Bcl-2 [57]. Of particular interest are triterpenes which are a class of natural compounds that are increasingly investigated for their metabolic capabilities [23, 73, 74]. Although these compounds demonstrate some antidiabetic properties [23], limited knowledge has been summarized relating to their cardioprotective potential against diabetes-induced complications.

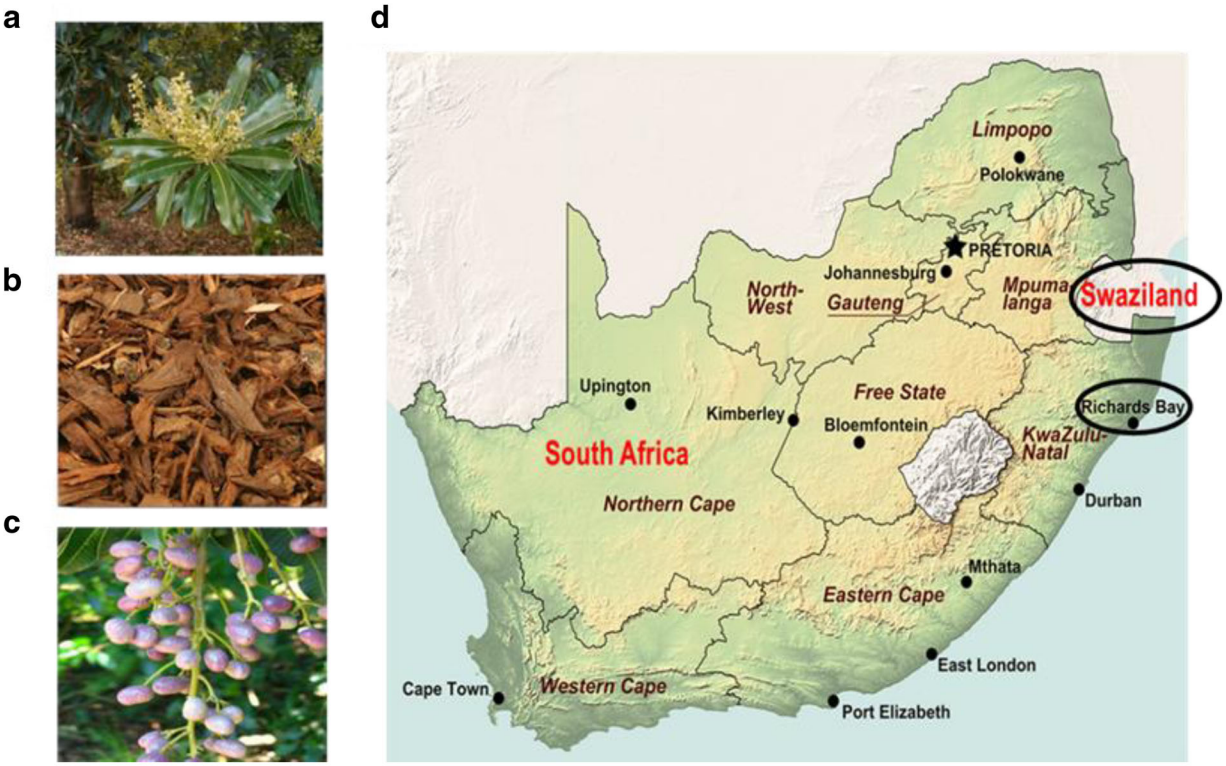
Triterpenoids and metabolic health

Triterpenes are compounds that are biosynthesized from squalene and possess diverse pharmacological properties. Several triterpenoids have been reported to ameliorate complications related to obesity, diabetes, and CVDs [75, 76]. For instance, in a phase 2 clinical trial, triterpenoid derivatives such as bardoxolone methyl and its analogue were shown to be more effective at improving renal and vascular damage in diabetic subjects than those receiving placebo [77]. Similarly, evidence describing the ability of ursolic acid and oleane triterpenoid to alleviate diabetes and stress-related myocardial dysfunction has been demonstrated [74]. However, recent research has increasingly focused on the specific branch of triterpenes known as lanostanes [78, 79]. This cluster of tetracyclic triterpenoid, resulting from lanosterol, is generated through

cyclization of squalene-2,3-epoxide in a chair-boat configuration, resulting in a protosterol [79]. Lanostanoids, including those from fungi and fruiting bodies of *Ganoderma leucocontextum*, are subject to increasing investigations for their ameliorative properties against metabolic diseases [80, 81]. The beneficial effects from some of these triterpenoids relevant to diabetes-associated complications include vasodilatory, antiinflammatory, and antithrombotic properties [74–76, 79, 80]. Equally important and of much interest are the pharmacological properties possessed by triterpenes found in the green aboriginal tall tree, *P. longifolia*.

