Food Bioscience 77 (2026) 108453

Contents lists available at ScienceDirect

Food Bioscience

journal homepage: www.elsevier.com/locate/fbio

Polydatin in rheumatological diseases: Multitarget mechanisms and therapeutic potential

Chiara Baggio [a,1], Paolo Sfriso [a,1], Amelia Carmela Damasco [a], Giacomo Cozzi [a], Giampietro Ravagnan [b], Roberta Ramonda [a], Francesca Oliviero [a,*]

[a] Rheumatology Unit, Department of Medicine - DIMED, University of Padova, Padova, Italy
[b] Institute of Translational Pharmacology-National Research Council, 00133, Rome, Italy

ARTICLE INFO

Keywords:
Polydatin
Polyphenols
Rheumatic diseases
Anti-inflammatory
Antioxidant
Immunomodulation

ABSTRACT

Rheumatological diseases encompass a wide range of conditions primarily affecting the musculoskeletal system. They represent a significant burden on modern society, affecting millions of people worldwide. These chronic and debilitating conditions require long-term management and a multidisciplinary approach that combines pharmacological interventions with lifestyle modifications for optimal patient outcomes. In this context, diet is emerging as a crucial support in managing rheumatological diseases. Certain dietary patterns and specific nutrients can play a significant role in reducing inflammation, alleviating symptoms, and potentially slowing disease progression. Bioactive compounds, which are found in many plant-based foods and are abundant in the Mediterranean diet, are increasingly being recognized as valuable supports to traditional treatments in arthritis. Among them, polydatin has shown potent antioxidant and anti-inflammatory properties.

This review aims to comprehensively examine the therapeutic potential of polydatin in various rheumatological diseases, including rheumatoid arthritis, osteoarthritis, crystal-induced arthritis, spondyloarthritis, and systemic lupus erythematosus. Articles included have been identified using keyword-based searches in multiple scientific databases, including PubMed and Scopus.

The review highlights polydatin's multi-targeted mechanisms, including antioxidant activity, modulation of inflammatory pathways, regulation of apoptosis and autophagy, and direct interactions with molecular targets like sirtuin 1 and chemokine receptor type 1. Although clinical studies specifically investigating polydatin in rheumatological conditions are scarce, the translational potential of this compound is supported by randomized controlled trials involving other human inflammatory and pain-related disorders. Polydatin's favorable pharmacokinetic profile, enhanced bioavailability, and diverse biological actions position it as a promising natural compound for managing rheumatological diseases.

1. Introduction

Rheumatological diseases encompass a wide range of conditions primarily affecting the musculoskeletal system, including joints, muscles, bones, and connective tissues. They represent a significant social burden, affecting millions of people worldwide. These conditions have a profound effect on patients' quality of life and healthcare systems (GBD 2021 Other Musculoskeletal Disorders Collaborators, 2023).

Clinically, rheumatic diseases are characterized by chronic pain, inflammation, and, in many cases, progressive disability. Among the most frequent, rheumatoid arthritis (RA), osteoarthritis (OA), spondyloarthritis (SpA), and crystal-induced arthritis (CIA) affect primarily the joint, while connective tissue diseases, including systemic lupus erythematosus (SLE), can affect various organs and tissues.

RA and SLE are autoimmune conditions characterized by a breakdown in immune tolerance, leading to the production of autoantibodies that target the body's own tissues: the synovium in RA, and multiple organs including the kidney, skin, and joints in SLE (Dai et al., 2025; Scherer et al., 2020). The pathological process begins with a complex interplay between genetic predisposition and environmental factors, including cigarette smoking, particulate matter and infections and is

* Corresponding author.
E-mail addresses: chiara.baggio@unipd.it (C. Baggio), paolo.sfriso@unipd.it (P. Sfriso), amelia.damasco@unipd.it (A.C. Damasco), giacomo.cozzi.1@studenti.unipd.it (G. Cozzi), gprav@unive.it (G. Ravagnan), roberta.ramonda@unipd.it (R. Ramonda), francesca.oliviero@unipd.it (F. Oliviero).
[1] These authors contributed equally and share first authorship.

https://doi.org/10.1016/j.fbio.2026.108453
Received 3 December 2025; Received in revised form 3 February 2026; Accepted 8 February 2026
Available online 9 February 2026

