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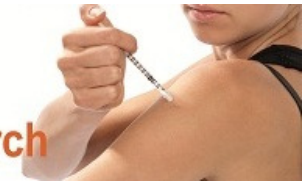

Review Article

High Fat Diet-Fed, Streptozotocin-Induced Diabetic Rat Model: Is It an Ideal Type 2 Diabetic Model?

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Abstract:
Type 2 diabetes mellitus (T2DM) is a complex chronic metabolic disorder with an epidemic prevalence, affecting 100 million people worldwide. To combat T2DM, more appropriate experimental animal models that mimic human T2DM conditions are needed. These animal models can be developed either spontaneously or induced by chemicals, diet or surgical manipulations individually or in combination. High fat diet-fed, streptozotocin (HFD/STZ)-treated rat model combines two different stressors, namely feeding the rats on HFD to induce dyslipidemia, hyperpreinsulinemia, insulin resistance and glucose intolerance followed by administering a β-cell toxin namely, streptozotocin (STZ) to reduce functional β-cell mass in order to simulate human diabetic condition.

This review primarily focuses on the suitability and effectiveness of HFD/STZ diabetic experimental obese rat model in simulating human T2DM. The use of HFD fed STZ-induced diabetic rat model for the last two decades of diabetic research undoubtedly establishes the relevance and effectiveness of this model. In this review, we discuss its development, rationale, underlying causes/mechanism(s) and merits and demerits.We hope that this review will lead to better understanding of the disease as well as developing more effective experimental animal model for diabetes research.

Keywords: β-cell; High-fat Diet; Natural Molecules; Streptozotocin; Type 2 Diabetes

Introduction: Type 2 diabetes mellitus (T2DM) is a complex chronic metabolic disorder increasing alarmingly in epidemic prevalence worldwide. T2DM is characterized by progressive deterioration in peripheral insulin resistance and subsequently insufficient insulin secretion due to pancreatic β-cell dysfunction and degeneration [1,2]. International diabetic federation has estimated that nearly 10% of adult population (415 million) in the world is affected by diabetes mellitus which is often manifested through related complications such as macroangiopathy (heart disease, stroke, atherosclerosis) and microangiopathy (nephropathy, neuropathy, retinopathy) [3,4].T2DM alone accounts for more than 95% of diabetes, comprising 8.3% of the total humanity [5]. T2DM is often initially linked with obesity associated insulin resistance followed by heightened β-cell compensatory mechanism like excess basal insulin secretion and hyperproinsulinemia with impaired metabolic profiles [6]. Insulin resistance also induces dispropotionate lipolysis in adipose tissue, impaired uptake of glucose by muscle, and uninhibited gluconeogenesis [7]. Insulin resistant people with obesity and T2DM have been identified with over-abundance of visceral adipose tissue which is resistant to the antilipolytic effect of insulin and subsequently releases excessive levels of free fatty acids (FFA) into blood circulation. Increased levels of FFA in blood is found to be a major contributor to the development of heightened insulin resistance leading to defective mitochondrial oxidative phosphorylation that relates to the accumulation of triacylglycerols and related lipid molecules in muscle as well [8].

Currently, insulin therapy and oral hypoglycemic drugs are the two of the most common treatments available for diabetes [9]. Even though the former

is effective for glycemic control, it leads to insulin resistance [10], anorexia nervosa, brain atrophy and fatty liver [11] on its prolonged use. The latter (biguanides and sulfonylureas) is also found to have adverse effects including haematological, cutaneous, gastrointestinal discomforts, diabetic coma, and hinder the proper functioning of kidney and liver [12]. Another group of oral drug namely, thiazoledinediones (TZDs) (Pioglitazone and Rosiglitazone) are synthetic insulin sensitizers used to treat insulin resistance related metabolic disorders like T2DM, high blood pressure, inflammation and obesity [13]. However they have also shown several undesirable complications such as weight gain, hepatotoxicity, edema, increased plasma lipoproteins and increased risk of congestive heart failure [14]. Hence, search for safer and more affordable oral hypoglycemic drugs from natural resources based on traditional knowledge has been intensified over the last two decades owing to the fact that natural products possess high diversity, bioavailability and contain bio-privileged structures.

Considering the complexity of impairments that T2DM plays in the human physiological process, more suitable T2DM experimental animal models are required to screen new drugs to combat T2DM. Despite of some limitations HFD/STZ induced T2DM experimental rat model which mimics the human T2DM, remains one of the most reasonable models available till date [1]. This model combines two different stressors, namely feeding the rats on high-fat diet to induce dyslipidemia, hyperpreinsulinemia, insulin resistance and glucose intolerance in them combined with the reduction of functional β-cell mass through the administration of a β-cell toxin, STZ, to simulate the pathological condition of human T2DM in them [15,16].

This review explores the suitability and effectiveness of HFD/STZ-induced diabetic experimental obese rat model through a chronological investigation of diabetic researches carried out using HFD/STZ-induced diabetic animal model for last two decades.

Modelling type 2 diabetes in rats using HFD/STZ: Rationale: HFD/STZ-induced diabetic experimental obese rat model synergistically simulates natural T2DM in human beings via a combination treatment of a diet high in fat to cause hyperinsulinemia, insulin resistance and glucose intolerance followed by STZ (β-cell toxin), injection to reduce functional β-cell mass [15,16]. Previous studies have shown that a metabolically healthy individual passes through a prediabetic obese transitional stage characterized by insulin resistance associated with impaired fasting blood glucose, glucose intolerance, hyperinsulinemia and dyslipidemia before becoming a T2DM patient [17,18]. In healthy individuals, glycogenesis and de novo lipogenesis maintain normoglycemia during hyperglycemia, where in the former case, excess glucose is stored as glycogen in the liver and muscle tissues and in the latter case, once glycogen stores are fully occupied, the excess circulating glucose levels bring about de novo lipogenesis mainly in the liver as well as in adipose tissues [19,20]. However persistent glucose overload could lead to obesity and consequently induce insulin resistance in liver and skeletal muscle due to decreased levels of glycogen synthesis, increased levels of gluconeogenesis and greater hepatic lipid accumulation through de novo lipogenesis [21,22]. Likewise, in healthy individuals excess lipid is stored in adipose tissue. However, very high lipid profile in the long term could cause severe adipocytes expansion and ectopic fat deposition in non-adipose tissue, such as muscle, liver and pancreatic β-cells, producing dysfunctional adipocytes characterized by insulin resistance, adipose inflammation, distorted adipokine profile (high leptin and low adiponectin) and hyperinsulinema [23-25]. Recent studies have shown that in obesity and T2DM, insulin resistance causes impairment of the endocrine function of the perivascular adipose tissue, an imbalance in the secretion of vasoconstrictor and vasodilator molecules, and an increased production of reactive oxygen species. Therefore, targeting plasma levels of adipokines or the expression of their receptors can increase insulin sensitivity, improve vascular function, and reduce the risk of cardiovascular morbidity and mortality [26].

Streptozotocin (STZ), is an antibiotic produced by *Streptomyces achromogenes* and has been widely used for developing diabetes in the experimental animals through its toxic effects on the pancreatic β-cells [27,28]. The cytotoxic action of STZ is associated with the generation of reactive oxygen species (ROS) causing oxidative damage that culminates in β-cell destruction through the induction of apoptosis and suppression of insulin biosynthesis [16,29]. Although cytotoxic activity of STZ on β-cells is still unclear, it is thought to be mediated by the inhibition of free radical scavenger-enzymes thereby enhancing the production of the superoxide radical which can damage pancreatic β-cells [29]. In addition, the intracellular metabolism of STZ produces nitric oxide (NO) that hastens DNA fragmentation, leading to hasty necrosis of the β-cells thereby the rate of insulin synthesis is diminished that ultimately results in a clinical condition known as hyperglycemia [30].

Hence HFD/STZ diabetic experimental obese rat modelis are designed to simulate the early stages of human T2DM pathology characterized by various complex metabolic dysfunctions such as β-cell compensatory mechanisms including increased functional β-cell mass and amplified β-cell function, hyperinsulinemia, insulin resistance, dyslipidemia, inflamed and dysfunctional adipocytes and ectopic fat deposition in liver and muscle [1].

