Molybdenum supplementation in rheumatic diseases: A systematic review

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Abstract. Molybdenum is an essential trace element involved in oxidative metabolism, detoxification pathways and in the regulation of inflammatory. However, despite biological plausibility, its role in rheumatic diseases remains unclear. The aim of the present study was to systematically review the available clinical evidence regarding molybdenum supplementation in rheumatic and autoimmune diseases. For this purpose, a systematic literature search was performed on the PubMed/MEDLINE, SciELO and LILACS databases from 1965 to June, 2024. Studies evaluating molybdenum supplementation in patients with rheumatic or autoimmune diseases were eligible. Screening and study selection followed the PRISMA recommendations. A total of 12 records were identified through database searching. Following screening and eligibility assessment, one clinical study fulfilled the inclusion criteria. That pilot crossover study included 14 patients with heterogeneous arthritic conditions and evaluated molybdenum amino acid chelate supplementation. Subjective improvements in pain and general health were reported; however, critical methodological limitations were identified, including the small sample size, heterogeneous diagnoses, lack of validated outcome measures and limited methodological reporting. On the whole, the current evidence is insufficient to support routine molybdenum supplementation in rheumatic diseases. Additional well-designed observational and interventional studies are warranted to clarify its potential clinical role.

Introduction

Molybdenum (Mo) is an essential trace element required in small amounts for normal human metabolism. It is widely distributed in plant-based foods, such as legumes, cereals and nuts, and the average dietary intake in the majority of populations exceeds the recommended dietary allowance of 45 μg/day for adults (1,2). Consequently, overt molybdenum deficiency is exceedingly rare in clinical practice, and dietary adequacy is generally maintained in diverse dietary patterns (1,2).

Physiologically, molybdenum acts as an indispensable cofactor for several molybdoenzymes, including xanthine oxidoreductase, aldehyde oxidase, sulfite oxidase and mitochondrial amidoxime reducing component (3,4). These enzymes are involved in purine metabolism, sulfur amino acid detoxification, redox balance and mitochondrial function. Through these pathways, molybdenum contributes indirectly to oxidative stress regulation, endothelial homeostasis and inflammatory signaling (3,4). From a rheumatology perspective, oxidative stress, redox imbalance and trace element disturbances have been consistently discussed as contributors to chronic inflammation, synovial pathology and systemic complications in rheumatoid arthritis (RA) and related rheumatic diseases (5,6).

Interest in micronutrients as potential adjunctive interventions has grown as the nutritional status may modulate inflammatory burden, antioxidant defenses, and possibly, symptom trajectories in chronic rheumatic disease. In this context, molybdenum has occasionally been proposed as a candidate supplement, largely on biochemical grounds. However, unlike other trace elements (e.g., zinc and selenium), for which the rheumatologic literature includes observational signals and some clinical discussion, the molybdenum-rheumatology interface remains poorly characterized (5-7). Therefore, the objective of the present systematic review was to critically evaluate the clinical evidence (if any) supporting molybdenum supplementation in rheumatic and autoimmune diseases, while situating the topic within current knowledge about trace elements, redox biology and inflammatory mechanisms relevant to rheumatology.

Biological and clinical rationale for the use of molybdenum. The putative relevance of molybdenum to rheumatic disease is primarily extrapolated from its enzymatic and metal-interaction biology. First, molybdoenzymes participate in oxidation-reduction pathways that can influence the generation of reactive oxygen species, detoxification processes and broader redox homeostasis (3,4). Xanthine oxidoreductase, for example, is central to purine metabolism and can contribute to oxidative reactions under certain conditions; this pathway has been considered

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therapeutically relevant in inflammatory and vascular contexts, supporting interest in xanthine oxidase inhibition as a strategy to modulate oxidative stress (8). While this does not directly imply that increasing molybdenum intake is beneficial, it illustrates why molybdenum-dependent enzymes are frequently mentioned when redox mechanisms are discussed.

