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Anti-diabetes and anti-obesity: A meta-analysis of different compounds

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ABSTRACT

Diabetes and obesity are chief health crisis and mainly age-related metabolic disorders. Diabetes is the main cause of morbidity and mortality worldwide. Obesity is linked with the progression of diabetes mellitus. High levels of glycerol, fatty acids, enzymes, pro-inflammatory markers and other obese entities build up insulin resistance in obese persons. The pathology of diabetes involves the dysfunction of β -islet cells of pancreas leading to deficient management of blood glucose level. This study demonstrates the anti-diabetic and anti-obesity effect of plant derived chemicals, some agonists, nutraceuticals, pharmaceutical drugs, some proteins and other compounds from 1998 to 2015. Plant derived from chemicals and other compounds were concluded to control diabetes and obesity by increasing number of glucose transporters, β -islet cells of pancreas, and lipid metabolism enzymes. In this way, the impairment of β -islet cells of pancreas is restored and the serum cholesterol and glucose levels of individuals are lowered. Further approaches are also needed to handle and cure diabetes and obesity.

1. Introduction

Sugar has been considered the essential component of human diet with most primitive rumor of its consumption from India and China since ancient times. High ingestion of sugar was linked with high risk situations such as cardiovascular diseases, dental caries, and obesity for decades[1]. Diabetes mellitus is a metabolic disorder which is connected with high levels of blood sugar throughout the world[2]. According to International Diabetes Federation, about 95% people are affected by diabetes out of 380 million. Diabetes (type 1 and 2) caused by impaired glucose homeostasis is due to insufficient production of insulin by pancreatic β -cell[3]. As communicable diseases, the status change is viewed in low and middle income countries. Chronic malady is more in high income countries. The most commonly examined condition is diabetes-obesity- hypertension nexus[4]. Diabetes mellitus is affecting many countries and its range is increasing vigorously. Depression risk in

diabetes type 2 patients increases with the increase of obesity[5]. Diabetes mellitus and obesity are the main causes of diseases and death in developing countries. In North American countries, diabetes mellitus reached about 10.2% in 2010 and will reach about 12.1% up till 2030, and also is rising in other countries[6]. The use of sugar beverages was associated with elevated incidence of type 2 diabetes[7]. Type 2 diabetes patients (60%–90%) were found obese by estimation. Insulin resistances and deficiency are the two main factors in obesity and diabetes. These factors are strongly connected with bi-fold dictatorial cycle. Ultimately, hyperglycemia excites insulin secretion and lowers the rise in glycemia. Both insulin confrontation and insulin deficiency might depict genetic action in the development of obese diabetes[8]. Body mass index and cardiovascular malfunctions associated death have been expansively premeditated[9]. Study was conducted to diagnose the reduction of body mass index and obesity with diabetes mellitus (type 2) extensively in rural areas as compared to urban areas[10]. Majority of people are affected by obesity and diabetes caused by over nutrition. Physical laziness also causes cardiovascular diseases[11]. High utilization of sugar and fat diet are considered as the main cause of obesity and diabetes. More than 50 kinds of rare sugars are present. D-allulose among these sugars has been studied to show reduced energy density exhibiting about zero calories[12].

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Endoplasmic reticulum is extended by protein rejoiner and become active in various condition. Hypothalamic and hepatic endoplasmic reticulum cause irritation and emerging steatosis due to detachment of insulin fusion and death of β -cells[13]. Protein convertase activates inactive pro-peptides to active peptides. Its two relatives of proprotein convertase subtilisin/kenin type 1 and type 2 are articulated in neuroendocrine tissues having prohormones like pro-opio-melano-cortin, thyroid-releasing hormone and gonadotropin releasing hormone. Its deficiency has been linked with hyperinsulinemia, malabsorptive diarrhea, incomplete vital imperfections in adrenal and thyroid glands, stern obesity hypogonadotropic hypogonadism[14]. Type 2 diabetes can also cause risk of macro-vascular complications and affect adipose tissues, liver, muscles and pancreas, which can cause irritation by the ingestion of macrophages[15]. The metabolism of glucose related to β -cells supports the production of normal glucose. But when it's not responded, normal glucose concentration would lower[16]. Metabolic syndrome caused by blood pressure, abnormal fasting, atherogenic dyslipidemia can cause cardiovascular diseases and obesity along with endothelinB receptor antagonists by endothelin-1 human vasculature involvement[17]. Obesity is rapidly becoming more common worldwide during pregnancy and considered the major medical concern. Gestational diabetes mellitus and maternal obesity are linked with modifications in the expression and activity of placental nutrient carrier[18]. Pregnant women metabolic state is essential in the offspring adiposity extension. Placenta passes on substrates modified in gestational diabetes mellitus such as amino acids and lipids, which ultimately lead to improve fetal weight, enzymes and proteins associated to placental metabolism of fatty acids. Placental composition might be changed and its association with diabetes mellitus and obesity will be revealed[19]. Obesity linked with co-morbidities like diabetes and cardiovascular diseases causes morbidity and death[20]. Various clinical conditions such as hypertension, insulin confrontation and dyslipidemia are related with central obesity[21]. Childhood obesity is under the concerns of US which causes chronic health problem in children (basically type-2 diabetes). Dental diseases and other oral problems are also concerned with the basic health problems. These increasing problems are in Native Americans and in native People[22]. Obesity is the major cause of colorectal cancer progression. Colorectal cancer prognosis after diagnosis might be affected by obesity[23]. The disorder of diabetes is caused by chronic hyperglycemia and other complications like atherosclerosis, coronary heart disease, macro- and micro-diseases[24]. The literature showed that plasma non-esterifies fatty acid called free fatty acids. Insulin suppressed the mobilization of fatty acids from adipose tissues[25]. The crowd of excessive amount of adipose tissue in body causes obesity measured by body mass index scale at a range of 18.8–24.9 kg/m²[26]. Atherosclerosis is the major cause of transience and morbidity in type 1 diabetes mellitus. Cardiovascular disease related with type 1 diabetes mellitus risk factors recognition is very significant[27]. Many reports predict that omega-3 poly unsaturated fatty acid has no or little action on metabolic control, while lowering hypertriglyceridemia in these patients, erythrocyte docosahexaenoic acid with eicosapentaenoic acid treatment significantly lowers the liver fat proportion in nonalcoholic fatty liver disease patients[28].