Induction of T2DM rat model using HFD/STZ; Procedure: The HFD/STZ - induced T2DM in experimental rats model was first reported by Reed in 2000 [31]. Thereafter, in search of an optimal strategy for developing human T2DM models, many reports have been found in literature on experimental T2DM rat models varying mostly only in their specifications, as shown in Table 1and Table 2, such as HFD feeding duration: 2-4 weeks to ≥ 3months prior to STZ induction, HFD nutritional content: carbohydrate, protein, fat, etc., Strain: wistar (W) and sprague-dawley (SD), etc., initial age: ≥8 weeks (W) and 5-12 weeks (SD), body weight: 180-250g (W) and 200-250g (SD), STZ dosage: 30-50 mg/kg (W) and 25-50mg/kg (SD), number of dose: single low dose or multiple lower doses, route of administration: intraperitonial(ip)/intravenous(iv).

Reference	Strain: Weight: initial age	Study period: Diet (prior to STZ)	HFD composition %	STZ dosage mg/kg b.wt: FBG; initial	Model	Results
Reed et al. (2000) [31]	SD 200 g 7 wk	3 wk 2 wk	C 41, P 18, F 40	1x50, ip 21.6±2.1 mmol/L	HFD/STZ	↑BG, INS, TG
Yang et al. (2003) [62]	SD	8 wk	C 40, P13, F 40	1x15,ip	HFD/STZ	↑FBG, TG, TC [32]
Zhang et al. (2003) [63]	SD 250±20 g 2 M	8 wk 2 m	C50, P13, F 30, Fb 7	1x15,ip	HFD/STZ	↑BW, FBG, INS, IR, TG, TC [33]
Danda et al. (2005) [64]	SD 175-200 g	14 wk 5 wk	F70	1x35,iv >250 mg/dL	HFD/STZ	↑BG, Hb1Ac, TC, TG, CR ↔ SINS [34]
Srinivasan et al. (2005) [2]	SD 160-180 g	4 wk 2 wk	F58, P25, C17	1x35, ip	HFD/STZ	↑BG, TG, TC [2]
Albersen et al. (2011) [65]	SD 12 wk	12 wk 2 wk	NPD 88, CHL 2, L10	2x30, ip >300mg/dL	HFD/STZ	↓BW, HDL-c, SI, testosterone ↑TG, TC, LDL-c, nNOS, smooth muscle/collagen, endothelial integrity [35]

Table 1: Data of the development of HFD fed STZ-induced diabetic rat model

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Zhou et al (2004) [36]	SD 83±5 g 4 wk	1 wk 4 wk	C 54, P 13, F 20%	1x40,ip	Protamine zinc insulin (1 - 2 U/kg)	↓FBG,TG, C ↑INS mRNA, INS (βcell)
Wu et al (2004) [37]	SD 8 wk	6 wk 2 wk	P18, F 41(%)	1x30, ip	Iosartan (4mg/kg)	↑GLUT4, PI3K ↓IR

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Tan et al (2005) [38]	SD 200–260 g 10 wk	14 d 2 wk	CA 200, S 528.4, CR 10, CB 150, Met 3, CC10,DL–α–toco-pherol10, Min/Vit, 10:35,CL51 (g/kg)	1x50, ip. ≥ 350 mg/dL	*Averrhoa bilimbi* Aq,BuOH Ext. (125 mg/kg)	↓FBG, TC, TG ↑Gln (L) ↔ BW, TBARS (L&K), CP_{450} (L)
Sahin et al (2007) [39]	SD 200-250 g 8 wk	8 wk 2 wk	CA 200,starch 150,s 150,F 400, CL50, V/M50, DIM3,CC2 (g/kg)	1x40, ip. ≥140 mg/dL	Chromium picolinate (8µg)	↑BW, INS, ISI, ↓ BG, TG, TC, FFA, PU, Cr, AST, ALT
Islam et al (2008) [40]	SD 120–140 g 5 wk	4 wk 2 wk	CN 37.7, s 10.0, CA 20.0, L 20.0 ,SB 2.0, CL 5.0,V/M 1 :4, L-Met 0.3(%)	1x 40, ip. ≥ 300 mg/dL	*Allium cepa* L. (0.5% and 2.0%)	↑FI, BW, FBG, FINS, HOMA-IR, HOMA-β, HbA1c, LW, LDL-c, TG, TC, HDL ↓Gln (L), βCF
Gao et al (2008) [41]	SD 210-220 g	4 wk 4 wk	S 30, L 15 (%)	1x25, ip.	Bis(α-furan carboxylato) oxovanadium(IV) (0.06,0.2 m moL/kg)	↓ BG, TG, TC, FFA, LEP
Zhang et al (2008) [42]	W 200–250 g	4 wk 4 wk	F22, P20, C48	Set 1;1x45,ip Set 2;2x30,ip (2W Inter.)	**Berberine** (100 mg/kg)	Set 1: T1DM (100%) Set 2: T2DM (35%) ↓BW, FBG, TC, TG, FINS, ISI
Zhou et al (2009) [43]	W 180–220 g	16 wk 16 wk	NPD 70, L 12, YO 9, s 9 (%)	1x35, ip. > 16.7 mM	*Rhizoma coptidis* Berberine (150, 300 mg/kg)	↓MDA, ISI, FINS ↑SOD, βCF, Pn/BW
Wang et al (2009) [44]	W 6 wk	8 wk 4 wk	Zhang et al (2008) [42]	1x 30, ip. ≥7.8 mmol/L	**Berberine** (100 mg/kg)	↓FBG, TC, TG, INS, NOX4 ptn in aorta, NADPH oxidase ↑endothelium-dep. vaso-relaxation in aorta, eNOS: (mRNA&Ptn), NO bioavailability
Xing et al (2009) [45]	SD (F) 170-200 g	8 wk 6 wk	L 10,s 20,CHL 2.5,cho 1,NPD 66.5 (%)	1x30, ip. ≥7.8 mmol/L	*Artemisia sphaerocephala* Krasch. Gum. (2.7%)	↓FBG, GSP, TC, TG, IR, FFA, F-accumulation ↑GK, Gln(L), HDL-c, ISI
Zou et al (2009) [46]	SD 220-250 g	8 wk 8 wk	F 58, C 25.6,P 16.4 (%)	1x25, ip ≥11.1 mmol/L	*Astragalus membranaceus* Huangqi. polysaccharides (700mg/kg)	↓FBG, SI, Hb1Ac, HOMA-IR ↑Gln(L), P-AMPKα, P-ACC, GLUT4(Skm)
Rajasekaran et al (2009) [47]	W 200-250 g	30 d 2 wk	CHL 2 %	1x50, ip.	*Monascus purpureus* Fermented rice aq. ext. (2.4mg/kg)	↓ FBG, TC, TG, LDL-c, VLDL-c ↑HDL-c, BW

