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Stevioside attenuates insulin resistance in skeletal muscle by facilitating IR/IRS-1/Akt/GLUT4 signaling pathways: an in vivo and in silico approach - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether stevioside, a glycoside extracted from *Stevia rebaudiana*, can improve insulin resistance in the gastrocnemius muscle of male rats rendered diabetic through a high-fat, high-sucrose diet. After 45 days of oral treatment, the treated animals showed an improvement in glucose tolerance, muscle glucose uptake, and markers linked to insulin signaling.In section 4.4 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that oxidative stress and reduced efficiency of the IRS-1–AKT–GLUT4 pathway accompany insulin resistance. Independent evidence confirms that cellular oxidation can reduce IRS-1/Akt signaling and GLUT4 translocation, and that AS160 links AKT to GLUT4 trafficking. However, the study did not directly measure AS160, AKT phosphorylation, or the amount of GLUT4 actually exposed on the membrane. The confirmation is therefore primarily mechanistic and experimental.

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether stevioside could attenuate diet-induced insulin resistance in skeletal muscle. The authors' hypothesis was that the compound would reduce oxidative stress and, alongside this change, recover components of the pathway through which insulin promotes glucose entry into the muscle fiber.The reason for the citation in paragraph 4.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is specific: in diabetic rats, stevioside was associated with a reduction in muscle oxidative markers, an increase in the expression of insulin receptor, IRS-1, AKT, and GLUT4, and greater glucose uptake. This places the research in the segment of the chain that goes from the intracellular redox environment to GLUT4 availability.The study can demonstrate that, in this animal model and under the experimental conditions adopted, these variations appeared together after treatment. However, it cannot establish that stevioside acted directly on IRS-1 or GLUT4, nor can it prove that the mechanism occurs through AS160. Molecular docking is a simulation that evaluates whether a molecule can fit into a specific area of a protein; it does not prove that the interaction occurs in the muscles of a living organism.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used 5–6-month-old male Wistar rats with an initial weight of 180 ± 20 g. Experimental type 2 diabetes was induced with a 60-day high-fat diet consisting of conventional feed, coconut oil, cholesterol, and cholic acid, plus water containing 30% sucrose. Animals with fasting glycemia above 120 mg/dL on day 58 were considered diabetic.The protocol describes five groups of six rats each: controls, controls treated with stevioside, untreated diabetic rats, diabetic rats treated with metformin, and diabetic rats treated with stevioside. Stevioside was administered orally at 20 mg/kg/day for 45 days; metformin at 50 mg/kg/day for the same period. However, the statistical analysis text refers to four groups, a methodological discrepancy compared to the study design description.Two days before euthanasia, fasting glycemia and an oral glucose tolerance test were performed. Insulin, lipids, and indicators of liver and kidney function were measured in the serum. In the gastrocnemius muscle, lipid peroxidation, hydrogen peroxide, hydroxyl radical, and antioxidant defenses—including catalase, superoxide dismutase, glutathione, and glutathione peroxidase—were evaluated.Glucose uptake and oxidation were measured in muscle fragments using radioactive tracers. The messenger RNA expression of the insulin receptor, IRS-1, AKT, and GLUT4 was analyzed using quantitative PCR, a technique that estimates how much a gene is transcribed into RNA. Data were analyzed using one-way analysis of variance and post-hoc tests; the authors considered a P-value of less than 0.05 to be statistically significant.

