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Short Communication

Role of Natural Products in the Treatment of Diabesity with Mechanism of Action-A Small Communication

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Earlier we have reviewed the role of natural products like flavonoids, monoterpenes, lentils like chickpenas and soya beans and walnuts for treating diabetes mellitus and insulin resistance besides importance of treating the 2 closely associated conditions that is obesity and diabetes mellitus (DM)together in view of which the term diabesity got coined [1-4]. Here we have further tried to explain the mechanism of some of the natural Chinese products in Diabetic nephropathy, cardiomyopathy and obesity besides taste problems.

Diabetic nephropathy (DN) is one of the causes of primary causes of end stage renal disease (ESRD), is increasingly diagnosed in patients secondary to increasing prevalence of diabetes mellitus (DM). Astragali –Radix, a chinese herb is widely shown to ameliorate symptoms of DM and DN, but its mechanics remain ill understood. Calycosin ($C_{16}H_{12}O_5$) is the major active component of Astragali – Radix. Zhang., et al. analyzed role of Calycosin in DN and explored its underlying mechanism. They examined cell activation, inflammatory cytokines expression and secretion, and protein levels in cultured mouse tubular epithelial cells (mTEC). db/dbmice were intraperitoneally injected with 10mg (kg-d) Calycosin or control saline for 4weeks followed by structure injury, inflammation and NFκB signaling activity. They found on analysis that TNF-α and IL1β were significantly induced by advanced glycation end-products (AGEs) but Calycosin markedly decreased the expression of TNF-α and IL1β in the mTEC. Calycosin effectively alleviated kidney injury in diabetic kidneys of db/db mice during the progression of diabetic renal injury as indicated by the reduction of histologic injury and immunohistochemistry regarding inflammatory cytokines. Mechanistically they identified Calycosin inhibited diabetes –induced inflammation in kidneys by suppressing the phosphorylation IKB-α and NFκB p65 in vitro as well as in vivo. Thus they concluded that Calycosin significantly ameliorated diabetes –induced renal inflammation in diabetic renal injury by inhibition of the NFκB dependent signaling pathway both *in vitro* as well as *in vivo* [5].

Glomerular fibrosis is caused by anaccumulation of intercellular spaces containing mesangial matrix proteins through either diffused or nodular changes. *Dianthus superbus* has been used in traditional medicine as a diuretic, a contraceptive, and an anti-inflammatory agent. Yoon., *et al*. aimed to investigate the effects of Dianthus superbus - EtOaC-soluble fraction (DS-EA) on glomerular fibrosis and renal dysfunction that has been implicated in DN in human renal mesangial cells and db/db mice. DS-EA reduced albumin excretion, creatinine clearance (Ccr)and plasma creatinine levels. DS-EA also ameliorated the levels of kidney injury molecules (KIM-1) and C-reactive protein. DSEA decreased the periodic –acid –Schiff (PAS) staining intensity and basement membrane thickening in glomeruli of the DN model. Additionally DS-EA, suppressed transforming growth factor –β (TGF-β)/Smad signaling. Collagen type IV, a glomerular fibrosis biomarker was markedly reduced on DS the EA administration, DS-EA pretreatment attenuated levels of inflammation factors like intracellular cell adhesion molecule (ICAM-1), and monocyte chemoattractant protein -1 (MCP-1). DS-EA inhibited the translocation of nuclear factor kappa B (NFκB) in Angiotensin II (Ang II)-stimulated mesangial cells. These findings support that DS-EA has protective effect against renal inflammation and fibrosis. Thus DS-EA might serve as a potential therapeutic agent targeting glomerulonephritis and glomerulosclerosis, that=> DN [6].

Chen., *et al*. examined that end stage renal disease (ESRD) and mortality among patients who use the traditional medicine (TCM) having DN. Of the total 125, 490 patients with incident DM patients from 2004-006were from the National Insurance Research Database in Taiwan and followed till 2012. The landmark method was applied to avoid immortal time bias, and propensity score matching was used to select 1: 1 baseline characteristics –matched cohort. The Kaplan-Meier method and competing risk analysis were used to assess mortality and ESRD rates separately. Among all eligible subjects, about 60% of patients were classified as TCM users (95% CI: 16.0-17.2). For the mortality rate, the 8 year cumulative incidence was 33. 8% for TCM users (95% CI: 33.1-34.6) and 49. 2%for

non users (95% CI: 48.5-49.9). After adjusting the confounding covariates, the cause specific hazard ratio of mortality for TCM users with ESRD (56. 8, 95%CI54. 6-59. 1)when compared with TCM users without ESRD (30.1, 95% CI 29.4-30.9). TCM Users who used TCM longer or initiated TCM treatments after being diagnosed with DN were associated with a lower risk of mortality. These results were consistent across sensitivity tests with different definitions of TCM users and inverse probability weighting of subjects. Thus concluding that the lower ESRD and mortality rates among patients with incident DN correlates with the use of TCM modalities or medication [7].

