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Dose-Dependent Outcomes of Streptozotocin–Nicotinamide Induction in Developing Diabetic Rat Models: A Literature Review

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin action, or both. Experimental rat models are widely used in preclinical diabetes research because they allow rapid and reproducible evaluation of disease mechanisms and therapeutic interventions. Among the available models, the combination of streptozotocin (STZ) and nicotinamide (NA) is commonly employed to induce a condition resembling type 2 diabetes mellitus (T2DM) through partial pancreatic β-cell damage while preserving residual insulin function. This literature review aimed to evaluate the effects of different STZ–NA induction doses on blood glucose levels in rats and to identify the most reproducible protocol for T2DM induction. A literature review was conducted using studies retrieved from scientific databases, including PubMed, NCBI, ScienceDirect, and PLOS One. A total of 21 studies met the inclusion criteria and were included in the qualitative synthesis. Across the included studies, successful diabetes induction was generally defined by hyperglycaemia; however, diagnostic thresholds varied, ranging from fasting blood glucose levels >126 mg/dL to random blood glucose levels ≥200 mg/dL. Most STZ–NA dose combinations successfully induced diabetic conditions, with post-induction glucose levels commonly exceeding 200 mg/dL. The combination of STZ 60 mg/kgBW and NA 120 mg/kgBW was the most frequently reported regimen and consistently produced stable hyperglycaemia, typically ≥200 mg/dL, while avoiding complete pancreatic β-cell destruction. Overall, the available evidence suggests that STZ 60 mg/kgBW combined with NA 120 mg/kgBW represents the most consistent protocol for establishing a T2DM rat model.

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ABSTRAK

Diabetes melitus (DM) merupakan gangguan metabolik kronis yang ditandai dengan hiperglikemia persisten akibat gangguan sekresi insulin, kerja insulin, atau keduanya. Model tikus eksperimental banyak digunakan dalam penelitian praklinis diabetes karena memungkinkan evaluasi yang cepat dan dapat direproduksi terhadap mekanisme penyakit serta intervensi terapeutik. Di antara berbagai model yang tersedia, kombinasi streptozotocin (STZ) dan nicotinamide (NA) sering digunakan untuk menginduksi kondisi yang menyerupai diabetes melitus tipe 2 melalui kerusakan parsial sel β pankreas dengan tetap mempertahankan sebagian fungsi insulin. Literature review ini bertujuan untuk mengevaluasi pengaruh berbagai dosis induksi STZ–NA terhadap kadar glukosa darah pada tikus serta mengidentifikasi protokol yang paling konsisten untuk induksi diabetes melitus tipe 2. Kajian komparatif dilakukan menggunakan artikel yang diperoleh dari berbagai basis data ilmiah, termasuk PubMed, NCBI, ScienceDirect, dan PLOS One. Sebanyak 21 studi memenuhi kriteria inklusi dan dimasukkan ke dalam sintesis kualitatif. Pada studi-studi yang ditinjau, keberhasilan induksi diabetes umumnya ditentukan berdasarkan kondisi hiperglikemia. Namun, ambang diagnostik yang digunakan bervariasi, mulai dari kadar glukosa darah puasa >126 mg/dL hingga kadar glukosa darah acak ≥200 mg/dL. Sebagian besar kombinasi dosis STZ–NA berhasil menginduksi kondisi diabetes, dengan kadar glukosa darah pascainduksi yang umumnya ≥200 mg/dL. Kombinasi STZ 60 mg/kgBB dan NA 120 mg/kgBB merupakan regimen yang paling sering dilaporkan dan secara konsisten menghasilkan hiperglikemia yang stabil, umumnya berkisar antara 250–350 mg/dL, tanpa menyebabkan kerusakan total sel β pankreas. Secara keseluruhan, bukti yang tersedia menunjukkan bahwa kombinasi STZ 60 mg/kgBB dan NA 120 mg/kgBB merupakan protokol yang paling konsisten untuk menghasilkan model tikus diabetes melitus tipe 2.

Kata Kunci: Diabetes melitus tipe 2, *Streptozotocin*, Nikotinamida, Dosis induksi, Hiperglikemia

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both [1], [2]. This condition affects the metabolism of carbohydrates, lipids, and proteins and is associated with various complications that significantly reduce patients' quality of life [3]–[5]. The American Diabetes Association (ADA) classifies DM into several categories, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and other specific types of diabetes [6], [7]. Among these, T2DM accounts for approximately 90–95% of all diabetes cases worldwide [8].

The global prevalence of diabetes continues to increase at an alarming rate. According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), the number of people living with diabetes has risen substantially over the past decades, reaching 529 million cases worldwide in 2021 and is projected to increase to 693 million by 2045 [9]–[13]. The development of diabetes is closely associated with insulin deficiency and/or insulin resistance. In T2DM, insulin resistance reduces glucose uptake by peripheral tissues and increases hepatic glucose production through gluconeogenesis and glycogenolysis, resulting in chronic hyperglycemia [14]–[18].

