

Therapeutic Insights against Oxidative Stress Induced Diabetic Nephropathy: A Review

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Abstract

Diabetes mellitus (DM) is an outcome of an absolute or relative deficiency of insulin which may be due to autoimmune destruction. It is mainly characterised by hyperglycemia, causes auto-oxidation of glucose, glycation of proteins and activation of polyol mechanism. This leads to oxidative stress, defined as an increase in the intracellular level of reactive oxygen species (ROS). Overproduction of ROS contributes to several microvascular and macrovascular complications of DM including diabetic nephropathy (DN). DN is a primary cause of chronic kidney disease and end-stage renal failure in various parts of the world. Minimizing the risk factors associated with DN is insufficient in lowering the vulnerability of this disorder. Henceforth, an increased knowledge on the role of oxidative stress would lead the way to the exploration of a number of molecules having antioxidant property as therapeutic option. These agents could reduce the severity of DN by decreasing the level of ROS and modulating an array of signalling cascade, thereby ameliorating oxidative stress via its antioxidative and immunomodulatory properties. This review provides valuable information concerning the recent advancements in understanding the role of well-known therapeutic agents in alleviating oxidative stress induced renovascular complications in DM. This review also encompasses the role of different natural products on their effect on the T-cell driven immune response in autoimmune diabetic nephropathy.

Keywords: Diabetic nephropathy; Oxidative stress; ROS; Antioxidant molecules

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Introduction

With the unhealthy nutritional transition and changes in human behavior and lifestyle, the incidence of diabetes mellitus (DM) in the society is rising out of the blue. DM, a common endocrine metabolic disorder, characterized by a state of chronic hyperglycemia, is a major concern as it is a universal cause of morbidity and mortality [1-3]. Globally, the number of diabetic patients is on alarming rise which will be heading to around 592 million by 2035 from the present scenario of 382 million affected people as estimated by International Diabetes Federation (IDF). Although it is a universal public health threat, present trend indicates that the Asian countries contribute to 60% of world's diabetic population due to the rapid occurrence of socio-economic growth and industrialization in many of these countries [4]. The countries which are at greater risk in Asia

include India, China and Japan [5]. Despite of the high mortality rate of diabetes patients, the more serious part is the painstaking morbidity associated with it [6]. The debilitating symptoms of DM include weight loss, polyuria, polydipsia and polyphagia [7]. Irrespective of such varied symptoms, onset of this disease is due to the body's inability to control blood glucose level. This is mainly because of the (i) failure of glucose access into the cells; (ii) reduction in the utilization of glucose by different tissues; and (iii) up turn of glucose synthesis by liver [8].

Universally, DM is classified into three different forms: type 1 DM (T1DM), type 2 DM (T2DM) and Gestational DM. Type 1 DM or insulin dependent diabetes mellitus (IDDM) occurs due to insulin deficiency as an after effect of autoimmune destruction of pancreatic β -cells; Type 2 DM, also called non-insulin dependent diabetes mellitus (NIDDM), occurs as a result of insensitivity of

cells to insulin and therefore subsequent loss of β -cell function [9]; and gestational diabetes mellitus, which develops during pregnancy, due to hormonal changes that alter the body's ability to make use of insulin leading to carbohydrate intolerance and usually vanishes after the birth of the child. It does not confirm the birth of a diabetic child [10-12]. It is well accepted that autoimmunity is a major factor in T1DM. In the pathogenesis and progression of several microvascular and macrovascular complications including diabetic nephropathy, a number of inflammatory and angiogenic molecules are important modulators in different pathways of these pathophysiological conditions. Like T1DM, T2DM is also being recognized for having autoimmune aspects because of the circulating autoantibodies against β cells and self-reactive T cells. Literature also suggests the presence of these β -cell autoantibodies in initially non-insulin dependent diabetic children with the clinical features of T2DM [13].

The major complications of DM include various macrovascular diseases like cardiovascular disease, stroke and peripheral vascular disease, all resulting from complications related to damaged blood vessels [14]. Whereas, the key microvascular complications involve damage to the eyes (diabetic retinopathy), kidneys (diabetic nephropathy) and nerves (diabetic neuropathy) [15-17] (Figure 1). Among the various complications of DM, approximately 40% of patients are affected by diabetic nephropathy (DN) [18]. DN is a major cause of death from diabetes [19] and also a leading cause of end stage renal disease in many developing countries [20]. Symptoms which are usually absent at an early stage develops with time [21] and are

characterized by the development of proteinuria and decrease in glomerular filtration rate (GFR) [22]. Patients suffering from such end stage complications require medical attentions like dialysis or even kidney transplant. Involvement of immune system and inflammatory processes in the development and progression of DN has been recently reported [23,24]. The activation of T cells in type 1 diabetes is also found to be associated with DN. Influx of T cells associates with albumin excretion rate and glomerular filtration surface. A number of cytokines like IL-18 and TNF- α have also been found to lead the way to DN [25,26]. Collectively immune system seems to be involved in causing structural and functional changes to kidney leading to DN. Also multiple publications suggest that free radicals originating from oxidative stress and failure of the intrinsic antioxidants during diabetes are the main culprits having a significant contribution in the development and progression of life threatening DN [27-29]. Apart from this, some other risk factors like increased blood pressure and genetic alterations also play a causal role in DN [30].

Oxidative stress is an imbalance between oxidant level i.e., pro-oxidants and antioxidants within the body. It results when harmful free radicals are generated in excess and body's natural antioxidants ability to detoxify them is perturbed [31]. This leads to inordinate formation and/or scanty removal of these free radicals which are mainly classified as Reactive oxygen species (ROS) and Reactive nitrogen species (RNS). ROS production occurs via divergent sources in a diabetic patient like enzymatic, non-enzymatic and mitochondrial pathways [32] and causes oxidation of various biomolecules including DNA, protein, carbohydrates

