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French maritime pine bark extract (*Pinus pinaster*, Pycnogenol®) as an adjunct therapy in osteoarthritis, systemic lupus erythematosus, and Behçet's disease: a narrative review

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Abstract

Background: Oxidative stress contributes to the pathogenesis of several rheumatic diseases. French maritime pine bark extract (Pycnogenol®) is a standardized polyphenolic compound with antioxidant, anti-inflammatory, and immunomodulatory properties.

Objective: To summarize clinical evidence on Pycnogenol as adjunct therapy in osteoarthritis, systemic lupus erythematosus (SLE), and Behçet's disease.

Methods: A structured narrative review was conducted following PRISMA guidance. Databases searched included PubMed/MEDLINE, EMBASE, Web of

Science, Scopus, and SciELO, from 1966 to May 2024. Search terms combined "Pycnogenol," "Pinus pinaster," and disease-specific keywords. Eligible studies were clinical trials or prospective investigations assessing Pycnogenol in human subjects with rheumatic diseases. Review articles and in vitro or animal studies were excluded.

Results: Eleven clinical studies were included, eight on osteoarthritis and three on SLE and Behçet's disease. Doses ranged from 100 to 220 mg/day, with follow-up from 3 weeks to 3 months. In osteoarthritis, most trials reported improved WOMAC scores, reduced CRP, ESR, pain, better physical function, and decreased analgesic use. In SLE, reductions in SLEDAI, anti-dsDNA antibodies, and oxidative stress markers were observed. In Behçet's disease, improvements in ulcer pain and inflammatory parameters were noted. Adverse effects were absent or mild.

Conclusions: Current evidence suggests that Pycnogenol may provide complementary benefits in osteoarthritis, SLE, and Behçet's disease through antioxidant and anti-inflammatory mechanisms. However, available studies are limited by small samples, short duration, and methodological heterogeneity. Larger, well-designed randomized controlled trials are required to confirm its efficacy and safety in rheumatologic practice.

Keywords: Pycnogenol, *Pinus pinaster*, French maritime pine bark extract, osteoarthritis, systemic lupus erythematosus, Behçet's disease, antioxidant, oxidative stress

Running title: Pycnogenol in rheumatic diseases.

Introduction

Oxidative stress has been implicated in the development of several conditions, including cancer, cardiovascular disease, and rheumatic diseases. Thus, reactive oxygen species (ROS) generation is a physiological defense against microbial infection. However, the inappropriate generation of ROS, as occurs in autoimmune inflammation, causes tissue damage and is involved in acute and chronic inflammation [1]. In fact, diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic sclerosis, Sjogren's syndrome, and vasculitis are directly related to oxidative stress [1].

French Maritime Pine Bark Extract **(**Pycnogenol®) (PYC), a herbal dietary supplement derived from French maritime pine bark extract, is a powerful antioxidant through procyanidin production. It is a subtype of proanthocyanidin, a member of the flavonoid subgroup of polyphenols, with powerful antioxidant properties [2].

This review focuses specifically on three rheumatic diseases for which clinical data on Pycnogenol are available — osteoarthritis, systemic lupus erythematosus, and Behçet's disease — representing degenerative, autoimmune, and vasculitic mechanisms, respectively..

Methods

A structured narrative review was performed to synthesize clinical evidence on *French maritime pine bark extract* (Pycnogenol®) in rheumatic diseases. The search followed the main steps of PRISMA guidelines to ensure transparency and reproducibility, although no quantitative synthesis (meta-analysis) was undertaken.

Data sources and search strategy: Electronic searches were conducted in PubMed/MEDLINE, EMBASE, Web of Science, Scopus, and SciELO, covering the period from 1966 to May 2024, without language restrictions. The search combined controlled vocabulary and free-text terms, using Boolean operators as follows:

("Pycnogenol" OR "*Pinus pinaster*" OR "pine bark extract") AND ("osteoarthritis" OR "lupus" OR "systemic lupus erythematosus" OR "Behçet" OR "rheumatic diseases").

