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Luteolin from Lonicera japonica Thunb. restores GLUT4-mediated glucose uptake via PI3K/Akt signaling in insulin resistance - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether luteolin, a flavonoid found in *Lonicera japonica*, can improve glucose uptake under conditions of insulin resistance. Using differentiated 3T3-L1 adipocytes and mice with diet-induced insulin resistance, the authors observed an increase in glucose entry and GLUT4 translocation to the cell membrane, associated with increased phosphorylation of IRS, PI3K, AKT, and AS160. Pharmacological blockade of PI3K with wortmannin abolished these effects.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that the recovery of glucose uptake requires the integrity of the PI3K–AKT–AS160–GLUT4 sequence. Independent studies confirm this axis with good consistency in adipose and muscle cells; human data also show alterations in specific AS160 signals in type 2 diabetes. However, other human studies indicate that reduced muscle glucose uptake in obesity can occur even without measurable differences in AKT and AS160 phosphorylation. The mechanism is therefore well-supported experimentally, while the clinical efficacy of luteolin requires human studies.

ONLINE ARTICLE

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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 luteolin could reactivate cellular glucose uptake when the insulin response is impaired. The authors' hypothesis was that the compound acts on the PI3K/AKT pathway, a sequence of proteins that transmits the insulin signal from inside the cell to glucose transporters.The key point is practical: GLUT4 is the transporter that carries glucose from the blood into cells, primarily in adipose tissue and muscle. In conditions of insulin resistance, GLUT4 tends to be less available on the cell membrane. The study therefore verified whether luteolin promotes the translocation of GLUT4 to the cell surface and, consequently, increases glucose uptake.The relevance to section 4.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns a specific segment of the insulin chain: PI3K AKT AS160 GLUT4 increased glucose uptake. The research documents this segment in experimental models. It does not, however, demonstrate that luteolin prevents or cures insulin resistance in humans, nor does it establish effective or safe doses for clinical use.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract; therefore, information not present in it must be considered as not reported in the available material.The authors combined network pharmacology analysis and molecular docking. Network pharmacology is a computational approach that links a substance to potential biological targets; molecular docking estimates whether a molecule can fit into a specific region of a protein. These tools identified luteolin as a potential compound relevant to insulin resistance pathways, including PI3K/AKT. Such analyses generate hypotheses and do not, by themselves, prove that the mechanism occurs in a living organism.Biological verification was conducted in differentiated 3T3-L1 adipocytes, murine cells frequently used as a model for adipose tissue, and in mice with insulin resistance induced by a high-fat diet. Glucose uptake, phosphorylation of insulin signaling proteins, and GLUT4 translocation to the membrane were evaluated using biochemical assays, Western blotting, immunofluorescence, and flow cytometry. Western blotting measures the relative quantity of proteins or their phosphorylated forms; phosphorylation is a chemical modification that can activate or regulate a protein.Wortmannin was used as a pharmacological inhibitor of PI3K. The number of cellular and animal experiments, the sex and age of the mice, the dosages of luteolin and wortmannin, the duration of treatment, inclusion criteria, specific metabolic endpoints, and detailed statistical analyses are not reported in the available material.

4. RESULTS

In cellular and animal models of insulin resistance, luteolin increased glucose uptake and promoted the translocation of GLUT4 to the plasma membrane. In simple terms, a greater proportion of the transporters required to move glucose into the cell were found to be located where they can perform their function.This increase was accompanied by greater phosphorylation of IRS, PI3K, AKT, and AS160. IRS is a protein that collects the signal from the insulin receptor; PI3K and AKT transmit the signal inward; AS160 regulates part of the trafficking of vesicles containing GLUT4. The direction of the result is therefore consistent with a reactivation of the insulin cascade that brings GLUT4 to the cell surface.The result most relevant to the book's paragraph was the effect of wortmannin: the inhibition of PI3K suppressed both the translocation of GLUT4 and the increase in glucose uptake induced by luteolin. This experiment reinforces the interpretation that, in the model studied, PI3K is necessary for luteolin to produce these effects.The abstract also reports that luteolin improved metabolic parameters and insulin signaling in insulin-resistant mice. However, absolute values, percentage differences, P-values, confidence intervals, the number of animals, and individual metabolic parameters are not reported in the available material. It is therefore not possible to quantify the effect size or precisely evaluate its statistical robustness.

5. INTERPRETATION

The biological significance of this work is that luteolin, in the models examined, reactivated a part of the system through which insulin allows cells to utilize glucose. The effect was not attributed solely to an increase in the total amount of GLUT4: the authors observed, above all, a greater transfer of the

