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THE HIGH FAT DIET- STREPTAZOTOCIN RAT MODEL OF TYPE 2 DIABETES: A COMPREHENSIVE REVIEW

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ABSTRACT
Diabetes is a metabolic condition, with Type 2 Diabetes (T2DM) being particularly complex. This review focuses on induction of T2DM using the high-fat diet (HFD) and streptozotocin (STZ) in rodents. The combination of HFD-STZ administration is a common method to induce T2DM in experimental animals. However, variations exist in the type of food, duration of the HFD, and doses of STZ injections. This method simulates the pathophysiology of human T2DM by initially inducing insulin resistance through extended high-fat diet exposure, followed by partial destruction of pancreatic β-cells with a low dose of STZ. The HFD-STZ model effectively mirrors the progressive nature of T2DM, marked by initial insulin resistance and subsequent β-cell dysfunction. The review aims to evaluate the mechanisms, pathophysiology, and pharmacology of diabetes mellitus.

KEYWORDS: Type 2 diabetes (T2D), Metabolic syndrome, High fat diet (HFD), Streptozotocin, Hyperinsulinemia, Hyperglycemia**.**

INTRODUCTION

Diabetes mellitus is a persistent metabolic condition marked by elevated blood sugar levels. It represents a type of metabolic disorder characterized by both insulin deficiency and insulin resistance. This long-lasting disease arises from the body's inability to effectively process and control blood glucose, either due to excessive insulin secretion by the pancreas or the failure of insulin to manage blood glucose levels.[1] Insulin, a polypeptide hormone produced by the beta cells in the islets of Langerhans within the pancreas, plays a crucial role in regulating blood glucose levels, as well as in the absorption and utilization of glucose.[2] In individuals with diabetes, a condition known as "insulin resistance" occurs, where the body's cells do not respond adequately to the hormone insulin. Insulin resistance is essentially a reduction in the body's sensitivity to insulin's biochemical effects and its ability to facilitate glucose disposal. This results in an accumulation of glucose in the bloodstream, eventually leading to type 2 diabetes.[3] While there are several forms of diabetes, the three primary types are type 1 diabetes, type 2 diabetes, and gestational diabetes, which is induced by pregnancy.

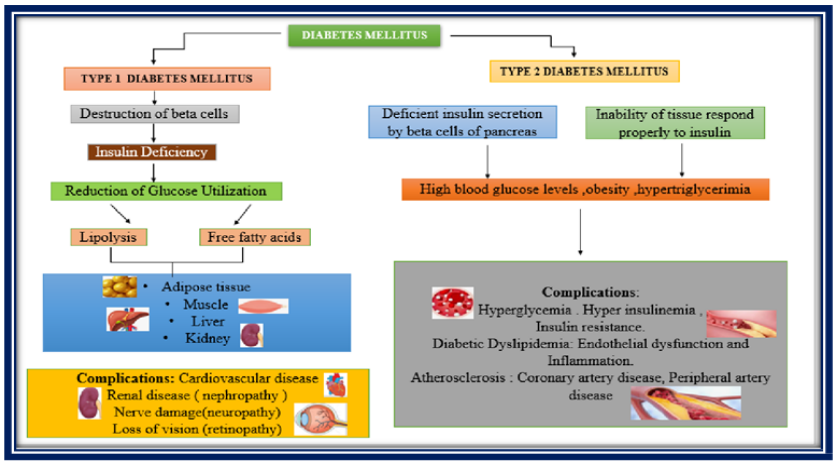

Fig. 1: Pathophysiological Differences and Complications of Type 1 and Type 2 Diabetes Mellitus.

The HFD/STZ rat model mirrors several features of human T2DM.

Hyperglycemia: This model shows increased fasting blood glucose (FBG) and post-meal glucose levels. Diabetes is typically characterized by FBG >126 mg/dl48 or HbA1c ≥ 7%. Impaired glucose tolerance is evident, with a notably higher area under the curve in OGTT, and hyperglycemia can be severe.

Insulin Resistance and Insulin Levels: A primary characteristic induced by the HFD is insulin resistance, which is measured by elevated HOMA-IR. Fasting plasma insulin levels may vary; they can remain unchanged, initially rise (hyperinsulinemia) due to insulin resistance, or decrease following STZ treatment. The drop in insulin after STZ in HFD rats might align levels with normal controls. The model is anticipated to progress from insulin resistance to beta-cell dysfunction and possibly hyperinsulinemia in later stages.

Dyslipidemia: Elevated triglycerides (TG) levels are frequently observed. Total cholesterol (TC) and low-density lipoprotein (LDL) levels may also rise, especially in groups receiving HFD and modeling agents together. Increased TG is considered a predictor for T2DM.

Weight and Body Composition: HFD feeding generally results in weight gain. However, after STZ administration, the weight gain in the HFD/STZ group may be less than in controls, sometimes leading to reductions in muscle mass and adipose tissue. Some protocols may produce non-obese diabetic animals, which could be more relevant to certain human populations. A significant weight loss following STZ injection is more indicative of type 1 diabetes.

Pancreatic Changes: Histopathological examination reveals damage to pancreatic islets, such as irregular borders and a reduced number of islets. Pancreatic islet hypertrophy can occur with HFD feeding as beta cells try to compensate for insulin resistance, followed by damage after STZ. A decrease in insulin-positive cells is also noted. Pancreatic necrosis can occur.

Liver Changes: Liver tissue may exhibit vacuolar degeneration, fat accumulation, and hydropic degeneration in hepatocytes. Liver inflammation might also be present, and necrosis can occur. The liver index may increase.

Other Metabolic Alterations: Increased water intake (polydipsia), urine volume, and urine glucose are classic signs of hyperglycemia seen in diabetic rats. Liver and muscle glycogen content may decrease, and serum glucagon levels might be lower. Reduced food intake and body weight compared to controls can be observed after STZ. Relative energy intake may rise in the HFD/STZ group.

Associated Complications: This model can be used to study complications such as oxidative stress and inflammation, gut microbiota dysbiosis, and bone abnormalities like osteoporosis.

Development of HFD-fed and STZ-treated type 2 diabetic rats

T2DM models were formerly produced using a combination of high-fat diet (HFD) and streptozotocin (STZ) injection. However, there were differences in the food type, duration of the HFD, and STZ injection doses. The proportion of fat, the type of fat (such as lard or palm oil), and the addition of other ingredients like sucrose or cholesterol can all differ significantly from one high-fat diet to the next. This may have an impact on other metabolic indicators and the level of insulin resistance. Rats may be given the HFD for a few weeks or for several months prior to receiving a STZ injection. Insulin resistance may become more noticeable with extended HFD eating. There are significant variations in the dosage of STZ used to cause partial beta-cell death. A single low dose is used in certain investigations, while several lower doses are used in others. Additionally, the administration method (e.g., intraperitoneal, intravenous) may vary. These differences in methodology can lead to T2DM models with varying degrees of hyperglycemia, insulin resistance, and beta-cell dysfunction, potentially affecting the translatability of research findings.

Composition of High-Fat -Diet

Variations in the HFD's nutrient composition (fat type/amount, presence of sugars) across studies significantly alter weight gain, fat distribution (e.g., visceral vs. subcutaneous), and the metabolic profile (glucose/lipid metabolism, inflammation, liver function) in T2DM rat models. This lack of standardization impacts the characteristics of the resulting diabetic phenotype and the comparability of research findings.

Table 1: Various Models of HFD-STZ of Past Literature.

