Diabetic nephropathy: A short review

Sulaiman Muhammad Sani

ABSTRACT

Diabetic nephropathy is the main complication in diabetic patients. It leads to renal failure and end stage renal disease (ESRD) worldwide. Increment of kidneys size, glomerulosis, and increase level of albumin in urine, glomerular hypertrophy and thickening of glomerular basement membrane Diabetic nephropathy are the main characteristic of Diabetic nephropathy (DN). Persistent high glucose level in the blood results in hemodynamic changes and mechanical changes in the glomerular which is responsible for gene expression changes as well as alteration downstream transcription factors. Oxidative stress can be defined as over production of reactive oxygen species. Different drugs such as simvastatin Andrographolide Schisandrin B, Diosmin, Lycium chinense and Lycium chinense have anti-oxidant property, Most of these drugs increase the production off exogenous antioxidant which include reduced glutathione (GSH) and catalase (CAT).

Key words: Oxidative stress, antioxidant, cytokines, inflammation, apoptosis, fibrosis, reactive oxygen species.

INTRODUCTION

Diabetes mellitus is a life threatening illness characterized by high blood glucose level which occurs as a result of reduction of insulin secretion or down regulation of insulin receptors. The incidence of diabetes is always increasing in which the number of patients can reach seven hundred million by 2045[1]. Persistent hyper-glycaemia is related to macromolecular complications which have impact on many organs such as kidneys and eyes. Diabetic nephropathy is the main complication in diabetic patients [2]. It leads to renal failure and end stage renal disease (ESRD) worldwide [3-4]. Increment of kidneys size, glomerulosis, and increase level of albumin in urine, glomerular hypertrophy and thickening of glomerular basement membrane Diabetic nephropathy are the main characteristic of Diabetic nephropathy (DN) [5-7]. Approximately 15–40% of diabetic patients experience DN [8]. Chronic persistent

hyperglycemia has more impact in DN pathogenesis, although other factors also take role in DN pathogenesis such as chronic inflammation, dyslipidemia, lack of insulin signaling, renal polyol formation, increase in oxidative stress and deposition of advanced glycation end product[9-11.] Hemodynamic and metabolic impairment occurs as a result of local inflammatory stress in DN. Tumor necrosis factor (TNF)-a and Interleukin-1b are the Inflammatory markers which increase in DN patients [12]

Pathogenesis of Diabetic nephropathy

Diabetic nephropathy pathogenesis is complex pathway; high blood glucose level is the main factor associate with progressive glomerular damage in diabetes. Persistent high glucose level in the blood results in hemodynamic changes and mechanical changes in the glomerular which is responsible for gene expression changes as well as alteration downstream transcription factors[13].Therefore, these changes result in liberation of several cytokines, growth factor as well as oxidative stress[14], increase in production of reactive oxygen specie occur as a result of hyperglycemia which leads to the activation of different redox-sensitve signaling molecules followed by macro and micro molecular complications. High production of ROS leads to the inactivation of endogenous antioxidant, and causes chromatin condensation, accelerated apoptosis and DNA fragmentation epithelial cell in the kidney [15].

What is oxidative stress?

Oxidative stress can be defined as over production of reactive oxygen species (ROS)[16]. ROS generation are counter-balance by endogenous antioxidants in the normal body function, ROS are chemical substances that have capacity to donate electron to several biological molecules. Oxidative stress occurs as a result of imbalance between endogenous antioxidants and ROS also known as pro-oxidants which lead to cellular damage [16]. The main souce of O2•- production mitochondrial electron transport chain complex .Xanthine oxidase produced via xanthine dehydrogenase, which utilize oxygen molecule as e- acceptor during catabolism of xanthine. Xanthine oxidase is the source of O2•-, H2O2 and OH•, NADPH catalized the conversion of molecular oxygen into Superoxide radical (O2•-) O2•- is converted to hydrogen peroxide (H_2O2). H_2O2 can be converted into water and O_2 glutathione peroxidases (GPx) and GSH, it

can also converted into hydroxyl radical (OH•) by autooxidation of Fe^{2+} Fenton and Harber Weiss reactions[35] Figure 1.

