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The effects of MCC950 on NLRP3 inflammasome and inflammatory biomarkers: a systematic review and meta-analysis on animal studies

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Abstract

Introduction: The NLRP3 inflammasome plays a key role in the regulation of inflammation and has been implicated in various inflammatory diseases. The present study evaluated the impact of MCC950 on NLRP3 and inflammatory biomarkers in systematic review and meta-analysis.

Methods: Searches were performed across databases including Medline (PubMed), Scopus, Web of Science, and Embase. The pooled effects of MCC950 on NLRP3, TNF-alpha, interleukin (IL)-16, IL-18, and IL-1β were analyzed using a random effects model.

Results: Twenty animal studies met the inclusion criteria. MCC950 did not significantly reduce NLRP3 (SMD = -0.88; 95% CI: -1.79,0.03; $P = 0.058$) and TNF-alpha levels (SMD= -1.18; 95% CI: -2.45, 0.09; $P = 0.069$). A significant reduction was observed in IL-18 (SMD= -1.22; 95% CI: -2.44, -0.00; $P = 0.049$), IL-16 (SMD= -1.225; 95% CI: -2.779, 0.329; $P = 0.122$) and IL-1β (SMD = -1.38; 95% CI: -2.44 to -0.32; $P = 0.011$) concentrations after MCC950 treatment.

Conclusion: MCC950 reduced serum levels of some inflammatory factors. However, NLRP3 did not change significantly. Further research is necessary to understand the function of pharmacological inhibition of NLRP3 activation.

Registration: This study was conducted in accordance with the PRISMA checklist, and its protocol was registered on both the PROSPERO website (ID: CRD42024567477) and the Research Registry website (UIN: reviewregistry1887).

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Introduction

Inflammation is a key factor in the pathophysiology of various chronic diseases. From birth, the human body uses innate and adaptive immunity to fight pathogens (1,2). When hazardous stimuli such as infections, dead cells, or contaminants are present, the innate immune system mounts a carefully controlled defensive response. While prolonged inflammation can result in chronic or systemic inflammatory disorders, inadequate inflammation might allow pathogens to persist. The innate immune system relies on germline-encoded pattern-recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs) from invading pathogens and danger-associated molecular patterns (DAMPs) from internal stress. This capability is essential for effective defense against infectious and harmful agents. Induction of PRR activity by these factors activates downstream inflammatory pathways and induces the production of inflammatory cytokines (3,4).

Recent findings have significantly enhanced our understanding of the macromolecular mechanisms that trigger inflammasomes, a vital function of the innate immune system (5,6). NOD-like receptors (NLRs), a key subgroup of PRRs, play a significant role in inflammasome function (7). The NLRP3 inflammasome is especially significant in conditions related to ischemia and other diseases characterized by sterile inflammation (8). This complex includes cytoplasmic PRRs, ASC (apoptosis-associated speck-like protein containing a CARD), and the enzyme caspase-1 (9). Experimental research has shown that activation of NLRP3 by

Key point
- MCC950 administration in animal models did not significantly affect NLRP3 expression or TNF-alpha levels.
- Noteworthy reductions in serum levels of IL-18, interleukin-1β, and IL-16 were observed following MCC950 treatment.
- This study underscores the complex interplay of MCC950 on various cytokines in animal models, shedding light on potential therapeutic avenues.

pathogenic agents leads to a cascade of events ultimately activating caspase-1. This enzyme then stimulates the activation of interleukin (IL)-1β and IL-18, which induce pro-inflammatory actions in tissues (2,10).

Preclinical research has found that small compounds, such as isoliquiritigenin, can decrease NLRP3 activity. These molecules reduce pro-IL-1 and NLRP3 expression and block lipopolysaccharide (LPS)-induced NF-κB activation, demonstrating multi-target action (11,12). MCC950, a diarylsulfonylurea-containing compound, was initially discovered as an IL-1β inhibitor and later categorized as a member of cytokine release inhibitory drugs. Recent research suggests that the NLRP3 inflammasome's canonical and non-canonical pathways can be inhibited by MCC950, a selective small molecule blocker of the NLRP3 inflammasome, both in vivo and in vitro (13,14). Preclinical studies report that MCC950 has therapeutic properties in several inflammatory-based diseases, such as cognitive disease (15), spontaneous colitis, arthritis, and atherosclerosis (12,16). This study aims to systematically review the effects of MCC950 on NLRP3 and certain inflammatory markers.

Methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17).

Eligibility criteria

Studies were selected for the meta-analysis based on the PECOS criteria—population, exposure, comparison, outcomes, and study design—as detailed below.

- Population: Animals (rats, mice, pig)
- Exposure: MCC950 treatment
- Outcomes: Evaluation of changes in inflammatory cytokines.
- Type of studies: Animal studies.

Search strategy

Two investigators (PKH and RA) independently searched major databases, including PubMed, Scopus, Web of Science, and Embase, from their inception until November 30, 2023, for relevant articles in any language. To ensure comprehensive coverage, the reference lists of the selected articles were also checked. The keywords used in the search process included: "NLRP3", "NLR Family Pyrin Domain Containing 3", "NLR Family, Pyrin Domain-Containing 3 Protein" [Mesh], "Tumor Necrosis Factor-alpha" [Mesh], TNF-alpha, IL-18, "Interleukin-18" [Mesh], "Interleukin-1beta" [Mesh], and other synonyms in combination with MCC950.

Study selection criteria

Studies were included if they met the following criteria: they were conducted on animal models, evaluated the effect of MCC950 on at least one of the outcomes (NLRP3 or TNF-α or IL-18 or IL-1β), and were designed as parallel group animal studies. Studies that were conducted on cells or human samples were excluded from the analysis. Moreover, studies that evaluated the effect of MCC950 simultaneously with another intervention, were excluded too.

Data extraction

From the selected papers, two researchers (PKH and RA) independently extracted data such as the first author's name, publication year, country, type of animal model, sample size, intervention type, disease, duration of intervention, evaluation method, and main outcomes. When numerical data were available only in figures, Engauge Digitizer (version 12.1; developed by Mark Mitchell, Torrance, Calif.) was used to extract and convert the data points. The primary aim of this study was to assess the impact of MCC950 on NLRP3. Secondary outcomes included levels of TNF-alpha, IL-18, and IL-1β. Any discrepancies were resolved through discussions with additional experts.

Statistical analysis

For continuous data, results were presented as forest plots using the standardized mean difference (SMD) with 95% confidence intervals (CIs). The heterogeneity between studies was assessed using I^2 statistics. An I^2 value below 25% indicated low heterogeneity, 25%-50% indicated moderate heterogeneity, and above 50% indicated substantial heterogeneity. For low heterogeneity ($I^2 \leq 50\%$), a fixed-effects model was applied, while a random-effects model was used for I^2 values exceeding 50%. Sensitivity analysis involved the removal of one study at a time. Meta-regression analysis was conducted to explore the relationship between outcomes and specific variables. Publication bias was assessed through funnel plots and Egger's test, with a *P* value over 0.05 indicating no significant publication bias. All analyses were performed using STATA (version 13.1), with statistical significance set at a *P* value below 0.05.

Results

Selection and recognition research

Figure 1 shows a flowchart of our search process and results. The initial search yielded 721 studies, with 560 articles moving to the first screening phase after duplicate records were removed. Following a review of titles and abstracts, 508 studies were excluded, and 53 studies

