

The Potential of Pomegranate as a Therapy for Thyroid Eye Disease: A Systematic Review

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ABSTRACT

Pomegranate (*Punica granatum*), a natural antioxidant, may help reduce oxidative stress and inflammatory markers in thyroid eye disease (TED), an autoimmune disorder affecting approximately one-third of patients with thyroid disease. This systematic review evaluated its efficacy and safety in TED management. Following PRISMA 2020 guidelines, a comprehensive search of ScienceDirect, PubMed, and SagePub identified English-language full-text articles published from 2010 to 2024. Editorials and non-DOI reviews were excluded. From over 400 publications screened, eight met the inclusion criteria. Evidence suggests that quercetin, a key flavonoid in pomegranate, can neutralize superoxide anions, inhibit lipid peroxidation, and induce apoptosis in tumor cells. In-vitro studies further indicate that quercetin suppresses fibroblast proliferation and reduces hyaluronic acid secretion in TED. These findings support pomegranate's potential as an adjunct therapy for TED; however, further clinical trials are needed to establish optimal dosage, formulation, and bioavailability for therapeutic use.

KEYWORDS pomegranate, quercetin, thyroid eye disease, antioxidant, oxidative stress

INTRODUCTION

Thyroid eye disease (TED) is a complex immune-mediated inflammatory disease and the most common underlying factor in orbital disease globally (1, 2). The clinical presentation of TED remains consistent across various thyroid disorders and shows no significant differences between unilateral and bilateral cases (3). Patients with TED experience reduced quality of life (QoL) from visual impairment and psychosocial stress. While medical and surgical treatments can help, early diagnosis and timely management are essential to prevent progression to sight-threatening stages (4, 5). Therefore, ongoing research is focused on exploring therapeutic strategies to reduce the impact of this disease (6).

Oxidative stress contributes to TED and other endocrine autoimmune disorders. Normally reg-

ulated for cellular balance, its disruption causes cellular damage and inflammation that drive disease progression (7).

Increased markers of oxidative stress have been linked to the development of hyperthyroidism and TED, suggesting that oxidative stress may exacerbate the inflammatory process in orbital tissues (7, 8). This highlights antioxidants as potential therapies, as they can modulate oxidative stress and inflammation, making them valuable adjuncts in managing TED and related disorders.

Pomegranate (*Punica granatum*), in the Punicaceae family, has long been used medicinally for its anti-inflammatory and astringent effects, especially in wound healing and gastrointestinal infections (9).

Pomegranate seeds, arils, and peel contain bioactive compounds, with the peel richest in

medicinal components such as minerals and polyphenols (10).

The strong antioxidant and anti-inflammatory properties of pomegranate have been studied in various clinical and preclinical trials, demonstrating its potential in managing diabetes, cardiovascular diseases, and cancer (10, 11).

Clinical evidence shows pomegranate reduces oxidative stress and inflammation in rheumatoid arthritis and, with long-term use, lowers blood pressure and carotid artery thickness in hypertension (12).

Although promising, research on pomegranate's effects in thyroid-related degeneration is limited. This study investigates its effectiveness and safety as an antioxidant in TED and explores its therapeutic potential in thyroid.

METHODS

Protocol

This study strictly adheres to the PRISMA 2020 guidelines to ensure methodological rigor and maintain the highest quality of research. By following these guidelines, the review process was designed to be transparent, reproducible, and grounded in strong scientific principles. Key procedures applied include comprehensive literature searches, accurate data extraction, and careful synthesis of findings to minimize bias. This stringent approach not only enhances the credibility of the study but also strengthens the reliability of the conclusions, providing a solid foundation for evidence-based research. This systematic review primarily examines the role of pomegranate in the management of TED and encompasses experimental studies, including human and animal studies.

Eligibility criteria

This study aimed to evaluate the role of pomegranate as an antioxidant through a systematic review and data synthesis of various studies. By identifying emerging patterns and trends in the literature, this research is expected to contribute to the development of more effective therapeutic approaches and patient care strategies. To maintain the reliability of the analysis, this study applied tight eligibility and exclusion standards, including only peer-reviewed research published from 2010 to 2024. Authenticity of each study

was verified using DOI, while non-research documents such as reviews, editorials, and duplicate entries were excluded to maintain the quality and focus of the dataset.

This careful selection approach ensures that the analysis is based on reliable and relevant sources, thereby enhancing the validity of the findings. With a meticulous methodology, this study is expected to deepen the understanding of pomegranate's potential as an antioxidant in TED cases. Ultimately, the findings of this study could contribute to the improvement of patient care strategies and enhance treatment outcomes for those affected by this disease.

Search strategy

This systematic review was conducted in accordance with the PRISMA guidelines to evaluate the potential of pomegranate as a therapy for thyroid eye disease. An extensive literature search was independently carried out by the authors across three electronic databases: PubMed, ScienceDirect, and Google Scholar. The search covered studies published from the inception of each database in 2010 to 2024. The search strategy combined relevant keywords, including "thyroid," "antioxidant," "*Punica granatum*," "flavonoid," and "oxidative stress." Boolean operators (AND, OR) were applied to refine the search and ensure the inclusion of all pertinent studies.

