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Experimental Animal Models in Diabetes Research: Emerging Tools for Herbal Antidiabetic Drug Discovery

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

Diabetes mellitus is a major metabolic disorder characterized by chronic hyperglycemia and associated complications such as nephropathy, retinopathy, and cardiovascular diseases. Experimental animal models are essential for understanding the pathogenesis of diabetes and for evaluating new antidiabetic drugs and medicinal plants. Various models, including chemical, dietary, genetic, and surgical models, are widely used in diabetes research. Among these, Streptozotocin and Alloxan induced diabetic models are the most commonly employed due to their simplicity and reproducibility. These models help in screening plant-derived compounds for antihyperglycemic and organ-protective activities. This review highlights the major experimental diabetic models, their principles, advantages, limitations, and their significance in medicinal plant-based antidiabetic drug discovery.

1. INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterized by chronic elevation of blood glucose levels due to impaired insulin secretion, defective insulin action, or both. The disease has emerged as a major global health concern because of its increasing prevalence and its association with severe complications such as nephropathy, retinopathy, neuropathy, and cardiovascular disorders. Consequently, researchers are increasingly focusing on medicinal plants as alternative sources for the development of safer and more effective antidiabetic therapies (King, 2012).

Experimental animal models are essential tools in diabetes research because they provide valuable insight into the pathogenesis of diabetes and help in evaluating the pharmacological potential of newly developed drugs and herbal formulations before clinical application. Different experimental methods are employed to induce diabetes in laboratory animals, including chemical, dietary, genetic, surgical, and hormonal approaches. (Szkudelski, 2001).

Diet-induced diabetic models are also widely employed for studying insulin resistance and metabolic syndrome. Feeding animals with a high-fat diet for prolonged periods produces obesity, glucose intolerance, hyperlipidemia, and insulin resistance, closely resembling Type 2 diabetes observed in humans. In many studies, a combination of high-fat diet and low-dose streptozotocin is used to establish a more reliable experimental model of Type 2 diabetes because it reproduces both insulin resistance and partial β-cell dysfunction (Winzell and Ahren, 2004; Reed et al., 2000).

In addition to chemical and dietary models, genetic diabetic models such as db/db mouse, ob/ob mouse, and Non-Obese Diabetic

mouse are frequently used in experimental research.(King, 2012).

2. ANTIDIABETIC MODELS

Experimental animal models are essential for studying the pathogenesis of diabetes mellitus and for evaluating the efficacy of antidiabetic drugs and medicinal plants. These models simulate either Type 1 or Type 2 diabetes through chemical, dietary, genetic, surgical, or hormonal methods.

2.1 Experimental Models Used to Induce Diabetes:

2.1.1 Streptozotocin (STZ)-Induced Diabetes Model

- **Principle:** Streptozotocin-induced diabetes is based on the selective destruction of pancreatic β-cells. STZ enters β-cells through the GLUT2 transporter and causes DNA alkylation, nitric oxide release, and oxidative stress, resulting in insulin deficiency and hyperglycemia (Szkudelski, 2001).
- **Procedure:** Experimental animals such as rats or mice are fasted overnight before STZ administration. Streptozotocin is freshly prepared in cold citrate buffer (pH 4.5) and administered either intraperitoneally or intravenously at a dose ranging from 35–65 mg/kg body weight. Blood glucose levels are measured after 48–72 hours, and animals showing hyperglycemia are considered diabetic.
- **Advantages**

a. Simple and rapid induction of diabetes
b. Highly reproducible model
c. Widely accepted for antidiabetic screening
d. Suitable for studying diabetic complications

- **Disadvantages**

a. High doses may cause mortality
b. Variable response among animal strains
c. Possibility of hepatic and renal toxicity

2.1.2 Alloxan-Induced Diabetes Model

- **Principle:** Alloxan induces diabetes by selectively destroying pancreatic β-cells through the formation of reactive oxygen species and free radicals, leading to oxidative damage and insulin deficiency (Lenzen, 2008).
- **Procedure:**Animals are fasted overnight before administration of alloxan monohydrate dissolved in normal saline. The drug is administered intraperitoneally or intravenously at doses ranging from 100–150 mg/kg body weight. Blood glucose levels are checked after 72 hours to confirm diabetes induction.
- **Advantages**

a. Economical and easy to use
b. Rapid induction of hyperglycemia
c. Useful for evaluating antihyperglycemic agents