Consequently, continuous efforts are being made to develop and evaluate new antidiabetic therapies.

Experimental animal models play an essential role in diabetes research because they enable the assessment of disease mechanisms and therapeutic interventions under controlled conditions. Rodents are commonly used due to their small size, relatively simple induction procedures, and cost-effectiveness [19]. Various diabetogenic agents have been employed to induce diabetes in laboratory animals, including streptozotocin (STZ), alloxan, vacor, dithizone, and 8-dihydroquinone [20], [21]. Among these agents, STZ is widely used because it effectively induces pancreatic β-cell damage and exhibits fewer adverse effects than alloxan [22].

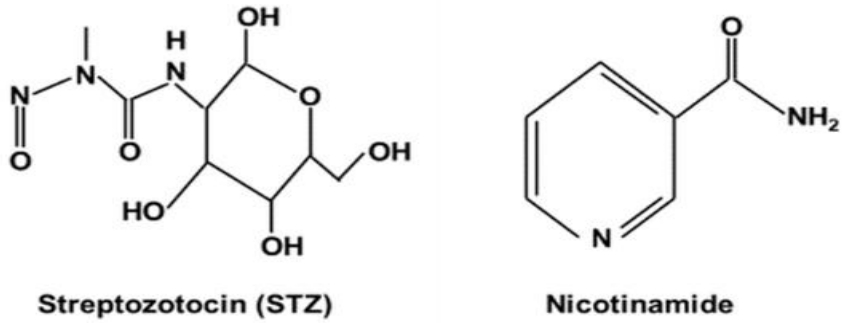

Figure 1. Structure of streptozotocin (STZ) and nicotinamide (NA) [23].

One of the most frequently utilized models for T2DM is the combination of streptozotocin and nicotinamide (STZ–NA). As illustrated in **Figure 1**, STZ and nicotinamide possess distinct chemical structures that contribute to their respective biological activities [23]. STZ acts as a diabetogenic compound with selective cytotoxic effects on pancreatic β-cells, whereas nicotinamide partially protects these cells from STZ-induced damage, thereby producing a diabetic state that more closely resembles T2DM in humans [24], [25]. This model has been widely adopted for evaluating the antidiabetic potential of novel therapeutic agents, including herbal medicines.

Although the STZ–NA model is extensively used in experimental diabetes studies, the induction protocols reported in the literature vary considerably in terms of STZ and nicotinamide doses. These variations may influence the severity of hyperglycemia and the reproducibility of the diabetic model, making it difficult to determine the most appropriate induction regimen. To date, a comprehensive review specifically comparing the effects of different STZ–NA dosing protocols on blood glucose levels in rats remains limited. Therefore, this review aims to analyze and compare the effects of various STZ–NA induction doses on blood glucose levels in rats and to provide a clearer reference for selecting suitable T2DM animal models in future studies.

2. Methods

Study Design and Review Framework

This study was conducted as a literature review to systematically identify, evaluate, and synthesize published evidence regarding the use of streptozotocin (STZ) and nicotinamide (NA) for the induction of Type 2 Diabetes Mellitus (T2DM) animal models. The review focused on comparing different STZ–NA induction protocols and their effects on blood glucose levels in rats. A descriptive-comparative approach was employed to analyze variations in induction doses, administration protocols, and

glycemic outcomes reported across studies. The review process consisted of literature identification, screening, eligibility assessment, data extraction, quality appraisal, and narrative synthesis to provide comprehensive evidence regarding the most reproducible STZ–NA induction regimen for establishing T2DM rat models.

Search Strategy and Information Sources

A comprehensive electronic search was performed across three major scientific databases: PubMed, NCBI, ScienceDirect and PLOS one. To ensure the inclusion of contemporary evidence, the publication period was strictly limited to peer-reviewed literature published within the last 10 years, spanning from 2015 to 2025.

Search Terms and Boolean Strings

To optimize retrieval accuracy and maximize search specificity, the search strategy utilized specific keywords combined as exact phrases. The precise search strings applied across the databases were as follows: streptozotocin-nicotinamide dose AND mechanism of streptozotocin AND mechanism of nicotinamide AND rat OR rats.

Eligibility Criteria

Articles were evaluated for inclusion in this review based on predefined eligibility criteria: Inclusion Criteria: (1) Original research articles published in clear, indexed national or international scientific journals within the 2015–2025 timeframe; (2) Studies utilizing rat models across any strains; (3) Experimental protocols evaluating the co-induction effects of STZ and NA; and (4) Quantitative data reporting on post-induction blood glucose levels or diabetes model success rates. Exclusion Criteria: (1) Articles published prior to 2015; (2) Studies that failed to demonstrate or measure the effects of STZ-NA on blood glucose levels in rats; (3) Incomplete articles, review articles, or conference abstracts-only; and (4) Duplicate publications across databases.