Abbreviations

ACLT	Anterior cruciate ligament transection
ADAMTS-5	A disintegrin and metalloproteinase with thrombospondin motifs 5
AMPK	AMP-activated protein kinase
AS	Ankylosing spondylitis
Bax	Bcl-2–associated X protein
Bcl-2	B-cell lymphoma 2
BLC	B lymphocyte chemoattractant
CIA	Crystal-induced arthritis
COX-2	Cyclooxygenase-2
CPP	Calcium pyrophosphate
CRP	C-reactive protein
CFA	Complete Freund's adjuvant
CXCL1	C-X-C motif chemokine ligand 1
DMM	Destabilization of the medial meniscus
EGCG	Epigallocatechin-3-gallate
ESR	Erythrocyte sedimentation rate
FLS	Fibroblast-like synoviocytes
GBD	Global Burden of Disease
HA	Hyaluronic acid
HPLC	High-performance liquid chromatography
iNOS	Inducible nitric oxide synthase
IL	Interleukin
MIA	Monosodium iodoacetate
MMP	Matrix metalloproteinase
MSU	Monosodium urate
mtROS	Mitochondrial reactive oxygen species
NETs/NETosis	Neutrophil extracellular traps/neutrophil extracellular trap formation
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-like receptor family pyrin domain-containing 3
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2–related factor 2
OA	Osteoarthritis
PBMCs	Peripheral blood mononuclear cells
PD	Polydatin
PGE_2	Prostaglandin E2
PIL	Pristane-induced lupus
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor κB ligand
ROS	Reactive oxygen species
SGLT1	Sodium-dependent glucose transporter 1
SIRT	Sirtuin
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
STAT3	Signal transducer and activator of transcription 3
SOD2	Superoxide dismutase 2
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

driven by the dysregulation and hyperactivity of both B and T lymphocytes. In contrast to these autoimmune conditions, SpA (Kocatürk et al., 2022) and CIA (Pascart et al., 2024) are inflammatory chronic diseases affecting, respectively, the spine, entheses, and peripheral joints. Both are characterized by the release of circulating inflammatory cytokines and metalloproteinases which progressively lead to tissue damage. In CIA these cytokines are induced after the deposition of pathogenic crystals into the articular and periarticular tissues. Finally, the hallmark of OA, which is the most common form of arthropathy, is the progressive degeneration and breakdown of cartilage and underlying bone, often accompanied by low-grade inflammation (He et al., 2020).

All these chronic and debilitating conditions require long-term management and a multidisciplinary approach that combines pharmacological interventions with lifestyle modifications for optimal patient outcomes. Although pharmacologic therapy remains the cornerstone of management, diet is emerging as a crucial support in managing these diseases. Recent studies have shown that certain dietary patterns and specific nutrients can play a significant role in reducing inflammation, alleviating symptoms, and potentially slowing disease progression (Ramonda et al., 2025). Bioactive compounds, which are found in many plant-based foods and are abundant in the Mediterranean diet, are increasingly being recognized as valuable supports to traditional treatments in arthritis (Long et al., 2023; Oliviero et al., 2018).

2. Literature search method

Articles included and discussed in this review were identified using keyword-based searches in multiple scientific databases, including PubMed and Scopus. Keywords encompassed the term “polydatin” associated with the different rheumatic disease including “osteoarthritis”, “rheumatoid arthritis”, “crystal-induced arthritis”, “spondyloarthritis”, “systemic lupus erythematosus”, “rheumatic diseases”. No restrictions were applied regarding publication year, language, or study design, and all relevant articles available up to the date of the search were considered. The selection of articles aimed at providing a comprehensive overview of current evidence, rather than following a formal systematic review or meta-analytic protocol. Therefore, a formal quantitative quality assessment or standardized data extraction protocol was not employed.

3. Bioactive compounds with a role in arthritis

A huge variety of bioactive compounds have been studied in *in vitro* and *in vivo* models of inflammation and arthritis, primarily for their effect in the modulation of inflammatory pathways. The ability of specific polyphenols like curcumin, quercetin, catechins and resveratrol, to target the fundamental processes of inflammation and oxidative stress makes polyphenols promising natural agents as a complementary therapy for managing the pain, stiffness, and joint damage associated with arthritis. This paragraph provides a brief overview of the role of these compounds in arthritis.

