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# Salidroside inhibits platelet function and thrombus formation via the AKT/GSK3b signaling pathway - A review of the evidence

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ARTICLE INFORMATION

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## 1. ABSTRACT

The analyzed study evaluated whether salidroside, a bioactive compound found in *Rhodiola rosea*, modifies the function of platelets—the blood cells that help stop bleeding but also contribute to the formation of thrombi. In human and murine platelets treated in the laboratory, the compound reduced aggregation, ATP release, surface spreading, and clot retraction. In mice, it prolonged bleeding time and reduced the experimental formation of arterial and venous thrombi.The research also observed a reduction in the phosphorylation of AKT and GSK-3b, consistent with the maintenance of GSK-3b inhibitory activity in platelets. This is the segment of the narrative covered in paragraph 4.12 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi. Independent genetic and pharmacological studies support the role of the PI3K/AKT/GSK-3 axis in platelet regulation. However, there is a previous conflicting result obtained with pharmacological inhibitors of GSK-3. Overall, the mechanism is well-supported at an experimental level, but it does not prove that salidroside prevents or treats thrombosis in humans.

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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 salidroside could reduce platelet activation and thrombus formation. The authors tested the hypothesis that this compound acts, at least in part, via the AKT/GSK-3b pathway. AKT is a protein that transmits signals within the platelet; GSK-3b is a kinase, a protein that modifies other proteins, which is normally active at rest and capable of exerting a brake on certain platelet responses.The relevance to the book's section concerns precisely the passage stating that, during platelet activation, AKT phosphorylates GSK-3b at a site that reduces its activity; if this brake is removed, aggregation and thrombus formation are favored. The analyzed study shows the opposite direction after exposure to salidroside: the phosphorylation of AKT and the inhibitory phosphorylation of GSK-3b decrease, while several platelet functions also decrease.It is important to distinguish what has been observed from what remains hypothetical. The research demonstrates effects in isolated platelets and in murine models of hemostasis and thrombosis. It does not prove that salidroside is an effective or safe antithrombotic treatment in humans, nor does it identify with certainty the initial direct molecular target of the compound.

## 3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors studied platelets isolated from human volunteers and 8-10-week-old C57BL/6 mice. The total number of human donors is not reported in the available material. Human platelets were incubated for one hour at 37 °C with salidroside at 0, 5, 10, or 20 µM; murine platelets were incubated with a vehicle or 20 µM. In some experiments, platelets were pretreated for two hours with SB216763, a GSK-3b inhibitor, at a concentration of 10 µM.Platelet function was evaluated by measuring aggregation and ATP release after stimulation with thrombin or collagen-related peptide. Alpha-granule release was also measured via P-selectin, as was the expression of GPIba, GPVI, and aIIbb3 receptors using flow cytometry, platelet spreading on fibrinogen or collagen, and clot retraction. The phosphorylation of c-Src, Syk, PLCγ2, AKT, and GSK-3b was analyzed via western blot, a technique that measures proteins and their modifications in cell extracts.In mice, salidroside was administered intraperitoneally at 20 mg/kg. After 30 minutes, platelet count and tail bleeding time were evaluated. Arterial thrombosis was induced with ferric chloride in mesenteric arterioles; venous thrombosis was studied via inferior vena cava stenosis and evaluated after 24 hours by thrombus weight and length. For in vivo tests, the reported groups ranged from five to seven animals. Statistical analyses included t-tests, one-way and two-way analysis of variance; the authors considered a P-value of less than 0.05 to be significant.

