Journal of Hunan University

(Natural Sciences)

Vol. 53 No. 6

June 2026

Available online at

https://jonuns.com

Open Access Article https://doi.org/10.55463/issn.1674-2974.53.6.11

Physical and Nutraceutical Interventions in Wistar Rat Models of Type 2 Diabetes Mellitus: A Scoping Review

Ikbal Gentar Alam [1*], Arta Farmawati[2], Lily Arsanti Lestari[3]

[1] **Clinical Nutrition Department, Faculty of Medicine, Universitas Pendidikan Indonesia, Bandung, Indonesia,**

[2] **Biochemistry Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia,**

[3] **Nutrition Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia,**

* Corresponding author: ikbalga@upi.edu

Article History:

Received: May 6, 2026
Revised: June 13, 2026
Accepted: June 17, 2026
Published: June 30, 2026

Abstract: This scoping review examines preclinical evidence on physical, probiotic, and nutraceutical interventions for type 2 diabetes mellitus using Wistar rat models. The distinctive contribution of this review lies in its explicit distinction between direct experimental evidence and a proposed future framework for a combined treadmill–Smallanthus sonchifolius–Lactobacillus acidophilus intervention. By systematically identifying the absence of direct evidence for this combined protocol, the review provides a focused rationale for future experimental studies rather than relying solely on extrapolation from separate intervention models. The study aimed to map intervention characteristics, animal models, outcomes, and evidence gaps related to glycemic control, insulin resistance, lipid metabolism, inflammation, gut microbiota, and molecular pathways. A scoping review was conducted according to the Arksey and O'Malley framework and the PRISMA-ScR guidelines. PubMed, Scopus, and Springer Nature databases/platforms were searched for studies published between 2015 and 2025 using terms related to Wistar rats, type 2 diabetes mellitus, treadmill exercise, yacon/Smallanthus sonchifolius, probiotics, and

Lactobacillus acidophilus. Records were screened using Rayyan, data were extracted using Microsoft Excel, and reporting quality and risk of bias were appraised using the ARRIVE reporting criteria and SYRCLE's risk of bias tool. The search identified 1,389 records; after duplicate removal, title and abstract screening, and full-text assessment, 23 studies were included in the review. The strongest direct evidence was found for treadmill exercise, with 21 studies reporting improvements in fasting blood glucose, glucose tolerance, insulin resistance indices, lipid or adiposity parameters, and metabolic-inflammatory pathways. Direct evidence for Lactobacillus acidophilus was limited to two studies, which reported improvements in glycemia, insulin sensitivity, inflammatory markers, body weight, and fecal lactobacilli counts. No eligible study directly examined Smallanthus sonchifolius or the full three-component combination. Therefore, treadmill exercise is directly supported by preclinical evidence, Lactobacillus acidophilus has limited supportive evidence, and yacon-based as well as combined physical–nutraceutical–probiotic protocols remain hypothesis-generating strategies requiring direct experimental validation.

Keywords: Type 2 diabetes mellitus; Wistar rats; treadmill exercise; probiotics; Lactobacillus acidophilus; Smallanthus sonchifolius; yacon; nutraceuticals; scoping review; inflammation.

基于 Wistar 大鼠 2 型糖尿病模型的物理干预与营养保健干预：一项范围综述

摘要：本范围综述考察了基于 Wistar 大鼠模型的 2 型糖尿病物理干预、 益生菌干预和营养保健干预的临床前证据。本综述的独特贡献在于明确区分了直接实验性证据与未来拟议的跑台运动-菊薯（Smallanthus sonchifolius）-嗜酸乳杆菌 （Lactobacillus acidophilus） 联合干预框架。 通过系统识别该联合方案目前缺乏直接证据， 本综述为未来实验研究提供了有针对性的依据，而不是仅依赖于不同单一干预模型结果的外推。本研究旨在梳理与血糖控制、胰岛素抵抗、脂质代谢、炎症、肠道微生物群和分子通路相关的干预特征、动物模型、结局指标和证据空白。本范围综述依据 Arksey 和 O'Malley 框架以及 PRISMA-ScR 指南开展。检索了 PubMed、Scopus 和 Springer Nature 数据库/平台中 2015 年至 2025 年发表的研究，检索词涉及 Wistar 大鼠、2 型糖尿病、跑台运动、菊薯/Smallanthus sonchifolius、益生菌和 Lactobacillus acidophilus。研究记录使用 Rayyan 进行筛选，数据采用 Microsoft Excel 提取，并使用 ARRIVE 报告规范和 SYRCLE 偏倚风险评估工具对报告质量和偏倚风险进行评价。检索共识别出 1,389 条记录；经去重、题名和摘要筛选以及全文评估后，最终纳入 23 项研究。最强的直接证据来自跑台运动，其中 21 项研究报告了空腹血糖、葡萄糖耐量、胰岛素抵抗指数、脂质或脂肪沉积参数以及代谢炎症通路的改善。关于 Lactobacillus acidophilus 的直接证据仅限于 2 项研究，这些研究报告了血糖水平、胰岛素敏感性、炎症标志物、体重和粪便乳杆菌计数的改善。未发现符合条件的研究直接考察 Smallanthus sonchifolius 或完整的三组分联合干预。因此， 跑台运动已获得临床前直接证据支持，Lactobacillus acidophilus 具有有限的支持性证据，而基于菊薯的干预以及物理-营养保健-益生菌联合方案仍属于假设生成性策略，需要进一步通过直接实验加以验证。

关键词：2 型糖尿病；Wistar 大鼠；跑台运动；益生菌；嗜酸乳杆菌；菊薯；Smallanthus sonchifolius；营养保健品；范围综述；炎症。

1. Introduction

Diabetes mellitus is a major global health problem, characterized by chronic hyperglycemia due to impaired insulin secretion or action, leading to multiple organ damage. Type 2 diabetes accounts for 90% of cases, marked by insulin resistance and secretion insufficiency, with contributions from diet, physical inactivity, obesity, and gut microbiota dysfunction. The burden of diabetes is rising worldwide, impacting mortality, morbidity, and healthcare costs. Diabetes is associated with metabolic disturbances, oxidative stress, inflammation, and immune alterations that accelerate vascular complications(1,2).

Diabetes management combines lifestyle interventions and pharmacotherapy, although no cure exists. Antidiabetic drugs lower glucose levels but have side effects, hypoglycemia risk, and narrow therapeutic windows. Conventional formulations cannot respond to glucose fluctuations or target specific organs, increasing toxicity risks. This has driven development of safer, multifactorial strategies focusing on metabolism, inflammation, and microbiota(2).

Structured aerobic exercise is key to non-pharmacological interventions. Endurance exercise increases glucose uptake, improves glycemic control, and enhances insulin sensitivity. In Wistar rat models, moderate treadmill exercise reduced fasting glucose and improved glucose tolerance. Studies have shown that high-intensity exercise reduces gluconeogenesis and increases liver glycogen storage. Treadmill exercise works at systemic and molecular levels in diabetes pathogenesis(2,3).

Nutraceuticals and functional foods have shown potential as complementary therapies by modulating metabolic pathways. Related literature suggests that herbal nutraceuticals may contain compounds with prebiotic and antihyperglycemic properties, potentially working by increasing short-chain fatty acid production and improving metabolic profiles. However, no eligible study in this review directly evaluated yacon-derived nutraceuticals in Wistar rat models of type 2 diabetes. Lactobacillus probiotics exert antidiabetic effects by modulating the microbiota and reducing inflammation. Synbiotic functional foods combining prebiotics and probiotics offer promise for normalizing gut ecosystem and metabolic function(1,2,4).

Specific solutions using functional foods have been evaluated in animal models. A synbiotic biscuit from banana tuber, sweet potato, and black soybean flours with L. acidophilus showed moderate glycemic index (65) and glycemic load. Daily consumption of 10 g for 15 days in alloxan-induced Wistar rats reduced fasting glucose to 97 mg/dL and increased fecal L. acidophilus to 6.5–7 log colony-forming units (CFU) / g. This glucose reduction is related to SCFA production, increased mucosal glutathione levels, and reduced oxidative stress, which improves insulin sensitivity(1).

One of the two included studies on Lactobacillus acidophilus evaluated a cell-free probiotic extract (LPE) from L. acidophilus and L. plantarum in STZ–nicotinamide diabetic rats and reported significant reduction in fasting glucose, insulin, TNF-α, and HOMA-IR index. This mechanisms include antioxidant activities of probiotic metabolites and suppression of hyperglycemic pathways. Studies on Euterpe oleracea polyphenols have shown reduced glucose, HOMA-IR, leptin, and cytokine levels, increased GLUT4 and pAKT expression, and activation of the adiponectin–AMPK pathway(2,4).

Physical and nutraceutical interventions show synergistic effects. Combining treadmill exercise with polyphenol-rich extracts leads to greater reductions in glucose and insulin resistance, with increased expression of key proteins. Similarly, the combination of HIIT and time-restricted feeding improved glucose markers in T2DM rats. Meta-analyses have shown that probiotics, prebiotics, and synbiotics benefit cardiometabolic risk factors in prediabetes and T2DM (2–4).

Although treadmill exercise, yacon-derived nutraceuticals, and *Lactobacillus acidophilus* have been investigated separately in experimental diabetes models, the evidence base remains fragmented. Most available studies have examined one intervention at a time, such as exercise alone, probiotic supplementation alone, or nutraceutical administration alone. A smaller number of studies have evaluated combined strategies, but these combinations generally involve different nutraceuticals, probiotic formulations, or dietary approaches that do not directly correspond to the combined intervention of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus*. Consequently, the extent to which these three modalities have been studied together in a single experimental protocol remains unclear (1–4).

The novelty of this scoping review lies in it explicit mapping of this evidence gap. This review does not merely summarize the independent effects of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus*. Rather, it systematically identifies whether direct experimental evidence exists for their combined use in Wistar rat models of type 2 diabetes mellitus and clarifies the absence or scarcity of studies applying these three interventions within an integrated protocol. To the authors' knowledge, no prior scoping or systematic review has explicitly mapped the evidence gap for this specific three-component combination in diabetic rat models. This review provides a structured evidence map that distinguishes between evidence for separate interventions, evidence for partial combinations, and the lack of direct evidence for the full combined protocol.

This study aimed to conduct a scoping review of physical and nutraceutical interventions for diabetes mellitus, focusing on these three modalities. The objectives are: (1) to map experimental findings on their impact on glycemic control, insulin resistance, and inflammatory biomarkers in diabetic animal models; and (2) to evaluate potential synergy when combining physical and nutraceutical interventions. The main contribution of this review is to demonstrate that while individual and partial-combination evidence exists for these interventions, direct evidence for a single integrated protocol combining treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus* remains lacking or insufficient. This evidence gap provides a clear rationale for future experimental studies designed to evaluate multimodal, mechanism-based intervention packages for type 2 diabetes mellitus (1–4).

2. Methods and Materials

2.1. Study Design

A scoping review was chosen as the appropriate method to answer the research question, "What are the characteristics of the interventions and the outcomes reported from the use of treadmill, Smallanthus sonchifolius, and Lactobacillus acidophilus in studies involving Wistar animal models of diabetes mellitus?" The protocol was conducted according to the Arksey and O'Malley framework, which includes the following steps: identifying the research question, identifying relevant studies, selecting studies, charting the data, and collecting, summarizing, and reporting the results (5). The scoping review manuscript was prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines (6).

2.2. Identifying Research Question

This scoping review aims to systematically describe and map the available scientific evidence regarding the effects of physical activity or exercise interventions using a treadmill, probiotic supplementation, especially Lactobacillus acidophilus, whether administered alone or together with other types of probiotics, and the administration of the herbal Smallanthus Sonchifolius, given either separately or in combination, on the management of diabetes mellitus. This was assessed by examining the clinical indicators of type 2 diabetes in Wistar rats as an animal model of type 2 diabetes mellitus. To achieve this objective, we seek to answer the question: "What are the characteristics and reported outcomes of treadmill exercise, Lactobacillus acidophilus, and Smallanthus sonchifolius interventions-wether used separately, in partial combinations, or as complete integrated protocol-in Wistar or Rattus Norvegicus models of type 2 diabetes mellitus? Does direct experimental evidence exist for the full three-component combination?"

2.3. Identifying Relevant Study

In this study, relevant articles were searched using the PubMed, Scopus, and Springer Nature databases, covering publications from 2015 to 2025. Searches in all three databases were conducted in mid-July 2025. To improve transparency and reproducibility, a complete search strategy was developed separately for each database and adapted to the syntax and indexing system of PubMed, Scopus, and Springer Nature. The search strategy combined four concept blocks: type 2 diabetes mellitus, treadmill exercise, Smallanthus sonchifolius, and Lactobacillus acidophilus intervention. Searches were performed using title, abstract, and keyword fields whenever the database allowed field restriction. In PubMed, searches used the title/abstract field tag `[Title/Abstract]` and relevant MeSH terms when applicable. In Scopus, searches used `TITLE-ABS-KEY`. In Springer Nature, searches were conducted using title, abstract, and keyword-related search functions available in the database interface.

The search terms included synonyms and spelling variants for each concept. For type 2 diabetes mellitus, the terms included "type 2 diabetes mellitus," "type II diabetes mellitus," "T2DM," "diabetes mellitus type 2," "diabetes mellitus type II," "type 2 diabetes," "type II diabetes," "non-insulin dependent," "non-insulin dependent diabetes mellitus," "diabetes type 2," "diabetes type II," "adult-onset diabetes mellitus," and "T2DM." For treadmill exercise, the terms included "treadmill," "treadmill exercise," and "treadmill training." For yacon, the terms included "Smallanthus sonchifolius," "yacon," and "yakon." For probiotic interventions, the terms included "Lactobacillus acidophilus."