Second, sulfite oxidase is required for the detoxification of sulfite, preventing the accumulation of potentially harmful intermediates; severe impairment of this pathway (typically genetic or profound cofactor deficiency states) can have major clinical consequences, reinforcing the essentiality of molybdenum biology (3,4). Third, aldehyde oxidase and related molybdenum enzymes participate in metabolism of various aldehydes and xenobiotics, adding a conceptual layer related to detoxification and oxidative pathways (3,4). Collectively, these mechanisms have been used to justify speculative hypotheses that molybdenum may indirectly influence inflammatory signaling, oxidative injury, or mitochondrial function in chronic inflammatory states. The proposed biological pathways through which molybdenum may theoretically influence oxidative stress, inflammatory signaling, mitochondrial function, and endothelial homeostasis relevant to rheumatic diseases are summarized in Fig. 1.

A more concrete clinical precedent for molybdenum-based interventions is its interaction with copper metabolism. Tetrathiomolybdate (and related compounds) plays a documented role in reducing copper bioavailability, with clinical use and extensive discussion in Wilson's disease management (9). Copper control strategies have also been explored in other settings (including antiangiogenic concepts in oncology), demonstrating that molybdenum compounds can have clinically meaningful biological effects, albeit via copper binding rather than 'nutritional supplementation' per se (10). As altered metal homeostasis and oxidative stress are relevant to rheumatic diseases, findings from studies evaluating oxidative stress and trace element disturbances in rheumatoid arthritis have led investigators to speculate that copper-modulating or redox-related mechanisms could theoretically intersect with rheumatic pathophysiology (5-7).

However, biochemical plausibility should be separated from evidence of clinical benefit. Notably, routine molybdenum intake is usually adequate, and indiscriminate supplementation could carry theoretical risks, including trace element imbalances, particularly through copper-related interactions (2,9). Therefore, any rationale for supplementation in rheumatology needs to be supported by controlled human data demonstrating improvements in validated clinical outcomes or objective inflammatory markers, alongside safety characterization.

Data and methods

Search strategy. A systematic literature search was conducted on the PubMed/MEDLINE, SciELO and LILACS databases, covering publications from 1965 to June, 2024. The search strategy combined controlled vocabulary terms and free-text keywords using Boolean operators. The principal search combinations included: ('molybdenum' OR 'trace elements') AND ('arthritis' OR 'rheumatoid arthritis' OR 'autoimmune diseases' OR 'rheumatic diseases'). The reference lists of relevant articles were also examined to identify additional clinical studies potentially missed by database indexing. The study selection process is summarized in Fig. 2.

Eligibility criteria. Eligible studies were original clinical investigations involving human participants that evaluated molybdenum supplementation (or molybdenum-containing interventions presented explicitly as supplementation) in any rheumatic or autoimmune disease. Review articles, experimental animal studies, *in vitro* investigations, case reports, conference abstracts and non-indexed publications were excluded. No restrictions were applied regarding language or study design.

Study selection. Duplicate records were manually identified and removed prior to study screening. Titles and abstracts were assessed for relevance according to predefined eligibility criteria, followed by full-text evaluation when appropriate. Given the anticipated scarcity of clinical trials, the present systematic review also considered whether molybdenum-related clinical evidence existed in adjacent immune-inflammatory contexts that could plausibly inform rheumatology; however, the principal scope remained supplementation studies in rheumatic and autoimmune disease populations.

Outcomes of interest. The primary outcomes of interest were validated measures of pain, disease activity (when applicable), functional status, patient-reported outcomes, inflammatory biomarkers and adverse events.

Data synthesis. As only one eligible study was identified, a meta-analysis could not be performed. Therefore, the results were summarized using a qualitative descriptive approach.

Results

Study selection. The literature search identified 12 records through database searching and manual review of reference lists. Following the removal of duplicates and screening of titles and abstracts, potentially relevant articles underwent full-text assessment. Only one study fulfilled the predefined eligibility criteria and was included in the final review (Fig. 2).

No randomized controlled trials, prospective cohort studies, or case-control studies specifically evaluating molybdenum supplementation in rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, vasculitis, or other autoimmune rheumatic diseases were identified.

Characteristics of included studies. The only eligible study identified was a pilot crossover investigation published by Moss in 1995 (11). That study enrolled 14 patients with heterogeneous arthritic conditions who received molybdenum amino acid chelate supplementation at doses of 200 or 500 μg/day.

That study reported subjective improvements in pain and general health following supplementation. However, several critical methodological limitations were identified. The patient population included mixed arthritic diagnoses without standardized disease classification, validated outcome measures were not employed, objective inflammatory biomarkers were not assessed, and methodological details regarding crossover procedures, randomization, and statistical analyses were incompletely reported (11).