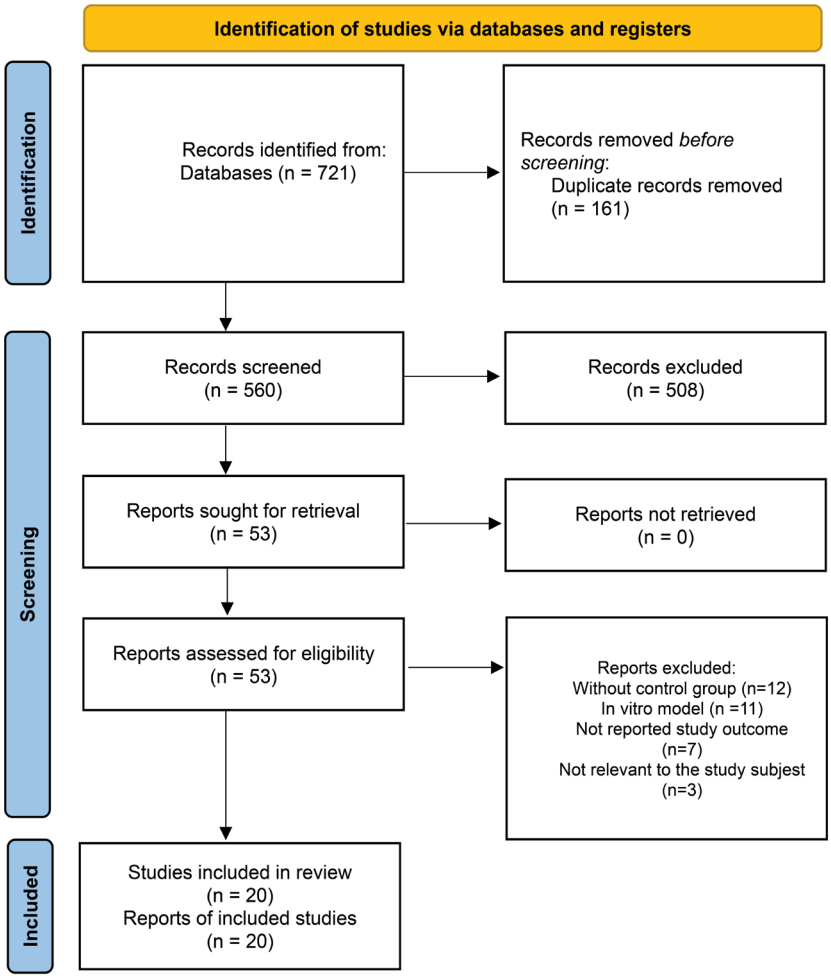

Figure 1. Flow chart of study selection for inclusion trials in the systematic review.

proceeded to the second screening phase. After full-text evaluation, 20 studies were ultimately included in the final analysis (18-37).

Table 1 presents the characteristics of the included studies, all published between 2016 and 2022. With the exception of the study by Luo et al which was conducted on rat sample, all other studies used mouse samples, all other studies used mouse samples. Sample sizes in these studies ranged from 3 to 18.

Effect of MCC950 on NLRP3 expression

The effect of MCC950 on NLRP3 expression was evaluated in 15 studies (20-22,24,25,28-33,35,37). It has been reported that MCC950 treatment could not cause a significant change in NLRP3 expression, with a significant heterogeneity (SMD = -0.88 95% CI: -1.79 to 0.03, $P = 0.058$; $I^2 = 83.3\%$, Figure 2). In order to evaluate the stability of the overall results, we applied the leave-one-out method in our sensitivity analysis. The leave-one-out sensitivity analysis showed that leaving studies which conducted by Chen et al (20) (SMD = -1.038 [95% CI: -2.003, -0.074, $P = 0.035$]), Dolunay et al (28) (SMD = -0.995 [95% CI: -1.959, -0.031, $P = 0.043$]), Fu et al (35) (SMD = -1.028 [95% CI: -2.001, -0.056, $P = 0.038$]), Ismael et al (29) (SMD = -1.148 [95% CI: -1.969, -0.327, $P = 0.0.006$]) and Xu et al (21) (SMD = -0.985 [95% CI: -1.952, -0.017, $P = 0.046$]) led to significant changes in results.

There was a significant publication bias using the funnel plots and Egger's and Begg's tests (Egger's test $P = 0.001$; Begg's test $P = 0.037$).

Effect of MCC950 on TNF-alpha levels

Seven studies described the effect of MCC950 on the TNF-alpha levels (20,22,23,27,29,35). The quantitative meta-analysis displayed a non-significant reduction in TNF-alpha levels after MCC950 administration (SMD = -1.18 [95% CI: -2.45, 0.09, $P = 0.069$]), with a significant heterogeneity ($I^2 = 83.3\%$, $P < 0.001$; Figure 3). The results of sensitivity analysis revealed that there was a significant change in results after removing Ismael et al (29) (SMD = -1.541 [95% CI: -2.837, -0.246, $P = 0.020$]) and Perera et al (27) (SMD = -1.453 [95% CI: -2.887, -0.018, $P = 0.047$]). Furthermore, we found considerable evidence of publication bias based on funnel plots and Egger's test (Egger's test $P = 0.003$).