4. RESULTS

In rats fed a high-fat and sucrose diet, fasting glycemia and fasting insulinemia were increased compared to controls. This pattern is consistent with a reduced tissue response to insulin: to keep glucose under control, the body tends to produce more insulin. Treatment with stevioside reduced these parameters toward control values and improved glucose tolerance; the available text does not report the absolute values of the individual measurements.In the diabetic gastrocnemius muscle, markers of oxidative stress were increased and antioxidant defenses were reduced. Stevioside reduced lipid peroxidation, hydrogen peroxide, and hydroxyl radicals, while increasing catalase, superoxide dismutase, glutathione, and glutathione peroxidase. In simple terms, the treatment was associated with fewer signs of oxidative damage and a greater capacity of the tissue to neutralize reactive species.The result most relevant to the book is that diabetic rats showed lower messenger RNA expression of insulin signaling components, including the insulin receptor, IRS-1, AKT, and GLUT4. After stevioside, the expression of these markers increased. In parallel, glucose uptake and its oxidation in the muscle increased compared to untreated diabetic rats. The authors report that the trend was similar to that observed with metformin, but the available material does not allow for the extraction of all numerical values from the graphs.Docking estimated an energetically favorable interaction of stevioside with IRS-1 and a structural model of GLUT4, with binding energies of –8.27 and –7.8 kcal/mol, respectively. A negative value indicates that

the binding predicted by the program is energetically possible in the model; it is not proof of physical binding in muscle cells.

5. INTERPRETATION

For a muscle fiber, responding to insulin means moving more GLUT4 transporters—the proteins that allow glucose to enter—toward the cell surface. The study suggests that, in the diabetic rat, stevioside is associated with a recovery of conditions favorable to this process: lower oxidative stress, higher expression of certain insulin signaling nodes, and greater glucose uptake.The segment of the chain documented by the publication is therefore: increased oxidative stress in diabetic muscle reduced expression of IR/IRS-1/AKT/GLUT4 components and glucose uptake; treatment with stevioside the opposite direction for these measures. However, the work does not demonstrate the entire functional sequence described in the book. It did not measure PI3K, AKT phosphorylation, AS160 phosphorylation, or the translocation of GLUT4 to the plasma membrane.The distinction is relevant. A greater amount of GLUT4 RNA does not necessarily equate to a greater amount of GLUT4 on the membrane, which is the data point most directly linked to glucose uptake. Furthermore, the association between lower oxidative stress and the recovery of signaling does not, by itself, prove that the reduction in oxidative stress was the cause of the improvement. Independent experiments that directly modify these steps help to evaluate how biologically consistent the narrative is.

6. INDEPENDENT SUPPORTING EVIDENCE

The link between AKT, AS160, and GLUT4 was tested directly by Thong and colleagues in cultured muscle cells. By making AS160 non-phosphorylatable, the authors nearly abolished the increase in GLUT4 on the cell surface induced by insulin and other stimuli that activate AKT. This experiment does not concern stevioside, but it confirms the central step of the book's narrative: AS160 is a necessary regulator of GLUT4 trafficking in response to signals involving AKT [1]. The limitation is that this is primarily a cellular model, not a demonstration of the same chain in human muscle under diabetic conditions.A second study verified the relationship between oxidative damage and insulin signaling in rat L6 myotubes exposed to palmitate. Protecting mitochondrial DNA reduced superoxide production, increased insulin-dependent phosphorylation of IRS-1 and AKT, and increased GLUT4 translocation to the membrane. The result supports the biological direction proposed in the paragraph: an unfavorable oxidative environment can compromise the signal that brings GLUT4 to the surface, while reducing that source of stress can recover it [2]. The limitation is the use of cultured cells and genetic manipulation, which is different from the administration of stevioside.Mohd-Radzman and colleagues studied stevioside in 3T3-L1 adipocytes rendered insulin-resistant by the TNF-a factor. The compound increased glucose uptake by up to 4.4 times and improved the signals detected by tyrosine phosphorylation and IRS-1. This is independent confirmation that stevioside can be associated with a greater cellular insulin response and increased glucose entry [3]. However, it does not measure AKT, AS160, or GLUT4 and concerns murine adipose tissue, not skeletal muscle.Overall, the independent evidence builds a coherent network: AS160 links AKT activation to the appearance of GLUT4 in the membrane; lipid-induced oxidative stress can weaken IRS-1/AKT and GLUT4 translocation; stevioside has shown favorable activity on glucose uptake even in an independent cellular model. This convergence supports the general mechanism, but does not prove a therapeutic action of stevioside in humans.

