Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Effects of selenium supplementation on PI3K/Akt/GLUT-4 insulin signaling pathway activation: a systematic review with meta-analysis of animal models of diabetes

Efeitos da suplementação de selênio na ativação da via de sinalização da insulina PI3K/Akt/GLUT-4: uma revisão sistemática com meta-análise de modelos animais de diabetes

Efectos de la suplementación con selenio sobre la activación de la vía de señalización de insulina PI3K/Akt/GLUT-4: una revisión sistemática con metanálisis de modelos animales de diabetes

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ABSTRACT

Objective: We aimed to elucidate, through systematic review and meta-analysis, how exposure to selenium can influence the activation of the PI3K/Akt/GLUT-4 signaling pathway in animal models of diabetes. **Methods:** Search was performed in the PubMed/Medline, Cochrane Library, LILACS, Web of Science, and Scopus databases, without a time limit, with a focus on studies conducted in animal models of diabetes. **Results:** 13 articles were included in this review. The findings show that selenium supplementation resulted in increased expression of the GLUT-4 protein, as well as improved fasting glucose, fasting insulin, and HOMA-IR in animal model, disregarding studies conducted on humans that show a diabetogenic effect of this mineral in many studies conducted. Similarly, this meta-analysis shows controversies results regarding modulation of the PI3K/Akt/GLUT-4 pathway and glucose metabolism in different animal models. **Final considerations:** The relationship between selenium and insulin signaling is complex and dependent on dose, compound, and tissue, is important to interpret these results carefully.

Keywords: Insulin, Selenium, Dietary supplements, Genomics.

RESUMO

Objetivo: Nosso objetivo foi elucidar, por meio de revisão sistemática e meta-análise, como a exposição ao selênio pode influenciar a ativação da via de sinalização PI3K/Akt/GLUT-4 em modelos animais de diabetes. **Métodos:** A busca foi realizada nas bases de dados PubMed/Medline, Cochrane Library, LILACS, Web of Science e Scopus, sem limite temporal, com foco em estudos conduzidos em modelos animais de diabetes. **Resultados:** Treze artigos foram incluídos nesta revisão. Os resultados mostram que a suplementação com

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SUBMETIDO EM: 12/2025 | **ACEITO EM: 1/2026** | **PUBLICADO EM: 3/2026**

selênio resultou em aumento da expressão da proteína GLUT-4, bem como melhora da glicemia de jejum, insulinemia de jejum e HOMA-IR em modelos animais, contrariando estudos conduzidos em humanos que demonstram um efeito diabetogênico desse mineral em muitos estudos realizados. Da mesma forma, esta meta-análise mostra resultados controversos em relação à modulação da via PI3K/Akt/GLUT-4 e ao metabolismo da glicose em diferentes modelos animais. **Considerações finais:** A relação entre o selênio e a sinalização da insulina é complexa e depende da dose, do composto e do tecido; é importante interpretar esses resultados com cautela.

Palavras-chave: Insulina, Selênio, Suplementos nutricionais, Genômica.

RESUMEN

Objetivo: Nos propusimos dilucidar, a través de una revisión sistemática y un metaanálisis, cómo la exposición al selenio puede influir en la activación de la vía de señalización PI3K/Akt/GLUT-4 en modelos animales de diabetes. **Métodos:** Se realizó una búsqueda en las bases de datos PubMed/Medline, Cochrane Library, LILACS, Web of Science y Scopus, sin límite de tiempo, con foco en estudios realizados en modelos animales de diabetes. **Resultados:** Se incluyeron 13 artículos en esta revisión. Los hallazgos muestran que la suplementación con selenio resultó en una mayor expresión de la proteína GLUT-4, así como una mejoría de la glucosa en ayunas, la insulina en ayunas y el HOMA-IR en el modelo animal, ignorando estudios realizados en humanos que muestran un efecto diabetogénico de este mineral en muchos estudios realizados. De igual manera, este metaanálisis muestra resultados controvertidos con respecto a la modulación de la vía PI3K/Akt/GLUT-4 y el metabolismo de la glucosa en diferentes modelos animales. **Consideraciones finales:** La relación entre el selenio y la señalización de insulina es compleja y depende de la dosis, el compuesto y el tejido, es importante interpretar estos resultados con cuidado.

Palabras clave: Insulina, Selenio, Suplementos dieteticos, Genómica.

INTRODUCTION

Insulin is a hormone synthesized in the β cells of the islets of Langerhans, located in the pancreas, which performs important functions, such as glucose uptake by adipose tissue and skeletal muscle, regulation of glucose production by the liver, as well as inhibiting lipolysis in adipose tissue and preventing the elevation of fatty acid concentrations in the bloodstream (NORTON L, et al., 2023).

Glucose uptake by target tissue cells occurs via the PI3K/Akt/GLUT-4 signaling pathway, which involves a cascade of chemical reactions that begin after insulin binds to the α subunits of its receptor, culminating in the autophosphorylation of the tyrosine kinase domain present in the β subunits of the same receptor, leading to the activation of proximal insulin receptor substrates (IRS-1, IRS-2, IRS-3, and IRS-4). Once phosphorylated, the IRSs activate phosphatidylinositol 3-kinase (PI3K), which in turn phosphorylates protein kinase B (Akt), culminating in the translocation of glucose transporter 4 (GLUT-4) from the intracellular compartments to the plasma membrane, allowing glucose to flow into the cell (LE TKC, et al., 2023).

In recent decades, there has been growing interest in understanding the cascades of insulin signaling, with an emphasis on the participation of nutrients such as selenium. This mineral performs important biological functions, such as antioxidant and anti-inflammatory action, in addition to acting on insulin metabolism by being incorporated into molecules called selenoproteins (LE TKC, et al., 2023; CAI X, et al., 2024).

In this regard, it should be noted that selenium stimulates insulin production by pancreatic β-cells, as well as stimulating insulin receptor activation, even in the absence of the hormone (MURANO K, et al., 2018). A study conducted in an animal model observed that selenium deficiency is related to reduced concentrations of insulin receptors, IRS-1, IRS-2, PI3K, Akt, and glucose transporters (YANG J, et al., 2017).

In this regard, the literature has presented controversial data about the role of selenium in insulin signaling, demonstrating that this mineral follows a very characteristic pattern, called the U-shaped effect in animal model (MURANO K, et al., 2018; DUBEY P, et al., 2020).

This effect shows that both selenium deficiency and excess are harmful to insulin metabolism. At optimal concentrations, selenium increases antioxidant activity and improves insulin response; however, when deficient or excessive, it reduces insulin sensitivity and impairs glucose metabolism in animal model (MURANO K, et al., 2018; DUBEY P, et al., 2020).

In this approach, it is important to consider a strong body of evidence indicating that selenium species and selenoproteins frequently impair glucose metabolism and insulin sensitivity (MITA Y, et al., 2014; MISU H, et al., 2012; SAITO Y, et al., 2020).

Thus, considering the complexity of the mechanisms involved in selenium's participation in the insulin signaling pathway, as well as the scarcity of robust data in the literature on the effects of supplementation with this trace element on the signaling of this hormone, the objective of this review is to systematically describe and analyze, using meta-analysis, the scientific data on the effect of selenium supplementation on the activation of the PI3K/Akt/GLUT-4 insulin signaling pathway in animal models of diabetes, as well as its repercussions on biochemical parameters of the glycemic profile.

METHODS

Presentation

This systematic review of the literature was developed to answer the guiding question: “Do animals with diabetes supplemented with selenium show changes in the expression of genes and proteins of the PI3K/Akt/GLUT-4 insulin signaling pathway compared to those not supplemented with this nutrient?”

This question was developed based on the PICO strategy (Population = animals; Exposure = selenium supplementation; Comparison = placebo group or no intervention; Outcome = changes in the expression of genes and proteins involved in the PI3K/Akt/GLUT-4 insulin signaling pathway).

This review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform, where it was approved under opinion number CRD42020220195.

This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in its conduct.

Eligibility criteria

Studies that evaluated the expression of classic genes and proteins of the PI3K/Akt/GLUT-4 signaling pathway, namely insulin, IR, IRS-1-4, PI3K, Akt (1, 2, and 3), and GLUT-4, were included. The inclusion criteria were: (1) original research studies; (2) only studies involving rodents with diabetes supplemented with selenium, diabetic or induced to insulin resistance, of both sexes, without age restrictions, compared to animals with the same clinical condition that were not treated with this mineral or received a placebo; (3) studies that evaluated the effect of selenium supplementation on the expression of genes and proteins in the insulin signaling pathway, using Polymerase Chain Reaction (PCR) and Western Blotting methodologies, respectively (4) placebo-controlled studies.

The following were excluded: (1) studies involving healthy animals; (2) literature review studies; (3) studies conducted in humans; (4) studies involving animals with liver, kidney, or heart disease, autoimmune diseases, cancer, diseases that compromise the digestion and absorption of selenium by the gastrointestinal tract, as well as other clinical conditions that may affect the homeostasis of this nutrient in animals; (5) studies conducted on pregnant or lactating animals; (6) studies involving animals other than mice and rats; (7) case studies. The literature review was conducted without restriction on the year of publication and included studies written in English.

