LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

LZ205, a newly synthesized flavonoid compound, exerts an anti-inflammatory effect by inhibiting M1 macrophage polarization through the regulation of the PI3K/AKT/mTOR signaling pathway - Evidence review

Dott. A. Conte[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether LZ205, a synthetic flavonoid, can attenuate inflammation by modifying the behavior of macrophages, immune cells capable of assuming different functional states. In cellular experiments, LZ205 reduced the secretion of cytokines associated with M1 macrophages, which have a pro-inflammatory profile. In mice, it also reduced M1 polarization markers in models of dextran sodium sulfate-induced colitis and alum-induced peritonitis. In parallel, there was a decrease in PI3K, phosphorylated AKT, and phosphorylated mTOR, components of a signaling network that links energy availability, cellular metabolism, and immune response.In section 6.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that the suppression of the PI3K/AKT/mTOR cascade can limit M1 macrophage polarization and reduce experimental inflammation. Independent studies in models of intestinal inflammation support this chain of events, but research on human macrophages treated with rapamycin shows an opposite outcome. Overall, the confirmation is mechanistic: it primarily concerns cells and animals, not a proven clinical benefit in humans.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 25, 2026
Updated: November 25, 2026

DOI 10.5281/zenodo.24531226

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 LZ205 could reduce inflammation by acting on macrophages. Macrophages are innate immune cells that eliminate microorganisms and debris, but they can also amplify or limit inflammation. The M1 definition conventionally indicates a set of characteristics associated with the production of pro-inflammatory mediators; M2, on the other hand, indicates a set of programs more associated with tissue repair and regulation of the immune response. This classification is useful in experiments, but in living organisms, macrophages can assume intermediate and changing states.The authors' hypothesis was that LZ205 inhibited the M1 program through PI3K/AKT/mTOR. This signaling pathway is a series of proteins that transmits information about nutrients, growth, and external stimuli to the cell. PI3K activates AKT, a protein kinase; AKT can then promote the activation of mTOR, a regulator of metabolism and protein synthesis. The publication is relevant to the passage in paragraph 6.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it documents, in the studied model, the segment: reduction of PI3K/AKT/mTOR activity lower M1 polarization fewer inflammatory signals.The study can demonstrate that LZ205 is associated with these variations under the experimental conditions used and that such variations are consistent with the proposed mechanism. However, it cannot establish that LZ205 is effective or safe in people with colitis, peritonitis, autoimmune diseases, or other inflammatory conditions. Nor can it demonstrate that every mTOR inhibitor necessarily produces the same effect on all macrophages and in all tissues.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract is available; the full text is not accessible. Consequently, numerous methodological details are not reported in the available material.The authors conducted *in vitro* experiments on macrophages, evaluating the secretion of cytokines associated with the M1 phenotype and the messenger RNA levels of cytokines associated with the M2 phenotype. The precise type of macrophages, the number of biological replicates, the concentrations of LZ205, the duration of treatments, pharmacological controls, and detailed analytical procedures are not reported in the available material.The *in vivo* portion used mice with dextran sodium sulfate-induced colitis, commonly abbreviated as DSS, and mice with alum-induced peritonitis. DSS colitis is an experimental model of colon damage and inflammation; alum-induced peritonitis, on the other hand, causes an inflammatory response in the abdominal cavity. The number of animals, sex, strain, dosages, route and frequency of LZ205 administration, duration of follow-up, and criteria for randomization and blinding are not reported in the available material.According to the abstract, PI3K, phosphorylated AKT (indicated as p-AKT), and phosphorylated mTOR (indicated as p-mTOR) were evaluated in colon tissues and peritoneal macrophages. Phosphorylation is a chemical modification that often signals the activation or change in function of a protein. The laboratory techniques and statistical methods used are not reported in the available material.