The Boolean operators `AND` and `OR` were used to combine the concept blocks. The general search structure was: ("type 2 diabetes mellitus" OR "type II diabetes mellitus" OR "T2DM" OR "diabetes mellitus type 2" OR "diabetes mellitus type II" OR "type 2 diabetes" OR "type II diabetes" OR "non-insulin dependent" OR "non-insulin dependent diabetes mellitus" OR "diabetes type 2" "diabetes type II" OR "adult-onset diabetes mellitus" OR "T2DM") AND (treadmill OR "treadmill exercise" OR "treadmill training" OR "Smallanthus sonchifolius" OR yacon OR yakon OR Lactobacillus). The complete database-specific search strings are provided in Supplementary Appendix A. This appendix includes the exact search syntax used in PubMed, Scopus, and Springer Nature, including field tags, Boolean operators, truncation where applicable, and date limits. Providing the full search strings allows the search process to be replicated and clarifies that synonyms for yacon, probiotics, physical exercise, and type 2 diabetes mellitus were included, to broaden our search to most medical and health journals. All citations found, along with their metadata (such as abstracts and author names), were managed using the online AI application

Rayan. The authors focused their search on these three databases and did not include gray literature or unpublished articles. All team members independently conducted scoping reviews.

2.4. Study Selection

The search results from the three databases were imported into the Rayyan application (Rayyan: AI-Powered Systematic Review Management Platform). Duplicate checking and selection of articles to be retained or removed, as well as screening based on titles and abstracts, were performed by two reviewers (IA and LL) for eligibility. Articles were considered eligible for inclusion in this review if they met the following criteria: (a) the study was conducted on Wistar animals (Rattus Norvegicus) induced with type 2 diabetes mellitus; (b) the study assessed one or more interventions, which included treadmill intervention, administration of simplisia or extracts from the leaves or tubers of Smallanthus sonchifolius, and/or administration of probiotics containing Lactobacillus acidophilus either alone or in combination with other probiotics; (c) the study was a quantitative experimental study; (d) the article was written in English or Indonesian; and (e) the article was published between 2015 and 2025. Studies on type 1 DM, gestational diabetes, or other types of diabetes, as well as editorials, opinions, and review articles, were excluded. Only completed articles were collected and filtered for relevance. Any disagreements regarding the inclusion of a study were discussed by the two reviewers (IA and LL) to reach a consensus. A third reviewer (AF) determined whether the study should be included if consensus could not be reached.

2.5. Data Charting

Data management of the eligible articles was performed using Microsoft Excel. The collected data included the authors and year of publication, research methods, characteristics of experimental animals, interventions (such as treadmill exercise, consumption of Lactobacillus acidophilus, consumption of simplicia, or extract of Smallanthus Sonchifolius with or without other interventions), and outcomes related to the clinical control of type 2 diabetes mellitus.

2.6. Collating, Summarizing, and Reporting Results

The data extracted in the previous stage were collected and summarized to provide a narrative overview of how existing research articles demonstrate the relationship between treadmill activity, supplementation with Lactobacillus acidophilus probiotics either alone or in combination with other probiotics, supplementation with simplicia or extracts from the tubers and/or leaves of Smalanthus sonchifolius, and clinical control of T2DM.

In the synthesis, search results were also interpreted according to the intervention terms captured during data charting. This enabled transparent reporting of whether evidence was retrieved through exercise-related terms, yacon-related terms, probiotic-related terms, or broader type 2 diabetes animal-model terms. This approach strengthened the ability of the review to identify not only available evidence, but also the absence of direct evidence for the complete combined protocol.

2.7. Ethical Considerations

This review used data from previously published studies and did not involve direct experimentation on animals or humans. Therefore, ethical approval was not required for this review. However, animal welfare-related reporting was considered during the appraisal of included studies through the assessment of methodological and reporting quality.

3. Critical Appraisal

A critical appraisal of intervention studies on animal models was conducted using SYRCLE's RoB approach, which covers ten domains (selection, performance, detection, attrition, reporting, and other biases). Each domain was assessed as "Yes," "No," "Unclear," or not applicable (Table 1). The appraisal was performed to map the quality and risk of bias of preclinical evidence and to inform the interpretation of results, not as an exclusion criterion (8,9). Additionally, compliance with key ARRIVE points (randomization, blinding, sample size, animal details, animal handling, and statistical analysis) was checked to describe the reporting quality (Table 2) (10–12).

4. Results

4.1. Study Selection

The overall literature search from the databases yielded 1,389 articles, consisting of 222 articles from the PubMed database (https://pubmed.ncbi.nlm.nih.gov/), 546 articles from Springer Nature (https://link.springer.com/), and 621 articles from Scopus (https://www.scopus.com). After the deduplication process, 1,135 articles remained for review. Screening based on titles and abstracts resulted in the exclusion of 871 articles, and 264 relevant full-text articles were evaluated for eligibility. Following the eligibility assessment, 241 articles did not meet the inclusion criteria, and 23 articles met the requirements and were analyzed (Figure 1)

4.2. Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 3. Data were obtained from 23 studies published between 2015 and 2025. The population in these studies consisted of Wistar experimental animals (Rattus Norvegicus) induced with type 2 diabetes. This was an interventional study on experimental animals. The types of interventions

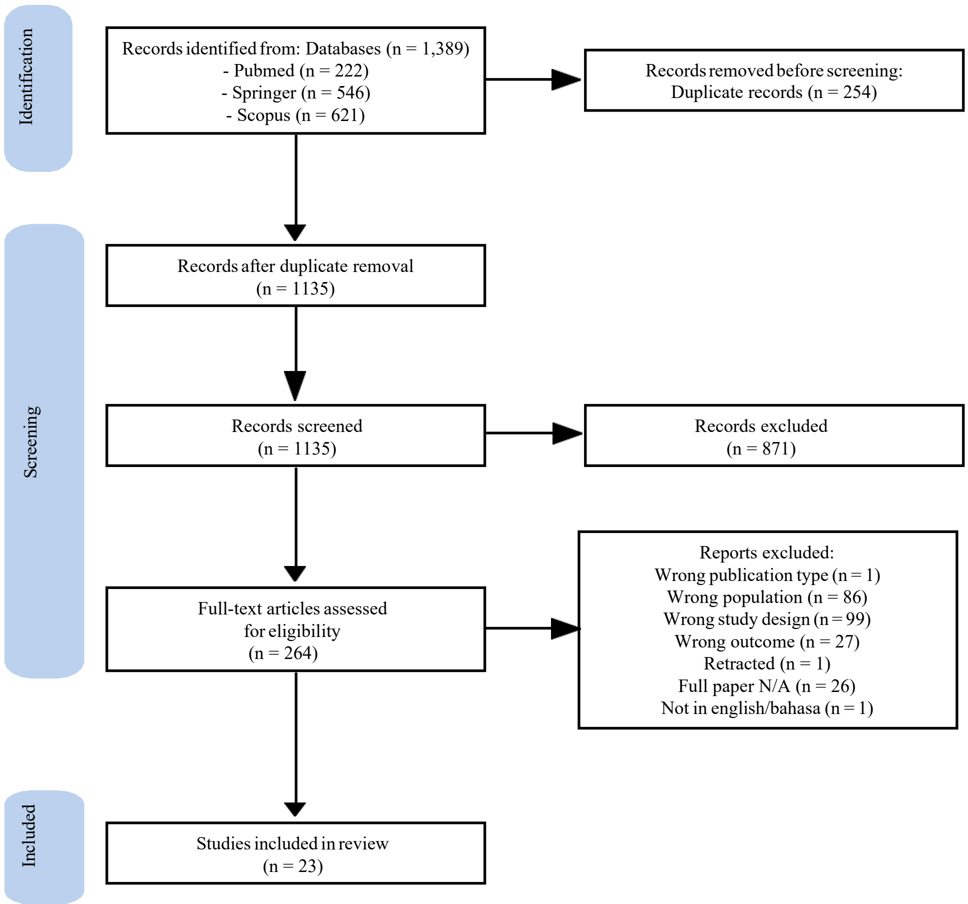

Figure 1: PRISMA flowchart for selected studies (7)

examined included exercise in the form of treadmill training at various intensity levels, supplementation with the probiotic Lactobacillus acidophilus either alone or in combination with other probiotics, and/or supplementation with simplicia or extracts from the leaves and/or tubers of Smallanthus sonchifolius. Among the 23 studies, 21 evaluated treadmill exercise protocols, either as a single intervention or in combination with other non-yacon nutraceuticals or dietary strategies. Two studies evaluated *Lactobacillus acidophilus*-containing interventions. No eligible study directly evaluated *Smallanthus sonchifolius* in Wistar rat models of type 2 diabetes mellitus according to the predefined inclusion criteria. Therefore, any interpretation of *Smallanthus sonchifolius* in this review should be considered indirect, theoretical, or hypothesis-generating rather than directly supported by the selected studies.

The outcomes observed were mainly clinical outcomes in T2DM control, such as blood glucose levels, plasma insulin levels, lipid profile, HOMA-IR, HOMA-B, and other outcomes correlated with morbidity and mortality control in type 2 diabetes along with its complications.

4.3. Treadmill Exercise

Treadmill exercise was the most frequently investigated intervention. Of the 23 included studies, 21 examined treadmill-based exercises. These include moderate-intensity continuous training, aerobic endurance training, high-intensity interval training, and other structured treadmill protocols with different intensities, frequencies, and durations. The intervention duration generally ranged from short-term protocols to longer interventions lasting approximately 14 weeks.

Aerobic treadmill exercise consistently reduces fasting blood glucose levels and improves insulin sensitivity (HOMA-IR) in diabetic rats (3,13–15). High-intensity interval training (HIIT) protocols improve glucose regulation and insulin signaling, increasing serum insulin levels and reducing insulin resistance (15,16). Moderate-intensity continuous treadmill training (MCT) improves glucose tolerance and reduces hyperglycemia (17,18). Aerobic training enhances mitochondrial biogenesis and oxidative capacity in the muscles and liver, contributing to improved glucose utilization (19). Longer duration

Table 1. SYRCLE's Risk of Bias assessment of the included animal studies

Author, year	Design	Score based on appropriate SYRCLE's RoB										Overall appraisal
		Seq. Gen.	Baseline	Alloc. conceal	Random housing	Inv. Blind.	Random outcome	Outcome blind	Incomplete data	Selective report	Other bias	
Ziarniak et al., 2021	Experimental	Y	Y	Y	Y	Y	Y	Y	N	U	N	Included
Zhao *et al.*, 2023	Experimental	Y	Y	Y	U	U	U	U	Y	Y	N	Included
Syahputra et al., 2023	Experimental	Y	Y	Y	Y	U	Y	U	U	U	U	Included
Sheikh et al., 2025	Experimental	Y	Y	Y	U	U	U	U	U	U	U	Included
Sharafifard et al., 2025	Experimental	Y	Y	Y	Y	U	Y	U	Y	U	N	Included
Saadatzadeh et al., 2025	Experimental	Y	Y	Y	U	U	Y	U	Y	U	N	Included
Hossein et al., 2023	Experimental	Y	Y	U	U	Y	Y	Y	Y	U	N	Included
Moody et al., 2024	Experimental	U	Y	U	U	U	U	U	N	U	U	Included
Hoseini & Gharzi, 2025	Experimental	Y	Y	Y	U	U	Y	U	Y	U	N	Included
Machrina et al., 2019	Experimental	U	Y	U	Y	U	Y	U	N	Y	U	Included
Lin et al., 2024	Experimental	Y	Y	Y	Y	U	Y	U	Y	U	N	Included
Kılıç et al., 2025	Experimental	Y	Y	Y	U	U	Y	U	N	Y	N	Included
Khaledi & Gharzi, 2023	Experimental	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Included
Kazemia & Zahediasl, 2018	Experimental	U	Y	U	U	U	U	U	N	U	N	Included
Hoseini et al., 2025	Experimental	Y	Y	U	U	U	Y	U	Y	U	N	Included
Hamid et al., 2024	Experimental	Y	Y	U	Y	U	Y	U	Y	Y	N	Included
Gharaat et al., 2024	Experimental	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included
Bem et al., 2018	Experimental	Y	Y	U	Y	U	Y	U	U	Y	U	Included
Freitas et al., 2018	Experimental	Y	Y	U	Y	U	Y	U	Y	U	N	Included
Dastaha et al., 2021	Experimental	Y	Y	Y	U	U	Y	U	U	U	Y	Included
Dareini et al., 2024	Experimental	Y	Y	Y	Y	U	Y	U	U	U	N	Included
Abreu et al., 2016	Experimental	Y	Y	Y	Y	U	Y	U	Y	U	Y	Included
Abdolmaleki and Heidarianpour, 2020	Experimental	Y	Y	Y	Y	U	Y	U	Y	U	N	Included

Abbreviations and interpretation: SYRCLE's RoB = Systematic Review Center for Laboratory Animal Experimentation's risk of bias tool; Seq. gen. = sequence generation; Alloc. conceal. = allocation concealment; Inv. blind. = investigator blinding; Y = Yes, indicating low risk of bias or adequate reporting; N = No, indicating high risk of bias or inadequate reporting; U = Unclear, indicating insufficient information to judge the domain.

improvements in glycemic control and insulin protocols (6–14 weeks) yield more pronounced sensitivity (3,13).