S. No	Reference /Source	Rodent strain and Body weight/Age	HFD Composition and Duration	STZ Frequency, Dose and Route of administration	Outcome
1.	***Yang et al. [2000]***[4]	Sprague- Dawley (SD), 8 weeks	***HFD composition*** 40% Fat (F), 13% protein, 40% carbohydrates, 7% vitamins. ***HFD Duration*** 8 weeks before STZ	1 x 15 mg/kg, i. v	FBG = ↑, TG =↑ C =. ↑
2.	***Reed et al. [2000]***[5]	Sprague- Dawley (SD), BW: 200 g	***HFD composition*** 40% Fat (F), 18% protein, 40% carbohydrates ***HFD duration:*** 2 weeks before STZ	1 x 50 mg/kg, i,p	BG = ↑, I =↑, TG =↑ Classified as **Early DS**
3.	***Zhang et al. [2003]***[6]	Sprague- Dawley (SD), 8 weeks	***HFD composition*** 30% of calories as fat (mostly zoosterol**),** 13% proteins, 50% carbohydrates ***HFD duration:*** 2 months (8 weeks) before STZ injection	1 x 15 mg/kg, i.v	FBG = ↑, FSI = S, TG = H, C = ↑. Classified as **Late DS**
4.	***Zhou et al. [2004]***[7]	Sprague- Dawley rats, 4 weeks, BW; 83-105g	***HFD composition***: 54%Carbohydrates, 13%Proteins, 20%Fat, 5%vitamins. ***HFD duration*** 4 weeks before injection	1 x 40 mg/kg, i. p	FBG = ↑, FSI = S, TG=↑ , C =↑ Classified as **Late DS**
5.	***Wu et al. [2004]***[8]	Sprague- Dawley (SD), 8 weeks	***HFD composition***: 41% Fat (F),18% protein, 41%carbohydrates HFD duration 2 weeks before STZ	1 x 30 mg/kg, i.v	FBG =↑, I = S. Classified as **Late DS**
6.	***Danda et al.[2005]***[9]	Sprague- Dawley rats, BW:175-200 g	***HFD composition*** 60% calories from fat and 70% animal fat. Fed for ***HFD duration*** 5 weeks before STZ injection	1 x 35 mg/kg, i.v	BG =↑, Hba1c ↑, C =↑, TG =, S↑I = 84.3.
7.	***Srinivasan et al. [2005]***[10]	Sprague- Dawley (SD),BW:160-180	***HFD composition***: 58% calories as fat, 25% protein, 17% carbohydrate. ***HFD Duration***: Fed HFD ad libitum for an initial period of 2 weeks. STZ injected after the initial 2 weeks of HFD	1 x 35 mg/kg, i.p	PGL = ↑, PI = S, PTG = ↑, PTC = ↑. Classified as **Late DS**
8.	***Sahin et al.[2007]***[11]	Sprague- Dawley rats, BW: 200-250g	***HFD composition:*** 40% fat,30% carbohydrate 20% protein (as % of total kilocalories) 10% vitamins. Fed for ***HFD duration*** 2 weeks before STZ injection	1 x 40 mg/kg , i.p	G = ↑, I = L, TG =↑, TC =↑. Classified as **Late DS**
9.	***Islam et al. [2008]***[12]	Sprague- Dawley Rats BW:120-140 g	***HFD composition*** 47% Carbohydrates, ST, 20% casein, 20%lard, 10% Other components ***HFD duration*** 2 weeks before STZ	1 x 40 mg/kg, i.p	FBG = 181.7 - 60.1 mg/dL, FBI = 61.8 -27.3 pmol/L, HbA1C % = 7.8.
10.	***Zhang et al. [2008]*** [13]	Wistar Rats BW: 200-250g	***HFD composition*** 22% Fat (F),48% carbohydrates,20% protein ***HFD duration*:** 4 weeks before STZ	2 x 30 mg/kg, i.p	FBG =↑, FI = S, TG = ↑, TC = ↑. Classified as **Late DS**
11.	***Gao et al [2008]***[14]	Sprague- Dawley rats, BW:210-220 g	***HFD composition*** 15% Fat (FL),30% carbohydrates. ***HFD duration:*** 4 weeks	1 x 25 mg/kg, i.p	BG =↑, TG =↑, C = S

			before STZ		
12.	***Zou et al. [2009]***[15]	Sprague- Dawley Rats BW: 220-250g	***HFD composition:*** HFD consisted of 58% fat, 25.6% carbohydrate, and 16.4% protein ***HFD duration:*** 8 weeks	1 x 25 mg/kg; i.p	FBG = 20, SI = 86, HbA1c = 7.
13.	***Xing et al. [2009]***[16]	Sprague- Dawley Rats BW:170-200 g	***HFD composition*** 10% Fat (FL), 66% normal diet, 20% carbohydrate, 1%vitamins ***HFD duration:*** 6 weeks before STZ	1 x 30 mg/kg ; i.p	FBG =↑, ISI = L.
14.	***Zhang et al. [2009]***[17]	Sprague- Dawley Rats BW:180-200 g	***HFD composition*** 60% Fat (FL), duration 8 weeks before STZ	1 x 25 mg/kg, i.p	FPG =↑ , FPI =↑, FTG=↑, PTC =↑. Classified as **Early DS**
15.	***Lu et al. [2010]***[18]	Wistar Rats BW: 250-270g	***HFD composition:*** 30% carbohydrates, 22% proteins, 12% lipids, and 3% vitamins ***HFD duration:*** 8 weeks	1 x 30 mg/kg, i.p	BG > 11, HbA1C = 8, TG = 1.4, C = 2.0, HDL = 1.5, LDL = 0.2.
16.	***Parveen et al [2010]***[19]	Wistar rats BW:160-200 g	***HFD composition:*** 40% fat, 18% protein and 41% carbohydrate, as a percentage of total kcal) ***HFD duration*: 2** weeks	1 x 40 mg/kg, i.p	HbA1c = 11.
17.	***Guo et al. [2011]***[20]	Wistar Rats BW: 140-180g	***HFD composition:*** 67% Normal diet, 20% Carbohysrates like sucrose, 10%Fat Lard, 1% Other components ***HFD duration*** 4 weeks before STZ	1 x 30 mg/kg , i.p	PG =↑, PI = ↑, TG =↑, TC =↑, IRI =↑. Classified as **Early (T2D)**.
18.	***Sharma et al. [2011]*** [21]	Wistar Rat, BW: 170-200	***HFD composition:*** 25% coconut oil, 2% cholesterol and 73% normal rat chow; provides 55% of the animal's energy as fat) ***HFD duration:*** 42 days (6 weeks)	1 x 40 mg/kg, i.p	BG =↑, I = ↑, APQ =↑, TG =↑, HDL = L, LDL = ↑, HOMA-IR =↑, HOMA-B = L. Classified as **Early (T2D)**.
19.	***Albersen et al [2011]***[22]	Sprague- Dawley Rats BW:12 weeks	***HFD composition:*** Rats were fed rat chow containing 2% cholesterol and 10% lard ***HFD duration***: 2 weeks prior to STZ injections	2 x 20 mg/kg , i.p	BG > 17, SI = L, TG = ↑, TC = ↑, LDL =↑ , HDL = ↑.
20.	***Si et al. [2012]***[23]	Sprague- Dawley Rats, BW: 200 g	***HFD composition*** 41% Carbohydrates, 18% Proteins, 40 Fats ***HFD duratio***n 2 weeks before STZ	1 x 50 mg/kg, i.v	Blood Glucose (BG) = ↑. **Not Available (NA)** for T2D stage classification due to lack of metabolic parameters
21.	***Guo et al. [2012]***[24]	Wistar (W), BW:140-180 g	***HFD composition:*** 67% Normal diet 20 Carbohydrates like sucrose, 10%Fat Lard, 1% Other components ***HFD duration*** 4 weeks before STZ	1 x 30 mg/kg, i.p	PG =↑, PI =↑, TG =↑, TC =↑, IRI =↑. Classified as **Early (T2D**
22.	***Hussein et al. [2012]***[25]	Sprague- Dawley rats BW: 15-21 weeks	***HFD composition:*** 22.5% hydrogenated vegetable oil, 22.5% milk powder, 51.5% ground soybean, 2% corn starch, 1% sucrose, and 0.5% vitamins and minerals ***HFD duration:* 2 weeks**	1 x 35 mg/kg, i. v	Fasting Glucose (FG) = 13, Fasting Insulin (FI) = 107, TG = 2.1, TC = 5.2, HD = 1.0, LDL = 3.7. **NA (T2D)**.