2. Anti-diabetic and anti-obesity agents

2.1. Effect of some agonists against diabetes and obesity

Anti-diabetic outcome of β 3-adrenergic agonist CL observation was accomplished in overweight Zucker diabetic fatty rats (ZDF)[29]. ZDF-rats aged 7 weeks were directed with CL at a dose of 1 mg/kg/day for 14 days with the help of osmotic minipumps. Intravenous glucose tolerance tests were carried out for 13 days after beginning of disodium salt (CL-316243) treatment in mindful and 3 h-fasted rats. Glucose consumption determination is accomplished by glucose metabolic index using [²⁻³H] deoxy glucose method. Then plasma levels of glucose with glucose analyzer, free fatty acids with a non esterified fatty acid kit, and insulin with radioimmunoassay were verified. Hyperinsulinemic-euglycemic clamps were done in aware, uncontrolled, unagitated rats[30]. At the end, they evaluated the facts obtained statistically. They winded up that in obese ZDF rats, CL handling normalizes the glycemia and increases insulin sensitivity[31]. β 3-agonists increase the defective mitochondrial oxidation due to the increase of energy expenditure and fat oxidation which reduce free fatty acid level in plasma. Glucose consumption by skeletal muscles is accomplished via glucose fatty acid cycle. Thus, this agonist (β 3/CL-316243) was found useful for type 2 diabetes and obesity treatment[32]. The β -adrenergic receptors agonistic action of SWR-0342SA in rats was studied by using segregated tissues and its anti-diabetic and anti-obesity consequences were studied in KK-Ay mice and C57BL mice[33-35]. They were provided with SWR-0342SA suspended in distilled water, then assessed body weight with food ingestion and blood glucose level with glucose B-test wok kit adjusted according glucose oxidase method and serum insulin level with Lbis mouse insulin enzyme immunoassay kit using streptavidin biotin method at regular intervals. Then they analyzed the values obtained statistically. They finished off that SWR-0342SA is a discerning β 3-adrenergic receptor agonist and owns more anti-diabetic activity than anti-obesity activity (Table 1). Although its mechanism is not obvious, it described that in white adipose tissue of the obese mice, β 3 adrenergic receptor agonists (*i.e.* BRL 26830A and CL-216347) increased the insulin receptors and returned the expression of glucose transporter type 4 (GLUT4)[36]. The reaction of tissue lipoprotein lipase to resupplying of food were described after delayed (4 h) fasting in weak and overweight Zucker rats. Lipoprotein lipase activity was studied in muscle and adipose tissues in fasted and fed conditions at various intervals along with or without propranolol during re-nourishing. They concluded that in lean rats, β -adrenergic pathway was activated by re-feeding after delayed fasting. This β -adrenergic pathway works against lipoprotein lipase modulation by insulin mediation. β -adrenergic pathway was enhanced by insulin mediated modulation, while in obese Zucker rats, the pathway was not activated by re-feeding in adipose tissues and muscles[37]. Linoleic acid was experimented for isomer-specific anti-diabetic activities. Lean and male Zucker diabetic fatty rats were taken at 6 weeks of age. Monitoring of animals was accomplished for glycemia after 7 days acclimation phase and allocated to dietary treatments. Fatty rat's weight was higher than lean rats initially but not diverse in different treatments. Intra-peritoneal glucose tolerance tests were accomplished on Day 11 to a subset of animals from

2.3. Anti-diabetic and anti-obesity effect of *Gymnema species* extracts

Gymnema sylvestre (Gurmar) is an important herb in Ayurvedic system of medicine for its sugar destroyer property. The phytochemicals such as gurmarin, gymnemic, polypeptide, and gymnema-saponins of the plant are accountable for sweet repression activity. The herb possesses a wide range of remedial effects as a natural remedy for diabetes treatment[45]. Obese mice were treated with *G. yunnanense* extracts in an experimental study. Extract effects on mice body weight was customized. Diabetic mice body weight was also decreased by the plant extract. Administration of *G. yunnanense* extract considerably decreased hyperglycemia and fatness in both animal models[46].