Exercise reduces or stabilizes body weight in diabetic rats, counteracting diabetes-induced weight loss (14,20). Treadmill exercise decreases visceral and epididymal fat mass (14,19). Treadmill exercise upregulates the expression of beneficial genes related to insulin signaling, metabolism, and inflammation (14,21). HIIT and moderate-intensity interval training modulate signaling pathways, such as the irisin/AMPK and leptin pathways, reducing pathological protein accumulation and inflammation (15,22,23). Exercise reduces pro-inflammatory markers and improves lipid profiles, although some lipid improvements may be non-significant (14,23).

In summary, the evidence-based conclusion from the included studies is that treadmill exercise has direct preclinical support for improving glycemic regulation, insulin sensitivity, adiposity-related outcomes, and selected molecular pathways in Wistar or *Rattus norvegicus* models of diabetes or diabetes-related metabolic dysfunctions.

4.4. Lactobacillus acidophilus and Probiotic-Related Interventions

Two studies discussing Lactobacillus acidophilus interventions were included in this review. The first involved the administration of a lyophilized probiotic extract (Lactobacillus acidophilus and Lactobacillus plantarum) at three different doses compared to metformin, and the second involved the administration of synbiotic biscuits (Lactobacillus acidophilus and a flour mix of sweet potatoes, banana corm, and black soybeans) at two different doses compared to metformin. Lyophilized probiotic extracts (Lactobacillus acidophilus and Lactobacillus plantarum) significantly lowered fasting blood sugar levels and improved insulin sensitivity in diabetic rats. Probiotics reduce inflammatory cytokines, such as TNF-α, and slow diabetes-associated weight loss. These effects are linked to the modulation of oxidative stress and innate inflammation, suggesting that probiotics are a complementary approach to improve gut microbiota and metabolic health in T2DM (2).The selected articles did not contain any information or data related to Smallanthus sonchifolius or its effects on type 2 Diabetes Mellitus (T2DM) control. No studies, interventions, or results involving Smallanthus sonchifolius were found in the selected studies. Comparing other herbal interventions with similar constituents, Smallanthus sonchifolius showed antidiabetic effects by reducing blood glucose, improving insulin signaling, increasing GLP-1, reducing inflammation, decreasing the HOMA-IR index, and improving β-cell function in diabetic rats.

Synbiotic biscuits (created with Lactobacillus acidophilus and a composite fluor mix of sweet potatoes, banana corm and black soybeans) exhibit a moderate glycemic index and load, supporting balanced energy release and blood sugar regulation. Daily consumption reduced fasting blood glucose levels and improved body weight in diabetic rats. The intervention increases survival and proliferation of beneficial gut bacteria (Lactobacillus acidophilus), contributing to improved glucose metabolism and antioxidant effects (1).

Probiotic formulations have demonstrated promising antidiabetic effects in preclinical T2DM models. The combination of these supplements with structured exercise amplifies metabolic improvements, including enhanced glycemic control, insulin sensitivity, lipid metabolism, and inflammation reduction. These findings support integrative lifestyle strategies incorporating nutraceutical supplementation for improved T2DM management.

4.5. Smallanthus sonchifolius and Related Nutraceutical Evidence

No eligible study in the final selected articles directly evaluated *Smallanthus sonchifolius* in Wistar rat models of type 2 diabetes mellitus. This is a key limitation of the evidence base and should be interpreted as an important negative finding in this scoping review.

Accordingly, this review cannot conclude that *Smallanthus sonchifolius* has a direct antidiabetic effect based on the selected studies. Statements regarding the potential role of *Smallanthus sonchifolius* must be framed as indirect or theoretical. Its proposed relevance is based on biological plausibility and evidence from related nutraceutical, polyphenol-rich, or prebiotic interventions rather than direct evidence from eligible *Smallanthus sonchifolius* studies.

Some included studies evaluated nutraceutical or functional interventions other than *Smallanthus sonchifolius*, including polyphenol-rich extracts or dietary strategies combined with exercise or used as metabolic interventions. These studies suggest that nutraceuticals with antioxidant, anti-inflammatory, or prebiotic properties may improve glucose regulation, insulin sensitivity, lipid metabolism, oxidative stress, and inflammatory pathways in diabetic animal models.

These nutraceutical findings provide only an indirect rationale for future investigations of *Smallanthus sonchifolius*. They did not establish the direct efficacy of *Smallanthus sonchifolius*. A more accurate interpretation is that evidence from polyphenol-rich or prebiotic-related nutraceutical interventions suggests a possible scientific basis for future studies testing yacon-derived preparations in Wistar rat models of type 2 diabetes mellitus.

4.6. Combined Interventions

Several included studies evaluated combined or multimodal interventions. However, the combinations identified in the selected studies generally involved treadmill exercise with other nutraceuticals, dietary strategies, or experimental approaches that did not directly correspond to the target combinations of this review.

No eligible study directly evaluated treadmill exercise combined with *Smallanthus sonchifolius*. No eligible study directly evaluated treadmill exercise combined with *Lactobacillus acidophilus*. No eligible study directly evaluated the combination of *Smallanthus sonchifolius* and *Lactobacillus acidophilus*. Most importantly, no eligible study directly investigated a single integrated protocol combining treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus* in Wistar rat models of type 2 diabetes mellitus.

This absence of direct evidence is a major finding of the present scoping review. The available studies support the individual role of treadmill exercise and provide limited direct evidence for *Lactobacillus acidophilus*-containing interventions. However, direct evidence for *Smallanthus sonchifolius* has not been identified, and no study has tested the full three-component intervention.

Therefore, the discussion of combined interventions should be separated into two levels. The first level is evidence-based: the selected studies show that treadmill exercise has direct support, and *Lactobacillus acidophilus* has limited direct support. The second level is conceptual: the proposed combination of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus* is biologically plausible because these interventions may target complementary pathways; however, this combination remains untested in the eligible literature.

Table 2. ARRIVE-based reporting quality assessment of the included animal studies

Author, Year	Score based on key point ARRIVE						Overall appraisal
	Randomization	Blinding	Sample size	Animal details	Housing/handling	Statistics	
Ziarniak et al., 2021	Y	Y	Y	Y	Y	Y	Included
Zhao *et al.*, 2023	U	Y	U	Y	Y	Y	Included
Syahputra et al., 2023	U	Y	U	Y	Y	Y	Included
Sheikh et al., 2025	U	Y	U	Y	Y	Y	Included
Sharafifard *et al.*, 2025	U	Y	U	Y	Y	Y	Included
Saadatzadeh et al., 2025	U	Y	U	Y	Y	Y	Included
Hossein et al., 2023	Y	Y	Y	Y	Y	Y	Included
Moody et al., 2024	U	U	Y	Y	Y	Y	Included
Hoseini & Gharzi, 2025	Y	Y	U	Y	Y	Y	Included
Machrina et al., 2019	U	U	U	Y	Y	Y	Included
Lin et al., 2024	U	Y	U	Y	Y	Y	Included
Kılıç et al., 2025	Y	Y	U	Y	Y	Y	Included
Khaledi & Gharzi, 2023	U	Y	Y	Y	Y	Y	Included
Kazemia and Zahediasl, 2018	Y	Y	U	Y	Y	Y	Included
Hoseini et al., 2025	U	Y	U	Y	Y	Y	Included
Hamid et al., 2024	Y	Y	U	Y	Y	Y	Included
Gharaat et al., 2024	U	Y	Y	Y	Y	Y	Included
Bem et al., 2018	U	Y	U	Y	Y	Y	Included
Freitas et al., 2018	U	Y	U	Y	Y	Y	Included
Dastaha et al., 2021	U	Y	U	Y	Y	Y	Included
Dareini et al., 2024	U	Y	U	Y	Y	Y	Included
Abreu et al., 2016	U	Y	U	Y	Y	Y	Included
Abdolmaleki & Heidarianpour, 2020	U	Y	U	Y	Y	Y	Included

Abbreviations and interpretation: ARRIVE = Animal Research: Reporting of In Vivo Experiments; Y = Yes, indicating that the item was adequately reported; N = No, indicating that the item was not reported or reported inadequately; U = Unclear, indicating that insufficient information was available to determine whether the item was adequately reported.

However, this proposed synergy is an extrapolation and should not be presented as an evidence-based finding. The appropriate conclusion is that the selected literature provides a rationale for future combined intervention studies but does not yet provide direct experimental confirmation of the combined protocol.

4.7. Risk of Bias and Reporting Quality

The methodological quality of the included animal studies was assessed using SYRCLE's Risk of Bias Tool. Overall, all included studies were retained for synthesis, although the risk of bias profiles varied across studies. Several studies adequately reported important methodological elements, such as experimental design, disease induction, intervention protocol, and outcome measurement. However, some domains were frequently judged as unclear because the articles did not provide sufficient details regarding allocation concealment, random housing, blinding of investigators, or outcome assessment.

Complementary reporting appraisal using ARRIVE-related key items showed that most studies reported animal characteristics, intervention details, outcome measures, and statistical analyses. However, the reporting of sample size calculation, randomization procedures, and blinding was inconsistent. These limitations did not lead to exclusion but were considered during interpretation of the evidence because incomplete reporting may reduce confidence in internal validity and reproducibility.

Risk of bias and reporting assessments indicate that the evidence base is useful for mapping intervention characteristics and biological outcomes; however, caution is required when interpreting the strength of causal inference. Incomplete reporting of randomization, allocation concealment, blinding, and sample size calculation limits reproducibility and may increase the possibility of bias in some studies.

4.8. Research Gaps and Future Directions

The most consistent evidence identified in this review was related to treadmill exercises. Treadmill-based interventions have beneficial effects on glycemic control, insulin sensitivity, body composition, lipid metabolism, oxidative stress, inflammatory markers, and selected molecular pathways. Evidence for *Lactobacillus acidophilus* was limited but suggested potential benefits on fasting blood glucose, insulin resistance, inflammation, body weight, and fecal *Lactobacillus* counts.

The major research gap was the absence of eligible studies directly examining *Smallanthus sonchifolius* in Wistar rat models of type 2 diabetes mellitus. Another major gap was the absence of direct studies evaluating combined protocols involving treadmill exercise and *Smallanthus sonchifolius*, treadmill exercise and *Lactobacillus acidophilus*, *Smallanthus sonchifolius* and *Lactobacillus acidophilus*, or the three-component combination.

Therefore, future studies should be designed to test these combinations directly rather than relying on extrapolation from separate intervention studies. Experimental protocols should clearly define the diabetes induction model, treadmill intensity and duration, *Smallanthus sonchifolius* preparation type and dose, *Lactobacillus acidophilus* strain and viable count, intervention duration, comparator groups, and primary outcomes.

Future research should also include mechanistic outcomes that reflect the proposed multimodal pathway, including fasting blood glucose, insulin, HOMA-IR, HOMA-β, lipid profile, body weight, gut microbiota composition, short-chain fatty acid concentrations, oxidative stress markers, inflammatory cytokines, and molecular markers such as NLRP3-related inflammatory signaling.

Such studies would allow investigators to determine whether the proposed treadmill–*Smallanthus sonchifolius*–*Lactobacillus acidophilus* protocol produces additive, synergistic, or non-superior effects compared with single or partial interventions. Until such studies are conducted, combined interventions should be described as promising but unconfirmed research directions.

4.9. Summary of Main Findings

This scoping review identified 23 eligible experimental studies involving Wistar or *Rattus norvegicus* models of diabetes or diabetes-related metabolic dysfunction. The evidence was dominated by treadmill exercise studies, which consistently showed improvements in glycemic control, insulin sensitivity, body composition, inflammatory regulation, and molecular pathways. Two studies evaluated *Lactobacillus acidophilus*-containing interventions and reported favorable effects on fasting blood glucose, insulin sensitivity, inflammatory markers, body weight, and fecal *Lactobacillus* counts.

In contrast, no eligible study directly evaluated *Smallanthus sonchifolius* according to the predefined criteria. Therefore, the potential antidiabetic role of *Smallanthus sonchifolius* should be presented as indirect and hypothesis-generating, based on related nutraceutical, polyphenol-rich, or prebiotic evidence rather than direct evidence from the included studies.

No eligible study tested treadmill exercise combined with *Smallanthus sonchifolius*, treadmill exercise combined with *Lactobacillus acidophilus*, *Smallanthus sonchifolius* combined with *Lactobacillus acidophilus*, or the complete protocol involving all three interventions. This absence of direct combined intervention evidence is one of the central findings of this review and should not be overstated as proof of synergy.

Overall, the findings show that treadmill exercise has the strongest direct preclinical evidence among the target interventions, *Lactobacillus acidophilus* has limited but supportive evidence, and *Smallanthus sonchifolius* as well as the full multimodal intervention remain underexplored. The main contribution of this review is to distinguish evidence-based findings from conceptual extrapolation and to identify a clear research gap for integrated physical–nutraceutical–probiotic protocols in Wistar rat models of type 2 diabetes mellitus.

5. Discussion

This scoping review mapped the available preclinical evidence on treadmill exercise, *Lactobacillus acidophilus*-containing interventions, *Smallanthus sonchifolius*-related nutraceutical evidence, and combined physical–nutraceutical–probiotic strategies in Wistar or *Rattus norvegicus* models of type 2 diabetes mellitus. The main finding was that the evidence base was uneven. Direct evidence was strongest for treadmill exercise, limited but supportive for *Lactobacillus acidophilus*, and absent for *Smallanthus sonchifolius* according to the predefined eligibility criteria. Most importantly, no eligible study directly tested the full combined protocol of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus*. Therefore, the combined intervention should be interpreted as a hypothesis-generating framework rather than an evidence-based therapeutic strategy.

