Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

LETTER

Geniposide Stabilized Atherosclerosis Plaque by Induced M2 Polarization via PPARγ Signaling Pathway [Letter]

Haizhen Guo[1,2], Yuke Zhao[1,2], Zidong Cong[2]

[1]Tianjin University of Traditional Chinese Medicine, Tianjin, 301617, People's Republic of China; [2]The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, 300150, People's Republic of China

Correspondence: Haizhen Guo; Zidong Cong, Email 2404392316@qq.com; czd1602630@sina.com

Drug Design, Development and Therapy downloaded from https://www.dovepress.com/
For personal use only.

Dear editor

We were very interested to read the article by Jin et al (2025) entitled "Geniposide Stabilized Atherosclerosis Plaque by Induced M2 Polarization via PPARγ Signaling Pathway" in Drug Design, Development and Therapy.[1] Through in vivo and in vitro experiments, the authors show that Geniposide (Gen) stabilizes atherosclerotic plaques by promoting macrophage M2 polarization via activation of the PPARγ signaling pathway. These findings offer valuable, albeit preliminary, insights into the anti-atherosclerotic actions of geniposide. However, we believe that several methodological aspects would benefit from greater clarification to enhance the mechanistic support for these various findings.

After carefully reading the manuscript, we feel that the reasons for choosing particular dose and treatment duration of the PPARγ antagonist GW9662 need further clarification. The in vitro studies were done using only one concentration (5 μM) and one pretreatment period (1 h), without testing whether the treatment affects cell viability under these conditions. Earlier findings suggest that GW9662 can be cytotoxic or exhibit off-target effects that are PPARγ non-inhibitory.[2] The downregulation of M2 marker expression may not only be due to specific PPARγ blockade, as it cannot be excluded that drug-induced effects on cellular state also caused this downregulation through nonspecific stress responses. In addition, GW9662 was given via intraperitoneal injection in the ApoE$^{-/-}$ mouse model 1 mg/kg/day. Nevertheless, the regimen was not validated by any pharmacokinetic or pharmacodynamic data. Since GW9662 is known to have a poor in vivo bioavailability,[3] and there is no information regarding systemic exposure, tissue distribution (in particular the aorta) or inhibition of the target pathway, it remains unclear whether this dose achieved effective and selective PPARγ blockade in vivo.

Moreover, it would be beneficial to strengthen the evidence for the necessity of PPARγ. Though GW9662 is commonly used as a selective PPARγ antagonist, it is prone to off-target effects with high concentrations or under specific experimental conditions, possibly affecting other nuclear receptors such as PPARα or PPARδ.[4,5] Accordingly, reliance on pharmacological inhibition alone may not fully rule out PPARγ-independent pathways. Using genetic methods like macrophage-specific PPARγ knockdown or knockout would significantly strengthen the conclusion that Gen acts mainly through PPARγ to promote M2 polarization.

The evaluation of plaque stability seems somewhat limited, and we observed a slight methodological flaw in the study. The study appears to equate reduced plaque area with enhanced stability. While plaque area is clinically relevant, stability is more strongly determined by key histopathological features of vulnerability—namely, fibrous-cap thickness, collagen content, and necrotic core size. The conclusion regarding plaque stabilization is therefore constrained by the absence of these critical parameters. In addition, the restriction enzyme listed as "HandIII" in the Methods section is presumably a typo for "HindIII."

Received: 4 November 2025
Accepted: 10 November 2025
Published: 14 November 2025

© 2025 Guo et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

The authors should be commended for providing valuable preliminary evidence on the anti-atherosclerotic mechanism of Gen. Addressing these points through further clarification or additional experimentation would considerably reinforce the study's conclusions and lay a firmer foundation for future research.

Disclosure

The authors report no conflicts of interest in this communication.

References

1. Jin Z, Chu Q, Du Z, et al. Geniposide stabilized atherosclerosis plaque by induced M2 polarization via PPARγ signaling pathway. *Drug Des Devel Ther*. 2025;19:8805–8821. doi:10.2147/DDDT.S499890
2. Tachachartvanich P, Sangsuwan R, Ngernpisutsilp N, et al. Structure-based discovery of a novel nuclear receptor PPARgamma inhibitor: implications for obesity and metabolic disease intervention. *Biomed Pharmacother*. 2025;192:118615. doi:10.1016/j.biopha.2025.118615
3. Kapetanovic IM, Lyubimov AV, Kabirova EV, et al. Effects of bacterial and presystemic nitroreductase metabolism of 2-chloro-5-nitro-N-phenylbenzamide on its mutagenicity and bioavailability. *Chem Biol Interact*. 2012;197:16–22. doi:10.1016/j.cbi.2012.03.002
4. Sharma S, Pathirajage KS, Johnson T, Battu JR, Dasgupta S. GW-9662, a peroxisome proliferator-activated receptor gamma (PPARgamma) inhibitor, impairs early embryonic development in zebrafish. *Comp Biochem Physiol C Toxicol Pharmacol*. 2025;298:110332. doi:10.1016/j.cbpc.2025.110332
5. Schubert M, Becher S, Wallert M, et al. The peroxisome proliferator-activated receptor (PPAR)-gamma antagonist 2-chloro-5-nitro-n-phenylbenzamide (GW9662) triggers perilipin 2 expression via ppardelta and induces lipogenesis and triglyceride accumulation in human THP-1 macrophages. *Mol Pharmacol*. 2020;97:212–225. doi:10.1124/mol.119.117887

Dove Medical Press encourages responsible, free and frank academic debate. The contentTxt of the Drug Design, Development and Therapy 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Drug Design, Development and Therapy editors. While all reasonable steps have been taken to confirm the contentTxt of each letter, Dove Medical Press accepts no liability in respect of the contentTxt of any letter, nor is it responsible for the contentTxt and accuracy of any letter to the editor.

Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/drug-design-development-and-therapy-journal

https://doi.org/10.2147/DDDT.S578934