Curcumin, the main active ingredient in turmeric, is one of the most widely studied polyphenols in the context of arthritis. Its anti-inflammatory properties are attributed to its ability to block key inflammatory pathways, such as the COX-2 pathway, the NF-κB inflammatory pathways and inflammasomes (Buhrmann et al., 2021; Pandey et al., 2025; Wang et al., 2019). Studies have shown that curcumin may be effective in reducing pain and improving functional assessment indices in patients with OA, as well as decreasing the use of pain-relieving medication (Lopresti et al., 2021). In a randomized, double-blind, placebo-controlled trial involving a small group of patients with RA, curcumin, administered for 90 days, has been shown to reduce inflammatory (ESR, CRP) and clinical indices, including the visual analog scale for pain, rheumatoid factor values, disease activity score 28, and American College of Rheumatology responses (Amalraj

et al., 2017).

Quercetin, a flavonoid found in many fruits, vegetables, and teas, has shown strong antioxidant and anti-inflammatory effects. Its mechanism of action relies in the inhibition of the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, and by suppressing the activation of transcription factors like NF-κB. Research, including some human clinical trials, has shown that quercetin supplementation can significantly improve clinical symptoms, reduce morning pain, and decrease disease activity in women with RA (Javadi et al., 2017). It also appears to have a protective effect against cartilage degradation (Kanzaki et al., 2012).

Epigallocatechin-3-Gallate (EGCG), the most abundant and well-known catechin found in green tea, is a potent antioxidant and anti-inflammatory compound. Studies suggest that EGCG may help reduce inflammation and cartilage degradation in experimental models of arthritis (Wang et al., 2025; Zhu et al., 2022). Its beneficial effects are thought to be mediated by the inhibition of inflammatory enzymes and the regulation of signaling pathways involved in joint destruction and new bone formation, including the nuclear factor erythroid 2-related factor 2 (Nrf2) and the Wnt/β-Catenin/COX-2 pathway (Oliviero et al., 2013; Wang et al., 2025; Zhang et al., 2021).

Resveratrol, found in grapes and berries, is a stilbene polyphenol with notable anti-inflammatory and antioxidant properties. In various preclinical and animal models of arthritis, resveratrol has been shown to have joint-protective effects. Its mechanisms include inhibiting the production of pro-inflammatory cytokines, protecting chondrocytes (Zhou et al., 2021), and suppressing synovial cell proliferation (Li et al., 2021), which is a hallmark of RA. Preliminary clinical evidence also suggests it may help reduce disease activity scores and improve quality of life for RA patients (Khojah et al., 2018). In OA, oral supplementation with resveratrol showed to reduce frailty, pain during walking, and the WOMAC score, and to increase the key regulator SIRT-1 (Karim, Khan, Ahmad, & Qaisar, 2025). The natural precursor of resveratrol, polydatin (PD), has gained increased attention for its diverse and superior benefits and will be the focus of the following paragraphs.

4. Polydatin

Polydatin, also known as piceid, is a natural stilbenoid polyphenol and a monocrystalline compound found in various plant species. The rhizomes and roots of Polygonum cuspidatum (Japanese knotweed) serve as the principal source of PD, a species long utilized in traditional medicine for managing inflammation, infections, jaundice, skin burns, and hyperlipemia (Karami et al., 2022). Beyond knotweed, PD is also present in other plant families such as Vitaceae, Liliaceae, and Leguminosae, and can be found in red wine (Potdar et al., 2018), nuts (Tang & Tan, 2019), vegetables, fruits, hop cones or pellets, and cocoa- and chocolate-based products (Bashmil et al., 2025; Binke et al., 2025; Chen, 2004; Du et al., 2013; Hurst et al., 2008; Tang et al., 2022; Wang, 2017; Wang et al., 2020; Zhao et al., 2010; Zhou et al., 2005) (Table 1). Owing to its broad distribution and diverse sources, PD has gained attention in scientific research due to its potential health benefits, which include antioxidant properties, anti-inflammatory effects, cardiovascular protection, neuroprotective, antiangiogenetic, and anti-cancer properties (Karami et al., 2022).

PD is a glycosylated derivative of resveratrol, chemically it's a stilbenoid with a glucose molecule (glucopyranoside) linked to the hydroxyl group at the 3-position of the first benzene ring. Furthermore, PD demonstrates superior antioxidant (Şöhretoğlu et al., 2018) and anti-inflammatory (Lanzilli et al., 2012) properties compared to those of resveratrol. Various techniques have been established for isolating resveratrol from its isomers in *P. cuspidatum*, including reflux extraction, filtration, hydrolysis, liquid-liquid extraction, elution, and high-performance liquid chromatography coupled with a UV-visible diode array detector (Romero-Pérez et al., 2001; Wang et al., 2013).

