

Rutin supplementation in osteoarthritis and tendinitis: A systematic review

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Abstract. Rutin supplementation (not kaempferol) has been traditionally used in several medical systems, including Iranian medicine, for inflammatory and degenerative disorders. The aim of the present systematic review was to provide a synthesized review of the available the clinical evidence on the use of rutin in rheumatic diseases. For this purpose, a systematic search was conducted on the PubMed and SciELO databases from 1966 to September, 2024 using terms related to rutin and rheumatic diseases, including osteoarthritis and tendinitis, with no language restrictions. Reference lists of eligible studies were also screened for additional publications. A total of six clinical studies comprising 558 patients were identified, including osteoarthritis (n=5) and rotator cuff tendinitis (n=1). All studies evaluated rutin/rutoside within multi-component oral enzyme formulations, including Phlogenzym® and Wobenzym, rather than as monotherapy. In osteoarthritis, rutin-containing enzyme formulations generally led to improvements in pain and function comparable to diclofenac, with additional placebo-controlled evidence supporting symptomatic benefit. Studies showing improvements in joint tenderness greater with Phlogenzym® than with diclofenac, and on rotator cuff tendinitis are available. Adverse events were predominantly mild and gastrointestinal. On the whole, the present systematic review demonstrates that clinical evidence for rutin in osteoarthritis and tendinitis is limited to a small number of studies evaluating rutin as part of the multi-component formulation Phlogenzym®. The available findings are preliminary and do not establish the efficacy of rutin monotherapy. Further high-quality randomized controlled trials are required.

Introduction

Rutin (also known as vitamin P or rutoside) is a flavonoid belonging to a ubiquitous group of naturally occurring polyphenolic compounds found in vegetables, fruits and plant-based beverages (1). It is particularly abundant in buckwheat, citrus fruits, apples, tea, onions and red wine.

Rutin, in the form of quercetin, is known for its anti-inflammatory, antimutagenic, antioxidant, anticancer, gastroprotective and neuroprotective effects (2,3). Its pharmacological activities are partly explained by the inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways, as well as by the modulation of oxidative stress and cytokine signaling.

Experimental evidence also highlights that rutin may exert cartilage-protective and anti-inflammatory actions through the activation of SIRT1 and reduction of oxidative damage, further supporting its potential relevance in osteoarthritis models (4,5). Recent experimental evidence has further demonstrated that rutin may inhibit the progression of osteoarthritis by reducing inflammatory mediators and cartilage degradation through cystathionine- β -synthase-mediated RhoA/ROCK signaling (6).

There are a few experimental studies available on the use of Rutin in animal osteoarthritis, demonstrating protective effects against cartilage degeneration (4,5). Beyond osteoarthritis, experimental evidence suggests that rutin may also exert potentially relevant effects on musculoskeletal tissues through the modulation of oxidative stress, inflammatory signaling, osteoclast activity and bone metabolism (4,6). These findings broaden the biological rationale for investigating rutin in rheumatic and musculoskeletal disorders. In tendinopathy, oxidative stress, inflammatory signaling, and impaired tissue repair are recognized components of disease pathophysiology, providing a biological rationale for investigating antioxidant and anti-inflammatory compounds, such as rutin in tendon disorders, including rotator cuff tendinitis. However, there are only a limited number of clinical trials evaluating the effects of Rutin in human rheumatic disorders (7-12).

Notably, all available clinical studies used Phlogenzym®, a fixed-dose combination of bromelain, trypsin and rutoside (a glycosylated form of rutin), enabling the determination of the isolated effects of rutin monotherapy. This limitation should be acknowledged when interpreting clinical outcomes.

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The aim of the present study was to conduct a systematic review on the use of rutin as a treatment for rheumatic diseases.