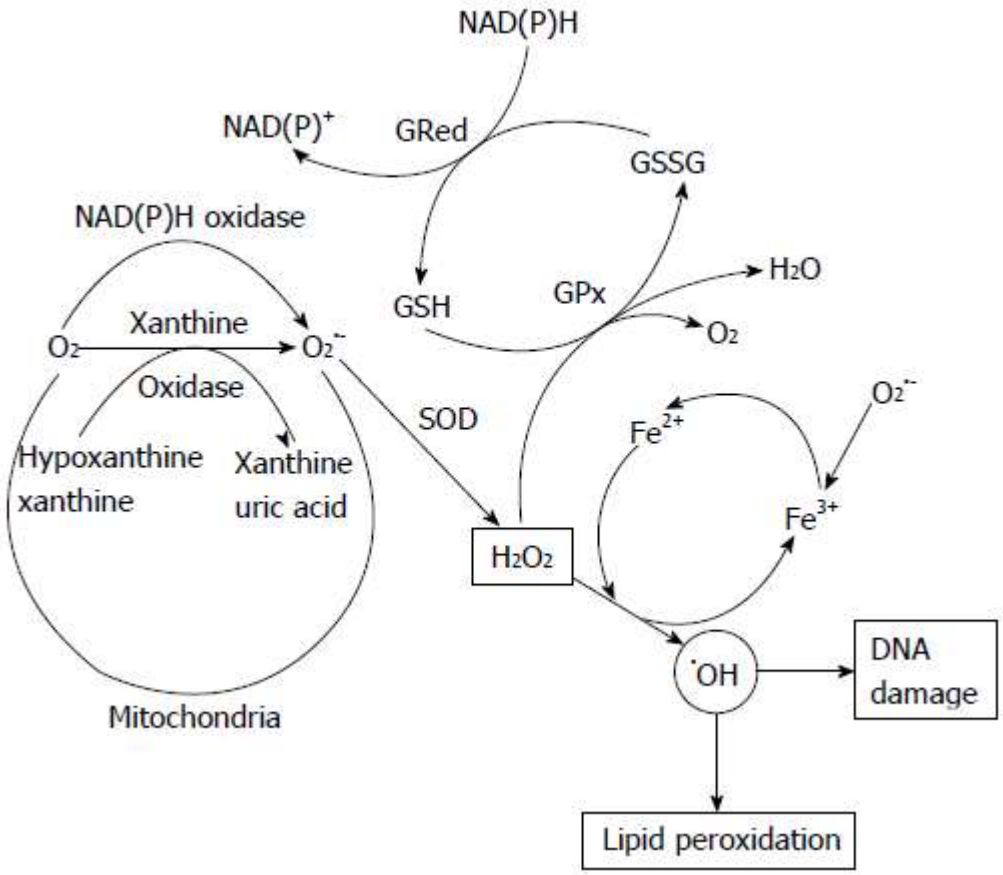

Fig.1

Role of different drugs use in diabetic nephropathy

Simvastatin

Statins are the class of drug for lowering-lipid in the body, Simvastatin maintain the glucose level and prevent weight loss in diabetic rat [18] , it also protect oxidative stress against pancreatic β-cells and increase secretion as well as sensitivity of insulin [19,20]. Hyper-glycaemia induced pro-oxidants production accelerates the generation of growth factors, transcription factors and cytokines which have implication in DN. Pro-oxidants trigger lipid peroxidation which lead to the tissue damage and renal fibrosis [21]. Overproduction of pro-oxidants which lead to oxidative stress in renal tissue which is associated with cellular antioxidants depletion such as GHS, herein, CAT and superoxide dismutase (SOD) [22,23]. Peroxynitrite produced as a result of the reaction between NO and superoxide radicals which leads to damage of DNA [24]