Study Selection Process

All records retrieved from the databases were exported and screened for duplicates. Titles and abstracts were subsequently reviewed for relevance, followed by full-text eligibility assessment. The initial database search identified 496 records (PubMed: 201, ScienceDirect: 259, and PLOS One: 36). After removing 14 duplicate records, 482 articles were screened based on titles and abstracts, resulting in the exclusion of 442 records. Subsequently, 40 full-text articles were assessed for eligibility. Of these, 19 articles were excluded due to wrong indication (n = 7) and wrong intervention (n = 12). Ultimately, 21 studies met the inclusion criteria and were included in the final qualitative synthesis (**Figure 2**).

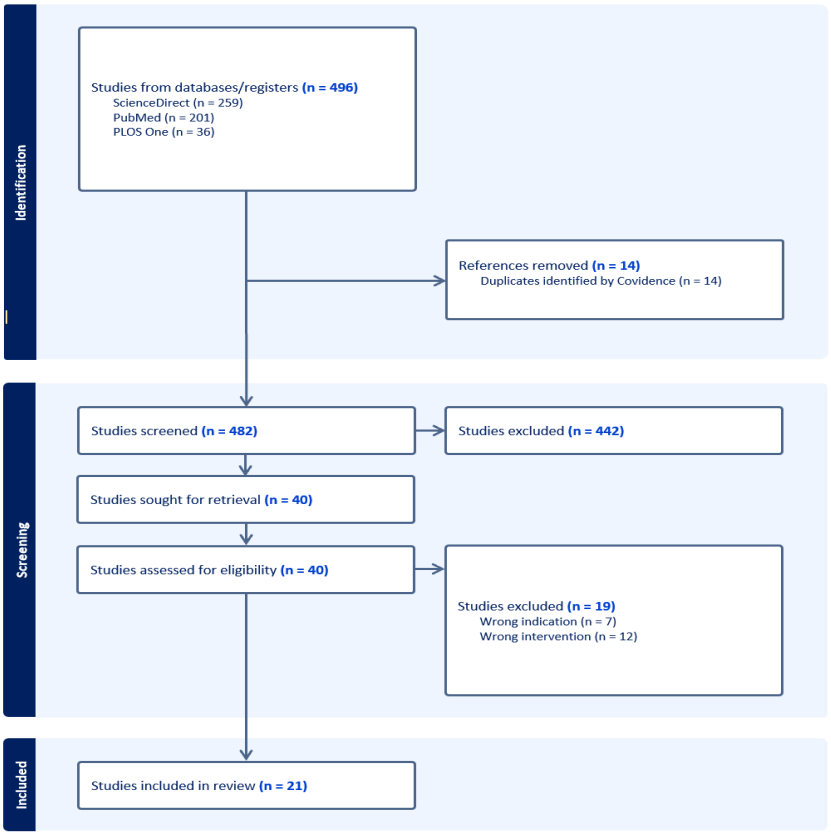

Figure 2. The flow chart of the identification and selection process.

Data Extraction and Data Items

Data extraction was performed independently using a standardized data extraction form. The extracted variables included the author and year of publication, streptozotocin (STZ) dose (mg/kg body weight), nicotinamide (NA) dose (mg/kg body weight), route of administration, and post-induction blood glucose levels reported in each study.

Quality Appraisal

The methodological quality of the included studies was evaluated using the SYRCLE Risk of Bias tool alongside adapted laboratory study quality criteria. Assessments were conducted across multiple domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias.

Data Synthesis and Analysis Approach

Due to the anticipated methodological heterogeneity across the literature (variations in rat strains, observation intervals, and glucose detection techniques), a qualitative narrative synthesis approach was adopted rather than a statistical meta-analysis. Quantitative data regarding chemical dosages and glycemic outcomes were compiled into comparative tables. The analysis focused on identifying descriptive patterns in induction success rates by grouping studies based on dose configurations and physiological responses to determine the most reproducible protocol.

Outcome Definitions

The primary outcome of interest was the successful establishment of a stable Type 2 Diabetes Mellitus (T2DM) model in rats. Reflecting the inherent heterogeneity across the reviewed literature, the diagnostic threshold defining successful

hyperglycemia varied across studies, ranging between >200 mg/dL. Optimal model success was defined as the achievement of these sustained hyperglycemia levels without inducing full necrosis or complete destruction of the pancreatic β cells populations.