Data and methods

A corrected and structured literature search was conducted on the PubMed and SciELO databases from 1966 to September, 2024 using the following Boolean strategy: ('rutin' OR 'rutoside' OR 'rutosid' OR 'vitamin P') AND ('rheumatologic' OR 'rheumatic disease' OR 'fibromyalgia' OR 'rheumatoid arthritis' OR 'spondyloarthritis' OR 'osteoarthritis' OR 'tendinitis' OR 'tendinopathy' OR 'tendon' OR 'rotator cuff' OR 'gout').

The search had no language restriction. The reference lists of the selected articles were analyzed to identify additional publications. The search results were screened to identify human clinical studies and to exclude preclinical studies conducted exclusively on animals or *in vitro*. Eligible studies included clinical studies evaluating rutin, either as monotherapy or as a component of a combination treatment, in patients with rheumatic or musculoskeletal diseases. Preclinical studies, reviews, editorials and studies without clinical data were excluded.

The author screened the titles and abstracts of the retrieved records and subsequently assessed potentially eligible full-text articles. Finally, a standardized form was designed to extract the information from relevant articles, including authors, year of publication, the number of patients studied, demographics, disease duration, follow-up, rutin posology, outcomes and side-effects.

The methodological quality and risk of bias of the included clinical trials were assessed according to their study design, considering the randomization process, deviations from intended interventions, missing outcome data, outcome measurement and the selection of reported results. Given the very small number of eligible studies and their clinical and methodological heterogeneity, the quantitative assessment of publication bias was considered inappropriate. The study selection process was documented in a PRISMA flow diagram to improve transparency in reporting, and is presented in Fig. 1. The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the risk of bias of the included randomized clinical trials. The results of the risk-of-bias assessment are presented in Table I.

Results

The present review identified six clinical studies encompassing a total of 558 patients, conducted across Austria, Canada, Germany and Pakistan, thereby providing a modest, yet geographically diverse body of evidence on the therapeutic effects of rutin as part of oral enzyme combinations in rheumatic conditions (7-12). In total, four studies evaluated Phlogenzym®, whereas the two additional studies by Singer and Oberleitner (7) and Bolten *et al* (12) evaluated Wobenzym, an oral enzyme formulation also containing rutin/rutoside. As all studies employed multi-component enzymatic formulations containing rutin/rutoside together with proteolytic enzymes, it is essential to emphasize that none of the included trials investigated rutin as a standalone intervention. This methodological constraint significantly limits the ability to isolate the specific pharmacological contribution of rutin itself, as bromelain and trypsin are known to exert independent anti-inflammatory and

proteolytic actions that may synergistically contribute to the observed clinical outcomes (7-12). The main characteristics of the included studies, including sample size, demographic characteristics, disease duration, follow-up, rutin/rutoside-containing formulation and dosage, clinical outcomes, and adverse events, are summarized in Table II.

The risk-of-bias assessment of the included randomized clinical trials is summarized in Table I. Methodological quality varied across studies, with concerns mainly related to incomplete reporting of the randomization process, lack of blinding in open or pragmatic trials, missing outcome data, and the measurement of subjective outcomes.

The demographic characteristics across studies were relatively consistent, with participants generally being middle-aged or older adults and with both sexes represented across the trials. Disease duration also varied substantially (from >6 weeks to 54 months), indicating that both early-stage and chronic presentations of osteoarthritis and tendinitis were represented. This diversity enhances external validity, while also introducing clinical heterogeneity that may influence treatment responsiveness.

Across the five osteoarthritis trials, rutin-containing oral enzyme therapy demonstrated clinical efficacy generally comparable to diclofenac in conventional measures of disease severity, including pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) domains, joint stiffness, physical function, Lequesne's index, and composite assessments of tenderness and swelling (7-10,12). The addition of the Singer and Oberleitner (7) and Bolten *et al* (12) trials strengthens the evidence base in knee osteoarthritis, as both were randomized controlled studies comparing an oral enzyme combination containing rutin/rutoside with diclofenac.