Search strategy

The search for articles was conducted in the PubMed/Medline, Cochrane Library, LILACs, Web of Science, and Scopus databases with the last update on October 3, 2025. The Boolean descriptors used in the search in all databases were: Strategy 1 – ((selenium) OR (selenoprotein) OR (selp) OR (selenomethionine) OR (selenocysteine) OR (glutathione peroxidase) OR (thioredoxin reductase)) AND ((insulin resistance) OR (insulin sensitivity) OR (diabetes)) AND ((gene expression) OR (protein expression)); Strategy 2 – (selenium OR selen* OR selenoprotein OR selp protein OR selp OR glutathione peroxidase OR selenomethionine OR selenocysteine OR thioredoxin reductase) AND (insulin resistance OR insulin sensitivity OR diabetes) AND (gene expression OR protein expression). Both strategies were used in each database in order to extract as many articles as possible.

Screening and data extration

References were imported into EndNote Web, and duplicates were removed. Titles, abstracts, and full texts were screened independently by two reviewers, with disagreements resolved by a third. Reference lists were manually searched for additional studies.

Extracted variables included authorship, publication year, animal characteristics, intervention details (dose, chemical form, route, duration), tissues analyzed, glycemic parameters, gene/protein expression results and outcomes.

Risk of bias assessment

The quality assessment was performed independently by two authors (TGVS and EHSO) using SYRCLE's risk of bias (RoB) tool for animal studies following the CAMARADES checklist for risk of bias assessment. This tool helps to systematically assess the risk of bias across several domains using the following questions: 1. Was the allocation sequence generated and applied appropriately? 2. Were the groups similar at the start of the study or were they adjusted for confounding factors in the analysis? 3. Was the allocation to different groups adequately concealed during the study? 4. Were the animals randomly housed during the experiment? 5. Were the caregivers and/or researchers unaware of which intervention each animal received during the experiment? 6. Were animals randomly selected for outcome assessment? 7. Was the outcome assessor blinded? 8. Were incomplete outcome data adequately addressed? 9. Are the study reports free of selective reporting of outcomes? 10. Was the study apparently free of other problems that could result in a high risk of bias?

Statistical analysis

Continuous outcomes were extracted as means and standard deviations. Depending on species heterogeneity, mean differences (MD) or standardized mean differences (SMD) were calculated using a random-effects model in RevMan. Heterogeneity was examined using I^2, Chi^2 and Tau^2 tests. Subgroup analyses were performed for rats versus mice, and $p < 0.05$ was considered significant.

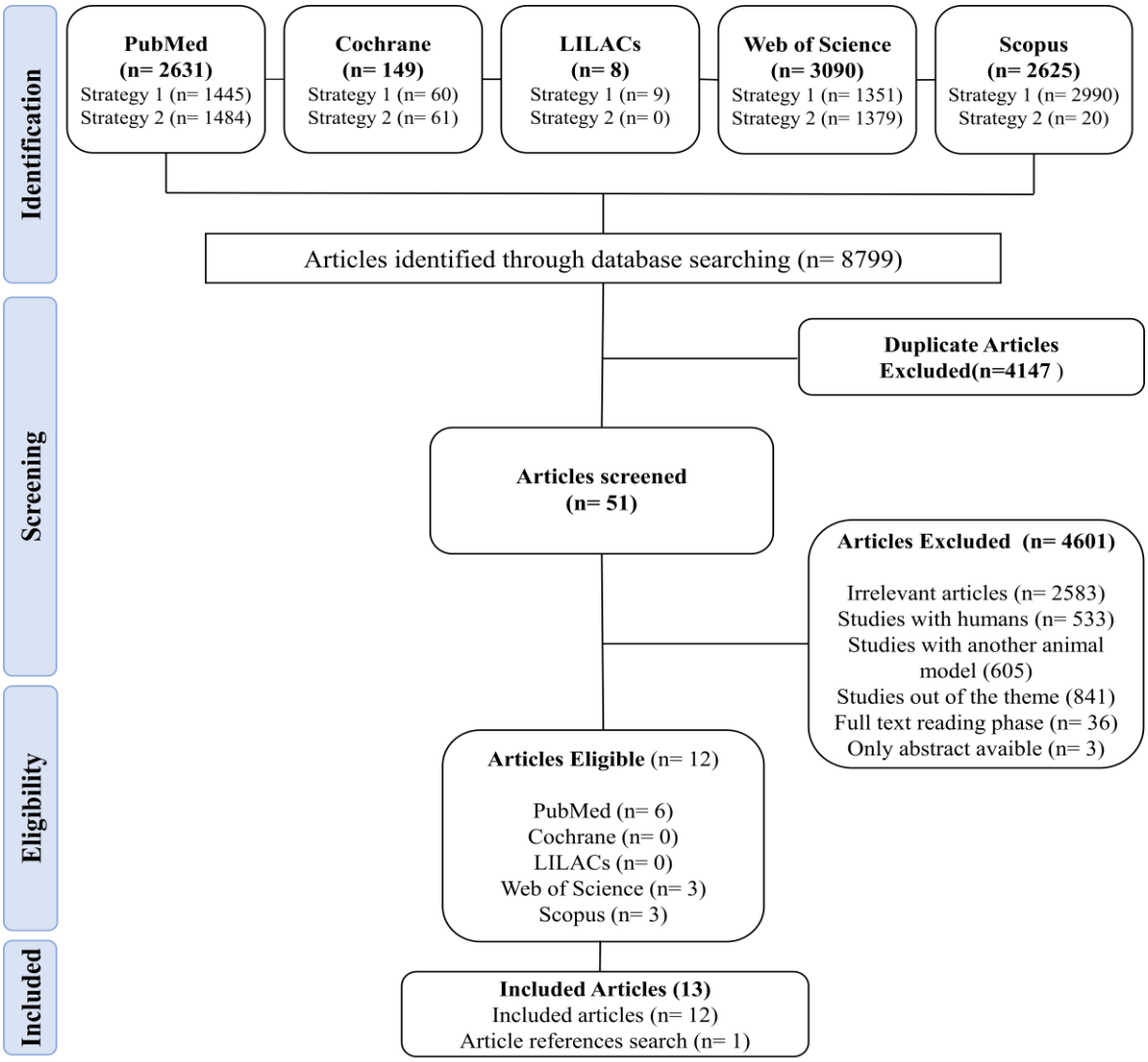
RESULTS

Screening and selection of articles

The database search retrieved a total of 8799 references. After removing 4147 duplicates, 4652 remaining references were evaluated, resulting in 51 articles, of which 3 had only the abstract available and 36 were not approved for full-text reading.

According to the eligibility criteria, 12 studies were included in this review. In addition, it should be noted that the manual evaluation of the article references resulted in the inclusion of one more study. Thus, this analysis includes 13 articles, and the search and analysis steps are illustrated in **Figure 1**. It is worth noting that the studies included in this review evaluated only animal models of diabetes involving rats and mice.

Figure 1 - Flowchart of the search steps and the study selection process conducted in an animal model with diabetes.



Source: Soares TC, et al., 2026.

Characteristics of the included studies in an animal model with diabetes

Of the studies included (n=13), six evaluated gene expression (CAI X, et al., 2024; HASSAN RM, et al., 2021; WANG C et al., 2014; AL-QURAISHY S, et al., 2015; BARAKAT G, et al., 2017; HWANG D, et al, 2007) and nine analyzed protein expression (HWANG D, et al, 2007; XU TJ, et al., 2010; KIM SS, et al., 2011; BARAKAT GM, et al., 2012; ZHOU X, et al., 2014a; ZHOU X, et al., 2014b; ZHOU J, et al., 2015; BARAKAT G, et al., 2017; ABDULMALEC and BALBAA, 2019) of the PI3K/Akt/GLUT-4 pathway. Among these studies, seven were conducted in rats and six in mice, both models are induced to develop diabetes. In addition, two studies were performed on male animals, none were performed on female animals, and one did not specify the sex of the animals.

As for experimental models, selenium dosages ranged from 45.65 µg/kg/day to 5000 µg/kg/day. The thirteen studies involved experimental models of diabetes, with streptozotocin being the most commonly used agent for inducing the disease. The chemical forms of selenium supplementation were sodium selenite (n=12) and sodium selenate (n=1), among which two studies used selenium nanoparticle technology. These compounds were administered orally (n=3), by gavage (n=5), intraperitoneal injection (n=2), through water (n=2), and diet (n=1). The supplementation period ranged from 3 to 12 months. **Table 1** presents a description of the studies included in this review.

Table 1 - Study characteristics of studies in animal diabetic.