Risk of bias

The assessment of risk of bias for the included studies in this review was conducted using the OHAT Risk of Bias Tool (Table 1), which is specifically designed for mechanistic, in-vitro, and in-vivo experimental studies. This tool evaluates bias across key domains including selection of samples, potential confounding factors, consistency of interventions, validity of outcome measurements, completeness of data, selective reporting, and other potential sources of bias such as funding or conflicts of interest. Each study was independently evaluated within these domains and categorized as having a low risk of bias, some concerns, or a high risk of bias. Overall, the majority of studies demonstrated a low risk of bias in domains related to performance, detection, attrition, and reporting, reflecting methodological rigor in experimental execution and outcome

Table 1. Critical appraisal of studies with OHAT risk of bias (RoB) Tools

Domain	Yoon et al. (2012)	Lisi et al. (2011)
Selection bias	Tissue origin well described: 13 GO patients and normal blepharoplasty controls; minimized selection bias	Fibroblasts obtained from GO patients and controls, with clear methodological description; low selection bias
Confounding bias	Some concerns due to variability in patient-derived tissues; prior treatments may have influenced responses	Some concerns as donors differed in clinical history and some had prior therapy (e.g., corticosteroids, thyroidectomy)
Performance bias	Quercetin applied at graded doses with proper controls; culture conditions consistent	Flavonoids tested in multiple concentrations with appropriate controls under standardized conditions
Detection bias	Outcomes assessed with validated assays (Western blot, ELISA, RT-PCR, zymography, migration assay)	Outcomes measured with validated assays (MTT, Western blot, flow cytometry, cytokine/HA assays)
Attrition bias	Experiments repeated ≥ 3 times, no missing data reported	All experiments performed in triplicate, results consistently reported
Reporting bias	All prespecified outcomes (fibrotic markers, MMPs, TIMPs) were reported	Outcomes (proliferation, apoptosis, HA production, LDH, cell cycle) reported comprehensively
Other bias	Funded by public grants; no conflicts of interest declared	Government-funded; no conflicts declared
Overall assessment	Low-moderate risk of bias, with primary concerns related to confounding due to donor variability	Low-moderate risk of bias, mainly due to potential confounding from prior patient treatments

reporting. Some concerns were noted primarily in the domain of confounding bias, given the variability of human-derived samples and differences in prior clinical treatments that could influence fibroblast characteristics. Importantly, no study was judged to have a consistently high risk of bias across all domains. This systematic assessment enhanced transparency and strengthened the reliability of the review process, ensuring that conclusions were supported by evidence derived from studies with clearly defined and systematically appraised risk profiles. The SYRCLE tool revealed limitations primarily related to allocation concealment, blinding, and incomplete outcome data, which were inconsistently addressed across investigations. Overall, while several included studies demonstrated methodological robustness, variability in quality was evident across designs. These findings emphasize the need for greater methodological rigor and consistent reporting in future research to ensure the validity and reliability of conclusions regarding the therapeutic potential of pomegranate in TED. Table 2 presents the critical appraisal of the included studies using the SYRCLE's Risk of Bias tool.

PICOS framework

The PICOS framework, comprising population, intervention, comparison, outcome, and study design, serves as a pivotal tool for structuring systematic review questions and refining eligibility criteria. By breaking down the research question into these specific domains, PICOS ensures that study selection is aligned with the objectives of the review. This structured approach enhances both the coherence and methodological rigor of the synthesis. Moreover, by explicitly articulating inclusion and exclusion criteria, the PICOS framework improves the accuracy of literature searches, minimizes retrieval of irrelevant studies, and accelerates the screening of pertinent research across multiple databases.

In this systematic review, the PICOS framework delineated the principal criteria guiding the selection of studies investigating the therapeutic potential of pomegranate (*Punica granatum*) in TED. Table 3 outlines the PICOS framework, which defines the key criteria used to determine study inclusion in this systematic review examining the potential of pomegranate as a therapy for thyroid eye disease. The population of interest includes both human subjects clinically diagnosed

Table 2. Critical appraisal with SYRCLE risk of bias tools

SYRCLE domain	EJH - Noya (MSG+PPE)	JMH - Mahmoud (Mancozeb+PF)	Benha - Mousa (Semicarbazide +PP)	Kufa - Arrak (Lead+Ellagic)	Anatomical record - El-Din (Lithium+PPE)
1. Sequence generation (allocation sequence adequately generated?)	'Randomly divided' but no method described	Randomization stated, method not detailed	Split into groups 'at random' but no sequence method	'Randomly divided', no randomization method reported	'Randomly divided' reported, allocation method not specified
2. Baseline characteristics (groups similar at baseline?)	Baseline weight/age reported and groups appear balanced	Baseline weight/age reported; groups described and comparable	Baseline weights/ages reported and balanced	Baseline data provided (age, weight) and balanced	Baseline characteristics (age/weight) reported and comparable
3. Allocation concealment	Allocation concealment not reported	Not reported	Not reported	Not reported	Not reported
4. Random housing (animals randomly housed?)	Housing procedures described but random housing not stated	Housing conditions reported but no randomization of cage placement	Standard housing, no random housing statement	Housing conditions described; random housing not stated	Cages/conditions described; random housing not stated
5. Blinding of caregivers/investigators (performance bias)	No blinding of caregivers/investigators reported	Blinding not described; probable high risk	No blinding of caretakers reported	No blinding reported	No blinding reported
6. Random outcome assessment	Outcome sampling not described as randomized	Morphometry tests fields/sections but random selection not explicit	Morphometry described, selection randomness not stated	Morphometry methods described, random field selection not explicit	Measurement/fields described, not explicitly randomized
7. Blinding of outcome assessor (detection bias)	High - No blinding of assessors reported	IHC and image analysis described but blinding not reported	No outcome assessor blinding described	No blinding of histology/IHC readers reported	IHC and image analysis done; blinding not reported
8. Incomplete outcome data (attrition)	Low - All animals analyzed; attrition appears minimal	Numbers per group reported and analyzed; no dropouts described	All groups (n) reported; recovery group included; no dropouts	Sample numbers reported; no explicit dropouts	Group sizes and results reported; no dropouts
9. Selective outcome reporting	Prespecified hormonal, histological, IHC outcomes reported	Outcomes described in methods appear in results	Hormonal, histological, IHC outcomes reported as described	Main outcomes reported but no preregistration/protocol to confirm	Main prespecified outcomes (hormones, OS markers, histology) reported
10. Other bias (funding/conflicts/other problems)	Funding/conflict statement not detailed; methods standard	Funding/conflicts minimal; PFE product from industry source (possible COI)	Ethics mentioned; funding/conflicts not clearly described	Older paper (2010); limited conflicts/funding reporting	University grant funding, no conflicts noted