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Kaviarasan and Pugalendi (2009) [48]	W 150-180 g 8wk	45 d 17 d	F 20, C 0.5, P 17.7, FI 3.4, M/V 6.7/1.7 (g/kg)	1x 50, ip. ≥ 140 mg/dL	*Spermacoce hispida* seed Extr. Fra. (40 mg/kg)	↓TC, LDL-c, VLDL-c, A/G, U, UA, Cr, TBARS, LOOH, ALT, AST, ALP ↑L (wt),TP, A, SOD, CAT, GPx, GSH, PPARα (m RNA)
Veerapur et al (2010) [49]	W 200-250 g 7-8 wk	2 wk 2 wk	Srinivasan et al (2005) [2]	1x 25, ip. ≥ 200 mg/dL	*Dodonaea viscosa L.* Jacq. (Aq. Ext. 400/200; EtOH Ext. 200/100 mg/kg)	↓BW, FBG, INS, HOMA IR, TG,TC, LDL-c, VLDL-c, TBARS, PTP-1B ↑HDL-c, GSH, Total thiol, GST, CAT, SOD, PPARγ Glu uptake (Skm)
Parveen et al (2010) [50]	W 160-200 g	4 wk 2 wk	Srinivasan et al (2005) [2]	1x40, ip	French maritime pine bark ext- Pycnogenol (10mg/kg)	↑ SOD, CAT, GPx, GSH, GST, CAT, Gln (L) ↓FBG, HbA1c, TBARS, MDA, PC
Zhang et al (2010) [29]	W 200–250 g	15 d 2 wk	Reed et al (2000) [31]	1x35, ip. 7.0 -33.3 mmol/L	*Potentilla discolor* Bunge (TFE; 369 mg/kg: TTE; 501 mg/kg)	↓FBG, GSP, TC, TG, LDL-c, MDA, NO ↑HDL-c, SOD, GSH
Zhang et al (2010) [51]	SD 200-220 g	6 wk 10 wk	L 19.75, s 7.79 NPD 72.46 (g/kg)	1x25, ip. > 140mg/dL/ 7.8 mmol/L	*Hippophae rhamnoides* L. seed aq. Ext. (400 mg/kg)	↓BW, FSG, TC, LDL-c ↑ISI ↔ FFA, TG, FFA, HDL-c
Lu et al (2010) [52]	W 250 ± 20 g 8 wk	2 m 2wk	HFD	1x30, ip. > 200 mg/dL	*Paceilomyces farinosus* (G30801)	↓BG
Lu et al (2010) [53]	SD 160-180 g	6 wk 4 wk	Wu et al (2004) [37]	1x30, ip. ≥ 16.7 mM	*Litsea coreana* leve. (400 mg/kg)	↓BW, FBG, HbA1c, FFA, TC, TG, LDL-c, CRP, MDA, W/BW (S,L), PTP1B (L) ↑FINS, ISI, HDL-c, SOD (S,L)
Sunil et al (2011) [54]	W 150-200 g	28 d 15 d	Reuter et al (2007) [55]	1x40, ip. ≥ 300 mg/ dL	*Symplocos cochinchinensis (Lour.) S. Moore.* Leaf Ext. (250,500 mg/kg)	↓BPG, PI, TC (S,L), TG (S,L), FFA (S,L) ↑BW, Gln (L)

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Hussein et al (2012) [56]	SD 230 ±10 g 4-6 M	10 d 2 wk	Shimoni et al (1998) [57]	1x35, ip ≥ 250 mg/ dL	Ghrelin (40 µg/kg)	↓BW, FBG, INS, HOMA-IR, TG, TC, LDL-c, ACOX (mRNA) ↑ GLUT4, HDL-c
Jung et al (2011) [58]	SD 8 wk	8 wk 2 wk	F 41.2%	1x40,ip. >126 mg/dL	*Allium cepa* L. peel ext. (Quercetin) 1%	↓FBG, HOMA-IR, PINS, MDA, FFA, TP; IL6 (mRNA&Ptn), TNFα mRNA(L) ↑SOD, IS, Gln (L, Skm); ISI, GLUT4 (L, Skm)
Parveen et al (2011) [59]	W 180-200 g	4 wk 2 wk	Reed et al (2000) [31]	1x 40, ip. ≥ 140 mg/dL	*Terminalia arjuna*ext. (500 mg/kg)	↓FBG, HbA1c, TG, TC, LDL-c, VLDL-c, TBARS, MDA, PC, BUN, Cr, ALP ↑HDL-c, Gln (L), GSH, GST, CAT (L,Pn)
Parveen & Siddiqui (2011) [60]	W 160–200 g	4 wk 2 wk	Reed et al (2000) [31]	1x 40, ip. ≥140 mg/dL	*Butea monosperma* flower ext. (300 mg/kg)	↓FBG, HbA1c, TC, TG, FFA, LDL-c, VLDL-c, TBARS, PC ↑INS, HDL-c, GSH, GST, CAT
Sharma et al (2011) [61]	W (M/F) 180-200 g	21 d 2 wk	Sharma et al (2011) [62]	1x40, ip > 13.9 mmol/L	*Aegle marmelos* fruit aq. Ext. (250, 500 and 1000 mg/kg)	↓FSG, SI, HOMA-IR, TNF-α, IL-6, TC, TG, LDL-c ↔BW ↑HDL-c, HOMA-B, SOD, TBARS, PPARγ
Sharma et al (2011) [62]	W 170-200 g	28 d 10 d	CO 25, CHL 2, NPD 73 (%)	1x40, ip ≥13.89 mmol/L	Naringin (100mg/kg)	↓BW, FBG, INS, TC,TG, LDL-c, IR, HOMA-IR, TNFα, IL6, CRP; NF-κB, SREBP-1c (L,K); LXR (L); TBARS (S,Pn,L,K); SOD, GSH-Px (S,Pn,L,K) ↑HDL, HOMA-B, βCF; PPARγ, HSP72, HSP27,P-IRS, (L,K), Adip, Islet area
Zhang et al (2011) [63]	SD 180-220 g	8 wk 4 wk	L 18, YO 8, CO 2, SC 0.2, NPD 71.8 (g/kg)	1x35, ip. ≥ 16.67 mmol/L	Yi-Qi-Zeng-Min-Tang (1.41,2.82 g/100g)	↓FBG, HOMA-IR, TG, TC, LDL-c, FFA,TNFα, IL-6 ↑HDL-c; FINS ↔BW
Mahmoud et al (2012) [64]	W 190±10 g	30 d 2 wk	Reed et al (2000) [31]	1x35, ip. ≥ 200 mg/dL	Hesperidin and Naringin (50mg/kg)	↓ FBG, HbA1c, MDA, TNF-α , IL-6, NO ↑INS, Vit C & E ↔ GSH, CAT, GPx, GR,SOD (L)
Ahmed et al (2012) [65]	W 190 ±10 g	30 d 2 wk	Reed et al (2000) [31]	1x35, ip. ≥ 200 mg/dL	Hesperidin and Naringin (50 mg/kg)	↓FBG, TC, TG, LDL-c, VLDL-c, FFA, HbA1c, AST, LDH, CK-MB, AdipR(S) ↑ INS, HDL, Gln (L&Skm)

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Khan et al (2012) [66]	SD 230 ± 20 g	30 d 2 wk	Xie & Du (2005) [67]	1x35, ip. ≥ 126 mg/dL	*Semecarpus anacardium* nut milk ext. (200 mg/kg)	↓FBG, FINS, HOMA-IR, HbA1c, AST, ALT, ALP, ACP, LDH (L&S), LPO, MDA ↑SOD, CAT, GPx, GST, GR, Vit C&E, GSH, T-SH (L&Skm)
Li et al (2012) [68]	ICR mice 18 - 22 g	4 wk 4 wk	F 22, C 48, P 20 (%)	1x100, ip. > 7.8 mmol/L	*Panax ginseng* (300 mg/kg PDG ; 30 mg/kg CK)	↓FBG , PEPCK, G6P: (gene) ↑INS
Bas et al (2012) [69]	SD 10-12 wk	12 wk 2 wk	VO 3, AF 37, CN 30.5, CA 20, SB 4.5, DCP 1.7, DIM 0.20, LS 1.6, NaCl 0.5 V/M 1 (g/kg)	1x35, ip. 300 mg/Dl	*Nerium oleander* distillate (3.75, 37.5, 375µg/mL)	↓FBG, HbA1c, HOMA-IR, HOMA-β, ALP, AST, ALT, TC, LDL-c, TG, AI, TG/HDL-c, FINS, LEP ↑β CF, BW, HDL-c, PPAR α,β,γ (Adip) α,γ (L): mRNA)
Bansal et al (2012) [70]	W 22 ± 3 g 4–6 wk	28 d 4 wk	Mu et al (2006) [71]	1x 125, ip.	*Pilea microphylla* (100 mg/kg)	↓BW, PG, TC, TG, MDA, DPP-IV ↑GSH, CAT, SOD (P), βcell protected
Kaur (2012) [72]	W 100-150 g 11wk	30 d 30 d	HFD	1x30,ip. >126 mg/dL	*Curcuma longa* Linn (curcumin), *Piper nigrum* (piperine), *Allium cepa* (quercetin) (100 mg/kg)	↓FBG, TG,TC, LDL-c ↑HDL-c, BW, SOD, CAT, GSH-Px
Latha et al (2012) [73]	W 170-180 g	15 d 2 wk	Srinivasan et al (2005) [2]	1x35,ip. >300 mg/dL	*Garcinia camogia, Commiphora wightii, Gymnema sylvestre,Terminalia Chebula,, Trigonella foenum-graecum* (250 ,500 mg/kg)	↓WB, FBG, TG, TC, LDL-c, VLDL-c, AST, ALT ↑HDL-c
Veerapur et al (2012) [74]	W 200–250 g 7–8 wk	2 wk 2 wk	Srinivasan et al (2005) [2]	HFD + STZ: 1x25, ip. ≥ 200 mg/dL	*Ficus racemosa* EtOH Ext. (200, 400 mg/kg)	↓FBG, FINS, HOMA IR, TG, TC, VLDL-c ,LDL-c, TC/HDL-c, LDL-c/HDL-c, TBARS, inhibited PTP-1B, DPPIV ↑HDL-c, GSH, T-SH, GST, CAT, SOD; PPARγ Glu uptake (Skm)