Elevated palmitic acid (PA) levels are associated with the development of inflammation, insulin resistance (IR) and endothelial dysfunction. Clinopodiumghinese (Benth) O Kuntze has been shown to lower blood glucose and attenuate high glucose induced vascular endothelial cells injury. Shi., *et al.* in the present study investigated the effects of ethyl acetate extract of C. chinense (CCE) on PA-induced inflammation and IR in the vascular endothelium and its molecular mechanisms. They found that CCE significantly inhibited PA-induced toll like receptor 4 (TLR4) expression in human umbilical vein endothelial cells (HUVECs). Thus this led to the inhibition of the following down stream adapted proteins myelod differentiation primary response gene 88, Toll/interleukin -1 receptor domain –containing adaptor-inducing interferon-β and TNF receptor –associated factor-6. Further CCE inhibited the phosphorylation of Ikappa B kinase β, nuclear factor kappa B (NFκB), c-Jun N terminal kinase, extracellular regular protein kinase, p38-mitogen activated protein kinase (MAPK)and subsequently suppressed the release of TNF-α, IL1β and IL-6. CCE also inhibited IRS 1 serine phosphorylation and ameliorated insulin mediated tyrosine phosphorylation of IRS1. Further CCE restored serine/threonine kinase and endothelial nitric oxide (ENOS) phosphorylation and NO production in PA-treated rat thoracic aortas. These results suggest that CCE can significantly restore and alleviate impaired insulin signaling in the vascular endothelium by suppressing TLR-4-mediated NFκB and MAPK pathways. Hence CCE can be considered as a potential therapeutic candidate for endothelial dysfunction associated with IR and DM [8].

Khan., *et al.* studied crude microcystins that were extracted from the blooming Microcystitis aeruginosa under stress conditions, by ultrasonication following by solvent extraction. The microcystins extract was evaluated for its potential of inhibiting adipogenesis and angiogenesis. The anti angiogenic activity of the microcystins extract was investigated using HUVECs and its anti-obesity action was determined in vitro by quantification of the accumulated lipids in mouse 3T3L1 cells via Oil Red O staining method. the microcystins extract suppressed HUVECs proliferation and tubes formation in matrigel in a dose dependent manner. RT-PCRanalysis showed the downregulation of the mRNA expression of angiogenesis –related signaling molecules, like PI3K, β-catenin, vascular endothelial growth factor receptor 2 (VEGFR-2), vascular endothelial-cadherin, Akt-1, and NFκB. Further, it inhibited adipogenesis and lipogenesis by decreasing the differentiation of premature 3T3 cells and lipid accumulation in a dose dependent manner. It suppressed adipogenesis and lipogenesis by decreasing the expression of peroxisome proliferator –activated receptor-γ, CCAAT/enhancer protein binding protein α-and sterol regulatory element binding protein. Thus concluding that microcystin exerts its antiangiogenic and antiobesity effects due to the inhibitory effects on the genes expression of associated signaling molecules and transcriptional factors [9].

Diabetic Cardiomyopathy (DCM)is characterized by cardiac hypertrophy, fibrosis, oxidative stress and inflammation. Trimetazidine (TMZ), a potent metabolism modulator, has been shown to be cardioprotective in experimental models of ischemia reperfusion and T2DM-induced CM. Tang., *et al.* examined whether TMZ inhibits CM induced by type1 DM, Wistar rats were randomly divided into control group (vehicle alone), DM (Diabetes induced by streptozotocin (STZInjection)group and DM treated with TMZ (DM/TMZ) group. Cardiac function, histology, plasma biochemistry and molecular mechanisms were assessed. STZ induced DM in rats as indicated by hyperglycaemia, increased and reduced levels of AGEs and insulin respectively. Diabetic rats were characterized by left ventricular dysfunction, cardiac hypertrophy and fibrosis as signs of inflammation and oxidative stress in the myocardium, that were accompanied by increased levels of NADPH oxidase2 (Nox2) and transient receptor potential channel 3 (TRPC3) in the heart. TMZ treatment ameliorate DM associated structural and functional alterations by inhibiting Nox2 and TRCP3 without having any effects on glucose, insulin and AGEs levels. Thus by these results it can be presumed that TMZ could be used to treat DCM associated with T1DM [10].

Further, Sakai C., *et al.* conducted a randomized placebo controlled trial of an oral preparation of high molecular weight Fucoidan, that is derived from seaweeds, used widely in Japanese cuisines. 30pts with T2M on diet therapy were recruited from OPD (n=22 men, n=8 women) Age was 59.10 ± 13.24 years, BMI; 25. 18 ± 3. 88, Hb A1c; 7.04 ± 1.24%). They were divided into2 groups and underwent 2 interventions with a 4week interval. One group received Fucoidan for 12 weeks (a daily 60ml test beverage containing 1620 mg of Fucoidan) and the placebo (60ml) for the subsequent 12weeksperiod while the order was reversed in the other group. Evaluation was done just before and after each intervention. Taste sensitivity was measured for 5 basic tastes by the filter disk method and food intake was evaluated with a validated diet questionnaire. They found no side effects occurred during the study period. Despite no change of the diet, stool frequency increased during Fucoidan intake (from 7.78 ± 4.64/week in Week 1 to 9.15 ± 5.03 week in week 5, $p<0.001$), and it increased more in lean subjects. In 11 subjects whose stool frequency exceeded the mean value the thresholds of sweet, salty, bitter and umami tastes were significantly reduced (increase of sensitivity) after fucoidan intake. In14

subjects with normal HOMA-IR (Homeostatic model assessment of IR, <2.5) HbA1c reduced after Fucoidan intake (from 6.73 ± 1.00 to 6.59 ± 1.00%, p<0.05)as did the fasting plasma levels of glucagon like peptide 1 (GLP-1) from 6.42 ± 3.52 to 4.93 ± 1.88 pmol/L, P<0.05). Thus concluding that fucoidan intake led to changes in gastrointestinal function, including increased stool frequency and enhanced taste sensitivity, that could attribute to better control of DM [11].

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