Chapter # 2 REVIEW OF LITERATURE

*Salvia miltiorrhiza* Bunge (Labiatae) (SM), slows the progression of renal function deterioration in DN rats induced by STZ. Significant renal dysfunction, as indicated by increased urine protein excretion and serum creatinine levels was observed in the DN rats. SM treatment reduced urine protein excretion. Moreover, immunohistological staining analysis revealed that SM reduced the expressions of TGF-β1, collagen IV, ED-1, and RAGE. These data indicate that SM attenuates the structural manifestations of renal disease progression and ameliorates the effects of renal dysfunction in DN rats [115]. Young Sook Kim *et al* [116] revealed that the extract of *Cassiae semen* (CS) attenuates DN via inhibition of advanced glycation end products accumulation in streptozotocin-induced diabetic rats. The preventive effect of CS was achieved via inhibition of AGEs accumulation and RAGE expression in experimental models of diabetic nephropathy. Furthermore, CS treatment inhibited COX-2 expression in the renal cortex of STZ-diabetic rats.

The administration of Icariin effectively ameliorated alterations in early diabetic nephropathy induced by STZ. The finding suggests that Icariin may not be useful in the prevention of hyperglycemia in early diabetic nephropathy. However, the inhibitory effects of Icariin on expressions of TGF-β, collagen IV and oxidative stress diabetic rat imply its potential efficacy in preventing the progression of DN [117].

Kelly DJ *et al* [118] showed that renin inhibition with aliskiren is renoprotective in experimental advanced diabetic nephropathy, with effects that are similar but not identical to those caused by ACE inhibition. At present it is uncertain whether additional effects might be achievable at higher dose or whether the
demonstrated changes are applicable to other disease models and to humans. It is also uncertain whether additional renoprotection can be achieved by combining renin inhibition with more conventional blockers of the RAS.

Eunjin Sohn et al [119] suggested that the inhibition of AGEs accumulation in the kidney and the anti-apoptotic effect on podocyte by Aster koraiensis extract (AKE) might ameliorate diabetic nephropathy. It seems likely that the treatment with AKE is effective for treatment for diabetic nephropathy due to inhibition of AGEs accumulation in the kidney and serum, and could be a valuable therapeutic approach in diabetic nephropathy.

Zuo-qi Xiao et al [120] concluded that the polysaccharides from Liriope spicata var. prolifera (LSP) could reduce the fasting blood glucose and HbA1c levels of diabetic rats. Furthermore, function related parameters and structural damages of kidney in diabetic rats were meliorated by LSP. Hypolipidemic, antioxidant and down-regulation the system of AGE-RAGE were responsible for the preventive effects on diabetic nephropathy. Therefore, LSP had preventive effects on diabetic nephropathy in high fat-fed and low-dose STZ-treated diabetic rats. LSP could be developed as a potential new anti-diabetic drug.

Jingtao Zou et al [121] showed that the total flavonoids extracted from Murraya paniculata (L.) Jack (TFMP) leaves as a new intervention that can effectively control or prevent the development of kidney damage in diabetic rats and the effects of TFMP on DN may be via its regulation of glucose, lipid metabolism and oxidative stress as well as inflammation cytokines. There are multi-target effects by ethanol extracts of Rehmannia complex RC combining a moderate glucose lowering effect with suppressing endothelin-1 system, oxidative stress, depressed MMP (matrix metalloproteinases) 2 and 9 activity in STZ-induced diabetic nephropathy [122].
Avijeet Jain et al [123] revealed that the *Tephrosia purpurea* (TP) leaf and *Momordica dioica* (MD) fruit can prevent or retard the development of drug-induced diabetic nephropathy via its beneficial effects by correcting the hyperglycemia, antioxidant enzyme system, renal dysfunction as well as cure diabetic nephropathy to some extent. It is further concluded that MD fruits are more potent than TP leaves. It is also concluded that phenolic compounds and flavonoids may be responsible for the observed activities.

The scientific reports on oleanolic acid (OA) conclusively demonstrate its efficacy to intervene the pathogenesis of diabetic nephropathy through multiple mechanisms. The lower systemic toxicity of OA and its ability to act on multiple biological targets is also well known. OA has a favorable safety profile and has already been tested clinically. It is proposed that OA deserves further investigations through clinical trials for its role in the treatment of diabetic nephropathy [124].

Sen Zhang et al[125] study suggests that the skimming can suppress diabetic nephropathy in rats effectively, and may slow down the renal fibrosis by regulating TGF-β1 signal pathway. Haojun Zhang et al [126] proved that the administration of Chaihuang-Yishen granule (CHYS) may slow the progression of DN by inhibiting the inflammatory and consequently fibrotic processes.