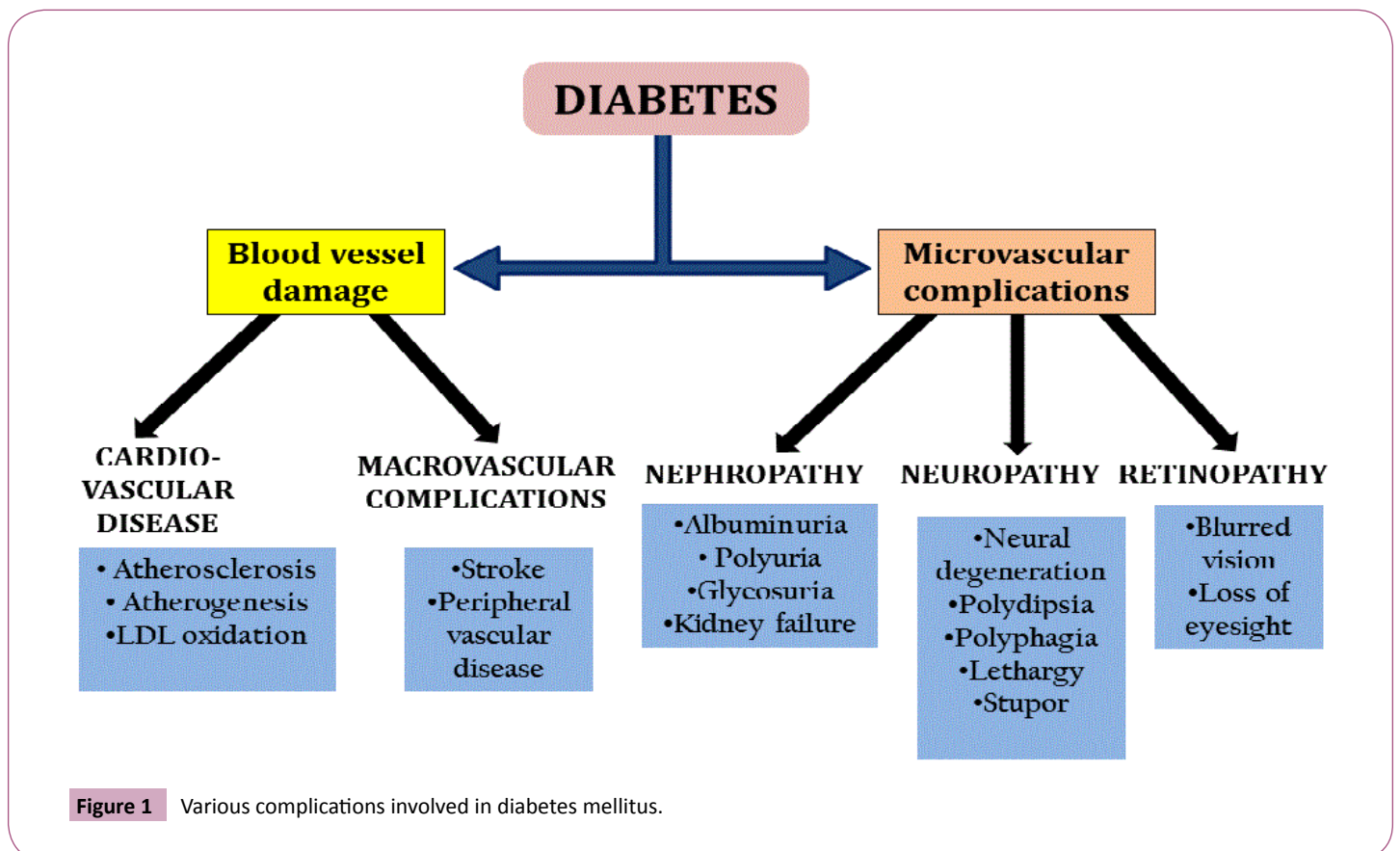


Figure 1 Various complications involved in diabetes mellitus.

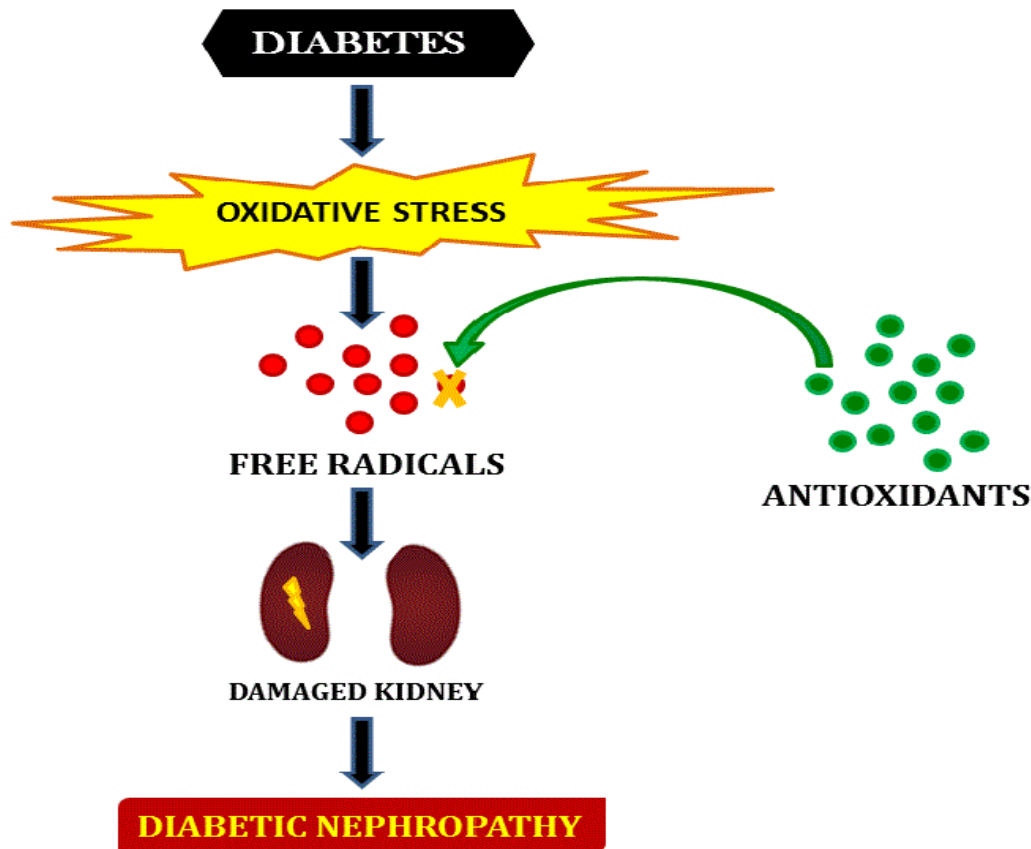


Figure 2 A graphical illustration on the role of free radicals and antioxidants in diabetic nephropathy.

and lipids [33]. Various cells like endothelial, vascular smooth muscle, tubular epithelial and mesangial cells starts producing ROS under hyperglycemic condition thereby increasing the complications of diabetes, especially DN [34]. This ROS causes thickening of basement membrane within kidney glomerulus besides the progressive accumulation of extracellular matrix components in the mesangium [35].

Oxidative stress plays a causal role in several pathological conditions in the body and targeting them with antioxidants has shown to reduce the deleterious effects of ROS [36]. This makes different molecules having antioxidant activity, as the savior in such stressed situation. Such molecules have been found to counteract the harmful effect that occurs due to increased ROS in various disorders like heart disease, Alzheimer disease, aging and many others by removing free radical intermediates and inhibiting oxidation of other molecules [37-39]. High glucose level during diabetes leads to oxidative stress through different signaling pathways which produces detrimental situations like DN in our body [40,41]. Therefore, treating DN with innumerable antioxidant molecules that can exhibit effective results, has opened a newer therapeutic approach [35,42,43]. Use of product from plants has demonstrated their antioxidants effects [44-46]. Recently, the potential of drugs as antioxidants in treating DN has also been proven [47-49]. This review highlights the role of several recently studied antioxidant therapies, thereby combining

the research reports of various studies, useful in preventing the pathogenesis of DN occurring due to oxidative stress.