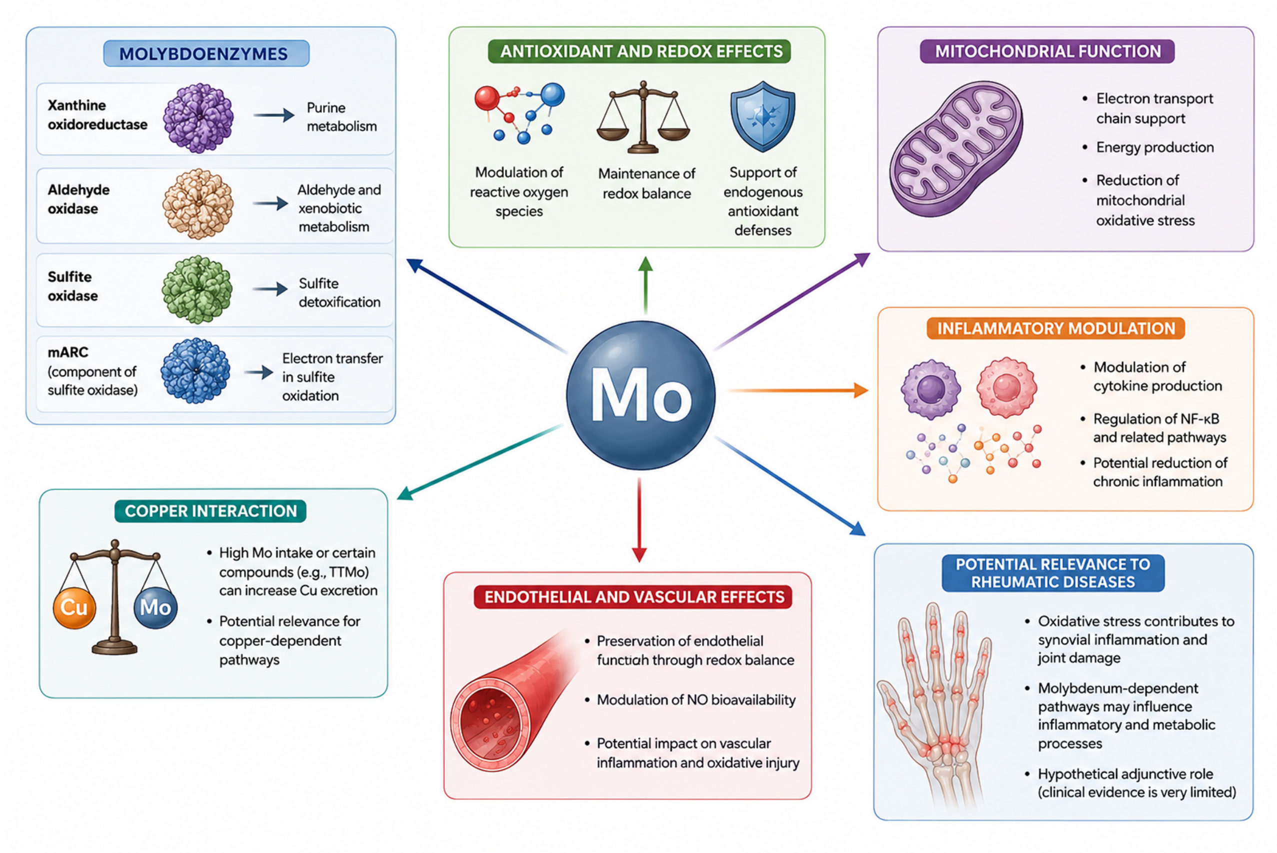

Figure 1. Proposed biological roles of molybdenum relevant to rheumatic diseases. Molybdenum is an essential trace element that acts as a cofactor for several molybdoenzymes involved in purine metabolism, sulfite detoxification, redox regulation, mitochondrial function, and endothelial homeostasis. Through these pathways, molybdenum-dependent enzymes may indirectly influence oxidative stress, inflammatory signaling, vascular function, and metabolic processes potentially relevant to rheumatic diseases. However, despite biochemical plausibility, current clinical evidence supporting molybdenum supplementation in rheumatology remains extremely limited. Mo, molybdenum; ROS, reactive oxygen species; NF-κB, nuclear factor κB; mARC, mitochondrial amidoxime reducing component; NO, nitric oxide; TTMo, tetrathiomolybdate.