5.1. Direct Evidence for Treadmill Exercise in Diabetic Rat Models

Treadmill exercise was the most consistently represented intervention in the studies included. Twenty-one of the 23 eligible studies evaluated treadmill-based exercise protocols, including moderate-intensity continuous training, endurance training, high-intensity interval training, and other structured aerobic protocols. Across studies, treadmill exercise generally improved fasting blood glucose, glucose tolerance, insulin resistance indices, body composition, lipid-related parameters, oxidative stress, inflammatory markers, and selected molecular pathways [3, 13-23, 25-32].

The biological plausibility of these findings is strong because aerobic exercise directly targets major metabolic defects in type 2 diabetes. Skeletal muscle is the largest site of insulin-stimulated glucose disposal, and repeated aerobic contractions can enhance glucose uptake through insulin-dependent and insulin-independent mechanisms. Exercise-induced activation of AMPK, improvement in mitochondrial oxidative capacity, and modulation of GLUT4-related pathways provide mechanistic explanations for the observed improvements in glycemic control and insulin sensitivity [17, 19, 22].

Several studies have shown that treadmill exercise affects hepatic glucose metabolism. Endurance or interval training modulates pathways such as AKT–FOXO1–PEPCK, reduces gluconeogenic signaling, increases liver glycogen storage, and improves insulin signaling [3, 16]. These mechanisms are relevant because excessive hepatic glucose production is a central contributor to fasting hyperglycemia in type 2 diabetes. Therefore, treadmill exercise appears to act at both peripheral and hepatic levels by increasing glucose utilization and reducing endogenous glucose output.

The benefits of exercise are not limited to glucose metabolism. Several studies reported reduced visceral or epididymal fat mass, improved lipid profiles, decreased inflammatory markers, and lower oxidative stress [14, 20, 22, 23, 25]. These effects are important because type 2 diabetes is not merely a hyperglycemic disorder but a systemic metabolic-inflammatory condition involving adipose tissue dysfunction, hepatic insulin resistance, mitochondrial stress, and chronic low-grade inflammation. The consistency of these findings supports treadmill exercise as the intervention with the strongest direct preclinical evidence in this study.

However, the interpretation of these results must be approached with caution. Treadmill protocols vary substantially in term of duration, frequency, speed, incline, and intensity. Diabetes induction methods also differed across studies, including streptozotocin, streptozotocin–nicotinamide, high-fat diet, and combined diet–chemical models. These methodological differences limit direct comparisons across studies and prevent quantitative synthesis. Nevertheless, the direction of effect across most studies supports treadmill exercise as a reproducible non-pharmacological intervention in diabetic rat models.

5.2. Limited Direct Evidence for Lactobacillus acidophilus and Probiotic Related Interventions

Only two eligible studies directly evaluated *Lactobacillus acidophilus*-containing interventions. One study used a lyophilized probiotic extract containing *Lactobacillus acidophilus* and *Lactobacillus plantarum*, while another used synbiotic biscuits containing *Lactobacillus acidophilus* in a fiber-rich food matrix [1, 2]. These studies reported improvements in fasting blood glucose, insulin sensitivity, inflammatory markers, body weight, and fecal *Lactobacillus* counts.

Therefore, the direct evidence for *Lactobacillus acidophilus* is supportive but limited. A study on probiotic extract suggests that bacterial metabolites may influence glycemic and inflammatory pathways through antioxidant activity, reduction of TNF-α, and improvement in insulin resistance [2]. A previous study on synbiotic biscuits suggested that a food matrix containing *Lactobacillus acidophilus* and fermentable substrates can improve glycemia and increase fecal lactobacilli counts [1]. These results are consistent with the broader concept that probiotics and synbiotics may influence diabetes-related outcomes by modulating the gut microbiota, intestinal barrier function, metabolic endotoxemia, short-chain fatty acid production, oxidative stress, and inflammatory signaling.

Despite these encouraging findings, the evidence remains limited. The two eligible studies differed in probiotic formulation, dosage, delivery matrix, duration, and comparator. One used a cell-free or lyophilized probiotic-derived preparation, whereas the other used a live probiotic-containing synbiotic food product. These differences make it difficult to isolate the specific effects of *Lactobacillus acidophilus*. In the synbiotic study, the observed metabolic effects may have resulted from the combined influence of probiotic organisms, prebiotic substrates, glycemic load, and food matrix. Therefore, *Lactobacillus acidophilus* should be described as having limited direct preclinical support, not as a fully established antidiabetic intervention in this evidence base.

5.3. Smallanthus sonchifolius: Abesence of Direct Evidence and Indirect Nutraceutical Rationale

A major finding of this review is that no eligible study directly evaluated *Smallanthus sonchifolius* in Wistar rat models of type 2 diabetes mellitus according to the predefined inclusion criteria. This absence of direct evidence should be emphasized as a central gap in the evidence. Consequently, this review cannot conclude that *Smallanthus sonchifolius* has a direct antidiabetic effect based on the selected studies.

Therefore, the potential relevance of *Smallanthus sonchifolius* should be discussed only as indirect and hypothesis-generating. Yacon contains fructo-oligosaccharides and polyphenolic compounds, which provide a theoretical basis for its possible metabolic effects. Based on general phytochemical knowledge, fructo-oligosaccharides in yacon are hypothesized to act as prebiotic substrates that support short-chain fatty acid production, while polyphenols are theorized to influence oxidative stress, inflammation, glucose transport, and insulin signaling. However, these mechanisms where not directly demonstrated in nay eligible study in this review.

Some included studies evaluated other nutraceuticals, particularly polyphenol-rich preparations such as *Euterpe oleracea* seed extract, either alone or in combination with exercise [4, 25]. These studies reported improvements in glucose metabolism, lipid profiles, hepatic steatosis, oxidative stress, inflammatory markers, and insulin signaling pathways. These findings suggest that polyphenol-rich or prebiotic-like interventions may provide a scientific rationale for future studies on yacon-derived products. However, these nutraceutical findings should not be interpreted as direct evidence for *Smallanthus sonchifolius*. They only support the plausibility of future investigations.

This distinction is important to avoid overinterpretation. The correct interpretation is not that *Smallanthus sonchifolius* has been proven effective in the selected Wistar rat studies, but that the biological characteristics of yacon and the indirect evidence from related nutraceuticals justify targeted experimental testing. Future studies should directly evaluate yacon leaf and tuber extracts, purified fructooligosaccharide fractions, and standardized yacon preparations using well-characterized type 2 diabetes models.

5.4. Combined Interventions: Evidence-Based Findings Versus Conceptual Extrapolation

This review also identified an important gap regarding combined interventions. No eligible study directly evaluated treadmill exercise combined with *Smallanthus sonchifolius*. No eligible study directly evaluated treadmill exercise combined with *Lactobacillus acidophilus*. No eligible studies evaluated the combination of *Smallanthus sonchifolius* and *Lactobacillus acidophilus*. Most importantly, no eligible study tested the full three-component intervention combining treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus*.

Therefore, the discussion of combined interventions must be separated into two levels. The first level is evidence-based. The selected studies support treadmill exercise as a direct intervention for improving metabolic outcomes in diabetic rat models. The selected studies also provided limited direct evidence for *Lactobacillus acidophilus*-containing interventions. The second level is conceptual. The proposed combination of treadmill exercise, yacon-derived nutraceuticals, and *Lactobacillus acidophilus* is mechanistically plausible but remains untested in eligible literature.

The proposed combination of treadmill exercise, yacon-derived nutraceuticals, and *Lactobacillus acidophilus* is mechanistically plausible but remains untested in the eligible literature. Conceptually, treadmill exercise may improve skeletal muscle glucose uptake, insulin sensitivity, mitochondrial function, and systemic inflammatory regulation. *Smallanthus sonchifolius* may provide prebiotic fructooligosaccharides and antioxidant phytochemicals, although this was not directly demonstrated in the selected studies. *Lactobacillus acidophilus* may contribute to gut microbial modulation, intestinal barrier function, and inflammatory regulation. Together, these interventions could theoretically target multiple organs and pathways involved in type 2 diabetes, including skeletal muscle, liver, adipose tissue, pancreas, gut microbiota, and immune-inflammatory signaling.

However, this proposed synergy remains an extrapolation. It should not be presented as an established finding of this review. The available literature provides a rationale for future combined intervention studies but does not provide direct experimental confirmation of additive or synergistic effects of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus*. This distinction strengthens the scientific validity of the manuscript and aligns the conclusions with the actual evidence mapped in the review.

5.5. Overall Interpretation

Overall, the findings indicate that treadmill exercise is directly supported by preclinical evidence as a non-pharmacological intervention for improving glycemic regulation, insulin sensitivity, adiposity-related outcomes, lipid metabolism, inflammation, oxidative stress, and selected molecular pathways in diabetic rats. *Lactobacillus acidophilus* has limited but supportive direct evidence, particularly for improving glycemia, insulin resistance, inflammation, body weight, and fecal lactobacilli counts. In contrast, *Smallanthus sonchifolius* was not directly evaluated in the eligible studies and should be discussed only as an indirect, biologically plausible, and hypothesis-generating nutraceutical candidate.

The proposed combination of treadmill exercise, *Smallanthus sonchifolius*, and *Lactobacillus acidophilus* remains untested. Its rationale is mechanistically coherent because the three interventions may target complementary aspects of type 2 diabetes pathophysiology, including muscle glucose uptake, hepatic glucose production, gut microbiota, short-chain fatty acid production, oxidative stress, and inflammatory signaling. However, direct experimental validation is required before this combined strategy can be described as effective. Future well-designed preclinical studies are needed to test this integrated physical–nutraceutical–probiotic protocol and determine whether it offers benefits beyond single or partial interventions.

6. Strength, Limitations, and Implication for Further Research

This scoping review had several strengths. It systematically mapped evidence from three databases over a ten-year publication window and used predefined eligibility criteria to identify relevant preclinical studies. It also incorporated SYRCLE and ARRIVE-based appraisals to evaluate methodological transparency and reporting completeness. Another strength is the explicit distinction between direct evidence and conceptual extrapolation, which is essential when discussing *Smallanthus sonchifolius* and combined interventions.

This review also has some limitations. First, only studies published in English or Indonesian were included. The authors did not search non-English database (e.g., Chinese, Spanish, or Portuguese databases), which may have excluded relevant studies on yacon or probiotics from regions where this interventions are more commonly studied. Second, gray literature and unpublished studies were not searched, which may have resulted in publication bias favoring positive findings. Third, substantial heterogeneity in animal models (e.g., STZ-only, STZ-nicotinamide, high-fat diet, combined diet-chemical models), diabetes induction protocols, intervention duration, exercise intensity, probiotic formulation, nutraceutical composition, and outcome measures prevented quantitative synthesis. Meta-analysis was not feasible due to inconsistent outcome reporting and lack of standardized protocols across studies. Therefore, narrative synthesis was the only appropriate approach. Fourth, the absence of eligible *Smallanthus sonchifolius* studies is a major limitation. The review's tittle and research question prospectively included yacon as a core intervention, but the search identified no eligible studies that directly evaluated yacon in Wistar rat models of type 2 diabetes according to the predefined criteria. Consequently, all statements about yacon in this review are indirect based on related nutraceutical evidence or biological plausibility, and should not be interpreted as evidence-based conclusions about yacon's efficacy. Fifth, because the included evidence was derived from animal models, translation to human type 2 diabetes requires caution.

The SYRCLE and ARRIVE assessments showed that the included studies were useful for mapping intervention characteristics and biological outcomes; however, several methodological and reporting limitations were identified. Many studies reported animal characteristics, intervention protocols, outcome measures, and statistical analyses. However, several domains related to allocation concealment, random housing, investigator blinding, random outcome assessment, outcome assessor blinding, and sample size calculation were often unclear.

These limitations are common in preclinical animal studies but have significant implications. Incomplete reporting of randomization and blinding may increase the risk of selection, performance, and detection bias. The lack of sample size justification may reduce confidence in the statistical robustness of the findings. Inconsistent reporting of housing, handling, and intervention details may reduce reproducibility, especially for exercise and probiotic protocols where environmental stress, intensity, strain viability, and dosing schedules can influence outcomes.

Methodological appraisal was not used as an exclusion criterion because the purpose of the scoping review was to map the available evidence rather than exclude studies based on quality. Nevertheless, these appraisal results should be considered when interpreting the strength of evidence. Treadmill exercise has the strongest direct evidence in terms of quantity and consistency; however, protocol heterogeneity and incomplete reporting still limit the ability to define an optimal regimen. *Lactobacillus acidophilus* has limited direct evidence, and the lack of direct *Smallanthus sonchifolius* studies prevents efficacy conclusions for yacon-based interventions.

The central contribution of this review is the identification of a clear research gap for integrated physical–nutraceutical–probiotic interventions in Wistar rat models of type 2 diabetes mellitus. Future studies should directly test the combined protocol rather than inferring its effects from separate intervention studies. Such studies should include appropriate comparator groups, including diabetic control, treadmill-only, yacon-only, *Lactobacillus acidophilus*-only, partial combination, and full three-component intervention groups. This design allows investigators to distinguish between additive, synergistic, neutral, or antagonistic interactions.