2.4. Anti-diabetic and anti-obesity action by irisin

Adipocyte browning (exercise mediated) regulation by irisin was reported. However, the effect of irisin on lipid and glucose metabolism in diabetes are unknown. The mechanism and role of irisin in the utilization of lipid and glucose in diabetic mice were evaluated. For establishment of diabetes, a mouse was fed with high fat diet and treated with irisin. Hepatocytes and monocytes cultured were carried out in high fat and glucose medium. Evaluation of protein expression, uptake of glucose and oxidation of fatty acids were accomplished. Results concluded that irisin has an important role in lipid metabolism, glucose consumption and diabetes treatment[47]. The investigation of muscles role in irisin as myokine hormone and hyper-lipidemia was accomplished. Healthy athlete men (22) of various kind of chronic activity and 40 healthy non-athlete men of normal activity were selected for the assessment. Enzyme immunoassay technique was used for serum irisin measurements. Lipid profile parameters such as total triglycerides, cholesterol, low and high density lipoprotein-cholesterol measurements were made by spectrophotometric techniques. Irisin was found as a defensive factor against hyper-lipidemia and obesity[48].

2.5. Anti-diabetic and anti-obesity effect of acacia polyphenol

Anti-diabetic and anti-obesity effects of extracts of acacia polyphenol were studied. Acacia polyphenol has anti-obesity effect by high energy consumption gene in skeletal muscles and liver. Acacia polyphenol acts as anti-diabetic in KKAY mice with inducing obesity by decreasing necrosis factor. Lower white adipocytes secretion and raise expression of GLUT4 work as anti obesity. The polyphenol decreases the secretion of white adipocytes and increases GLUT4 expression. The transcriptional machinery regulated by peroxisome proliferator-activated receptors (PPAR- γ and retinoid X receptor) increases the production of adiponectin[49,50].

2.6. Anti-diabetic and obesity effect of *Plantago husk fiber*

Plantago psyllium (*P. psyllium*) leaves were dried and stored in polyethylene bags. Albino rats were fed orally for 10 days by cholesterol powder (1%). Hypoglycemic agents were used

for alloxan induced hyperglycemia treatment[51]. Alloxan intraperitoneal injection was injected for diabetes induction. Albino rats (20/each sex) weighing 200–300 g were used for this assessment. Hypocholesterolemic and anti-diabetic activities of *P. psyllium* were investigated on cholesterol and serum glucose levels in albino diabetic rats[52]. Normalization of liver size and production of lower and higher cholesterol level were carried out by *P. psyllium* husk. It also lowers glucose and lipid concentrations in type 2 diabetic patients[53].

2.7. Anti-diabetic and anti-obesity effect of *Nigella sativa* (*N. sativa*) seed extract

N. sativa seed ethanol extract treatment activates the insulin, adenosine monophosphate kinase, and PPARs- γ signaling pathway in skeletal muscles, hepatocytes, adipocytes and liver cells. It also increases phosphorylation in muscles cells. Production of metabolic stress is accomplished by ethanol extract of disruption of mitochondrial energy transduction. So *N. sativa* seed ethanol extract behaves as an agonist of PPARs- γ . Metabolic syndrome, diabetes and obesity treatment are carried out by *N. sativa* seed oil[54].

2.8. Anti-diabetic and anti-obesity consequence of *Jasonia montana* (*J. montana*) ethanolic extract

Ethanolic extract of *J. montana* consisted of essential oils, polyphenols, mono- and sesquiterpenes, flavonoids and other di, tri, tetra-queretin derivatives. The body weight of regular diet group increased rats due to high fat diet but is comparatively less than prolonged high fat diet. Plant extracts were fed to rats which higher food intake reduced the body weight. This experimental procedure revealed that *J. montana* extract could be used against obesity as herbal drug. Blood glucose level was also reduced by the use of *J. montana* extract due to enhancement in insulin resistance[55].

2.9. Anti-diabetic and anti-obesity result of decaffeinated green tea extracts

The decaffeinated green tea extract had cellulose, EGCG, epicatechin, epicatechin gallate, gallic acid, epigallocatechin, gallic acid, and caffeine in different percentages by weight and dosage in milligram. Placebo consisted of pure microcrystalline cellulose. Evaluations of creatinine, blood pressure, uric acid, glucose, body mass index, Hemoglobin A1C, waist circumference, alanine transaminase, plasma lipoproteins, and hormone peptides were carried out at Day 0 and after conduct of 16 weeks. Caffeinated green tea causes body mass index consistent reduction, while caffeine green tea did not show any activity against obesity[56]. Green tea catechins revealed *in vitro* anti-diabetic as well anti-obesity activities[57].

2.10. Anti-diabetic and anti-obesity upshot of cambuci fruit

The anti-diabetic and anti-obesity effects of cambuci fruit were studied on mice. They were provided with water and extractions every day for 8 weeks. The body weight and food ingestion

were checked every 2 days and glucose level was checked after every 6 h. Plasma was separated by centrifugation after 8th week to check plasma cholesterol. Glucose tolerance test was performed after 7 weeks. Phenolic compounds from the cambuci fruit prevent the metabolic complications related with obesity by increasing high density lipid and decreasing the low density lipid cholesterol. While those compounds also improve glucose metabolism and make better for glucose tolerance by maintaining the glucose level. Tumor necrosis factor- α , interleukin-6 and macrophage play a role in obesity to control associative pathway, while phenolic compounds have therapeutic ability to make these pathways better for reducing obesity and related complications. Recently, phenolic compounds from bergamot (*Citrus bergamia*) fruit were isolated, which was found helpful in the treatment of hypercholesterolemia[58,59]

2.11. Folic acid utilization in obesity and diabetes

Folic acid supplementation was found effective against neural tube defects and some congenital disorders. Patients exposed to medications with anti-folate activity, diabetics, obese and smokers were benefited by the treatment of folic acid higher doses[60]. Feeding of high fat diet activates 3-hydroxy-3-methylglutaryl-CoA reductase. This causes the accumulation of hepatic cholesterol in 3-hydroxy-3-methylglutaryl-CoA reductase, which is metabolic disorder controlling by folic acid activating the AMPK[61]. During high fat feeding, folic acid restores AMPK activation by phosphorylation and improves glucose and cholesterol metabolism[62].