The cardioprotective potential of lanosteryl triterpenes from *Protorhus longifolia*

The genus *Protorhus* constitutes one of the diverse species of flowering plants that includes *Protorhus ditimena* and *Protorhus longifolia*, which are endemic to Madagascar and Southern Africa, respectively (Fig. 4). Despite the limited medicinal knowledge on *P. ditimena*, scientific data on *P. longifolia* has come to the forefront reporting on the traditional health benefits of this plant. The species has been used traditionally as a blood-thinning agent and in the treatment of



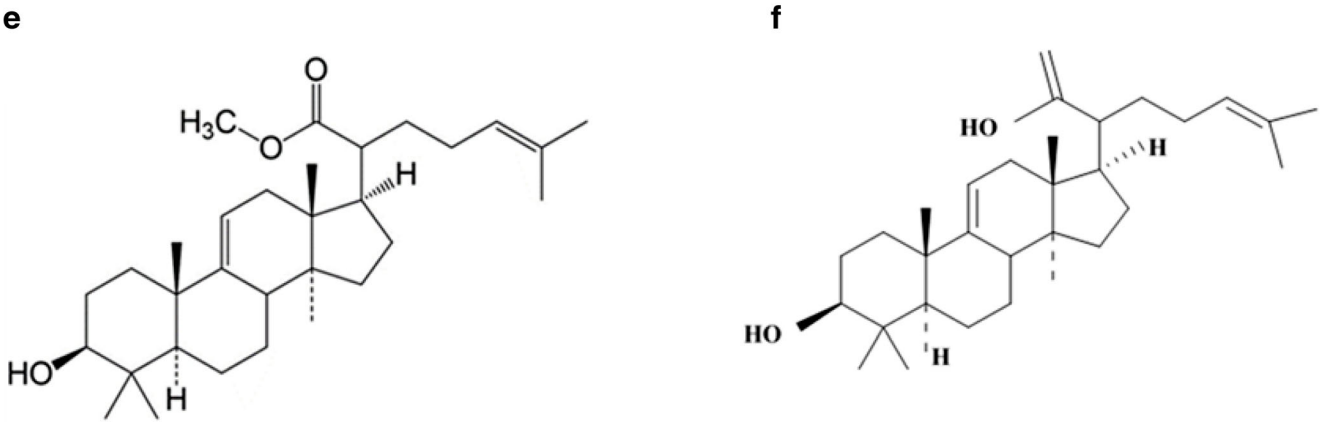


Fig. 4 Representative image of the **a** leaves, **b** stem barks, and **c** fruits of *Protorhus longifolia*. *P. longifolia* (Benrh.) Engl. (Anacardiaceae), also known as unhlangothi (Zulu), a green tall tree that is indigenous to Southern Africa, is mostly found in the **d** Zululand region of KwaZulu-Natal and parts of Swaziland. The chemical structure of **e** methyl-3β-hydroxylanosta-9,24-dien-21-oate (RA3) and **f** 3β-hydroxylanosta-9,24-dien-21-oic acid (RA5). Sources: https://pza.sanbi.org/Protorhus-longifolia and Mosa et al. [26]