Singer and Oberleitner (7) evaluated 80 patients with painful knee osteoarthritis in an acute phase in a double-blind trial. Patients received Wobenzym or diclofenac for 28 days, followed by a 28-day treatment-free observation period. Pain at rest, during motion, while walking, at night and tenderness improved significantly ($P < 0.05$) following treatment, with no significant difference between the two treatment groups. A tendency toward relapse was observed during the subsequent treatment-free period. Global assessments of efficacy and tolerability by physicians and patients were predominantly rated as 'very good' or 'good'.

Bolten *et al* (12) evaluated 150 patients with moderate-to-severe painful knee osteoarthritis in a randomized, double-blind, placebo-controlled trial comparing Wobenzym, diclofenac and a placebo over a period of 12 weeks. Both active treatments led to significant improvements in the Lequesne algofunctional index compared with the placebo, with no significant difference between Wobenzym and diclofenac. WOMAC scores also improved in both active-treatment groups, and rescue paracetamol consumption was significantly lower with Wobenzym than with the placebo. These findings provide additional placebo-controlled evidence supporting the symptomatic efficacy of a Rutin-containing enzyme combination in knee osteoarthritis (12).

One clinically notable observation emerged from the German study by Tilwe *et al* (10), in which improvement in joint tenderness was significantly greater in the Phlogenzym® group compared with diclofenac. Although mechanistic

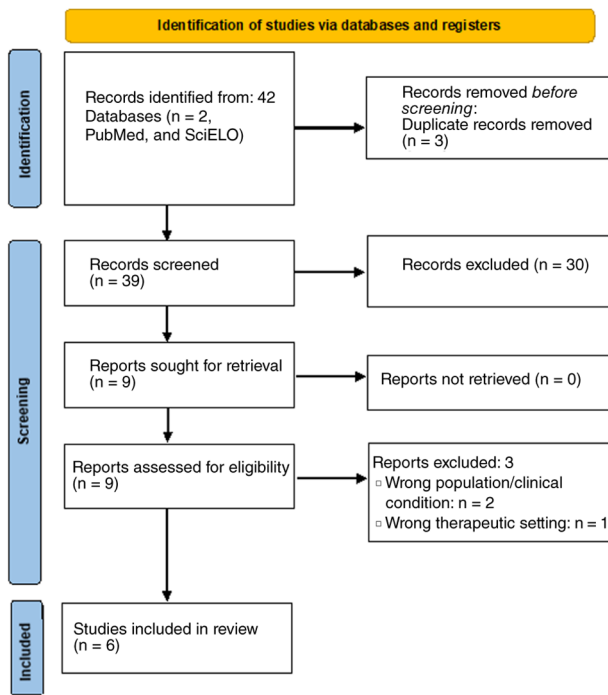


Figure 1. PRISMA flow diagram of the literature search and study selection process. PRISMA flow diagram illustrating the identification, screening, eligibility assessment and final inclusion of studies evaluating rutin/ruto-side-containing interventions in rheumatic diseases. Following the literature search and application of the predefined eligibility criteria, six clinical studies were included in the final review.

interpretations remain speculative, this finding may reflect the unique enzymatic activity of bromelain and trypsin in modulating inflammatory edema and tissue sensitivity, effects not typically associated with diclofenac.

In the randomized study by Akhtar *et al* (8), global physician-assessed treatment efficacy demonstrated favorable ratings for 51.4% of the patients in the rutin/Phlogenzym® group compared with 37.2% in the diclofenac group. Although the difference did not reach statistical significance, the numerical trend suggests potential clinical advantages, particularly when combined with the favorable safety profile observed in the enzymatic therapy group. Disease severity reductions were paralleled by measurable functional improvements, reinforcing the consistency of benefit across trials.