In addition, the small sample size and short treatment duration limited the ability to evaluate efficacy and safety outcomes reliably. The principal characteristics, findings and methodological limitations of the included study are summarized in Table I.

Summary of available evidence. The currently available evidence should not be interpreted as demonstrating either efficacy or lack of efficacy of molybdenum supplementation in rheumatic diseases. Rather, it reflects the remarkable scarcity of adequately designed clinical investigations in this field.

The available data are insufficient to determine whether molybdenum supplementation exerts clinically meaningful effects on pain, disease activity, functional outcomes, inflammatory biomarkers, or other clinically relevant endpoints in rheumatic diseases. Furthermore, the heterogeneity of the arthritic conditions included in the only available study substantially limits disease-specific interpretation, since pathogenic mechanisms, clinical manifestations, and treatment responses differ considerably among rheumatic disorders.

No replication studies, confirmatory trials, long-term follow-up investigations, or formal safety evaluations in rheumatic populations were identified. Consequently, the current clinical evidence base remains limited to a single small pilot study with substantial methodological limitations, precluding evidence-based recommendations regarding routine molybdenum supplementation in rheumatology.

Discussion

The present systematic review highlights a clear mismatch between biochemical plausibility and clinical evidence for molybdenum supplementation in rheumatology. Molybdenum is indisputably essential for human physiology through its molybdoenzyme cofactor role, with well-described functions in redox metabolism, detoxification processes, and mitochondrial-related pathways (3,4). These domains are mechanistically relevant to chronic inflammatory diseases, including RA, where oxidative stress, redox dysregulation, immunometabolic alterations, and metabolic-inflammatory coupling are increasingly recognized as important contributors (5,6). Nonetheless, the existence of relevant pathways does not establish that increasing molybdenum exposure confers benefit, particularly in populations where intake is already sufficient.

A central issue is that supplementation hypotheses often assume deficiency or functional insufficiency. Yet, dietary surveys and nutritional guidance suggest that average molybdenum intake in a number of settings exceeds recommended