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
Hwang D, et al, (2007)	Mice (NI)	NI	IPI	Diabetic + Sodium selenite (865 µg/kg/day)	Diabetic + water	3 weeks	**Fasting glucose:** 7.02±0.29 Vs 7,28±0.29 mmol/L **Fasting insulin** 98.0±8.5 Vs 95.0±7.8pmol/mL	Liver	NI	**Akt:** 0.73±0.11 Vs 5.58±0.42 **p-Akt:** 1.0±1.1 Vs 6.63±0.63 **PI3K:** 9.1±0.8. Vs 7.57±0.64 **p-PI3K** 0.95±0.11 Vs 3.19±0.32
Xu TJ, et al. (2010)	Sprague-Dawly rats (35)	M	Gavage	Diabetic + Sodium selenite (180 µg/kg/day)	Diabetic control group	4 weeks	**Fasting glucose:** 15.4±2.1 Vs 25.0±1.6 mmol/L **HbA1c:** 7.0±0.4 Vs 8.1±0.3%	Cardiac muscle	NI	**GLUT-4:** 80.91±20.83
Kim SS, et al. (2011)	Goto-Kakizaki rats (40)	M	IPI	Sodium selenite (865 µg/kg/day)	Diabetic sedentary control	6 weeks	**Fasting glucose:** 6.91±0.63 Vs 8.73±0.1 mmol/L **Fasting insulin:** 14.21±2.58 Vs 19.9±2.0 µU/mL **HOMA-IR:** 4.36±0.71 Vs 7.72±0.76 mg/dL	Soleus an plantaris muscle	NI	**GLUT-4 (Soleus muscle):** 137.87±7.63 Vs 100.46±0.1 **GLUT-4 (Plantaris muscle):** 123.62±5.74 Vs 99.78±1.3
Barakat GM, et al. (2012)	Sprague-Dawly rats (40)	M	Oral (water)	Sodium selenite (5000 µg/kg/day)	Diabetic controls	4 weeks	**Fasting glucose:** 12.79±2,14 Vs 5.01±0.46 mmol/L	Liver	**IRS-1:** 0.67±0.24	**IRS-1:** 0.36±0.01 Vs 8±0.39

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
Wang C, et al., (2014)	Db/Db mice (16)	M	Gavage	Sodium selenate (800 µg/kg/dia)	Diabetic control group	9 weeks	**Fasting glucose:** 29.26±15.99 Vs 15.99±5.21 mmol/L **Fasting insulin:** 3,57±1,36 Vs 1.96±0.28 µU/mL **HbA1c** 5;9±0.6 Vs 4.0±0.5% **HOMA-IR:** 13.56±1.91 mg/dL	Liver Pancreas	**IR:** 0.64±0.07 Vs 1.01±0.23 (Liver)	NI
Zhou X, et al. (2014a)	KKAy mice and C57BL/6J mice (NI)	M	Gavage	Diabetic group + Se-ExPS (200 µg/kg/day of sodium selenite)	Diabetic group	6 weeks	NI	Skeletal muscle	NI	**↑GLUT-4*** *(The article did not provide numerical results, only images of the expression)
Zhou X, et al. (2014b)	KKAy mice and C57BL/6J mice (NI)	M	Gavage	Diabetic group + Se-ExPS (228.25 µg/kg/day sodium selenite)	Diabetic group	6 weeks	NI	VAT	NI	**↑GLUT-4*** *(The article did not provide numerical results, only images of the expression)
Al-quraishy S, et al., (2015)	Albino Wistar rats (49)	M	Oral	Sodium selenite (45.65 µg/kg/day)	Diabetic control	28 days	**Fasting glucose** 8.06±1.27 Vs 16.71±15.15 mmol/L **Fasting insulin:** 6.05±0.58 Vs 22,18±0.58	Liver and kidney	**IR (Liver):** -1.99±-0.28 Vs 1.29±0.16 **IR (Kigney):** -1.43±0.38 Vs -5.01±-1.14 **IRS-1 (liver, kidney):** 12.94±0.8 Vs 9.34±0.63 8.36±0.2 Vs 3.42±0.17	NI

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
Zhou J, et al. (2015)	C57BL/6 mice (50)	M	Gavage	Diabetic + Low-sodium selenite (228.25 µg/kg/day) Diabetic + High-sodium selenite (2000 µg/kg/day)	Diabetic control group	6 weeks	**Fasting glucose:** Se 0.5mg/kg - 17.62±2.91 Vs 17.04±0.4 mmol/L Se 2.0 mg/kg – 18,59±2.28 Vs 17.04±2.33 mmol/L **Fasting insulin:** Se 0.5mg/kg – 34.62±4.08 Vs 32.69±3.15 µU/mL Se 2.0 mg/kg – 40.94±3.25 Vs 32.69±3.15 µU/mL **HOMA-IR:** Se 0.5 mg/kg- 27.0±4.88 Vs 24.71±3.74 Se 2.0 mg/kg – 33.49±3.75Vs 24.71±3.74	Liver	NI	**p-Akt:** Se 2.0 mg/kg 0.29±0.32 Vs 0.45±0.45
Barakat G, et al., (2017)	Sprague-Dawly rats (40)	M	Oral (Water)	Diabetic + 5000 µg/kg/day of Sodium selenite	Diabetic control group	4 weeks	NI	Pancreas	**IRS-1:** 0.36±0.01 Vs 0.19±0.01	**IRS-1:** 0.17±0.01 Vs 8.0±0.19
Abdulmaleck and Balbaa (2019)	Wistar rats (120)	M	Oral	Se-NPs (100 µg/kg/day of sodium selenite) Se-NPs (400 µg/kg/day)	Diabetic control group	8 weeks	**Fasting glucose:** Se 0.1mg/kg - 6.11±0.19 Vs 19.33±19.33±0,31 mmol/L Se 0.4mg/kg - 6.0±0.18 Vs 19.33±0.31 mmol/L **Fasting insulin:** Se 0.1mg/kg -15.63±0.23 Vs 35.12±0.35	Liver	NI	**p-IRS-1:** Se 0.1mg/kg - 0.89±0.04 Vs 0.26±0.4 Se 0.4mg/kg – 0.55±0.04 Vs 0.26±0.04 **p-Akt:**

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
							µU/mL Se 0.4mg/kg – 14.84±0.16 Vs 35.12±35.12 µU/mL **HOMA-IR** Se 0.1mg/kg – 4.24±0.14 Vs 3.95±0.17 mg/dL Se 0.4mg/kg –3.95±0.17 Vs 30.17±0.21 mg/dL **HOMA-β:** Se 0.1mg/kg – 119.71±1.03 Vs 44,66±0.95 Se 0.4mg/kg – 118.72±1.05 Vs 44,66±0.95			0.75±0.04 Vs 0.04 Vs 0.96±0.03 Vs 0.23±0.23
Hassan RM, et al., (2021)	Albino rats (60)	M	Oral	Diabetic + Sodium selenite (400 µg/kg/day)	Diabetic control group	6 weeks	**Fasting glucose:** 6.51±0.06 Vs 15.28±2.86 mmol/L **Fasting insulin:** 38.21±0.48 Vs 25.02±0.48 µU/mL **HbA1c:** 7.38±0.7 Vs 9.5±0.04% **HOMA-IR** 11.05±0.19 Vs 15.75±1.16 mg-dL	Liver	**IRS-1:** 0.8±0.0 Vs 0.26±0.02	NI

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
Cai X, et al., (2024)	Db/db and Db/m Mice (100)	M	Diet	**(Db/Db)** Db/db group Sodium selenite 100 µg/kg/day Db/db group Sodium selenite 300 µg/kg/day Db/db group Sodium selenite 900 µg/kg/day Db/db group Sodium selenite 2700 µg/kg/day **(Db/m)** Db/m droup Sodium selenite 100 µg/kg/day Db/m group Sodium selenite 300 µg/kg/day Db/m group Sodium selenite 0.9 mg/kg Db/m group Sodium selenite 2700 µg/kg/day	Db/db diabetic control (Se 0) Db/m diabetic control (Se 0)	12 weeks	**Fasting glucose (Db/db)** Se 100 µg/kg/day - 28.67±1.89 Vs 29.71±2.86 mmol/L 300 µg/kg/day – 30.33±3.16 Vs 29.71±2.86 mmol/L Se 900 µg/kg/day – 28.67±3.32 Vs 29.71±2.86 mmol/L Se 2700 µg/kg/day - 30.43±2.39 Vs 29.71 Vs 2.89 mmol/L **(Db/m)** Se 100 µg/kg/day - 4.04±0.5 Vs 4.37±1.12 mmol/L Se 300 µg/kg/day – 4,93±0,81 Vs 4.37±1.12 mmol/L Se 900 µg/kg/day – 5.34±0.62 Vs 4.37±1.12 mmol/L Se 2700 µg/kg/day – 5.1±0.67 Vs 4.37±1.12 mmol/L (↑ Fasting glucose Only in db/db mice) **Fasting insulin:** **(Db/db)** Se 100 µg/kg/day – 9.67±2.73 Vs 6.8±1.23 µU/mL Se 300 µg/kg/day – 9.43±2.37 Vs 6.8±1.23 µU/mL	Liver	**IR:** **(Db/Db)** Se 100 µg/kg/day – 1.57±0.58 Vs 1.69±1.51 Se 300 µg/kg/day – 4.44±2.66 Vs 1.69±1.51 Se 900 µg/kg/day – 1.57±0.65 Vs 1.69±1.51 Se 2700 µg/kg/day – 1.44±0.76 Vs 1.69±1.51 **(Db/m)** Se 100 µg/kg/day – 1.65±1.08 Vs 1.11±0.89 Se 300 µg/kg/day – 1.43±0.4 Vs 1.11±0.89 Se 900 µg/kg/day – 0.94±0.46 Vs 1.11±0.89	NI