The study on rotator cuff tendinitis conducted in Canada by Szczurko *et al* (11) also demonstrated clinically relevant improvements with enzyme-based therapy. The Shoulder Pain and Disability Index (SPADI) decreased by 54.5% in the Phlogenzym® group compared to only 18% in the exercise-based control group. This substantial improvement suggests a potential therapeutic role for rutin-containing enzymatic formulations in tendinopathy; however, as only one study evaluated rotator cuff tendinitis, comparisons of treatment responsiveness between tendinitis and osteoarthritis cannot be established. Additional outcomes, including reductions in pain (visual analog scale), enhancements in the MYMOP, measure yourself medical outcome profile (MYMOP) and SF-36 scores, and measurable gains in shoulder extension, flexion and abduction, reinforce the robustness of the findings and point toward meaningful improvements in both symptoms and function.

Table I. Risk-of-bias assessment of the included randomized clinical trials.

Authors, year of publication	D1. Randomization process	D2. Deviations from intended interventions	D3. Missing outcome data	D4. Measurement of the outcome	D5. Selection of reported result	Overall risk (Refs.)
Akhtar <i>et al</i> , 2004	Some concerns	Low	Some concerns	Low	Some concerns	(8)
Klein <i>et al</i> , 2006	Some concerns	Low	Low	Low	Some concerns	(9)
Tilwe <i>et al</i> , 2001	Some concerns	High	Low	High	Some concerns	(10)
Szczurko <i>et al</i> , 2009	Low	High	Some concerns	High	Low	(11)
Bolten <i>et al</i> , 2015	Some concerns	Low	High	Low	High	(12)
Singer and Oberleitner, 1996	Pending full-text assessment	Pending	Pending	Pending	Pending	(7)

D1, bias arising from the randomization process; D2, bias due to deviations from intended interventions; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result.

Table II. Clinical studies of rutin-containing enzyme formulations in rheumatic diseases.

Authors, year of publication	No. of patients	Demographics	Disease duration	Follow-up	Rutin posology	Outcomes	Side effects	(Refs.)
Singer and Oberleitner, 1996	80	Patients with painful knee OA in an acute phase; groups comparable regarding age and sex	Groups comparable regarding OA duration; exact values not reported in the abstract	28 days treatment + 28 days treatment-free observation	Wobenzym, 4x7 capsules/day	Significant improvement (P<0.05) in pain at rest, during motion, walking, at night, and tenderness; no significant difference versus diclofenac	AEs in 14 patients, mainly gastrointestinal; allergic rash and dizziness also reported; 6 discontinued	(7)
Akhtar <i>et al</i> , 2004	103	58 females/45 males; mean age, 52 years	18-20 months	6 weeks	Phlogenzym® (bromelain, 90 mg; trypsin, 48 mg; rutoside, 100 mg), two tablets three times daily	WOMAC pain, stiffness, and physical function improved; overall efficacy comparable to diclofenac	Mild gastrointestinal adverse events; no severe adverse events	(8)
Klein <i>et al</i> , 2006	90	48 females/42 males; mean age, 55 years	24-26 months	12 weeks	Phlogenzym® (bromelain, 90 mg; trypsin, 48 mg; rutoside, 100 mg), two tablets three times daily	Improvement in pain and function comparable to diclofenac; improvement in joint tenderness favored enzyme therapy	Mainly mild gastrointestinal symptoms; no serious adverse events	(9)
Tilwe <i>et al</i> , 2001	50	33 females/17 males; mean age, ~50 years	12-14 months	6 weeks	Phlogenzym® (bromelain, 90 mg; trypsin, 48 mg; rutoside, 100 mg), two tablets three times daily	Significant improvement in OA symptoms; efficacy generally comparable to diclofenac	Predominantly mild gastrointestinal adverse events	(10)
Szczurko <i>et al</i> , 2009	85	Adults with rotator cuff tendinitis	>6 weeks	12 weeks	Phlogenzym® containing bromelain, trypsin and rutoside	SPADI decreased by 54.5 vs. 18% in the controls; improvements also observed in pain VAS, MYMOP, SF-36, and shoulder range of motion	Predominantly mild adverse events; no major safety concerns	(11)

Table II. Continued.