transporter to the membrane, which is the site where it can facilitate glucose entry.In detail, the documented segment is PI3K AKT AS160 GLUT4 translocation increased glucose uptake. The loss of the effect after treatment with wortmannin supports a dependence on PI3K in the experimental system. Since PI3K is located upstream of AKT and AS160, the result is consistent with the idea that luteolin does not bypass the insulin cascade, but rather promotes its functional recovery.However, this interpretation does not equate to proof that every component of the sequence is the sole determinant of glucose uptake. Wortmannin can have effects that require cautious interpretation, and the regulation of GLUT4 also includes other proteins, the cytoskeleton, and vesicle fusion processes with the membrane. Furthermore, murine adipose cells and mice fed a high-fat diet do not completely reproduce insulin resistance in humans.Regarding the passage cited in "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study does not need to demonstrate the entire pathophysiology of insulin resistance. Instead, it specifically documents that the reactivation of PI3K is associated with the activation of AKT and AS160, a greater presence of GLUT4 in the membrane, and increased glucose uptake in the experimental models examined.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Independent confirmation of the initial step in the chain comes from an experiment on 3T3-L1 adipocytes. In these cells, insulin increased GLUT4 translocation to the surface and glucose uptake. Inhibition of PI3K with wortmannin, pharmacological blockade of AKT, and experimental reduction of PI3K or AKT prevented insulin-induced GLUT4 translocation. The study therefore directly confirms that, in murine adipocytes, PI3K and AKT are necessary for the transition from insulin signaling to GLUT4 mobilization [1]. The limitation is that this is a cellular model, not human tissue under physiological conditions.A second study investigated the link between AKT, AS160, and GLUT4. In 3T3-L1 adipocytes, insulin increased the phosphorylation of AS160 at multiple sites. Expression of non-phosphorylatable forms of AS160 markedly reduced insulin-induced GLUT4 translocation. This data supports an experimental causal relationship: AS160 phosphorylation contributes to releasing the traffic of GLUT4-containing vesicles toward the membrane [2]. This completes the AKT AS160 GLUT4 segment of the book's narrative, while still remaining cellular evidence.Relevance in humans was assessed in a study using a hyperinsulinemic-euglycemic clamp, a procedure that measures the response to insulin while maintaining stable glycemia. The study included 8 lean adults with normal glucose tolerance, 9 obese adults without diabetes, and 10 obese adults with type 2 diabetes. In participants with type 2 diabetes, insulin-stimulated AS160 phosphorylation at the Thr642 site was reduced compared to lean subjects; this alteration accompanied lower insulin sensitivity [3]. The study is observational and does not prove that the AS160 defect is the sole cause of reduced glucose uptake, but it brings the molecular chain into a human context.Taken together, these studies are independent of the publication under review and converge on a functional sequence: PI3K and AKT promote GLUT4 mobilization, while AS160 represents an important regulator of vesicle trafficking. The publication on luteolin adds to this structure an experimental verification of a natural compound under conditions of insulin resistance, but it does not represent a clinical demonstration of its therapeutic use.

7. CONFLICTING EVIDENCE

Important contextual evidence comes from a clinical study on individuals with obesity and non-obese individuals who underwent clamps and muscle biopsies. In the main protocol, the group with obesity showed a reduction of more than 60% in insulin-stimulated glucose disposal compared to the non-obese group, but showed no differences in the phosphorylation of AKT or AS160 [4].This result does not negate the role of the PI3K–AKT–AS160–GLUT4 axis in cellular models. However, it indicates that, in human muscle during obesity, lower glucose uptake may also depend on other levels of regulation: GLUT4 quantity, vesicular trafficking downstream of AS160, nutrient availability, mitochondrial function, or tissue characteristics. In the same study, the total amount of GLUT4 in the muscle was 17% lower in obese participants, and the increase in AKT2 phosphorylation was positively correlated with insulin

sensitivity [4].This evidence therefore suggests that we should not transform a well-defined biological chain into a single universal explanation for insulin resistance. The general direction of the narrative remains consistent, but its application to humans depends on the tissue, the metabolic condition, and the specific point in the cascade that is altered.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the PI3K–AKT–AS160–GLUT4 pathway.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	3T3-L1 adipocytes and mice with high-fat diet-induced insulin resistance	Luteolin increased phosphorylation of IRS, PI3K, AKT, and AS160, GLUT4 translocation, and glucose uptake; wortmannin abolished the effects.	direct confirmation	moderate
[1]	Cellular	3T3-L1 adipocytes	Blocking or reducing PI3K and AKT prevented insulin-induced GLUT4 translocation and increased glucose uptake.	direct confirmation	moderate
[2]	Cellular	3T3-L1 adipocytes	Non-phosphorylatable mutations of AS160 markedly reduced insulin-stimulated GLUT4 translocation.	direct confirmation	moderate
[3]	Observational with physiological intervention	8 lean adults, 9 obese adults without diabetes, and 10 obese adults with type 2 diabetes	In type 2 diabetes, insulin-stimulated AS160 Thr642 phosphorylation in muscle was reduced and accompanied insulin resistance.	indirect confirmation	moderate

[4]	Observational with clamp	Main protocol: 16 non-obese adults and 25 obese adults	In obesity, insulin-induced glucose disposal was reduced by over 60%, with no differences in AKT and AS160 phosphorylation.	conflicting evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study consistently supports the idea that luteolin may increase glucose uptake in experimental models of insulin resistance by promoting the PI3K–AKT–AS160–GLUT4 pathway. The blocking of PI3K reinforces the mechanistic nature of this observation.Independent literature confirms that PI3K, AKT, and AS160 participate in the translocation of GLUT4 to the cell membrane. The role of this axis is therefore well-supported at the cellular and biological level, with associative signals also present in human muscle. However, insulin resistance in humans does not necessarily depend on a single defect in the cascade, and the clinical efficacy of luteolin requires validation in controlled human studies.

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.

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