Table 1. General characteristics of eligible studies

Author, year	Subject	Sample size	Sample type	Disease type	Intervention duration	MCC950 dose	Control type
Ludwig-Portugall, I. 2016 (26)	Mice	8	Renal DCs from wild-type mice	Crystal-induced kidney fibrosis	21 days	200 mg/kg	PBS
Chen, W. 2017 (20)	Mice	10	Hind limbs	Alpha virus induced inflammation	10 days	20 mg/kg	PBS
Dolunay, A. 2017 (28)	Mice	6	Brain	LPS induced inflammatory hyperalgesia	NA	3 mg/kg	PBS
Perera, P. 2017 (27)	Mice	20	Proximal colon	Spontaneous colitis	21 days	40 mg/kg	PBS
Jiang, X.B. 2017 (30)	Mice	8	Heart	Heart failure	21 days	10 mg/kg	PBS
Ismael, S. 2017 (29)	Mice	16	Pericontusional cerebral cortex	Traumatic brain injury	3 days	50 mg/kg	Saline
Xu, K.Y. 2018 (21)	Mice	18	lung ischemia-reperfusion (IR)	Lung ischemia	12 hours	50 mg/kg	Saline
Hong, P. 2018 (31)	Mice	6	Brain	Cerebral ischemia-reperfusion injury in diabetic mice	24 hours	50 mg/kg	PBS
Fan, Y. 2018 (32)	Mice	36	Hippocamp	Induced proptosis and cognitive impairment	7 days	10 mg/kg	PBS
Perera, A.P. 2018 (27)	Mice	8	Mesenteric lymph node	Spontaneous colitis	21 days	40 mg/kg	PBS
Chen, L. 2018 (18)	Mice	12	Distal colon	Spontaneous colitis	49 days	40 mg/kg	PBS
Ismael, S. 2018 (29)	Mice	10	Brain cerebral cortex	Traumatic brain injury	3 days	50 mg/kg	Saline
Perera, P. 2018 (27)	Mice	20	Distal colon	Spontaneous colitis	21 days	40 mg/kg	PBS
Luo, Y. 2019 (22)	Rat	18	Brain	Early brain injury after subarachnoid hemorrhage	24 hours	10 mg/kg	PBS
Chen, S. 2019 (24)	Mice	12	Spleen	Head and neck squamous cell	21 days	15 mg/kg	PBS
Krishnan, M. 2019 (33)	Mice	16	Kidney	Hypertension	25 days	10 mg/kg	Saline
Jiao, J. 2020 (23)	Mice	28	Spinal cord	Spinal cord injury	28 days	10-50 mg/kg	PBS
Jiang, M. 2020 (34)	Mice	8	Brain cortex	Cardiac arrest	14 days	10 mg/kg	PBS
Fu, Q. 2020 (35)	Mice	12	Brain	Preoperative neurocognitive disorder	7 days	10 mg/kg	Saline
Chen, Y.Q. 2020 (38)	Mice	12	Spinal cord	Spinal cord injury	7 days	50 mg/kg	PBS
Dong, J. 2021 (36)	Mice	12	Serum	Wilson disease	30 days	20 mg/kg	PBS
Ni, B. 2021 (37)	Mice	12	Knee joint (upper tibia and lower femur)	Osteoarthritis	8 weeks	3 mg/kg	Saline
Jiang, X. 2022 (30)	Mice	8	Heart	HF induced ventricular arrythmia	3 weeks	10 mg/kg	PBS
Chen, X. 2022 (25)	Mice	12	Liver tissue	Induced liver injury	NA	10 mg/kg	PBS

PBS: Phosphate-buffered saline.

