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Anti-arthritic effect of berberine associated with the regulation of macrophage energy metabolism through the AMPK/HIF-1a pathway - Review of the evidence

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1. ABSTRACT

The analyzed study evaluated whether berberine, a plant-derived alkaloid, could attenuate joint inflammation by modifying the metabolism of macrophages, immune cells capable of adopting either more pro-inflammatory or more regulatory characteristics. In rats with experimentally induced arthritis and in laboratory-stimulated rat macrophages, berberine increased the proportion of cells with M2 characteristics, reduced that of M1 cells, increased AMPK activation, and reduced HIF-1a expression. It was also associated with a decrease in certain indicators of glycolysis.The research contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, according to which berberine can metabolically reprogram inflammatory macrophages without eliminating them. Independent studies confirm that AMPK can limit pro-inflammatory metabolic programs and that HIF-1a can promote glycolysis and M1 polarization. However, another study observed that berberine can increase glycolysis in different cellular contexts. Overall, the narrative is supported primarily at the mechanistic and preclinical level.

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 berberine could reduce inflammation in experimental arthritis by intervening in how macrophages produce and use energy. The authors' hypothesis was that the substance promotes the shift from M1 macrophages—cells generally associated with an intense inflammatory response—to M2 macrophages, which are more linked to the regulation of the immune system and tissue repair.The specific reason for the citation in paragraph 6.2.1 is the segment of the chain that connects the activation of AMPK, a sensor of cellular energy status, to the reduction of HIF-1α, a transcription factor that promotes the expression of genes involved in the response to hypoxia and glycolysis. The analyzed study documents this association in an animal model of arthritis and in rat macrophages cultured in the laboratory. However, it cannot demonstrate that berberine has the same effect in people with rheumatoid arthritis, nor that it directly reduces HIF-1α through a direct molecular bond.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication, available only as an abstract, describes two experimental parts. The first used rats with adjuvant-induced arthritis, an animal model employed to study inflammatory joint processes. In the joint tissues, the total number of macrophages, the proportion of M1 and M2 cells, AMPK phosphorylation, and HIF-1α expression were evaluated.The second part used peritoneal macrophages obtained from normal rats and stimulated with lipopolysaccharide, or LPS, a bacterial component used in the laboratory to induce an inflammatory response. The cells were pretreated with berberine; in some experiments, Compound C, a pharmacological inhibitor of AMPK, was added. Cell migration, glucose consumption, lactate export, and intracellular content of ATP, the main cellular energy molecule, were measured.The number of animals and cultures, dosages, duration of treatments, inclusion criteria, detailed analytical techniques, clinical endpoints of arthritis, and complete statistical analyses are not reported in the available material.

4. RESULTS

In rats with arthritis, treatment with berberine had little influence on the total number of joint macrophages. The practical significance is that the substance does not appear to have acted simply by eliminating these cells. Instead, it increased the proportion of M2 macrophages and decreased the proportion of M1 macrophages, thereby shifting the cell population toward less pro-inflammatory characteristics.In the same tissue, berberine increased the phosphorylation of AMPK, an indicator of its activation, and reduced the expression of HIF-1α in synovial macrophages. In macrophages stimulated with LPS in the laboratory, pretreatment with berberine showed the same trend: an increase in p-AMPK, a reduction in HIF-1α, and a shift from M1 to M2 characteristics.From an energy perspective, berberine reduced glucose consumption and lactate export, both of which are consistent with a reduction in glycolysis, and increased intracellular ATP. Compound C significantly reversed these metabolic effects and abolished the inhibition of macrophage migration induced by berberine. This result makes AMPK a plausibly necessary step in the experimental model. The abstract does not report absolute values, percentages, confidence intervals, or P-values.