3. Results and Discussion

Study Selection Results

The literature search identified studies investigating the induction of type 2 diabetes mellitus (T2DM) using combinations of streptozotocin (STZ) and nicotinamide (NA) in Wistar rats. After screening and eligibility assessment, studies meeting the predefined inclusion criteria were included for qualitative synthesis. The selected studies employed various STZ–NA dose combinations administered intraperitoneally and reported fasting blood glucose outcomes as indicators of successful T2DM induction. The characteristics of the included studies, including the STZ–NA dosage combinations, route of administration, and fasting blood glucose outcomes following induction, are summarized in **Table 1**.

Table 1. Characteristics of Included Studies and STZ–NA Induction Outcomes

Research Title	Method	Dosage	Results	Literature
Amelioration of diabetes and its complications by Manilkara zapota (L) P. Royen fruit peel extract and its fractions in alloxan and STZ-NA induced diabetes in Wistar rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	Following induction, blood glucose levels increased, averaging between 268 and 290 mg/dL.	[26]
Blood glucose lowering and anti-oxidant potential of erythritol: An in vitro and in vivo study	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 55 mg/kgBW and NA 100 mg/kgBW	The investigation's findings demonstrated that the rats in the induced group had hyperglycemia, with an average blood glucose level of around 270 mg/dL.	[27]
Antidiabetic and antihyperlipidemic effects of aqueous extract of Parquetina nigrescens in streptozotocin–nicotinamide induced type 2 diabetic rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	The results of the investigation showed that the induced rats had hyperglycemia, with average blood glucose levels above 200 mg/dL.	[28]
Resveratrol attenuates visfatin and vaspin genes expression in adipose tissue of rats with type 2 diabetes	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	Following STZ-Na induction, rats' fasting blood glucose levels rose to 219.37–289.75 mg/dL.	[29]
Comparison of the anti-diabetic effects of various grain and	Intraperitoneal Induction of Streptozotocin	STZ 60 mg/kgBW and	The efficacy of the diabetes model was demonstrated by the	[30]

legume extracts in high-fat diet and streptozotocin-nicotinamide-induced diabetic rats	and Nicotinamide	NA 120 mg/kgBW	MC group's much higher fasting blood glucose levels (271.0 ± 15.4 mg/dL) than those of the NC group (97.6 ± 1.43 mg/dL). Additionally, the glucose levels of the PC, OE, and SE groups were greater than those of the NC group.	
Antihyperglycemic and antihyperlipidemic activities of wild musk melon (Cucumis melo var. agrestis) in streptozotocin-nicotinamide induced diabetic rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	There was an increase in blood glucose levels in groups 2, 3, 4, and 5 with averages of 300.63±3.52, 330.00±1.85, 328.00±1.08, and 338.33±5.57, respectively.	[31]
Phenolic enriched fraction of Clerodendrum glandulosum Lindl. leaf extract ameliorates hyperglycemia and oxidative stress in streptozotocin-nicotinamide induced diabetic rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	When the rats were given STZ for 72 hours, their blood glucose levels rose to > 300 mg/dL, which is regarded as diabetic.	[32]
Effects of Red Spinach Extract Mira Variety on Fasting Blood Glucose and Malondialdehyde of DMT2 Model Rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 45 mg/kgBW and NA 110 mg/kgBW	A increase was indicated by the average blood glucose level of 273 mg/dL.	[33]
Effect of Ramania Leaf Ethanol Extract on Insulin and FBG in Obese Type 2 DM Wistar Rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 45 mg/kgBW and NA 110 mg/kgBW	Blood glucose levels increased following the delivery of STZ-NA, and they ranged from 255 to 265 mg/dL.	[34]
A pre-clinical study to investigate the anti-diabetic potential of p-propoxybenzoic acid as a multi-target inhibitor in streptozotocin-nicotinamide induced type-2 diabetic rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 65 mg/kgBW and NA 230 mg/kgBW	The difference between the sick control group and the normal control group was statistically significant (P value < 0.001). Following induction, blood glucose levels typically increased by 240–265 mg/dL.	[35]