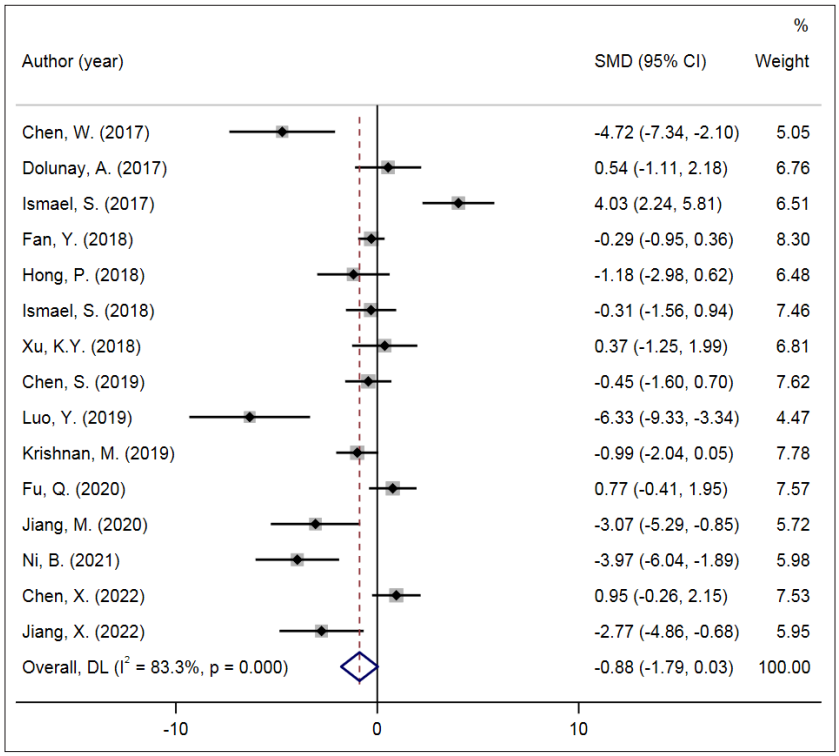

Figure 2. The forest plot of the effect of MCC950 on the NLRP3 expression.

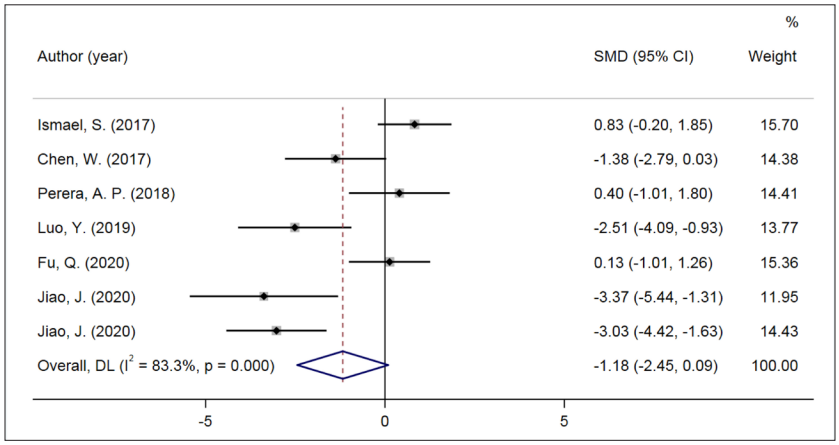

Figure 3. The forest plot of the effect of MCC950 on the TNF-alpha levels.

Effect of MCC950 on IL-18 levels

Ten studies with 11 effect sizes have reported the effect of MCC950 administration on IL-18 levels (Figure 4) (20,21,23,25,26,30,35,36,38). The quantitative meta-analysis displayed a significant effect of MCC950 on IL-18 levels (SMD = -1.22 [95% CI: -2.44, -0.00, $P=0.049$]), with a significant heterogeneity ($I^2=85.5$, $P<0.001$). It has been reported in sensitivity analysis that left out of studies which conducted by Jiang et al (30), Chen et al (20), Jiao et al (23), Dong et al (36) and Ludwig-Portugal et al (26) caused the results to shift towards insignificance. There was not any evidence of publication bias between evaluated studies (Egger's test $P=0.55$; Begg's test $P=0.161$).