conditions such as hemiplegic paralysis, heart burn, and abdominal hemorrhaging [27]. Although the commercial value of *P. longifolia* has not yet been established, its increased traditional usage can potentially add to its commercial value as it is one of the top 10 most frequently traded medicinal plants in the Eastern Cape Province (South Africa (SA) and highly retailed in the KwaZulu-Natal (SA) region to manage high blood sugar levels [82, 83]. The latter findings are important for the botanical and plant-derived therapeutic market as this international market is expected to escalate from $29.4 billion to approximately $39.6 billion with a compound annual growth rate (CAGR) of 6.1% for the period of 2017–2022 [84]. This has been related to the recent commercial success of products such as green tea (*Camellia sinensis*) and rooibos (*Aspalathus linearis*). In the case of rooibos, although previously considered to be of insignificant economic importance, rooibos is now part of the highly consumed beverages worldwide behind green tea [14, 85]. Therefore, scientific validation of medicinal plants such as *P. longifolia* may be of similar value for the development of herbal health care, plant-based cosmetics, and nutraceutical supplements for the South African market.

While *P. longifolia* is gradually gaining popularity due to its medicinal benefits in an array of diseases, very limited work has been done on this plant and its triterpenes, RA3 and RA5 (Fig. 4), to accentuate its antidiabetic and cardioprotective properties. The leaf extracts of *P. longifolia*, along with RA3 and RA5, have been individually reported to possess in vitro antimicrobial and antibacterial activities [19, 86, 87]. Here, both RA3 and RA5 displayed chemotherapeutic potential against *Listeria* as well as bactericidal activity on antibiotic-resistant strains, thereby suggesting their potential use to combat drug-resistant infectious diseases. The hexane extract of the stem barks of *P. longifolia* revealed it could inhibit thrombin- and epinephrine-induced platelet aggregations in vitro [27]. These findings were confirmed in a carrageenan-induced rat paw edema model, where RA5 effectively alleviated thrombin-induced plate aggregation, which plays a pivotal role in blood clotting in both physiological and pathophysiological conditions such as atherothrombosis [26]. In the same rat model, RA3 demonstrated anticoagulant and antiinflammatory activities by inhibiting cyclooxygenase (COX) which is involved in the synthesis of prostaglandins and the subsequent release of prostanoids and thromboxane [26]. The effects of prostanoids and thromboxane are often opposing as they are imperative for maintaining homeostasis between arterial vasoconstriction and vasodilation as well as in antithrombotic and prothrombotic events [88]. Thus, the properties exhibited by RA3 and RA5 could be especially important in regulating myocardial homeostasis.

The oral administration of RA3 at 100 and 200 mg/kg body weight for 15 days significantly lowered the levels of total cholesterol and low-density lipoproteins whilst increasing high-density lipoproteins in high-fat diet-induced hyperlipidemic rats [25]. In the same study, RA3 effectively reduced the levels of the following liver enzymes: alkaline phosphatase (ALP), alkaline aminotransferase (ALT), and aspartate aminotransferase (AST), which have been implicated in the development of cardiovascular diseases [25, 89]. These results were concomitant with the significant reduction in atherogenic and coronary risk index in the same rat model. In a different study, streptozotocin-induced diabetic rats, administration of RA3 at 100 mg/kg body weight daily for 14 days revealed significantly reduced blood glucose levels by 37% when compared to untreated controls, thereby indicating the compounds' hypoglycemic potential [21]. This antihyperglycemic effect was further substantiated by the triterpenes' ability to improve glucose tolerance in the diabetic animals in a manner comparable to that of the

Table 1 The protective effect of *Protorhus longifolia* and its lanosteryl triterpenes, including methyl-3β-hydroxylanosta-9,24-dien-21-oate (RA3) and 3β-hydroxylanosta-9,24-dien-21-oic acid (RA5), against diabetes-associated compilations

Treatment	Model	Outcome	Reference
RA3 and RA5	Thrombin- and epinephrine-induced platelet aggregation	Anti-inflammatory effect (IC_{50} of 0.59 mg/mL)	[27]
100 mg/kg and 200 mg/kg of RA3	High-fat-fed Sprague Dawley rats	Improved lipid profiles and atherogenic index	[25, 91]
100 mg/kg of RA3	Type II diabetes was induced through STZ injection and feeding Sprague Dawley rats a high-fat diet	Improved glucose tolerance, pancreatic beta cell ultrastructure, and fasting c-peptide levels, while reducing oxidative stress and inflammation	[91]
RA3	Cotton pellet-induced granuloma model in rats	Anticoagulant and anti-inflammatory activity	[20, 27]
100 mg/kg of RA3	Streptozotocin-induced diabetic Sprague Dawley rats	Improved glucose tolerance and antioxidant while reducing lipid peroxidation	[21]
100 mg/kg of RA3	Isoproterenol-induced myocardial injury in hyperlipidemic Sprague Dawley rats	Decreased fat deposition, LDH, and lipid peroxidation while improving antioxidant capacity in the heart	[24]