Decrease in lipid peroxidation and Nitric oxide (NO) was observe during Simvastatin supplementation, it also enhance the generation of endogenous anti-oxidant such CAT, GHS and SOD in diabetic rat's kidneys [17] previous studies reported that; oxidative stress is prevented by Simvastatin, it also has renoprotective effects as a result of decrease in oxidative stress and prevent the depletion of endogenous anti-oxidant. The effect of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is inhibited by simvastatin which is the main enzyme responsible for ROS generation [17]. Simvastatin decreased albuminuria and urine volume, it also increases clearance of creatinine as well as creatinine levels in urine [17]. Creatinine clearance is the renal function biomarker which is proportional to the glomerular filtration rate (GFR) [17]. Albuminuria is the main clinical manifestation in renal damage, the rate of albumin level in the urine determines the severity of renal damage [25]. Foot process effacement and podocytes hypertrophy leads to albuminuria [26]. Therefore, urine albumin level can be deceased by reduction of glomerular hyper permeability and kidney damage[27]. Simvastatin prevented renal apoptosis by decrease the expression of pro-apoptotic protein BAX and increases the expression of anti-apoptotic protein Bcl-2 significantly [17].

Sulforaphane (SF)

Sulforaphane (SF) is an isothiocyanate isolated from cauli flower and broccoli. It increased the activity of nuclear factor erythroid 2-related factor 2 **(Nrf2)** (Nrf2 is a redox-sensitive transcription factor) Nrf2 combines to antioxidant response elements (ARE) present in the promoter region of coded genes for various related stress-responsive proteins and antioxidant enzymes [27]. SF has protective activity against acute kidney injury (AKI) as a result of the stimulation of Nrf2-dependent antioxidant, the expression of heme oxygenase-1 , quinone oxidoreductase 1, NADPH and level of GSH by SF[28]. SF also prevent the damage of tissue by maintaining GHS level and oxidative damage reduction [29] and maintaining the mitochondrial respiration [30]. SF prevents acidophilic necrosis which occurs as a result proximal tubular damage in maleic acid induced nephropathy. Renal vasoconstriction result in reduction of renal blood flow, renal vascular resistance (RVR) and renal plasma flow (RPF) observed in nephropathy induced by maleic acid (MA) was prevented by SF[31]. Oxidative stress was reduced as a result of the generation of antioxidant enzyme like Heme-oxygenase

HO-1. The inductions of these enzymes significantly prevent proximal tubular apoptosis [32]. Nitric oxide synthase (NOS) is the main source of pro-oxidants; the activity of NOS can be terminated by SF. Thus isothiocyanate not only enhance antioxidants activity but also prevents the generation of ROS by preventing the activity of NOS [33].

Andrographolide

Andrographolide decreased albumin excretion I diabetic mice. NADPH oxygenase-1 (NOXI) is an enzyme responsible for the production of reactive oxygen species (ROS), Andrographolide inhibits the expression of NOX1, and therefore DN can be prevented by decreasing the production of ROS through NOX1 inhibition. Glomerular fibrosis and mesangial hypertrophy occur due resident inflammation and proliferation of mesangial cells which observed in diabetic mice, the inflammatory gene transcription is regulated by NF-κB pathway, high level of NF-κB was observed in diabetic mice which decresed by Andrographolide. Activation of protein kines B(Akt) mediated Mesangial cell hypertrophy, Andrographolide prevents the actvation of Akt. Thus, Andrographolide prevents DN through the inhibition of NF-κB and Akt.[34]

Schisandrin B (SchB)

Schisandrin B (SchB) is obtained from Chinese Schisandra chinensis, SchB is abundant in the fruit part of the plant, and it's the main chemical constituent present in the plant [35]. Many studies reported that fibrosis is among the pathological pathway of DN, fibrosis is associated with narrowing of capillary lumen which occurs as a result of accumulation of collagen and connective tissue, SchB prevent fibrosis by decreasing the accumulation of collagen and connective tissue. It prevents renal apoptosis through the restore of BAX and up regulation of BCL2. , it also prevents inflammation via up regulation of IkBa (NF-kB inhibitor), inhibition of TNF-a protein and VCAM-1 down regulation [36].