7. CONFLICTING EVIDENCE

An important result for defining the interpretation comes from a study on Zucker rats, in which stevioside modestly increased insulin-stimulated muscle glucose transport at low concentrations between 0.01 and 0.1 mmol/L. However, at 0.5 mmol/L or higher concentrations, the effect was reversed in the muscle of lean rats: glucose transport did not increase further, but rather decreased compared to the benefit observed at lower doses [4].This evidence does not directly contradict the result of the analyzed study, because the model, duration of exposure, and dosage are different. However, it shows that the response to stevioside at the muscle level is
concentration-dependent and cannot be described as automatically favorable under all conditions. No directly conflicting evidence sufficiently relevant to the same long-term rat protocol with a high-fat and

sucrose diet has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent evidence that confirms or defines individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and molecular docking	Male Wistar rats with diet-induced diabetes (high-fat and sucrose); six rats per group	Stevioside reduced oxidative stress markers, increased IR/IRS-1/AKT/GLUT4 expression, and increased muscle glucose uptake	biologically consistent evidence	preliminary
[1]	Cellular and mechanistic	Cultured muscle cells and CHO-IR cells	Non-phosphorylatable AS160 almost abolished the increase in membrane GLUT4 induced by stimuli that activate AKT	direct confirmation	moderate
[2]	Cellular and mechanistic	Rat L6 myotubes exposed to palmitate	Reducing mitochondrial damage and superoxide increased phosphorylated IRS-1 and AKT and GLUT4 translocation	indirect confirmation	moderate
[3]	Cellular	Insulin-resistant 3T3-L1 murine adipocytes	Stevioside increased glucose uptake and IRS-1-associated signaling	indirect confirmation	low
[4]	Animal and ex vivo	Soleus and epitrochlearis muscles of lean and obese Zucker rats	Low concentrations increased insulin-stimulated transport; higher concentrations reversed the effect in lean rat muscle	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed shows that stevioside, in rats with diet-induced metabolic alterations, is associated with lower oxidative stress in the muscle, higher expression of insulin signaling markers, and increased glucose uptake. The narrative regarding the link between the redox environment, IRS-1/AKT, and GLUT4 is mechanistically supported by independent studies.However, the evidence remains experimental. It is not possible to infer from these results that stevioside prevents or cures diabetes in humans, nor that it acts directly on AS160 or GLUT4 in human muscle. The mechanism is biologically plausible and moderately supported in preclinical models, but it requires clinical validation and studies that directly measure GLUT4 translocation and AS160 phosphorylation.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **The Rab GTPase-Activating Protein AS160 Integrates Akt, Protein Kinase C, and AMP-Activated Protein Kinase Signals Regulating GLUT4 Traffic**
Thong et al., 2007
Diabetes
DOI: https://doi.org/10.2337/db06-0900

[2] **Protection from Palmitate-Induced Mitochondrial DNA Damage Prevents from Mitochondrial Oxidative Stress, Mitochondrial Dysfunction, Apoptosis, and Impaired Insulin Signaling in Rat L6 Skeletal Muscle Cells**
Yuzefovych et al., 2012
Endocrinology
DOI: https://doi.org/10.1210/en.2011-1442

[3] **Stevioside fromStevia rebaudianaBertoni Increases Insulin Sensitivity in 3T3-L1 Adipocytes**
Mohd-Radzman et al., 2013
Evidence-Based Complementary and Alternative Medicine
DOI: https://doi.org/10.1155/2013/938081

[4] **Effects of stevioside on glucose transport activity in insulin-sensitive and insulin-resistant rat skeletal muscle**
Lailerd et al., 2004
Metabolism
DOI: https://doi.org/10.1016/j.metabol.2003.07.014