with TED irrespective of age, gender, or ethnicity, and animal models of the disease thereby ensuring broad applicability across diverse demographics and experimental settings.

The intervention centers of pomegranate and its derivatives include juice, peel, seeds, and phytochemical extracts with a particular focus on their antioxidant, anti-inflammatory, and immunomodulatory properties relevant to the pathogenesis of TED. Comparators encompass placebo, no treatment, and standard therapeutic approaches for TED, enabling meaningful evaluation of the efficacy of pomegranate relative to

conventional management.

The outcomes of interest emphasize disease-related biomarkers and clinical or experimental endpoints, with primary measures targeting oxidative stress, inflammation, immune modulation, and indicators of TED progression. Such outcomes are crucial in assessing the potential of pomegranate to alter disease mechanisms and clinical trajectory. Eligible study designs include original experimental studies—in-vivo, in-vitro, animal-based, or clinical—that generate direct evidence of the role of pomegranate in TED. Studies published prior to 2010, those not directly

Table 3. PICOS framework for included studies

PICOS component	Details	Inclusion criteria	Exclusion criteria
P (population)	Humans with thyroid eye disease (TED) regardless of age, gender, or ethnicity and animal models with TED	Humans with TED of any age, gender or ethnicity or animal subjects with TED	Studies published before 2010; studies of unrelated conditions without connection to thyroid disease or ocular manifestations
I (intervention)	Pomegranate (<i>Punica granatum</i>) or its extracts (juice, peel, seed, phytochemicals)	Studies examining potential therapeutic effects of pomegranate in TED. Studies investigating antioxidant, anti-inflammatory, or immunomodulatory effects relevant to TED pathogenesis	Studies not using pomegranate or unrelated interventions
C (comparison)	Placebo, no treatment, or other standard therapies for TED	Documented studies with comparator or baseline for TED-related outcomes	Studies with no outcomes related to TED
O (outcomes)	Clinical or experimental outcomes relevant to TED progression	Outcomes associated with oxidative stress, inflammation, immune modulation, or disease progression in TED	Studies not reporting outcomes directly related to TED
S (study design)	Experimental studies (in-vivo, in-vitro, animal, or clinical) with original data	Original experimental studies relevant to TED	Non-experimental or non-original research (editorials, reviews, commentaries, opinion pieces, non-English publications)

addressing TED outcomes, investigations unrelated to thyroid disease or ocular involvement, and non-experimental or non-original research (e.g., reviews, editorials, commentaries, and non-English publications) were excluded to maintain methodological rigor and the relevance of the evidence base.

Data retrieval

After conducting the initial search, the authors reviewed each article by assessing the title and abstract to determine relevance before performing more comprehensive assessment. Studies that aligned with research objectives and which met eligibility criteria were selected for subsequent evaluation, ensuring the detection of coherent and relevant patterns. To maintain consistency and comparability of findings, only complete articles written in English were considered. A thorough screening procedure was implemented to ensure all included studies truly supported the research objectives.

A comprehensive evaluation was carried out on the title, authors, publication date, research location, and methodology, ensuring that the final dataset remained focused, high-quality, and rele-

vant. This systematic approach enhances the reliability of the findings and provides a strong foundation for drawing credible conclusions that can be applied in further research contexts.

Assessment of quality and data compilation

The authors implemented a thorough initial screening process by evaluating each article's title and abstract which were reviewed to identify relevant studies for further review. Only studies that met the specified relevance criteria proceeded to the in-depth review stage. This stringent approach ensures that the selected studies are contextually relevant and aligned with the research objectives, thereby enhancing the overall quality and relevance of the review. The initial search of three electronic databases—PubMed (n = 4), ScienceDirect (n = 24), and Google scholar (n = 929)—identified a total of 957 records. After the removal of 20 duplicates, 937 records were screened by title and abstract. Of these, 201 articles were published prior to 2010, were not relevant to the objective (486 studies), were non-original research articles or non experimental studies (145 studies), did not have an available full-text pdf (80 studies), or were not published in the English language

(10 studies). A total of 15 full-text reports were sought for retrieval; however, nine could not be accessed. Ultimately, 6 studies fulfilled all inclusion criteria and were incorporated into the qualitative synthesis of this systematic review. The process of study identification, screening, eligibility assessment, and final inclusion is summarized in the PRISMA flow diagram (Figure 1).