Diosmin

Diosmin obtained from hesperidin by dehydrogenation, its abundant in the pericarp of many citrus family [37]. Diosmin decreases the level of Malondialdehyde (MDA) which is the natural product of lipid peroxidation, many studies have been reported that metabolic syndroms are associated with Advanced glycation end products (AGEs) decreased by Diosmin[38].

Lycium chinense (LC)

Lycium chinense is a popular Chinese traditional medicine, it belongs to Solanaceae family. Whole part of the plant can be used as a medicine but leaf is mostly used as medicine [39, 40, 41]. LC reduces inflammation through the inhibition of inflammatory cytokines such as IL-1β, TNF-α and IL-6 , decreases the production of MDA in the lipid peroxidation path way and increases the activity of endogenous antioxidant such as GSH and CAT [42]

Ergosterol (EGR)

According to *leu et al*.EGR decreased the serum level of inflammatory cytokines such as MCP-1 IL-6 and TNF-α. It also reduced the level of blood urea nitrogen (BUN), albumin and albumin/creatinine ratio (ACR) which indicated the reduction of liver damage. EGR is significantly increased the level of insulinwhich is associated with decrease of blood glucose level [43].

Curculigo orchiodies (CO)

Curculigo orchioides is a traditional medicine which widely used, it possesses powerful antioxidant activity, and it belongs to Amaryllidaceae family [44]. The hydroalcoholic extract reduced blood glucsose level significantly, its also reported that the level of SOD, GSH and CAT were significantly increased by CO in dose related manner. Albumin, urea and creatinine are the biomarkers which indicate the extent of renal damage, their level were decreased after administration of CO. Thus, CO reduces renal damage [45]

S. no	Drug	Mode of action
1	**Simvastatin**	➢ Increased the level of endogenous antioxidant such GSH and CAT. ➢ It also decreased the level of ROS by 2NADPH inhibition
2	**Sulforaphane**	➢ It has protective activity against acute kidney injury (AKI) as a result of the stimulation of Nrf2-dependent antioxidant
3	**Andrographolide**	➢ It decreased the level of ROS through the inhibition of NOX. ➢ It prevents DN through the inhibition of NF-κB and Akt
4	**Schisandrin B**	➢ it a prevents inflammation via up regulation of IkBa, inhibition of TNF-a protein and VCAM-1 down regulation. ➢ It also prevents DN by decreasing fibrosis in the renal tissue
5	**Diosmin**	➢ It decreases the of Malondialdehyde (MDA) which is the natural product of lipid peroxidation
6	**Lycium chinense**	➢ It reduces inflammation through the inhibition of inflammatory cytokines such as IL-1β, TNF-α and IL-6
7	**Ergosterol**	➢ It decreases the serum level of inflammatory cytokines such as MCP-1 IL-6 and TNF-α
8	**Curculigo orchiodies**	➢ its decrease the level of SOD, GSH and CAT significantly.

CONCLUSION

Diabetic nephropathy is among the complication of diabetes mellitus, it occurs as a result of imbalance between ROS and endogenous anti-oxidants this condition is known as oxidative stress, different drugs show the anti-oxidants property be enhancing the generation of endogenous anti-oxidants such as glutathione, SOD and catalase e.t.c. and induced the depletion of ROS such as superoxide anion (O2•-) and NOX. In this review I discussed about the relationship between oxidative stess and renal damage in hyperglycemic condition, different studies indicated the activies of many drugs such as simvastatin Andrographolide Schisandrin B, Diosmin, Lycium chinense and Lycium chinense. Some of these drugs showed direct antioxidant activity by increasing th production of endogenous antioxidant such as GSH and CAT while some possessed anti-inflammatory activity through the inhibition of pro-inflammatory cytokines which are associated with oxidative stress.