Effect of MCC950 on IL-1β levels

Overall, 12 studies (20,21,23,25,26,30,35,36,38) with 20 effect sizes considered the effect of MCC950 on IL-1β levels. As shown in Figure 5, MCC950 administration caused a significant reduction in IL-1β concentration (SMD = -1.38 95% CI: −2.44 to -0.32, $P=0.011$; $I^2=88.4\%$, $P<0.001$). The results of sensitivity analysis based on leave-one-out method showed that leaving each of study in a range from (SMD = -1.666 [95% CI: -2.682, -0.65, $P=0.001$]) by Dong et al (36) to (SMD= -1.666 [95% CI: -2.682, -0.65, $P=0.001$]) to (SMD = -1.043 [95% CI: -2.032, -0.053, $P=0.039$]) by Jiao et al (23) had no significant effect on the pooled effect size. There was a significant evidence of publication bias (Egger's test $P=0.002$).

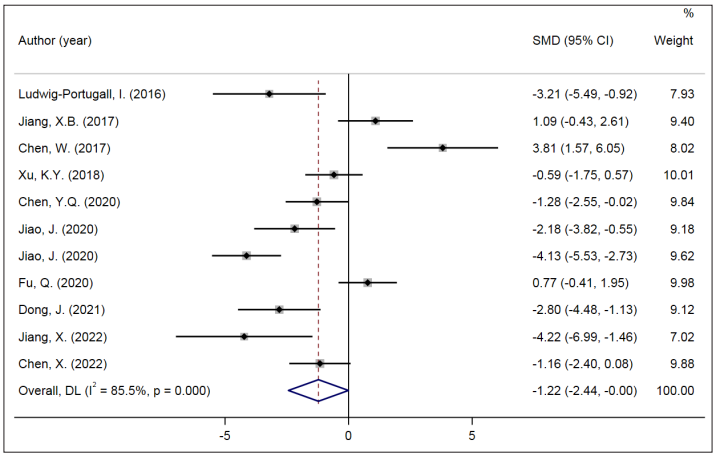

Figure 4. The forest plot of the effect of MCC950 on the IL-18 levels.

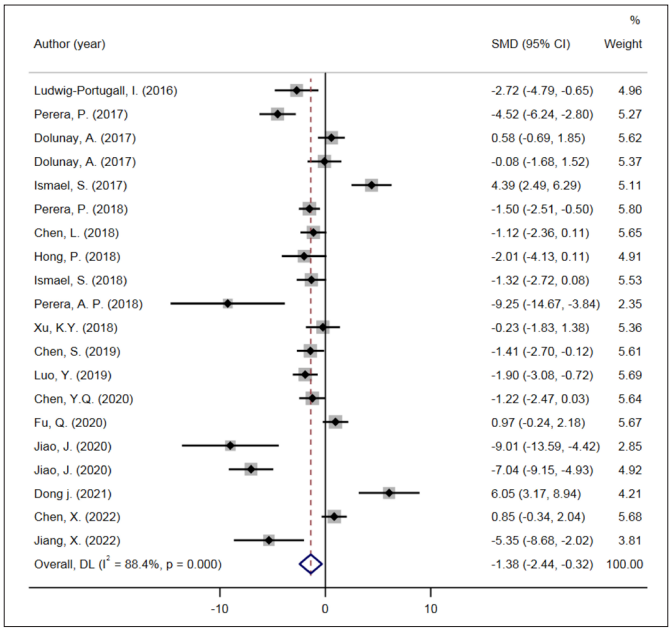

Figure 5. The forest plot of the effect of MCC950 on the IL-1β levels.

Effect of MCC950 on IL-16 levels

Four studies have reported the effects of MCC950 on IL-16 levels (Figure 6) (20,22,26,36). We found a significant reduction in IL-16 following MCC950 treatment (SMD = -1.41 95% CI: -2.66 to -0.15, $P = 0.028$; $I^2 = 64.6\%$, $P = 0.037$). The sensitivity analysis indicated that removing Luo et al (22) (SMD = -1.599 [95% CI: -3.528, 0.331, $P = 0.104$]) and Chen et al (20) (SMD = -1.225 [95% CI: -2.779, 0.329, $P = 0.122$]) resulted in non-significant findings. There was a significant evidence of publication bias (Egger's test $P = 0.007$).

Discussion

This study demonstrated that MCC950 administration in animal models did not significantly affect NLRP3 expression or TNF-alpha levels. However, it led to a significant reduction in serum levels of IL-18, IL-1β, and IL-16.