23.	***Hu et al. [2013]***[26]	Male Wistar rats 10-12 weeks	***HFD composition*** 26% carbohydrates, 15.2% proteins, 58% fat ***HFD duration:*** 12week***s***	1 x 30 mg/kg, ip	Plasma Glucose (PG) = Higher (H) ↑, Plasma Insulin (PI) = ↑, HOMA-IR = ↑. Classified as **Early (T2D**
24.	***Abo-Elmatty et al. [2013]***[27]	Male Albino rats,200 ± 35 g	***HFD composition:*** HFD provided 58% of total calories from fat, 25% from protein, and 17% from carbohydrate ***HFD duration:*** 2 weeks before STZ	1 x 35 mg/kg, i.p	Fasting Blood Glucose (FBG) =↑, SI = Same (S), HbA1c =↑, Triglycerides (TG) =↑, LDL =↑ , HDL = Lower (L). Classified as **Late (T2D**
25.	***Gandhij et al. [2013]***[28]	Wistar rats, BW:180-210 g	***HFD composition*** 25% Fat-coconut oil (FCN), 73% normal diet, 2% cholesterol ***HFD duration***: 2 weeks before STZ	1 x 40 mg/kg, i.p	FBG =↑ , PI =↑ , TG =↑ , TC = ↑. Classified as **Early (T2D)**.
26.	***Khan et al. [2013]***[29]	Male Wistar rats BW:190- 210 g	***HFD composition*** 20% sucrose, 10% Lard, 2.5% Cholestrol, 1% Other components ***HFD duratio***n 2 weeks before STZ	1 x 35 mg/kg, i.p	RNG =↑ , HbA1c =↑ , I = L, HOMA-IR =↑ Classified as **Late (T2D)**.
27.	***Subhasree, N., et al*. (2015)**[30]	Adult Sprague–Dawley rats of either sex. BW: 150–170g	***HFD composition***: 58% calories as fat, 25% protein, 17% carbohydrate. ***Duration***: 4 weeks	1 x 35 mg/kg, i.p	After 28 days of Type II DM induction Blood glucose levels Plasma insulin Serum lipid profile, triglycerides (TG), total-cholesterol (TC), low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), and VLDL. Gluconeogenic enzyme activities (glucose-6-phosphatase and fructose-1,6-bisphosphatase) in liver and kidney tissues. Histopathological changes in pancreas, liver, and kidney tissues
28.	***Gheibi et al. [2017]***[31]	Male Wistar rats BW: 190 -210g	***HFD composition***: (carbohydrate: 27.5%; protein: 14.7%; fat: 58.8%; lipid source: butter) ***HFD duration***: 14 days	1x 25mg/kg, i.p	***Glycemic control***: ↑Serum glucose, ↑ serum insulin, ↑ HbA1c; ↑ area under the curve of serum glucose and serum insulin in the intraperitoneal (i.p.) glucose tolerance test; ↑ area under the curve of serum glucose in the i.p. pyruvate tolerance test; ↑ area under the curve of serum glucose in the i.p. insulin tolerance test. ***Lipid profile***: ↑ TG, ↑ TC, ↑ LDL-c, ↑ HDL-c.
29.	***Sohrabipour et al [2018]***[32]	Male Wistar rats aged 4 weeks	***HFD composition*** (carbohydrate: 17%; protein: 25%; fat: 58%; lipid source: (not disclosed) ***HFD duration***:28 days	1x 25mg/kg, i.p	***Glycemic control***:↑random blood glucose over 90 days of intervention; ↑ area under the serum glucose curve in the i.p. glucose tolerance test after 30 and 90 days of intervention; ↑ area under the serum glucose curve in the i.p. insulin tolerance test after 30 and 90 days of intervention; ↓ glucose infusion rate necessary to maintain normoglycemia

					during insulin infusion in the euglycemic– hypersulinemic clamp; ↓ plasma insulin, ↑ plasma glucagon
30.	***de Bem, Graziele Freitas, et al. (2018)***[33]	Male Wistar rats BW: 180– 200 g.	***HFD composition*:** (HF; 55% energy from lipids, 31% from carbohydrate, 14% from protein; 5.2 kcal/g) for 3 weeks before STZ	1 x 35 mg/kg, i.p Administered after 3 weeks of experimental diet and 12h fasting	Diabetic groups had ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL- c, ***Glycemic control***: ↑ insulin, ↑ HOMA-IR
31.	***Fallahnejad, Habib, et al. (2018).***[34]	Male Wistar rats BW: 200gr	***HFD Composition***: 32% of total energy from fat, 48% carbohydrate, and 20% protein. Other components listed by weight include Rump oil (25%), Sucrose (12%), Chickpea flour (1%), Wheat flour (10%), Cholice acid (1%), and Cholesterol (1%), mixed with Powdered NPD (50%) ***HFD duration***: 2 weeks	1 x 35 mg/kg, i.p	***Glycemic control***: ↑HDL-c, ↑HOMA-IR in the diabetic subgroups. HFD/STZ-treated rats did not show evidence of hyperlipidemia, possibly due to a pre- diabetic condition
32.	***Zhuo, Juncheng, et al. (2018).***[35]	Male Wistar rats 8 weeks, 180-220g	***HFD Composition***: [HFSD] 20% sucrose, 12% lard oil, 5% milk powder, 2% egg, 61% normal fodder. ***HFD Duration***: 8 weeks	1 x 35 mg/kg, i.p	↑serum glucose, ↑ serum insulin, ↑ HOMA-IR, ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c. pathological traits of T2DM (dyslipidemia, hyperglycemia**).** ***Histopathology*** showed inflammation in pancreas and liver.
33.	***Guo, Xiao-xuan, et al. " (2018)***[36]	Wistar rats	***HFD Composition***: carbohydrates (17%), and protein (25%). ***HFD Duration***: 13 weeks (8 wks HFD + STZ + 4 wks diet	1 x 25mg/kg, i.p [or] 1 x 35mg/kg, i.p	HFD+STZ rat model effectively simulates T2DM, exhibits ***Glycemic control***: insulin resistance, moderate hyperglycemia, and ***Histopathological*** *partial β-cell dysfunction*
34.	***Tarighat-Esfanjani et al. [2018]***[37]	Male Wistar rats BW: above 220g	***HFD composition*** (carbohydrate: 48%; protein: 20%; fat: 32%; lipid source: rump oil) for ***HFD duration***: 30 days	1x 35mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↔ insulin; ↑ HOMA-IR. ***Lipid profile:*** ↔ TG; ↔TC; ↔VLDL; ↔LDL-c.
35.	***Xiang, Jiamei, et al. (2019)***[38]	Male Wistar rats BW:200–220g	***HFD composition*:** consisting of 45% fat, 35% carbohydrate, and 20% protein for four- weeks prior to STZ. ***HFD duration***: 8 weeks	1 x 30 mg/kg, i.p	***Glycemic control:*** ↑Serum GLU, ↑HbA1c, and ↑insulin levels. HOMA-IR index increased, ↓QUICKI
36.	***Zhang, Qinghua, et al. " (2019)***[39]	**Male Wistar rats**, weighing **180–220 g**	**High-fat diet** (60% fat, 20% protein, 20% carbohydrate) ***HFD duration:***12 weeks	1 x 28 mg/kg, i.p Administered after 12 weeks of HFD	***Glycemic control***: ↑ fasting blood glucose, ↑ oral glucose tolerance, ↑ fasting ↑ serum insulin, ↑ insulin resistance index ↑ lipid levels. Impaired glucose tolerance. Hyperinsulinemia. ↑ HOMA-IR, ↓ HOMA-IS. ***Lipid profile:*** ↑ Serum TC, ↑ TG levels ↑hepatic TG level
37.	***Cai, Huan, et al (2019)***[40]	male adult Wistar rats 250–280 g	***HFD Composition***: 57.5% fat, 26.9% carbohydrate, 15.6% protein ***HFD duration***: 4 weeks	1 x 35 mg/kg, i.p	***Glycemic control:*** ↑FBG, ↑HOMA-IR, ↑OGTT AUC, ↑TG, and ↑LDL-C levels ($P < 0.05$). ↓HOMA-β and ↓ HDL-C significantly ($P < 0.05$) in DCM rats. DCM rats