Eligibility criteria: We included human studies evaluating oral or topical Pycnogenol, either as monotherapy or as part of combination supplements, in patients fulfilling recognized diagnostic criteria for rheumatic diseases. Exclusion criteria were: animal or in vitro studies, review papers, case reports, and editorials.

Study selection and data extraction: Two independent reviewers screened titles and abstracts for relevance, retrieved full texts, and extracted study characteristics, sample size, design, intervention, outcomes, and adverse events. Disagreements were resolved by consensus. To enhance clarity, studies were grouped as:

1. *Monocomponent interventions* (Pycnogenol alone), and
2. *Multicomponent interventions* (Pycnogenol combined with other supplements).

Risk of bias and quality assessment: Because of the heterogeneous nature and small number of studies, a formal quantitative risk-of-bias or GRADE analysis was not feasible. However, each study's design (randomized, openlabel, observational) and control group characteristics were qualitatively appraised.

Data synthesis: Results were summarized descriptively, highlighting patterns of clinical and biochemical outcomes across osteoarthritis, lupus, and Behçet's

disease. A PRISMA-style flow diagram will be provided to illustrate the study selection process.

Results

Table 1 summarizes the studies of PYC in osteoarthritis [4-11]. Eight articles were found, including 602 patients. The countries that reported those selected articles were Germany (n=4), followed by Australia (n=1), Italy (n=1), Israel (n=1), and Slovakia (n=1). Two studies were double-blinded randomized and controlled trials; one was a double-blinded cross-over trial, 1was an observational registry study, 1 was a randomized controlled trial, and 1 was an internet-based randomized controlled trial. Age varied from 48.6 ± 8 to 65.1±6.94 years old, and female gender ranged from 47% to 85% in the included articles. Disease duration ranged from 1 to 10 years, although in 5/8 articles, this datum was not available. The PYC dosage ranged from 100 to 220mg/day. The follow-up of all studies ranged from 3 weeks to 3 months.

Concerning outcomes, 7/8 articles showed improvements. WOMAC, CRP, ESR, treadmill test, and the timed-up-to-go test improved, and the need for analgesics and non-steroidal anti-inflammatory drugs was reduced after supplementation. In 2/8 articles, biochemical parameters improved after

supplementation. One study showed that costs were reduced after PYC [ref]. In 1/8, the effects were equal to placebo.

In addition, the side effects were present in 3/8 articles and were all mild, characterized by flatulence and gastrointestinal symptoms; equal to placebo in 1/8, absent in 1/8, and 2/8, they were good effects (reduced limb edema and gastrointestinal symptoms).

Table 2 summarizes the studies of PYC on systemic lupus erythematosus and Behçet disease [12-14]. Three articles were found, two on lupus and one on Behçet disease; they included 71 patients. The countries that reported those selected articles were Italy (n=2) and Romania(n=1). Two studies were open prospective studies and one was a double-blinded prospective trial. Age varied from 30 (19-41) to 59.7 ± 8.2 years old, and female gender ranged from 91% to 100% in the included articles. Disease duration ranged from 1 to 10 years, although in 6/8 articles, this datum was not available. The PYC dosage ranged from 120 to 150 mg/day. The follow-up of all studies ranged from 4 to 9 weeks.

Concerning outcomes, all papes showed benefits. In lupus, a r SLEDAI reduction was seen, as was a decrease in ESR, oxidant substances (ROS), apoptosis, cytopenias, hematuria, anti-dsDNA, and antiphospholipid antibodies. In Behçet diseases, improvements in pain and burning in ulcers

were verified, as were ESR, leucocytosis, and Pathergy test reduction. In addition, the side effects were absent in 1/3 and not described in 2/3.

Discussion

French maritime pine bark extract (Pycnogenol®) has been investigated in a few rheumatic conditions—mainly osteoarthritis, systemic lupus erythematosus, and Behçet's disease—with most studies reporting clinical or biochemical improvement and mild or absent adverse effects. Nevertheless, these results must be interpreted cautiously due to methodological heterogeneity, small samples, and short follow-up.