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
							Se 900 µg/kg/day - 8.04±2.92 Vs 6.8±1.23 µU/mL Se 2700 µg/kg/day – 13,38±5.97 Vs 6.8±1.23 µU/mL (Db/m) Se 100 µg/kg/day – 28,82±3.51 Vs 6.8±1.23 µU/mL Se 300 µg/kg/day - 27.05±1.68 Vs 6.8±1.23 µU/mL Se 900 µg/kg/day – 26.29±4.4.02 Vs 6.8±1.23 µU/mL Se 2700 µg/kg/day – 21.27±0.88 Vs 6.8±1.23 µU/mL (Only in db/m mice) **HbA1c** **(Db/db)** Se 100 µg/kg/day – 7.8±0.8 Vs 8.6±0.5% Se 300 µg/kg/day – 8.0±0.72 Vs 8.6±0.5% Se 900 µg/kg/day - 8.13±0.76Vs 8.6±0.5% Se 2700 µg/kg/day - 7.93±0.5 Vs 8.6±0.5% **(Db/m)** Se 100 µg/kg/day –3.4 ±0.09 Vs 3.43±0.08% Se 300 µg/kg/day – 3.47 ±0.08 Vs 3.43±0.08% Se 900 µg/kg/day - 3.45±0.05 –Vs 3.43±0.08%		Se 2700 µg/kg/day – 1.42±0.69 Vs 0.69 Vs 1.11±0.89 **GLUT4:** **(Db/Db)** Se 100 µg/kg/day - 1.51±0.46 Vs 1.37±1.04 Se 300 µg/kg/day – 4.81±2.84 Vs 1.37±1.04 Se 900 µg/kg/day – 1.51±3.48 Vs 1.37±1.04 Se 2700 µg/kg/day – 1.79±0.72 Vs 1.37±1.04 **(Db/m)** Se 100 µg/kg/day – 2.89±0.59 Vs 1.16±0.69 Se 300 µg/kg/day – 1.22±0;29 Vs 1.16±0.69	

	Animals		Rout	Intervention	Comparator	Duration	Glycemic Control Parameters Intervention Vs Comparator	Sample	Gene expression	Protein expression
	Species (n)	Gender								
							Se 2700 µg/kg/day – 3.38±0.08 Vs 3.43±0.08% **HOMA-IR (Db/Db)** Se 100 µg/kg/day – 12.7±3.37 Vs 8.57±1.53 mg/dL Se 300 µg/kg/day – 12.64±3.37 Vs 8.57±1.53 mg/dL Se 900 µg/kg/day – 10.12±3.64 Vs 8.57±1.53 mg/dL 2700 µg/kg/day – 14.14±6.7 Vs 8.57±1.53 mg/dL **(Db/Db)** Se 100 µg/kg/day – 5,44±0.49 Vs 4.85±0.83 mg/dL Se 300 µg/kg/day – 4.96±0.63 Vs 4.85±0.83 mg/dL Se 900 µg/kg/day - 5.54±0.98 Vs 4.85±0.83 mg/dL Se 2700 µg/kg/day – 4.51±0.37 Vs 4.85±0.83 mg/dL		Se Se 900 µg/kg/day – 0.82±0.13 Vs 1.16±0.69 Se 2700 µg/kg/day – 1.45±0.93 Vs 1.16±0.69	

NI: no information, IPI: intraperitoneal injection, M: male, IR: insulin receptor, IRS-1: insulin receptor substrate 1, p-IRS1: phosphorylated IRS-1, Akt: protein kinase B, p-Akt: phosphorylated Akt, PI3K: phosphatidylinositol 3-kinase, p-PI3K: phosphorylated PI3K, GLUT-4: glucose transporter 4, HbA1c: Glycated haemoglobin, HOMA-IR: homeostasis model assessment of insulin resistance, HOMA- β: homeostasis model assessment of β-cell funtion, Se-ExPS: selenium enriched exopolysaccharide, Se-NPs: selenium nanoparticles, VAT: visceral adipose tissue.

Source: Soares TC, et al., 2026.

Methodological quality assessment

Most studies presented medium risk of bias. Reporting deficiencies were common in allocation, concealment, randomization, and blinding. However, selective reporting bias was generally low, and no major additional sources of bias were identified (**Table 2**).

Table 2 - Risk assessment using the SYRCLE tool for bias risk assessment.

Autores, Ano	1	2	3	4	5	6	7	8	9	10
Hwang D, et al. (2007)	ND	S	ND	ND	ND	ND	ND	ND	ND	S
Xu TJ, et al. (2007)	ND	N	ND	ND	ND	ND	ND	S	ND	S
Kim SS, et al. (2011)	ND	S	ND	ND	ND	ND	ND	N	S	S
Barakat GM, et al. (2012)	ND	ND	ND	ND	ND	ND	ND	S	S	S
Wang C, et al. (2014)	ND	ND	ND	ND	ND	ND	ND	ND	S	S
Zhou X, et al. (2014a)	ND	ND	ND	ND	ND	ND	ND	S	S	S
Zhou X, et al. (2014b)	ND	ND	ND	ND	ND	ND	ND	ND	S	S
Al-Quraishy S, et al. (2015)	ND	S	ND	ND	ND	ND	ND	S	S	S
Zhou J, et al. (2015)	ND	ND	ND	ND	ND	ND	ND	N	S	S
Barakat G, et al. (2017)	ND	ND	ND	ND	ND	ND	ND	S	S	S
Abdulmalek AS and Balbaa M (2019)	ND	ND	ND	ND	ND	ND	ND	S	S	S
Hassan RM, et al. (2021)	ND	ND	ND	ND	ND	ND	S	S	S	S
Cai X, et al. (2024)	ND	S	ND	ND	ND	ND	ND	N	S	S

Note: (Y): green code indicates compliance; (N): red code indicates non-compliance; (ND): yellow code indicates that data are not available. (1): Allocation sequence; (2): Baseline characteristics; (3): Allocation concealment; (4): Randomization of accommodation; (5): Caregiver blinding; (6): Randomization in outcome assessment; (7): Outcome assessment blinding; (8): Incomplete outcome data; (9): Selective outcome reporting; (10): Other sources of bias.
Source: Soares TC, et al., 2026.

Effects of selenium supplementation on glycemic control parameters

Among the studies included in this review, ten evaluated glycemic control parameters, which involved blood glucose (CAI X, et al., 2024; HASSAN RM, et al., 2021; WANG C et al., 2014; AL-QURAISHY S, et al., 2015; BARAKAT G, et al., 2017; HWANG D, et al, 2007; XU TJ, et al., 2010; KIM SS, et al., 2011; ZHOU J, et al., 2015; ABDULMALEC AS and BALBAA M, 2019), eight evaluated fasting insulin (CAI X, et al., 2024; HASSAN RM, et al., 2021; WANG C, et al., 2014; AL-QURAISHY S, et al., 2015; HWANG D, et al, 2007; KIM SS, et al., 2011; ZHOU J, et al., 2015), four evaluated glycated haemoglobin (CAI X, et al., 2024; HASSAN RM, et al., 2021; WANG C et al., 2014; XU TJ, et al., 2010), six evaluated HOMA-IR (CAI X, et al., 2024; HASSAN RM, et al., 2021; WANG C et al., 2014; KIM SS, et al., 2011; ZHOU J, et al., 2015; ABDULMALEC AS and BALBAA M, 2019), and one evaluated HOMA-β in animal model of diabetes (ABDULMALEC AS and BALBAA M, 2019).

Regarding fasting blood glucose, eight studies demonstrated that selenium supplementation reduced the concentrations of this marker in diabetic rodents compared to non-supplementation (HASSAN RM, et al., 2021; WANG C et al., 2014; AL-QURAISHY S, et al., 2015; BARAKAT G, et al., 2017; HWANG D, et al, 2007; XU TJ, et al., 2010; KIM SS, et al., 2011).

On the other hand, this mineral was associated with increased fasting blood glucose in diabetic rodents in two studies (CAI X, et al., 2024; ABDULMALEC AS and BALBAA M, 2019). The meta-analysis (nine studies, 260 animals) found no overall significant effect, though selenium reduced glycemia in the rat subgroup (**Figure 2A**).

Eight studies evaluated fasting insulin (**Figure 2B**). Selenium increased insulin in some models and decreased it in others. Meta-analysis (seven studies) revealed no global effect; rats showed reduced insulin, while mice showed increased insulin.