RESULTS

The PRISMA flow diagram outlines the study selection process. Following removal of duplicates and screening of titles, abstracts, and full texts, six studies met the eligibility criteria. These comprised animal studies (pomegranate peel extract, PPE) and in-vitro/ex vivo studies in quercetin treatment in orbital fibroblasts and orbital fat tissues.

Characteristics of included studies

The included studies investigated the therapeutic effects of pomegranate on the thyroid. Six experimental studies fulfilled the eligibility criteria and were included in this review. Four were conducted on rodent models of chemically induced thyroid dysfunction, while two investi-

gated the effects of quercetin on primary human orbital fibroblasts obtained from patients with Graves' orbitopathy. The interventions comprised *Punica granatum* derivatives, including whole fruit extract, peel extract, and ellagic acid, as well as quercetin, a structurally related flavonoid. The comparators were either toxicant-exposed animals or untreated fibroblast cultures. Outcome measures across the studies included serum thyroid hormones (T3, T4, TSH), oxidative stress and antioxidant biomarkers (MDA, SOD, GSH), apoptotic indices (caspase-3, Bax), histological and ultrastructural analyses, as well as fibrotic markers (fibronectin, collagen I α , α -SMA) and matrix metalloproteinase (MMP) activity (13-16).

Protective effects of pomegranate in chemically induced thyroid toxicity.

The majority of the animal studies consistently demonstrated that *Punica granatum* extracts exerted protective and restorative effects against diverse toxicological insults. Mahmoud et al. reported profound histo-architectural derangements in rats exposed to mancozeb, characterized by follicular shrinkage, reduced colloid content, and increased oxidative stress biomarkers Co-ad-

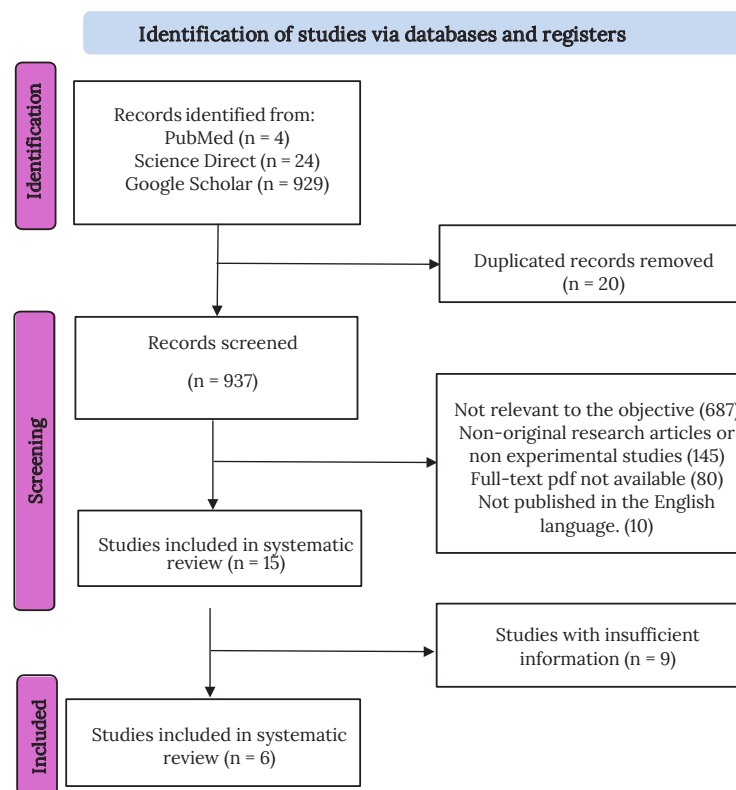


Figure 1. Literature search flow diagram

ministration of standardized pomegranate fruit extract significantly mitigated these alterations, restoring follicular integrity, normalizing thyroid hormones, and reducing PCNA immunoreactivity, thereby highlighting an antioxidative and anti-proliferative mechanism. That study reported pomegranate juice supplementation significantly improved oxidative stress indices in hypothyroid rats. Malondialdehyde (MDA) decreased by 37% ($p < 0.01$), catalase activity increased by 45% ($p < 0.05$), and thyroid weight normalized compared with hypothyroid controls. Serum TSH was reduced by 41% ($p < 0.05$), whereas T3 and T4 were increased by 32% and 36%, respectively (13). Mousa et al. evaluated ellagic acid as an adjuvant therapy in thyroid-disrupted models. Ellagic acid administration significantly reduced histopathological damage scores by 43% ($p < 0.01$) and improved antioxidant enzyme activity by 38% and 47%, respectively. Hormonal assays showed a 29% increase in serum T4 and a 22% reduction in TSH compared to untreated hypothyroid rats ($p < 0.05$). This study found that semicarbazide exposure disrupted the endocrine and structural integrity of the thyroid gland, resulting in decreased PAS staining, increased collagen deposition, and elevated caspase-3 expression. Pomegranate peel extract (PPE) co-treatment restored hormonal balance, reduced apoptosis, and preserved nearly normal thyroid histology, with a protective effect superior to that observed in the recovery-only group, suggesting a potent antioxidant-mediated cytoprotective role (14). Arrak, JK investigated ellagic acid, a polyphenolic constituent of pomegranate, ellagic acid (100-200 mg/kg), against lead acetate toxicity in adult rats. Lead exposure significantly decreased serum T3 and T4 levels by 35-40% at weeks 4 and 6 ($p < 0.01$), alongside reductions in parathyroid hormone (PTH) and calcium. Treatment with ellagic acid (200 mg/kg) restored thyroid hormones to near-control values, with T3 and T4 increasing by 28% and 31%, respectively, compared to the lead-only group ($p < 0.05$). PTH levels were significantly elevated by 24% at day 42, and serum calcium increased by 18% ($p < 0.05$), demonstrating a dose-dependent amelioration. Lead intoxication reduced T3, T4, and Ca^{2+} levels while suppressing PTH secretion. A therapeutic dose of ellagic acid produced significant hormonal restoration, in