					showed polydipsia, polyuria, and slow weight gain
38.	***Yu, Songyan, et al. (2019)***[41]	Male SD 8 weeks old rats	***HFD composition***: 60% fat HFD Duration: HFD for 8 weeks before STZ, Total 32 weeks HFD.	1 x 25mg/kg, i.p	Rats showed ***Glycemic control***: hyperglycemia, decreased FBI/C- partial β-cell dysfunction peptide, Histopathological: pancreatic islet destruction, decreased HOMA-β.
39.	***Abel-Hamid et al [2019]***[42]	Male Wistar rats BW: 150–180g and aged	***HFD composition***: (carbohydrate: 24%; protein: 20%; fat: 46%; lipid source: corn oil and beef tallow) ***HFD duration***; 28 days	1x 35mg/kg, i.p	***Glycemic control***: ↑fasting glucose, ↓ serum insulin, ↑ HOMA-IR ***Histopathological:*** ↓ hepatic glycogen content
40.	***Ghiasi et al. [2019]***[43]	Male Wistar rats BW: 200 and 250g	***HFD composition*** (carbohydrate: 48%; protein: 20%; fat: 22% (does not amount to 100%) ***HFD duration***; 28 days	1x 35mg/kg, i.p	***Glycemic control***: ↑fasting glucose, ↑ serum insulin, ↓ QUICKI. LIPID PROFILE: ↑ TG, ↑ TC, ↓ HDL-c. ***Hepatic function***: ↓ serum albumin. ***Oxidative and antioxidant markers:*** ↑MDA, ↓SOD, ↓Gpx, ↓pancreatic CAT. ***Histopathological:*** ↓ pancreatic beta-cell density
41.	***Omidi et al. [2019]***[44]	Male Wistar rats BW: 250 g	***HFD composition*** (carbohydrate: 48%; protein: 20%; fat: 32%;) ***HFD duration***; 30 days	1x 35mg/kg, i.p	***Glycemic control***: ↑fasting glucose, ↑ serum insulin, ↑ HOMA-IR. ***Lipid profile:*** TG, TC, LDL-c, and HDL-c
42.	***Magalhães, Diego A. DE, et al. (2019).***[45]	Male Wistar rats BW: 200-240g	***HFD composition:*** High-Fat Diet (HFD) (58.0% energy from fat, in-house mix). Fed for 1 week before STZ, **HFD** duration 4 weeks	1 x 30 mg/kg, ip. Injected after 1-week HFD	***Glycemic control***: ↑body weight, ↑blood glucose, ↑plasma insulin, ↑HOMA-IR index. ↑HbA1C. Significant increase in ↑plasma insulin and ↑HOMA-IR at week. **Histopathological:** Liver histology showed fat droplets in hepatocytes (Non- alcoholic fatty liver disease). Large glomerulus size in kidney pathology (early diabetic nephropathy).
43.	***Stott, Nicole L., and Joseph S. Marino. (2020):***[46]	Male Wistar rats BW: 180-220g	***HFD composition:*** High Fat and Sugar Diet (HFSD).20% sucrose, 12% lard oil, 5% milk powder, 2% egg, 61% normal fodder. ***HFD duration***: **8 weeks**	1x 35mg/kg, i.m	(HFSDSTZ model induces insulin resistance and partial pancreatic β-cell dysfunction, leading to elevated ↑ blood glucose, ↑ insulin, and ↑ lipid levels. It also disrupts insulin signaling pathways, particularly in the liver and pancreas, while pro-inflammatory markers like ↑ TNFα and ↑ IL6. ***Histopathologica***l: inflammation and structural damage in pancreatic and

					hepatic tissues
44.	***Lv, Qiuyue, et al (2020)***[47]	Male Wistar rats BW: 200 ± 20 g.	**High-fat and glucose diet** (HFD; **45% fat**, 20% protein, 35% carbohydrate) for **4 weeks** ***HFD duration***: 8 weeks	1 x 30 mg/kg, i.p Administered after 4 weeks of HFD	Model of T2D group: ↑blood glucose, ↑HbA1c, ↑TG, ↑CHO, ↑TNF-α, ↑IL-1β, ↑IL-6, and ↑IL-8 levels compared to controls. ↑ LDL-c, ↑ NEFA
45.	***Lv et al [2020]***[48]	Male Wistar rats BW:180 and 220g.	***HFD composition*** (carbohydrate: 35%; protein: 20%; fat: 45 %;) ***HFD duration*** 28 days	1x 30mg/kg, i.p	***Glycemic control:*** ↑serum glucose, ↑ HbA1c, ↑ serum insulin, ↑ HOMA-IR; ↑ the area under the serum glucose curve in the i.p. glucose tolerance test, ↑ the area under the serum glucose curve in the i.p. insulin tolerance test. **Lipid profile:** ↑ TG, ↑ TC, ↔ HDL-c, LDL-c, and non-esterified fatty acids (NEFAs). **Histopathological:** Altered architecture of the hepatic lobules; hepatocytes increased their sizes and exhibited blurred borders. Cytoplasm filled with fat vacuoles of different sizes, pushing the nucleus to the periphery after 30, 60, and 90 min. **Lipid profile:** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c, ↑ free fatty acids (FFAs)
46.	***Mangali et al [2020]***[49]	Male Wistar rats BW:180–220g	***HFD composition (carbohydrate:*** 17%; protein: 25%; fat: 58%; ***HFD duration*** 28 days	1x 35mg/kg, i.p	***Glycemic control:*** ↑blood glucose; ↑ serum glucose after 120 min in the i.p. glucose tolerance test; ↑ serum glucose after 120 min in the i.p. insulin tolerance test. **Lipid profile:** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c.
47.	**Xu et al. [2020]**[50]	Male Wistar rats weighing between 180 and 220g	***HFD composition (carbohydrate:*** *41%; protein: 24%; fat: 24%;* ***HFD duration*** *28 days*	1x 30mg/kg, i.p dose)	***Glycemic control:*** ↑fasting glucose; ↑ insulin; ↑ HOMA-IR; ↓ insulin sensitivity index (ISI); ↑ HbA1c; ↓ hepatic glycogen; ↑ area under the serum glucose curve in the oral glucose tolerance test; ↑ % of serum glucose in the i.p. insulin tolerance test after 30, 60, and 90 min. ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c, ↑ free fatty acids (FFAs)
48.	***Rezazadeh et al [2021]***[51]	Male and female Wistar rats aged 4 weeks	***HFD composition*** (carbohydrate: 17%; protein: 25%; fat: 58%; lipid source: lard and cholesterol) ***HFD duration*** 84 days	1x 35mg/kg, i.p	***Glycemic control:*** ↑glycemia after confirmation of diabetes and over 140 days of intervention. ↑ HbA1cat the end of the intervention; ↑ area under the serum glucose curve in the i.p. glucose tolerance test at 28 days, 56 days, and 84 days

					after the intervention; ↓ glucose infusion rate required to maintain normoglycemia during insulin infusion in the euglycemic– hypersulinemic clamp at the end of the intervention.
49.	***Zelinskaya et al. [2021]***[52]	Male Wistar rats aged 8 weeks	***HFD composition*** (carbohydrate: 38%; protein: 18%; fat: 22%; ***HFD duration*** 20 days	1x 20mg/kg, i.p	***Glycemic control:*** ↑area under the serum glucose curve in the oral glucose tolerance test
50.	***Bowonsomsarit, Wirin, et al (2021).***[53]	Male Wistar rats, BW: 200-240grams	***HFD Composition***: 58.0% energy from fat (in-house mix of chow, lard, casein) ***HFD Duration***: 5 weeks (1 wk pre + 4 wks post-STZ)	1 x 30 mg/kg, i.p	HFD+STZ rat model induces type 2 T2DM in rodents within 4 weeks. exhibits ***Glycemic control***: ↑ body weight, elevated ↑ plasma insulin levels, ↑ insulin resistance, and ↑ hepatic steatosis.
51.	***Kolefer, Kilenma, David Miaffo (2021)***[54]	Male albino Wistar rats 200-250g.	***HFD Composition*** Fat (58%), carbohydrates (17%), and protein (25%). ***HFD duration***: 30 days	1 x 35 mg/kg, i.p	The untreated diabetic rat model demonstrated hallmark features of type 2 diabetes, including sustained hyperglycemia, insulin resistance, β-cell dysfunction, dyslipidemia, organ dysfunction, and oxidative stress
52.	***Ghasemi, Asghar, et al. (2023)***[55]	Male Wistar rats BW: 150-200g	***HFD Composition***: ~4900 kcal/kg total caloric value; calories from fat- 58.8%; Carbohydrate- 27.0%; protein 14.2% ***HFD duration***: 8 weeks	1 x 25 mg/kg, i.p	At the end of the study (week 8), ↑ serum glucose, ↑serum insulin, ↑HOMA1-IR, ↑HOMA2-IR, and ↓QUICKI detected in diabetic rats compared to controls. Lower GIIS from isolated islets in diabetic rats.
53.	***Ghasemi et al [2023]***[56]	Male Wistar rats 190 - 210 g.	***HFD composition*** (carbohydrate: 27%; protein: 14,2%; fat: 58,8%; lipid source: sheep butter) ***HFD duration*** 14 days	1x 25mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↑ insulin; ↓ Islets GIIS; ↑ HOMA1-IR, ↑HOMA2-IR, ↓ QUICKI
54.	***Swain et al [2023]***[57]	Male and female Wistar rats weighing between 150 and 180 g.	***HFD composition*** (carbohydrate: 17%; protein: 25%; fat: 58%; ***HFD duration*** 15 days	1x 40mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↓ insulin; ↑ HbA1c, ↑ HOMA-IR, ↓ HOMA- β,↓ QUICKI
55.	***Khoramipour et al [2023]***[58]	Male Wistar rats BW:189- 210g	***HFD composition***: (carbohydrate: 20%; protein: 19%; fat: 60%; lipid source: lard and soybean oil) ***HFD duration***: 56 days	1x 35mg/kg, i.p	***Glycemic control:*** ↑fasting glucose after the high-fat diet and STZ injection, ↑ fasting glucose after the 56 days of intervention, ↓ insulin; ↑ HOMA-IR
56.	***Vijay; Vellapandian et al [2023]***[59]	Male Wistar rats BW: 150 -200g.	Consumption of HFD (carbohydrate: 17%; protein: 25%; fat: 58%; lipid source: lard) ***HFD duration***: 21 days	1x 35mg/kg, i.p	***Glycemic control:*** ↑glycemia over the 21 days of intervention, ↓ insulin; ↑ HOMA-IR; ↑ area under the serum glucose curve in the oral glucose tolerance test. ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL- c. LIVER FUNCTION: ↑ ALT, ↑ AST, ↑ ALP