Osteoarthritis

Oxidative stress plays a key role in osteoarthritis (OA) pathogenesis by promoting chondrocyte apoptosis, activation of matrix metalloproteinases (MMP-3, MMP-13), and degradation of the extracellular matrix. Reactive oxygen species (ROS) interact with pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), sustaining inflammation and cartilage damage [15]. Pycnogenol, rich in procyanidins and other polyphenols, exerts potent antioxidant and anti-inflammatory actions by inhibiting NF-κB activation and reducing cytokine-induced ROS [2, 8]. Clinical trials have shown that daily doses

between 100 and 220 mg for 3 weeks to 3 months improve WOMAC, CRP, ESR, and pain scores, and decrease the use of non-steroidal antiinflammatory drugs [4-11]. In the SVOS randomized study, Pycnogenol improved WOMAC by 56% and treadmill performance [9], while another trial demonstrated significant reductions in plasma free radicals, CRP, and

fibrinogen [10].

However, several studies evaluated multicomponent formulations (e.g., Pycnogenol with methylsulfonylmethane or glucosamine) [5], precluding attribution of benefits exclusively to the extract.

Systemic Lupus Erythematosus

Oxidative stress contributes to DNA damage and the generation of autoantigens that trigger anti-dsDNA antibodies in SLE [16]. Through antioxidant and endothelial-protective mechanisms, Pycnogenol may attenuate these processes. In two prospective studies, supplementation with 120–150 mg/day for 8–9 weeks reduced SLEDAI scores, ESR, ROS, apoptosis, cytopenias, hematuria, anti-dsDNA, and antiphospholipid antibodies [12, 13]. Although these findings suggest an adjunctive benefit, both trials were openlabel or pilot in nature, with short duration and small cohorts.

Behçet's Disease

In Behçet's disease (BD), excessive ROS generation by activated neutrophils and endothelial dysfunction are central to vascular inflammation [17]. In a controlled study of 34 patients, Pycnogenol (150 mg/day for 4 weeks) improved oral ulcer pain and burning and decreased ESR, leukocytosis, and

Pathergy-test positivity [14]. These preliminary observations support further exploration of Pycnogenol as a complementary antioxidant and antiinflammatory therapy in BD.

Safety and Methodological Considerations

Across all included trials, adverse events were absent or mild—mostly flatulence or transient gastrointestinal discomfort—comparable to placebo [68]. No serious adverse reactions were reported. Nevertheless, most studies used the commercial formulation Pycnogenol®, raising the possibility of sponsor-related bias and selective reporting. Moreover, the limited number of randomized, double-blind, placebo-controlled trials and the short follow-up (≤3 months) preclude conclusions regarding long-term efficacy or safety.

Conclusion

This narrative review identified 11 clinical studies assessing *French maritime pine bark extract* (Pycnogenol®) in rheumatic diseases, specifically osteoarthritis, systemic lupus erythematosus, and Behçet's disease. Preliminary evidence

indicates that Pycnogenol may improve clinical symptoms and inflammatory or oxidative biomarkers in these conditions,

acting as a **complementary or adjunctive** therapy. However, the available data derive mainly from small, short-term studies with heterogeneous methodologies and potential conflicts of interest.

Future **large, double-blind, randomized controlled trials** with standardized outcomes and longer follow-up are required to establish its true therapeutic value and safety profile in rheumatologic practice.

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JFC: Conception, analysis, writing, interpretation, revision.

ATAM: analysis, writing, interpretation

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Table 1 – Clinical studies on *French maritime pine bark extract* (Pycnogenol®) in osteoarthritis.