4. RESULTS

In cellular experiments, LZ205 statistically significantly reduced the secretion of pro-inflammatory cytokines associated with M1 macrophages. Simply put, the cells released fewer chemical messengers typical of an inflammatory response. The abstract does not indicate which specific cytokines were measured, nor does it report absolute values, percentage changes, *P* values, or confidence intervals.In the same experimental system, LZ205 did not alter the messenger RNA levels of cytokines associated with M2 macrophages. This finding suggests that the observed effect was more evident on the M1 program than on the M2 markers considered by the authors. However, without the full text, it is not possible to know which M2 markers were analyzed or to rule out effects on other aspects of macrophage function.In mice, LZ205 statistically significantly inhibited M1 polarization in both the DSS-induced colitis model and the alum-induced peritonitis model. In parallel, it reduced the expression of PI3K and p-AKT and p-mTOR signals in the colon and peritoneal macrophages. The biological significance is consistent with lower activity of the PI3K/AKT/mTOR network in inflamed sites and a

reduced M1 profile. The abstract does not report histological scores for colitis, body weight, clinical severity, survival, compound concentrations, effect size, or quantitative data on inflammation.The central result, relevant to the book, is therefore not a clinical demonstration of colitis or peritonitis treatment. It is the experimental observation that the decrease in PI3K/AKT/mTOR signals accompanies the reduction of pro-inflammatory M1 macrophage polarization and inflammatory signals in the models examined.

5. INTERPRETATION

For a non-technical reader, the essential message is that macrophages are not simply "on" or "off": they receive metabolic and immune signals that modify their behavior. In the study, LZ205 was associated with lower activation of a cellular network, PI3K/AKT/mTOR, and a lower presence or activity of the pro-inflammatory M1 program.The relationship proposed by the authors is biologically plausible. PI3K, AKT, and mTOR can influence nutrient consumption, protein synthesis, and the production of inflammatory mediators. However, the simultaneous reduction of p-AKT, p-mTOR, and M1 markers does not, by itself, prove that blocking this pathway is the sole cause of the effect of LZ205. A compound can act on multiple targets, and a reduction in general inflammation can, in turn, secondarily reduce the activation of this pathway.The segment documented by the publication subject to the Evidence Review coincides with that reported in the book: in the cellular and murine models considered, LZ205 reduced M1 polarization and inflammation along with the suppression of the PI3K/AKT/mTOR cascade. The publication does not prove the broader thesis that intervening on mTOR is universally useful in immune-mediated diseases, nor does it allow for the automatic transfer of the effects of LZ205 to rapamycin or other drugs that act on mTOR.

6. INDEPENDENT CONFIRMING EVIDENCE

Particularly relevant confirmation comes from an independent study on intestinal inflammation and macrophages. Liao and colleagues observed that advanced oxidized protein products increased the activation of the PI3K/AKT/mTOR pathway, promoted M1 polarization, and impaired autophagy, the cellular system that removes and recycles damaged components. The experiments included RAW264.7 cells, bone marrow-derived macrophages, and mice exposed to oxidized products. Inhibition of PI3K attenuated the impairment of autophagy, reduced M1 polarization, and reduced intestinal inflammation in mice. This study directly supports the chain segment related to PI3K/AKT/mTOR M1 intestinal inflammation, with pharmacological intervention on the pathway. The limitation is that the model reproduces an experimental context of Crohn's disease and does not demonstrate the efficacy of LZ205 in humans [1].A second study examined mice with DSS-induced colitis treated with sphingosine-1-phosphate, a lipid signaling molecule. Compared to untreated mice with colitis, the treated animals showed fewer signs of colon damage and inflammation, a lower proportion of F4/80+CD86+ macrophages, used as an indicator of M1, and a higher proportion of F4/80+CD206+ macrophages, used as an indicator of M2. In the same comparison, gene expression analysis and protein experiments revealed a reduction in PI3K-AKT signals in the treated group. This result is consistent with the book's narrative and the original study: in experimental colitis, lower pathway activity is associated with lower M1 signals and less inflammation. However, the authors themselves specify that the direct causal link between PI3K-AKT and sphingosine-1-phosphate-induced polarization has not been defined; the confirmation is therefore convergent, but not definitive [2].Taken together, these independent studies do not validate LZ205 as a therapy. Instead, they reinforce the specific mechanistic point: in some models of intestinal inflammation, increased PI3K/AKT/mTOR signaling is associated with M1 characteristics, and the inhibition or reduction of this signal can be accompanied by a decrease in inflammation. The strength of the confirmation remains limited by the fact that the data come primarily from cell cultures and rodents.