57.	***Wickramasinghe et al. (2024)***[60]	Male Wistar rats, BW: 150 ± 15g	***HFD composition:*** 60% calories from fat (butter), fed for 4 weeks before STZ ***HFD duration*** 4 weeks after STZ	4 weeks after STZ 1 x 30, 40, or 50 mg/kg, ip	***Glycemic control:*** ↑Body weight. ↑glucose intolerance. ↑HOMA-IR > 2.5 (insulin resistance). ↑HOMA-β < 50% (impaired β-cell function). ↑TG, ↑TC, ↑VLDL-C, ↑LDL-C (dyslipidemia). ***Histopathological changes:*** loss of pancreatic islets, islet hypertrophy, mild fatty change in exocrine pancreas. Prominent hydropic degeneration in liver hepatocytes
58.	***Khosravi et al [2024]***[61]	Male Wistar rats BW:188 and 212g	***HFD composition*** (carbohydrate: 20%; protein: 20%; fat: 60%; ***HFD duration*** 56 days	1x 35mg/kg, i.p	***Glycemic control:*** ↔fasting glucose before induction, ↑ fasting glucose after induction and after intervention; ↔ insulin before induction, ↑ insulin after induction and after intervention; ↔ HOMA-IR before induction, ↑ HOMA- IR after induction and after intervention.
59.	***A-Elgadir et al [2024]***[62]	Male Wistar rats BW: 200 and 210 g and aged 8–9 weeks	***HFD composition*** (carbohydrate: 20%; protein: 20%; fat: 60%; ***HFD duration*** 91 days	1x 45mg/kg, i.p	***Metabolic control:*** ↓bodyweight. ***Glycemic control:*** ↑fasting glucose; ↑ insulin; ↑ HOMA-IR. ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c.
60.	***Gharaat; Choobdari; Sheykhlouvand [2024]***[63]	Male Wistar rats BW:170 and 190g	***HFD composition*** (carbohydrate: 35%; protein: 10%; fat: 55%; lipid source: animal fat oil) ***HFD duration*** 28 days	1x 45mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↔ insulin; ↑ HOMA-IR in pre-intervention, at the end of 42-day intervention, and after physical exercise
61.	***Salem et al [2024]***[64]	Male Wistar rats BW:150 and 180g	***HFD composition*** (carbohydrate: 17%; protein: 25%; fat: 58%; lipid source: lard) ***HFD duration*** 14 day	1x 35mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↑ insulin; ↑ HbA1c, ↑ HOMA-IR ***Histopathological:*** Frontal cerebral cortex tissue—disorganization of the layers, deformed neurons, the depletion of the cellular elements, inflammatory cell infiltration, and dilated congested blood vessels, ↓ QUICKI
62.	***Bagheripour***	Female (170–180g) and male Wistar rats (190–210 g)	***HFD composition*** (carbohydrate: 27.5%; protein: 14.5%; fat: 58%; lipid source: butter) for ***HFD duration*** 91 days	1x 30mg/kg, i.p	***Glycemic control:*** ↑fasting glucose; ↑ area under the curve of serum glucose in the intraperitoneal (i.p.) glucose tolerance test; ↑ area under the curve of serum glucose in the i.p. pyruvate tolerance test immediately and after 28 days or 56 days of the intervention.

					Lipid profile: ↑ TG, ↑ TC, ↑ LDL-c, ↑ HDL-c immediately and after 28 days or 56 days of the intervention
63.	***Gharaat, Mohammad Ali, (2024)***[66]	Male Wistar rats; BW: 170-190g	***HFD Composition***: 55% of total fat energy (derived from animal fat oil), 10% protein, and 35% carbohydrate. ***HFD duration***: 4 weeks	1 x 40 mg/kg, i.p	Diabetic rats exhibited ↑glucose and ↑ HOMA-IR
64.	***Mahmoud, Lamiaa Mohamed, et al. (2024)***[67]	Male Wistar rats BW:150 to 160g	***HFD Composition***: 57% fat, 25% protein, 17% carbohydrate. ***HFD duration***: 6 weeks	1 x 35 mg/kg, i.p	serum glucose, ↑ HbA1c, ↑ serum insulin, ↑ HOMA-IR
65.	***Khosravi, Pouria, et al. (2024).***[68]	Wistar male rats. BW:200±10.25g	***HFD Composition***: 60% fat, 20% protein, and 20% carbohydrate. ***HFD duration***: 8 weeks	1 x 35 mg/kg, i.p	The untreated diabetic rat model effectively replicates key features of type 2 diabetes mellitus (T2DM), including persistent hyperglycemia (FBG >300 mg/dL), increased body weight, and insulin resistance
66.	***Arifah, Fitriana Hayyu, et al. (2025).***[69]	Wistar rats	***HFD Composition***: (HFFD) 2 ml egg yolk, 2 ml lard, and fructose (3.6 g/kg BW). ***HFD Duration***: 3 weeks	1 x 35 mg/kg, i.p	***Glycemic control***: ↑fasting glucose, ↓ serum insulin, ↑HOMA-IR ***Histopathological:*** ↓ hepatic glycogen content
67.	***Fitriana Hayyu Arifah, et al. [2025]***[70]	Wistar rats,	***HFD composition:*** High-Fat High-Fructose Diet (HFFD) (2ml egg yolk, 2ml lard, fructose 3.6 g/kg BW).	1 x 35 mg/kg BW, i.p. Injected after 2, 4, or 6 weeks of HFFD.	↑body weight, ↑FBG, ↑triglyceride, ↑TyG index. Increased necrosis score in pancreas, kidney, liver, heart. ↓ number of insulin-positive cells, ↑insulin-negative cells
67.	***Fitriana Hayyu Arifah, et al. [2025]***[70]	Wistar rats,	***HFD composition:*** High-Fat High-Fructose Diet (HFFD) (2ml egg yolk, 2ml lard, fructose 3.6 g/kg BW). ***HFD duration*** 3 weeks	1 x 35 mg/kg BW, i.p. Injected after 2, 4, or 6 weeks of HFFD.	↑body weight, ↑FBG, ↑triglyceride, ↑TyG index. Increased necrosis score in pancreas, kidney, liver, heart. ↓ number of insulin-positive cells, ↑insulin-negative cells
68.	***Rajiv Gandhi Sathiyabama et al (2008)***[71]	Male Wistar rats BW: 180-200g	***HFD composition*:** (55% energy from fat, 31% from carbohydrates, 14% from proteins; 5.9 kcal/g) ***Duration***: 2 weeks prior to STZ	1 x 40 mg/kg, i.p	***Glycemic control***: ↑ FBG, ↑plasma insulin, and ↑ HOMA-IR. ***Lipid profile:*** ↑ TG, ↑ TC, ↑ LDL-c, ↓ HDL-c ↑ SGOT, ↑ SGPT, ↑ALP, ↑ urea, and ↑ creatinine. ***Histopathological:*** Pancreatic tissue showed degranulated β-cells, widespread vacuolization, disordered islet architecture.

ADVANTAGES AND DISADVANTAGES OF HFD-STZ MODEL

1. Pathophysiological Relevance Advantages:

The HFD + STZ model effectively mirrors key aspects of human T2DM by combining diet-induced insulin resistance with partial β-cell dysfunction. This dual approach closely resembles the progression of T2DM in humans, where insulin resistance is often followed by β-cell failure. The model exhibits metabolic disturbances such as hyperglycemia, hyperinsulinemia, and dyslipidemia, aligning with human disease characteristics.