REFERENCES

[1] N.H. Cho, J.E. Shaw, S. Karuranga, Y. Huang, J.D. da Rocha Fernandes, A.W. Ohlrogge, B. Malanda, IDF diabetes atlas: global estimates of diabetes prevalencefor 2017 and projections for 2045, Diabetes Res. Clin. Pract. 138 (2018)271–281.

[2] A.T. Reutens, R.C. Atkins, Epidemiology of diabetic nephropathy, Contrib. Nephrol.170 (2011) 1–7.

[3]N. Bhattacharjee, S. Barma, N. Konwar, S. Dewanjee, P. Manna, Mechanistic insight of diabetic nephropathy and its pharmacotherapeutic targets: an update, Eur. J. Pharmacol. 791 (2016) 8–24.

[4] W.F. Keane, B.M. Brenner, D. de Zeeuw, J.P. Grunfeld, J. McGill, W.E. Mitch, A.B. Ribeiro, S. Shahinfar, R.L. Simpson, S.M. Snapinn, R. Toto, RENAAL Study Investigators, The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study, Kidney Int. 63 (2003) 1499–1507.

[5] S. Hou, F. Zheng, Y. Li, L. Gao, J. Zhang, The protective effect of glycyrrhizic acid on renal tubular epithelial cell injury induced by high glucose, Int. J. Mol. Sci. 15
(2014) 15026–15043

[6] J.S. Saulnier-Blache, E. Feigerlova, J.M. Halimi, P. Gourdy, R. Roussel, B. Guerci, A. Dupuy, J. Bertrand-Michel, J.L. Bascands, S. Hadjadj, J.P. Schanstra, Urinary
lysophopholipids are increased in diabetic patients with nephropathy, J. Diabetes Complicat. 31 (2017) 1103–1108.

[7] X. Zhang, H. He, D. Liang, Y. Jiang, W. Liang, Z.H. Chi, J. Ma, Protective effects of berberine on renal injury in streptozotocin (STZ)-induced diabetic mice, Int. J. Mol.
Sci. 17 (2016) 1327

[8]S. Yagihashi, H. Mizukami, K. Sugimoto, Mechanism of diabetic neuropathy: where are we now and where to go? J. Diabetes Invest. 2 (2011) 18–32.

[9] S. Yamagishi, T. Matsui, Advanced glycation end products, oxidative stress and diabetic nephropathy, Oxid. Med. Cell. Longev. 3 (2010) 101–108.

[10] J.M. Forbes, M.E. Cooper, M.D. Oldfield, M.C. Thomas, Role of advanced glycation end products in diabetic nephropathy, J. Am. Soc. Nephrol. 14 (2003) S254–258.

[11] M. Brownlee, The pathobiology of diabetic complications a unifying mechanism, Diabetes 54 (2005) 1615–1625.

[12]S. Ogawa, T. Mori, K. Nako, S. Ito, Combination therapy with renin-angiotensin system inhibitors and the calcium channel blocker azelnidipine decreases plasma inflammatory markers and urinary oxidative stress markers in patients with diabetic nephropathy, Hypertens. Res. : Offic. J. Jpn. Soc. Hypertens. 31 (2008) 1147e1155.

[13] F.A. Wagener, D. Dekker, J.H. Berden, A. Scharstuhl, J. van der Vlag, The role of reactive oxygen species in apoptosis of the diabetic kidney, Apoptosis : Int. J. Program. Cell Death 14 (12) (2009) 1451–1458.

[14] N.K. Foundation, KDOQI clinical practice guideline for diabetes and CKD, Am. J. Kidney Dis. 60 (5) (2012) 850–886.

[15] K. Kachhawa, M. Varma, P. Kachhawa, D. Agrawal, M. Shaikh, S. Kumar, Study of dyslipidemia and antioxidant status in chronic kidney disease patients at a hospital in South East Asia, J. Health Res. Rev. 3 (1) (2016) 28–30.