Chronic diseases are often driven by early-stage cellular events, many of which are based on inflammatory processes (39). Previous studies have documented the activation of nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) in response to various stimuli such as LPS. This activation significantly increases the production and secretion of various pro-inflammatory cytokines, creating conditions that can worsen several chronic diseases (40).

Among these, NLRP3 is a notable component, as it forms part of multi-protein complexes called inflammasomes, which play critical roles in inflammation and immunity (12). In this study, MCC950 administration did not significantly impact NLRP3. However, in the sensitivity analysis, after removing some studies, this effect became significant. A previous systematic review and meta-analysis conducted by Gao et al found that NLRP3 inhibition led to a significant reduction in some inflammatory factors in experimental acute pancreatitis (41).

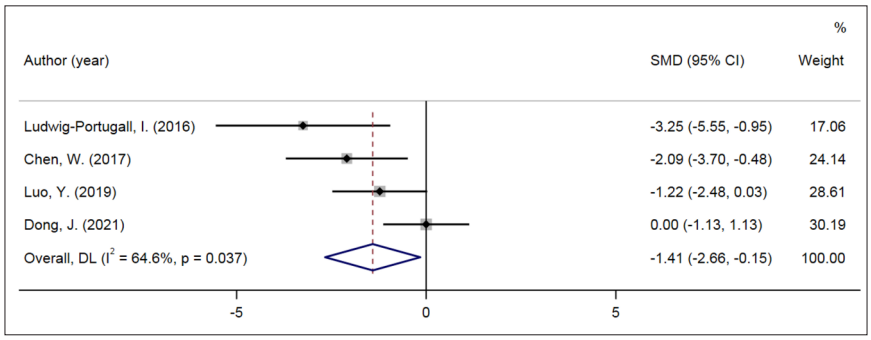

Figure 6. The forest plot of the effect of MCC950 on the IL-16 levels.

Despite NLRP3 inflammasome being recognized as a crucial factor in inflammatory processes, the exact mechanism remains unknown. Generally, the formation of the NLRP3 inflammasome involves two processes: priming and assembly. In the priming phase, toll-like receptors (TLRs) detect inflammatory stimuli such as PAMPs and DAMPs. This detection leads to the NF-κB -mediated expression of NLRP3, pro-caspase-1, pro-IL-1, and pro-IL-18. In the subsequent stage, the NLRP3 inflammasome assembles following NLRP3 activation (12, 42). This activation results in the maturation and release of potent pro-inflammatory cytokines like IL-18 and IL-1β (43).

Our findings showed that MCC950 led to a significant reduction in levels of IL-1β, IL-18, and IL-16 in animal models, but did not significantly affect TNF-α levels. Coll et al demonstrated that MCC950 administration does not inhibit TLR signaling but exerts its effects in the NLRP3 inflammasome assembly phase (44). These results are consistent with our study and suggest that MCC950's inhibitory effects are focused on the processes stimulated by NLRP3 inflammasomes, rather than the expression of NLRP3 itself.

Additionally, our pooled analysis revealed a significant reduction in serum levels of IL-1β in animal models treated with MCC950. The activation of the NLRP3 inflammasome and subsequent release of IL-1β were initially observed in pancreatic beta-cells and islet-infiltrating macrophages (45). IL-1β, a crucial pro-inflammatory cytokine, can induce the production of other cytokines and chemokines. Endothelial cells stimulated by IL-1β express cell membrane adhesion molecules and pro-coagulant properties. The transcription of IL-1β is regulated by PRR proteins in the NLRP3 inflammasome in response to PAMPs or DAMPs (46,47). In addition to immune cells such as monocytes and macrophages, non-immune cells like keratinocytes also secrete IL-1β. Several studies have implicated IL-1β in the pathogenesis of chronic disorders like diabetes and metabolic syndrome (42,48). Thus, the suppression of IL-1β by MCC950 may provide protective effects against these chronic conditions.

