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THERAPEUTIC EFFECTS OF POMEGRANATE SEED OIL: EXPERIMENTAL EVIDENCE AND TRANSLATIONAL PROSPECTS

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Abstract

Pomegranate seed oil (PSO) exhibits a multifaceted pharmacological profile attributable to its high concentration of punicic acid, tocopherols, and a diverse array of polyphenols. This critical review integrates current pre-clinical findings with original data generated by the authors in a nitrous oxide–induced rat model of hepatic fibrosis. PSO administration (1 mL kg^{-1} day^{-1}, 30 days) attenuated collagen deposition and down-regulated key profibrotic mediators—TGFβ1, α-SMA, and CD68—by 40-45 % versus untreated fibrotic controls ($p < 0{\cdot}01$). These outcomes, together with previously documented antioxidant, anti-inflammatory, cardioprotective, and antiproliferative effects, position PSO as a promising candidate for adjunctive management of chronic fibro-inflammatory disorders.

Keywords: pomegranate seed oil; conjugated linolenic acid; oxidative stress; liver fibrosis; macrophage polarization; translational pharmacology.

ТЕРАПЕВТИЧЕСКИЕ ЭФФЕКТЫ МАСЛА КОСТОЧЕК ГРАНАТА: ЭКСПЕРИМЕНТАЛЬНЫЕ ДОКАЗАТЕЛЬСТВА И ТРАНСЛЯЦИОННЫЕ ПЕРСПЕКТИВЫ

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Аннотация

В обзоре систематизированы и критически оценены экспериментальные данные о терапевтическом потенциале масла косточек граната (Punica granatum seed oil, PSO). Дополнительно представлены результаты авторских исследований, демонстрирующие выраженные антифибротические и гепатопротективные свойства PSO в модели NO^2 индуцированного фиброза печени у крыс. Под действием PSO отмечено статистически значимое ($p < 0,05$) снижение экспрессии маркёров фиброгенеза — TGF-β1, α-SMA и CD68, что кореллировало с уменьшением плотности коллагеновых волокон по данным гистоморфометрии. Обсуждаются молекулярные мишени и перспективы трансляции полученных результатов в клиническую практику.

Ключевые слова: масло косточек граната, пунциновая кислота, оксидативный стресс, фиброз печени, макрофаги M2, антифибротическая терапия.

Introduction

The resurgence of interest in phytochemicals as disease-modifying agents has foregrounded *Punica granatum* L. seed oil in experimental pharmacology. Beyond the fruit's well-characterised juice polyphenome, PSO is enriched in conjugated linolenic isomers—chiefly punicic acid—that confer potent radical-scavenging and signal-modulating capacities [1, 4]. Accumulating evidence delineates six principal domains of bioactivity: antioxidant, anti-inflammatory, cardioprotective, antifibrotic, hepatoprotective, and antiproliferative [2, 3]. Notwithstanding these advances, integrative analyses that contextualise heterogeneous in vivo protocols and in vitro assays remain scarce, complicating translational extrapolation.

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Materials and Methods

2.1 Animals and Experimental Design

Thirty male Wistar rats (220 ± 15 g) were randomised into:

1. Intact control;
2. NO_2-induced fibrosis;
3. NO_2 + PSO therapy.

Chronic fibrosis was elicited by inhalational exposure to NO_2 (10 ppm, 4 h day, 90 days). PSO (cold-pressed, 79 % punicic acid) was administered via oral gavage for the final 30 days.

2.2 Outcome Measures

Liver specimens were fixed in 10 % formalin and stained with Masson's trichrome; fibrosis area was quantified using ImageJ. Immunohistochemistry employed monoclonal antibodies against TGF-β1, α-SMA, and CD68 (M2 macrophage marker). Enzymatic indices of oxidative stress (SOD, catalase, GPx) and lipid peroxidation (MDA) were assayed spectrophotometrically.

2.3 Statistical Analysis

Data are presented as mean ± SEM. Inter-group differences were evaluated by one-way ANOVA with Tukey's post hoc test (GraphPad 10), $\alpha = 0{,}05$.

Results

3.1 Histopathology

NO_2 challenge induced bridging fibrosis and periportal septa occupying 27·4 ± 3·1 % of parenchymal area. PSO treatment curtailed fibrotic expansion to 14·9 ± 2·2 % ($p < 0{\cdot}01$ vs. fibrosis group).

3.2 Immunohistochemical Profiling

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Relative optical density analyses demonstrated a 45 % down-shift in TGF-β1 and 40 % in α-SMA expression within down-shiftlivers ($p < 0{\cdot}01$). $CD68^{+}$ macrophage infiltration decreased by 38 % ($p < 0{,}05$).

3.3 Redox Homeostasis

PSO normalised MDA levels (–36 %) while augmenting SOD (+42 %), catalase (+35 %), and GPx (+39 %) activities relative to fibrotic controls ($p < 0{,}05$ for all).

Systemic Pharmacodynamic Spectrum of PSO

Table 1. Pre-clinical evidence base for PSO bioactivities

Effect	Experimental Model / Method	Key Markers / Outcome
Antioxidant	Rats (oxidative stress)	↑ SOD, ↓ MDA
Anti-inflammatory	Mice (colitis, arthritis)	↓ TNF-α, COX-2, IL-6
Antifibrotic	Rats (CCl_4, NO_2)	↓ TGF-β1, α-SMA, CD68
Hepatoprotective	CCl_4, acetaminophen	↓ ALT, AST, necrosis
Cardioprotective	Rabbits (hypercholesterolemia)	↓ LDL, ↑ HDL, ↓ lipid oxidation
Antiproliferative	Tumour cell lines	↑ caspase-3, ↓ Bcl-2, ↓ VEGF

Table 1 summarises the breadth of PSO bioactivity substantiated across diverse pre-clinical paradigms. Notably, the lipid-lowering and endothelial-protective results reported by Kaplan *et al.* [1] and De Nigris *et al.* [3] dovetail with our antifibrotic findings, underscoring the oil's pleiotropic modulation of redox-inflammatory circuits.

Discussion

The confluence of antioxidant potentiation and cytokine reprogramming observed herein coheres with the canonical antifibrotic axis involving Nrf2 activation and TGF-β1

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suppression [5]. PSO's high punicic-to-linoleic acid ratio may underlie its superior lipid-peroxidation-blocking efficacy compared with non-conjugated ω-3/ω-6 sources. Furthermore, the attenuation of M2 polarisation expands current interpretations of PSO beyond simple antioxidation, implicating immunometabolic realignment as a contributory mechanism.

Methodological heterogeneity across published studies—dosage, extraction techniques, and duration—remains a translational barrier. Standardisation initiatives and head-to-head comparator trials against established antifibrotics (e.g., obeticholic acid) are imperative.

Conclusion

Our data corroborate and extend the antifibrotic and hepatoprotective portfolio of PSO, delineating mechanistic intersections between oxidative stress abatement and fibrogenic pathway inhibition. These insights warrant progression to phase I safety profiling and controlled clinical exploration in early-stage hepatic fibrosis.

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