Glycated haemoglobin was evaluated in three studies (**Figure 3A**); two reported reductions. Meta-analysis found no significant effect between the groups (**Figure 3A**). Six studies (146 animals) evaluated the effect of selenium supplementation on the HOMA-IR index in animal models of diabetes (**Figure 3B**). Pooled analysis showed no significant difference (p = 0.59), with high heterogeneity (I^2 = 88%). Three studies (70 animals) were conducted with rats and three (146 animals) with mice. In subgroup analysis, supplementation was associated with a reduction in HOMA-IR in the rat studies (p = 0.02), although with high heterogeneity (I^2 = 93%).

Figure 2A e 2B - Fasting glucose and fasting insulin levels in animals with diabetes undergoing selenium Supplementation.

Figure 2A

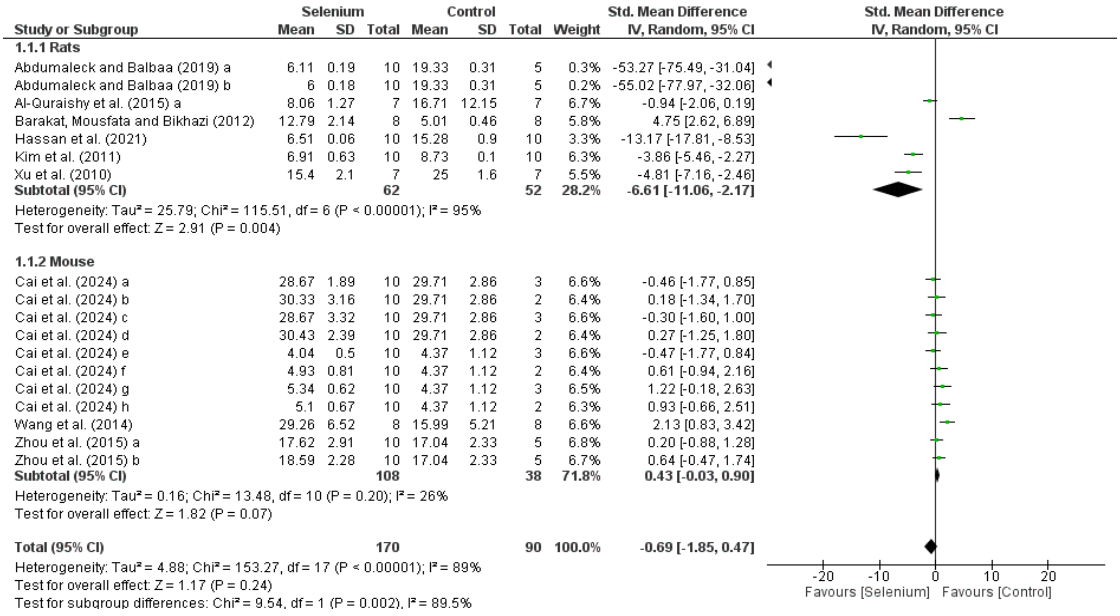
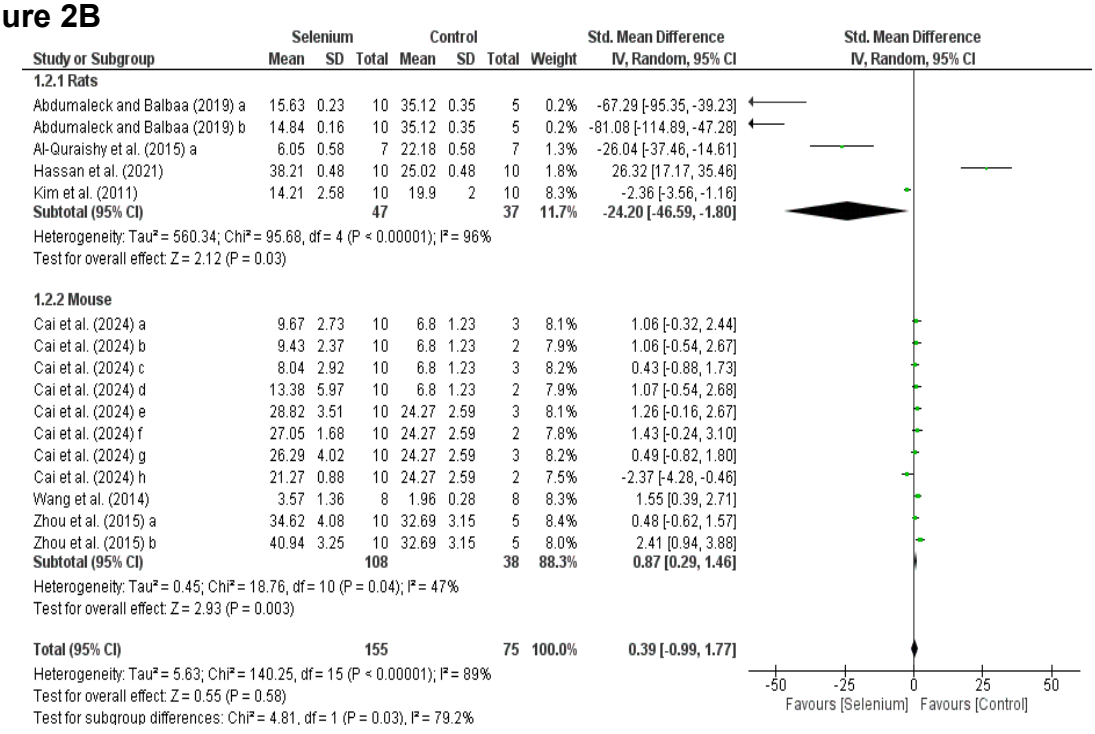


Figure 2B



Source: Soares TC, et al., 2026.

Figure 3A e 3B - Glycated haemoglobine HOMA-IR index in animals with diabetes undergoing selenium supplementation.