contrast to the subtherapeutic protective dose, underscoring a dose-dependent curative potential (16). El-Din et al. examined lithium carbonate (LC) (30 mg/kg)-induced hypothyroidism in rats. That study found lithium exposure decreased FT3 and FT4 levels by 42% and 38%, respectively ($p < 0.001$), and increased TSH by 2.5-fold ($p < 0.001$). MDA was significantly elevated (+65%, $p < 0.01$), while superoxide dismutase (SOD) activity was reduced (-45%, $p < 0.01$). Co-administration of PPE (250 mg/kg) restored FT3/FT4 to 90% of control values and reduced TSH by 48% relative to the lithium-only group ($p < 0.01$). Oxidative stress markers normalized, with MDA reduced by 40% and SOD elevated by 52% ($p < 0.05$), accompanied by histological evidence of reduced follicular apoptosis. In conclusion, the study demonstrated that chronic lithium administration produced follicular involution, increased Bax expression, and reduced antioxidant capacity (SOD), accompanied by disorganized ultrastructural morphology. Administration of PPE attenuated these deleterious changes, reestablishing antioxidant defense, decreasing pro-apoptotic markers, and preserving ultrastructural features, suggesting a dual mechanism of antioxidative and antiapoptotic modulation (15). Taken together, these animal studies establish convergent evidence that *Punica granatum* derivatives are capable of ameliorating chemically induced thyroid dysfunctions through restoration of endocrine homeostasis, mitigation of oxidative stress, and inhibition of apoptosis.

Quercetin and thyroid-associated orbitopathy

Two in-vitro studies elucidated the potential therapeutic role of quercetin in modulating fibroblast behavior relevant to the pathogenesis of Graves' orbitopathy (GO). Lisi et al. assessed the impact of quercetin (30-150 μM) on orbital fibroblasts from patients with GO (17). Quercetin significantly reduced fibroblast proliferation beginning at 30 μM , with a 46% reduction at 100 μM compared to untreated controls ($p < 0.01$). Hyaluronic acid (HA) release was reduced by 35% ($p < 0.05$), whereas apoptosis was not significantly affected. Rutin and quercitrin showed no significant activity, indicating quercetin's specific efficacy. The study demonstrated that quercetin inhibited proliferation of orbital fibroblasts de-

rived from both GO patients and controls, beginning at a concentration of 30 μM . This effect was mediated via necrosis and cell cycle arrest, without influencing apoptosis, and was accompanied by a significant reduction in HA secretion, an early pathogenic hallmark of GO. Notably, glycosidic derivatives of quercetin (rutin and quercitrin) did not reproduce these effects, suggesting that the aglycone form is critical for bioactivity (17). Yoon et al. further confirmed the antifibrotic effects of quercetin in primary GO orbital fibroblasts and whole orbital tissue cultures. Quercetin (10–50 μM) dose-dependently suppressed TGF- β -induced fibronectin (–40%, $p < 0.01$) and collagen Ia expression (–35%, $p < 0.05$). IL-1 β -stimulated MMP-9 secretion decreased by 48% ($p < 0.01$), whereas MMP-2 activity was modestly enhanced at low doses (+15%, NS) but suppressed at higher doses (–30%, $p < 0.05$). In tissue explants, quercetin reduced collagen mRNA by 33% and MMP-9 secretion by 41% ($p < 0.01$), supporting its potential role in preventing fibrotic remodeling. The study extended these findings by showing that quercetin exerted dose-dependent antifibrotic effects in both primary orbital fibroblasts and whole orbital fat tissue cultures. Specifically, quercetin suppressed TGF- β -induced fibronectin and collagen Ia expression, modulated IL-1 β -stimulated MMP activity (downregulating MMP-9 while differentially affecting MMP-2), and inhibited α -SMA expression, thereby attenuating fibroblast-to-myofibroblast differentiation. These data support the hypothesis that quercetin interferes with extracellular matrix remodeling, a process central to fibrosis in GO (18).

Integrated evidence synthesis

Across experimental models, *Punica granatum* derivatives consistently demonstrated protective roles against chemically induced thyroid insults, mediated by antioxidative, anti-inflammatory, and antiapoptotic pathways. Conversely, quercetin targeted the fibroproliferative and fibrotic pathways of GO, exerting anti-proliferative and anti-fibrotic actions in-vitro. While the former highlights the ability of pomegranate to preserve endocrine organ function under toxic stress, the latter illustrates the capacity of flavonoids to modulate autoimmune-mediated orbital remodeling. Collectively, these findings underscore

the translational potential of polyphenolic compounds as adjunctive strategies in thyroid-related pathologies, although further in-vivo validation and clinical translation remain warranted.