5. INTERPRETATION

In layman's terms, the results suggest that berberine shifted macrophages from a state that tends to support inflammation toward a more regulatory state by modifying their energy program. Glycolysis is a rapid pathway for obtaining energy from glucose; in activated immune cells, it can also provide materials useful for the production of inflammatory mediators.The pathway documented by the study is: berberine increased AMPK activation decreased HIF-1α expression and lower indicators of glycolysis reduction of M1 characteristics and increase of M2 characteristics. The use of Compound C strengthens the hypothesis that AMPK participates in the observed mechanism, but it does not prove a complete linear sequence nor does it exclude the effects of berberine on other cellular targets.The book's phrasing that berberine "shuts off" the energy supply of inflammatory cells is a useful popular simplification, provided it is not taken literally. The study does not

show that all energy functions of macrophages are shut off; instead, it shows a reduction in specific indicators of glycolysis in rat models. Furthermore, the available data documents a reduction in HIF-1α expression, not a demonstration of direct inhibition of the protein by berberine.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the link between HIF-1α, glycolysis, and the pro-inflammatory activation of macrophages comes from a cellular study in which the experimental increase of HIF-1α boosted the expression of glycolysis genes and promoted M1 characteristics. This supports the book's passage stating that HIF-1α can steer macrophages toward a more glycolytic metabolism and an inflammatory response. However, this is an experimental cellular model: it demonstrates a plausible biological relationship, not the efficacy of a treatment in human arthritis [1].A second study, conducted in murine models of sepsis and in immune cells, showed that AMPK deficiency increases PKM2-dependent aerobic glycolysis and promotes the release of HMGB1, a mediator associated with systemic inflammation. Conversely, pharmacological activation of AMPK protected the animals from endotoxic shock and polymicrobial sepsis. Although this is a different disease than arthritis, this result confirms the general step in the chain: higher AMPK activity can counterbalance pro-inflammatory energy reprogramming in macrophages and monocytes [2].Taken together, these independent studies do not exactly replicate the original experiment with berberine in adjuvant-induced arthritis. However, they reinforce the two mechanistic nodes necessary for the narrative: HIF-1α can support glycolysis and M1 characteristics, while AMPK can limit excessive metabolic and inflammatory programs. The convergence is therefore biologically consistent, but it remains primarily preclinical.

7. CONFLICTING EVIDENCE

Directly relevant evidence suggests that the reduction of glycolysis should not be considered a universal effect of berberine. In mouse bone marrow-derived macrophages and human peripheral blood mononuclear cells, berberine induced aerobic glycolysis by blocking the tricarboxylic acid cycle, with an increase in GLUT1 expression and hexokinase activity. In the same study, it modulated cytokine secretion and attenuated certain inflammatory outcomes in mouse models of infection and endotoxic shock [3].This result does not negate the data from the analyzed study, but it shows that the effect of berberine on macrophage metabolism can depend on the cell type, the inflammatory stimulus, the observation time, and the pathological context. Specifically, an increase in glycolysis in cell cultures does not automatically equate to an increase in inflammation, because the relationship between metabolism and immune function is modulated by many cellular pathways.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication that is the subject of the Evidence Review from the independent research used to confirm or define the scope of the book's narrative passage.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Rats with adjuvant-induced arthritis; rat peritoneal macrophages stimulated with LPS	Berberine increased p-AMPK and M2 macrophages, reduced HIF-1α, M1 macrophages, and glycolysis indicators	direct confirmation	moderate
[1]	Cellular	Macrophages subjected to experimental manipulation of HIF-1α	Increased HIF-1α boosted glycolytic genes and M1 polarization characteristics	direct confirmation	moderate
[2]	Animal and cellular	Murine models of sepsis, macrophages, and monocytes	AMPK deficiency increased aerobic glycolysis and pro-inflammatory signals; AMPK activation provided protection in sepsis models	indirect confirmation	moderate
[3]	Cellular and animal	Murine macrophages, human mononuclear cells, and murine models of infection	Berberine induced aerobic glycolysis in some macrophages, while modulating cytokines and attenuating inflammatory outcomes in murine models	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed suggests that, in experimental rat arthritis, berberine does not reduce the total number of joint macrophages but modifies their profile, increasing M2 characteristics and reducing M1 ones. This change was accompanied by greater AMPK activation, lower HIF-1a expression, and a reduction in glycolysis indicators.The proposed biological chain is confirmed by independent evidence, particularly at a mechanistic level: HIF-1a can promote glycolysis and inflammatory activation of macrophages, while AMPK can limit pro-inflammatory metabolic programs. However, the interpretation requires caution because the available data are preclinical and because berberine can produce different metabolic responses in other cell models. Therefore, it is not possible to infer proven therapeutic efficacy in people with rheumatoid arthritis.

Aggiornato al 25/11/2026. 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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