Oxidative stress and diabetic nephropathy

Oxidative stress is a deleterious phenomenon within the body, mainly characterized by imbalance of cellular oxidation/reduction levels. It reduces the normal antioxidant defense system of the human body by decreasing the cellular antioxidant levels and lowering the activity and expression of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) etc. to scavenge free radicals [50-52]. The presence of high glucose level either due to resistance of cells to insulin or lack of insulin synthesis by pancreatic β cells leads to the condition commonly known as diabetes [3]. As discussed earlier, this condition plays an important role in the production of ROS by activating several cellular responses through different signaling pathways thereby leading to detrimental effects like DN. Quite a number of factors are involved in generation of oxidative stress during diabetes but the dominant role is played by increase in the production of several reactive radicals (peroxyl, hydroxyl and superoxide) and many other reactive compounds (hydrogen peroxide (H_2O_2), nitric oxide (NO), nitrogen dioxide (NO_2), nitrous oxide (HNO_2), hydrochlorous acid (HOCl) etc.) [53,54]. It is well established that

oxidative stress during DM ultimately leads to the knocking down of normal kidney homeostasis and proper functioning [21].

Evidence of increased ROS production in kidneys of both type 1 and type 2 DM affected patients via both enzymatic and non-enzymatic pathways have also been reported [55-57]. High glucose appears to act through the activation of protein kinase C (PKC) in diabetic glomeruli through de novo synthesis of diacylglycerol (DAG). This PKC produces ROS which in turn causes activation of PKC thereby causing increment of mesangial expansion, basement membrane thickening and dysfunction of endothelial cells leading to DN [15,58]. ROS formation also occurs due to the isoforms of nicotinamide adenine dinucleotide phosphate oxidases (NOXs), especially NOX-4, activated under hyperglycemic condition, which leads to endothelial dysfunction, inflammation and apoptosis [59,60]. Others like auto-oxidation of glucose, polyol pathway flux, increased formation of advanced glycation end (AGE) products and glycation of proteins under hyperglycemic conditions are also involved in causing direct and indirect renal damage by producing extensive amount of ROS [61,62].

Diabetes has also been found to be associated with an increment of renin-angiotensin system (RAS) activity including aldosterone production which plays an important and direct role in the production and activation of ROS leading to renal damage [63,64]. Elevated level of glucose leads to the activation of transforming growth factor-(TGF- β). Over expression of TGF- β or TGF- β type II receptor in the glomerular and tubulointerstitial compartments of the diabetic kidney has been reported in many studies. Enhanced level of TGF- β leads to renal hypertrophy, glomerulosclerosis and tubulointerstitial fibrosis in diabetic kidney [65,66]. Multiple literatures suggest that vascular endothelial growth factor (VEGF), a protein secreted by the podocytes and the mesangial cells of kidney, plays a role in the progression of DN [67,68]. Under oxidative stress condition, VEGF is increased and expressed by the activity of hypoxia-inducible factor (HIF-1 α), notch signaling and increased level of Angiotensin II [69-71]. VEGF interferes with the phosphoinositide 3-kinase/protein kinase B (PI3K/PKB) pathway and modulates the expression of endothelial nitric oxide synthase (eNOS) [72-74]. Thus VEGF indirectly elevates the level of intracellular ROS by stimulating the generation of peroxynitrite (ONOO⁻) [75]. Several studies have also revealed that inadequate glycemic control increases the inflammatory activities by activating macrophages as an after effect of protein glycation. These activated macrophages enhance the ROS production leading the way to DN [76].

Excessive ROS production by different pathways leads to the activation of downstream molecules like p38 mitogen activated protein kinases (p38 MAPK), nuclear factor- κ B (NF- κ B) and TGF- β causing development of DN [35,42]. Growing evidence suggests that oxidative stress during hyperglycemic condition leads to the overproduction of superoxides (\bullet O₂⁻) by the uncoupling of eNOS [77]. This diminishes the level of an antioxidant enzyme SOD, the first metallo protein enzyme, which is involved in the conversion of super oxide anion radical (O₂⁻) to H₂O₂ thereby removing the superoxide anions. Also the production of VEGF leads to the proteinuria thereby adding complications to DN [78,79]. On an

overall perspective, it is found that under diabetic conditions, intracellular ROS is elevated due to many converging pathways and finally leads to nephropathic situation by activating an array of diverging signaling cascades (Figure 3).

Antioxidant therapies in amelioration of diabetic nephropathy

Antioxidants are the class of compounds which can potentially inhibit the oxidation of other intracellular molecules, protecting our body from the detrimental effects of free radicals [80]. Free radicals are the electron deficient, highly reactive molecules that can oxidize the cellular macromolecules causing severe damage to subcellular organelles [81,82]. It is necessary to timely scavenge these free radicals otherwise persistent exposure to them can lead to tissue degradation directing its way to a state of organ pathophysiology. To prevent the deleterious effects of free radicals, the effects of antioxidants are extensively studied [83-86]. Antioxidants act through different mechanisms at various sites exerting a number of biochemical effects. Researchers suggest that the hyperglycemia during DM often interfere with the intracellular ascorbate metabolism and results in the generation of free radicals thereby increasing the susceptibility of oxidative damage [87]. It has been experimentally shown in different diabetic models that the level of different antioxidants got decreased, both transcriptionally and post-transcriptionally, in kidney tissue [88,89]. It is also shown that prevention of the overproduction of ROS by the administration of exogenous antioxidants is an effective strategy in combating DN [35,90,91]. Numerous studies suggest that antioxidants improve the renal physiology in DN by acting directly against oxidative damage. Moreover, exogenous administration of antioxidants is capable of preventing the progression of DN. They can also effectively block the formation of excessive ROS and scavenge the preformed intracellular ROS. Some antioxidant molecules can even modulate the signaling cascade to resume the normal cellular homeostasis [15,21,42,92] (Figure 3).

Human body possesses natural antioxidants to control the level of ROS by scavenging them both enzymatically and non-enzymatically [93]. Enzymatic pathways include a platter of enzymes namely SOD, CAT, GPx, GR etc. Different nonenzymatic antioxidants include various vitamins (like vitamin A, C, E, carotenoids, α -lipoic acid, etc.), trace elements [like coenzyme Q10 (CoQ10), copper, selenium, zinc, etc.] and cofactors (like uric acid, folic acid, albumin, etc.). Antioxidant enzymes either readily converts the reactive free radical \bullet O₂⁻ into H₂O₂ or activates intracellular pathways to regenerate other antioxidative metabolites [33]. These metabolites then react with the reactive radicals and change them into the stabilized form. Other than this metabolites or enzymes, certain genes (e.g., nuclear factor erythroid 2-related factor 2 (Nrf-2) and heme oxygenase-1 (HO-1)) and their end products are also capable in maintaining cellular homeostasis in oxidative stress related organ pathophysiological conditions including DN [94].