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Khan et al (2012) [66]	SD 230±20 g	30 d 2 wk	Xie & Du (2005) [67]	1x35, ip > 200 mg/dL	*Semecarpus anacardium* Linn nut milk ext (200 mg/kg)	↓FBG, HbA1c, TC, TG, FFA ↑INS
Guo et al (2012) [75]	W 140-180 g	12 wk 4 wk	L 10, s 20, CHL 2,SC 1, NPD 67 (%)	1x30, ip ≥7.8 mmol/L	Rosiglitazone (3mg/kg)	↓PG, PINS, TC, TG, IR, IRI, HW/BW; p22phox, NOX_4, MCP1, CTGF1(H) ↑BW; Adi-R1,2 (mRNA-P,H);GLUT4, AMPKα, NADPH Oxidase (Ptn-H)
Guo et al (2012) [76]	W 140-180 g	12 wk 4 wk	L10, s20, CHL2, SC1,NPD 67 (%)	1x 30,ip. ≥ 7.8 mmol/L	Telmisartan (5mg/kg)	↓FBG, PI, TC, TG, FFA (S); CTGF, NF-κB , MCP1, NOX4, p22phox(H), Hwt/BW ↑ GLUT4, adipoR1, adipoR2 (H)
Wen et al (2012) [77]	W 150-170 g 8 wk	8 wk 4 wk	Guo et al (2002) [78]	1x30, ip. ≥15.00 mmol/L	*Fructus Ligustri Lucidi, Eclipta Prostrata, Dioscorea opposite* Oleanolic acid (4,8g/kg)	↓KW, FBG, TC, TG, TG(Kl); AER, CR, U; Fib, TGF (Ptn), SREBP-1c, ACC, FAS (K-mRNA & Ptn) ↑BW, KFn (Histopathology)
Hou et al (2012) [79]	SD 200–220 g	8 wk 8 wk	F 59.8, P 20.1, C 20.1 (%)	1x25, ip. ≥ 11.1 mmol/L	n-3 PUFAs(3-eicosapentaenoic acid, 3-doco sahexaenoic acid)	↑ FFA, TG (S,H), β-oxidation (H-mitochondria, Peroxisome), PPARα, LBP , mCPT-1, ACOX1, ACOX3, DBP, THLA/B, SCPx (mRNA)
Fang et al (2012) [80]	SD 150-180 g	3 wk 5 wk	F 58.3, P 7.9, C 33.8 (%)	1x40, ip. ≥16.70 mmol/L	Fufang Xue Shuan Tong capsule (900,1800mg/kg)	↓UPE, Cr clearance, MMI, MDA ↑SOD ↔ FBG,BW
Ren et al (2012) [81]	SD 180-220 g 8 wk	6 wk	NPD 67, s 20, L 10, CHL 2, BS 1(%)	1x30, ip ≥ 7.0 mmol/L	Vit (1,25-$(OH)_2$ D3	↓ VEGF, TGF-β1
Si et al (2012) [82]	SD 200 g 7 wk	6 wk 2 wk	Reed et al (2000) [31]	1x50, iv ≥8.0 mmol/L	Mesenchyman stem cells ($2x10^6$)	↓ FBG, IR ↑INS, C-peptide(S), βCF, GLUT4, IRS1, AKt (L,Sk,H)
Zhou et al (2013) [83]	W 180-200 g	16 wk 4 wk	NPD 67.5, L 15, s 15, CHL 2,Bile salt 0.5 (%)	1x30,ip	Hu-Lu-Ba-Wan *Trigonella foenum-graecum*L., *Psoralea corylifolia* L. (18g/kg)	↓FBG, TG, TC, LDLc (S); K/BW, BUN, Cr, UTP, A; NADPH activity(K); Phosphorylated PKC-α, $P47^{phox}$, Fib (mRNA&ptn) ↑HDLc, Renal morphology

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Wu et al (2013) [84]	SD 90-100 g	12 wk 4 wk	HFD	1x40, ip. ≥16.70 mmol/L	Xiexin decoction *Rheum palmatum* L. *Coptis chinensis* Franch, *Scutellaria baicalensis* Georgi (2 : 1 : 1 (w/w) (1.25,2.5 g/kg)	↓FBG, GAUC, HbA1c, TC, TG, UAE, Cr clearance, Kw/BW; MCP-1, ICAM-1, TNF-α, IL-6, TGF-β1; AGEs , RAGE; IKKα, phospho-IκBα, phospho-NF-κBp65, NF-κBp65(K mRNA& Ptn) ↑IκBα, RFn
Wang et al (2013) [85]	SD 180-200 g	8 wk 6 wk	NPD 84.5, L 5, YO 10, SC0.5 (%)	1x35, ip. ≥11.10 mmol/L	*Coptidis rhizome* Berberine (200 mg/kg)	↓FBG, KW/BW, U.A/C, UP/C, BUN, Cr, TG, TC, LDL-c; GRK2, GRK3(Ptn) ↑BW,HDL-c, GRK4, GRK6, cAMP (Ptn) ↔ GRK5(Ptn)
Wang et al (2013) [86]	W 180-220 g	8 wk	Guo et al (2002) [78]	1x25, ip	*Rhodiola rosea* (10,20g/kg)	↓FBG, TC, TG, Cr, A, KW/BW, glomerular area, TGF-β1
Chaudhari et al (2013) [87]	W 150-200 g	21 d 2 wk	Chaudhari et al (2012) [88]	1x35, ip. >200 mg/dL	*Embelia ribes* fruit Embelin (100, 200 mg/kg)	↓BW, FBG, BP, LDH, Cr, ALP, TC, TG, TBARS ↑A, TP (S); SOD, CAT, GSH (K)
Hsu et al (2013) [89]	ICR mice 4 wk	4 wk 8 wk	L 60% kcal	1x100,ip. >400 mg/dL	*Hypolepis punctata* (Thunb.) Mett Pterosin A (100mg/kg)	↓TC, LDL-c, BUN, Cr, AST, ALT, IR, HOMA-IR, HbA1c, INS
Naik et al (2013) [90]	SD 160-180 g	3 wk 4 wk	Srinivasan et al (2005) [2]	1x35, ip. ≥380mg/dL	*Embelia basal* Embelin (50mg/kg)	↓FBG, HbA1c, IL6, TNFα, MDA, TC, TG, LDL-c, VLDL-c ↑HDL-c; GSH, SOD, CAT(L)
Hu et al (2013) [91]	SD 150-180 g 10-12 wk	4 wk	C 26, P 15.2, L 58.8 (%)	1x 30-35,ip ≥ 16.7 mmol/L	Pioglitazone 20 mg	↓PI, BG, CSF-INS, HOMA-IR, GSK-3β, Tau protein hyperphosphorylation ↑AKT(hippocampal)
Prangthip et al (2013) [92]	SD 147 ± 9 g 5 wk	12 wk 2 wk	CA 20; CN 3, s 10.75 CL 5, DL-Met 0.30, M/V 3.50: 1, cb 0.20 ,CR 28 (%)	1x20 & 1x30, ip. ≥ 16.65 mM	Riceberry supplement	↓FBG, HbA1c, TNF-α, IL-6, TBARS, TC, TG, LDL-c, Protected Pn, Sp ↑BW, INS, GLUT4, SOD, CAT, GPx
Rahuja et al (2013) [93]	SD 200±10 g 8-10 wk	15 d 6 wk	Fructose 60, CA 21, F 13, V/M 1,NaCl 2 (%)	1x35, ip. ≥300mg/dL	*Jatropha gossypifolia* L. Stem Ext. (250mg/kg)	↓FBG,TC,TG,LDL-c, Bil, AST, ALT, U, UA, Cr ↑INS, HDL-c