Figure 3A

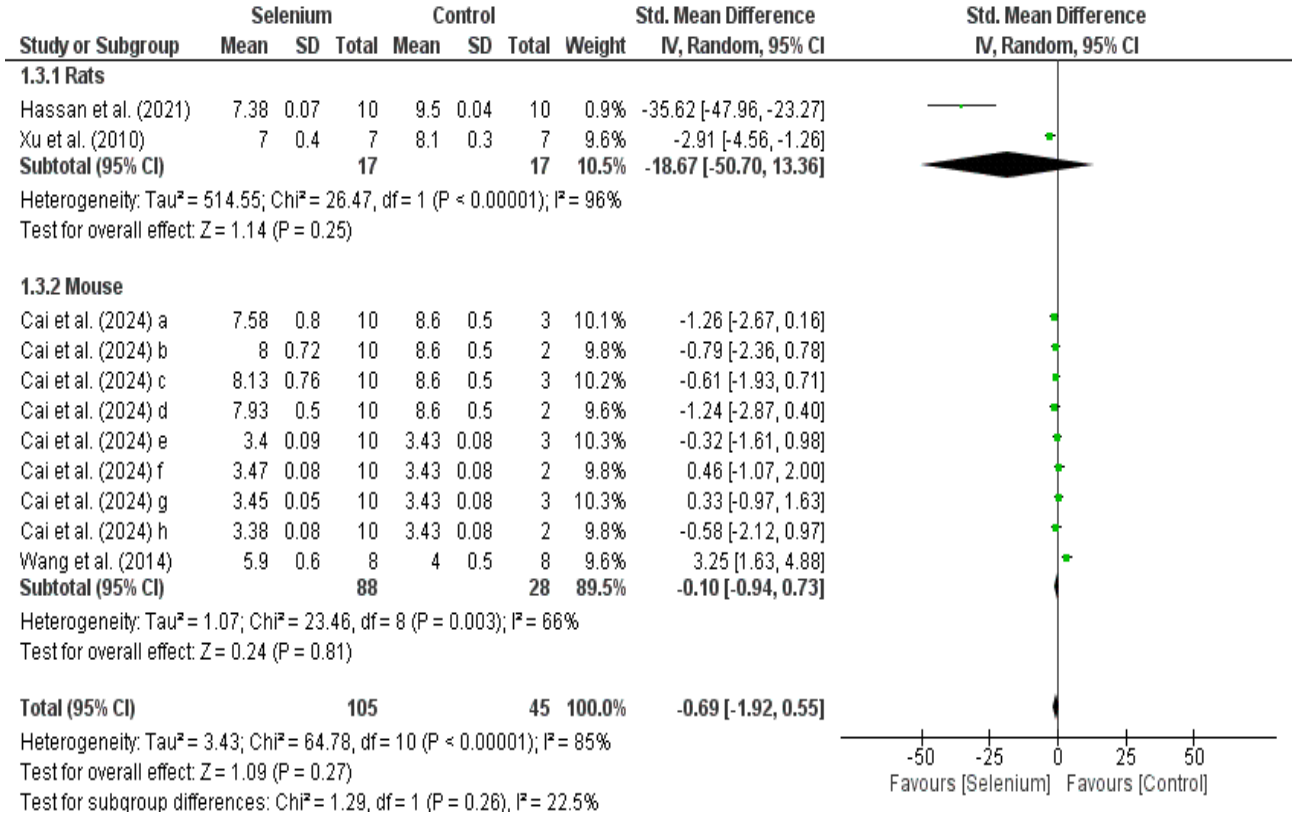
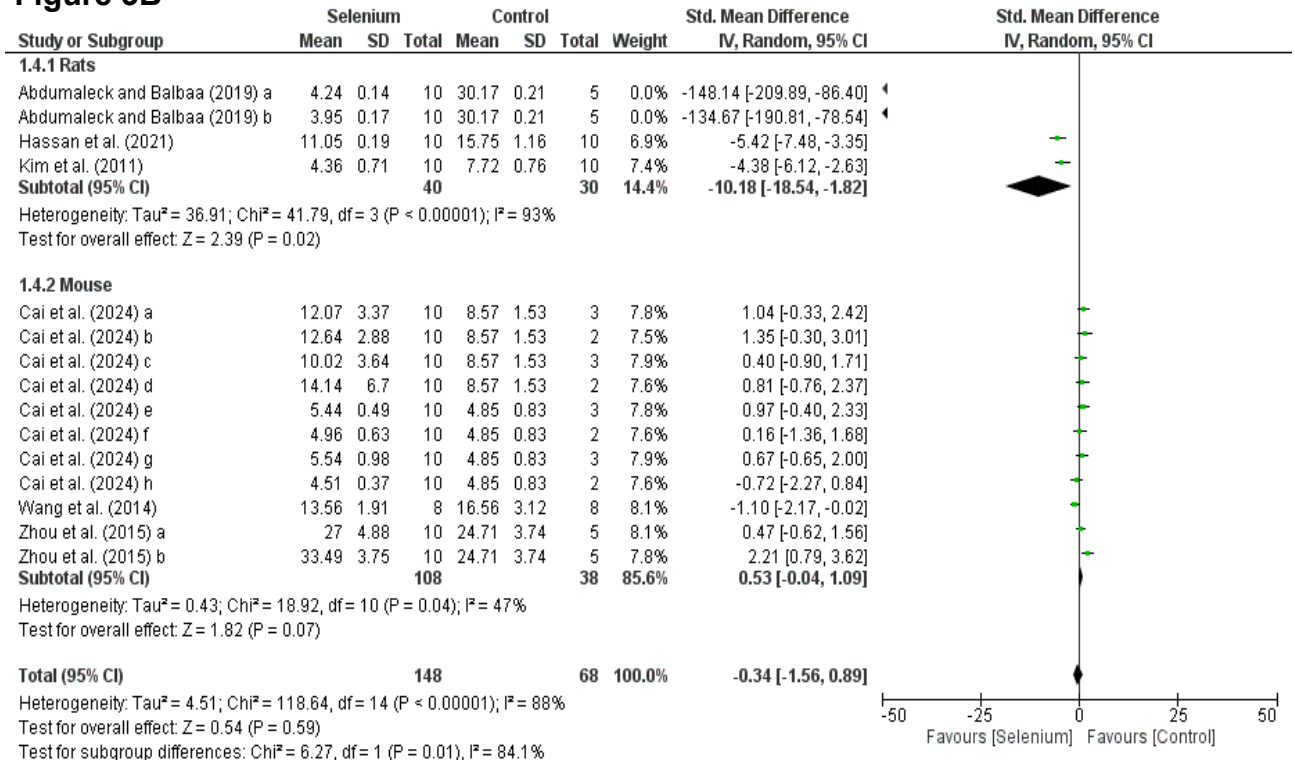


Figure 3B



Source: Soares TC, et al., 2026.

Effect of selenium supplementation on the expression of genes encoding proteins of the PI3K/Akt/GLUT-4 pathway

Regarding the study conducted by Wang C, et al. (2014) showed lower insulin receptor gene expression in the liver and kidney tissues of mice, Al-Quraishy S, et al. (2015) found increased gene expression in the liver of rats, and Cai X, et al. (2024) observed no difference in the liver of supplemented mice compared to non-supplemented mice with diabetes.

Regarding the analysis of IRS-1 gene expression, three studies demonstrated higher gene expression of this substrate in the liver, kidneys, and/or pancreas of rats treated with selenium (AL-QURAISHY S, et al., 2015; BARAKAT G, et al., 2017; HASSAN RM, et al., 2021), and one study showed lower expression in the liver of rats (BARAKAT GM, et al., 2012) (**Figure 4A**). The study by Cai X, et al. (2024) showed reduced GLUT-4 expression in the liver of supplemented mice.

Effect of selenium supplementation on the expression of proteins in the PI3K/Akt/GLUT-4 pathway

One study found increased expression in pancreatic tissue in mice (WANG C et al., 2014). Regarding IRS-1, one study found increased expression in the liver of rats (ABDULMALEC AS and BALBAA M, 2019), one study observed reduced expression of this protein in the liver of rats (BARAKAT GM, et al., 2012), and one study found no difference in the expression of this protein in the pancreas of rats (BARAKAT G, et al., 2017).

One study found increased expression of the Akt protein in the liver of mice (HWANG D, et al, 2007). Regarding phosphorylated Akt protein (p-Akt), two studies showed higher expression in the liver of rats (ABDULMALEC AS and BALBAA M, 2019) and mice (HWANG D, et al, 2007).

One study observed lower pAkt expression in the liver of mice supplemented with selenium compared to those not supplemented. The study by Hwang D, et al. (2007) showed lower PI3K expression but higher pPI3K expression in the liver of mice supplemented with selenium compared to those not supplemented.

Other studies have shown an increase in GLUT-4 in the skeletal muscle of diabetic mice (HWANG D, et al, 2007; ZHOU X, et al., 2014a) supplemented with this nutrient, as well as in the visceral adipose tissue of diabetic mice (ZHOU X, et al., 2014b). However, there was no statistical difference between groups in terms of GLUT-4 expression in the heart muscle of diabetic rats (XU TJ, et al., 2010) after selenium supplementation.

Meta-analyses of gene and protein expression in the PI3K/Akt/GLUT-4 pathway

The meta-analysis also investigated the gene and protein expression of IRS-1 (**Figure 4A** and **4B**). There was no significant difference between the groups in gene expression ($p = 0.10$), with high heterogeneity ($I^2 = 92\%$). The studies included in the review also evaluated the levels of Akt protein not (**Figure 4C** and **4D**) and GLUT-4 (**Figure 4E**) proteins in animal models of diabetes.

The meta-analysis of two studies encompassing 54 animals demonstrated a significant increase in GLUT-4 protein levels in the supplemented group (Figure 9; $p < 0.05$), although with high heterogeneity ($I^2 = 93\%$). Finally, two studies evaluated insulin receptor expression in animal models of diabetes supplemented with selenium.

The combined analysis did not identify significant differences between the groups ($p = 0.75$), with heterogeneity considered acceptable ($I^2 = 38\%$). It should be noted that it was not possible to analyze other proteins of the PI3K/Akt/GLUT-4 signaling pathway due to the insufficient number of studies.

Figure 4A, 4B, 4C, 4D E 4E - Expression of the IRS-1 gene (4A), IRS1 protein (4B), Akt protein (4C) and GLUT-4 protein (4D) and insulin receptor (4E) in diabetic animals supplemented with selenium.

Figure 4A

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Al-Quraishy et al. (2015) a	12.94	0.8	7	9.34	0.63	7	24.8%	3.60 [2.85, 4.35]
Al-Quraishy et al. (2015) b	8.36	0.2	7	3.42	0.17	7	25.1%	4.94 [4.75, 5.13]
Barakat, Mousfata and Bikhazi (2012)	0.67	0.24	8	1.44	0.96	8	24.9%	-0.77 [-1.46, -0.08]
Barakat et al. (2017)	0.08	0.01	8	0.08	0.01	8	25.2%	0.00 [-0.01, 0.01]
Hassan et al. (2021)	0.8	0	10	0.26	0.02	10		Not estimable
Total (95% CI)			**40**			**40**	**100.0%**	**1.94 [-1.32, 5.21]**

Heterogeneity: Tau² = 11.02; Chi² = 2564.92, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.17 (P = 0.24)

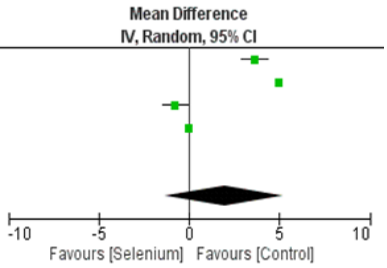


Figure 4B

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdumaleck and Balbaa (2019) a	0.89	0.04	10	0.26	0.4	5	0.6%	0.63 [0.28, 0.98]
Abdumaleck and Balbaa (2019) b	0.55	0.04	10	0.26	0.4	5	0.6%	0.29 [-0.06, 0.64]
Barakat, Mousfata and Bikhazi (2012)	0.36	0.01	8	0.39	0.01	8	49.4%	-0.03 [-0.04, -0.02]
Barakat et al. (2017)	0.17	0.01	8	0.19	0.01	8	49.4%	-0.02 [-0.03, -0.01]
Total (95% CI)			**36**			**26**	**100.0%**	**-0.02 [-0.05, 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 18.41, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 1.33 (P = 0.18)