Author, year [Ref] / Country	Study design	N (patients)	Type of intervention	Dose and	Main outcomes	Adverse events

				duration	
Liu et al., 2021 [4]	Internet-based, randomized clinical trial / Australia	106	**Multicomponent:** Pycnogenol 100 mg + Boswellia serrata 250 mg + MSM 1.5 g + Curcumin 168 mg vs placebo	3 months	No significant differences vs placebo	Not reported
Heffernan et al., 2020 [5]	Double-blind, cross-over pilot trial / Ireland	30	**Multicomponent:** 120 go, Mineral-rich algae mg/day, + Pycnogenol vs glucosamine	3 months	Improved pain, timed-up-and-go, KOOS, physical function; reduced analgesic use	1 (3 %) GI discomfort
Feragalli et al., 2019 [6]	Observational described	67	Topical patch with Pycnogenol	**Monocomponent:** 220 mg/day, 3 weeks	Reduced OA symptoms, NSAID use, CRP and ESR	Not registry / Italy

Author, year [Ref] / Country	**Study design**	**N (patients)**	**Type of intervention**	**Dose and duration**	**Main outcomes**	**Adverse events**

duration

Mülek et al., 2017 [7]	Randomized controlled trial / Germany	**Monocomponent**	33	200 mg/day, 3 weeks (pre-surgery)	Polyphenols detected in serum, blood cells, and synovial fluid
Jessberger et al., 2017 [8]	Randomized controlled / Germany	**Monocomponent**	33	100 mg of MMP-3, twice daily, 3 months	Downregulation of MMP-13, IL-1β 1 (3 %) gene expression; ↓ ADAMTS-5
Belcaro et al., 2008 (SVOS) [9]	Double-blind, placebo-controlled / Germany	**Monocomponent**	156	100 mg/day, 3 months	↑ WOMAC (56 %); ↑ treadmill distance; ↓ analgesic use and costs	Mild GI symptoms and limb edema reduction

Belcaro et al., 2008 [10]	Double-blind, ↓ Plasma free radicals (70 %), CRP, fibrinogen placebo-controlled / Germany	77	**Monocomponent**	100 mg/day, 3 months	None

Author, year [Ref]	**Study design / Country**	**N (patients)**	**Type of intervention**	**Dose Main and outcomes duration**	**Adverse events**
Císař et al., 2008 [11]	Double-blind, randomized, placebo-controlled / Slovakia	100	**Monocomponent**	150 mg/day, 3 months	↓ Pain (VAS), ↑ WOMAC, ↓ BP in hypertensive subjects Not described

Abbreviations: OA = osteoarthritis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; KOOS = Knee Injury and Osteoarthritis Outcome Score; NSAID = non-steroidal anti-inflammatory drug; VAS = visual analog scale; GI = gastrointestinal; MSM = methylsulfonylmethane.

Table 2 – Clinical studies on *French maritime pine bark extract* (Pycnogenol®) in systemic lupus erythematosus and Behçet's disease.

Author, year [Ref]	Study design / Country	Disease	N (patients)	Type of intervention	Dose and duration	Main outcomes	Adverse events
Cesarone et al., 2020 [12]	Open prospective controlled trial / Italy	SLE	26	**Monocomponent**	150 mg/day, 8 weeks	↓ Photosensitivity, oral ulcers, hematuria, cytopenias, anti-dsDNA, aPL; ↓ oxidative stress and microcirculatory disturbance	None
Stefanescu et al., 2001 [13]	Open prospective trial / Romania	SLE	11	**Monocomponent**	120 mg/day (30 days) → 60 mg/day (30	↓ SLEDAI, ROS, apoptosis, p56lck activity, ESR	Not described

Author, year [Ref]	Study design / Disease / Country	N (patients)	Type of intervention	Dose and duration	Main outcomes	Adverse events
					days)	
Hu et al., 2018 [14]	Double-blind **Monocomponent** trial / Behçet' disease / Italy	34	ESR, leukocytosis, e	150 mg/day, 4 weeks	↓ Ulcer pain and burning; ↓ Pathergy test response	Not described

Abbreviations: SLE = systemic lupus erythematosus; aPL = antiphospholipid antibodies; ROS = reactive oxygen species; ESR = erythrocyte sedimentation rate.