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Abo-elmatty et al (2013) [94]	A 150±20 g	4 wk 2 wk	Srinivasan et al (2005) [2]	1x35, ip. > 250-300 mg/dL	*Urtica pilulifera* EA Ext. (250 and 500mg/kg)	↓BG, HbA1c, FINS, HOMA IR, TG, TC, LDL-c, 8-OHdG, TNF-α, MDA ↑HDL-c, R-QUICKI, GSH, SOD,CAT ↔ALT, AST, ALP, BUN, Cr, TP
Gandhi et al (2013) [95]	W 180±10 g	30 d 2 wk	Sharma et al (2011) [62]	1x 40, ip. ≥ 250 mg/dL	Embelin (50 mg/kg)	↓ BW, FBG, PI, FFA,TC, TG,LDL-c ↑SOD, CAT, GPx, βCF, HDL-c, PPARγ, GLUT4, PI3K, p-Akt (Adip, Skm,L: mRNA& ptn)
Khan et al (2013) [96]	SD 230±20 g	30 d 2 wk	Xie & Du (2005) [67]	1x35, ip > 200 mg/dL	*Semecarpus anacardium* Linn nut milk ext (200 mg/kg)	↓FSG, PI, HOMA IR, TNF-α, IL-6 CRP, CHL, TGL, LDL-c, (P); TC, TG, FFA, FC (L,Sk); LCAT, CES (L) ↑PL (L,Sk), HDL-c, HOMA-β, CEH, LPL, PPARγ (L mRNA)
Priscilla et al (2014) [97]	W 75–100 g 5–6 wk	16 h 3 wk	NPD 365, GH 310, CA 250, CO10, Vit/Min 60, L-Cys 3,YE 1,NaCl1 (g/kg)	1x40, ip. ≥ 250 mg/dL	Naringenin (25 mg/kg)	↓ α-glucosidase, carbohydrates absorption, BG (PP), Well docked
Tharaheswari et al (2014) [98]	SD 150-200 g 8-10 wk	8 wk 4 wk	Srinivasan et al (2005) [2]	1x35,ip. >350 mg/dL	*Trigonella foenumgraecum* (150.300g/kg)	↓FBG, HbA1c, TG, TC, LDL-c, CK, CK-MB ↑Hb, INS, HDL-c, HK, Gln (Skm), DPPH inhibition, PPARγ (mRNA-Adip), PPARα (mRNA-L), GLUT4 (mRNA-Skm)
Li et al (2014) [99]	SD 180-220 g 6-8 wk	6 wk 4 wk	F 22, C 58, P 20 (%)	1x30,ip.(or x2) ≥7.8 mmol/L	Sequoyitol (25, 50 g/kg)	↓FBG, BUN, Cr, MDA, ROS; TGF-β1, NF-κB,$p22^{phox}$, $p27^{phox}$ (K- mRNA& Ptn) ↑TAOC

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Chang et al (2014) [100]	SD 8 wk	14 wk 4 wk	HFD	1x35,ip.	*Paeonia lactiflora Pall.* root glucosides (100,200mg/kg)	↓UPtn,Cr, BUN; Wnt-1, β-catenin (K-mRNA&Ptn) ↑ K protected and delayed DN
Ahad et al (2014) [101]	W 150-180 g	16 wk 5 wk	F 70%	1x35,ip ≥350mg/dL	*Passiflora caerulea* L., *Pelargonium peltatum* L., *Tilia tomentosa*Moench, *Pelargonium quercifolium* L.f., *Pelargonium crispum* (Berg.), *Oroxylum indicum* L. Benth. ex Kurz Chrysin (40mg/kg)	↓BW, FBG; TNF-α, NF-κB, TGF-β, fib and collagen-IV (Ptn); UPtn, BUN, Cr; IL-1β, IL-6, TNFα, MDA ↑ Cr clearance , K protection (histology); GSH, GPx, GR, SOD,CAT ↔SINS
Ahad et al (2014) [102]	W 130-150 g	16 wk 5 wk	F 70%	1x35,ip.	*Scutellaria baicalensis Georgi* (root), *Oroxylum indicum* L. (fruit) Baicalein (20mg/kg)	↓BW, FBG, HOMA IR, HbA1c, AST, ALT, ALP; NO (S,U); NF- κB,I NOS,TGF-β1, (K); UPtn; IL-1β, IL-6,TNFα ↑ Cr clearance , K protection ↔SINS
Sherif (2014) [103]	SD 150-180 g	4 wk 2 wk	Srinivasan et al (2005) [2]	1x35,ip. >350 mg/dL	Secoisolariciresinol diglucoside (10,20mg/kg)	↓FBG, Cr, BUN, Fructosamine, MAD, NO; NF-kB, TNF-α, iNOS (mRNA) ↑INS, GSH, SOD(K), Survivin, Bcl-2(mRNA)
Chen et al (2014) [104]	C57BL/6J 16 - 19 g 4 wk	13 wk 3 wk	NPD 54.7, L 16.9,s 14.0, CA 10.2, MD 2.1 (g/kg)	1x100, ip.	*Lactobacillus rhamnosus* CCFM0528 10^9 cfu	↓FBG, BG (PP), α glucosidase inhibition, HbA1c, Endotoxin, TNF-α, IL-6, IL-8 ↑BW, INS, Gln, IL-4, IL-10 Sp), βCF
Jiang et al (2014) [105]	W 200–250 g	28 d 4 wk	F 22, C 48, P 20%	1x30, ip. > 7.8 mmol/L	Panax ginseng (300, 100 mg/kg)	↓FBG,TG, TC ↑BW,FINS, ISI, InsR, IRS1, PI3Kp85, pAkt, Glut4 (Skm: mRNA& ptn)

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Gandhi et al (2014) [5]	W 180–200 g 5 wk	30 d 2 wk	Gandhi et al (2014) [106]	1x 40, ip. ≥ 250 mg/dL	Gallic acid (20 mg/kg)	↓ BW, BSG, PI, HOMA-IR, TC,TG, G6P, F1,6BP ↑ βCF, HK, Gln (L), PPARγ, GLUT4, PI3K, p-Akt (Aep, Sk,L: mRNA& ptn)
Gandhi et al (2014) [106]	W 180–200 g 5 wk	30 d 2 wk	Srinivasan et al (2005) [2]	1x 40, ip. ≥ 250 mg/dL	*Cyamopsis tetragonoloba* L. beans MeOH ext. (200,400 mg/kg)	↓ BW, FBG, HOMA-IR, PI, TC, TG, G6P, F1,6BP ↑ Gln (L), HK, G6P, F1, 6BP, βCF
Kumar et al (2014) [107]	W 150-200g 8-10 wk	4 wk 4 wk	Srinivasan et al (2005) [2]	1x35,ip >350 mg/dL	*Cassia auriculata* L. flower ext. (500mg/Kg)	↓FBG, SGPT, SGOT, ALP, LPO, LDL-c, TG, TC ↑HDL-c, Gln (L), CAT, SOD, GPx, GSH (P,L,Pn)
Kumar et al (2014) [108]	W 150-200 g	21 wk 28 d	CA 342, cystine 3, starch 172, s 172,CE 50, GN. oil 25, tallow 90, min oil 37, vit 1 (g/kg)	1x45,iv. >200 mg/dL	*Gymnema sylvestre* EtOH ext. (120mg/kg)	↓H rate, Arterial pressure, LEP, INS, Apolipoprotein B, TC, TG, LDL-c, VLDL-c, Glu, HbA1c, Cardiac Casapase-3, ATPase, Visceral fat, AI, TBARS, MDA ↑ BW, SOD, CAT, GSH, GPx, GST, GR, HDL-c, Na+/K+
Niture et al (2014) [109]	SD 160-180 g	3 wk 4 wk	Srinivasan et al (2005) [2]	1x35, ip. ≥300mg/dL	Rutin (50.100mg)	↓FBG, HbA1c, IL6, TNFα, MDA, TC, TG, LDL-c, VLDL-c ↑HDL-c; GSH, SOD, CAT(L)
Zhang et al (2014) [110]	SD 180-220 g	1 m	NPD 68.8, L 5, s 10, CHL 1, SC 0.2, Egg yolk 10	1x30, ip. ≥20 mM	*Paeonia suffruticosa* Andr, (Moutan Cortex: root bark) (5, 2.5 g/kg)	↓FBG, Cr, UPtn, KW, MDA; TGF-β2 (K-Ptn) ↑BW, SOD, GSH-Px, CAT
Priscilla et al (2015) [111]	W 75–100 g 12–13 wk	45 d 6 wk	Priscilla et al (2014) [97]	1x40, ip. ≥ 250 mg/dL	Naringenin (25 mg/kg)	↓BW, FBG, Pl, TG, FA,TC, LDL-c, VLDL-c, TBARS, LP(S); AST, ALT, ALP(L); TNFα (mRNA& ptn) ↑HDL-c(S), SOD, CAT, GPx (L&Pn); GLUT 4 (mRNA& ptn)