PD exists in four structural derivatives, trans-polydatin, trans-resveratrol, cis-polydatin, and cis-resveratrol, of which the trans-isomers exhibit significantly higher bioactivity and stability than their cis counterparts. Trans-polydatin, itself, can be biosynthesized from 4-coumaroyl-CoA via a stilbene synthase–catalyzed reaction (Du et al., 2013; Mikulski & Molski, 2010) (Fig. 1).

Owing to the presence of three hydroxyl phenolic groups, PD readily interacts with reactive oxygen species (ROS) and acts as a potent antioxidant. These hydroxyl groups can donate hydrogen atoms to neutralize free radicals, forming resonance-stabilized phenoxyl radicals that prevent oxidative chain reactions. In addition, the glucosidic moiety enhances the compound's stability and aqueous solubility, contributing to a more sustained antioxidant effect compared to resveratrol (Aboul-Enein et al., 2007; Fabris et al., 2008; Rudrapal et al., 2022). Beyond its radical-scavenging activity, the structural configuration of PD also contributes to other biological effects, likely mediated by its polyphenolic framework and glucosidic linkage, which enable hydrogen bonding and hydrophobic interactions with key molecular targets (Cerezo et al., 2015; Perez-Moral et al., 2019). Recent studies suggest that PD may interact with VEGF, as indicated by HerboChip screening and supported by HPLC, ultrafiltration, and Biacore assays and functional studies in endothelial cells. Molecular docking further predicted favorable binding at the VEGF receptor-binding domain (−6.9 to −6.5 kcal/mol) consistent with a mechanistic hypothesis of direct interaction, which could potentially inhibit VEGF–VEGFR2 signaling and suppress VEGF-induced endothelial cell proliferation, contributing to anti-angiogenic effects (Hu et al., 2019). While these findings support a mechanistic hypothesis of direct PD–VEGF interaction, further validation using structural biology approaches, such as X-ray crystallography or NMR, and functional biomarker studies in cellular or clinical settings

Table 1
Content of polydatin (trans-piceid) in various food sources.

Food Source	Polydatin (trans-Piceid) Concentration (μg/g)	Notes
Polygonum cuspidatum	14430	Highest concentration, often used for extraction The concentration of polydatin varies by plant part, with roots and rhizomes containing the highest levels [29,30]
Mulberry	39.7 - 133.8	[30, 31]
Grape peel	11.2 - 11.7	Grapes, red wine, and berries are general sources [30, 32]
Polygoni Multiflori (Tuber Fleeceflower)	33.7	[30, 33]
Banana Flour	6.6 ± 0.3 3.2 ± 0.2 2.6 ± 1.2	15 % Cavendish [34] 15 % Ladyfinger [34] 10 % Ducasse [34]
Peanuts	0.22 - 1.44	Nuts are a general source *[30, 35]*
Soybeans	Mentioned as a source	Specific concentration data is variable and not readily quantified in standard literature *[36]*
Hop Flowers (*Humulus lupulus*)	Mentioned as a source	Specific concentration data is variable and not readily quantified in standard literature *[30]*
Cocoa Powder	7.14 ± 0.80	Highest concentration among cocoa products *[37]*
Unsweetened Baking Chocolate	4.04 ± 0.14	*[37]*
Semisweet Chocolate Baking Chips	2.01 ± 0.18	*[37]*
Dark Chocolate	1.82 ± 0.36	Concentration is highly dependent on cocoa content *[37]*
Milk Chocolate	0.44 ± 0.06	Significantly lower due to lower cocoa solid content *[37]*
Chocolate Syrups	0.35 ± 0.06	Lowest concentration *[37]*