2.12. Anti-obesity and anti-diabetic role of flavonoid derivative (Fla-CN)

Fla-CN anti-diabetic and anti-obesity activities were studied through micro RNA in fat diet induced obesity mice. Standard methodology was used for the preparation of a semi-synthesized flavonoid derivative of tiliroside called kaempferol (Fla-CN)[63]. The C57BL/6 mice (aged 4 weeks) were divided into high and low fat diet groups. Insulin resistance in obesity was shown by high fat diet group after 8 weeks. Five mice groups were made. Three clusters among those groups got Fla-CN containing diet, while two of them got high fat diet for 4 weeks. These mice's food intake was monitored regularly. Epididymal adipose tissues, muscle, serum and liver samples were taken and accumulated at optimum conditions. High and low density lipoprotein, total cholesterol, mice's serum concentration of triglycerides, malondialdehyde, nonesterified fatty acid, and superoxide dismutase via enzymatic assays using commercial kits were analyzed. Interleukin 1 β , insulin, adiponectin, tumor necrosis factor and leptin were found out with the help of ELISA kits. Intraperitoneal insulin tolerance test was carried out on 25th day to find glucose concentration, and then executed hyperinsulinemic-euglycemic clamps. Histology of liver and epididymis adipose tissues were performed. Proteins were taken out through immune blotting. It was concluded that Fla-CN decreased fatness efficiently, developed insulin sensitivity and improved metabolic lipid disarray in a dose-reliant way. In the HFD⁺ Fla-CN

groups, Fla-CN extremely decreased adipocytes size in epididymal white adipose tissue. Furthermore, Fla-CN treatment also improved AMPK commencement, liver and systemic lipid contents, leptin and high Adiponectin levels which makes glucose and lipid metabolism better[64].

3. Remedial effects of anti-diabetic agents

3.1. Effect of HE3286 treatment

Insulin injected to experimental animals was accomplished intra-peritoneally and glucose was orally administered. Rats were implanted with one carotid arterial and two jugular venous cannulae. With constant infusion and injection, hyperinsulinemic euglycemic clamp experiments were started after 4 to 5 days of revitalization. Insulin was injected into jugular vein after 1 h. Free fatty acid, glucose specific activity and insulin levels were monitored from blood samples. After blood samples centrifugation, the plasma was stored for analysis at -80°C . They investigated the treatment of fatty diabetic rats by compound HF3268 in liver and adipose tissues. Its treatment normalized the fasting and it also improved glucose tolerance and liver insulin sensitivity. HF3286 treatment led to increase human insulin sensitivity. Treatment with HE3286 reduced the serum level as well as the gluconeogenic ability. Lipidomic analysis showed that HE3286 treatment reduced liver cholesterol[65].

3.2. Anti-diabetic effect of Chloroxylon swietenia bark extracts

Glucagon and insulin hormones control blood glucose level within the physiological range (70–120 mg/dL)[66]. The anti-diabetic activity of the bark extract of *Chloroxylon swietenia* was investigated against diabetic rats. Streptozotocin (50 mg/kg) intra-peritoneal injections were made for diabetes induction in male albino rats. Oral administrations of plant bark methanolic and aqueous extracts were made to diabetic rats. Glibenclamide (600 $\mu\text{g}/\text{kg}$) was injected intragastrically for 45 days. Enhancement of blood pressure, weight loss, and hemoglobin glycosylation were recorded. Decline was experimented in total hemoglobin content and plasma insulin level[67].

3.3. Anti-diabetic results of anthocyanins from maqui berry

Maqui berry anthocyanins were evaluated for anti-diabetic properties. The concentrations of anthocyanins in crude extracts, maqui berry post amberlite extract and anthocyanins-rich were determined by high pressure liquid chromatography using commercial anthocyanins standards[68]. Synthesis of DNA, extraction and purification of RNA were accomplished. Cytotoxic effects of maqui berry anthocyanins and cell membrane alterations to H4II cells and L6 myo-tubes were investigated. Delphinidin 3-sambubioside-5-glucoside isolated from anthocyanin was studied for anti-diabetic potential. Anthocyanins oral administration was found significant for blood glucose level and tolerance in hyper-glycemic obese mice, which were fed with a high fat diet. Glucose uptake was enhanced

by anthocyanins. The results suggest that anthocyanins of maqui berry could be used for adipogenesis and inflammation inhibition in diabetic patients[69].

