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

Najeeb Ullah, Kinza Hafeez, Samia Farooq, Amna Batool, Noreen Aslam, Marzia Hussain, Sohail Ahmad

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].
Endoplasmic reticulum is extended by protein rejoinder 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 subtilisine/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 non-esterified 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/m^2[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 β3-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 [2^1H] 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]. β3-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 (β3/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 work 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 β3-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, β3 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 treatment nonalcoholic fatty liver disease patients[28].
acceptance in ZDF rats and reconciles the anti-diabetic effects by linoleic acid by diet significantly progresses weakened glucose and glucose metabolism of CLA iso-forms were found regular nutritional CLA isoforms on food ingestion, escalation rate, adiposity, particular CLA isomers. They observed the function of particular synthesis and western blotting[38-40] . Utilization of conjugated 3-kinase activity, Akt phosphorylation, Northern blot analysis, Probe glycogen synthase activity, tyrosine-associated phosphidylinositol muscle incubations, glucose transport activity, glycogen content, and organs were collected for hormone and metabolite assays, each handling. Animals were killed on 15th day and tissues, blood and organs were collected for hormone and metabolite assays, muscle incubations, glucose transport activity, glycogen content, glycogen synthase activity, tyrosine-associated phosphidylinositol 3-kinase activity, Akt phosphorylation, Northern blot analysis, Probe synthesis and western blotting[38-40]. Utilization of conjugated linoleic acid by diet significantly progresses weakened glucose acceptance in ZDF rats and reconciles the anti-diabetic effects by particular CLA isomers. They observed the function of particular nutritional CLA isoforms on food ingestion, escalation rate, adiposity, action of insulin in skeletal muscle and genes expression considered to be vital in lipid and glucose metabolism, and possibly, thermo genesis. According to the enhanced glucose tolerance, insulin-excited glucose transportation was better in soleus muscle. Glycogen synthase insulin stimulated action was found in muscles and soleus of rats (50/50). In ZDF rat model, the pleiotropic results of lipid and glucose metabolism of CLA iso-forms were found regular with introduction of peroxisome proliferator-activated receptors (PPARs). While pancreatic islets enhanced the insulin secretion by mechanism of up-regulation of uncoupling protein genes which was also an anti-diabetic effect[41]. A compound SR-202 was prepared via transcriptional assessment. They inspected in vivo action of antagonist SR-202 and checked the results by blocking PPAR-γ disorder. Metabolic disorders therapy can be improved by SR-202 antagonist[42].

2.2. Anti-diabetic and anti-obesity effect of phytoestrogens

Phytoestrogens are structurally analogous polyphenols to endogenous estrogen. Studies revealed the anti-diabetic properties of phytoestrogens through estrogen dependent and independent trails[43]. Adipogenic genes of high fat diet induced up-regulation are inhibited by prunetin and liver tissues of lipid metabolism relevant genes expression are suppressed. Adiponectin receptors 1 and 2 expression and AMP-activated protein kinase (AMPK) were induced by prunetin in adipose and liver tissues. It was concluded from the experimental results that anti-obesity effects were mediated via suppressing the obesity relevant transcription by prunetin. The feedback mechanism was followed for this suppression which regulates adiponectin, AMPK, adipR1 and adipoR2[44].

Table 1
Remedial effects of phytochemicals, agonists, plant extracts and some other compounds.

<table>
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CLA: Conjugated linoleic acid; EGCG: Epigallocatechin gallate; G. yunnanense: Gymnema yunnanense.

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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 guarmin, 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 is reported. However, the effect of irisin on lipid and glucose metabolism in diabetes is 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 myokin hormone and hyper-lipidemia was accomplished. Healthy athletes men (22) of various kind of chronic activity and 40 healthy non-athlete men of normal activity were selected for the assessment. Enzyme immunosorbent technique was used for serum irisin measurements. Lipid profile parameters such as total triglycerides, cholesterol, low and high density lipo-protein-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/either sex) weighing 200–300 g were used for this assessment. Hypcholesterolemic 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-quercein 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, gallocatechin, epigallocatechin, gallocatechin gallate, 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-methyl-glutaryl-CoA reductase. This causes the accumulation of hepatic triglycerides, malondialdehyde, non-esterified fatty acid, and superoxide dismutase via enzymatic assays using 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 from bergamot (Citrus bergamia) fruit were isolated, which was found helpful in the treatment of hypercholesterolemia[58,59].

**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, nonestesterified fatty acid, and superoxide dismutase via enzymatic assays using commercial kits were analyzed. Interleukin 1β, insulin, adiponectin, tumor necrosis factor and leptin were found out with the help of ELISA kits. Intrapерitoneal 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 HFD7 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 μg/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 H4I4 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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