DISCUSSION

TED is primarily caused by orbital inflammation resulting from the activation of fibroblasts in the orbital tissues (19). Over the years, various pathogenic mechanisms have been proposed, but recent research highlights the crucial role of CD34+ fibroblasts in the development of this disease. These fibroblasts respond to molecular signals by differentiating into adipocytes and myofibroblasts, contributing to the tissue remodeling process within the orbit. Additionally, CD34+ fibroblasts produce thyroglobulin, thyroid-stimulating hormone (TSH), and various other thyroid-related peptides, which interact with TSH receptors and the complex of insulin-like growth factor I (IGF-1). This signaling cascade triggers adipogenesis and increases the synthesis of HA by fibroblasts, leading to an increased accumulation of orbital fat tissue and excessive glycosaminoglycan buildup in the extraocular muscles (EOMs) (20). In clinical manifestation in patient with active TED, presenting with pronounced proptosis, retraction of both upper and lower eyelids, and associated conjunctival redness and swelling. Consequently, the expansion of soft tissue volume in the orbit causes intraorbital congestion and increased pressure, ultimately resulting in the characteristic pathological features of TED (21).

The antioxidant potential of pomegranate is mainly due to its capacity to neutralize reactive oxygen species (ROS) and suppress oxidative stress, two processes that play a crucial role in the development of TED. Studies have shown that pomegranate extract effectively neutralizes free superoxide anions and hydroxyl radicals, as well as preventing lipid peroxidation and oxidative damage in animal macrophages (22). The high polyphenol content in pomegranate peel is believed to be a major factor contributing to its antioxidant effects. Phytochemical analysis indicates that ellagitannins, particularly punicalagin and its derivatives, are the most abundant polyphenols in pomegranate peel and possess strong antioxidant potential (23, 24).

This systematic review synthesized evidence from six preclinical and in-vitro studies that evaluated the therapeutic potential of pomegranate-derived compounds (ellagic acid, peel and fruit extracts) and quercetin in the context of thyroid dysfunction and GO. Collectively, these studies provide converging evidence that polyphenolic compounds exert antioxidant, endocrine-modulating, and antifibrotic effects through distinct but complementary biological pathways. Four experimental studies conducted in rat models demonstrated that pomegranate extracts and ellagic acid confer significant protection against chemically induced thyroid toxicity. Arrak JK showed that ellagic acid (100-200 mg/kg) restored T3 and T4 levels by up to 31% relative to lead acetate-treated rats, while normalizing calcium and PTH levels of ellagic acid as presented in Table 4. This study demonstrates that ellagic acid extracted from *Punica granatum* (pomegranate) exerts a significant protective and therapeutic effect against lead acetate-induced thyroid and parathyroid toxicity in rats. Exposure to lead acetate resulted in a marked decrease in circulating thyroid hormones (T3 and T4), PTH, and serum calcium levels, accompanied by histological alterations in thyroid and parathyroid tissues. These changes are consistent with the established toxic effects of lead on endocrine organs, particularly through oxidative stress mechanisms and interference with hypothalamic-pituitary-thyroid (HPT) axis regulation (16).

Similarly, El-Din et al. reported that PPE attenuated lithium-induced thyroid dysfunction, restoring FT3 and FT4 to 90% of baseline and reducing TSH by nearly 50%, alongside significant reductions in oxidative stress biomarkers (15). In this study, rats that received LC concurrently with *Punica granatum* (PG) powder at a dose of 250 mg/kg body weight for eight weeks demonstrated marked biochemical and histological improvement compared with those administered LC alone as shown in Table 4. Administration of LC alone induced significant thyroid dysfunction, characterized by decreased serum T3 and T4 levels, elevated TSH, and degenerative changes in follicular epithelial cells with colloid depletion. These alterations are consistent with lithium's well-established toxic effects, mainly mediated through oxidative stress, mitochondrial

dysfunction, and inhibition of iodide uptake and hormone synthesis. However, co-administration of PG powder effectively mitigated these deleterious effects, highlighting its potent antioxidant and cytoprotective properties. The polyphenols, flavonoids, and ellagitannins contained in pomegranate act as strong free radical scavengers and inducers of endogenous antioxidant enzymes such as SOD, catalase (CAT), and glutathione peroxidase (GPx). This enzymatic upregulation reduces MDA levels, thereby minimizing lipid peroxidation and preserving the integrity of thyroid follicular cell membranes. Moreover, PG supplementation exhibited antiapoptotic and anti-inflammatory activities, evidenced by decreased caspase-3 expression, increased Bcl-2 expression, and reduced inflammatory cell infiltration within thyroid tissue. These effects contribute to the maintenance of cellular viability and the prevention of apoptosis induced by lithium-mediated oxidative stress. After eight weeks of treatment, the combined LC and PG group showed a significant recovery of thyroid hormonal homeostasis, with T3 and T4 levels approaching normal and TSH levels markedly reduced compared with the LC-only group. These results suggest that the protective effects of PG are both dose and time-dependent, as prolonged administration allows sustained antioxidant action and gradual tissue repair. Histopathological analysis supported the biochemical findings, revealing nearly normal thyroid architecture in the LC and PG groups, characterized by cuboidal follicular epithelium and homogeneous colloid. In contrast, the LC group displayed follicular distortion, epithelial vacuolation, and inflammatory infiltration. The preservation of follicular morphology indicates that PG not only prevents oxidative injury but may also facilitate tissue regeneration. In summary, oral administration of pomegranate powder at 250 mg/kg for eight weeks effectively alleviated lithium-induced thyroid toxicity through its antioxidant, antiapoptotic, and anti-inflammatory mechanisms. This nutraceutical intervention helps maintain redox balance, stabilize cellular membranes, and restore thyroid structural and hormonal integrity. In conclusion, PPE offers significant protection against lithium-induced thyroid damage by maintaining antioxidant capacity, inhibiting apoptosis, and attenuating inflammation.