first-line antidiabetic drug, metformin. These observations are suggestive of the triterpenes' ability to protect against diabetes-induced complications as hyperglycemia is linked with increased oxidative stress and subsequent tissue damage. As summarized in Table 1, the pharmaceutical properties exhibited by these lanosteryl triterpenes are indicative of their potential role in the development of diabetes-induced cardiac injury. In a recent study, the cardioprotective effect of RA3 was determined by establishing the effect of the triterpene in isoproterenol-induced myocardial injury in high-fat diet (HFD)-fed rats [24]. Briefly, isoproterenol causes severe stress in the myocardium, compromising cardiac membrane integrity [90], thereby resulting in the leakage of cardiac biomarker enzymes (lactate dehydrogenase (LDH), creatine kinase (CK), and CK-MB) into the bloodstream. Here, RA3 effectively decreased serum LDH activity that was used, in the study, as a diagnostic tool for cardiac damage. This reduction was associated with the triterpenes' ability to maintain the membrane integrity of the cardiomyocytes. Furthermore, a noticeable improvement, few lesions of acute hyaline degeneration, and decreased lipid deposits were seen in the hearts of these animals, which further confirmed the cardioprotective potential of the lanosteryl triterpenes [24]. In addition, the myocardial necrotic effect of isoproterenol has been shown to be mediated by oxidative stress in these animals. Either than those extracted from *P. longifolia*, the cardioprotective effect of triterpenes has been credited to their ability to elevate endogenous antioxidant levels while subsequently preventing lipid peroxidation. In accordance, RA3 has been shown to increase serum glutathione content and catalase, and superoxide activity in both non-diabetic and diabetic animals [20, 91], confirming the triterpenes' ability to increase the endogenous antioxidant content of the myocardium. This apparent increase was proportional to the reduction in lipid peroxidation and inflammatory cytokines accompanied with improved pancreatic beta cell ultrastructure in the muscles and pancreatic islets of diabetic animals, respectively [91]. As summarized in Table 1, the lanosteryl triterpenes presented in this review have consistently demonstrated metabolic benefits against diabetes and its associated cardiovascular complications. However, the mechanistic insights by which these compounds apply their pharmaceutical effects are yet to be established. Nonetheless, we propose that these