Synergistic effect of micronutrients and metformin in alleviating diabetic nephropathy and cardiovascular Dysfunctioning in diabetic rat	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 55 mg/kgBW and NA 230 mg/kgBW	Blood glucose levels in rats in groups 2, 3, 4, and 5 after STZ-NA induction increased with an average of 230-270 mg/dL.	[36]
Hepatoprotective Effects of Polydatin-Loaded Chitosan Nanoparticles in Diabetic Rats: Modulation of Glucose Metabolism, Oxidative Stress, and Inflammation Biomarkers	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 50 mg/kgBW and NA 110 mg/kgBW	A rise in blood sugar levels of at least 250 mg/dL on average	[37]
Aqueous Ajwa dates seeds extract improves memory impairment in type-2 diabetes mellitus rats by reducing blood glucose levels and enhancing brain cholinergic transmission	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	Following STZ-NA induction, diabetic rats, diabetic rats treated with metformin, diabetic rats treated with AASE (200 mg), and diabetic rats treated with AASE (400 mg) all had an average rise in blood glucose levels of 300–400 mg/dL.	[38]
Hydroethanolic Extract from Bridelia atroviridis M¨ ull. Arg. Bark Improves Haematological and Biochemical Parameters in Nicotinamide-/Streptozotocin-Induced Diabetic Rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 55 mg/kgBW and NA 110 mg/kgBW	After STZ-NA induction, rats in the diabetic control group, Met 200 mg/kg treatment group, B. atroviridis 50 mg/kg, B. atroviridis 100 mg/kgBW, and B. atroviridis 200 mg/kg treatment groups saw an average increase in blood glucose levels of 250–300 mg/dL.	[39]
Antidiabetic and hepatoprotection effect of butterfly pea flower (Clitoria ternatea L.) through antioxidant, anti-inflammatory, lower LDH, ACP, AST, and ALT on diabetes mellitus and dyslipidemia rat	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	According to the findings of the STZ-NA induction study, the rats' blood glucose levels exceeded 250 mg/dL.	[40]

Ageratina adenophora (Spreng.) King & H. Rob. Standardized leaf extract as an antidiabetic agent for type 2 diabetes: An in vitro and in vivo evaluation	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 50 mg/kgBW and NA 110 mg/kgBW	The fasting blood glucose levels of the STZ-NA-induced diabetic rats increased significantly from 337 to 372 mg/dL during the experimental research in comparison to the normal control rats (group I).	[41]
Musa paradisiaca L. leaf and fruit peel hydroethanolic extracts improved the lipid profile, glycemic index and oxidative stress in nicotinamide/streptozotocin-induced diabetic rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	Following STZ-Na induction, rats' fasting blood glucose levels rose to 263.95–317.83 mg/dL.	[42]
Mitigation of Diabetes Mellitus Using Euphorbia helioscopia Leaf Ethanolic Extract by Modulating GCK, GLUT4, IGF, and G6P Expressions in Streptozotocin-Induced Diabetic Rats	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	The experimental group of rats produced by streptozotocin-nicotinamide showed a significant risk of hypoglycemia; on the first day, the glucose level of the EH500 group was 285.4 mg/dL, whereas that of the positive control group PC was 278.2 mg/dL.	[43]
Antidiabetic and antihyperlipidemic effects of Premna spinosa bark in experimental animal models	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	After receiving STZ, each rat's blood glucose levels were tested and found to be between 240 and 293 mg/dL, which is regarded as severe diabetes.	[44]
Formulation and evaluation of SGLT2 inhibitory effect of a polyherbal mixture inspired from Ayurvedic system of medicine	Intraperitoneal Induction of Streptozotocin and Nicotinamide	STZ 60 mg/kgBW and NA 120 mg/kgBW	The rats were deemed hyperglycemic following STZ-NA induction because their fasting glucose levels were between 250 and 450 mg/dL.	[45]
Study of Antidiabetic Properties of Berberis asiatica and Withania somnifera in	Intraperitoneal Induction of Streptozotocin	STZ 50 mg/kgBW and NA 110	Blood glucose levels in DM rats increased to more than 350 mg/dL on day 7 after STZ NA	[46]

Streptozotocin-Nicotinamide-Induced Type II Diabetes Mellitus in Wistar Rats	and Nicotinamide	mg/kgBW	induction in all groups except the control group.

Characteristics of Included Studies

As presented in Table 1, all included studies used intraperitoneal administration of streptozotocin and nicotinamide to induce T2DM in Wistar rats, although variations were observed in the dosage combinations and resulting blood glucose levels. Administration of both streptozotocin and nicotinamide regimens successfully induced a type 2 diabetes mellitus model in rats [24]. Compared with other experimental diabetic models, particularly the use of STZ alone, the STZ–NA model more closely resembles the pathophysiological characteristics of T2DM because residual pancreatic β-cell function is preserved. Streptozotocin alone is commonly used to induce type 1 diabetes through selective destruction of pancreatic β-cells in the islets of Langerhans, whereas the combination of STZ and nicotinamide produces moderate insulin deficiency accompanied by persistent hyperglycaemia, which better reflects human T2DM [47]–[49].

When compared with the combination of STZ and NA, the use of STZ alone tends to result in several disadvantages, including lower glucose sensitivity, a longer induction process, and a greater risk of toxicity to vital organs such as the liver and kidneys [48]. Meanwhile, db/db rats are widely recognized as a commonly used genetic animal model of T2DM; however, the STZ–NA model provides a more economical and experimentally flexible alternative while still reproducing important diabetic characteristics [47]. The induction process was generally performed via intraperitoneal injection through the abdominal cavity with the objective of producing diabetic rats with blood glucose levels exceeding 200 mg/dL [50]. Intraperitoneal administration is the most widely used route in studies involving Wistar rats because the procedure is relatively simple, rapid, and effective in generating a stable diabetic model [51].