Disadvantages

The β-cell damage induced by STZ is due to its cytotoxic effects, differing from the gradual β- cell decline seen in human T2DM, which is typically due to chronic metabolic stress and inflammation. Additionally, if the STZ dose is too high, it can lead to extensive β-cell destruction, resembling type 1 diabetes rather than type 2.

2. Speed and Simplicity of Onset Advantages

This model allows for the rapid induction of diabetic symptoms, typically within 2–4 weeks.

Such a swift onset is beneficial for high-throughput drug screening and short-term studies.

Disadvantages
The accelerated development of diabetes in this model does not capture the prolonged prediabetic phase observed in humans, potentially overlooking early pathogenic events.

3. Reproducibility Advantages
When standardized protocols are followed—considering factors like animal strain, age, STZ dosage, and diet composition—the model yields consistent and reproducible results across different studies.

Disadvantages
Variability in response can occur due to differences in animal genetics, sex, age, and even slight alterations in diet or STZ preparation, necessitating careful calibration for each experimental setup.

4. Cost and Practicality Advantages
Compared to genetically modified models like db/db mice or Zucker diabetic rats, the HFD + STZ model is more cost-effective and doesn't require specialized breeding, making it accessible for many laboratories.

Disadvantages
Handling STZ requires caution due to its toxicity to humans and animals. Additionally, long- term maintenance of diabetic animals can become costly, especially when monitoring and managing diabetes-related complications.

5. Suitability for Drug Testing Advantages
This model is suitable for evaluating a range of antidiabetic agents, including insulin sensitizers, hypoglycemic drugs, and compounds targeting metabolic syndrome. Its flexibility allows for testing interventions at various stages of disease progression.

Disadvantages
It is less appropriate for studying therapies targeting autoimmune mechanisms or immune pathways, as the model lacks an autoimmune component. Furthermore, the chemical-induced β- cell damage may limit studies on β-cell regeneration.

6. Ethical and Welfare Considerations Advantages
The shorter duration and straightforward procedures of this model can reduce overall animal use.
Well-defined endpoints help in minimizing animal suffering.

Disadvantages
STZ is toxic to organs beyond the pancreas, particularly the kidneys and liver, raising ethical concerns. This necessitates careful monitoring to ensure animal welfare throughout the study.

7. Model Flexibility Advantages
Researchers can adjust the STZ dose and duration of HFD feeding to induce varying degrees of hyperglycemia and insulin resistance, allowing the modeling of different stages of T2DM.

Disadvantages
High variability in responses may require frequent optimization of dosing and diet protocols for each study, complicating comparisons across different experiments.

8. Autoimmune and Inflammatory Aspects Advantages
The model focuses on metabolic aspects of T2DM without the confounding effects of autoimmune processes, making it ideal for studying non-autoimmune diabetes.

Disadvantages
It lacks an autoimmune component, rendering it unsuitable for investigating the role of inflammation or immune dysfunction in diabetes pathogenesis.

9. Modeling of Diabetic Complications Advantages
Over time, animals in this model can develop complications such as neuropathy, nephropathy, and fatty liver, providing a platform to study chronic outcomes of diabetes.

Disadvantages
The onset and severity of these complications can be inconsistent, and the underlying mechanisms may differ from those in human disease, potentially limiting translational relevance.

10. Translation to Human T2DM Advantages
The model effectively mimics key aspects of human T2DM, particularly diet-induced insulin resistance and β-cell decline, reflecting lifestyle-related diabetes.

Disadvantages
It does not account for the complex interplay of environmental and genetic factors present in human T2DM. Additionally, comorbidities commonly associated with human diabetes, such as hypertension and dyslipidemia, may not be well-represented.

CONCLUSION

The HFD/STZ rat model is a widely used and valuable tool for preclinical research into the pathogenesis and treatment of T2DM. It is relatively inexpensive, straightforward to develop, and can induce a diabetic state that mimics key aspects of human T2DM, including the progression from insulin resistance to beta-cell dysfunction, within a relatively short timeframe. The model is suitable for testing potential therapeutic agents. The HFD/STZ model remains a relevant tool for advancing the understanding of T2DM. Detailed characterization of the metabolic and pathological state, including glucose and insulin/C-peptide levels, beta-cell

function, and histopathological changes, is crucial for enhancing the translatability of research findings and better defining the specific stage of T2DM being modeled.

List of Abbreviations

SD- Sprague Dawley rats, HFD-high fat diet, BG- blood glucose, FBG –fasting blood glucose HOMA-IR - Homeostatic Model Assessment for Insulin Resistance, C-carbohydrates,

TG-triglycerides, TC- total cholesterol, LDL-low density lipoproteins, HDL-high density lipoprotein, VLDL-very low-density lipoprotein, Hba1c-glycated hemoglobin, FSI- fasting sugar index, DS -diabetic stage.

PGI-post glucose index, PI -plasma glucose index, FBI-fasting blood glucose index, FPG-fasting plasma glucose, FPI-fasting plasma index, IRI-immunoreactive insulin, APQ-polydipsia/polyurea, NA-not applicable.

PI-plasma insulin, OGTT-oral glucose tolerance, SOD-superoxide dismutase, MDA-diabetes mellitus.

REFERENCE

1. Ojo, O. A., Ibrahim, H. S., Rotimi, D. E., Ogunlakin, A. D., & Ojo, A. B. Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology. Medicine in Novel Technology and Devices, 2023; 19: 100247.
2. Kiconco, R., Lumumba, S. A., Bagenda, C. N., Atwine, R., Ndarubweine, J., & Rugera, S. P. (2024). Insulin therapy among diabetic patients in rural communities of Sub-Saharan Africa: a perspective review. Therapeutic Advances in Endocrinology and Metabolism, 15, 20420188241232280.
3. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metabolism, 2021; 119(0026 0495): 154766.
4. Yang J, Li G, Zhang F, et al. Identification of variations of gene expression of visceral adipose and renal tissue in type 2 diabetic rats using cDNA representational difference analysis. Chin Med J (Engl) 2003; 116: 529–533.
5. Reed MJ, Meszaros K, Entes LJ, et al. Anewratmodelof type 2 diabetes: the fat-fed, streptozotocin-treated rat. Metabolism, 2000; 49: 1390–1394.
6. Zhang F, Ye C, Li G, et al. Theratmodelof type2diabetic mellitus and its glycometabolism characters. Exp Anim., 2003; 52: 401–407.
7. Zhou YS, Gao Y, Guo XH, et al. Effects of timely insulin treatment on protection of beta cells in a rat model of type 2 diabetes mellitus. Chin Med J (Engl), 2004; 117: 1523–1529.
8. Wu Y, Ouyang JP, Zhou YF, et al. Mechanism of improving effect of losartan on insulin sensitivity of non-insulin dependent diabetes mellitus rats. Acta Physiologica Sinica, 2004; 56: 539–549.
9. Danda RS, Habiba NM, Rincon-Choles H, et al. Kidney involvement in a nongenetic rat model of type 2 diabetes. Kidney Int., 2005; 68: 2562–2571.
10. Srinivasan K, Viswanad B, Asrat L, et al. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. Pharmacol Res., 2005; 52: 313–320.
11. Sahin K, Onderci M, Tuzcu M, et al. Effect of chromium on carbohydrate and lipid metabolism in a rat model of type 2 diabetes mellitus: the fat-fed, streptozotocin-treated rat. Metabolism, 2007; 56: 1233–1240.
12. Islam MS, Choi H, Loots DT. Effects of dietary onion (Allium cepa L.) in a high-fat diet streptozotocin-induced diabetes rodent model. Ann Nutr Metab., 2008; 53: 6–12.
13. Zhang M, Lv XY, Li J, et al. The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. Exp Diabetes Res., 2008; 2008: 704045.
14. Gao L, Niu Y, Liu W, et al. The antilipolytic action of bis (alpha-furancarboxylato) oxo vanadium (IV) in adipocytes. Clin Chim Acta., 2008; 388: 89–94.
15. Zou F, Mao XQ, Wang N, et al. Astragalus polysaccharides alleviates glucose toxicity and restores glucose homeostasis in diabetic states via activation of AMPK. Acta Pharmacol Sin., 2009; 30: 1607–1615.
16. Xing XH, Zhang ZM, Hu XZ, et al. Antidiabetic effects of Artemisia sphaerocephala Krasch. gum, a novel food additive in China, on streptozotocin-induced type 2 diabetic rats. JEthnopharmacol., 2009; 125: 410–416.
17. Zhang T, Pan BS, Zhao B, et al. Exacerbation of poststroke dementia by type 2 diabetes is associated with synergistic increases of beta-secretase activation and beta-amyloid generation in rat brains. Neuroscience, 2009; 161: 1045–1056.
18. Lu HE, Jian CH, Chen SF, et al. Hypoglycaemic effects of fermented mycelium of Paecilomyces farinosus (G30801) on high-fat fed rats with streptozotocin-induced diabetes. Indian J Med Res., 2010; 131: 696–701.
19. Parveen K, Khan MR, Mujeeb M, et al. Protective effects of Pycnogenol on hyperglycemia- induced oxidative damage in the liver of type 2 diabetic rats. Chem Biol Interact, 2010; 186: 219– 227.
20. GuoZ, ZhengC, QinZ, et al. Effect of telmisartan on the expression of cardiac adiponectin and its receptor 1 in type 2 diabetic rats. JPharmPharmacol, 2011; 63: 87–94.
21. SharmaAK, BhartiS, OjhaS, et al. Up-regulation of PPARgamma, heat shock protein-27 and- 72 by naringin attenuates insulin resistance, beta-cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes. Br J Nutr., 2011; 106: 1713–1723.
22. Albersen M, Lin G, Fandel TM, et al. Functional,