7. CONFLICTING EVIDENCE

The direction of the effect is not identical in every experimental context. Mercalli and colleagues studied macrophages obtained from the blood of six healthy donors and found that rapamycin, an mTOR inhibitor, increased certain M1 markers and cytokines in M1-polarized macrophages. Specifically, CD86, CCR7, interleukin-6, TNF-a, and interleukin-1b increased, while some markers associated with M2 decreased. In

a small group of 12 people treated with rapamycin before pancreatic islet transplantation, the authors also described a quantitative shift toward an M1 profile following treatment [3].This result is directly at odds with a simple interpretation that inhibiting mTOR always reduces M1 polarization. It does not invalidate the correspondence between the original study and the book's paragraph, but it shows that the effect depends on the type of inhibitor, the macrophage differentiation stage, the inflammatory stimulus, the tissue, and likely the balance between the mTORC1 and mTORC2 complexes. Furthermore, rapamycin is not LZ205 and acts with a different pharmacology. The small human sample size and the absence of a randomized clinical comparison further reduce the possibility of generalizing that result.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent research. The strength of the evidence refers to the specific pathway described in the book's paragraph, not to therapeutic efficacy in humans.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	Macrophages; mice with DSS-induced colitis and alum-induced peritonitis	LZ205 reduced M1-associated cytokines, M1 polarization, and PI3K, p-AKT, and p-mTOR signaling.	direct confirmation	moderate
[1]	Cellular, animal, and observational	RAW264.7 macrophages, bone marrow-derived macrophages, mice exposed to oxidized protein products; observations in people with Crohn's disease	PI3K inhibition reduced M1 polarization and intestinal inflammation in the mouse model.	direct confirmation	moderate
[2]	Animal	C57BL/6 mice with DSS-induced colitis	Treatment reduced PI3K-AKT signaling, M1 macrophages, and colon inflammation, while increasing M2 markers.	indirect confirmation	moderate
[3]	Cellular and observational	Macrophages from six healthy donors; 12 people treated with rapamycin before pancreatic islet transplantation	Rapamycin increased M1 markers and cytokines under specific experimental conditions.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study consistently supports the specific pathway for which it is cited: LZ205 reduced PI3K/AKT/mTOR signaling, M1 macrophage polarization, and inflammation in cellular systems and two mouse models. Independent evidence confirms that this network can contribute to the pro-inflammatory polarization of macrophages and experimental colitis.The most balanced conclusion is that the link is confirmed at a mechanistic level. It has not been proven that LZ205 prevents or treats inflammatory diseases in humans, nor that simple mTOR inhibition always has an anti-inflammatory effect. Effects may vary depending on the compound used, the biological context, and the type of macrophage involved.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Advanced oxidation protein products impair autophagic flux in macrophage by inducing lysosomal dysfunction via activation of PI3K-Akt-mTOR pathway in Crohn's disease**
Liao et al., 2021
Free Radical Biology and Medicine
DOI: https://doi.org/10.1016/j.freeradbiomed.2021.05.018

[2] **Rapamycin unbalances the polarization of human macrophages to M1**
Mercalli et al., 2013
Immunology
DOI: https://doi.org/10.1111/imm.12126

[3] **Sphingosine-1-phosphate alleviates colitis by regulating macrophage polarization and PI3k-Akt signaling**
Hu et al., 2025
Frontiers in Immunology
DOI: https://doi.org/10.3389/fimmu.2025.1622094