Although the induction method was consistent across studies, substantial variation was observed in the dosages of STZ and NA. The most frequently reported combinations included STZ 45 mg/kgBW + NA 110 mg/kgBW, STZ 50 mg/kgBW + NA 110 mg/kgBW, STZ 55 mg/kgBW combined with different NA doses, and STZ 60 mg/kgBW + NA 120 mg/kgBW. Blood glucose levels following induction generally exceeded 200 mg/dL, indicating successful establishment of hyperglycaemia and diabetic conditions.

Dose–Response Patterns of STZ–NA Induction

Analysis of the included studies revealed a dose-dependent relationship between STZ–NA administration and hyperglycaemic outcomes. Lower STZ doses combined with moderate NA concentrations generally produced moderate hyperglycaemia, whereas higher STZ doses tended to generate more pronounced increases in blood glucose levels. The combination of STZ 45 mg/kgBW and NA 110 mg/kgBW produced fasting blood glucose values ranging from approximately 255–273 mg/dL [33], [34]. Increasing the STZ dose to 50 mg/kgBW while maintaining NA at 110 mg/kgBW resulted in broader glucose ranges, extending from approximately 250 mg/dL to more than 370 mg/dL [37], [41], [46]. Studies utilizing STZ doses of 55–60 mg/kgBW

consistently generated hyperglycaemia above 250 mg/dL [26], [27], [40]–[45], [28]–[32], [36], [38], [39], demonstrating reliable induction of diabetic conditions.

The observed dose–response pattern may be explained by the opposing actions of STZ and NA. Increasing STZ doses enhances β-cell toxicity and consequently elevates blood glucose levels, whereas increasing NA doses attenuate β-cell destruction through their protective action. Therefore, the final glycaemic outcome depends not only on the STZ dose but also on the balance between the diabetogenic effect of STZ and the cytoprotective effect of nicotinamide [23], [49]. These findings suggest that the diabetogenic effect of STZ increases with dose, while NA modulates the severity of β-cell damage through its protective effect on pancreatic tissue.

Comparison of STZ–NA Dose Combinations

STZ 45 mg/kgBW + NA 110 mg/kgBW

Two studies employed this regimen and reported blood glucose levels between 255 and 273 mg/dL [33], [34]. The relatively narrow glucose range indicates a moderate and reproducible diabetic phenotype. However, the achieved hyperglycaemia was generally lower than that reported with higher STZ doses. Although the dosage protocol was identical, minor differences in glycaemic outcomes were observed. Study [33] reported average glucose levels of approximately 273 mg/dL, whereas study [34] reported values ranging from 255 to 265 mg/dL. These variations may be attributed to differences in animal physiological conditions, fasting duration, administration procedures, experimental environments, and individual biological responses to STZ and NA exposure [52].

STZ 50 mg/kgBW + NA 110 mg/kgBW

Three studies utilized this combination and observed glucose levels ranging from approximately 250 mg/dL to more than 370 mg/dL [37], [41], [46]. Although successful induction was achieved, substantial inter-study variability was observed. Study [37] reported blood glucose levels exceeding 250 mg/dL, whereas [41] observed fasting blood glucose concentrations between 337 and 372 mg/dL. Similarly, study [46] reported glucose levels exceeding 350 mg/dL following induction. This variability suggests that factors beyond dosage contribute significantly to glycaemic outcomes. Differences in strain susceptibility, metabolic status before induction, injection accuracy, and timing of glucose assessment may influence the degree of β-cell damage and subsequent hyperglycaemia [52]. These findings indicate that even relatively small changes in experimental conditions may result in marked differences in blood glucose responses.

STZ 55 mg/kgBW with Variable NA Doses

Studies using STZ 55 mg/kgBW combined with NA doses of 100, 110, or 230 mg/kgBW generally reported blood glucose levels between 230 and 300 mg/dL [27], [36], [39]. Despite variations in NA concentration, hyperglycaemia was consistently induced. Study [36] reported blood glucose levels around 270 mg/dL, while [39] observed values between 230 and 270 mg/dL. Similarly, [27] reported glucose levels ranging from 250 to 300 mg/dL. Variations in NA dosage appear to affect the extent of β-cell protection. At higher concentrations, nicotinamide may reduce STZ-induced cellular damage more effectively, resulting in lower glucose elevations despite the use of higher STZ doses. Nevertheless, all reviewed studies demonstrated successful

diabetes induction, indicating that STZ at 55 mg/kgBW maintains sufficient diabetogenic activity despite differences in NA administration [23], [49].