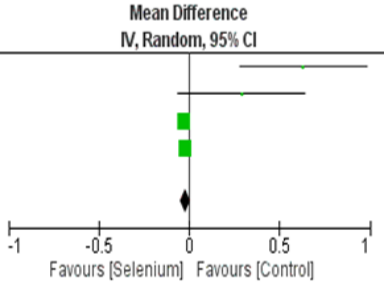


Figure 4C

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abdumaleck and Balbaa (2019) a	0.75	0.04	10	0.23	0.03	5	33.8%	13.15 [7.57, 18.74]
Abdumaleck and Balbaa (2019) b	0.96	0.03	10	0.23	0.03	5	30.5%	22.90 [13.30, 32.51]
Zhou et al. (2015) a	0.29	0.31	8	0.99	1.1	8	35.7%	-0.82 [-1.85, 0.21]
Total (95% CI)			**28**			**18**	**100.0%**	**11.13 [-2.59, 24.85]**

Heterogeneity: Tau² = 136.92; Chi² = 45.52, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.59 (P = 0.11)

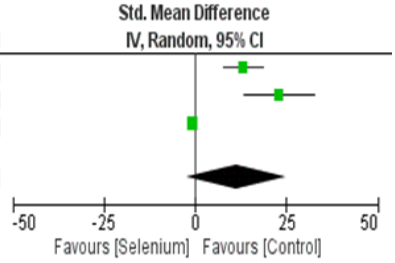


Figure 4D

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kim et al. (2011) a	137.87	7.63	10	100.46	0.1	10	40.0%	37.41 [32.68, 42.14]
Kim et al. (2011) b	123.62	5.74	10	99.78	1.3	10	41.0%	23.84 [20.19, 27.49]
Xu et al. (2010)	80.91	20.83	7	67.92	18.12	7	19.0%	12.99 [-7.46, 33.44]
Total (95% CI)			**27**			**27**	**100.0%**	**27.20 [15.21, 39.19]**

Heterogeneity: Tau² = 87.75; Chi² = 22.11, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 4.45 (P < 0.00001)

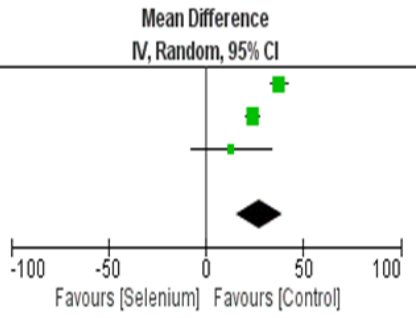
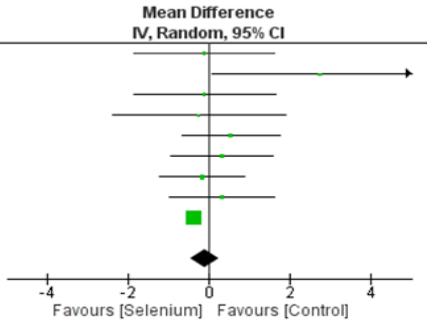


Figure 4E

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cai et al. (2024) a	1.57	0.58	10	1.69	1.51	3	4.0%	-0.12 [-1.87, 1.63]
Cai et al. (2024) b	4.44	2.66	10	1.69	1.51	2	1.8%	2.75 [0.09, 5.41]
Cai et al. (2024) c	1.57	0.65	10	1.69	1.51	3	3.9%	-0.12 [-1.88, 1.64]
Cai et al. (2024) d	1.44	0.76	10	1.69	1.51	2	2.7%	-0.25 [-2.40, 1.90]
Cai et al. (2024) e	1.65	1.08	10	1.11	0.89	3	7.7%	0.54 [-0.67, 1.75]
Cai et al. (2024) f	1.43	0.4	10	1.11	0.89	2	7.2%	0.32 [-0.94, 1.58]
Cai et al. (2024) g	0.94	0.46	10	1.11	0.89	3	9.9%	-0.17 [-1.22, 0.88]
Cai et al. (2024) h	1.42	0.69	10	1.11	0.89	2	6.7%	0.31 [-1.00, 1.62]
Wang et al. (2014)	0.64	0.07	8	1.01	0.23	8	56.1%	-0.37 [-0.54, -0.20]
Total (95% CI)			**88**			**28**	**100.0%**	**-0.11 [-0.46, 0.25]**

Heterogeneity: Tau² = 0.05; Chi² = 9.45, df = 8 (P = 0.31); I² = 15%
Test for overall effect: Z = 0.58 (P = 0.56)



Source: Soares TC, et al., 2026.

DISCUSSION

This review examined the effects of selenium supplementation on PI3K/Akt/GLUT-4 insulin signaling in diabetic animal models. Variability among studies may be explained by species-specific differences, since rats and mice differ in bile acid profiles and metabolic responses (ZHOU J, et al., 2015; ABDULMALEC AS and BALBAA M, 2019), as well as in genetic and phenotypic traits that affect protein expression and insulin-pathway regulation (ZHENG D, et al., 2024; ZHOU J, et al., 2015).

A consistent finding is the U-shaped, dose-dependent action of selenium, where both deficiency and excess impair insulin sensitivity. Physiological selenium levels favor Akt phosphorylation and GLUT-4 translocation, but high doses trigger oxidative and epigenetic disturbances leading to insulin resistance (LIU T, et al., 2023). Selenium deficiency reduces IR, IRS-1, IRS-2, PI3K, Akt, and glucose transporter expression (YANG J, et al., 2017), whereas excessive intake (2000 µg/kg/day) decreases IRS-1, IRS-2, PI3K, Akt and p-Akt, promoting insulin resistance in healthy rats (STAHEL P, et al., 2017).

Beyond its antioxidant role, selenium influences selenoprotein-dependent pathways involved in endoplasmic reticulum stress, autophagy, and insulin sensitivity (WANG Z, et al., 2022). Its interaction with transcription factors such as PPARγ and NRF2 (STAPLETON SR, et al., 1997) may explain improved GLUT-4 expression after moderate supplementation. Classic studies showed selenium-induced phosphorylation of IR, IRS-1 and Akt (HEI YJ, et al., 1998; MCNEIL JH, 1991), increased PI3K expression and positive correlations with GLP-1R, IRS-1 and preproinsulin (WANG C et al., 2014; HWANG D, et al, 2007).

Selenium may enhance glycemic control by reducing oxidative stress and inflammatory cytokines such as IL-1, IL-6 and TNF-α (FARROKHIAN A, et al., 2016; STRÓŻYK A, et al., 2019). Individuals with insulin resistance exhibit reduced selenium and lower GPx1, GPx3 and SelP levels (ALHARITHY M and ALAFIF N, 2023; LABUNSKY VM, et al., 2014). Selenium also modulates NF-κB and PPARs (Mattmiller et al., 2013; Shi et al., 2020) and influences insulin-related gene expression via epigenetic mechanisms such as DNA methylation (JABŁOŃSKA E and RESZKA E, 2017; SPECKMANN B, et al., 2017). Effects differ according to selenium form, with nanoparticles showing greater bioactivity and lower toxicity (HE J, et al., 2019; LABUNSKY VM, et al., 2014). Our meta-analysis identified increased GLUT-4 protein expression following supplementation.

Nonetheless, considerable evidence indicates detrimental effects of selenium on insulin metabolism. High selenium exposure and increased selenoprotein P can impair insulin signaling and worsen glycemic control (MITA Y, et al 2014; MISU H, et al., 2012; SAITO Y, et al., 2020). Hepatic overproduction of selenoprotein P induces insulin resistance (MISU H, et al., 2010), and its excess is inversely correlated with adiponectin in type 2 diabetes (MISU H, et al., 2012). Some selenium compounds delay insulin signaling in skeletal muscle, and excessive selenoprotein P disrupts metabolic redox balance (SAITO Y, 2020). Recent findings show that high selenium intake upregulates PHGDH, causing metabolic dysfunction, while serine supplementation attenuates selenium-induced insulin resistance (WANG C et al., 2014). These results highlight that selenium's effects depend on dose, chemical form, duration, metabolic state, and species-specific characteristics.

This review is limited by the small number of available studies and substantial heterogeneity in doses, forms, routes and duration of supplementation, as well as differences in experimental models and molecular analyses. Nonetheless, the systematic approach and meta-analysis strengthen the integration of molecular and biochemical data, emphasizing selenium's complex and context-dependent influence on insulin signaling.