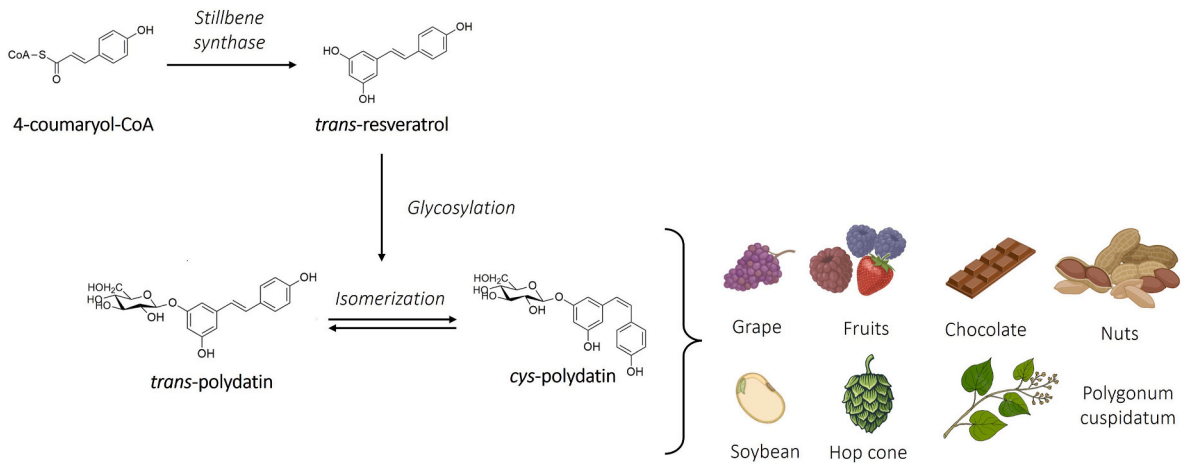

Fig. 1. Structural derivatives of polydatin.

is warranted to substantiate the interaction and confirm its physiological relevance.

In addition, *in silico* studies have demonstrated that PD can effectively bind to the active sites of human Sirtuins (SIRT1 - SIRT7), forming multiple stabilizing interactions, including hydrogen bonds and hydrophobic contacts with key residues. Molecular docking analyses indicate that PD exhibits higher binding affinity than resveratrol and comparable or superior affinity to curcumin, particularly toward mitochondrial SIRT-3 and SIRT-5. Molecular dynamics simulations further support the stability of these interactions, highlighting consistent hydrogen bonding, hydrophobic contacts, and water-mediated bridges between PD and Sirtuin residues. These findings suggest that PD may modulate SIRT-dependent pathways, potentially enhancing mitochondrial function, regulating cellular stress responses, and maintaining metabolic homeostasis. By influencing these pathways, PD could contribute to its reported anti-inflammatory and cytoprotective effects (Ferrari et al., 2023).

However, it is important to note that these findings are based entirely on *in silico* modeling. Experimental validation, including *in vitro* enzymatic assays, cell-based studies, and eventually clinical biomarker investigations, is essential to confirm whether PD truly engages Sirtuins in a biologically meaningful manner and to determine the functional consequences of such interactions.

Thus, the combination of polyphenolic hydroxyl groups and the glucosidic moiety not only contributes to PD's antioxidant and stabilizing properties but also enables its multi-target interactions, including potential modulation of VEGF and Sirtuin pathways, thereby linking its chemical structure directly to its diverse pharmacological effects.

4.1. Bioavailability, absorption and metabolism

The glycosylation of PD, through the attachment of a glucose moiety, enhances its water solubility and chemical stability, providing distinct pharmacokinetic advantages over the aglycone resveratrol. Resveratrol is characterized by high intestinal absorption but very low systemic bioavailability (<1%) due to extensive first-pass metabolism involving glucuronidation and sulfation in the intestinal mucosa and liver (Walle, 2011).

Unlike resveratrol, which crosses cell membranes mainly by passive diffusion, the glucose residue of PD allows also for active transport via sodium-dependent glucose transporter (SGLT1), primarily present in the stomach and intestines (Henry et al., 2005).

After absorption, PD can undergo enzymatic deglycosylation through two different mechanisms, which allow the release of free resveratrol within intestinal cells or into the systemic circulation. The first involves cytosolic β-glucosidases which cleaves the molecule after it crosses the brush-border membrane via SGLT1. The second pathway takes place on the luminal side of the epithelium, where the membrane-bound enzyme lactase–phlorizin hydrolase removes the glucose residue, allowing the released aglycone to passively diffuse into the cell, where it undergoes further metabolism (Henry-Vitrac et al., 2006).

Pharmacokinetic and biodistribution studies reveal that, following either oral or intravenous administration, PD reaches high concentrations in the kidney, liver, lung, and heart, with peak tissue levels typically achieved within 10 min post-dose. This rapid distribution pattern suggests efficient systemic diffusion and a strong affinity for metabolically active and excretory organs (Du et al., 2013).