3.4. Anti-diabetic effect of ethanol extract of *Caulerpa lentillifera* (*C. lentillifera*)

C. lentillifera ethanol extract were examined for anti-diabetic potential. Adipocytes (3T3-L1) were grown in 96 black well plates. Incubation was carried with sample and rosiglitazone (5 µmol/L) at 37 °C under 5% CO₂ atmospheric pressure for 24 h. It was experimented to evaluate anti-diabetic effect of *C. lentillifera*. Dipeptidyl peptidase-IV inhibitors stimulated insulin secretion, whereas α-glucosidase inhibitors decreased blood glucose. *C. lentillifera* extract inhibited enzyme activity. The addition of *C. lentillifera* extract increased cell capability. The combination of interleukin-1β and interferon-γ caused pancreatic β-cell death and decreased insulin secretion. ELISA rat insulin kit was used for determination of insulin secretion in cell culture. *C. lentillifera* extract did not cause cell cytotoxicity and enhance glucose uptake[70].

3.5. Anti-diabetic effect of plants essential oils

Essential oils of *Syzygium aromaticum* and *Cuminum cyminum* were evaluated for anti-diabetic activities. The anti-diabetic potential was assessed in dose dependent mode (1–100 µg/mL). At 100 µg/mL dose, the maximum activity was displayed by the plant essential oils[71]. *Foeniculum vulgare* essential oil was used for the treatment of hyperglycemia and pathological diseases in diabetic rats. This was done by the redox homeostasis restoring and anti-oxidant potential of plant essential oils. The result of these experimental activities made essential oils as antidiabetic drug in industry[72].

4. Conclusion

High expenditure of sugar and high fat diet are considered as contributing dietary factory of chronic disorders of obesity and diabetes along with genetic, metabolic and psychosocial factors. It is concluded that anti-diabetic and anti-obesity compounds work by increasing glucose responsiveness. These compounds decrease the amount of glycerol, non-esterified fatty acids, proinflammatory substances and cytokines. Several compounds were reported for the improving function of pancreas beta cells and enzymes involved in lipid metabolism. Further approaches are needed to control the unceasing disorders of obesity and diabetes.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

- [1] Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 2012; **346**: e7492.
- [2] Deepak KKG, Nageswara Rao Reddy N, Surekha C. Role of antidiabetic compounds on glucose metabolism? A special focus on medicinal plant: *Salacia* spp. *Med Chem* 2014; **4**: 373-81.
- [3] Bruin JE, Saber N, Braun N, Fox JK, Mojibian M, Asadi A, et al. Treating diet-induced diabetes and obesity with human embryonic stem cell-derived pancreatic progenitor cells and antidiabetic drugs. *Stem Cell Reports* 2015; **4**: 605-20.
- [4] Ali FMH, Nikoloski Z, Reka H, Gjebrea O, Mossialos E. The diabetes-obesity-hypertension nexus in Qatar: evidence from the World Health Survey. *Popul Health Metr* 2014; **12**: 18.
- [5] De la Cruz-Cano E, Tovilla-Zarate CA, Reyes-Ramos E, Gonzalez-Castro TB, Juarez-Castro I, López-Narváez ML, et al. Association between obesity and depression in patients with diabetes mellitus type 2; a study protocol. *F1000Res* 2015; **4**: 7.
- [6] Gucciardi E, Chan VW, Manuel L, Sidani S. A systematic literature review of diabetes self-management education features to improve diabetes education in women of Black African/Caribbean and Hispanic/Latin American ethnicity. *Patient Educ Couns* 2013; **92**(2): 235-45.
- [7] Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ* 2015; **351**: h3576.
- [8] Felber JP, Golay A. Pathways from obesity to diabetes. *Int J Obes Relat Metab Disord* 2002; **26**(Suppl 2): S39-45.
- [9] Lim RB, Chen C, Naidoo N, Gay G, Tang WE, Seah D, et al. Anthropometrics indices of obesity, and all-cause and cardiovascular disease-related mortality, in an Asian cohort with type 2 diabetes mellitus. *Diabetes Metab* 2015; **41**(4): 291-300.
- [10] Feng X, Astell-Burt T. Does area of residence influence weight loss following a diagnosis of type 2 diabetes? Fixed effects longitudinal analysis of 54,707 middle-to-older aged Australians. *Diabetes Res Clin Pract* 2016; **116**: 123-6.
- [11] Henry RR, Chilton R, Garvey WT. New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). *J Diabetes Complications* 2013; **27**: 508-18.
- [12] Hossain A, Yamaguchi F, Matsuo T, Tsukamoto I, Toyoda Y, Ogawa M, et al. Rare sugar D-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus. *Pharmacol Ther* 2015; **155**: 49-59.
- [13] Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. *Trends Mol Med* 2012; **18**(1): 59-68.
- [14] Frank GR, Fox J, Candela N, Jovanovic Z, Bochukova E, Levine J, et al. Severe obesity and diabetes insipidus in a patient with PCSK1 deficiency. *Mol Genet Metab* 2013; **110**: 191-4.
- [15] Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation

- as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 2014; **105**: 141-50.
- [16] Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014; **383**: 1068-83.
- [17] Campia U, Tesauro M, Di Daniele N, Cardillo C. The vascular endothelin system in obesity and type 2 diabetes: pathophysiology and therapeutic implications. *Life Sci* 2014; **118**: 149-55.
- [18] Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta* 2015; **36**(7): 709-15.
- [19] Uhl O, Demmelmair H, Segura MT, Florido J, Rueda R, Campoy C, et al. Effects of obesity and gestational diabetes mellitus on placental phospholipids. *Diabetes Res Clin Pract* 2015; **109**(2): 364-71.
- [20] Abdali D, Samson SE, Grover AK. How effective are antioxidant supplements in obesity and diabetes? *Med Princ Pract* 2015; **24**: 201-15.
- [21] Tyrovolas S, Koyanagi A, Garin N, Olaya B, Ayuso-Mateos JL, Miret M, et al. Diabetes mellitus and its association with central obesity and disability among older adults: a global perspective. *Exp Gerontol* 2015; **64**: 70-7.
- [22] Haring RC, Skye W Jr, Battleson BL, Brings-Him-Back-Janis M, Teufel-Shone N. Teeth and heavysset kids: intervention similarities between childhood obesity and oral health interventions within native American societies. *J Indig Res* 2014; **3**(1): 1-22.
- [23] Amptoulach S, Gross G, Kalaitzakis E. Differential impact of obesity and diabetes mellitus on survival after liver resection for colorectal cancer metastases. *J Surg Res* 2015; **199**(2): 378-85.
- [24] Verma S, Chandra H, Banerjee M. Cyclooxygenase 1 (COX1) expression in type 2 diabetes mellitus: a preliminary study from North India. *Egypt J Med Hum Genet* 2016; **17**(1): 41-5.
- [25] Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes* 2011; **60**: 2441-9.
- [26] Shearer P, Mus C, Mgt GCR. Literature review – Canine, feline and human overweight and obesity. Vancouver, WA: Banfield Pet Hospital; 2010. [Online] Available from: <https://www.banfield.com/getmedia/aa3b125b-18a7-4422-8f68-7861db3385b4/e15ce5a8-f5df-4864-9b51-58383540372b-pdf0> [Accessed on 10th April, 2016]
- [27] Akyürek N, Atabek ME, Eklioglu BS, Alp H. Evaluation of the relationship between cardiovascular risk factors and periaortic fat thickness in children with type 1 diabetes mellitus. *Diabetes Metab* 2015; **41**: 338-41.
- [28] Yessoufou A, Nekoua MP, Gbankoto A, Mashalla Y, Moutairou K. Beneficial effects of omega-3 polyunsaturated fatty acids in gestational diabetes: consequences in macrosomia and adulthood obesity. *J Diabetes Res* 2015; **2015**: 731434.
- [29] Hempe J, Elvert R, Schmidts HL, Kramer W, Herling AW. Appropriateness of the Zucker diabetic fatty rat as a model for diabetic microvascular late complications. *Lab Anim* 2012; **46**(1): 32-9.
- [30] Ayala JE, Bracy DP, Malabanan C, James FD, Ansari T, Fueger, PT, et al. Hyperinsulinemic-euglycemic clamps in conscious, unrestrained mice. *J Vis Exp* 2011; doi: 10.3791/3188.
- [31] Crist GH, Xu B, Lanoue KF, Lang CH. Tissue-specific effects of *in vivo* adenosine receptor blockade on glucose uptake in Zucker rats. *FASEB J* 1998; **12**(13): 1301-8.
- [32] Liu X, Pérusse F, Bukowiecki LJ. Mechanisms of the antidiabetic effects of the beta 3-adrenergic agonist CL-316243 in obese Zucker-ZDF rats. *Am J Physiol* 1998; **274**(5 Pt 2): R1212-9.
- [33] Katsuda Y, Ohta T, Shinohara M, Bin T, Yamada T. Diabetic mouse models. *Open J Anim Sci* 2013; **3**(4): 334-42.
- [34] Tomino Y. Lessons from the KK-Ay mouse, a spontaneous animal model for the treatment of human type 2 diabetic nephropathy. *Nephrourol Mon* 2012; **4**(3): 524-29.
- [35] Heaberlin JR, Ma Y, Zhang J, Ahuja SS, Lindsey ML, Halade GV. Obese and diabetic KKAY mice show increased mortality but improved cardiac function following myocardial infarction. *Cardiovasc Pathol* 2013; **22**(6): 481-7.
- [36] Kiso T, Namikawn T, Tokunaga T, Sawada K, Kakita T, Shogaki T, et al. Anti-obesity and anti-diabetic activities of β_3 -adrenergic receptor agonist (S)(Z)-[4-[[1-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]-1-propenyl]phenoxy] acetic acid ethanedioic acid (SWR-0342SA), in KK-A^y mice. *Biol Pharm Bull* 1999; **22**(10): 1073-8.
- [37] Picard F, Richard D, Timofeeva E, Deshaies Y. Abnormal insulin and beta-adrenergic modulation of lipoprotein lipase during refeeding after prolonged fasting in the Zucker rat. *Diabetologia* 2000; **43**(7): 866-74.
- [38] Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm* 2010; **2010**: 802078.
- [39] Hart JR, Vogt PK. Phosphorylation of AKT: a mutational analysis. *Oncotarget* 2011; **2**(6): 467-76.
- [40] Mahmood T, Yang PC. Western blot: technique, theory, and trouble shooting. *N Am J Med Sci* 2012; **4**(9): 429-34.
- [41] Ryder JW, Portocarrero CP, Song XM, Cui L, Yu M, Combatsiaris T, et al. Isomer-specific antidiabetic properties of conjugated linoleic acid. Improved glucose tolerance, skeletal muscle insulin action, and UCP-2 gene expression. *Diabetes* 2001; **50**(5): 1149-57.
- [42] Rieusset J, Touri F, Michalik L, Escher P, Desvergne B, Niesor E, et al. A new selective peroxisome proliferator-activated receptor gamma antagonist with antiobesity and antidiabetic activity. *Mol Endocrinol* 2002; **16**(11): 2628-44.
- [43] Talaei M, Pan A. Role of phytoestrogens in prevention and management of type 2 diabetes. *World J Diabetes* 2015; **6**(2): 271-83.
- [44] Ahn TG, Yang G, Lee HM, Kim MD, Choi HY, Park KS, et al. Molecular mechanisms underlying the anti-obesity potential of prunetin, an O-methylated isoflavone. *Biochem Pharmacol* 2013; **85**(10): 1525-33.
- [45] Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of *Gymnema sylvestris*: an important medicinal plant. *BioMed Res Int* 2014; **2014**: 830285.
- [46] Xie JT, Wang A, Mehendale S, Wu J, Aung HH, Dey L, et al. Anti-diabetic effects of *Gymnema yunnanense* extract. *Pharmacol Res* 2003; **47**(4): 323-9.
- [47] Xin C, Liu J, Zhang J, Zhu D, Wang H, Xiong L, et al. Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. *Int J Obes (Lond)* 2016; **40**(3): 443-51.
- [48] Saleh BO, Majeed MJ, Oreaby GM. Irisin peptide is myokine, anti-obesity and anti-lipidemic factor. *Am J Res Commun* 2015; **3**(1): 20-30.
- [49] Ikarashi N, Toda T, Okaniwa T, Ito K, Ochiai W, Sugiyama K. Anti-obesity and anti-diabetic effect of acacia polyphenol in obese diabetic KKAY mice fed high-fat diet. *Evid Based Complement Alternat Med* 2011; **2011**: 952031.
- [50] Zorzano, Palacín M, Gumà A. Mechanisms regulating GLUT4 glucose transporter expression and glucose transport in skeletal muscle. *Acta Physiol Scand* 2005; **183**(1): 43-58.
- [51] Islam T, Rahman A, Islam AU. Effects of aqueous extract of fresh leaves