Reference	Strain Weight initial age	Study period: Diet (prior to STZ)	HFD composition	STZ dosage mg/kg b. wt: FBG; initial	Extract/compound/ Derivatives	Results
Maheswari & Vennarasi (2015) [112]	W 200±10 g	4 wk 2 wk	Srinivasan et al (2005) [2]	1x40,ip. >140mg/dL	*Tribulus terrestris* Lvs. Aq. Ext (50mg/kg)	↓FBG, HbA1c, TC, TG, LDL-c, VLDL-c, BUN, Cr, ALP, TBARS, MDA, PC (L, Pn) ↑HDLc, Gln (L), GSH, GST, CAT, SOD (L, Pn)
Naidu et al (2015) [113]	W 150-180 g	30 d 2 wk	CA 200, starch 152, s 152,CE 50, tallow 400,V/M 50,DIM 3,CC 2(g/kg)	1x35,ip. ≥200mg/dL	*Trigonella foenum* Diosgenin (60mg/kg)	↓FBG, BW, INS, IR, LDL-c, VLDL-c(S); TC,TG, FFA, PL (L,H,B) ↑HDL-c
Irudayaraj et al (2016) [114]	W 180-200g	28d 15d	Gandhi et al (2014) [106]	1x40, ip. ≥200 mg/dL	*Ficus carica* Linn. Ficusin (20 and 40 mg/kg)	↓FBG, TC, TG, FFA, U ,Cr , AST, ALT, ALP (P) ↑BW, INS, SOD, CAT, GPx, Gln(L), GLUT4,PPARγ (Adip-mRNA), Docked well with GLUT4, PPARγ
Shah et al (2016) [115]	SD 150-200 g 6-12 wk	28 d 4 wk	F 20,C 46,P 20 (%)	1x35, ip >17.0 mmol/L	*Brassica oleracea* var. Italica (400,800mg/kg)	↓FBG, HbA1c ↑INS, Hb, BW
Stalin et al (2016) [14]	W 180 ±10 g 5 wk	30 d 2 wk	Gandhi et al (2014) [106]	1x40, ip. > 250 mg/dL	6-bromoembelin and Vilangin; (30 mg/kg)	↓FPG, PI, BW, TC, TG, LDL-c, FFA, G6P, F1,6BP ↑HK, HDL-c ; PPARγ, GLUT4, PI3K, p-Akt (Adip, Skm, L: mRNA& ptn)
Antony et al (2017) [116]	W 180-200 g	28 d 2 wk	Gandhi et al (2014) [106]	1x40,ip ≥250mg/dL	*Mimosa pudica Linn.* Myoinositol (25,50 mg/kg)	↓FI, WI, FBG, HOMA-IR, TC, TG, LDL-c, SGOT, SGPT, ALP,U, Cr ↔BW; L,H, K, Pan protected ↑HDL-c, PINS, β-CF, PPARγ, GLUT4, IR (mRNA&Ptn , docked well)
Stephen et al (2017) [117]	W 170-190g	28d 15d	NPD 68, D 30, CHL 2 (%)	1x40, ip. ≥250 mg/dL	*Ficus carica Linn.* EA lvs ext.. 250,500 mg/dL	↓FBG,TC,TG, BW,PINS ↑G6Pase, F1,6BPase, HK, Gln (L), βcells protected

Table 2: Data of HFD fed STZ-induced diabetic rat model studies for pharmacological screening

Abbreviation:↑, Raised; ↓, Lowered; ↔, Ameliorated; 8-OHdG, 8-hydroxy-2-deoxyguanosine; A, Albumin; ACC, Acetyl-CoA carboxylase; ACOX, Acyl-CoA oxidase; ACP, Acid phosphatase; Adip, Adipose; Adipo, Adiponectin; AdipoE, Adipose epididymal; AdipoR, Adiponectin receptor; AER, Albumin excretion rate; AF, Animal fat; AGE, Advanced glycation end-product; AGI, α-glucosidase inhibition; AI, Atherogenic index; ALP, Alkaline phosphatase; ALPL, Apolipoprotein lipase; AMPK, AMP activated protein kinase; Bcl, β- cell function; Bcl-2, B-cell lymphoma-2; BG, Blood glucose; Bil, Bilirubin; BS, Bile salt; BW, Body weight; C, Carbohydrate; CA, Casein; CAT, Catalase; CB, Cocoa Butter; Cb, Cholinebitartate; CC, Choline chloride; CEH, Cholesterol ester hydrolase; CES, Cholesterol ester synthetase; CK-MB, Creatine kinase; CL, Cellulose; CN, Corn; CO, Coconut oil; CP450, Cytochrome P450; Cr, Creatinine; CR, Corn oil; CRP, C-reactive protein; D, Dalda; d, Day; DBP, D-bifunctional protein; DCP, Dicalcium phosphate; DIM, DI-methionine; DPPIV, Dipeptidyl peptidase 4; F, Female; F, Fibre; F1, 6BP, Fructose-1,6-bisphosphatase;FAS, Fatty acid synthase; FBG, Fasting blood glucose; Fbn, Fibronectin; FC, Free cholesterol; FC, Free cholesterol; FINS, Fasting serum insulin; FSG, Fasting Serum Glucose; FTG, Fasting Triglycerides; G, Globulin; G6P, Glucose-6-phosphatase; GH, Ghee; Gln, Glycogen; Glu, Glucose; Glut4, Glucose transporter 4; GPx, Glutathione peroxidase; GR, Glutathione reductase; GSH, Reduced glutathione; GSK-3β, Glycogen synthase kinase-3β; GSP, Glycosylated serum protein; GST, Glutathione-s-transferase; H, Heart; HbA1c, Glycosylated haemoglobin; HDL-c, High-density lipoprotein cholesterol; HK, Hexokinase; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model of assessment of β-cell function; HP, Lipid, hydroperoxidase; IL, Interleukin; INS, Insulin; InsR, Insulin receptor; IR, Insulin resistance;IRI, Insulin resistance index; IRS, Insulin receptor substrates; ISI, Insulin sensitivity index; K, Kidney; L, Liver; LBP, L-bifunctional protein; LCAT, Lecithin cholesteryl acyl transferase; LDH, Lactate dehydrogenase; LDL-c, Low-density lipoprotein cholesterol; LDL-c, Very low-density lipoprotein cholesterol; LEP, Leptin; M, Male; m, Month; mCPT-1, Muscle carnitine palmitoyltransferase 1; MD, Maltodextrin; MDA, Malondialdehyde; Mi, Mitochondria; MMI, Mesangial matrix index; NaCl, Salt NO, Nitric oxide; NP-SH, Nonprotein thiol; p-Akt, Phosphorylated protein kinase; PC, Protein carbonyl; PEPCK, Phosphoenolpyruvate carboxykinase; PG, Plasma glucose; PI, Plasma insulin; PI3K, Phosphatidylinositol 3-kinase; PL, Phospholipid; Pn, Pancreas; PP, Post Prandial; PPAR, Peroxisome proliferator-activated-receptor; PTC, Plasma Total Cholesterol; PTG, Plasma Triglycerides; PTP, Protein tyrosine phosphatase; PU, Plasma urea; Res, Resistin; RFn, Renal function; R-QUICKI, Revised quantitative insulin sensitivity check index; SC, Sodium cholate; SCPx, Sterol carrier protein x; SD, Sprague-Dawley ICR mice; SGOT/AST, Serum glutamic oxaloacetic transaminase; SGPT/ALT, Serum glutamic pyruvic transaminase; Skm, Skeletal muscle; SOD, Superoxide dismutase; SP, Soya pulp; Sp, Spleen; TAOC, Total antioxidant capacity; TBARS, Thiobarbituric reactive substances; THL, 3-Ketoacyl-CoA thiolase; TNF-α, Tumor necrosis factor-alpha; T-SH, Total thiol; UA, Uric acid; UAE, Urinary albumin excretion; V/M, Vitamins and minerals; VEGF, Vascular endothelial growth factor; VO, Vegetable oil; w, Week; W,Wistar; YE, Yeast; YO, Yolk powder

