

Rubimaillin targets NLRP3 R167/Y381 to ameliorate inflammatory and neurodegenerative diseases

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INTRODUCTION	RESULTS	CONCLUSIONS
Rubimaillin (Rub) is a naphthoquinone from <i>Rubia cordifolia</i> L. with known anti-inflammatory and neuroprotective activities. The NLRP3 inflammasome drives pyroptosis and IL-1β release; and its hyperactivation underlies gout, sepsis, and Alzheimer's disease (AD). However, the underlying mechanisms are not fully defined.	Rub dose-dependently suppressed pyroptosis and IL-1β release in mouse primary microglia, BMDMs, and THP-1 cells, without affecting AIM2 or NLRC4 inflammasome pathways. Mechanistically, Rub directly bound to NLRP3, blocking NLRP3 and ASC oligomerization, caspase-1 activation, and GSDMD cleavage. Mutagenesis studies identified arginine 167 and tyrosine 381 as the critical residues for Rub-NLRP3 binding. In vivo, Rub treatment significantly prolonged survival and attenuated lung injury in LPS-induced sepsis, reduced paw swelling and bone erosion in MSU-induced gout, and ameliorated cognitive deficits and neuroinflammation in APP/PS1 model.	Rub selectively targets the NLRP3 inflammasome via direct binding to its NACHT domain at residues R167 and Y381, effectively blocking NLRP3 and ASC oligomerization, ASC speck formation, caspase-1 activation, and GSDMD-mediated pyroptosis. Rub exerts therapeutic effects in sepsis, gout, and AD models without affecting AIM2 or NLRC4 pathways. This study provides a molecular basis for the traditional anti-inflammatory use of <i>Rubia cordifolia</i> L. and establishes Rub as a promising natural lead compound for the treatment of NLRP3-driven inflammatory and neurodegenerative disorders.

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