[16]Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol 1997; 82: 291-295 [PMID: 9129943

][17] N.M.]Al-Rasheed et al. Biomedicine & Pharmacotherapy 105 (2018) 290–298

[18] A.M. Mohamadin, A.A. Elberry, H.S. Abdel Gawad, G.M. Morsy, F.A. Al-Abbasi, Protective effects of simvastatin, a lipid lowering agent, against oxidative damage in experimental diabetic rats, J. Lipids 2011 (2011) 167958.

[19] S.I. McFarlane, R. Muniyappa, R. Francisco, J.R. Sowers, Clinical review 145: pleiotropic effects of statins: lipid reduction and beyond, J. Clin. Endocrinol. Metab.87 (4) (2002) 1451–1458.

[20] K.K. Ray, C.P. Cannon, The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes, J. Am. Coll. Cardiol. 46 (8) (2005) 1425–1433.

[21]E. Ozbek, Induction of oxidative stress in kidney, Int. J. Nephrol. 2012 (2012) 465897.

[22] S. Zhang, H. Xu, X. Yu, Y. Wu, D. Sui, Metformin ameliorates diabetic nephropathy in a rat model of low-dose streptozotocin-induced diabetes, Exp. Ther. Med. 14 (1) (2017) 383–390.

[23] X. Chen, R. Wu, Y. Kong, Y. Yang, Y. Gao, D. Sun, Q. Liu, D. Dai, Z. Lu, N. Wang, S. Ge, F. Wang, Tanshinone II aattenuates renal damage in STZ-induced diabetic rats via inhibiting oxidative stress and inflammation, Oncotarget 8 (19) (2017)

[24] K. Stadler, M.G. Bonini, S. Dallas, J. Jiang, R. Radi, R.P. Mason, M.B. Kadiiska, Involvement of inducible nitric oxide synthase in hydroxyl radical-mediated lipid peroxidation in streptozotocin-induced diabetes, Free Radical Bio. Med. 45 (6) (2008) 866–874.

[25] G. Viberti, N.M. Wheeldon, Microalbuminuria reduction with valsartan in patients

with type 2 diabetes mellitus: a blood pressure-independent effect, Circulation 106 (6) (2002) 672–678.

[26] K. Reidy, H.M. Kang, T. Hostetter, K. Susztak, Molecular mechanisms of diabetic kidney disease, J. Clin. Invest. 124 (6) (2014) 2333–2340.

[27] J.M. Lee, J.A. Johnson, An important role of Nrf2–ARE pathway in the cellular defense mechanism, J. Biochem. Mol. Biol. 37 (2004) 139–143.

[28]Shelton, L.M., Park, B.K., Copple, I.M., et al., 2013. Role of Nrf2 in protection against acute kidney injury. Kidney Int. 84, 1090–1095.

[29]Santana-Martínez, R.A., Galván-Arzáte, S., Hernández-Pando, R., Chánez-Cárdenas, M.E., Avila-Chávez, E., López-Acosta, G., Pedraza-Chaverrí, J., Santamaría, A., Maldonado, P.D., 2014. Sulforaphane reduces the alterations induced by quinolinic acid: modulation of glutathione levels. Neuroscience 272, 188–198

[30] Negrette-Guzmán, M., Huerta-Yepez, S., Vega, M.I., León-Contreras, J.C., Hernández-Pando, R., Medina-Campos, O.N., Rodríguez, E., Tapia, E., Pedraza-Chaverri, J.,2017. Sulforaphane induces differential modulation of mitochondrial biogenesis and dynamics in normal cells and tumor cells. Food Chem. Toxicol. 100, 90–102.

[31] A. Briones-Herrera et al. Food and Chemical Toxicology 115 (2018) 185–197.