Both PD and its aglycone metabolite are subject to hepatic glucuronidation and sulfation, which rapidly converts the active compounds into inactive glucuronide conjugates. These conjugates are then quickly eliminated from the body via renal excretion, significantly reducing the systemic concentration and thus the bioavailability of PD. However, PD exhibits a longer half-life and a higher maximal plasma concentration than resveratrol when administered at equivalent doses (Du et al., 2013).

Collectively, these pharmacokinetic properties confer on PD enhanced bioavailability and systemic exposure compared with resveratrol, supporting its potential as a more pharmacologically stable and therapeutically effective form of this polyphenol in models of oxidative stress, inflammation, and metabolic disorders (Du et al., 2013).

Recent advances in pharmaceutical nanotechnology have led to the development of multiple delivery systems aimed at overcoming the pharmacokinetic limitations of PD, including liposomes, micelles, and polymeric or inorganic nanoparticles. However, these approaches differ substantially in their impact on PD bioavailability and systemic exposure. Liposomal formulations have been shown to significantly enhance the oral bioavailability of PD, likely due to high encapsulation efficiency and prolonged circulation time (Wang et al., 2015). In contrast, micellar systems have been primarily designed to achieve tissue-specific delivery rather than to increase systemic bioavailability; ROS- and pH-responsive PD-loaded micelles demonstrated marked therapeutic efficacy in liver fibrosis models through targeted release, despite the lack of direct pharmacokinetic evidence for increased plasma exposure (Lin et al., 2020). Similarly, polymeric nanocapsules have been shown to preserve the anti-inflammatory and antioxidant properties of PD in ex vivo models, although their effects on *in vivo* bioavailability remain to be established (Basta-Kaim et al., 2019). Chitosan-based PD nanoparticles exhibited superior therapeutic efficacy compared with free PD in diabetic liver injury, an effect attributed to improved absorption and prolonged release, albeit without direct quantitative assessment of systemic bioavailability (Abd El-Hameed et al., 2021). Notably, not all nanoparticle-based strategies are beneficial, as inorganic quantum dot

heterojunctions were reported to increase PD binding to plasma proteins, thereby reducing the free circulating fraction and potentially attenuating its pharmacological activity (Xiao et al., 2011). Collectively, these findings highlight that the enhancement of PD bioavailability is highly dependent on the delivery platform, with substantial variability across systems and a critical distinction between improved systemic exposure and targeted tissue accumulation.

4.2. Safety, tolerability, and potential drug–nutrient interactions of polydatin

Clinical studies indicate that PD, alone or in combination with palmitoylethanolamide (PEA), is generally well tolerated and exhibits a favorable safety profile across diverse patient populations. In trials evaluating chronic pelvic pain associated with endometriosis, administration of PEA/polydatin (400/40 mg twice daily for 80-90 days) significantly improved pain, dysmenorrhea, dyspareunia, and quality of life without reported adverse events (Indraccolo et al., 2017; Loi et al., 2019; Soave et al., 2013). Similarly, in patients with irritable bowel syndrome, PEA/polydatin supplementation (200/20 mg twice daily for 12 weeks) reduced abdominal pain severity and modulated cannabinoid receptor expression, again with no significant side effects observed (Cremon et al., 2017).

PD has also been evaluated in the context of liver disease, cardiovascular disorders, and oxidative stress. In alcoholic patients, oral administration of PD-containing nutritional supplements reduced liver enzymes and lipid peroxidation while improving cognitive performance, with no adverse events reported (Pace et al., 2015). Moreover, clinical evaluation in elderly patients with coronary heart disease showed that PD significantly improved treatment outcomes (Zhang & Li, 2018). PD injections have also entered phase II clinical trials for cardiovascular and cerebrovascular disorders (Zeng et al., 2015). Topical PD formulations (0.8-1.5%) were well tolerated in patients receiving EGFR inhibitors, reducing the incidence and severity of cutaneous adverse effects without causing systemic toxicity (Bavetta et al., 2021; Fuggetta et al., 2019).