In addition to the ROS scavenging properties, exogenous antioxidant molecules are also capable of modulating different gene expression to improve the oxidative stress induced DN [95-

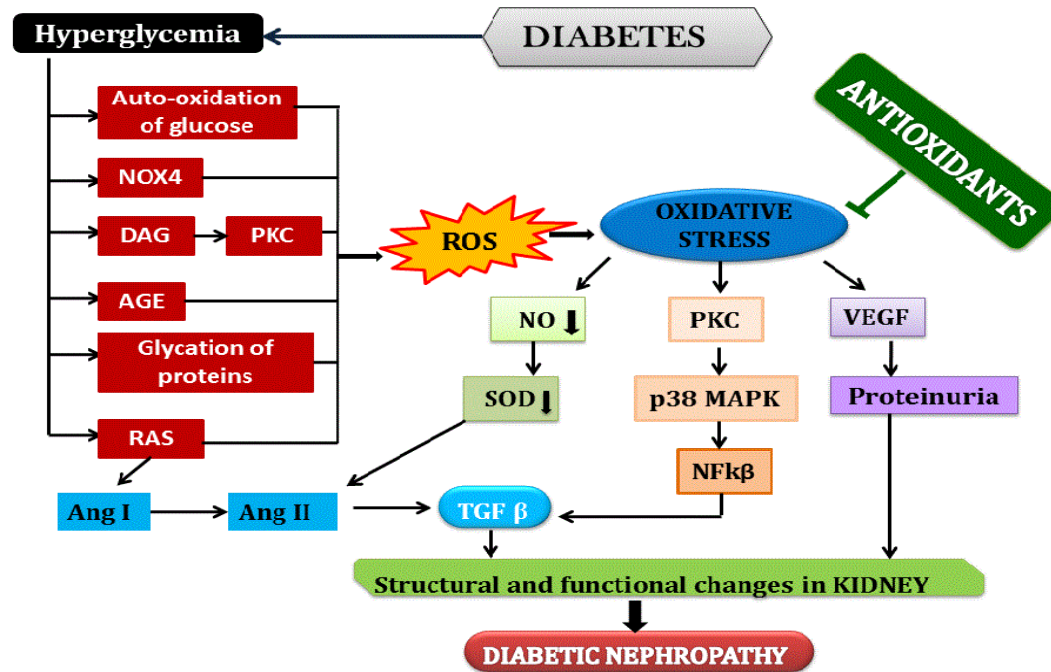


Figure 3 Schematic representation of signaling cascade involved in diabetic nephropathy and its modulation by antioxidants.

97]. Antioxidants including various dietary phytochemicals have been shown to exhibit immunomodulatory effect by reducing destruction of pancreatic β -cells, enhancing immunotolerance and autoimmunity suppression [98]. Reports suggest that the inhibitors of NOXs are very helpful in reducing the level of blood glucose and urinary protein content [99,100]. Some antioxidants are also known to reduce the expression of VEGF and they can even diminish the 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) contents in urine [101]. They can improve the functionality of the glomerular and mesangial cells in kidney. Besides, different antioxidants can also regulate the glomerular expression of TGF- β 1 and collagen IV proteins in the kidney under diabetic conditions [102,103]. Apart from these functions, antioxidants also inhibit high glucose induced activation of hexosamine, PKC, AGE pathways and NF- κ B [62,104]. In addition, numerous reports have been published on antioxidants about their potential in down-regulating different pro-apoptotic genes and simultaneous up-regulation of different anti-apoptotic genes along with maintaining the normal mitochondrial homeostasis [105-107].

Antioxidants are pleiotropic biomolecules. Along with the control in the serum blood glucose level, some antioxidants are very effective in inhibiting some crucial signaling intermediates like angiotensin-2 converting enzyme (ACE), angiotensin-2 receptor blockers (ARB), and aldosterone blockers [108,109]. Selective antioxidants molecules can also activate eNOS, which in turn increases the bioavailability of nitric oxide and blocks the expression of angiotensin 2 and TGF- β thus inhibiting the progression of diabetes in kidney [93,110].

A number of antioxidants are known to ameliorate oxidative stress induced renovascular complications. The follow up study

covers an area highlighting the recent literature on the detailing of the alleviating role of several antioxidants molecules against DN.

Therapeutic plants

A number of studies are going on to determine the importance of plants and their active ingredients all over the world [111,112]. Among these, several natural antioxidants have been reported to show beneficial consequences in putting a halt to the fatality of renal dysfunctions in DN. The active phytochemicals responsible for the activities of plant products have been identified in some and yet to be identified in others. Several molecules show their protective effects on kidney by lowering glucose level near to normal while some show direct effects on kidney [113,114]. Recent studies suggest that these compounds reduce the AGE levels, expression of TGF- β and other cytokines, etc. [115,116]. Moreover they also ameliorate the oxidative stress by modulating the functions of glomerular cells in the kidney. The therapeutic potential of different plants is under investigation to assess their anti-inflammatory and immunomodulatory activities. Many scientists are keenly engrossed to prevent and recover people from DN and a number of studies are going on for suitable inexpensive active principles capable of counteracting it with minimum side effects. Investigation of plant products for their pharmacological properties in the regulation of oxidative stress induced renovascular complications has become prime importance. An overview of some recent plants (their whole extracts or active compounds) playing a protective role in DN and their mechanistic implications are mentioned below.

Terminalia arjuna

Belonging to the family of Combretaceae, *Terminalia arjuna* (*T. arjuna*) has been well known among ayurvedic medicinal plants. The entire plant is full of many bioactive constituents like tannins, triterpenoid saponins, flavonoids, ellagic acid, gallic acid, oligomeric proanthocyanidins (OPCs), phytosterols etc. [117,118]. They are useful as therapeutic agents for the treatment of various physiological disorders [119]. A pentacyclic triterpenoid saponin, arjunolic acid (2,3,23-trihydroxyolean-12-en-28-oic acid; AA), isolated from the bark of this tree, is popularly known for its radical scavenging activity and potential antioxidant power [120] due to its hydrogen donation, metal ion chelating and the resonance stabilization of carboxyl radical property [120]. P. Manna et al. have portrayed the efficacy of AA in ameliorating STZ induced hyperglycemia and associated renal pathophysiology. This is due to the effect of AA in reducing oxidative as well as nitrosative stress and suppressing the activation of polyol pathway. Treatment of STZ induced diabetes rats with AA maintains kidney histology sound by preventing renal ultra-structure damage, loss of brush border, extensive tubular casts and debris as well as tubular dilatations. Administration of AA to diabetic rats has been shown to prevent hyperglycemia, peroxidation of lipids, protein carbonylation and restores the antioxidant defense machineries including antioxidant enzyme activities and the redox ratio of reduced glutathione to oxidized glutathione (GSH/GSSG). Its administration, both prior and post, has also been shown to inhibit or reduce the activation of MAPKs (phospho-ERK1/2, phospho-p38) and NF- κ B (p65) [42]. This result suggests that AA could potentially suppress hyperglycemia induced oxidative stress thereby preventing the initiation of DN.