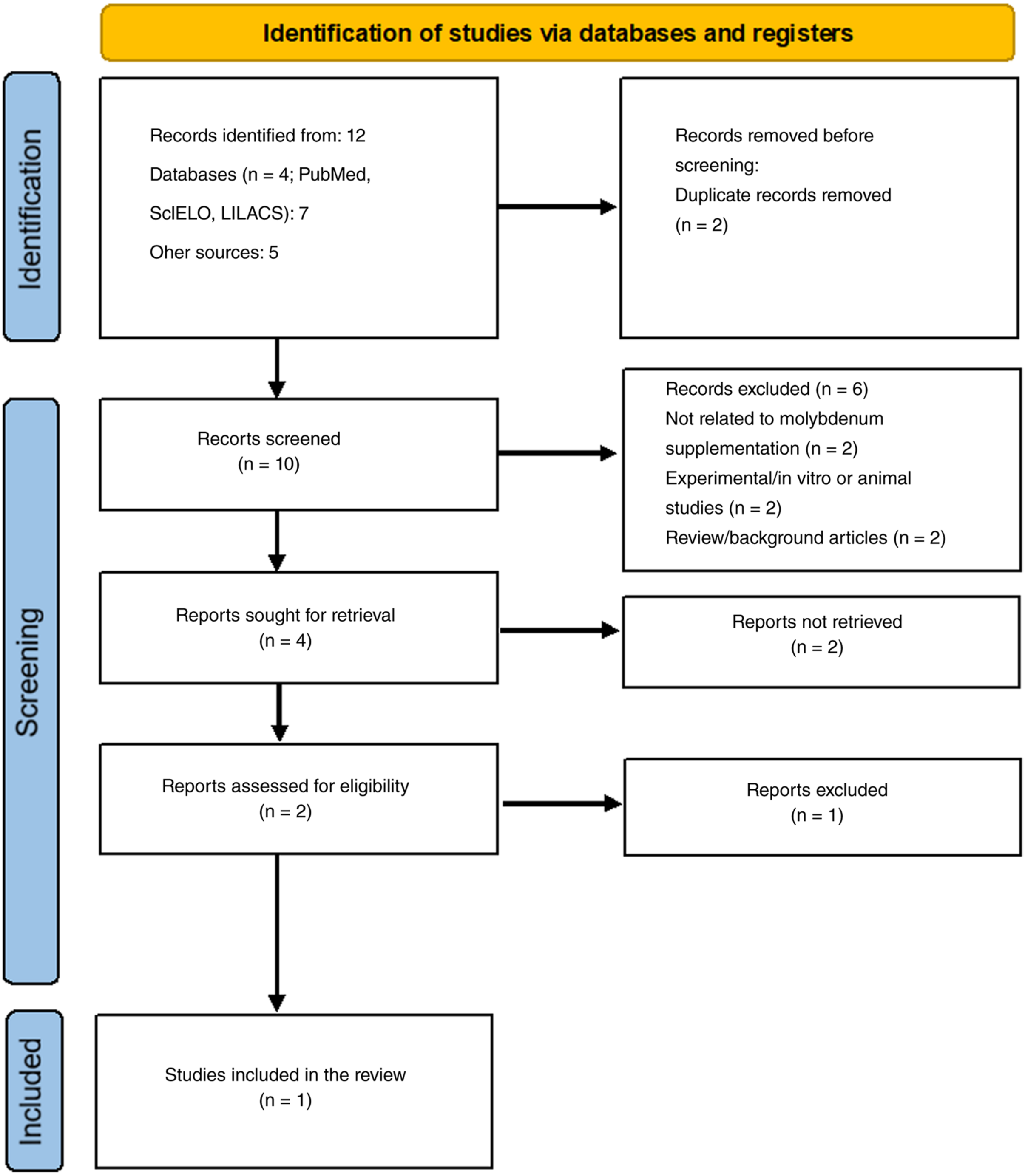

Figure 2. PRISMA flow diagram of study selection for the systematic review. PRISMA flowchart illustrating the study selection process for the systematic review. A total of 12 records were identified, and one study fulfilled the eligibility criteria and was included in the final review.

intakes, and frank deficiency is rare (1,2). In such a context, 'more' is not necessarily better; supplementation may merely increase exposure without addressing a biologically relevant deficiency. From a clinical standpoint, an intervention is most plausible when there is evidence that: i) Baseline levels are low or functionally inadequate in the target population; ii) repletion changes a relevant biological marker; and iii) such changes translate into improved clinical outcomes. None of these steps has been convincingly demonstrated for molybdenum in rheumatic diseases.

The contrast with other trace elements is instructive. Zinc and selenium have been discussed in RA and other inflammatory conditions, with studies reporting associations between serum levels and disease activity or oxidative stress parameters, and with some clinical attention to inadequate intake patterns in chronic disease populations (5-7). While that literature is not uniformly definitive, it provides a framework for how micronutrient hypotheses can be explored and tested. While the literature regarding zinc and selenium status in rheumatoid arthritis and other inflammatory conditions is not uniformly definitive (5-7), it provides a framework for how micronutrient hypotheses can be explored and tested. This relative lack of research attention may also reflect the rarity of clinically significant molybdenum deficiency compared with

Table I. Available clinical evidence evaluating molybdenum supplementation in arthritis-related conditions.

Author, year of publication	Population/ disease	Sample size	Intervention	Main findings	Major limitations	(Refs.)
Moss, 1995	Heterogeneous arthritis conditions	14 patients	Molybdenum amino acid chelate supplementation (200 or 500 μg/day) in a crossover pilot design	Subjective improvements in pain and general health were reported by some participants	Very small sample size; heterogeneous diagnoses; absence of standardized rheumatologic classification criteria; lack of validated outcome instruments; no objective inflammatory biomarkers; limited methodological transparency regarding randomization and statistical analysis; short follow-up duration; insufficient safety evaluation	(11)

other trace elements more frequently implicated in inflammatory and nutritional disorders.