- of *Abroma augusta* L. on oral absorption of glucose and metformin hydrochloride in experimental rats. *ISRN Pharm* 2012; **2012**: 472586.
- [52] Wang Z, Wang J, Chan P. Treating type 2 diabetes mellitus with traditional Chinese and Indian medicinal herbs. *Evid Based Complement Alternat Med* 2013; **2013**: 343594.
- [53] Ahmed I, Naeem M, Shakoor A, Ahmed Z, Iqbal HMN. Investigation of anti-diabetic and hypocholesterolemic potential of *Psyllium* husk fiber (*Plantago psyllium*) in diabetic and Hypercholesterolemic albino rats. *Int J Med Health Biomed Bioeng Pharm Eng* 2010; **4**(1): 30-4.
- [54] Benhaddou-Andaloussi A, Martineau LC, Vallerand D, Haddad Y, Afshar A, Settaf A, et al. Multiple molecular targets underlie the antidiabetic effect of *Nigella sativa* seed extract in skeletal muscle, adipocyte and liver cells. *Diabetes Obes Metab* 2010; **12**(2): 148-57.
- [55] Hussein MA. Anti-obesity, antiatherogenic, anti-diabetic and antioxidant activities of *J. montana* ethanolic formulation in obese diabetic rats fed high-fat diet. *Free Radic Antioxid* 2011; **1**(1): 49-60.
- [56] Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. *Am J Clin Nutr* 2010; **91**: 73-81.
- [57] Hsu CH1, Liao YL, Lin SC, Tsai TH, Huang CJ, Chou P. Does supplementation with green tea extract improve insulin resistance in obese type 2 diabetics? A randomized, double-blind, and placebo-controlled clinical trial. *Altern Med Rev* 2011; **16**(2): 157-63.
- [58] Donado-Pestana CM, Belchior T, Festuccia WT, Genovese MI. Phenolic compounds from cambuci (*Campomanesia phaea* O. Berg) fruit attenuate glucose intolerance and adipose tissue inflammation induced by a high-fat, high-sucrose diet. *Food Res Int* 2015; **69**: 170-8.
- [59] Di Donna L, Iacopetta D, Cappello AR, Gallucci G, Martello E, Fiorillo M, et al. Hypocholesterolemic activity of 3-hydroxy-3-methyl-glutaryl flavanones enriched fraction from bergamot fruit (*Citrus bergamia*): "In vivo" studies. *J Funct Foods* 2014; **7**: 558-68.
- [60] Chitayat D, Matsui D, Amitai Y, Kennedy D, Vohra S, Rieder M, et al. Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. *J Clin Pharmacol* 2016; **56**(2): 170-5.
- [61] Wu N, Sarna LK, Hwang SY, Zhu Q, Wang P, Siow YL, O K. Activation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase during high fat diet feeding. *Biochim Biophys Acta* 2013; **1832**: 1560-8.
- [62] Sid V, Wu N, Sarna LK, Siow YL, House JD, O K. Folic acid supplementation during high-fat diet feeding restores AMPK activation via an AMP-LKB1-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 2015; **309**: R1215-25.
- [63] Qin N, Li CB, Jin MN, Shi LH, Duan HQ, Niu WY. Synthesis and biological activity of novel tiliroside derivants. *Eur J Med Chem* 2011; **46**(10): 5189-95.
- [64] Qin N, Chen Y, Jin MN, Zhang C, Qiao W, Yue XL, et al. Anti-obesity and anti-diabetic effects of flavonoid derivative (Fla-CN) via microRNA in high fat diet induced obesity mice. *Eur J Pharm Sci* 2016; **82**: 52-63.
- [65] Lu M, Patsouris D, Li P, Flores-Riveros J, Frincke JM, Watkins S, et al. A new antidiabetic compound attenuates inflammation and insulin resistance in Zucker diabetic fatty rats. *Am J Physiol Endocrinol Metab* 2010; **298**(5): E1036-48.
- [66] Lunze K, Singh T, Walter M, Brendel MD, Leonhardt S. Blood glucose control algorithms for type 1 diabetic patients: a methodological review. *Biomed Signal Process Control* 2013; **8**: 107-19.