Curcuma longa

It is a *rhizomatous herbaceous* perennial plant of the ginger family, Zingiberaceae [121]. The yellow phenolic pigment of this medicinal plant, called *curcumin* [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], widely present in spice turmeric, is of great therapeutic value. Curcumin has caught scientific attention as a potential treatment for DN as it is a commonly consumed natural foodstuff and considered safe compared to the available expensive commercial drugs. Its diverse properties of regulating different signaling pathways, intracellular components and key enzymes are due to its inbuilt antidiabetic, antioxidant and anti-inflammatory properties [90,122,123]. Its antioxidant property generally comes up due to its hydroxyl group or the methylene group of the α -diketone (heptadiene-dione) moiety [123].

The renoprotective effect of curcumin on DN has recently been discovered by many researchers [124]. Its treatment restores the increased BUN level to normal and enhances the clearance of creatinine and urea [125,126]. It also modulates the levels of aspartate aminotransferase, N-acetyl D-glucosaminidase, alkaline as well as acid phosphatases and alanine aminotransferase. Renal integrity has been found to be repaired by *curcumin* via its effect in normalizing the levels of aldose reductase, ATPases, SOD, CAT, glucose-6-phosphate dehydrogenase, glutathione, transaminases, lactate dehydrogenase (LDH), and membrane polyunsaturated fatty acid/saturated fatty acid (PUFA/SFA) ratio [127]. A further study has revealed that it leads to the activation of adenosine monophosphate (AMP) [128] which in turn reduces

the expression of VEGF and VEGF receptor [129] thereby inhibiting PKC- α and PKC- β 1 oxidative activities [58]. This causes inhibition of peroxidation of lipids and subsequent restoration of structure and function of renal tissue by standardizing antioxidant defense systems [58]. Moreover, its ability to inhibit NF- κ B and p300 and thereby alteration in the expression of p38 MAPK and heat shock protein-27 (HSP-27), induces posttranslational modification of histone H3 in diabetic kidneys, subsequently reducing oxidative insult mediated renal damage [130,131]. Curcumin also reduces the level of Nox4 and p67 phox thereby decreasing oxidative stress [132]. Clinical trials have shown the reduction of TGF- β , IL-8 and urinary protein levels further confirming the positive effect of curcumin on end-stage renal disease [133]. Despite of showing such pleiotropic effect, it has not yet been approved as a therapeutic agent due to its poor water solubility, low bioavailability and intense staining colour [134]. Along with the antioxidant and antidiabetic effects, curcumin has also been found to be effective in suppressing T-cell mediated destruction of the pancreatic β cells in auto immune diabetes model [25].

Trigonella foenum-graecum

Belonging to the family of Fabaceae, *Trigonella foenum-graecum* (Fenugreek) is an ancient curative plant widely distributed in Asia, Africa and the Mediterranean countries [135]. Its seeds, which mature into long pods, are used as a time-honored remedy for the treatment of diabetes [136]. Several studies has shown it's hypoglycemic, hypocholesterolemic and hyperinsulinemic effects both in patients with IDDM and NIDDM as well as in experimental diabetic animals [137]. Treatment of diabetic rats with fenugreek seed powder for 12 weeks has found to elevate the activity of CAT and SOD as well as the concentration of GSH thereby reversing oxidative damage. In addition, fenugreek supplementation is shown to reduce the level of MDA and peroxide lipids in the kidney homogenates of diabetic animals, indicating its antioxidant activity [138]. Its ability to decrease ROS production and activate antioxidant enzymes leads to attenuation of AGE production followed by reduction of NF- κ B activation, which in turn down regulates the expression of genes like IL-6 [139]. Decrease in the level of IL-6 and inflammation could be correlated to the improvement of the antioxidant enzymes. Furthermore, it also protects kidney from functional and histopathologic abnormalities of DM [137,140]. Studies have also demonstrated the role of fenugreek seeds in improving glucose homeostasis and renal function in alloxan induced diabetic rats by delaying carbohydrate digestion and absorption thereby improving kidney's antioxidant status [138]. Being a commonly used edible item and relative lack of toxicity, fenugreek stands for a positive dietary adjunct for the treatment of DN and may be considered as a potentially active oral antidiabetic agent in future.

Psidium guajava

Psidium guajava of the family Myrtaceae, commonly called guava, is a semi deciduous tropical tree which is widely grown throughout Asia for its fruit [141]. Its use is limited not only as food but it is widely used as folk medicine in subtropical areas all around the globe due of its pharmacologic activities. The various part of the plant has been known to possesses many

pharmacological properties like anti-spasmodic, antimicrobial, hypoglycaemic, antiamebic, antioxidant, anti-inflammatory, anti-cancer, analgesic, endothelial progenitor cells, anti-diarrhea, anti-stomachache and so on [142,143]. In particular, the leaf extract and fruit has traditionally been used as a hyperglycemic agent. The essential constituents of guava leaves are phenolic compounds, isoflavonoids, gallic acid, catechin, epicatechin, rutin, naringenin and kaempferol. The pulp is rich in ascorbic acid and carotenoids (β -carotene, lycopene and β -cryptoxanthin) [142,144]. Report suggests that guava extract is effective against DN in various ways. The attenuation of systemic oxidative stress and hyperglycemia occurs in diabetic rats as a consequence of guava fruit intake [145]. Its renal protective activity is mainly due to its ability to decrease malondialdehyde and ROS levels and to retain the activity of antioxidant enzymes. It improves body weight loss, hypo-insulinemia and renal functions in diabetic mice [146]. Study by Lin et al. has shown that guava extract suppresses renal aldose reductase activity, the rate limiting enzyme in polyol pathway, thereby reducing the synthesis of sorbitol and as a consequence of which AGE generation decreases. This indicates that it can intercede aldose reductase and repress polyol pathway [146].