Deng Pan et al [127] conclude that Fudan–Yueyang–G. lucidum (FYGL) confers protection against the renal functional and morphologic injuries by increasing activities of antioxidants and inhibiting accumulation of oxidation, suggesting a potential nutritional supplement for the prevention and therapy of DN. Haseena BHK et al [128] suggests that Semecarpus anacardium demonstrated antioxidant activity in diabetic nephropathy rats. The potential nephroprotective effect is plausibly due to its underlying antioxidant role.
Majid Tavafi et al[129] concluded that the *Satureja khozestanica* essential oil significantly can ameliorate glomerular hypertrophy, loss of glomerular number, glomerulosclerosis and attenuated serum urea and serum creatinine in diabetic rats. Wei Ma et al[130] suggested that the multiple components in Shanzhuyu could synergistically decrease the accumulation of ECM in mesangial cells by inhibiting the expression of Col IV, FN and IL-6. This provided partial evidences for the clinic practices of *Cornus officinalis* fruit (Shanzhuyu) in DN therapy. The review initially demonstrated the therapeutic effects of Astragalus injection in DN patients such as reducing urine protein and improving renal function [131].

Juqian Zhang et al[132] systematic review demonstrates that *Astragalus membranaceus* (root) and its effective components (APS and AS I) can reduce fasting blood glucose and albuminuria levels, reverse the glomerular hyperfiltration state and ameliorate proliferative glomerular pathological changes during the early stages of DN in rat models. Cong-Cong Zeng et al [133] demonstrate that rhein has the ability to mediate multiple molecular targets, particularly oxidative stress and inflammation, which makes rhein a potential candidate for the therapy of some diseases, such as DN.

Elhussainy E M et al [134] revealed that tannic acid which is identified as a one of the active compounds of *Ganoderma lucidum* aqueous extract showed highly antioxidant, antidiabetic and antihyperlipidemic activities and it can be used in treatment of diabetic nephropathy. STZ-induced diabetes male rats with the low doses of Moringa revealed a safe and an excellent antidiabetic activity due to its content of antioxidant compounds such as glucormoringin, phenols, and flavonoids and almost restored the diabetic rats to the normal healthy state. In addition, lower doses of Moringa under study may have greater medical benefits when used as food supplement for diabetic people’s diet [135].
Tzeng et al [136] propose the reduced accumulation of glomerular extracellular matrix in zerumbone-treated diabetic rats is a consequence of reduced infiltration of inflammatory cells, in addition to the antifibrotic effect of zerumbone. The beneficial effect of zerumbone in rats with DN is at least in part through antihyperglycemia which was accompanied by inhibition of macrophage infiltration via reducing p38 mediated inflammatory response.

Rajavel V et al[137] indicate that chronic administration of Oil palm (Elaeis guineensis) leaves extract (OPLE) exerts both antioxidant and pro-oxidant effects depending on the duration of treatment as assessed by levels of oxidative stress markers, renal dysfunction and renal pathology in DN. Lu et al[138] showed that the anti-inflammatory and antifibrotic effects of ruscogenin in DN may be attributable to prevention of NF-κB activation, by which inflammatory cell infiltration is abrogated, in turn ameliorating ECM accumulation. This study provides an important pharmacological and therapeutic basis for the treatment of DN. The beneficial effects of Oryzanol supplementation in preventing the development of DN may be attributed to its anti-hyperglycemic and antioxidant effect, coupled with its renoprotective action against functional and morphologic injuries, restoration of the altered lipid profile and reduction of renal oxidative and or nitrosative stress induced by hyperglycemia [139].

North American ginseng is effective in the prevention of diabetic nephropathy both in type 1 and type 2 animal models through a combination of mechanisms namely, it’s anti-hyperglycemic and antioxidant effects [140]. Elbe H et al[141] suggested that melatonin, quercetin, and resveratrol are beneficial in improving diabetic nephropathy by preventing oxidative stress.
Catalpol ameliorated the early diabetic nephropathy. It improved the renal function and decreased the overproduction of fibronectin and Col IV expressions in renal cortex of diabetic rats [142]. Naja naja atra venom reduces hyperglycemia, decreases urinary protein, improves renal function and structure, restrains oxidative stress and lipid metabolism products, and prevents inflammatory factor infiltration. The present study provides details about the effect of naja naja atra venom in the early stage of DN, suggesting that it could be a potential renoprotective pharmaceutical for DN patients [143]

Zhi-sen WANG et al[144] concluded that Rhodiola rosea played important roles in relieving DN injuries by decreasing the TGF-β1 expression in renal tissues. The renoprotective effects of curcumin seem to result from its inhibitory effect on ROS, lipid peroxidation and the production of vasoactive mediators, which play a role in improving renal dysfunction in diabetes [145].

Muthenna P et al [146] suggested that cinnamon and particularly its active principle procyanidin-B2 ameliorated STZ-induced proteinuria and podocyte injury in rats. This effect, at least in part, could be attributed to suppressing renal AGE-RAGE stimulated MCP-1 and PKC-α expression. Safranal was found to reduce dysfunction (its effect on BUN and Creatinin levels) and damage (histopathological data) that occur in renal tissue, by means of its both antioxidative and anti-inflammatory effects diabetic nephropathy. Thus, safranal may be considered to be anti-inflammatory by preventing free radicals, inducing cytokine synthesis [147].