[32] Ray, P.D., Huang, B.W., Tsuji, Y., 2012. Reactive oxygen species (ROS) homeostasis and

redox regulation in cellular signaling. Cell. Signal. 24, 981–990. http://dx.doi.org/

10.1016/j.cellsig.2012.01.008

[33] Loomis, E.D., 2005. Endothelin mediates superoxide production and vasoconstriction through activation of NADPH oxidase and uncoupled nitric-oxide synthase in the rat aorta. J. Pharmacol. Exp. Therapeut. 315, 1058–1064.

[34] Ji, X., Li, C., Ou, Y., Li, N., Yuan, K., Yang, G., Chen, X., Yang, Z., Liu, B., Cheung, W.W., Wang, L., Huang, R., Lan, T., Andrographolide ameliorates diabetic nephropathy by attenuating hyperglycemia-mediated renal oxidative stress and inflammation via Akt/NF-κB pathway, Molecular and Cellular Endocrinology (2016),

[35] Savaskan NE, Ufer C, Kühn H, Borchert A. Molecular biology of glutathione peroxidase 4: from genomic structure to developmental expression and neural function. Biol Chem 2007; 388: 1007-1017[PMID: 17937614 DOI: 10.1515/BC.2007.126]57 Djordjević VB. Free radicals in cell biology. Int Rev

[36]X. Zhao, Y. Xiang, C. Cai, A. Zhou, N. Zhu, C. Zeng, Schisandrin B protects against myocardial ischemia/reperfusion injury via the PI3K/Akt pathway inrats, Mol. Med. Rep. 17 (2018) 556e561

[37] M.E. Waltner-Law, X.L. Wang, B.K. Law, R.K. Hall, M. Nawano, D.K. Granner, Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production, J. Biol. Chem. 277 (2002) 34933–34940.

Pharmacother. 83 (2016) 392–396.

[38]Liu, Chunyan, et al. "Ergosterol Ameliorates Renal Inflammatory Responses in Mice Model of Diabetic Nephropathy." *Biomedicine and Pharmacotherapy*, vol. 128, no. February, Elsevier, 2020, p. 110252, doi:10.1016/j.biopha.2020.110252.

[39] R. Yao, M. Heinrich, C.S. Weckerle, The genus Lycium as food and medicine: a botanical, ethnobotanical and historical review, J. Ethnopharmacol. 212 (2018) 50–66.

[40] S.Y. Kim, K.H. Lee, K.S. Chang, J.Y. Bock, M.Y. Jung, Taste and flavor compounds in box thorn (Lycium chinense Miller) leaves, Food Chem. 58 (1997) 297–303

[41]Y.C. Yeh, T.S. Hahm, C.M. Sabliov, Y.M. Lo, Effects of Chinese wolfberry (Lycium chinense P. Mill.) leaf hydrolysates on the growth of Pediococcus acidilactici, Bioresour. Technol. 99 (2008) 1383–1393

[42] Olatunji, Opeyemi Joshua, et al. "Lycium Chinense Leaves Extract Ameliorates Diabetic Nephropathy by Suppressing Hyperglycemia Mediated Renal Oxidative Stress and Inflammation." *Biomedicine and Pharmacotherapy*, vol. 102, no. March, Elsevier, 2018, pp. 1145–51, doi:10.1016/j.biopha.2018.03.037

[43]Liu, Chunyan, et al. "Ergosterol Ameliorates Renal Inflammatory Responses in Mice Model of Diabetic Nephropathy." *Biomedicine and Pharmacotherapy*, vol. 128, no. February, Elsevier, 2020, p. 110252, doi:10.1016/j.biopha.2020.110252.

[44]Wen C, Chen H, Yang NS. Developing phytocompounds from medicinal plants as immunomodulators. Adv Bot Res 2012;62:197e272.

[45]Singla K, Singh R, Nephroprotective effect of Curculigo orchiodies in streptozotocinenicotinamide induced diabetic nephropathy in wistar rats, J Ayurveda Integr Med, https://doi.org/10.1016/j.jaim.2020.05.0