Zingiber officinale

Amelioration of endogenous oxidative damage occurs to some extent by consumption of nutritional antioxidants through diet. Addition of spices to perk up the flavour of foods is a long back tradition. A very well-known spice widely consumed by humans and possessing antioxidant property is ginger, a rhizome of *Zingiber officinale* plant of the family Zingiberaceae [147]. This medicinal herb seems to be an excellent oral remedy for different pathological conditions due to its affectivity and lack of serious side effects. Its chemical constituents include gingerols, shogaols, some phenolic ketone derivatives, volatile oils, alkaloids, saponins and flavonoids [148] but whether one or more of these components are actually responsible for the protective action is yet to be identified. Nowadays, researchers are shifting their attention towards the protective role of ginger in DN. With this respect, a study by Tzeng et al. has shown the remedial effects of ginger on renal damage in diabetic rats [149]. Administration of ginger to diabetic animals has shown to reverse the disturbed antioxidant and lipid peroxidation levels thereby significantly reducing the nephropathy [150]. Alteration in the activities of cytosolic and mitochondrial enzymes like glucose-6-phosphate dehydrogenase (G6PD), LDH, sorbitol dehydrogenase (SDH), malate dehydrogenase (MDH) and glutamate dehydrogenase (GDH), responsible for maintaining favourable condition in the cells, during DM results in severe malfunctioning of kidney. A study by Ramuduet al. has shown the reversal of all these enzyme activities to normal after the oral administration of ginger for 30 days [151]. One of the foremost symptom of diabetes i.e. weight loss occurs due to (i) enormous breakdown of tissue proteins; (ii) unavailability of carbohydrate as an energy source leading to wastage of protein; and (iii) excretion of glucose through urine [152,153]. Administration of ginger brings up the body weights near to normal by lowering glucose level, polyurea and also by preventing osmotic degradation [151]. The beneficial role of ginger in DN makes it a possible nutraceutical supplement to

cope up with diabetes-induced detrimental effects and to protect renal cells from damages.

Aloe vera

Another very well acknowledged plant in the management of DN is *Aloe vera*, also called “secret plant originated from ancient Egypt” of family Liliaceae. It is enormously used as a traditional medicine by Indians for skin diseases, constipation, worm infestation, colic and infections and by Chinese for the treatment of fungal diseases [154]. The presence of high amount of phenolic compounds like glycosides (aloin), β -1,4 acetylated mannan, 1,8-dihydroxyanthraquinone derivatives, mannose phosphate and alproglucoprotein are responsible for its biological activity [155]. Availability of *Aloe vera* as pharmaceutical products like gels and ointments for topical applications and tablets and capsules for oral use has increased up its use [156]. Oral administration of *Aloe vera* has been shown to significantly reduce the level of lipid peroxides and stimulate the β -cells of the pancreatic islets thereby lowering the glucose level and thus ameliorating DN [155]. Study of the effect of *Aloe vera* gel extract in STZ induced diabetic rats has shown its positive effect in normalizing the levels of fasting blood glucose and plasma insulin. Its treatment also reduces the concentration of triglycerides, cholesterol and free fatty acids in the plasma, liver and kidney of diabetic rats [157]. Oral administration of *Aloe vera* causes detoxification of H_2O_2 and its subsequent decomposition into H_2O and O_2 mainly by elevating antioxidant profile of CAT, GPx, etc. to a significant extent [158,159]. Thus *Aloe vera* has been found to be potential candidate for alleviating DN, a global cause of mortality and morbidity, by reducing oxidative damage and modulating antioxidant enzymes.

It can, therefore, be said that the above mentioned plants can turn out as potential anti diabetic agents by targeting the molecules of oxidative stress and glucose metabolism pathway, showing ameliorating effects on DN. (Figure 4) shows the schematic representation of different plant extracts affecting a wide array of downstream molecules and events while exhibiting antioxidant activity.

Drugs

In addition to naturally occurring antioxidants, research related to the antioxidant activity of drugs and their ability to ameliorate oxidative stress induced renal damage during diabetes are being conducted in many laboratories. A few recently studied drugs and their mechanistic action in alleviating DN has been tinted in the forthcoming studies.

Telmisartan

Telmisartan is a well-known unique angiotensin II (Ang II) type 1 receptor blocker (ARB) that exerts a powerful antioxidant effect in patients with DN. A recent clinical study has shown it to be more effective in renoprotection as compared to other ARB class of drugs like losartan and valsartan owing to the difference in their intrinsic pharmacokinetic and physiochemical properties [160]. Furthermore, a number of properties like the best binding affinity to Ang II type 1 receptors, the maximum plasma half-life and the highest lipophilicity among the presently available