Future experimental protocols should clearly define the diabetes induction model, animal strain, sex, age, diet composition, treadmill intensity, duration, frequency, yacon preparation, yacon dose, probiotic strain, viable count, formulation stability, intervention duration, and timing of outcome measurements. Standardization is essential because variations in treadmill intensity, yacon phytochemical composition, fructooligosaccharide content, probiotic viability, and diabetes induction method may substantially affect outcomes.

Outcome selection should reflect the proposed multimodal mechanisms. At a minimum, future studies should measure fasting blood glucose, insulin, HOMA-IR, HOMA-β, glucose tolerance, lipid profile, body weight, visceral adiposity, inflammatory cytokines, oxidative stress markers, gut microbiota composition, short-chain fatty acid concentrations, and pancreatic or hepatic molecular markers. Given the role of inflammation in type 2 diabetes, NLRP3 inflammasome-related markers may also be important mechanistic endpoints. These outcomes will allow future studies to determine whether the combined intervention affects the metabolic, microbial, inflammatory, and molecular dimensions of diabetes simultaneously.

7. Conclusion

This scoping review mapped 23 eligible preclinical studies on physical, probiotic, and nutraceutical interventions in Wistar or *Rattus norvegicus* models of type 2 diabetes mellitus. The principal finding was that the available evidence was not evenly distributed across the target interventions. Treadmill exercise had the strongest direct evidence, while *Lactobacillus acidophilus*-containing interventions had limited but supportive direct evidence. No eligible study directly evaluated the *Smallanthus sonchifolius* or the full combined treadmill–*Smallanthus sonchifolius*–*Lactobacillus acidophilus* protocol.

The most generalizable principle revealed by the included studies is that structured treadmill exercise can improve several interrelated components of diabetic metabolic dysfunction in rats. Across the selected studies, treadmill-based protocols were associated with improved fasting blood glucose, glucose tolerance, insulin resistance indices, lipid or adiposity-related parameters, oxidative stress, inflammatory regulation, and molecular pathways related to skeletal muscle and hepatic metabolism. These findings are consistent with the established role of aerobic exercise in enhancing peripheral glucose uptake, improving insulin signalling, and reducing metabolic inflammatory stress.

Direct evidence for *Lactobacillus acidophilus* was limited to two eligible studies. These studies reported favourable effects on glycaemia, insulin sensitivity, inflammatory markers, body weight, and faecal lactobacilli counts. However, differences in formulation, dose, delivery matrix, and intervention duration limit the generalizability of this finding. Therefore, *Lactobacillus acidophilus* should be considered as a promising but preliminary probiotic or synbiotic candidate for diabetic rat models.

A major exception and unresolved problem identified in this review is the absence of eligible direct evidence for *Smallanthus sonchifolius*. Therefore, this review cannot conclude that *Smallanthus sonchifolius* has a direct antidiabetic effect in Wistar rats. Its potential relevance remains indirect and hypothesis-generating, based on its known fructo-oligosaccharide and polyphenol content and related evidence from other prebiotic or polyphenol-rich nutraceutical interventions.

Another central research gap is the absence of direct studies evaluating treadmill exercise combined with *Smallanthus sonchifolius*, treadmill exercise combined with *Lactobacillus acidophilus*, *Smallanthus sonchifolius* combined with *Lactobacillus acidophilus*, or the complete three-component protocol. Thus, the proposed combined intervention should not be described as an evidence-based synergistic strategy. The theoretical value of this lies in providing a mechanistically plausible framework for targeting multiple dimensions of type 2 diabetes pathophysiology, including skeletal muscle glucose uptake, hepatic glucose production, gut microbiota modulation, short-chain fatty acid production, oxidative stress, and inflammatory signaling.

The theoretical and practical significance of this review lies in its clear distinction between direct preclinical evidence and conceptual extrapolation. Unlike studies that evaluate single interventions or partial combinations, this scoping review identified the lack of direct evidence for an integrated physical–nutraceutical–probiotic protocol. This finding provides a focused rationale for future experimental work rather than a definitive conclusion regarding the combined efficacy.

Future studies should directly test the proposed combined protocol using a standardized and reproducible design. The recommended elements include a clearly defined type 2 diabetes induction model, standardized treadmill intensity and duration, chemically characterized *Smallanthus sonchifolius* preparations, specified *Lactobacillus acidophilus* strains and viable counts, adequate comparator groups, and mechanistic outcomes such as fasting blood glucose, insulin, HOMA-IR, HOMA-β, lipid profile, gut microbiota composition, short-chain fatty acids, oxidative stress markers, inflammatory cytokines, and NLRP3-related signalling. Such studies are required to determine whether the combined protocol produces additive, synergistic, neutral, or non-superior effects compared to single or partial interventions.

Declarations

Author Contributions

Conceptualization, IG Alam and A Farmawati; methodology, IG Alam and A Farmawati; software, IG Alam; validation, IG Alam, A Farmawati and LA Lestari; formal analysis, IG Alam; investigation, LA Lestari; resources, IG Alam; data curation, IG Alam; writing—original draft preparation, IG Alam; writing—review and editing, A Farmawati and LA Lestari; visualization, IG Alam; supervision, A Farmawati; project administration, IG Alam. All authors have read and agreed to the published version of this manuscript.

Funding

This work was not supported by any funding agency

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript. In addition, the authors have completely observed the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies.

Acknowledgements

During the preparation of this manuscript, the authors used AI to enhance writing clarity. After using the AI, the authors reviewed and edited the content as needed and took full responsibility for its publication.

References

[1] MOODY S. D., HANIDAH I., LEMBONG E., WULANDARI E., HARLINA P. W., KHARISMA S. F., YARLINA V. P., and LANI M. N. Synbiotic biscuit potential reducing blood sugar levels in Wistar white rats. *Current Research in Nutrition and Food Science,* 2024,12(1): 339-348. https://dx.doi.org/10.12944/CRNFSJ.12.1.28

[2] SAADATZADEH A., EMAMIFAR S. M. K., MARD S. A., AHANGARPOUR A., ANGALI K. A., and MEHDIALAMDARLOU S. Probiotic preserving extract supplementation as a novel attitude in managing diabetes mellitus. *BMC Complementary Medicine and Therapies*. 2025, 25(243): 1-10. https://doi.org/10.1186/s12906-025-04974-z

[3] ABDOLMALEKI F., and HEIDARIANPOUR A. Endurance exercise training restores diabetes - induced alteration in circulating Glycosylphosphatidylinositol - specific phospholipase D levels in rats. *Diabetol Metab Syndr*. 2020, 12: 43. https://doi.org/10.1186/s13098-020-00553-z

[4] DE BEM G. F., COSTA C. A., SANTOS I. B., CORDEIRO V. S. C., COSTA L., CARVALHO L. C. R. M., DE SOUZA M. A. V., SOARES R. A., DE SOUSA P. J. C., OGNIBENE D. T., RESENDE A. C., and DE MOURA R. S. Antidiabetic effect of Euterpe oleracea Mart extract and exercise training on high-fat diet and streptozotocin-induced diabetic rats : A positive interaction. *Plos ONE*, 2018, 13(6): e0199207. https://doi.org/10.1371/journal.pone.0199207

[5] ARKSEY H., and O’MALLEY L. Scoping studies : towards a methodological framework. *International Journal of Social Research*

Methodology, 2005, 8(1): 19-32. https://doi.org/10.1080/1364557032000119616
[6] TRICCO A. C., LILLIE E., ZARIN W., O'BRIEN K. K., COLQUHOUN H., LEVAC D., MOHER D., PETERS M. D. J., HORSLEY T., WEEKS L., HEMPEL S., AKL E. A., CHANG C., MCGOWAN J., STEWART L., HARTLING L., ALDCROFT A., WILSON M. G., GARRITTY C., LEWIN S., GODFREY C. M., MACDONALD M. T., LANGLOIS E. V., SOARES-WEISER K., MORIARTY J., CLIFFORD T., TUNÇALP Ö., and STRAUS S. E. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine*, 2018, 169(7): 467-473. https://doi.org/10.7326/M18-0850
[7] HADDAWAY N. R., PAGE M. J., PRITCHARD C. C., and MCGUINNESS L. A. PRISMA2020 An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*, 2022, 18(2):e1230). https://doi.org/10.1002/cl2.1230
[8] HOOIJMANS C. R., ROVERS M. M., DE VRIES R. B. M., LEENAARS M., RITSKES-HOITINGA M., and LANGENDAM M. W. SYRCLE ' s risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014, 14:43. https://doi.org/10.1186/1471-2288-14-43
[9] SARGEANT J. M., and O'CONNOR A. M. Scoping Reviews , Systematic Reviews , and Meta-Analysis : Applications in Veterinary Medicine. *Frontiers in Veterinary Science*, 2020, 7:11. https://doi.org/10.3389/fvets.2020.00011
[10] LIN L., LI S., GUO Z., FANG P., FENG Y., QI C., WANG M., XIAO L., CHEN M., and WANG T. The efficacy and potential mechanism of the acupuncture treatment for type 2 diabetes mellitus : A systematic review and meta-analysis of data from animal models. *Front. Endocrinol*. 2025, 16:1627061. https:// doi.org/10.3389/fendo.2025.1627061.
[11] PERCIE DU SERT N., AHLUWALIA A., ALAM S., AVEY M. T., BAKER M., BROWNE W. J., CLARK A., CUTHILL I. C., DIRNAGL U., EMERSON M., GARNER P., HOLGATE S. T., HOWELLS D. W., HURST V., KARP N. A., LAZIC S. E., LIDSTER K., MACCALLUM C. J., MACLEOD M., PEARL E. J., PETERSEN O. H., RAWLE F., REYNOLDS P., ROONEY K., SENA E. S., SILBERBERG S. D., STECKLER T., and WÜRbel H. Reporting animal research : Explanation and elaboration for the ARRIVE guidelines 2.0. *PLOS BIOLOGY*, 2020. 18(7): e3000411. https://doi.org/10.1371/journal.pbio.3000411
[12] PERCIE DU SERT N., HURST V., AHLUWALIA A., ALAM S., AVEY M. T., BAKER M., BROWNE W. J., CLARK A., CUTHILL I. C., DIRNAGL U., EMERSON M., GARNER P., HOLGATE S. T., HOWELLS D. W., KARP N. A., LAZIC S. E., LIDSTER K., MACCALLUM C. J., MACLEOD M., PEARL E. J., PETERSEN O. H., RAWLE F., REYNOLDS P., ROONEY K., SENA E. S., SILBERBERG S. D., STECKLER T., and WÜRbel H. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLOS BIOLOGY,* 2020. 18(7): e3000410. https://doi.org/10.1371/journal.pbio.3000410
[13] DASTAH S., TOFIGHI A., and BABAEI S. The effect of aerobic exercise on the expression of mir-126 and related target genes in the endothelial tissue of the cardiac muscle of diabetic rats. *Microvasc Res,* 2021, 138: 104212. https://doi.org/10.1016/j.mvr.2021.104212
[14] KAZEMI F., and ZAHEDIASL S. Effects of exercise training on adipose tissue apelin expression in streptozotocin-nicotinamide induced diabetic rats. *Gene*, 2018, 662: 97–102. https://doi.org/10.1016/j.gene.2018.04.003
[15] REZAEI M. H., RASHIDIAN E., MADADIZADEH M., AMIRI M., and AALI J. Leptin Signaling Could Mediate Hippocampal Decumulation of Beta - Amyloid and Tau Induced by High - Intensity Interval Training in Rats with Type 2 Diabetes. *Cell Mol Neurobiol*, 2023, 43(7): 3465–78. https://doi.org/10.1007/s10571-023-01357-1
[16] SHARAFIFARD F., KAZEMINASAB F., GHANBARI M., GHAEDI K., and ROSENKRANZ S. K. The combined effects of high- intensity interval training and time-restricted feeding on the AKT / FOXO1 / PEPCK pathway in diabetic rats. *Nature Portfolio-Sci Rep.* 2025, 15: 13898. https://doi.org/10.1038/s41598-025-96703-2
[17] MACHRINA Y., PURBA A., LINDARTO D., and MASKOEN A. M. Exercise Intensity Alter Insulin Receptor Gene Expression in Diabetic Type - 2 Rat Model. *Macedonian Journal of Medical Sciences*, 2019, 7(20): 3370–5. https://doi.org/10.3889/oamjms.2019.425
[18] SYAHPUTRA M., LINDARTO D., and RAMAYANI O. R. Effect of Moderate Intensity Continuous Training and Slow Type Interval Training to Gene Expression of TGF-β in Type 2 Diabetes Mellitus Model Wistar Rats. *MEd ARCH*, 2023, 77(1): 4–7. https://doi.org/10.5455/medarh.2023.77.4-7
[19] ABREU P., VITZEL K. F., MONTEIRO I. C. C. R., LIMA T. I., and QUEIROZ A. N. Effects of endurance training on reduction of plasma glucose during high intensity constant and incremental speed tests in Wistar rats. *Brazilian Journal of Medical and Biological Research*, 2016, 49(11): e5226. http://dx.doi.org/10.1590/1414-431X20165226
[20] GHARAAT M. A., CHOOBDARI H. R., and SHEYKLOUVAND M. Reducing cardiac apoptotic