## 4. RESULTS

In human platelets, salidroside dose-dependently reduced aggregation induced by thrombin or collagen-related peptide and decreased ATP release, a marker of dense granule secretion. These data indicate that platelets responded less intensely to pro-aggregatory stimuli. The data were obtained from four to six experiments for aggregation and ATP, with differences reported by the authors as statistically significant compared to the vehicle. Surface P-selectin, an indicator of alpha-granule release, did not change significantly.Salidroside did not alter the surface expression of the main platelet receptors GPIba, GPVI, and aIIbb3. However, it reduced platelet spreading on fibrinogen and collagen, clot retraction, and the phosphorylation of c-Src, Syk, and PLCγ2. In simple terms, the compound did not reduce the number of major receptors, but it attenuated certain intracellular signals necessary for the platelet to adhere stably and make the clot more compact.In murine platelets treated with 20 µM of salidroside, aggregation, ATP release, and clot retraction were reduced compared to the vehicle. In mice treated with 20 mg/kg, the platelet count did not change, while the bleeding time increased. This result is consistent with a reduced hemostatic capacity, meaning a greater difficulty in stopping bleeding, and represents a relevant safety finding.In murine models, salidroside prolonged the time required for arterial occlusion induced by ferric chloride and reduced the weight and length of venous thrombi following inferior vena cava stenosis. Coagulation factors VIII and IX and prothrombin time showed no significant differences between the vehicle and salidroside. The authors therefore interpreted the reduction in thrombi primarily as an effect on platelet

function, rather than a measurable change in the coagulation parameters examined.The central result for this section of the book is that, after stimulation with thrombin, salidroside reduced AKT phosphorylation at the Thr308 and Ser473 sites and GSK-3b phosphorylation at the Ser9 site in both human and murine platelets. Since Ser9 phosphorylation normally reduces GSK-3b activity, its decrease is consistent with a more active GSK-3b. Furthermore, the GSK-3b inhibitor SB216763 abolished the inhibitory effect of salidroside on aggregation and clot retraction. This functional rescue experiment reinforces the involvement of GSK-3b, but does not prove that AKT/GSK-3b is the only pathway through which salidroside acts.

## 5. INTERPRETATION

The biological significance of the data is that salidroside made platelets less prone to aggregating and consolidating a clot in the studied models. The proposed mechanism is consistent with a brake kept active: if AKT is less phosphorylated, the inhibitory phosphorylation of GSK-3b also decreases; GSK-3b can therefore maintain greater activity and limit certain platelet responses.The pathway documented by the study is therefore: reduction of AKT signaling reduction of inhibitory phosphorylation of GSK-3b reduction of aggregation, clot retraction, and experimental thrombus formation. The part regarding the relationship between AKT and GSK-3b is directly supported by the phosphorylation data and the use of the GSK-3b inhibitor. The conclusion that salidroside acts exclusively through this pathway would, however, be broader than what the data allows us to state.The relationship with "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is therefore specific: the publication does not serve to demonstrate the entire physiology of insulin or cell survival, but documents in a platelet context that AKT and GSK-3b act as functionally linked regulators. However, the model is not equivalent to the insulin pathway in muscle or brain and does not allow for the automatic transfer of these results to those tissues.

## 6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the inhibitory role of GSK-3b in platelets comes from an independent genetic study. Li and colleagues compared mice with only one functional copy of the *Gsk3b* gene to normal controls. Platelets from mice with reduced GSK-3b expression showed increased aggregation, greater dense granule secretion, and increased fibrinogen binding. After carotid injury with ferric chloride, 80% of the mice with reduced GSK-3b formed stable occlusive thrombi, whereas 67% of the controls did not form occlusive thrombi. The authors also observed that GSK-3b phosphorylation depended in part on AKT. This study confirms, using a genetic model and two murine thrombosis models, that reducing GSK-3b promotes platelet activation and thrombosis [1].Moore and colleagues investigated the molecular link further. In human platelets, in mice lacking PKCa, and in mice with mutated GSK-3 phosphorylation sites, they showed that GSK-3a/b phosphorylation during the response to thrombin occurs in two stages: an early phase primarily dependent on PKCa and a late phase dependent on the PI3K/AKT pathway. In mice with non-phosphorylatable GSK-3a Ser21 and GSK-3b Ser9, aggregation, fibrinogen binding, and P-selectin expression induced by the PAR4 receptor were reduced. Conversely, the GSK-3 inhibitor CHIR99021 increased these responses. This work confirms the AKT inhibitory phosphorylation of GSK-3 increased platelet function pathway, while clarifying that AKT is not the only regulator of GSK-3 phosphorylation [2].Laurent and colleagues examined the role of platelet PI3Kb, an enzyme located upstream of AKT. In mice with selective deletion of PI3Kb in the megakaryocytic lineage and in human blood treated with a selective PI3Kb inhibitor, thrombus formation under high flow was unstable, with a greater tendency for emboli to detach. In the same context, the activating phosphorylation of AKT and the inhibitory phosphorylation of GSK-3 decreased; pharmacological inhibition of GSK-3 restored thrombus stability. This independent evidence extends the upstream chain: PI3Kb AKT inactivation of GSK-3 thrombus stability, in a model particularly relevant to high arterial flow [3].Taken together, these studies do not evaluate salidroside and do not validate its clinical use. However, they independently confirm the direction of the molecular chain described in the paragraph: keeping GSK-3 functionally active tends to limit certain platelet responses, while its inhibitory phosphorylation downstream of AKT promotes aggregation, secretion, and thrombus stability.