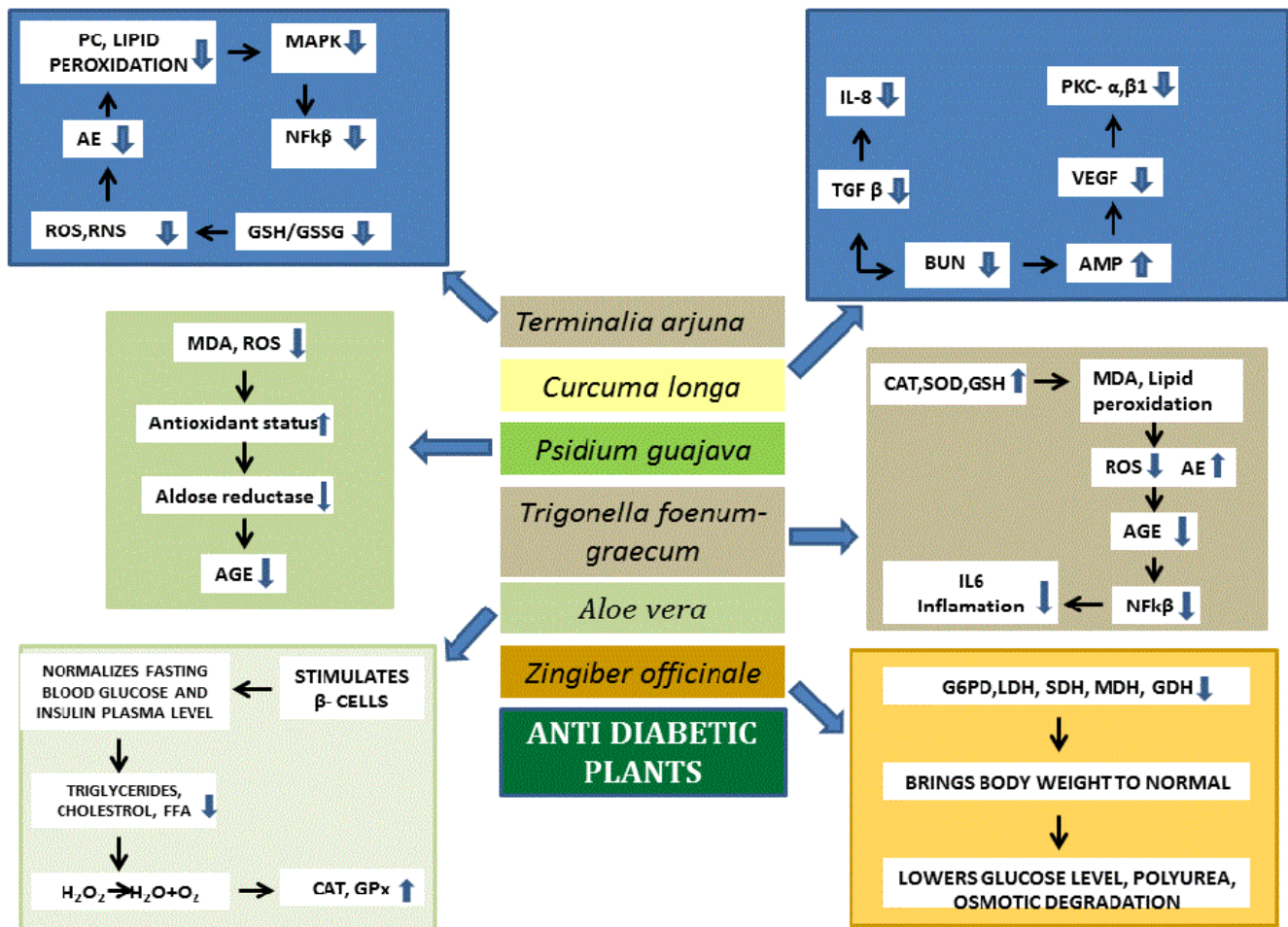


Figure 4 The mechanistic aspect of individual plants in amelioration of oxidative stress induced diabetic nephropathy by targeting different signaling intermediates. PC: protein carbonylation; AE: antioxidant enzyme; FFA: free fatty acid.

ARBs make this molecule a long lasting antioxidant [161,162]. It basically functions by enhancing the activity of superoxide scavenging enzyme i.e., SOD, by down regulating NOX, an enzyme responsible for superoxide production [163,164]. It has also been shown to reduce albuminuria in DN patients [165] and decrease DN conversion from the early to the evident form [166]. Ang II directs the synthesis of superoxide through the activation of NOX. Therefore, blockage of Ang II pathway through Ang II type 1 receptors by telmisartan ameliorates oxidative stress induced renal injury in DN.

Metformin

Metformin, an aminoguanidine derivative and an oral hypoglycemic drug, is a first-line therapy for controlling NIDDM and preventing its complications, especially DN [167,168]. It possesses antioxidant property and causes reduction of albumin excretion rate in the urine of diabetic patients. In addition, it decreases the production of AGE, improves free radical defense system by its ability to directly scavenge oxygenated free radicals and thereby reduces intracellular ROS levels [169]. By reducing the generation of ROS, metformin shows renoprotective effect in diabetic patients which has been confirmed by an increment in

the ratio of adenosine triphosphate/adenosine monophosphate (ATP/AMP) in the renal tissue of normoglycemic rats treated with drug after 8 weeks as compared to STZ induce diabetic rats which shows decrease in the level of both ATP and AMP [170]. Recent research also indicates that metformin intake can ameliorate the increased MDA level [171] and can restore the biochemical alteration and modulation of both enzymatic and non-enzymatic antioxidants [172] thereby indicating the clinical use of this antidiabetic drug in the treatment of DN.

Paricalcitol

Paricalcitol (19-nor-1,2,5-dihydroxyvitamin D2) is an active, third generation vitamin D analog that shows biological activity similar to vitamin D [173,174]. It binds and activates vitamin D receptor and thereby produces albuminuria reducing effect and slows down the progression of kidney disease [175]. A number of researches in experimental diabetic nephropathy models have shown the improvement of glomerular damage as an after effect of paricalcitol administration. Moreover, subsequent studies also suggest the involvement of RAS in the development of DN. The increment in rennin activity during DN leads to the conversion of AngI and AngII which increases ROS production thereby causing

renal damage. Therefore, drugs having the ability to inhibit renin-angiotensin system (RAS) is currently used for treatment of DN. It has been shown that paricalcitol suppresses RAS in the kidney of diabetic rats thereby showing anti-oxidative effects [176].

Pioglitazone

Positive and protective effects of thiazolidinedione (TZD) group of drugs, like pioglitazone, in the amelioration of antioxidant enzyme levels in renal histopathology and renal tissue associated with DN has recently been investigated by many researchers. Though pioglitazone does not bring up any changes in the blood glucose level of diabetic rats, it mitigates the renal histopathological lesions like glomerular focal necrosis, tubular epithelial necrosis, tubular dilation and vascular wall consolidation [177]. Tanimoto et al. have reported that treatment of rats with pioglitazone normalizes bowman capsular volume, drops down the amount of endothelial constitutive nitric oxide synthase (ecNOS) in the glomerular vascular endothelium, and improves the glomerular hyperfiltration [178]. Increased expression of NF- κ B p65 in renal tubules and glomeruli during DN has been reduced by pioglitazone therapy thereby showing protection from renal pathophysiology [179]. But TZDs has limited clinical uses due to the occurrence of fluid retention, hemodilution, and heart failure in about 15% of patients [180].

Spironolactone

A number of clinical and animal model studies related to the beneficial role of aldosterone receptor blocker like Spironolactone (SPL) against DN are currently going on. SPL plays a positive role in the attenuation of renal injury and proteinuria thereby helping in ameliorating DN [181]. The increased up expression level of NOX-4 during diabetes which causes renal damage by directing the synthesis of ROS has been found to decrease after SPL treatment [182]. Increased glucose level leads to activation of glomerular TGF- β expression which in turn also produces ROS. SPL exposure has shown to down regulate TGF- β expression and hence it inhibits oxidative stress in renal cortex of diabetic rats [183]. Therefore, it can be said that SPL can function as an antioxidant compound by elevating anti-oxidative defense systems (like GSH level) and thereby reducing oxidative stress [184]. However, the limitation of SPL administration is that its protective action is effective at early stages of DN but it has no beneficial effect at later stages of the disease [185,186].

Berberine

Berberine (BBR), an isoquinoline alkaloid and one of the key constituents of *Coptidis rhizoma* and *Cortex phellodendri*, has been well known for multiple pharmacological activities. Antibiotic, hypolipidemic, antitumor, antiviral, anti-arrhythmia, and cytotoxic effects are certain properties exhibited by BBR [187]. Several animal and clinical studies have been there to show that BBR improves hyperglycemic condition and also alleviates insulin resistance, thereby indicating its antidiabetic property [188].

Treatment of diabetic rats with BBR significantly decreases fasting blood glucose, creatinine, blood urea nitrogen and urine protein level. It also leads to the decrease in the activity of aldose

reductase at both mRNA and protein levels as reported by Liu et al. [189]. Studies also confirm the increment in the activity of SOD and the decrease in superoxide anion and MDA level after BBR treatment, suggesting the ameliorative role of BBR against renal dysfunction in DN rats [190].