Preclinical toxicology studies support these clinical observations. PD exhibits low acute and subchronic toxicity in animals, with an LD50 of approximately 1000 ± 57.3 mg/kg intraperitoneally (Tang et al., 2022) and is well tolerated up to 200 mg/kg. At very high intraperitoneal doses (50-700 mg/kg for 42 days), adverse effects such as peritonitis, mild liver cell necrosis, and bone marrow fat hyperplasia were observed (Zong et al., 2002). Oral administration at maximal gavage concentrations showed 100% survival in mice, with a maximum tolerable dose of 75.5 g/kg/day (Tang et al., 2022). Additionally, the IC50 for human normal liver cells (L02) is 263.05 μg/mL, indicating low cytotoxicity at physiologically relevant concentrations. Safety evaluation after intravenous injection for 30 days in humans confirmed no significant toxic effects (Li et al., 2015).

Although these studies demonstrate a high tolerability of PD, its pharmacokinetic properties, such as hepatic glucuronidation and sulfation, suggest potential interactions with drugs metabolized via the same pathways. To date, no clinically relevant drug-drug interactions involving PD have been reported. In patients with rheumatological conditions, who often require chronic administration of immunosuppressants, corticosteroids, or nonsteroidal anti-inflammatory drugs, careful monitoring is advisable, as co-administration could theoretically alter drug exposure or efficacy. Furthermore, PD's modulation of antioxidant and signaling pathways raises the possibility of interactions with nutrient supplements commonly used by these patients, such as vitamins C and E, selenium, or glutathione precursors, which may synergistically enhance its antioxidant effects (Biswas et al., 2020).

Overall, preclinical and clinical evidence supports PD as a safe and well-tolerated compound suitable for long-term administration, with a wide therapeutic window and minimal toxicity. Its favorable safety profile, together with the low incidence of adverse events, suggests potential for chronic use in patients with rheumatological conditions, provided that drug-drug and drug-nutrient interactions are carefully monitored.

5. Polydatin in rheumatological diseases

Building upon its favorable pharmacokinetic profile and established anti-inflammatory, anti-angiogenic and antioxidant properties, the therapeutic potential of PD has been explored in a variety of rheumatological diseases (Table 2). Although conditions such as RA, OA, SpA, and SLE differ substantially in their clinical presentation, they often share common pathological drivers, including chronic inflammation, oxidative stress, and immune dysregulation. The following sections will

Table 2
Polydatin's primary mechanism of action in rheumatic diseases.

Disease	Mechanism of action	Observed effects	References
Rheumatoid Arthritis	1. Anti-oxidative effects 2. Anti-inflammatory effects 3. Inhibition of NETosis	1. ↓ Oxidative stress markers. 2. ↓ Pro-inflammatory cytokines ↓ IL-6/STAT-3/IL-17/NF-κB signaling Regulated expression of MMP-9/3 ↓ VEGF 3. ↓ NET formation.	[47 - 50]
Osteoarthritis	1. Chondroprotective effects 2. Anti-inflammatory effects 3. Inhibition of autophagy 4. Bone/immune balance	1. ↓ Inflammatory cascade in chondrocytes ↑ Promoted anabolism ↓ Inhibited catabolism 2. ↓ Pro-inflammatory mediators 3. ↑ Autophagy flux Regulated (AMPK/mTOR) 4. Maintained bone metabolic balance ↓ Polarization of macrophages (M1) ↓ NF-κB signaling pathway	[51 - 55]
Crystal-Induced Arthritis	1. Inhibition of inflammation 2. Inhibition of inflammasome	1. ↓ Ankle swelling, synovitis ↓ Leukocyte infiltration (CXCL1) 2. ↓ ROS and NO ↓ NLRP3 inflammasome (IL-1β) ↓ Ferritin activation ↑ PPAR-γ pathway. 3. ↓ Hyperuricemia	[56 - 62]
Spondyloarthritis	Regulation of cell proliferation apoptosis, and autophagy in fibroblasts	↓ Fibroblast proliferation ↑ Fibroblast apoptosis ↑ Autophagy	[63]
Systemic Lupus Erythematosus	Blocking ROS-mediated NET formation	↓ NET formation ↓ Blocked ROS production ↓ Decreased proteinuria ↓ Serum autoantibodies (anti-dsDNA,-Sm) ↓ Austin scores ↓ IgG and NET deposition in the kidneys	[64 - 66]

summarize the preclinical evidence detailing the specific mechanisms by which PD exerts its effects in models of RA, OA, CIA, SpA, and SLE.