- **Disadvantages**

a. Less stable diabetic condition
b. High mortality rate
c. Risk of spontaneous recovery from diabetes

2.1.3 High-Fat Diet (HFD)-Induced Diabetes Model

- **Principle:**A prolonged high-fat diet causes obesity, insulin resistance, impaired glucose tolerance, and hyperlipidemia, mimicking human Type 2 diabetes mellitus (Winzell and Ahren, 2004).
- **Procedure:**Animals are fed a diet containing 40–60% fat for 4–20 weeks. Body weight, fasting blood glucose, insulin levels, and lipid profile are monitored regularly to evaluate diabetic status.
- **Advantages**

a. Closely resembles human Type 2 diabetes
b. Useful for studying obesity-related insulin resistance
c. Suitable for metabolic syndrome research

- **Disadvantages**

a. Slow induction process
b. Requires long experimental duration
c. Diabetes severity may vary among animals

2.1.4 High-Fat Diet Plus Streptozotocin Model

- **Principle:**This model combines insulin resistance induced by a high-fat diet with partial pancreatic β-cell dysfunction induced by low-dose STZ, thereby closely resembling human Type 2 diabetes mellitus (Reed et al., 2000).
- **Procedure:**Animals are initially fed a high-fat diet for 2–4 weeks to induce insulin resistance. Subsequently, low-dose STZ (25–40 mg/kg) is administered intraperitoneally. Hyperglycemia is confirmed after several days through blood glucose estimation.

- **Advantages:**

a. Mimics human Type 2 diabetes effectively
b. Produces stable hyperglycemia
c. Useful for studying diabetic complications and drug screening

- **Disadvantages**

a. Requires longer study duration
b. Experimental variability may occur
c. More expensive than chemical models alone

2.1.5 Nicotinamide-Streptozotocin Model

- **Principle:** Nicotinamide partially protects pancreatic β-cells against STZ-induced damage, resulting in moderate hyperglycemia and partial insulin deficiency similar to Type 2 diabetes mellitus (Masiello et al., 1998).
- **Procedure:**Nicotinamide (110–120 mg/kg) is administered intraperitoneally before STZ injection (45–65 mg/kg). Blood glucose levels are monitored after 72 hours to confirm diabetic status.
- **Advantages**

a. Stable Type 2 diabetic model
b. Retains partial pancreatic function
c. Useful for oral hypoglycemic studies

- **Disadvantages**

a. Requires precise dosing
b. Less severe hyperglycemia
c. Variability in β-cell protection

2.1.6 Genetic Diabetic Models

db/db Mouse

- **Principle:**This model develops diabetes due to mutation of the leptin receptor gene, causing obesity, insulin resistance, and severe hyperglycemia.**(**King AJF. 2012)
- **Procedure:**Animals naturally develop diabetic symptoms with age; no chemical induction is required. Blood glucose and body weight are monitored periodically.
- **Advantages**

a. Spontaneous and stable diabetes
b. Closely mimics human obesity-associated Type 2 diabetes

- **Disadvantages**

a. Expensive maintenance
b. Limited availability

Non-Obese Diabetic (NOD) Mouse

- **Principle:**NOD mice develop autoimmune destruction of pancreatic β-cells, resembling human Type 1 diabetes.**(**King AJF. 2012)
- **Procedure:**Animals are maintained under controlled conditions and monitored regularly for blood glucose elevation.
- **Advantages**

a. Useful for autoimmune diabetes research
b. Mimics human Type 1 diabetes closely

- **Disadvantages**

a. Time-consuming model
b. Expensive and genetically sensitive

Pancreatectomy Model

- **Principle:**Partial or complete surgical removal of the pancreas leads to insulin deficiency and hyperglycemia.**(**Bonner-Weir S et al. 1989).
- **Procedure:**Animals undergo surgical pancreatectomy under anesthesia followed by postoperative monitoring of blood glucose and physiological parameters.
- **Advantages:**

a. Useful for studying severe insulin deficiency
b. Suitable for pancreatic physiology research