Authors, year of publication	No. of patients	Demographics	Disease duration	Follow-up	Rutin posology	Outcomes	Side effects	(Refs.)
Bolten <i>et al</i> , 2015	150	Adults with moderate-to-severe painful knee OA; middle-aged/older population	Variable; chronic knee OA	12 weeks	Wobenzym, six tablets/day (288 mg trypsin + 540 mg bromelain + 600 mg rutoside trihydrate/day)	Lequesne index significantly improved vs. placebo with Wobenzym and diclofenac; no significant difference between active treatments; WOMAC also improved	Treatment-related AEs: 7.2% with Wobenzym, 15.6% with diclofenac, and 9.1% with placebo; mainly gastrointestinal	(12)

AE, adverse event; MYMOP, measure yourself medical outcome profile; OA, osteoarthritis; SPADI, shoulder pain and disability index; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Adverse events were generally mild and predominantly gastrointestinal across the six studies, although their frequency varied considerably among trials. In the study by Singer and Oberleitner (7), adverse events were reported in 14 patients receiving Wobenzym, including gastrointestinal complaints, dizziness and one allergic rash; 6 patients discontinued treatment due to adverse events. In the study by Bolten *et al* (12), treatment-related adverse events occurred in 7.2% of patients receiving Wobenzym, compared with 15.6% receiving diclofenac and 9.1% receiving the placebo, and were predominantly mild-to-moderate gastrointestinal events. Across the overall evidence base, no new major safety signal emerged for the rutin-containing enzyme combinations.

Overall, the expanded evidence base of six clinical studies indicates that rutin-containing enzyme combinations provide symptomatic improvement in osteoarthritis, with efficacy generally comparable to diclofenac in the available comparative trials (7-10,12). The single study on rotator cuff tendinitis also reported substantial improvements in pain and function (11); however, the limited evidence does not permit conclusions regarding differential efficacy across rheumatic conditions. As Rutin was administered exclusively as part of multi-component enzyme formulations, these results cannot establish the efficacy of rutin monotherapy.

Discussion

The present systematic review provides a detailed synthesis of the existing clinical evidence on the use of rutin, administered exclusively as a component of multi-enzyme formulations containing proteolytic enzymes, including Phlogenzym® and Wobenzym, in the management of osteoarthritis and rotator cuff tendinitis. Although the number of available studies remains limited, the collective findings allow for a nuanced interpretation of both the therapeutic potential and the inherent methodological constraints of the current evidence base. Notably, the available clinical evidence cannot be interpreted as evidence of efficacy of rutin monotherapy, as none of the included studies evaluated rutin as a standalone therapeutic agent. Moreover, the evidence is restricted to osteoarthritis and rotator cuff tendinitis, and therefore cannot be extrapolated to other rheumatic diseases (7-12).

Across the five osteoarthritis trials, the results generally demonstrate that rutin-containing multi-enzyme formulations provide symptomatic improvement, with efficacy comparable to diclofenac in the available head-to-head trials (7-10,12). The inclusion of the studies by Singer and Oberleitner (7) and Bolten *et al* (12) strengthens this observation by adding randomized evidence in knee osteoarthritis, including placebo-controlled data from Bolten *et al* (12). Diclofenac, as one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) worldwide, remains a benchmark for the symptomatic treatment of osteoarthritis; thus, any alternative demonstrating comparable efficacy with a more favorable safety profile warrants clinical attention. The superiority of enzyme therapy in joint tenderness observed in the German randomized trial (10) suggests possible advantages in specific inflammatory parameters, potentially mediated through pathways distinct from traditional NSAIDs. Nevertheless, these findings should be interpreted cautiously due to the