indices oxidative stress for a healthier heart: Cardioprotective effects of aerobic training in diabetic rats. *ARYA Atheroscler*, 2024, 20(2):50–60. https://doi.org/10.48305/arya.2024.41976.2911
[21] KILIÇ Y., DALKILIÇ S., DALKILIÇ L. K., ÖZDEMIR E., UĞURLU F. M., and PALA R. Effects of aerobic and anaerobic exercise on glucose , lipid , and inflammation- related gene expression in the brain tissue of streptozotocin-induced diabetic rat model. *Diabetology & Metabolic Syndrome,* 2025, 17:324. https://doi.org/10.1186/s13098-025-01893-4
[22] LIN J., ZHANG X., SUN Y., XU H., LI N., WANG Y., TIAN X., ZHAO C., WANG B., ZHU B., and ZHAO R. Exercise ameliorates muscular excessive mitochondrial fission , insulin resistance and inflammation in diabetic rats via irisin / AMPK activation. *Nature Portfolio-Sci Rep*. 2024, 14: 10658. https://doi.org/10.1038/s41598-024-61415-6
[23] SHEIKH R., REZA M., ABOLFATHI F., REZA S., and TABATABAEI F. The impact of moderate - intensity interval training on the NLR family pyrin domain - containing protein - 3 inflammasome pathway in the liver tissue of male rats with type 2 diabetes. *Sport Sci Health,* 2025: 1-9. https://doi.org/10.1007/s11332-025-01477-9
[24] DÍAZ-NÚÑEZ D., and RIVERA-TORRES B. Review Article Exploratory Review On The Evidence of Andean Crops With Hypoglycemic Effect And Their Bioactive Components. *Rev Peru Med Exp Salud Publica*, 2023, 40(4): 474–84. https://doi.org/10.17843/rpmesp.2023.404.12672
[25] FREITAS G., DE BEM G. F., DA COSTA C. A., CORDEIRO V. S. C., SANTOS I. B., DE CARVALHO L. C. R. M., SOARES R. A., RIBEIRO J. H., DE SOUZA M. A. V., DE SOUSA P. J. C., OGNIBENE D. T., RESENDE A. C., and DE MOURA R. S. Euterpe oleracea Mart . (açaí) seed extract associated with exercise training reduces hepatic steatosis in type 2 diabetic male rats. *J Nutr Biochem,* 2018, 52: 70–81. https://doi.org/10.1016/j.jnutbio.2017.09.021
[26] HOSEINI R., and GHARZI A. Vitamin D and exercise improve VEGF-B production and IGF-1 levels in diabetic rats : insights the role of miR-1 suppression. *Nature report Sci Reports,* 2025, 15: 1328. https://doi.org/10.1038/s41598-024-81230-3
[27] HOSEINI Z., BEHPOUR N., and HOSEINI R. Aerobic training and vitamin D modulate hepatic miRNA expression to improve lipid metabolism and insulin resistance in type 2 diabetes. *Nature report Sci Rep,* 2025, 15: 16764. https://doi.org/10.1038/s41598-025-01757-x
[28] KHALEDI K., and GHARZI A. Effects of aerobic training and vitamin D supplementation on glycemic indices and adipose tissue gene expression in type 2 diabetic rats. *Nature report Sci Rep,* 2023, 13: 10218. https://doi.org/10.1038/s41598-023-37489-z
[29] HAMID R. R., HOSEINI R., and AHMED H. Impact of Combined Aerobic Training and Magnesium Supplementation on Serum Biomarkers and microRNA - 155 and microRNA - 21 Expression in Adipose Tissue of Type 2 Diabetic Rats : An Eight - Week Interventional Study. *Biol Trace Elem Res*, 2025, 203(2): 861–71. https://doi.org/10.1007/s12011-024-04186-5
[30] ZIARNIAK K., DUDEK M., MATUSZEWSKA J., BIJOCH Ł., SKRZYPSKI M., CELICHOWSKI J., and ŚLIWOWSKA J. H. Two weeks of moderate intensity locomotor training increased corticosterone concentrations but did not alter the number of adropin-immunoreactive cells in the hippocampus of diabetic type 2 and control rats. *Acta Histochemica,* 2021, 123(7): 151751. https://doi.org/10.1016/j.acthis.2021.151751
[31] Dareini F, Bijeh N, Alireza S, Kakhak H, Haj M. The impact of six weeks of continuous training and high - intensity intermittent training on pancreatic functions of Streptozocin - induced diabetic rats. *Sport Sci Health,* 2025, 21(2): 565–74. https://doi.org/10.1007/s11332-024-01288-4

参考文:

[1] MOODY S. D., HANIDAH I., LEMBONG E., WULANDARI E., HARLINA P. W., KHARISMA S. F., YARLINA V. P., and LANI M. N. 具有降低 Wistar 白鼠血糖水平潜力的合生元饼干。Current Research in Nutrition and Food Science, 2024, 12(1): 339-348. https://dx.doi.org/10.12944/CRNFSJ.12.1.28
[2] SAADATZADEH A., EMAMIFAR S. M. K., MARD S. A., AHANGARPOUR A., ANGALI K. A., and MEHDIALAMDARLOU S. 益生菌保存提取物补充作为管理糖尿病的一种新方法。BMC Complementary Medicine and Therapies, 2025, 25(243): 1-10. https://doi.org/10.1186/s12906-025-04974-z
[3] ABDOLMALEKI F., and HEIDARIANPOUR A. 耐力运动训练可恢复糖尿病诱导的大鼠循环糖基磷脂酰肌醇特异性磷脂酶 D 水平改变。Diabetology & Metabolic Syndrome, 2020, 12: 43. https://doi.org/10.1186/s13098-020-00553-z
[4] DE BEM G. F., COSTA C. A., SANTOS I. B., CORDEIRO V. S. C., COSTA L., CARVALHO L. C. R. M., DE SOUZA M. A. V., SOARES R. A., DE SOUSA P. J. C., OGNIBENE D. T., RESENDE A. C., and DE MOURA R. S. Euterpe oleracea Mart. 提取物与运动训练对高脂饮食和链脲佐菌素诱导糖尿病大鼠的抗糖尿病作用：一种积极的相互作用。PLOS ONE, 2018, 13(6): e0199207. https://doi.org/10.1371/journal.pone.0199207
[5] ARKSEY H., and O'MALLEY L. 范围研究：走向一种方法学框架。International

Journal of Social Research Methodology, 2005, 8(1): 19-32. https://doi.org/10.1080/1364557032000119616
[6] TRICCO A. C., LILLIE E., ZARIN W., O'BRIEN K. K., COLQUHOUN H., LEVAC D., MOHER D., PETERS M. D. J., HORSLEY T., WEEKS L., HEMPEL S., AKL E. A., CHANG C., MCGOWAN J., STEWART L., HARTLING L., ALDCROFT A., WILSON M. G., GARRITTY C., LEWIN S., GODFREY C. M., MACDONALD M. T., LANGLOIS E. V., SOARES-WEISER K., MORIARTY J., CLIFFORD T., TUNÇALP Ö., and STRAUS S. E. 范围综述 PRISMA 扩展版（PRISMA-ScR）：清单与说明。Annals of Internal Medicine, 2018, 169(7): 467-473. https://doi.org/10.7326/M18-0850
[7] HADDAWAY N. R., PAGE M. J., PRITCHARD C. C., and MCGUINNESS L. A. PRISMA2020：用于生成符合 PRISMA 2020 标准流程图的 R 软件包和 Shiny 应用程序，并通过交互性优化数字透明度和开放综合。Campbell Systematic Reviews, 2022, 18(2): e1230. https://doi.org/10.1002/cl2.1230
[8] HOOIJMANS C. R., ROVERS M. M., DE VRIES R. B. M., LEENAARS M., RITSKES-HOITINGA M., and LANGENDAM M. W. 用于动物研究的 SYRCLE 偏倚风险评估工具。BMC Medical Research Methodology, 2014, 14: 43. https://doi.org/10.1186/1471-2288-14-43
[9] SARGEANT J. M., and O'CONNOR A. M. 范围综述、系统综述和荟萃分析：在兽医学中的应用。Frontiers in Veterinary Science, 2020, 7: 11. https://doi.org/10.3389/fvets.2020.00011
[10] LIN L., LI S., GUO Z., FANG P., FENG Y., QI C., WANG M., XIAO L., CHEN M., and WANG T. 针灸治疗 2 型糖尿病的疗效及潜在机制：基于动物模型数据的系统综述与荟萃分析。Frontiers in Endocrinology, 2025, 16: 1627061. https://doi.org/10.3389/fendo.2025.1627061
[11] PERCIE DU SERT N., AHLUWALIA A., ALAM S., AVEY M. T., BAKER M., BROWNE W. J., CLARK A., CUTHILL I. C., DIRNAGL U., EMERSON M., GARNER P., HOLGATE S. T., HOWELLS D. W., HURST V., KARP N. A., LAZIC S. E., LIDSTER K., MACCALLUM C. J., MACLEOD M., PEARL E. J., PETERSEN O. H., RAWLE F., REYNOLDS P., ROONEY K., SENA E. S., SILBERBERG S. D., STECKLER T., and WÜRbel H. 动物研究报告：ARRIVE 指南 2.0 的解释与阐述。PLOS Biology, 2020, 18(7): e3000411. https://doi.org/10.1371/journal.pbio.3000411
[12] PERCIE DU SERT N., HURST V., AHLUWALIA A., ALAM S., AVEY M. T., BAKER M., BROWNE W. J., CLARK A., CUTHILL I. C., DIRNAGL U., EMERSON M., GARNER P., HOLGATE S. T., HOWELLS D. W., KARP N. A., LAZIC S. E., LIDSTER K., MACCALLUM C. J., MACLEOD M., PEARL E. J., PETERSEN O. H., RAWLE F., REYNOLDS P., ROONEY K., SENA E. S., SILBERBERG S. D., STECKLER T., and WÜRbel H. ARRIVE 指南 2.0：动物研究报告的更新指南。PLOS Biology, 2020, 18(7): e3000410. https://doi.org/10.1371/journal.pbio.3000410
[13] DASTAH S., TOFIGHI A., and BABAEI S. 有氧运动对糖尿病大鼠心肌内皮组织中 miR-126 及相关靶基因表达的影响。Microvascular Research, 2021, 138: 104212. https://doi.org/10.1016/j.mvr.2021.104212
[14] KAZEMI F., and ZAHEDIASL S. 运动训练对链脲佐菌素-烟酰胺诱导糖尿病大鼠脂肪组织 apelin 表达的影响。Gene, 2018, 662: 97-102. https://doi.org/10.1016/j.gene.2018.04.003
[15] REZAEI M. H., RASHIDIAN E., MADADIZADEH M., AMIRI M., and AALI J. 瘦素信号可能介导高强度间歇训练诱导的 2 型糖尿病大鼠海马 β-淀粉样蛋白和 Tau 蛋白蓄积减少。Cellular and Molecular Neurobiology, 2023, 43(7): 3465-3478. https://doi.org/10.1007/s10571-023-01357-1
[16] SHARAFIFARD F., KAZEMINASAB F., GHANBARI M., GHAEDI K., and ROSENKRANZ S. K. 高强度间歇训练与限时进食对糖尿病大鼠 AKT/FOXO1/PEPCK 通路的联合影响。Scientific Reports, 2025, 15: 13898. https://doi.org/10.1038/s41598-025-96703-2
[17] MACHRINA Y., PURBA A., LINDARTO D., and MASKOEN A. M. 运动强度改变 2 型糖尿病大鼠模型中的胰岛素受体基因表达。Macedonian Journal of Medical Sciences, 2019, 7(20): 3370-3375. https://doi.org/10.3889/oamjms.2019.425
[18] SYAHPUTRA M., LINDARTO D., and RAMAYANI O. R. 中等强度持续训练和慢速间歇训练对 2 型糖尿病 Wistar 大鼠模型中 TGF-β 基因表达的影响。Medical Archives, 2023, 77(1): 4-7. https://doi.org/10.5455/medarh.2023.77.4-7
[19] ABREU P., VITZEL K. F., MONTEIRO I. C. C. R., LIMA T. I., and QUEIROZ A. N. 耐力训练对 Wistar 大鼠在高强度恒速和递增速度测试中血浆葡萄糖降低的影响。Brazilian Journal of Medical and Biological Research, 2016, 49(11): e5226. http://dx.doi.org/10.1590/1414-431X20165226
[20] GHARAAT M. A., CHOOBDARI H. R., and