Recent studies underscore the significance of NLRP3 inflammasome inhibition in reducing inflammation-related chronic diseases. Zhang et al highlighted that the suppression of the NLRP3 inflammasome can mitigate the inflammatory response in various disease models, including metabolic and autoimmune disorders (49). These findings support the therapeutic potential of MCC950, which appears to selectively inhibit NLRP3 without broadly affecting other immune pathways. This specificity could minimize adverse effects and provide a targeted approach to treating conditions characterized by chronic inflammation. Future research should focus on the long-term outcomes of MCC950 administration and its efficacy across different models to fully elucidate its therapeutic potential and mechanisms of action.

The current investigation found that MCC950 significantly lowered IL-18 levels. NLRP3 activation leads to the caspase-1 enzyme triggering the maturation of IL-1β and IL-18 precursors, resulting in the release of these active cytokines. IL-18's binding to the IL-18R complex activates several signaling pathways, including NF-κB, STAT1, and MAPKs (50,51). Furthermore, IL-18, also known as the IFN-γ-inducing factor, increases IFN-γ secretion from activated T cells and NK cells, contributing to Th1 cell polarization (52).

Conclusion

Our meta-analysis demonstrated that MCC950 treatment in animal models led to a significant reduction in IL-18, IL-1β, and IL-16 levels, but did not significantly affect NLRP3 and TNF-α levels. Further research is necessary to understand the function of pharmacological inhibition of NLRP3 activation and its therapeutic use.

In this time, it has been reported in pre-clinical studies that MCC950 has therapeutical properties in some of the inflammatory based diseases such as cognitive disease, spontaneous colitis, arthritis and atherosclerosis. So, the aim of this systematic review and meta-analysis study was to investigate the effect of MCC950 on NLRP3 and some of the inflammatory biomarkers.

This study showed that treating animal models with MCC950 significantly reduces levels of IL-18, IL-1β, and IL-16. Besides immune cells like monocytes, macrophages, neutrophils, B lymphocytes, dendritic cells, and NK cells, non-immune cells such as keratinocytes also secrete IL-

1β. Several studies have indicated that IL-1β plays a role in the development of chronic disorders like diabetes and metabolic syndrome. Therefore, IL-1β suppression by MCC950 might serve as a protective measure against these chronic conditions.

Recent studies underscore the significance of NLRP3 inflammasome inhibition in reducing inflammation-related chronic diseases. For instance, Bauernfeind et al (53) highlighted that the suppression of the NLRP3 inflammasome can mitigate the inflammatory response in a variety of disease models, including metabolic disorders and autoimmune diseases. These findings support the potential therapeutic role of MCC950, which appears to selectively inhibit NLRP3 without broadly affecting other immune pathways. This specificity could minimize adverse effects and provide a targeted approach to treating conditions characterized by chronic inflammation. Future research should focus on long-term outcomes of MCC950 administration and its efficacy across different models to fully elucidate its therapeutic potential and mechanisms of action.

Limitations of the study

To our knowledge, this study is the first systematic review and meta-analysis to assess the effects of MCC950 on NLRP3 and various inflammatory markers in animal studies. This meta-analysis benefited from detailed search strategy, selecting accurate inclusion and exclusion criteria and not having language restrictions. Nevertheless, there are several limitations to this study. First, the animal samples used are different in terms of the type of disease induced and this can affect the accuracy of the results. Second, we found a considerable publication bias in term of some evaluated outcomes. Finally, although most of the studies were conducted on mouse samples, the type of animal sample was different in some studies.

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Authors' contribution

Conceptualization: Parisa Khodabandeh Shahraki, Amirhossein Ramezani Ahmadi, Mojtaba Akbari, Atousa Masoud, Aghileh Panahi.
Data curation: Atousa Masoud, Mojtaba Akbari, Roya Adelnia, Aghileh Panahi.
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Investigation: Atousa Masoud, Roya Adelnia, Parisa Khodabandeh Shahraki, Aghileh Panahi.
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Software: Mojtaba Akbari, Lida Jamal Ashini
Supervision: Mojtaba Akbari, Amirhossein Ramezani Ahmadi.
Validation: Roya Adelnia, Aghileh Panahi.
Visualization: Amirhossein Ramezani Ahmadi, Aghileh Panahi.
Writing–original draft: Atousa Masoud, Roya Adelnia, Lida Jamal Ashini, Parisa Khodabandeh Shahraki.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42024567477) and Research Registry website (Unique Identifying Number (UIN): reviewregistry1887). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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