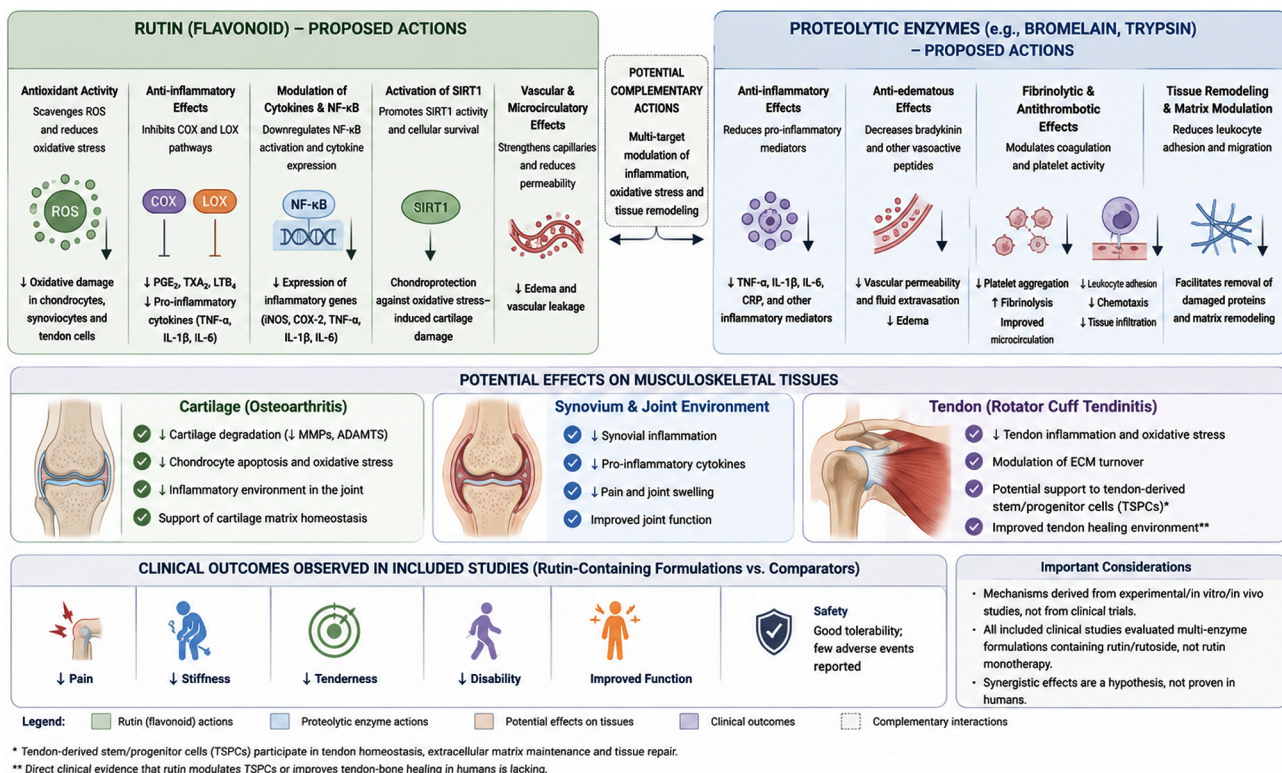


Figure 2. Proposed mechanisms of action of rutin and rutin-containing multi-enzyme formulations in osteoarthritis and rotator cuff tendinitis. Schematic representation of the proposed biological actions of rutin and proteolytic enzymes, including bromelain and trypsin, in musculoskeletal tissues. Rutin may exert antioxidant and anti-inflammatory effects through modulation of oxidative stress, COX/LOX pathways, inflammatory cytokines, NF-κB signaling and SIRT1 activation, whereas proteolytic enzymes may contribute additional anti-inflammatory, anti-edematous, and tissue-remodeling effects. These potentially complementary mechanisms may influence cartilage, synovial and tendon homeostasis. The figure also summarizes the main clinical outcomes reported with rutin-containing multi-enzyme formulations in the included studies. Mechanistic pathways are primarily based on experimental evidence and should not be interpreted as demonstrating the clinical efficacy of rutin monotherapy. TSPCs, tendon-derived stem/progenitor cells; COX, cyclooxygenase; LOX, lipoxygenase; NF-κB, nuclear factor kappa B; SIRT1, sirtuin 1; ROS, reactive oxygen species; ECM, extracellular matrix.