## 7. CONFLICTING EVIDENCE

There is directly conflicting evidence, which is significant because it concerns the same biological node. Barry and colleagues observed in human platelets that collagen, convulxin, and thrombin increased the phosphorylation of GSK-3a/b in a PI3K-dependent manner, which was associated with reduced GSK-3 activity. However, three pharmacological inhibitors of GSK-3—lithium, SB415286, and TDZD-8—reduced platelet aggregation, thus suggesting a positive, rather than inhibitory, role for GSK-3 in aggregation [4].This contrast does not eliminate the correspondence between the original study and the book's paragraph, but it does require caution. Subsequent studies have indicated that the effects of inhibitors may depend on incomplete selectivity, incubation duration, the agonist used, and the differing contributions of the GSK-3a and GSK-3b isoforms. More recent literature, also based on genetic models, tends to support an inhibitory function of GSK-3b in platelets, but the role of the enzyme is not identical under every experimental condition. No sufficiently relevant directly conflicting evidence regarding the specific effect of salidroside 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 Evidence Review from the independent research used to evaluate the AKT/GSK-3b pathway in platelet function.

### Quadro comparativo

| Reference | Study type | Population or model | Main result | Direction of evidence | Strength of evidence |
|---|---|---|---|---|---|
| Original study | Cellular, human and animal | Human and murine platelets; C57BL/6 mice | Salidroside reduced AKT and GSK-3b phosphorylation, platelet function, and experimental thrombosis; it increased bleeding in mice. | biologically consistent evidence | moderate |
| [1] | Genetic, cellular and animal | Human platelets and GSK-3b+/− mice | GSK-3b reduction increased aggregation, secretion, and susceptibility to thrombosis. | direct confirmation | moderate |
| [2] | Cellular and genetic animal | Human platelets; PKCa-null and GSK-3 knock-in mice | AKT contributes to the inhibitory phosphorylation of GSK-3; preventing this phosphorylation reduces platelet activation. | direct confirmation | moderate |
| [3] | Animal, ex vivo and human blood | Mice with platelet-specific PI3Kb deletion; human blood | Loss of PI3Kb reduced AKT and inhibitory GSK-3 phosphorylation, destabilizing high-flow thrombi. | indirect confirmation | moderate |

| | | | | | |
|---|---|---|---|---|---|
| [4] | Human cellular | Human platelets | Pharmacological GSK-3 inhibitors reduced aggregation, in the opposite direction to subsequent studies. | discordant evidence | preliminary |

## 9. SINTESI EDITORIALE E CONCLUSIONI

### CONCLUSIONS

The study analyzed consistently supports that salidroside reduces certain platelet functions and experimental thrombosis in mice, in association with decreased phosphorylation of AKT and GSK-3b. Independent evidence confirms at a mechanistic level that AKT promotes platelet activation, including through the inactivation of GSK-3. The narrative of the paragraph is therefore well-supported within the experimental context of platelets.Substantial limitations remain: the compound has not been evaluated in clinical antithrombotic studies, the increase in bleeding time in mice signals a potential hemostatic cost, and the role of GSK-3 may vary according to the model, isoform, and stimulus. Any therapeutic hypothesis therefore requires validation in humans, with particular attention to the balance between thrombus prevention and bleeding risk.

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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