

Dear respected editor;

Regarding the article titled (**The NLRP3 Inflammasome and Pyroptosis in Multisystem Diseases**)

This research designed is good and the methodology well explained. Also, the results and conclusion are clear, but there are some comments need to be revised.

I am suggesting this title; **"NLRP3 Inflammasome and Pyroptosis: Implications in Inflammation and Multisystem Disorders"**

Major Comments:

1. Design & Structure

- The manuscript is well-structured and provides an in-depth analysis of the NLRP3 inflammasome and its role in multisystem diseases. However, some sections could benefit from improved organization for enhanced clarity and readability.
- The transition between sections is sometimes abrupt, particularly in the **"Survey Methodology"** and **"Research Progress on the NLRP3 Inflammasome and Pyroptosis in Multiple Systems"** sections. A clear transition statement summarizing previous points and introducing the new topic would improve coherence.
- The manuscript lacks clear **subsection headings** in the discussion of different organ systems (e.g., Nervous System, Endocrine System, etc.). Although each system is discussed separately, better formatting (bold headings or numbered subsections) would improve readability.
- Figures and tables are mentioned but not adequately referenced in the text (e.g., "Figure 1"). If they are included in the final version, they should be explicitly referred to in relevant paragraphs with explanations.

2. Language & Grammar

- The language is generally **comprehensive but overly technical**, sometimes making it difficult for a broader scientific audience to grasp key concepts quickly. Simplifying some complex sentences without losing depth could enhance clarity.
- Numerous **grammatical errors, awkward phrasing, and typographical mistakes** are present throughout the manuscript. Some examples include:
 - **Abstract:**
 - *"Pyroptosis is a programmed cell death that plays a crucial role in immune response and inflammation processes."*
 - Suggested revision: *"Pyroptosis is a form of programmed cell death that plays a crucial role in immune responses and inflammatory processes."*
 - *"At the same time, combined with the research progress of multiple physiological systems, the key roles of the NLRP3 inflammasome and pyroptosis in the pathogenesis of diseases have been revealed..."*

- Suggested revision: *"Additionally, integrating findings from multiple physiological systems highlights the key roles of the NLRP3 inflammasome and pyroptosis in disease pathogenesis..."*

- **Introduction:**

- *"pyroptosis is a novel form of cell death that plays a unique role in physiological and pathological processes compared to traditional apoptosis and necrosis."*
- "Pyroptosis" should be capitalized at the beginning of the sentence.
- More concise phrasing could improve readability:
"Pyroptosis is a distinct form of cell death with unique physiological and pathological roles compared to apoptosis and necrosis."

- **Survey Methodology:**

- *"The search was optimized by removing duplicate articles, evaluating the full text for usability, and prioritizing high-impact studies."*
- The phrase "evaluating the full text for usability" is vague. Consider specifying criteria for usability.

3. Scientific Rigor

- The manuscript is **well-referenced** and includes an extensive citation list, which supports claims and findings.
- However, some statements need **stronger justification with direct references**. For instance:
 - In the **"Upstream of Pyroptosis: The NLRP3 Inflammasome"** section, the mechanism by which the **NEK7 protein regulates NLRP3** activation is not fully detailed. Including more molecular details or referring to **specific studies** would improve credibility.
 - The **"Digestive System"** section briefly mentions **anthocyanins** inhibiting NLRP3 activation in non-alcoholic fatty liver disease but lacks mechanistic details.
 - The **"Respiratory System"** section states, *"The NLRP3 inflammasome is a potential combination therapy target that can be used for both COVID-19 management and intervention for fertility issues."* This is a broad claim and should be backed by specific studies explaining the mechanisms in both cases.

4. Conceptual & Logical Issues

- Some **redundancy** exists in the description of **GSDMD**, **NINJ1**, and **NLRP3**, leading to repetition of similar concepts in different sections.
- The **"Conclusions"** section **repeats** many findings instead of providing **insights or future directions**. Consider focusing on:
 - The **therapeutic implications** of targeting the NLRP3 inflammasome.
 - **Knowledge gaps** that require further research.
 - How **different disease models** have contributed to current understanding.
 - Please rewrite it professionally.

5. References

- The reference list appears **comprehensive** but should be formatted according to the target journal's citation style. Please manage it to be unified for all references according to journal format.

Final Assessment & Suggestions for Improvement

1. **Revise the manuscript for grammatical accuracy and technical clarity.**
2. **Improve transitions between sections** for better logical flow.
3. **Enhance formatting with clear subsection headings** in the disease-specific discussions.
4. **Ensure all claims are well-supported with direct references.**
5. **Reduce redundancy in descriptions of molecular mechanisms** (especially for inflammasome activation and pyroptosis execution).
6. **Strengthen the conclusion** by focusing on future directions and therapeutic prospects.

This review identifies **critical areas for improvement** while acknowledging the manuscript's **scientific depth and relevance**. With structural and linguistic refinements, it can achieve a **higher standard of clarity, rigor, and impact** in the field.