limited number of studies, variable sample sizes, relatively short follow-up periods, and clinical and methodological heterogeneity of the available trials.

These mechanistic distinctions merit deeper consideration. Rutin possesses well-established anti-inflammatory and antioxidant activities, including the inhibition of COX and LOX pathways, the reduction of reactive oxygen species, and the modulation of cytokine expression (2-5). Preclinical studies highlight that rutin can activate SIRT1, contributing to chondroprotection against oxidative stress-induced cartilage damage, a mechanism highly relevant to the pathophysiology of osteoarthritis (5). However, it is important to recognize that all clinical studies evaluated rutin within multi-component enzyme formulations, rather than as a monotherapy. Phlogenzym® contains bromelain and trypsin in addition to rutin/rutoside, while Wobenzym formulations also combine rutin/rutoside with proteolytic enzymes. Therefore, other active components likely contribute substantially to the observed clinical outcomes. Bromelain has demonstrated the capacity to reduce the level of pro-inflammatory cytokines, such as TNF-α and IL-1β, to inhibit platelet aggregation and to modulate leukocyte trafficking (13). Trypsin and other proteolytic enzymes have been reported to regulate tissue remodeling and edema reduction. These findings are consistent with broader evidence on nutraceutical combinations in osteoarthritis, in which multiple bioactive compounds may act synergistically

to modulate inflammation and joint metabolism (14). Thus, the potential mechanism of these rutin-containing enzyme formulations may involve complementary, rather than isolated actions of their components: Rutin may contribute predominantly antioxidant and anti-inflammatory effects, whereas the proteolytic enzymes may provide additional anti-inflammatory, edema-modulating and tissue-remodeling effects. Such complementary actions could theoretically explain why these combinations may produce clinical effects that cannot be attributed to rutin alone. However, the available trials were not designed to determine pharmacological synergy or the individual contribution of each component; therefore, a synergistic effect remains a hypothesis rather than an established clinical mechanism.

These proposed and potentially complementary mechanisms of rutin/rutoside and proteolytic enzymes, together with their possible effects on cartilage, synovial and tendon tissues, and the principal clinical outcomes observed in the included studies, are summarized in Fig. 2. Notably, the mechanistic pathways depicted in Fig. 2 are derived predominantly from experimental evidence and should not be interpreted as demonstrating the clinical efficacy of rutin monotherapy or a clinically proven synergistic interaction among the formulation components.

Rutin should also be considered within the broader biological context of flavonoids with potential effects on

musculoskeletal tissues. Experimental studies on flavonoid and flavonoid-like compounds, including trifolirhizin, corylifol A, isosinensetin, chrysin, oroxylin A, tiliroside and scutellarein have reported the modulation of pathways involved in osteoblast and osteoclast activity, oxidative stress, inflammation and bone remodeling (15-17). These findings provide a useful mechanistic framework for considering the potential effects of rutin on bone and joint tissues. Nevertheless, direct comparisons between rutin and these compounds remain limited, and an ample amount of the available evidence is derived from *in vitro* or animal models; consequently, these observations should not be interpreted as evidence of equivalent clinical efficacy.