Thus it can be concluded that the above mentioned drugs can turn out as potential anti diabetic agents by targeting oxidative stress and glucose metabolism pathway molecules, showing ameliorating effects on DN. (Figure 5) shows the schematic representation of different drugs affecting a wide array of downstream molecules and events while exhibiting antioxidant activity.

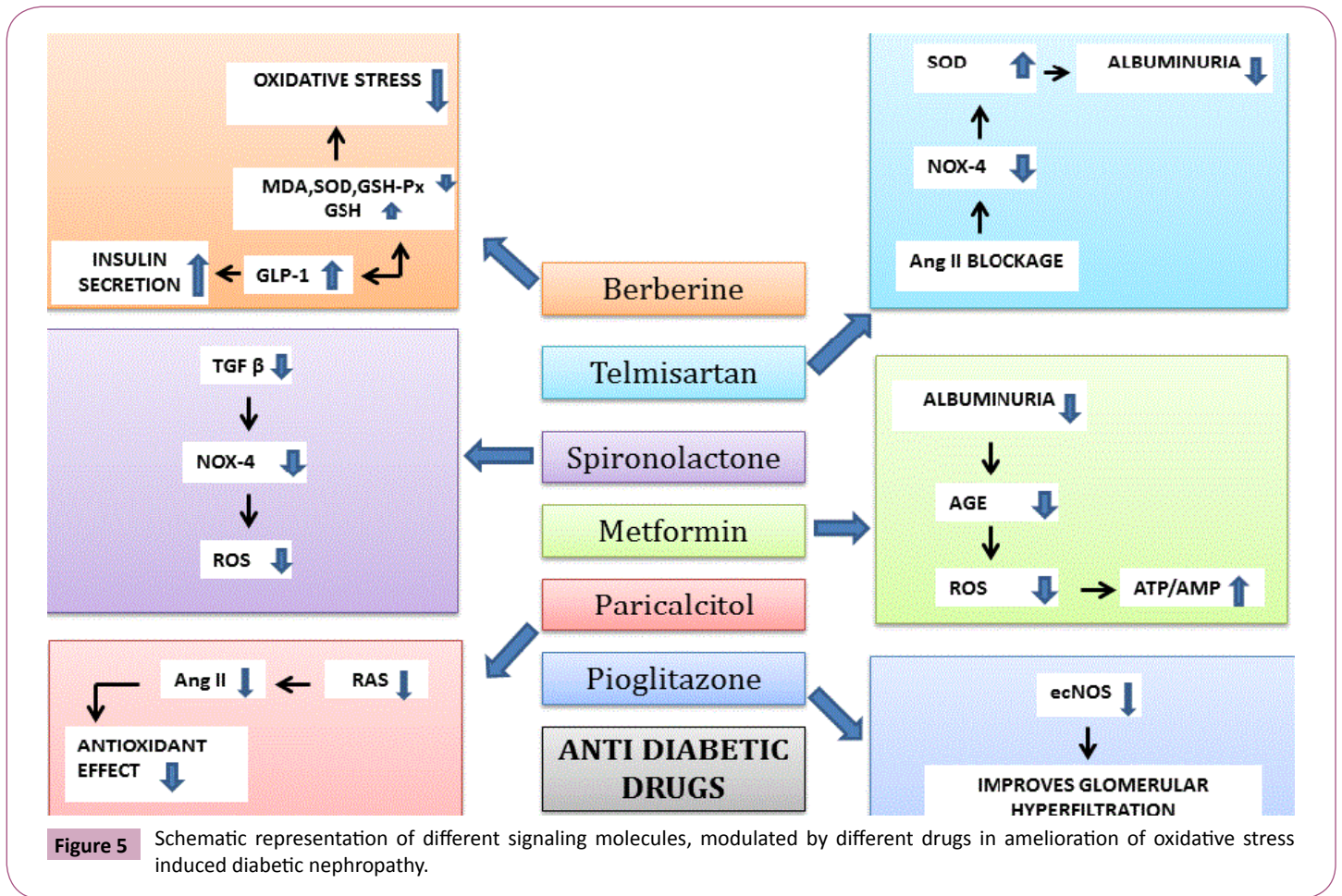
Current status and future prospect of antioxidant therapies against diabetic nephropathy

Type 1 diabetes is considered as one of the most studied organ-specific pathophysiology associated with the phenomenon of autoimmunity. However, with the emergence of numerous strategies for its prevention or cure, some distance still remains between the theoretical and realistic approach of immunotherapy. Different antioxidant molecules are found to be effective against different diabetic complications including nephropathy. In addition to the radical scavenging activity, some antioxidants are also capable of modulating an array of signaling cascade, which helps to restore the normal kidney tissue homeostasis. A number of antioxidants that are effective in treating autoimmune disease can play a beneficial role against DN. So far we have discussed the anti-diabetic properties of different therapeutic agents via their antioxidant property focusing a little bit on their immunomodulatory properties. Researches are being focused on targeting different T-regulatory cells which can suppress pro-inflammatory response via attenuation of respective signalling cascades. Experiments on different animal models have demonstrated their efficacy in treating oxidative stress induced DN [184]. Interestingly, studies on human with some of these molecules have also shown positive results. The effects of plant extracts on diabetic patients have shown to reduce the level of ROS, blood glucose level along with the improvement of antioxidants activity [113,191]. Studies on human also indicate the renal protective effect of above mentioned drugs by decreasing the expression of TGF- β and AGE, thereby preventing albuminuria [160,192]. But to increase the efficacy of above mentioned molecules, a targeted drug delivery system is essential and that is lacking in present scenario.

Current research projects, therefore, need to be focused on an effective delivery of antioxidant molecules to the target site specifically in the kidney for a better and proficient mode of action of antioxidants in preventive treatment of renal complications in DM. Moreover, over expression and endogenous administration of different antioxidant genes and/or molecules will also result in positive reversal of diabetes induced defects in renal cells that are affected due to excessive amount of reactive free radicals.

Conclusion

The advancement in the knowledge of potent antioxidants has



covered the way for greater insight in the treatment of DN. In this review, we had primarily focused on providing the understanding of diabetes induced oxidative stress via different signalling pathways. ROS formation contributes to the activation of various downstream signaling cascade leading the way to structural and functional changes in kidney. Activation of VEGF, PKC, T-reg cells and down regulation of nitric oxide production leads to DN. Increasing evidence in literatures suggest that the administration of therapeutic agents restores the antioxidant defense system thereby preventing ROS mediated damages. The anti-oxidative property of various vitamins, plants and their active ingredients

and drugs in combating such complications has been portrayed in this review. A detailed study in the potential protective role of these agents needs to be carried out for the effective treatment of DN. Moreover, a better understanding of immune signalling between T cell and pancreatic β -cell interaction for auto antigen processing is also necessary to develop new therapeutic strategies.

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