metabolic, and morphologic characteristics of a novel rat model of type 2 diabetes-associated erectile dysfunction. Urology, 2011; 78: 476– 478.
23. Si Y, Zhao Y, Hao H, et al. Infusion of mesenchymal stem cells ameliorates hyperglycemia in type 2 diabetic rats: identification of a novel role in improving insulin sensitivity. Diabetes., 2012; 61: 1616–1625.
24. Guo Z, Qin Z, Zhang R, et al. Effect of rosiglitazone on the expression of cardiac adiponectin receptors and NADPH oxidaseintype2diabeticrats. Eur J Pharmacol., 2012; 685: 116–125.
25. Hussein AA, Abdel-Aziz A, Gabr M, et al. Myocardial and metabolic dysfunction in type 2 diabetic rats: impact of ghrelin. Can J Physiol Pharmacol., 2012; 90: 99–111.'
26. Hu SH, Jiang T, Yang SS, et al. Pioglitazone ameliorates intracerebral insulin resistance and tau-protein hyperphosphorylation in rats with type 2 diabetes. Exp Clin Endocrinol Diabetes., 2013; 121: 220–224.
27. Abo-elmatty DM, Essawy SS, Badr JM, et al. Antioxidant and anti-inflammatory effects of Urtica pilulifera extracts in type 2 diabetic rats. J Ethnopharmacol, 2013; 145: 269–277.
28. Gandhi GR, Stalin A, Balakrishna K, et al. Insulin sensitization via partial agonism of PPARgamma and glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway by embelin in type 2 diabetic rats. Biochim Biophys Acta, 2013; 1830: 2243– 2255.
29. Khan HB, Vinayagam KS, Moorthy BT, et al. Anti-inflammatory and anti-hyperlipidemic effect of Semecarpus anacardium in a high fat diet: STZ-induced type 2 diabetic rat model. Inflammopharmacology, 2013; 21: 37–46.
30. Subhasree, N., Kamella, A., Kaliappan, I., Agrawal, A., & Dubey, G. P. Antidiabetic and antihyperlipidemic activities of a novel polyherbal formulation in high fat diet/streptozotocin induced diabetic rat model. Indian journal of pharmacology, 2015; 47(5): 509-513.
31. Gheibi, S.; Kashfi, K.; Ghasemi, A. A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. Biomed. Pharmacother., 2017; 95: 605–613.
32. Sohrabipour, S.; Sharifi, M.R.; Talebi, A.; Soltani, N. GABA dramatically improves glucose tolerance in streptozotocin-induced diabetic rats fed with high-fat diet. Eur. J. Pharmacol., 2018; 826: 75–84.
33. de Bem, G. F., Costa, C. A., Santos, I. B., Cristino Cordeiro, V. D. S., de Carvalho, L. C. R. M., de Souza, M. A. V., & de Moura, R. S. Antidiabetic effect of Euterpe oleracea Mart.(açaí) extract and exercise training on high-fat diet and streptozotocin-induced diabetic rats: A positive interaction. PLoS One, 2018; 13(6): e0199207.
34. Fallahnejad, H., Omidi, H., Khorram, S., Mesgari, M., Asghari-Jafarabadi, M., & Tarighat- Esfanjani, A. The effects of natural nano-sized clinoptilolite and metformin on the levels of serum glucose, lipid profile, and minerals in rats with type 2 diabetes mellitus. Iran Red Crescent Med J, 2018; 20(10).
35. Zhuo, J., Zeng, Q., Cai, D., Zeng, X., Chen, Y., Gan, H., & Zhang, C. Evaluation of type 2 diabetic mellitus animal models via interactions between insulin and mitogen-activated protein kinase signaling pathways induced by a high fat and sugar diet and streptozotocin. Molecular Medicine Reports, 2018; 17(4): 5132-5142.
36. Guo, X. X., Wang, Y., Wang, K., Ji, B. P., & Zhou, F. Stability of a type 2 diabetes rat model induced by high-fat diet feeding with low-dose streptozotocin injection. Journal of Zhejiang University. Science. B, 2018; 19(7): 559.
37. Tarighat-Esfanjani, A.; Fallahnejad, H.; Omidi, H.; Jafarabadi, M.A.; Abbasi, M.M.; Khorram, S. The Effects of Natural Nano-Sized Clinoptilolite and Metformin on the Levels of Serum Glucose, Lipid Profile, and Minerals in Rats with Type 2 Diabetes Mellitus. Iran. Red. Crescent Med. J., 2018; 20: e74365.
38. Xiang, J., Lv, Q., Yi, F., Song, Y., Le, L., Jiang, B., ... & Xiao, P. Dietary supplementation of vine tea ameliorates glucose and lipid metabolic disorder via akt signaling pathway in diabetic rats. Molecules, 2019; 24(10): 1866.
39. Zhang, Q., Huang, Y., Li, X., Liu, H., He, B., Wang, B., & Wu, S. Tangduqing granules attenuate insulin resistance and abnormal lipid metabolism through the coordinated regulation of PPARγ and DGAT2 in type 2 diabetic rats. Journal of diabetes research, 2019; (1): 7403978.
40. Cai, H., Chen, S., Liu, J., & He, Y. An attempt to reverse cardiac lipotoxicity by aerobic interval training in a high-fat diet-and streptozotocin-induced type 2 diabetes rat model. Diabetology & metabolic syndrome, 2019; 11: 1-12.
41. Yu, S., Cheng, Y., Zhang, L., Yin, Y., Xue, J., Li, B., ... & Mu, Y. Treatment with adipose tissue-derived mesenchymal stem cells exerts anti-diabetic effects, improves long-term complications, and attenuates inflammation in type 2 diabetic rats. Stem cell research & therapy, 2019; 10: 1-18.
42. Abdel-Hamid, H.A.; Abdalla, M.M.I.; Zenhom, N.M.; Ahmed, R.F. The effect of peptide tyrosine tyrosine (PYY3–36), a selective Y2 receptor agonist on streptozotocin-induced diabetes in albino rats. Endocr. Regul., 2019; 53: 26–33.
43. Ghiasi, R.; Naderi, R.; Sheervalilou, R.; Alipour, M.R. Swimming training by affecting the pancreatic Sirtuin1 (SIRT1) and oxidative stress, improves insulin sensitivity in diabetic male rats. Horm. Mol. Biol. Clin. Investig., 2019; 40: 20190011.
44. Omidi,H.; Khorram, S.; Mesgari, M.; Asghari-Jafarabadi, M.; Tarighat-Esfanjani, A. The effects of natural nano-sized clinoptilolite and Nigella sativa supplementation on blood glucose and lipid profile in rats with type 2 diabetes mellitus. Prog. Nutr., 2019; 21: 147–153.