FINAL CONSIDERATIONS

The findings of this review indicate that selenium supplementation may exert modulatory effects on the PI3K/Akt/GLUT-4 signaling pathway and on glucose metabolism parameters in animal models. However, these effects are not uniform among the species studied, and the magnitude of the responses varies according to the type of compound used, the dose administered, the exposure time, and the tissue analyzed. Although some studies show improvement in the glycemic profile and increased expression of a protein related to insulin action, other studies report no significant effect or even divergent responses, especially when comparing rats

and mice. These results suggest that the relationship between selenium and insulin signaling is complex and multifactorial and cannot be interpreted in a linear or causal manner. Therefore, although there is evidence of a beneficial role for selenium, especially when administered in physiological doses, current data do not allow for a definitive conclusion about its efficacy or safety in the context of insulin resistance. Additional studies, with standardized protocols, omic analyses, and translational approaches, are needed to clarify the molecular mechanisms involved and verify the applicability of these findings in animal models.

ACKNOWLEDGEMENTS AND FUNDING

This study was funded by the Piauí State Research Support Foundation – FAPEPI.

REFERENCES

1. ALHARITHY M, ALAFIF N. Association of Selenium Intake and Selenium Concentrations with Risk of Type 2 Diabetes in Adults: A Narrative Review. Metabolites, 2023; 13: 767.
2. ABDULMALEK AS, BALBAA M. Synergistic effect of nano-selenium and metformin on type 2 diabetic rat model: Diabetic complications alleviation through insulin sensitivity, oxidative mediators and inflammatory markers. PLoS One, 2019; 14: e0220779.
3. AL-QURAISHY S, et al. Anti-hyperglycemic activity of selenium nanoparticles in streptozotocin-induced diabetic rats. International Journal of Nanomedicine, 2015; 10: 6741–6756.
4. BARAKAT GM, et al. Effects of Selenium and Exendin-4 on Glucagon-Like Peptide-1 Receptor, IRS-1, and Raf-1 in the Liver of Diabetic Rats. Biochemical Genetits, 2012; 50: 922–935.
5. BARAKAT G, et al. Effects of exendin-4 and selenium on the expression of GLP-1R, IRS-1, and preproinsulin in the pancreas of diabetic rats. Journal of Physiology Biochemistry, 2017; 73: 387-394.
6. CAI X, et al. Dosage-effect of selenium supplementation on blood glucose and oxidative stress in type 2 diabetes mellitus and normal mice. Journal of Trace Elements in Medicine and Biology, 2024; 3: 127410.
7. DUBEY P, et al. Role of Minerals and Trace Elements in Diabetes and Insulin Resistance. Nutrients, 2020; 12: 1864.
8. FARROKHIAN A, et al. Selenium Supplementation Affects Insulin Resistance and Serum hs-CRP in Patients with Type 2 Diabetes and Coronary Heart Disease. Hormone and Metabolic Research, 2016; 48: 263-268.
9. HASSAN RM, et al. Mitigating effect of single or combined administration of nanoparticles of zinc oxide, chromium oxide, and selenium on genotoxicity and metabolic insult in fructose/streptozotocin diabetic rat model. Environmental Science and Pollution Research, 2021; 28: 48517-48534.
10. HE J, et al. Nano-selenium modulates glucose metabolism and reduces insulin resistance through activation of the PI3K/Akt pathway in diabetic mice. Journal of Trace Element in Medicine and Biology, 2019; 81: 127130.
11. HEI YJ, et al. Stimulation of MAP kinase and S6 kinase by vanadium and selenium in rat adipocytes. Molecular and Cellular Biochemistry, 1998; 178: 367-375.
12. HWANG D, et al. Selenium acts as an insulin-like molecule for the down-regulation of diabetic symptoms via endoplasmic reticulum stress and insulin signalling proteins in diabetes-induced non-obese diabetic mice. Journal of Biosciences, 2007; 32: 723–735.
13. JABŁOŃSKA E, RESZKA E. Selenium and Epigenetics in Cancer: Focus on DNA Methylation. Advances in Cancer Research, 2017; 136 :193-234.
14. KIM SS, et al. Exercise training and selenium or a combined treatment ameliorates aberrant expression of glucose and lactate metabolic proteins in skeletal muscle in a rodent model of diabetes. Nutrition Research and Practice, 2011; 5: 205-213.
15. LABUNSKYY VM, et al. Selenoproteins: molecular pathways and physiological roles. Physiological Reviews, 2014; 94: 739-777.
16. LE TKC, et al. Insulin signaling and its application. Frontiers in Endocrinology, 2023; 14: 1226655.

17. LIU T, et al. Dual role of selenium in oxidative stress and insulin signaling: dose-dependent effects in metabolic disorders. Free Radical Biology and Medicine, 2023; 207: 146–157.
18. MATTMILLER SA, et al. Regulation of inflammation by selenium and selenoproteins: impact on eicosanoid biosynthesis. Journal of Nutritional Science, 2013; 2: e28.
19. MCNEILL JH, et al. Insulinlike effects of sodium selenate in streptozocin-induced diabetic rats. Diabetes 1991; 40: 1675-1678.
20. MISU H, et al. Inverse correlation between serum levels of selenoprotein P and adiponectin in patients with type 2 diabetes. PLoS One, 2012; 7: e34952.
21. MISU H, et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metabolism, 2010; 12: 483-495.
22. MITA, Y., et al. Selenoprotein P-neutralizing antibodies improve insulin secretion and glucose sensitivity in type 2 diabetes mouse models. Nature Communications, 2017; 8: 1658.
23. MURANO K, et al. Role of supplementary selenium on the induction of insulin resistance and oxidative stress in NSY mice fed a high fat diet. Biolpgical & Pharmaceutical Bulletin, 2018; 41: 92-98.
24. NORTON L, et al. Insulin: The master regulator of glucose metabolism. Metabolism, 2022; 129: 155142.
25. SAITO Y. Selenoprotein P as an in vivo redox regulator: disorders related to its deficiency and excess. Journal of Clinical Biochemistry and Nutrition, 2020; 66: 1-7.
26. SHI Y, et al. Trace Elements, PPARs, and Metabolic Syndrome. International Journal of Molecular Sciences, 2020; 21: 2612.
27. SPECKMANN B, et al. Selenium increases hepatic DNA methylation and modulates one-carbon metabolism in the liver of mice. The Journal of Nutritional Biochemistry, 2017; 48: 112-119.
28. STAHEL P, et al. Supranutritional selenium intake from enriched milk casein impairs hepatic insulin sensitivity via attenuated IRS/PI3K/AKT signaling and decreased PGC-1α expression in male Sprague–Dawley rats. The Journal of Nutritional Biochemistry, 2017; 41: 142–150.
29. STAPLETON SR, et al. Selenium: potent stimulator of tyrosyl phosphorylation and activator of MAP kinase. Biochimica et Biophysica Acta, 1997; 1355: 259-269.
30. STRÓŻYK A, et al. Effectiveness and safety of selenium supplementation for type 2 diabetes mellitus in adults: a systematic review of randomised controlled trials. J Human Nut and Dietetics, 2019; 32: 635-645.
31. WANG Q, et al. Increased Expression of PHGDH Under High-Selenium Stress In Vivo. Biological Trace Element Research, 2024; 202: 5145-5156.
32. WANG C, et al. Long-Term Supranutritional Supplementation with Selenate Decreases Hyperglycemia and Promotes Fatty Liver Degeneration by Inducing Hyperinsulinemia in Diabetic db/db Mice. PLoS One, 2014; 9: e101315.
33. WANG Z, et al. Selenium supplementation improves hepatic insulin sensitivity via NRF2 and PPARγ activation in diabetic models. Redox Biology, 2022; 224:102311.
34. XU, TJ, et al. The effect of insulin in combination with selenium on blood glucose and GLUT4 expression in the cardiac muscle of streptozotocin-induced diabetic rats. Fund & Clinical Pharm, 2010; 24: 199-204.
35. YANG J, et al. Selenium deficiency-induced thioredoxin suppression and thioredoxin knock down disbalanced insulin responsiveness in chicken cardiomyocytes through PI3K/Akt pathway inhibition. Cellular Signalling, 2017; 38: 192-200.
36. ZHENG D, et al. Comparative profiling of serum, urine, and feces bile acids in humans, rats, and mice. Communications Biology, 2024; 7: 641.
37. ZHOU X, et al. Selenium-enriched exopolysaccharides improve skeletal muscle glucose uptake of diabetic KKAy mice via AMPK pathway. Journal of Physiology and Biochemistry, 2014a; 70: 547–554.
38. ZHOU J, et al. Selenite exacerbates hepatic insulin resistance in mouse model of type 2 diabetes through oxidative stress-mediated JNK pathway. Toxicology and Applied Pharmacology, 2015; 289:409-418.
39. ZHOU J, et al. Selenite exacerbates hepatic insulin resistance in mouse model of type 2 diabetes through oxidative stress-mediated JNK pathway. Toxicol Appl Pharmacol, 2015; 289: 409-418.
40. ZHOU X, et al. Selenium enriched exopolysaccharides produced by Enterobacter cloacae Z0206 alleviate adipose inflammation in diabetic KKAy mice through the AMPK/SirT1 pathway. Molecular Medicine Reports, 2014b; 9: 683-688.