STZ 60 mg/kgBW + NA 120 mg/kgBW

This was the most frequently used regimen among the included studies [26], [28], [30]–[32], [38], [40], [43]–[45]. Most studies reported fasting blood glucose levels ranging from 250 to 350 mg/dL, while several studies observed values exceeding 300 mg/dL. The consistency of these findings suggests that this protocol provides reliable induction of hyperglycaemia while maintaining partial pancreatic β-cell function. The slightly higher NA concentration may provide adequate protection against complete β-cell destruction, allowing preservation of residual insulin secretion while maintaining diabetic characteristics. Consequently, this protocol closely mimics the pathophysiological features of human T2DM and is frequently selected for evaluating antidiabetic drugs and natural products [26]. Other distinguishing characteristics of this model include impaired glucose tolerance, reduced glucose-stimulated insulin secretion, decreased pancreatic insulin reserves, reduction of pancreatic β-cell mass, responsiveness to sulfonylurea therapy such as glibenclamide, and stable moderate hyperglycaemia without the requirement for exogenous insulin administration [26].

Higher NA Regimens (STZ 55–65 mg/kgBW + NA 230 mg/kgBW)

Studies employing higher NA doses generally produced moderate hyperglycaemia, ranging from approximately 230 to 270 mg/dL [35], [36]. The stronger protective effect of NA may reduce excessive β-cell destruction, thereby preserving residual insulin secretion while maintaining diabetic characteristics. These findings further support the notion that NA dosage plays a critical role in determining the severity of hyperglycaemia induced by STZ.

Overall, the available evidence indicates that STZ 60 mg/kgBW combined with NA 120 mg/kgBW provides the most consistent and reproducible induction protocol among the reviewed studies.

Consistency of Hyperglycaemia Thresholds Across Studies

Although diagnostic thresholds varied slightly among studies, successful diabetes induction was generally defined by fasting blood glucose levels exceeding 126 mg/dL. For non-fasting measurements, random blood glucose levels of at least 200 mg/dL were commonly used as the criterion for diabetes [50]. Nearly all reviewed dose combinations surpassed this threshold, confirming successful establishment of diabetic models. Notably, studies using STZ 60 mg/kgBW + NA 120 mg/kgBW consistently produced glucose levels well above the minimum threshold while avoiding extreme hyperglycaemia associated with complete β-cell destruction. This balance is particularly important because T2DM is characterized by partial β-cell dysfunction rather than absolute insulin deficiency.

Mechanistic Interpretation of the STZ–NA Model

The STZ–NA model reproduces key features of human T2DM through the interaction between the cytotoxic effects of STZ and the protective actions of NA. Streptozotocin (2-deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose), a nitrosourea derivative, enters pancreatic β-cells through the GLUT2 glucose transporter [38]. Once inside the cell, STZ induces DNA alkylation and fragmentation, triggering activation of poly(ADP-ribose) polymerase-1 (PARP-1) as part of the DNA repair process. Excessive PARP-1 activation promotes conversion of NAD+ into ADP-ribose polymers, resulting

in depletion of intracellular NAD+ and ATP stores [38]. Reduced ATP availability impairs insulin synthesis and secretion, ultimately causing β-cell dysfunction and necrosis. In addition, STZ stimulates the generation of reactive oxygen species (ROS) and nitric oxide (NO), both of which contribute to oxidative stress and DNA damage [53]. These reactive molecules may combine to form peroxynitrite ($ONOO^-$), a highly toxic oxidant capable of exacerbating β-cell injury.

In contrast, nicotinamide (NA), also known as pyridine-3-carboxamide and an amide derivative of vitamin B3, acts as a protective agent against STZ-induced β-cell destruction [49]. NA inhibits excessive PARP-1 activation, thereby preserving intracellular NAD+ concentrations and preventing ATP depletion. By maintaining cellular energy metabolism, NA reduces β-cell necrosis and preserves partial insulin secretory capacity [49], [54], [55]. The protective effect of NA is highly dose dependent. When administered at insufficient concentrations, NA cannot adequately protect β-cells from STZ toxicity. Conversely, excessively high doses may completely prevent β-cell destruction and inhibit diabetes development. Therefore, careful optimization of both STZ and NA dosages is essential to achieve a reproducible T2DM phenotype [23], [49].

For this reason, NA is typically administered 15–30 minutes before STZ injection to maximize β-cell protection and establish a model characterized by partial β-cell dysfunction rather than complete β-cell loss [49], [54], [55]. The proposed mechanism of STZ toxicity and NA-mediated protection is illustrated in **Figure 3**.