However, from our extensive review of literature, we have drawn an outline for a standard procedural strategy followed in most HFD/STZ obese hyperglycemic rats model in developing T2DM. As shown in Table 2, after acclimatization for few weeks the experimental rats excluding the normal control rats had free access to standardized HFD varying from two to eight weeks prior to intraperitoneal/ intravenous injection with freshly prepared STZ (30-50 mg/kg BW (W) and 25-50mg/kg BW (SD) [14,59,63,64,66,79,84,85,118,119]. Initial drug-induced hypoglycemic mortality was avoided in STZ injected rats by administering them with 20% glucose solution for 24h. 0.1 M citrate buffer (pH 4.5) (carrier) alone was injected to normal control rats [64,84,119]. Hyperglycaemia was assessed five to seven days after STZ induction by measuring fasting blood glucose (FBG) level. The rats with FBG levels above ≥200 mg/dL were classified as diabetic [14,59,63,64,66,79,84,85,118,119]. Five to seven days after the induction of diabetes, the experiment was commenced (day 0). HFD treatment continued throughout the experimentation period.

HFD/STZ Experimental group design: Animals were randomly divided into five groups of six diabetic persisting and normal rats respectively. Group I: Normal control rats received vehicle (0.5% sodium carboxy methyl cellulose (CMC-Na) in warm water) alone at 1 ml/100 g BW. Group II: Diabetic control rats treated with vehicle alone. Group III: Diabetic rats treated with lower dose of testing extract or compound suspended in vehicle. Group IV: Diabetic rats treated with higherdose of testing extract or compound drug suspended in vehicle. Group V: Diabetic rats treated with commercial diabetic drugs suspended in vehicle. The drugs were administered orally once a day at a fixed time [14,59,63,64,66,79,84,85,118,119].

Physiological and Biochemical analysis: Food and water intakes were estimated daily during the course of the experiment. FBG and body weights (BW) were measured on regular intervals.

Plasma insulin (PI), total cholesterol (TC), triacylglycerols (TAG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and homeostasis model assessment of insulin resistance (HOMA-IR) were determined. After two weeks from the commencement of the experiment, oral glucose tolerance test (OGTT) was carried out. Briefly, the rats excluding the normal control group were fasted for 6 h and a glucose solution (2 g/kg) was orally administered exactly at 30 min after the administration of drugs to be tested orcommercial diabetic standard drugs. Blood glucose of each rat was analyzed at time 0 (prior to the glucose administration) and 30, 60 and 120 min after the glucose infusion. On the 25th day, insulin tolerance test (ITT) was carried out. Briefly, after fasting for 6 h, blood samples were obtained from the tail vein with heparin-coated tubes. Then, the animals were treated with a dose of 1.2 U/kg of insulin in normal saline intraperitoneally. Blood samples were collected at 30 and 60 min after the insulin injection for estimation of glucose. On the last day, animals were anaesthetized, sacrificed and blood was collected. Serum was separated by centrifugation at 2000 rpm for 10 min for estimating serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). Activity of serum alkaline phosphatase (ALP) was determined. Serum urea and creatinine were measured. Histology and immunohistochemical analysis were also carried out at the end of the study. Protein and mRNA expression analyses were also part of HFD/STZ-induced experimental obese rat model (Table 2).

Is HFD-STZ an ideal type 2 diabetic model?

Appropriate experimental models are essential tools for understanding the pathogenesis, complications, and genetic or environmental influences that increase the risks of type 2 diabetes and for testing various therapeutic agents. The animal models of T2DM can be obtained either spontaneously or induced by chemicals or dietary or surgical manipulations and/or by combination thereof. In recent years, large number of new genetically modified animal models including transgenic, generalized knock-out and tissuespecific knockout mice have been engineered for the study of diabetes. Table 3 summarizes the various T2DM animal modelswith their advantages and disadvantages.

Model Category	Advantages	Disadvantages
Spontaneous or genetically derived diabetic animals	Development of T2DM is spontaneous involving genetic factors Resemble human T2DM Inbred animals with homogeneous genetic background Environmental factors can be controlled Minimum variability of results and require small sample size	Animals are homogenous, highly inbred with monogenic inheritance Development of diabetes is genetically determined Limited availability and expensive for the diabetes study High mortality due to ketosis Require sophisticated maintenance
Chemically induced diabetic animals	Selective destruction of pancreatic β-cells using chemicals (alloxan/STZ) Residual insulin secretion makes the animals live longer Ketosis and resulting mortality is relatively less Comparatively cheaper, easier to develop and maintain	Hyperglycaemia develops predominantly by direct cytotoxic reduction of β-cells Development of T2DM is by insulin deficiency rather than of insulin resistance Diabetes induced by chemicals is mostly less stable and at times reversible because of spontaneous regeneration of β-cells Chemical toxicity to other body organs besides its cytotoxic action on β-cells High variability of results
Surgical diabetic animals	Minimum cytotoxic effects of chemical diabetogens on other organs Resemble human T2DM due to reduced islet β-cell mass	Complicated technical and surgical procedures involved Occurrence of some other digestive problems due to surgery Lose of α-islets along with β-cells leading to irregularities in glycemic balance High mortality

Model Category	Advantages	Disadvantages
Transgenic/knock-out diabetic animals	Effect of single gene or mutation on diabetes can be investigated in vivo Easier comprehension of complex genetics of T2DM	Highly sophisticated and costly procedure for the production and maintenance Expensive for regular screening experiments
Diet/nutrition induced diabetic animals	Develop diabetes associated with obesity Simulates human diabesity syndrome as a result of overnutrition Minimum chemical toxicity on other vital organs	Require long period of dietary treatment No frank hyperglycaemia develops upon simple dietary treatment in genetically normal animals Not suitable for screening antidiabetic agents on circulating glucose parameter
HFD/STZ rat model	Quick simulation of natural disease progression, cost-effective Simulate natural T2DM disease progression like obesity, insulin resistance, glucose intolerance *in vivo* Investigation of anti-diabetic potential of novel therapeutics Sensitive to T2DM drugs	STZ should be regarded to be a human carcinogen Poor standardization

Table 3: Advantages and disadvantages of different categories of type 2 diabetic animal models(Srinivasan & Ramarao (2007)

HFD/STZ-induced T2DM rat model is developed by a combination treatment of diet-induced dyslipidemia associated insulin resistance and a reduction in functional β-cell mass by a low-dose streptozotocin (STZ) injection [2,31]. High dietary fat (HFD) with a dense caloric content promotes obesity triggered impaired glucose tolerance and an increased risk for developing T2DM [120]. HFD feeding initially triggers increased levels of insulin secretion by the pancreatic β-cell which is then lowered by the partial destruction of the functional β-cell mass by the STZ injection. After the decrease in insulin levels, HFD-fed animals become significantly hyperglycemic. Hence, they simulate natural disease progression and metabolic symptoms characteristic of individuals at increased risk of developing T2DM because of insulin resistance and obesity [55].