SHEYKLOUVAND M. 通过降低心脏凋亡指标和氧化应激促进心脏健康：有氧训练对糖尿病大鼠的心脏保护作用。ARYA Atherosclerosis, 2024, 20(2): 50-60. https://doi.org/10.48305/arya.2024.41976.2911
[21] KILIÇ Y., DALKILIÇ S., DALKILIÇ L. K., ÖZDEMIR E., UĞURLU F. M., and PALA R. 有氧和无氧运动对链脲佐菌素诱导糖尿病大鼠模型脑组织中葡萄糖、脂质和炎症相关基因表达的影响。Diabetology & Metabolic Syndrome, 2025, 17: 324. https://doi.org/10.1186/s13098-025-01893-4
[22] LIN J., ZHANG X., SUN Y., XU H., LI N., WANG Y., TIAN X., ZHAO C., WANG B., ZHU B., and ZHAO R. 运动通过 irisin/AMPK 激活改善糖尿病大鼠肌肉中过度线粒体分裂、胰岛素抵抗和炎症。Scientific Reports, 2024, 14: 10658. https://doi.org/10.1038/s41598-024-61415-6
[23] SHEIKH R., REZA M., ABOLFATHI F., REZA S., and TABATABAEI F. 中等强度间歇训练对 2 型糖尿病雄性大鼠肝组织中 NLR 家族 pyrin 结构域蛋白 3 炎症小体通路的影响。Sport Sciences for Health, 2025: 1-9. https://doi.org/10.1007/s11332-025-01477-9
[24] DÍAZ-NÚÑEZ D., and RIVERA-TORRES B. 综述文章：具有降血糖作用的安第斯作物及其生物活性成分证据的探索性综述。Revista Peruana de Medicina Experimental y Salud Pública, 2023, 40(4): 474-484. https://doi.org/10.17843/rpmesp.2023.404.12672
[25] FREITAS G., DE BEM G. F., DA COSTA C. A., CORDEIRO V. S. C., SANTOS I. B., DE CARVALHO L. C. R. M., SOARES R. A., RIBEIRO J. H., DE SOUZA M. A. V., DE SOUSA P. J. C., OGNIBENE D. T., RESENDE A. C., and DE MOURA R. S. 与运动训练联合的 Euterpe oleracea Mart.（阿萨伊）种子提取物可减少 2 型糖尿病雄性大鼠的肝脂肪变性。Journal of Nutritional Biochemistry, 2018, 52: 70-81. https://doi.org/10.1016/j.jnutbio.2017.09.021
[26] HOSEINI R., and GHARZI A. 维生素 D 和运动改善糖尿病大鼠 VEGF-B 生成和 IGF-1 水平：关于 miR-1 抑制作用的见解。Scientific Reports, 2025, 15: 1328. https://doi.org/10.1038/s41598-024-81230-3
[27] HOSEINI Z., BEHPOUR N., and HOSEINI R. 有氧训练和维生素 D 通过调节肝脏 miRNA 表达改善 2 型糖尿病中的脂质代谢和胰岛素抵抗。Scientific Reports, 2025, 15: 16764. https://doi.org/10.1038/s41598-025-01757-x
[28] KHALEDI K., and GHARZI A. 有氧训练和维生素 D 补充对 2 型糖尿病大鼠血糖指标和脂肪组织基因表达的影响。Scientific Reports, 2023, 13: 10218. https://doi.org/10.1038/s41598-023-37489-z
[29] HAMID R. R., HOSEINI R., and AHMED H. 有氧训练联合镁补充对 2 型糖尿病大鼠血清生物标志物以及脂肪组织中 microRNA-155 和 microRNA-21 表达的影响：一项为期八周的干预研究。Biological Trace Element Research, 2025, 203(2): 861-871. https://doi.org/10.1007/s12011-024-04186-5
[30] ZIARNIAK K., DUDEK M., MATUSZEWSKA J., BIJOCH Ł., SKRZYPSKI M., CELICHOWSKI J., and ŚLIWOWSKA J. H. 两周中等强度运动训练增加皮质酮浓度，但未改变 2 型糖尿病和对照大鼠海马中 adropin 免疫反应细胞的数量。Acta Histochemica, 2021, 123(7): 151751. https://doi.org/10.1016/j.acthis.2021.151751
[31] DAREINI F., BIJEH N., ALIREZA S., KAKHAK H., and HAJ M. 六周连续训练和高强度间歇训练对链脲佐菌素诱导糖尿病大鼠胰腺功能的影响。Sport Sciences for Health, 2025, 21(2): 565-574. https://doi.org/10.1007/s11332-024-01288-4

Manuscript Information
Word count: 15,982 words (excluding references).
Peer-Review Record

Fast-track status: Not fast-tracked.
First-round reviews received: 3 reports.
Revision cycles completed: 3 rounds.
Final version submitted: June 17, 2026

Appendix A. Complete Search Strategy

Database	#	Search syntax	Citations found
Pubmed Article title, Abstract Filters: 10 years Full text	1	treadmill OR "treadmill exercise" OR "Treadmill training"	14028
	2	**"Smallanthus sonchifolius" OR Yacon OR Yakon**	111
	3	**"Lactobacillus acidophilus"**	1156
		"Type 2 Diabetes Mellitus" OR "Type II Diabetes Mellitus" OR "Diabetes Mellitus Type 2" OR "Diabetes Mellitus type II" OR "Type 2 Diabetes" OR "Type II Diabetes" OR "Non-Insulin Dependent" OR "Noninsulin Dependent Diabetes Mellitus" OR "Diabetes Type 2" OR "Diabetes Type II" OR "Adult-Onset Diabetes Mellitus" OR T2DM	114084
	5	#1 OR #2 OR #3 AND #4	222
Scopus Article title, Abstract, Keywords Filters: 2015-2025 Article	1	treadmill OR "treadmill exercise" OR "Treadmill training"	59968
	2	**"Smallanthus sonchifolius" OR Yacon OR Yakon**	726
	3	**"Lactobacillus acidophilus"**	12975
	4	"Type 2 Diabetes Mellitus" OR "Type II Diabetes Mellitus" OR "Diabetes Mellitus Type 2" OR "Diabetes Mellitus type II" OR "Type 2 Diabetes" OR "Type II Diabetes" OR "Non-Insulin Dependent" OR "Noninsulin Dependent Diabetes Mellitus" OR "Diabetes Type 2" OR "Diabetes Type II" OR "Adult-Onset Diabetes Mellitus" OR T2DM	395422
	5	#1 OR #2 OR #3 AND #4	621
Springer link Reserach article, Abstract English Date: 2015-2025	1	treadmill OR "treadmill exercise" OR "Treadmill training"	6851
	2	**"Smallanthus sonchifolius" OR Yacon OR Yakon**	193
	3	**"Lactobacillus acidophilus"**	3480
	4	"Type 2 Diabetes Mellitus" OR "Type II Diabetes Mellitus" OR "Diabetes Mellitus Type 2" OR "Diabetes Mellitus type II" OR "Type 2 Diabetes" OR "Type II Diabetes" OR "Non-Insulin Dependent" OR "Noninsulin Dependent Diabetes Mellitus" OR "Diabetes Type 2" OR "Diabetes Type II" OR "Adult-Onset Diabetes Mellitus" OR T2DM	55692
	5	#1 OR #2 OR #3 AND #4	546
		Total	1389
		Duplicate removal	254

Appendix B.

	Reference, year	Population Sample	Type of Intervention	Results
	Intervention: Exercise			
1	(Dastah *et al.*, 2021)	Wistar rats aged 12-24 weeks, 180-240 g	diabetes control: walking on a treadmill for 5 minutes per week, low intensity (acclimatization) diabetes exercise: aerobic exercise protocol for 8 weeks, 5 days a week using a treadmill with a 5-degree incline, starting at 10 m/min for 15 minutes, gradually increasing to 25 m/min for 30 minutes in the final week.	Fasting blood glucose and HOMA-IR were significantly lower in the trained diabetic group versus controls ($p<0.0001$ and $p=0.029$ respectively). Conversely, serum insulin was higher in the exercise group ($p< 0.04$).
2	(Ziarniak *et al.*, 2021)	Adult male Wistar rats (200 +- 30g)	Control: Standard diet HFD: Diet with 50% of calories from pork fat for 10 weeks DM2: High-fat diet followed by streptozotocin injection for diabetes induction then each group is divided into: Run: 2 weeks of treadmill training Non Run: no treadmill training Training used a treadmill 5 days a week for 2 weeks, with duration starting from 10 minutes up to 60 minutes, and speed starting from 4.2 cm/second up to 26 cm/second	Forced running for two weeks decreased insulin in both control (C-RUN) and diabetic (DM2-RUN) rats versus non-running groups.
3	(Kazemi & Zahediasl, 2018)	Adult male Wistar rats (230 - 250g), usia 8 minggu	Sedentary nondiabetic: Trained nondiabetic: Sedentary diabetic: Trained diabetic: Training using a treadmill for 8 weeks, 5 days a week, with a 5-degree incline, starting at 12 m/min for 15 minutes. Each week, the duration increases by 5 minutes; every 2 weeks, the intensity increases by 4 m/min until reaching 20 m/min for 40 minutes.	Body weight was lower in trained diabetic rats versus sedentary diabetic and non-diabetic groups from weeks 5-8. Fat weight and ratio were higher in diabetic groups, though exercise reduced fat in trained diabetic rats. Plasma glucose, insulin, and HOMA-IR were higher in diabetic groups but decreased with exercise. Sedentary diabetic rats showed higher TC, TG, LDL-C, and lower HDL-C than non-diabetic rats. During IPGTT, diabetic rats had higher glucose, though exercise improved their glucose tolerance.
4	(Hossein *et al.*, 2023)	Male Wistar rats, 8 weeks old, 200 +- 10,25g	Consists of 4 groups: CON: Healthy control T2D: Type 2 diabetes Ex: Exercise T2D + Ex: Type 2 diabetes + exercise Training uses a treadmill with a HIIT program of 2 minutes high intensity followed by 1 minute low intensity, starting with 4 intervals and increasing by 2 intervals every 2 weeks until a maximum of 10 intervals in the last 2 weeks, over a period of 8 weeks, 5 days a week.	Blood glucose was higher in T2D and T2D+EX groups after diabetes induction, but HIIT reduced glucose levels in T2D+EX after 8 weeks. T2D group showing decreased weight by study end. HIIT increased insulin in T2D+EX compared to T2D group. HIIT reduced HOMA-IR in T2D+EX compared to T2D. Leptin levels in serum and hippocampus were higher in T2D+EX versus T2D group.
5	(Abdolmaleki & Heidarianpour, 2020)	male Wistar rats, 3 months old, 210-230g	Consisting of 3 groups: Sedentary control: Sedentary diabetes: Diabetes training: Training: moderate-intensity endurance exercise on a treadmill for 14 weeks, 5 days	The 14-week endurance exercise training program improved glycemic control and restored GPLD1 levels in diabetic rats. The trained diabetic (TD) group showed decreased blood glucose and

	Reference, year	Population Sample	Type of Intervention	Results
			a week. The training starts at an intensity of 8 m/min for 15 minutes; each week, the intensity increases gradually by 2 m/min and the duration increases gradually by 5 minutes, until the last 4 weeks, which are 26 m/min for 60 minutes.	increased insulin compared to sedentary diabetic (SD) rats. TD rats demonstrated lower 2hOGTT and AUC values than the SD group. Sedentary diabetic rats had elevated GPLD1, which exercise reversed, correlating with improved glycemic profiles.
6	(Kılıç *et al.*, 2025)	male Wistar rats, aged 8-10 weeks, 200-250g	Consists of 4 groups: Control: not induced with diabetes, no exercise given Sedentary diabetes: induced with diabetes, no exercise given Diabetes with intense exercise: induced with diabetes, intense exercise protocol Diabetes with light exercise: induced with diabetes, light exercise protocol Exercise intervention for 6 weeks, 5 days per week Light exercise: treadmill for 30 minutes, 0 degree incline, speed 0.5 km/h, approximately 45-60% VO2 max Intense exercise: treadmill for 30 minutes, 15 degree incline, speed 1.62 km/h, approximately 80-100% VO2 max	Exercise protocols altered gene expression in diabetic rats' brain tissue and affected blood glucose. Blood glucose was lower in exercise groups versus diabetic sedentary group ($p=0.001$), with differences between groups ($F=581.786$; $p<0.05$). Post-test showed differences in body weight ($F=112.761$; $p<0.05$) and height ($F=14.320$; $p<0.05$). Both exercise types improved gene expression and lowered blood glucose, though not to control levels.
7	(Gharaat *et al.*, 2024)	male Wistar rats, 10 weeks old, weighed 170-190g	Consists of 3 groups: ND: Non-diabetic, normal diet Diabetic control: high-fat diet, diabetes-induced, no aerobic exercise Diabetic training: same as diabetic control, given aerobic exercise for 6 weeks using a treadmill, with the first week on the treadmill for 10 minutes at a speed of 10 m/min. Subsequently, a 6-week exercise protocol is given, starting at 65% in the first week, then gradually increasing to 85% by the sixth week (65%, 70%, 70%, 75%, 75%, 85%) with the duration of exercise increased by 1 minute each session.	Training mitigated diabetes by improving fitness, lowering glucose and insulin resistance, reducing apoptosis markers (Caspase-9 and P53), and enhancing heart function (LVEF).
8	(Abreu *et al.*, 2016)	male Wistar rats, 10 weeks old, weighed 200-230g	Consists of 2 groups: Control: no physical activity intervention given Training group: training provided using a treadmill, given for 6 weeks, 5 days per week, at 60% intensity, speed of 15, 20, and 25 m/min for 28 minutes.	Six-week endurance training in Wistar rats produced physiological adaptations. Exercised rats showed reduced plasma glucose, improved endurance, and enhanced oxidative capacity versus sedentary rats. Training decreased retroperitoneal and epididymal fat mass without changing body mass.
9	(Syahputra *et al.*, 2023)	male Wistar rats, 8 weeks old, 180-200g	Consists of 3 groups: Control: Diabetes group with no intervention MCT: Moderate intensity continuous training, exercise for 8 weeks, 3 days per week, using a treadmill at a speed of 20 m/min for 30 minutes SIT: Slow type interval training, exercise for 8 weeks, 3 days per week, using a treadmill at a speed of 20 m/min for 2 minutes followed by 1 minute of rest, repeated for 10 repetitions	The study's results show that both moderate intensity continuous training (MCT) and slow type interval training (SIT) affected TGF-β gene expression in Wistar rats with Type 2 Diabetes Mellitus (T2DM). MCT was more effective at decreasing TGF-β gene expression than SIT, though this difference was not statistically significant ($p = 0.965$).
10	(Machrina *et*	male Wistar	Consists of 3 groups:	Eight weeks of exercise impacted