- **Disadvantages**

a. Technically difficult
b. High mortality and postoperative complications

2.1.7 Glucocorticoid-Induced Diabetes Model

- **Principle:** The glucocorticoid-induced diabetes model is based on the ability of glucocorticoids to produce **insulin resistance and hyperglycemia** by altering carbohydrate, lipid, and protein metabolism. Glucocorticoids increase hepatic glucose production (gluconeogenesis), reduce peripheral glucose uptake in skeletal muscle and adipose tissue, impair insulin signaling, and may reduce pancreatic β-cell function. As a result, prolonged exposure produces metabolic changes resembling Type 2 diabetes mellitus (Andrews and Walker, 1999; Ferris and Kahn, 2012).
- **Procedure:** Healthy experimental animals (commonly rats or mice) are acclimatized under standard laboratory conditions. Glucocorticoids such as **dexamethasone**, **prednisolone**, or **corticosterone** are administered through intraperitoneal, subcutaneous, or oral routes for a defined period (commonly 5–21 days depending on study design).

Typical experimental steps include:

a. Selection and acclimatization of animals.
b. Administration of glucocorticoid at an appropriate dose and duration.
c. Monitoring of body weight and fasting blood glucose.
d. Evaluation of insulin resistance, glucose tolerance, lipid profile, and biochemical parameters.
e. Confirmation of diabetic status based on sustained elevation of blood glucose levels.

- **Advantages**

a. Simple and non-surgical method of diabetes induction.
b. Useful for studying **insulin resistance and Type 2 diabetes mechanisms**.
c. Mimics **steroid-induced diabetes** observed clinically.
d. Suitable for screening antihyperglycemic and insulin-sensitizing agents.
e. Allows investigation of glucose metabolism and endocrine regulation.

- **Disadvantages**

a. Hyperglycemia may be **reversible after discontinuation** of glucocorticoid treatment.
b. Does not completely reproduce all pathological features of human diabetes.
c. Response varies according to animal strain, dose, and treatment duration.
d. Long-term administration may produce secondary systemic effects such as immunosuppression and altered lipid metabolism.

2.1.8 Fructose/Sucrose-Induced Diabetes Model

- **Principle:** The fructose/sucrose-induced diabetes model is based on prolonged intake of a diet rich in fructose or sucrose, which leads to **insulin resistance, impaired glucose metabolism, hyperinsulinemia, dyslipidemia, and oxidative stress**. Excess dietary sugar increases hepatic lipogenesis and decreases insulin sensitivity, resulting in metabolic disturbances that resemble early-stage Type 2 diabetes mellitus and metabolic syndrome (Tran et al., 2009; Tappy and Lê, 2010).
- **Procedure:** Experimental animals (commonly rats or mice) are acclimatized and divided into control and treatment groups. Animals in the experimental group receive a **fructose-enriched diet (typically 40–70%) or sucrose-rich diet (30–60%)** through feed or drinking water for several weeks (commonly 2–12 weeks depending on the protocol).

Typical procedure includes:

a. Selection and acclimatization of animals.
b. Administration of fructose or sucrose through diet or drinking water.
c. Monitoring body weight and food intake.
d. Measurement of fasting blood glucose and insulin levels.
e. Evaluation of lipid profile and insulin resistance markers.
f. Confirmation of diabetic or prediabetic status.

- **Advantages**

a. Non-invasive and easy to establish.
b. Closely resembles dietary and lifestyle-related Type 2 diabetes.
c. Useful for studying insulin resistance and metabolic syndrome.
d. Suitable for evaluation of antidiabetic and antihyperlipidemic agents.
e. Allows investigation of obesity-associated diabetic changes.

- **Disadvantages**

a. Requires a relatively long induction period.
b. Diabetes severity may vary among animal species and strains.
c. Often produces moderate hyperglycemia rather than severe diabetes.
d. Experimental outcomes may depend on diet composition and duration.

Table:1. Mechanisms of Experimental Diabetic Models Used in Antidiabetic and Medicinal Plant Research