- [67] Jayaprasad B, Sharavanan PS, Sivaraj R. Antidiabetic effect of *Chloroxylon swietenia* bark extracts on streptozotocin induced diabetic rats. *Beni-Suef Univ J Basic Appl Sci* 2016; **5**(1): 61-9.
- [68] Raghavendra GNB, Bhat SG. Glucometer as a chairside device to assess blood glucose in periodontal patients. *J Int Clin Dent Res Organ* 2010; **2**(3): 130-3.
- [69] Rojo LE, Ribnicky D, Logendra S, Poulev A, Rojas-Silva P, Kuhn P, et al. In vitro and in-vivo anti-diabetic effects of anthocyanins from Maqui Berry (*Aristotelia chilensis*). *Food Chem* 2012; **131**(2): 387-96.
- [70] Sharma BR, Rhyu DY. Anti-diabetic effects of *Caulerpa lentillifera*: stimulation of insulin secretion in pancreatic β -cells and enhancement of glucose uptake in adipocytes. *Asian Pac J Trop Biomed* 2014; **4**(7): 575-80.
- [71] Yen HF, Hsieh CT, Hsieh TJ, Chang FR, Wang CK. In vitro anti-diabetic effect and chemical component analysis of 29 essential oils products. *J Food Drug Anal* 2015; **23**(1): 124-9.
- [72] El-Soud N, El-Laithy N, El-Saeed G, Wahby M, Khalil M, Morsy F, et al. Antidiabetic activities of *Foeniculum vulgare* Mill. essential oil in streptozotocin-induced diabetic rats. *Maced J Med Sci* 2011; **4**(2): 139-46.
- [73] Fang X, Sweeney G. Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes. *Biochem Soc Trans* 2006; **34**(Pt 5): 798-801.
- [74] Li TH, Hou CC, Chang CL, Yang WC. Anti-hyperglycemic properties of crude extract and triterpenes from *Poria cocos*. *Evid Based Complement Alternat Med* 2011; doi: 10.1155/2011/128402.
- [75] Rodriguez-Hernandez CJ, Guinovart JJ, Murguía JR. Anti-diabetic and anti-obesity agent sodium tungstate enhances GCN pathway activation through Glc7p inhibition. *FEBS Lett* 2012; **586**: 270-6.
- [76] You Q, Chen F, Wang X, Jiang Y, Lin S. Anti-diabetic activities of phenolic compounds in muscadine against alpha-glucosidase and pancreatic lipase. *LWT Food Sci Technol* 2012; **46**: 164-8.
- [77] Okumura T, Tsukui T, Hosokawa M, Miyashita K. Effect of caffeine and capsaicin on the blood glucose levels of obese/diabetic KK-A(y) mice. *J Oleo Sci* 2012; **61**: 515-23.
- [78] Sergent T, Vanderstraeten J, Winand J, Beguin P, Schneider YJ. Phenolic compounds and plant extracts as potential natural anti-obesity substances. *Food Chem* 2012; **135**: 68-73.
- [79] Kwak HJ, Pyun YM, Kim JY, Pagire HS, Kim KY, Kim KR, et al. Synthesis and biological evaluation of aminobenzimidazole derivatives with a phenylcyclohexyl acetic acid group as anti-obesity and anti-diabetic agents. *Bioorg Med Chem Lett* 2013; **23**: 4713-8.
- [80] Chang CL, Liu HY, Kuo TF, Hsu YJ, Shen MY, Pan CY, et al. Antidiabetic effect and mode of action of cytopiloyne. *Evid Based Complement Alternat Med* 2013; **2013**: 685642.
- [81] Keskes H, Mnafigui K, Hamden K, Damak M, El Feki A, Allouche N. In vitro anti-diabetic, anti-obesity and antioxidant proprieties of *Juniperus phoenicea* L. leaves from Tunisia. *Asian Pac J Trop Biomed* 2014; **4**: S649-55.
- [82] Irondi EA, Oboh G, Akindahunsi AA, Boligon AA, Athayde ML. Phenolic composition and inhibitory activity of *Mangifera indica* and *Mucuna urens* seeds extracts against key enzymes linked to the pathology and complications of type 2 diabetes. *Asian Pac J Trop Biomed* 2014; **4**(11): 903-10.
- [83] Yen HF, Hsieh CT, Hsieh TJ, Chang FR, Wang CK. In vitro anti-diabetic effect and chemical component analysis of 29 essential oils products. *J Food Drug Anal* 2015; **23**: 124-9.