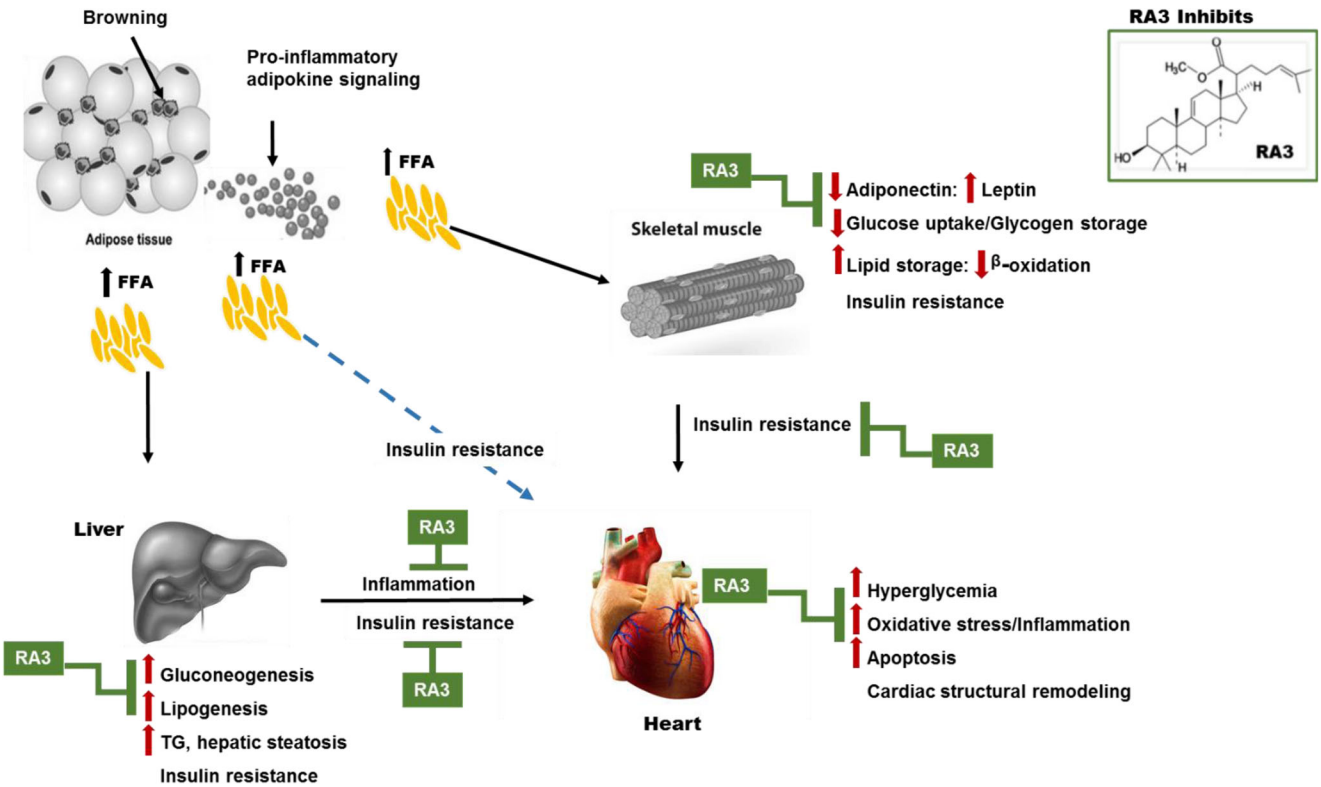


Fig. 5 The proposed mechanism of action of methyl-3β-hydroxylanosta-9,24-dien-21-oate (RA3). Numerous studies have demonstrated that lanosteryl triterpenoids isolated from *Protorhus longifolia* present with numerous medicinal benefits. Notably, RA3 has demonstrated anticoagulant and antiinflammatory activities by inhibiting cyclooxygenase which primarily involved in thrombosis. This triterpene also displayed antihyperglycemic and antihyperlipidemic properties in both diabetic and nondiabetic Sprague Dawley rat models. Furthermore, RA3 has been shown to improve myocardial structural impairments while improving insulin signaling and regulating energy efficiency in the cardiac muscle, thereby preventing cardiac injury

triterpenes, more importantly RA3, might exert their cardioprotective potential through their apparent inhibition of lipogenesis, improved insulin sensitivity, and resultant increase in the uptake of glucose in the liver and the skeletal and heart muscles.

Conclusion

CAD and DCM remain the foremost cardiovascular complications implicated in accelerated myocardial infarction within a diabetic state. Some of the pathophysiological mechanisms linked with the development of these complications are highlighted in this review. These include non-oxidative glucose pathways such as impaired myocardial substrate metabolism that eventually lead to oxidative stress- and proinflammatory-induced myocardial injuries. Moreover, it is evident that oxidative stress-induced tissue damage, through persistent exposure to hyperglycemia, remains the major factor associated with cardiac injury in a diabetic state. Alternatively, medicinal plants and their derivative constituents present abundant antioxidant properties that could potentially protect against such complications. Numerous studies have demonstrated that lanosteryl triterpenoids isolated from *Protorhus longifolia* present similar effects. Notably RA3 has previously presented anticoagulant, antiinflammatory, antihyperglycemic, and antihyperlipidemic properties (Fig. 5). However, this review clearly highlights the evidence gap that is required pertaining to the molecular mechanisms associated with the cardioprotective effect of these compounds. Once that is established, clinical studies can be conducted, which may be a significant step in enhancing the market value of *Protorhus longifolia*.

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Compliance with ethical standards

The manuscript does not contain clinical studies or patient data.

Conflict of interest The authors declare that they have no conflicts of interest.

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