S. No.	Experimental Model	Mechanism of Diabetes Induction	References
1.	**STZ-Induced Diabetes Model** Streptozotocin	Streptozotocin enters pancreatic β-cells through the GLUT2 transporter and causes DNA alkylation, oxidative stress, and nitric oxide generation, leading to β-cell destruction and insulin deficiency.	Szkudelski T. (2001).
2.	**Alloxan-Induced Diabetes Model** Alloxan	Alloxan generates reactive oxygen species within pancreatic β-cells, causing oxidative damage, β-cell necrosis, and reduced insulin secretion.	Lenzen S. (2008).
3.	**High-Fat Diet (HFD) Model**	Long-term intake of a high-fat diet induces obesity, insulin resistance, lipid accumulation, and impaired glucose metabolism.	Winzell MS, Ahren B. (2004).
4.	**HFD + STZ Model** Streptozotocin	High-fat diet produces insulin resistance, while low-dose streptozotocin partially impairs pancreatic β-cell function, mimicking Type 2 diabetes mellitus.	Reed MJ et al. (2000).
5.	**Nicotinamide + STZ Model** Nicotinamide	Nicotinamide partially protects β-cells against STZ toxicity, resulting in moderate insulin deficiency and hyperglycemia similar to Type 2 diabetes.	Masiello P et al. (1998).
6.	**db/db Mouse Model**db/db mouse	Mutation in the leptin receptor gene causes obesity, insulin resistance, hyperphagia, and progressive hyperglycemia.	King AJF. (2012).
7.	**ob/ob Mouse Model**ob/ob mouse	Deficiency of leptin hormone results in obesity, excessive food intake, insulin resistance,	King AJF. (2012).

		and hyperglycemia.	
8.	**NOD Mouse Model** Non-Obese Diabetic mouse	Autoimmune destruction of pancreatic β-cells mediated by T-lymphocytes leads to insulin deficiency and Type 1 diabetes mellitus.	Anderson MS, Bluestone JA. (2005).
9.	**Pancreatectomy Model**	Surgical removal of pancreatic tissue decreases insulin secretion, resulting in persistent hyperglycemia.	Bonner-Weir S et al. (1983).
10.	**Glucocorticoid-Induced Diabetes Model**	Glucocorticoids stimulate gluconeogenesis and reduce peripheral glucose utilization, causing insulin resistance and hyperglycemia.	Andrews RC, Walker BR. (1999).
11.	**Fructose/Sucrose-Induced Diabetes Model**	Excess fructose or sucrose intake causes oxidative stress, dyslipidemia, insulin resistance, and impaired glucose metabolism.	Tran LT, Yuen VG, McNeill JH. (2009).

3. RESULT

The reviewed experimental diabetic models successfully reproduced important clinical and metabolic features of diabetes mellitus in laboratory animals. Chemical models induced by Streptozotocin and Alloxan consistently produced hyperglycemia through pancreatic β-cell damage, making them reliable and widely accepted models for antidiabetic research. Dietary models, particularly high-fat diet-induced diabetes, effectively simulated insulin resistance, obesity, and metabolic disturbances associated with Type 2 diabetes mellitus. In addition, genetic models such as db/db mouse and Non-Obese Diabetic mouse provided stable and progressive diabetic conditions suitable for long-term studies.

The comparative evaluation of these models revealed that each model exhibits specific pathological characteristics, advantages, and limitations depending on the experimental objective. Overall, the findings demonstrate that experimental diabetic models remain highly effective tools for studying diabetic mechanisms, evaluating pharmacological responses, and supporting the preclinical development of new therapeutic agents.

4. FUTURE PERSPECTIVES

Future research in experimental diabetic models will focus on developing more **clinically relevant and mechanism-based models** to better mimic human diabetes mellitus. While chemical models such as Streptozotocin and Alloxan remain widely used, they are expected to be increasingly combined with dietary and genetic models like db/db mouse and Non-Obese Diabetic mouse for improved disease representation.

Advances in omics technologies, computational biology, and AI-based drug discovery will further enhance the understanding of diabetic mechanisms and accelerate screening of plant-derived compounds. In addition, greater emphasis will be placed on ethical research practices and refinement of animal models to improve translational outcomes for antidiabetic drug development.

5. CONCLUSION

Experimental models of diabetes are valuable research tools for reproducing the metabolic and pathological changes associated

with human diabetes mellitus. Different models, including chemical, dietary, genetic, and surgical approaches, provide reliable systems for studying the onset and progression of diabetic conditions. Among these, Streptozotocin and Alloxan induced models are extensively preferred because they are simple, economical, and reproducible. High-fat diet and genetic models further offer better simulation of insulin resistance and Type 2 diabetes. Each experimental model possesses distinct advantages and limitations; therefore, the selection of an appropriate model depends on the objective of the study. Overall, experimental diabetic models continue to serve as essential platforms for investigating disease mechanisms and evaluating potential therapeutic agents in preclinical research.

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