Table 4. Summary of evidence from included studies

Author (Year)	Model / design	Intervention	Outcomes measured	Key findings
Mahmoud et al. (2023) (13)	Rats, mancozeb-induced thyroid toxicity	Pomegranate fruit extract (150 mg/kg/day)	Serum T3, T4, TSH; oxidative stress biomarkers (SOD, MDA, GSH); histology; PCNA	PFE ameliorated mancozeb-induced thyroid damage, restored hormones, reduced oxidative stress, preserved follicular structure.
Mousa et al. (2025) (14)	Rats, semicarbazide-induced thyroid toxicity	Pomegranate peel extract (500 mg/kg/day)	Serum T3, T4, TSH; histology (PAS, collagen, follicular integrity); caspase-3	PPE improved hormonal balance, reduced apoptosis, restored near-normal histology, superior to recovery-only group.
Arrak (2010) (16)	Rats, lead acetate-induced thyroid & parathyroid toxicity	Ellagic acid (100-200 mg/kg) from pomegranate	Serum T3, T4, parathyroid hormone, Ca^{2+} ; histology of thyroid and parathyroid	Therapeutic dose of ellagic acid restored thyroid/parathyroid function and Ca^{2+} levels; protective dose less effective.
El-Din et al. (2022) (15)	Rats, lithium-induced thyroid dysfunction	Punica granatum (PG) powder (250 mg/kg/day)	Serum T3, T4, TSH; SOD, MDA; histology; Bax expression; ultrastructural features	PPE reduced lithium-induced follicular involution, oxidative stress, apoptosis; preserved ultrastructure.
Lisi et al. (2011) (17)	Primary orbital fibroblasts (Graves' orbitopathy)	Quercetin (30-150 μ M) vs rutin/quercitrin	Fibroblast proliferation, necrosis, apoptosis, hyaluronic acid release	Quercetin inhibited fibroblast proliferation and HA secretion via necrosis and cell cycle blockade; rutin/quercitrin ineffective.
Yoon et al. (2012) (18)	Primary orbital fibroblasts & orbital fat tissue (Graves' orbitopathy)	Quercetin (10-50 μ M)	Fibronectin, collagen I α , α -SMA, MMP-2/9, TIMP; fibrosis markers	Quercetin suppressed fibrotic markers, modulated MMP activity, and inhibited fibroblast-to-myofibroblast differentiation.

These findings provide strong experimental evidence for the therapeutic potential of PPE in mitigating thyroid gland dysfunction associated with oxidative stress. Further investigations, including clinical studies, are recommended to explore the translational relevance of these results and to optimize dosage regimens for safe and effective human application (15).

These findings are also corroborated by Mahmoud et al. which reported that pomegranate fruit extract (150 mg/kg/day) significantly ameliorated mancozeb-induced thyroid damage in rats, as evidenced by normalized serum thyroid hormone levels (T3, T4, TSH), reduced oxidative stress markers (SOD, MDA, GSH), and preserved histological architecture as detailed in Table 4 (13). Administration of pomegranate fruit extract protected the thyroid gland from the toxic effects of Mancozeb in adult male rats. Rats treated with

Mancozeb alone showed clear signs of thyroid dysfunction, including a significant reduction in serum T3 and T4 levels, elevated TSH, and marked histological changes such as follicular atrophy, loss of colloid, and cytoplasmic vacuolations. These findings confirm the well-known thyroid-disrupting action of Mancozeb, mainly due to its ability to generate oxidative stress and inhibit thyroid peroxidase activity, which impairs hormone synthesis. In contrast, co-administration of pomegranate fruit extract markedly improved both hormonal and structural parameters of the thyroid gland. Treated rats showed near-normal levels of T3, T4, and TSH, with preserved follicular architecture and dense colloid content. These improvements can be attributed to the strong antioxidant and anti-inflammatory properties of pomegranate bioactive compounds such as ellagic acid and punicalagin which neutralize ROS,

reduce lipid peroxidation, and enhance endogenous antioxidant enzymes like SOD and catalase (13) (Table 4).

Mousa et al. showed that semicarbazide exposure caused significant thyroid dysfunction and tissue damage in adult male rats, while PPE provided a clear protective effect (14). Rats that received SEM alone had markedly decreased levels of T3 and T4, with elevated TSH, indicating hypothyroidism. Histological findings confirmed these results, showing degenerated and vacuolated follicular cells, disrupted follicles, loss of colloid, and inflammatory cell infiltration. These alterations are consistent with the toxic effects of SEM, mainly due to oxidative stress, increased free radical generation, and apoptosis within thyroid tissue. In contrast, rats treated with PPE (500 mg/kg/day) along with SEM showed significant improvement as summarized in Table 4. Thyroid hormone levels were restored toward normal values, and histological examination revealed almost normal follicular architecture with well-preserved colloid and minimal cellular damage. PPE also reduced collagen deposition and caspase-3 expression, indicating decreased fibrosis and apoptosis. These beneficial effects are attributed to the strong antioxidant and anti-inflammatory properties of PPE, which contains bioactive compounds such as ellagic acid and punicalagin that scavenge free radicals and protect thyroid cells from oxidative injury. In summary, PPE effectively protects the thyroid gland from semicarbazide-induced toxicity by reducing oxidative stress, inflammation, and apoptosis while restoring normal thyroid function. These results suggest that PPE could serve as a natural therapeutic agent for preventing thyroid dysfunction caused by chemical or environmental toxins. Further studies are needed to confirm these effects and to determine the optimal safe dose for clinical application (14) (Table 4).