The single study evaluating rotator cuff tendinitis reported substantial improvements in pain, disability and shoulder function with Phlogenzym® (11). Rotator cuff tendinitis is characterized by soft-tissue and tendon pathology rather than the cartilage degeneration characteristic of osteoarthritis, providing a biological rationale for considering the potential effects of anti-inflammatory and proteolytic enzyme therapy in this setting. The marked improvement in SPADI scores in the Rutin/Phlogenzym® group compared with physical exercise alone (11) is clinically noteworthy. However, because only one included study evaluated tendinitis, the available evidence does not permit conclusions regarding whether Rutin-containing enzyme therapy is more effective in tendinopathy than in osteoarthritis. Tendon healing is also influenced by tendon-derived stem/progenitor cells (TSPCs), which participate in tendon homeostasis, extracellular matrix maintenance, and tissue repair (18,19). Oxidative stress and persistent inflammatory signaling may impair the regenerative capacity of these cells and contribute to abnormal tendon healing. Given the antioxidant and anti-inflammatory properties attributed to rutin, a potential interaction with biological pathways relevant to TSPC function and tendon repair is plausible. However, direct evidence demonstrating that rutin modulates TSPCs or improves tendon-bone healing in humans is currently lacking, and this association should therefore be regarded as a mechanistic hypothesis requiring experimental confirmation.

Despite these favorable signals, several limitations within the existing evidence base warrant emphasis. First, despite the inclusion of two additional trials, the overall number of studies remains limited, and follow-up periods were relatively short, restricting conclusions regarding long-term safety, sustained efficacy, or disease-modifying potential. Second, the use of combination therapy prohibits understanding the isolated contribution of rutin. Furthermore, most trials lacked detailed reporting of statistical significance levels (e.g., P-values, confidence intervals), risk-of-bias assessments and standardized evaluations of heterogeneity. These methodological gaps underscore the need for rigorously designed randomized controlled trials that incorporate validated outcome measures, adequate blinding, longer follow-up periods, and modern statistical methodologies. In addition, the small number of studies and their clinical and methodological heterogeneity preclude robust generalization of the findings and meaningful assessment of publication bias. Therefore, the evidence presented herein should be considered preliminary and hypothesis-generating rather than confirmatory.

Another key consideration pertains to the pharmacokinetic limitations of oral rutin, which is known to have poor intestinal absorption, rapid metabolism to quercetin derivatives, and limited systemic bioavailability (3). These characteristics may blunt its therapeutic potential in systemic inflammatory diseases and help explain the modest effects observed in osteoarthritis, where deeper intra-articular penetration may be required for significant symptom relief. Future research should explore enhanced delivery systems, such as nanoparticle formulations, liposomal encapsulation, or combination therapy with bioavailability enhancers, to optimize rutin absorption and bioactivity. These pharmacokinetic limitations may be particularly relevant when considering rutin as a stand-alone therapeutic agent and provide an additional rationale for investigating whether combination formulations can enhance its biological or clinical effects.

Looking ahead, there is substantial rationale to investigate rutin-containing therapies not only in osteoarthritis and tendinitis, but also in other rheumatic diseases characterized by oxidative stress and inflammatory cytokine cascades, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and crystal arthropathies (2,3). The preclinical literature strongly supports the potential of rutin to modulate pathways relevant to these diseases, but clinical validation is entirely lacking. Accordingly, future studies are warranted to distinguish clearly between rutin monotherapy and multi-component formulations, and to determine whether the effects observed with rutin-containing enzyme combinations are attributable to rutin, to the proteolytic enzymes, or to complementary interactions among their components.

In conclusion, the available clinical evidence on rutin is limited to a small number of studies evaluating it as a component of multi-component enzyme formulations, including Phlogenzym® and Wobenzym, in osteoarthritis and rotator cuff tendinitis. Although preliminary clinical benefits have been reported, the limited sample sizes, short follow-up periods, and inability to isolate the effects of rutin preclude definitive conclusions regarding its efficacy as monotherapy. Further high-quality randomized controlled trials are warranted.

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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 conceptualized the study, was involved in the data analysis, literature search, and in the writing and revision of the manuscript. 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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