STZ (2-deoxy-2-(3-methyl-3-nitrosourea) 1-D-glucopyranose) (MF:$C_8H_{15}N_3O_7$) (MW: 265 g/mol) is a naturally occurring cytotoxic glucose analogue, produced by *Streptomyces achromogenes* that inhibits DNA synthesis in mammalian cells [121]. Since the discovery by Rakieten [122] that STZ is a diabetogenic chemical agent, it has been widely used for inducing diabetes in experimental animals [123]. STZ is cytotoxic to pancreatic β-cells and its effects can be seen within seventy two hours after administration depending on the dose administered [124]. Unlike other nitrosourea compounds, STZ is hydrophilic due to the glucose moiety in its chemical structure which enables it to enter the β-cell via the low affinity glucose 2 transporter (GLUT2) in the plasma membrane making it a selective pancreatic β-cell toxic chemical. β-cells of the pancreas are more active than other cells in taking up glucose and so are more sensitive to STZ toxicity than insulin producing cells that do not express GLUT2 [125]. Similarly, cells that express GLUT2 such as the hepatocytes and the renal tubular cells are also susceptible to STZ [123,126]. In addition, STZ causes cardiac and adipose tissue damage and increases oxidative stress, inflammation and endothelial dysfunction [40] in a dose dependant manner or its metabolites in the liver, kidney, intestine and pancreas are consistently higher than those in the plasma. However, non β-cells such as α-cells and the extra-pancreatic parenchyma remain intact even after STZ treatment, indicating the β-cell selectivity of STZ [15].

STZ is taken up by pancreatic β-cells via the GLUT2 transporter where it causes β-cell death by DNA fragmentation due to the presence of nitrosourea moiety. There are three major explanations for β-cell toxicity associated with STZ. Firstly, the DNA methylating activity of the methylnitrosourea moiety of STZ [127], especially at the O_6 position of guanine, leads to DNA damage and pancreatic β-cell necrosis, through the depletion of cellular energy stores. DNA methylation is involved in the formation of carbonium ion (CH_3^+) resulting in the activation of the nuclear enzyme poly ADP-ribose synthetase as part of the cell repair mechanism and consequently, NAD^+ depletion [128]. Secondly, diabetogenic action of STZ that results in β-cell death has been attributed to its ability to act as nitric oxide donor in pancreatic cells [129] which inhibits aconitase activity, leading to DNA alkylation and damage

[130]. β-cells are particularly sensitive to damage by nitric oxide and free radicals because of their low levels of free radical scavenging enzymes [131]. Thirdly, oxidative stress due to excess production of free radicals as hydrogen peroxide [132,133] leads to pancreatic β-cell dysfunction caused by glucose toxicity in hyperglycemic conditions. Previously published reports showed that STZ treatment caused significant increase in malonaldehyde and decrease in antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase activities when compared with control animals in experiments, indicating the susceptibility of pancreas to STZ induced oxidative stress [134,135]. A recent study has suggested that certain food supplementation improved diabetic conditions in mouse model through the regulation of insulin and blood glucose levels, the decrease of oxidative stress and the restoration of the levels of proinflammatory cytokines and β-defensin that accelerated cutaneous wound healing [136]. The PI3K/AKT signaling pathway is important for insulin signaling and glucose metabolism, lymphocyte migration, proliferation, and differentiation, and TGF-β signaling regulation, making it an important therapeutic target for the treatment of cancer, diabetes, and other diseases. Impaired PI3K/AKT signaling pathway is characterized by complications, such as a marked increase in their levels of blood glucose, free radicals, plasma pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), and lipids, and a tendency toward abnormal obesity along with a marked reduction in plasma cytokine levels (IL-2, -4 and -7), in the number of circulating lymphocytes, decreased proliferation of superantigen (SEB)- stimulated lymphocytes and aberrant AKT phosphorylation [137].

In spite of the many advantages of this model such as being cost-effective, faster investigation procedure for screening the anti-diabetic potential of novel therapeutics, simulating natural T2DM disease progression like obesity, insulin resistance, glucose intolerance *in vivo*, being sensitive to T2DM drugs such as TZDs and insulinotropic agents, metformin and 11β-hydroxysteroid dehydrogenase type 1 inhibitors, many researchers have raised questions on the levels of effectiveness and reliability of this model (Table 1).

The following issues illustrate some of the major drawbacks with HFD/STZ-induced experimental obese rat model as shown in our studies (Table 2). One of the main objections is its poor standardisation method. The experimental conditions used for this model differ from lab to lab; for example diets containing fat as calories varies from 40 to 60%, STZ injection ranges from 35–50 mg/kg in either single or multiple dose, HFD feeding period prior to STZ induction varies from 2 to 4 weeks, etc. [55]. Hence initial standardization could be a laborious and time consuming task.

The type of diabetes induced by STZ has been a controversial issue because STZ-hyperglycemia can be similar to either type I or type II diabetes mellitus [118,133]. The dose of STZ required for inducing diabetes depends on factors such as the animal species, age of animal, route of administration, weight of animal, nutritional status, etc (Table 2). For injection in experimental animals and for optimum results, it is best to administer at fasting state and freshly prepared, dissolved in citrate buffer (pH 4.4-4.5). When administered intravenously, the binding of STZ to its target site is completed within a short time and plasma levels of STZ rapidly decrease within 15 minutes and concentrate in the liver and kidney [138]. According to the pharmaceuticals material safety data sheet of Sicor Pharmaceuticals Inc: Irvine CA [139], as much as twenty percent of the drug or metabolites containing an N-nitrosourea group is metabolized or excreted by the kidneys. Thus the biochemical changes observed after 15 minutes of STZ induction are secondary changes and not due to a direct effect of STZ [123]. Complications or deaths caused by any toxic effect of STZ were minimized by carrying out the experiments four to five weeks after the initial STZ injection [140]. Junod et al. [124], have hypothesized three stages of response in blood glucose after STZ administration. According to them, in the first two hours of STZ induction, blood glucose rises due to sudden breakdown of liver glycogen. Then, starting at about 6 hours after STZ induction, there is a hypoglycemic period, which could even be fatal. In the final stage permanent hyperglycemia begins at about 10 to 12 hours after STZ administration. Structural alterations in pancreatic beta cells (total degranulation) occur within 48 h after the treatment of STZ and could last for up to four months [141-143]; they have also reported that the destruction of the insulin secreting β-cells in rats starts three days after STZ administration, climaxing in 2 to 4 weeks, leaving less active cells that result in a diabetic condition.

Our review (Table 2) revealed that in HFD/STZ-induced diabetic animal model the experimentation can be commenced about two weeks post STZ induction since some animals could return to normoglycemic levels even after initial hyperglycemic levels. Thus if such considerations are not taken seriously, they could lead to wrong conclusions regarding the antidiabetic ability of a drug rather than the animal's ability to withstand the initial STZ

challenge. This review has also shown that intraperitoneal dose of STZ (35-40 mg/kg) to HFD fed rat model is best suited to represent the pathophysiological state of T2DM as drug treatment was accompanied by marginal increase in body weight in contrast to the catabolic loss of body weight, characteristic of diabetic condition produced by high dose of STZ (Table 2).

Finally, there are reports that STZ can lead to acute complications such as irritation, nausea, headache, vomiting and chronic complications such as reproductive disorders and general deterioration of health as well as blindness if in contact with the eyes. STZ has also been shown to induce tumors in rat kidney, liver and pancreas and cause neoplastic transformation in primary human kidney cells at doses of 1 mM [119,142,144]. Moreover, International Agency for Research on Cancer (IARC) has warned that STZ should be regarded as a human carcinogen and accidental exposure to it could be a serious health and safety concern to the researcher [145]. Special care must be taken in preparing STZ for practical use.

Conclusion:

Although having an animal model that mimics all of the human metabolic syndromes of T2DM is not realistic, the HFD-fed STZ-induced rat model, in which obesity and T2DM are induced by feeding a diet enriched in caloric content and injecting STZ, seems to be the optimal model to develop new therapeutic strategies with respect to pharmacological screening for type 2 diabetes. Furthermore, this model also combines the interplay between the influence of environmental changes involving high fat dietary life style habit of the modern times and the genetic changes that are responsible for the progression of human T2DM. To conclude, most of our studies showed (refer our papers in Table 2) that in spite of some limitations and disparities in the methodology, HFD-fed STZ-induced rat model still remains one of the optimal rat models available for pharmacological screening for type 2 diabetes research and will be invaluable for future research to target and test therapeutic interventions in pre-clinical trials.

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