45. Magalhães, D. A. D., Kume, W. T., Correia, F. S., Queiroz, T. S., Allebrandt, E. W., SANTOS, M. P. D., ... & França, S. A. D. High-fat diet and streptozotocin in the induction of type 2 diabetes mellitus: a new proposal. Anais da Academia Brasileira de Ciências, 2019; 91(01): e20180314.
46. Stott, N. L., & Marino, J. S. High fat rodent models of type 2 diabetes: from rodent to human. Nutrients, 2020; 12(12): 3650.
47. Lv, Q., Le, L., Xiang, J., Jiang, B., Chen, S., & Xiao, P. Liver transcriptomic reveals novel pathways of empagliflozin associated with type 2 diabetic rats. Frontiers in endocrinology, 2020; 11: 111.
48. Lv, Q.; Le, L.; Xiang, J.; Jiang, B.; Chen, S.; Xiao, P. Liver transcriptomic reveals novel pathways of empagliflozin associated with type 2 diabetic rats. Front. Endocrinol. 2020; 11: 111.
49. Mangali, S.; Bhat, A.; Jadhav, K.; Kalra, J.; Sriram, D.; Venuganti, V.V.K.; Dhar, A. Upregulation of PKR pathway mediates glucolipotoxicity induced diabetic cardiomyopathy in vivo in wistar rats and in vitro in cultured cardiomyocytes. Biochem. Pharmacol., 2020; 177: 113948.
50. Xu,L.-N.; Yin, L.-H.; Jin, Y.; Qi, Y.; Han, X.; Xu, Y.-W.; Liu, K.-X.; Zhao, Y.-Y.; Peng, J.-Y. Effect and possible mechanisms of dioscin on ameliorating metabolic glycolipid metabolic disorder in type-2-diabetes. Phytomedicine 2020, 67, 153139.
51. Rezazadeh, H.; Sharifi, M.R.; Soltani, N. Gamma-aminobutyric acid attenuates insulin resistance in type 2 diabetic patients and reduces the risk of insulin resistance in their offspring. Biomed. Pharmacother., 2021; 138: 111440.
52. Zelinskaya, I.; Kornushin, O.; Savochkina, E.; Dyachuk, V.; Vasyutina, M.; Galagudza, M.; Toropova, Y. Vascular region-specific changesinarterial tone in rats with type 2diabetes mellitus: Opposite responses of mesenteric andfemoralarteries to acetylcholine and 5-hydroxytryptamine. Life Sci., 2021; 286: 120011.
53. Bowonsomsarit, W., Anegkamol, W., Chuaypen, N., Kaewwongse, M., Tosukhowong, P., Prapunwattana, P., & Dissayabutra, T. Four-week induction of type 2 diabetes mellitus in rats by streptozotocin and high-fat diet. Chulalongkorn Medical Journal, 2021; 65(4).
54. Kolefer, K., Miaffo, D., & Ponka, R. (2021). Evaluation of Antidiabetic Properties of the Leaves Extract of Ficus vallis-choudae Delile in a Model of Type 2 Diabetes Induced by High-Fat Diet and Streptozotocin. The Scientific World Journal, 2021; (1): 1502230.
55. Ghasemi, A., Gheibi, S., Kashfi, K., & Jeddi, S. Anti-oxidant effect of nitrite in the pancreatic islets of type 2 diabetic male rats. Iranian Journal of Basic Medical Sciences, 2023; 26(4): 420.
56. Ghasemi, A.; Gheibi, S.; Kashfi, K.; Jeddi, S. Anti-oxidant effect of nitrite in the pancreatic islets of type 2 diabetic male rats. Iran. J. Basic Med. Sci., 2023; 26: 420.
57. Swain, S.K.; Dash, U.C.; Kanhar, S.; Sahoo, A.K. Network pharmacology-based elucidation of bioactive compounds and experimental exploration of antidiabetic mechanisms of Hydrolea zeylanica. Cell. Signal., 2023; 114: 110999.
58. Khoramipour, K.; Rezaei, M.H.; Madadizadeh, E.; Hosseini, M.S.; Soltani, Z.; Schierbauer, J.; Moser, O. High Intensity Interval Training can Ameliorate Hypothalamic Appetite Regulation in Male Rats with Type 2 Diabetes: The Role of Leptin. Cell. Mol. Neurobiol., 2023; 43: 4295– 4307.
59. Vijay, N.K.G.; Vellapandian, C. Ameliorative effects of phlorotannin-rich fraction of Sargassum tenerrimum in high-fat diet and low dose streptozotocin-induced metabolic changes and oxidative stress in diabetic rats. J. Herbmed Pharmacol., 2023; 12: 367–379.
60. Wickramasinghe, A. S. D., Attanayake, A. P., Wijesiri, T. W., Peiris, H. H., & Mudduwa, L. K. B. Pancreatic and hepatic histopathology of high-fat diet fed streptozotocin-induced Wistar rat model of type 2 diabetes mellitus. Ceylon Journal of Science, 2024; 53(2).
61. Khosravi, P.; Shahidi, F.; Eskandari, A.; Khoramipour, K. High-intensity interval training reduces Tau and beta-amyloid accumulation by improving lactate-dependent mitophagy in rats with type 2 diabetes. Iran. J. Basic Med. Sci., 2024; 27: 1430–1439.
62. A-Elgadir, T.M.E.; Shati, A.A.; Alqahtani, S.A.; Ebrahim, H.A.; Almohaimeed, H.M.; ShamsEldeeen, A.M.; Haidara, M.A.; Kamar, S.S.; Dawood, A.F.; El-Bidawy, M.H. Mesenchymal stem cells improve cardiac function in diabetic rats by reducing cardiac injury biomarkers and downregulating JAK/STAT/iNOS and iNOS/Apoptosis signaling pathways. Mol. Cell. Endocrinol., 2024; 591: 112280.
63. Gharaat, M.A.; Choobdari, H.R.; Sheykhlouvand, M. Cardioprotective effects of aerobic training in diabetic rats Reducing cardiac apoptotic indices and oxidative stress for a healthier heart. ARYA Atheroscler. J., 2024; 20: 50–60. and oxidative stress in diabetic rats. J. Herbmed Pharmacol. 2023; 12: 367–379.
64. Salem, H.R.; Hanna, G.S.; Hassan, M.H.; El-Kotb, S.; Rashad, S.; Yassien, R.I.; Selim, M.; Amer, G.S. Combined metformin and insulin therapy improves neurocognitive dysfunction in type 2 diabetic rat model via anti-inflammatory and antioxidant mechanisms. Physiol. Pharmacol., 2024; 28: 141–156.
65. Bagheripour, F.; Jeddi, S.; Kashfi, K.; Ghasemi, A. Anti-obesity and anti-diabetic effects of L-citrulline are sex-dependent. Life Sci., 2024; 339: 122432.
66. Gharaat, M. A., Choobdari, H. R., & Sheykhlouvand, M. Cardioprotective effects of aerobic training in diabetic rats: Reducing cardiac apoptotic indices and oxidative stress for a healthier heart. ARYA atherosclerosis, 2024; 20(2): 50.

67. Mahmoud, L. M., Mageed, A. A. A. A., Saadallah, J. M., Youssef, M. F., Rashed, L. A., & Ammar, H. I. Interleukin 1β receptor blocker (Anakinra) and regenerative stem cell therapy: two novel approaches effectively ameliorating diabetic cardiomyopathy. Naunyn- Schmiedeberg's Archives of Pharmacology, 2024; 397(10): 8023-8041.
68. Khosravi, P., Shahidi, F., Eskandari, A., & Khoramipour, K. High-intensity interval training reduces Tau and beta-amyloid accumulation by improving lactate-dependent mitophagy in rats with type 2 diabetes. Iranian Journal of Basic Medical Sciences, 2024; 27(11): 1430.
69. Arifah, F. H., Nugroho, A. E., Rohman, A., & Sujarwo, W. (2025). The Characterization of Fructose-Based High-Fat Diet and Low-Dose Streptozotocin in A Type 2 Diabetes Mellitus Rat Model.
70. Arifah, F. H., Nugroho, A. E., Rohman, A., & Sujarwo, W. (2025). The Characterization of Fructose-Based High-Fat Diet and Low-Dose Streptozotocin in A Type 2 Diabetes Mellitus Rat Model.
71. Sathiyabama, R. G., Gandhi, G. R., Denadai, M., Sridharan, G., Jothi, G., Sasikumar, P., & Gurgel, R. Q. Evidence of insulin-dependent signalling mechanisms produced by Citrus sinensis (L.) Osbeck fruit peel in an insulin resistant diabetic animal model. Food and chemical toxicology, 2018; 116: 86-99.