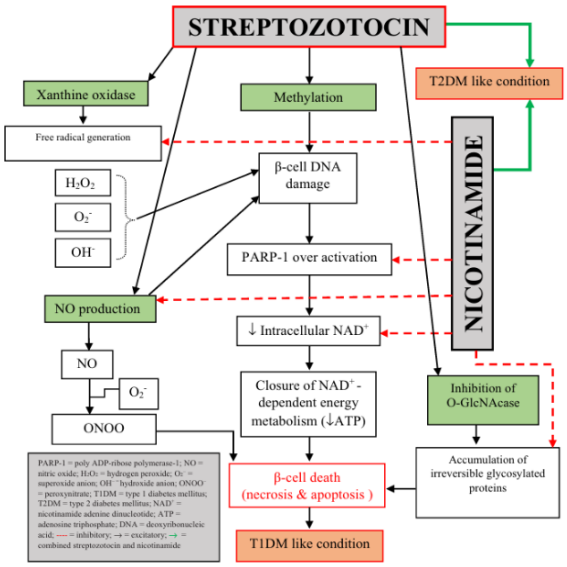

Figure 3. Representation of the toxicity mechanism of streptozotocin (STZ) through nicotinamide protection [49].

Nicotinamide protects pancreatic β-cells through multiple biochemical pathways. In addition to PARP-1 inhibition, NA functions as a free radical scavenger and reduces oxidative stress within pancreatic tissue. NA also prevents excessive accumulation of glycosylated proteins through maintenance of O-GlcNAcase activity and acts as a methyl-group acceptor, reducing DNA damage caused by alkylation. These mechanisms support β-cell regeneration, preserve islet architecture, enhance NAD+ synthesis, promote Langerhans islet development, and reduce apoptosis [49]. Consequently, NA moderates the diabetogenic effects of STZ and enables the development of a T2DM model that more closely resembles the human disease condition. Furthermore, the extent

of this protective effect is highly dependent on the concentration of NA administered [23].

Implications for Preclinical T2DM Model Standardization

The findings of this review suggest that standardization of STZ–NA protocols is necessary to improve reproducibility across preclinical studies. Among the reviewed regimens, STZ 60 mg/kgBW combined with NA 120 mg/kgBW demonstrated the most consistent performance, generating stable hyperglycaemia while preserving residual β-cell function. Compared with alternative animal models such as db/db rats, which possess spontaneous genetic mutations associated with obesity and diabetes, the STZ–NA model offers a more economical, practical, and experimentally flexible approach while still reproducing important features of T2DM [47]. Therefore, standardization of STZ–NA induction protocols may improve comparability among studies and facilitate broader application of this model in preclinical antidiabetic research. Adopting STZ 60 mg/kgBW + NA 120 mg/kgBW as a reference protocol may facilitate comparison between studies, improve reproducibility of therapeutic evaluations, and enhance translational relevance for T2DM research. Nevertheless, investigators should continue to consider animal characteristics, fasting duration, administration techniques, and timing of glucose measurements because these factors contribute to inter-study variability.

Limitations and Future Directions

This review has several limitations. First, the included studies exhibited methodological heterogeneity regarding animal age, body weight, fasting periods, timing of glucose measurements, and study duration, which may influence observed glycaemic outcomes. Second, the analysis relied primarily on reported blood glucose values and did not quantitatively compare insulin levels, β-cell histopathology, or insulin resistance markers. Third, the limited number of studies for certain dose combinations restricted direct comparisons between induction protocols. Future studies should incorporate standardized reporting guidelines and evaluate additional metabolic parameters, including insulin concentrations, HOMA-IR indices, pancreatic histopathology, oxidative stress biomarkers, and inflammatory mediators. Meta-analytic approaches may also help determine the optimal STZ–NA dosage combination for establishing reproducible T2DM models and improve translational applicability of preclinical diabetes research.

4. Conclusion

The combination of streptozotocin (STZ) and nicotinamide (NA) administered intraperitoneally is an effective and widely used method for inducing a type 2 diabetes mellitus (T2DM) model in rats. STZ induces partial pancreatic β-cell damage, while NA provides a protective effect that preserves residual β-cell function and insulin secretion, thereby mimicking key characteristics of human T2DM. Among the various induction protocols identified, the combination of STZ 60 mg/kgBW and NA 120 mg/kgBW consistently produced stable hyperglycaemia, with blood glucose levels generally exceeding ≥200 mg/dL, while avoiding complete β-cell destruction. This balance makes the STZ–NA model particularly suitable for investigating T2DM pathophysiology and evaluating the efficacy of potential antidiabetic therapies. However, the findings should be interpreted with caution due to methodological heterogeneity among the included studies, including differences in rat strains, animal characteristics, fasting periods, timing of NA and STZ administration, glucose measurement schedules, and diagnostic glucose cut-off values used to define successful diabetes induction. Furthermore, the

limited availability of studies for certain dose combinations restricted direct comparisons across induction protocols. Future research should adopt standardized induction and reporting protocols and evaluate additional metabolic parameters, such as insulin concentrations, insulin resistance indices, and pancreatic histopathological changes, to improve the reproducibility and translational relevance of experimental T2DM models.

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Conflicts of Interest:

The authors declare no conflicts of interest related to this study or its publication.

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