The single pilot study from 1995 reporting subjective improvements needs to be interpreted cautiously (11). Subjective symptom changes can occur due to regression to the mean, placebo effects, natural disease fluctuation, concurrent treatment changes and measurement artifacts. Potential placebo and expectancy effects should also be considered, particularly given the subjective nature of pain assessment and the absence of validated outcome measures. Without standardized diagnostic criteria, validated instruments (e.g., visual analog scale) anchored to protocol timing, functional indices) and transparent statistical reporting, it is impossible to determine whether the observed improvements reflect a true treatment effect or nonspecific factors (11). Additionally, heterogeneous 'arthritis' populations dilute interpretability: Mechanisms and symptom dynamics differ substantially among RA, osteoarthritis, crystalline arthropathies and spondyloarthritis; pooling such conditions obscures disease-specific effects and creates confounding.

Safety and biological trade-offs also warrant emphasis. Molybdenum can interact with copper homeostasis, particularly at higher exposures or in pharmacological formulations such as tetrathiomolybdate (9). Although the modulation of copper metabolism may be therapeutically useful in specific conditions, such as Wilson's disease, extrapolation of these mechanisms to routine rheumatology supplementation strategies remains speculative. While nutritional molybdenum doses are generally considered safe within recommended upper limits, safety cannot be assumed in all contexts, especially when supplement formulations vary, doses may exceed dietary norms, or patients take multiple micronutrients simultaneously (2,9). Moreover, rheumatology patients frequently have comorbidities (e.g., renal disease, cardiovascular risk, anemia) and polypharmacy, factors that can modify trace element handling and risk-benefit balance.

Notably, the current absence of robust clinical evidence should not be interpreted as a definitive evidence of lack of efficacy. Rather, the available literature is insufficient in quantity and methodological quality to support reliable conclusions regarding therapeutic benefit, absence of benefit, or long-term safety. Accordingly, current evidence remains inadequate to support routine molybdenum supplementation in rheumatic diseases.

From a research standpoint, the appropriate following steps could include: i) Observational studies assessing molybdenum status (dietary intake and, where feasible, biomarkers) in well-defined rheumatic cohorts; ii) mechanistic studies evaluating whether the molybdenum status correlates with redox markers, inflammatory pathways, endothelial measures, or mitochondrial function relevant to rheumatic disease activity; and iii) only after compelling signals, randomized trials using standardized outcomes (e.g., pain scales, disease activity indices where appropriate, functional outcomes and biomarkers), with careful safety monitoring and consideration of copper status (1-4,9). Until such data exist, any clinical use would remain speculative.

Recent advances in rheumatology research have further reinforced the importance of oxidative stress, redox dysregulation and immunometabolic alterations in the pathogenesis of autoimmune and inflammatory rheumatic diseases. Emerging evidence suggests that the metabolic reprogramming of immune cells, mitochondrial dysfunction and reactive oxygen species generation contribute to chronic inflammation, tissue damage and disease progression in rheumatoid arthritis, and related disorders. Furthermore, growing interest in nutritional and micronutrient-based interventions reflects the recognition that trace elements and metabolic pathways may influence inflammatory responses and immune homeostasis. Although no direct evidence currently supports a therapeutic role for molybdenum supplementation, these developments provide a contemporary biological framework for future investigations exploring potential links between molybdenum-dependent pathways and rheumatic disease mechanisms (12-15).

In conclusion, at present, there is no robust clinical evidence available supporting molybdenum supplementation in rheumatic diseases. Although molybdenum-dependent enzymes participate in pathways relevant to oxidative metabolism and redox biology, these mechanisms have not yet translated into demonstrable clinical benefit in autoimmune or inflammatory rheumatic conditions (3,4,11).

Current evidence remains insufficient to support routine molybdenum supplementation in rheumatic diseases, particularly considering the scarcity of adequately designed clinical studies and the generally sufficient dietary intake observed in most populations.

Potential interactions with copper homeostasis and the absence of long-term safety data further support a cautious interpretation of the currently available evidence (1,2,9).

Future studies are warranted to prioritize well-designed observational, mechanistic and translational investigations in carefully characterized rheumatic cohorts to determine whether molybdenum status is clinically relevant and potentially modifiable in ways that influence validated clinical outcomes. At present, molybdenum supplementation should be considered investigational in rheumatic diseases and cannot be recommended for routine clinical use outside research settings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

JFDC contributed to the conceptualization of the study, to the study methodology, investigation, data curation, writing of the original draft, the critical revision of the manuscript, and supervision. JFDC confirms the authenticity of all the raw data. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

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