	Reference, year	Population Sample	Type of Intervention	Results
	al., 2019)	rats, 8 weeks old, 150-180g	Control: Diabetes without intervention MCT: moderate intensity continuous training, exercise for 8 weeks, 3 days per week, using a treadmill at a speed of 25 m/min for 30 minutes SIT: slow type interval training, exercise for 8 weeks, 3 days per week, using a treadmill at a speed of 30 m/min for 30 minutes	metabolic markers in T2DM rats. Both moderate and severe continuous training reduced HOMA-IR and FBG levels. SCT showed significantly lower HOMA-IR versus control and MCT groups (p=0.001), while MCT demonstrated lower FBG levels than SCT.
11	(Dareini *et al.*, 2025)	male Wistar rats, 3-4 months old, 200-250g	Divided into 4 groups: Non-diabetic: healthy rats, no intervention given Diabetes: diabetes-induced, no exercise intervention HIIT: Exercise for 6 weeks, 6 days a week, initial speed of 26 m/min with 10.1 m/min intervals for 1 minute, the overload principle applied by increasing the number of intervals and the protocol provided varied CT: exercise for 6 weeks, 6 days a week, exercise duration gradually increased from 20 minutes on the first day up to 60 minutes in the fourth week and maintained until completion, constant speed of 15 m/min	Diabetic rats showed higher insulin resistance (HOMA-IR), while beta-cell function (HOMA-β) and insulin sensitivity (QUICKI) were lower. Neither HIIT nor CT improved HOMA-IR, HOMA-β, or QUICKI versus non-exercising diabetic rats.
12	(Sheikh *et al.*, 2025)	male Wistar rats, 10 weeks old, 190-210g	Divided into 4 groups: Control: healthy control MIIT: given moderate-intensity interval training intervention Di: diabetes induced Training for 8 weeks, 4 days a week, for 45 minutes each session, with 4 minutes of running at 60-70% VO2 max intensity followed by 3 minutes at 45-55% VO2 max intensity, 0-degree incline, 5 minutes of warm-up and cool-down Di + MIIT: diabetes induced and given moderate-intensity interval training intervention	The diabetic MIIT group showed lower NLRP3 and ASC protein expression compared to the non-exercise diabetic group ($p<0.05$). NLRP3 expression showed no difference between healthy training and control groups ($p>0.05$), though MIIT increased ASC protein expression versus controls ($p<0.05$). Diabetes induction increased serum LDL, triglycerides (TG), and cholesterol ($p<0.05$).
	Intervention: Lactobacillus acidophilus			
13	(Saadatzadeh *et al.*, 2025)	Adult male Wistar rats, 200-250g	Consists of 6 groups: Sham: Negative control: diabetes without intervention Positive control: given metformin LPE 60mg/ml LPE 120mg/ml LPE 240mg/ml LPE (lyophilized probiotic extract) is derived from probiotic strains Lactobacillus acidophilus and Lactobacillus plantarum. LPE 60mg/ml is equivalent to 270 mg/kg body weight, LPE 120mg/ml is equivalent to 540 mg/kg, and LPE 240mg/ml is equivalent to 1080 mg/kg. The metformin dose is 200 mg/kg.	LPE supplementation reduced blood sugar, inflammation (TNF-α), and insulin resistance in diabetic rats, with highest doses most effective.
14	(Moody *et al.*, 2024)	male Wistar rats, 2-3 months old, 150-200g	Consists of 4 groups: Negative control: only given distilled water Positive control: given metformin 45 mg/kg Intervention 3: given synbiotic biscuits, 5g Intervention 4: given synbiotic biscuits, 10g	Synbiotic biscuit treatment improved body weight in diabetic rats, with the 10g daily group reaching 216.33g after 15 days. The 10g treatment reduced fasting blood

	Reference, year	Population Sample	Type of Intervention	Results
				glucose to 96.97 mg/dl, showing decreasing glucose levels. Treatment increased L. acidophilus in rat faeces from 5.11-5.15 to 6.56-7.02 Log CFU/g by day 15, with the 10g group showing 6.56 log CFU/g, indicating gastrointestinal survival.
	Intervention: Exercise + Nutraceutical			
15	(Bem *et al.*, 2018)	male Wistar rats, 180-200g	Divided into 2 main groups, then each group is further divided into 4 treatment groups, namely: Control: Standard diet Control sedentary: Control training: Control ASE sedentary: Control ASE training HFD: diet with 55% of energy derived from fat HFD sedentary HFD training HFD ASE sedentary HFD ASE training Training: Exercise program of 30 minutes per day, 5 days per week, for 4 weeks, at 0-degree incline. Speed increases gradually up to 50%-60% of the maximum speed during the stress test ASE: Hydroalcoholic extract of Acai Seed (rich in polyphenols, especially catechin and polymeric proanthocyanidins), daily dose of 200 mg/kg	ASE shows antidiabetic effects by improving insulin-signaling, increasing GLP-1, and reducing inflammation, while exercise enhances these benefits through adiponectin-AMPK activation and IR expression.
16	(Freitas *et al.*, 2018)	Adult male Wistar rats, 180-200g	Divided into 2 major groups, then each group was further divided into 4 treatment groups, namely: Control: Standard diet Sedentary control: Training control: Sedentary ASE control: Training ASE control HFD: diet with 55% of energy derived from fat Sedentary HFD Training HFD Sedentary HFD ASE Training HFD ASE Training: Exercise program for 30 minutes per day, 5 days a week, with 0 degree incline. Speed is gradually increased up to 50%-60% of the maximum speed during the stress test. ASE: Hydroalcoholic extract of Acai Seed (rich in polyphenols, mainly catechin and polymeric proanthocyanidins) at a daily dose of 200 mg/kg	Exercise training alone in type 2 diabetic rats showed benefits but was less effective than when combined with açaí seed extract (ASE). Blood Glucose: Exercise significantly reduced blood glucose in diabetic rats versus the sedentary group. Serum Lipids and Liver Enzymes: Exercise reduced serum levels of total cholesterol, triglycerides, VLDL, ALT, and AST. AMPK Pathway: Exercise increased the pAMPK/AMPK ratio for metabolism regulation. Lipogenesis: It decreased SREBP-1c protein expression. Hepatic Oxidative Damage: Exercise reduced hepatic oxidative markers like MDA, carbonyl protein, and 8-isoprostane
	Intervention: Exercise + Other			
17	(Zhao *et al.*, 2023)	male Wistar rats, 8 weeks old,	Consists of 4 groups: Control: Diabetes: Diabetes exercise: Diabetes exercise Cyclo RGDyk:	An 8-week exercise program benefited type 2 diabetic (T2DM) rats via the irisin pathway. Exercise reduced weight loss, hyperlipidemia, hyperglycemia, and

	Reference, year	Population Sample	Type of Intervention	Results
			Exercise intervention: aerobic treadmill for 8 weeks, 5 days a week, starting in the first week with a gradually increasing duration of 10–45 minutes, with speed gradually increasing from 10–18 m/min; weeks 2–8 duration is 45 minutes, speed 18 m/min, and a 5-degree incline. Injection of Cyclo RGDyk at a dose of 2.5 mg/kg, twice a week for 8 weeks, administered intravenously through the tail vein.	insulin resistance. T2DM rats showed disorganized myocardial fibers and high cardiac injury markers, but exercise improved heart structure. Exercise reduces myocardial injury by increasing irisin expression and AMPK phosphorylation, inhibiting mitochondrial fission.
18	(Lin *et al.*, 2024)	male Wistar rats, 8 weeks old	Consists of 4 groups, namely: CON: Healthy control DM: Sedentary type 2 diabetes Ex: Exercise; treadmill for 8 weeks, 5 days a week, moderate intensity, in the first week the treadmill speed gradually increased from 10 m/min to 18 m/min with a duration starting from 10 minutes up to 45 minutes. In the second to eighth weeks, 5 minutes of warm-up at 10 m/min, followed by 35 minutes at a speed of 18 m/min, and cooling down at 0 m/min. ExRg: Treatment group, injected with cycloRGDyk (irisin inhibitor) at a dose of 2.5 mg/kg body weight.	Eight weeks of treadmill exercise training improved diabetic rats' health through the irisin/AMPK signaling pathway. Exercise training ameliorated hyperglycemia, hyperlipidemia, and insulin resistance.
19	(Khaledi & Gharzi, 2023)	male Wistar rats, 4-5 weeks old, 180 +- 10g	divided into 5 groups: Non-diabetic control: not induced with diabetes, no intervention given Diabetic control: induced with diabetes, no intervention given Aerobic exercise: treadmill running, 8 weeks, 5 days a week, 0 degree inclination, gradually increased starting from 30 minutes at a speed of 15 m/minute up to 60 minutes at a speed of 25 m/minute in the 8th week, exercise intensity maintained at 50-60% VO2 max, warm-up and cool-down performed for 10 minutes at a speed of 5 m/minute Vit D: given 5000 IU of Vit D per week as a single-dose injection Exercise + Vit D: induced with diabetes, given both exercise intervention and Vit D	Aerobic training (AT) and vitamin D (Vit D) supplementation, both separately and combined, improved metabolic and genetic markers in diabetic rats, with the combined intervention showing the best outcomes. The AT + Vit D, AT, and Vit D groups showed significant reductions in body weight, BMI, and food intake, with AT + Vit D showing the greatest decrease. Compared to controls, intervention groups had lower visceral fat, insulin, glucose, and HOMA-IR levels, with AT + Vit D showing the lowest levels.
20	(Hoseini & Gharzi, 2025)	male Wistar rats, 4-5 weeks old, 180 +- 10g	Consists of 4 groups, namely: Diabetic control; Aerobic training; Vit D; Aerobic training + Vit D: treadmill exercise regimen for 8 weeks, 5 days a week, intensity 50-60% VO2 max or speed of 15-25 m/min with 0-degree incline, 30-60 minutes per day, warm-up and cool-down each for 10 minutes at a speed of 5 m/min. Vit D is administered for 8 weeks as a single dose injection of 5000 IU once a week.	The study showed Aerobic Training (AT) and Vitamin D supplementation (Vit D), particularly combined, significantly benefited diabetic rats' physiological parameters. The AT + Vit D, AT, and Vit D groups showed decreased BW, BMI, and FI from baseline ($p=0.001$), with AT + Vit D showing the strongest effect. Visceral fat, insulin, glucose, and HOMA-IR were significantly lower in treatment groups versus the Control Diabetic (C) group.
21	(Hoseini *et al.*, 2025)	male Wistar rats, 8-10 weeks	Consists of 4 groups: Control: no intervention	Eight-week aerobic training (AT) and high-dose vitamin D

	Reference, year	Population Sample	Type of Intervention	Results
		old, weighed 200-250g	Aerobic training: first week adaptation with treadmill for 5 minutes, speed 8-10 m/min with 0 degree incline, followed by a formal 8-week program, 5 days a week, starting with 15 minutes at 10 m/min gradually increased so that at the end of the program 30 minutes at a speed of 25 m/min, with an intensity of 60-70% VO2 max. Each session includes a 10-minute warm-up and cool-down at a speed of 5 m/min. Moderate Vit D: given 5000 IU Vit D intraperitoneally per week High Vit D: given 10000 IU Vit D intraperitoneally per week	supplementation improved insulin resistance, lipid profiles, and hepatic microRNAs in diabetic rats. The AT group showed lower body weight, BMI, food intake, glucose, insulin, and HOMA-IR compared to control, moderate-dose and high-dose vitamin D groups. AT group also had lower total cholesterol, triglycerides and higher HDL/LDL ratio versus other groups.
22	(Hamid *et al.*, 2025)	male Wistar rats, 10-12 weeks old, 180+-10g	Divided into 4 groups: Control: diabetes without intervention Aerobic exercise: exercise using a treadmill for 8 weeks, 5 days per week, 0-degree incline, starting at a speed of 15 m/min for 30 minutes and gradually increasing up to 25 m/min for 60 minutes by the eighth week, with a target exercise intensity of 50-60% of VO2 max, warm-up and cool-down at a speed of 5 m/min for 10 minutes Magnesium supplementation: intervention with 1000 mg/kg Magnesium chloride provided in the diet AT+Mg: given both aerobic intervention and Magnesium	Aerobic training and magnesium supplementation (AT + Mg) had the strongest effects on metabolic and inflammatory markers. The AT + Mg and AT groups demonstrated significant body weight reduction post-intervention (p=0.001) The AT + Mg group showed optimal improvement with decreased insulin, glucose, and HOMA-IR, and increased serum Mg versus other groups. AT and Mg groups improved versus controls.
23	(Sharafifard *et al.*, 2025)	male Wistar rats, 4-5 weeks old, 200 +- 20g	divided into 6 groups: Non-diabetic control: not induced with diabetes, no intervention given Diabetic control: induced with diabetes, no intervention given Exercise: 10-week HIIT program, 5 days a week, 5-degree incline, consisting of 8 intervals, intensity at 85-90% VO2 max (22 m/min) for 3 minutes followed by intensity at 30-40% VO2 max (8 m/min); warm-up and cool-down at 30-40% intensity (8 m/min), speed increased in the 5th week RF: given an 8-hour eating window Exercise + RF: given both exercise and diet interventions Metformin: given 300 mg/kg metformin orally	Exercise groups (D-EX, D-TRF&EX) and TRF groups (D-TRF, D-TRF&EX) showed lower FBG levels compared to non-exercised and non-TRF groups. Exercise and TRF interventions led to significant differences in insulin levels versus control groups. Exercise and TRF interventions improved HOMA-IR compared to non-treated groups. D-NT group showed higher blood glucose during IPGTT and larger area under curve versus non-diabetic group, confirming impaired glucose tolerance.