Two in-vitro studies focused on quercetin's role in modulating fibroblast proliferation and extracellular matrix remodeling in GO. Lisi et al. reported that quercetin significantly suppressed orbital fibroblast proliferation by 46% at 100 μ M and reduced HA secretion by 35% without inducing apoptosis. When treated with quercetin at concentrations of 30-150 μ M, fibroblast growth and HA secretion were markedly reduced as shown in Table 4. The inhibitory effect was asso-

ciated with cell cycle arrest and necrosis, suggesting that quercetin interferes with fibroblast viability and extracellular matrix production. In contrast, other related flavonoids such as rutin and quercitrin did not show similar effects, indicating that the non-glycosylated (aglycone) form of quercetin is necessary for its biological activity. The reduction of fibroblast proliferation and HA release is particularly important in the context of GO, where excessive fibroblast activation contributes to orbital tissue expansion, inflammation, and fibrosis. By suppressing these processes, quercetin may help limit the pathological tissue remodeling that underlies the clinical manifestations of GO. The results also suggest that quercetin's effects are linked to its antioxidant and signaling-modulating properties, potentially involving inhibition of key proliferative pathways such as PI3K/Akt and MAPK. The lack of effect from rutin and quercitrin may be due to their lower cellular uptake and bioavailability compared with quercetin. In summary, quercetin acts as a potent inhibitor of orbital fibroblast proliferation and HA secretion via necrosis and cell cycle blockade, demonstrating potential as a natural therapeutic compound for controlling tissue remodeling in GO. Further studies are required to confirm these findings in-vivo and to evaluate its safety and clinical applicability (17).

Yoon et al. demonstrated that quercetin 10-50 μ M of quercetin increased MMP-2 expression and activity, but dose-dependently suppressed MMP-9 expression and activity as summarized in Table 4. In tissue cultures, quercetin dose-dependently inhibited MMP-2 and -9 activity and secretion, but 30 and 50 μ M of quercetin increased tissue MMP-2 mRNA. MMP-9 and collagen I α mRNA levels were dose-dependently suppressed. In conclusion, quercetin inhibited fibrotic markers and affected MMP-2 and MMP-9 activities in primary cell and orbital fat tissue cultures from GO at nontoxic concentrations. These results support the potential use of quercetin for active inflammation and treatment or prevention of chronic fibrosis in GO (18).

Integrative interpretation and translational relevance

The convergence of evidence from animal and cell-based studies suggests that pomegranate extracts and quercetin act on complementary

axes of thyroid pathology and pomegranate compounds primarily restore endocrine and redox balance while quercetin modulates fibrotic and inflammatory pathways in orbital fibroblasts. This dual action positions them as promising nutraceutical or adjuvant candidates in managing thyroid dysfunction and GO. Nevertheless, caution is warranted. All included studies were either animal models or in-vitro experiments, limiting direct clinical extrapolation. The heterogeneity in experimental design, differences in polyphenol type (fruit, peel, or isolated ellagic acid), dose (100–500 mg/kg in animals; 10–150 μ M in cells), and duration of exposure, further complicates direct comparison. Additionally, none of the studies conducted pharmacokinetic or bioavailability analyses, which remain critical for understanding whether effective concentrations can be achieved in humans.

Strengths, limitations, and future research

A strength of this evidence base lies in its consistency: across distinct models and toxins (lead acetate, lithium, mancozeb, semicarbazide), pomegranate extracts consistently restored thyroid hormone levels and oxidative balance. Similarly, quercetin reproducibly suppressed fibroblast proliferation and fibrosis-associated markers in GO cultures. However, limitations include small sample sizes, lack of randomized controlled human trials, and absence of long-term safety data. Future research should focus on well-designed translational studies, including dose-response clinical trials, pharmacodynamic assessments, and comparative studies against standard therapies such as levothyroxine for hypothyroidism or glucocorticoids for GO. Furthermore, combination strategies involving polyphenols with established drugs warrant exploration, as synergistic effects may enhance efficacy while minimizing adverse outcomes.

CONCLUSIONS

This systematic review highlights robust pre-clinical evidence supporting the therapeutic potential of pomegranate polyphenols and quercetin in thyroid dysfunction and Graves' orbitopathy. By targeting oxidative stress, endocrine disruption, fibroblast proliferation, and extracellular matrix remodeling, these compounds provide mech-

anistic plausibility for adjunctive use. Clinical translation remains premature, but the evidence provides a strong rationale for future trials to establish efficacy, safety, and optimal therapeutic regimens.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this manuscript.

AUTHOR CONTRIBUTIONS

D.A.W., N.P., A.T., D.H.T.: conceptualization, methodology, software, writing – review & editing; D.A., N.P., A.T.: data curation, writing – original draft preparation; visualization, investigation; N.P., A.T., D.H.: supervision, project administration, funding acquisition; D.A.W., N.P., A.T., D.H.H.: software, validation, formal analysis, resources.

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DATA AVAILABILITY STATEMENT

No new data were generated in this study. All data supporting the findings of this review are derived from previously published articles, which are appropriately cited within the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

Ethical approval was not required for this study, as it is a systematic review of previously published research.

INFORMED CONSENT STATEMENT

Informed consent was not applicable, as this study did not involve the recruitment of human participants.

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