5.1. Polydatin in rheumatoid arthritis (RA)

Polydatin has demonstrated significant therapeutic potential in preclinical models of RA through a multi-faceted mechanism of action (Fig. 2). In a collagen-induced arthritis mouse model, treatment with 30 or 45 mg/kg PD markedly inhibited the clinical arthritis score and hind-paw thickness in mice. PD was shown to effectively mitigate disease symptoms by leveraging its anti-oxidative and anti-inflammatory properties, specifically by reducing levels of oxidative stress markers such as malondialdehyde and superoxide dismutase, pro-inflammatory cytokines such as TNF-α and IL-1β, and by regulating the expression of matrix metalloproteinase-9 (MMP-9) (Li et al., 2016). A separate study utilizing a complete Freund's adjuvant (CFA)-induced arthritis rat model further elucidated its anti-arthritic effects, showing that administration of 200 mg/kg PD for 21 days attenuates joint damage by modulating the critical IL-6/STAT-3/IL-17/NF-κB signaling cascade (Kamel et al., 2018). Specifically, PD reduced the levels of pro-inflammatory cytokines in paw homogenates, including TNF-α, IL-6, IL-17, and matrix metalloproteinase-3 (MMP-3), the gene expression of STAT3 and RANKL, and hindered the immunohistochemical staining of vascular endothelial growth factor (VEGF), a crucial mediator responsible for microvasculature changes, and nuclear factor-κB (NF-κB) that is fundamental in regulating immuno-inflammatory response (Kamel et al., 2018).

Moreover, research has also revealed a mechanism involving the inhibition of neutrophil extracellular trap (NET) formation (NETosis) (Yang et al., 2019). NETosis has been found to contribute to the inflammatory and autoimmune responses characteristic of RA. In both *in vitro* experiments with human and murine neutrophils and *in vivo* in the collagen-induced arthritis mouse model, PD was shown to suppress NET formation, thereby delaying the onset and reducing the severity of arthritis (Yang et al., 2019).

Notably, the inhibitory effect on NETosis observed for PD does not appear to be unique to this compound, but rather reflects a broader class effect shared by polyphenolic and phytochemical antioxidants. Accumulating evidence demonstrates that several plant-derived bioactive compounds, including polyphenols such as resveratrol, catechin, quercetin and curcumin, are capable of modulating NET formation, release, and stability through convergent mechanisms (Askarizadeh et al., 2025; Liu et al., 2024). These mechanisms include attenuation of reactive oxygen species production, inhibition of key signaling pathways involved in neutrophil activation, such as NF-κB, PI3K, MAPK, and P2X7R-dependent signaling, and downregulation of NET-associated enzymes, including myeloperoxidase and neutrophil elastase (De Souza Andrade et al., 2022; Liu et al., 2024; Muñoz-Sánchez et al., 2023). *In vitro* studies have shown that resveratrol and catechin, as well as their conformationally constrained analogues, suppress NET formation in a dose-dependent manner by inhibiting DNA and MPO release from activated neutrophils, highlighting a structure–activity relationship underlying their anti-NET effects (Ohinata et al., 2024). Moreover, quercetin has been demonstrated to mitigate oxidized lipid–induced NETosis by inhibiting the P2X7R/p38MAPK/NOX2 signaling axis, further supporting the concept that polyphenols interfere with shared upstream pathways driving pathological NET formation (Liu et al., 2024). By restoring redox homeostasis and limiting excessive neutrophil activation, these phytochemicals impair chromatin decondensation and extracellular trap release, thereby reducing NET-driven tissue damage across multiple inflammatory and autoimmune disease models (De Souza Andrade et al., 2022; Muñoz-Sánchez et al., 2023). In this context, PD-mediated NETosis inhibition in rheumatoid arthritis aligns with a well-established antioxidant-driven framework, while its efficacy demonstrated specifically in experimental arthritis models underscores its translational relevance for RA.

Recently, Su et al. developed a novel multifunctional nanodrug system, HA-M@PB@Ag@PD NPs, designed for the treatment of RA. This system integrates PD and chitosan-silver (Chi-Ag) onto Prussian blue nanoparticles (PB NPs), with a hybrid membrane (M) and hyaluronic acid (HA) to improve targeting and circulation. Within this system, PD plays a central role in modulating the inflammatory microenvironment. *In vitro* studies demonstrated that PD effectively scavenges reactive oxygen species (ROS), promotes the repolarization of inflammatory macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, and reduces the production of pro-inflammatory cytokines. Meanwhile, Chi-Ag induces apoptosis in RA fibroblast-like synoviocytes (RA-FLS), further contributing to anti-arthritic effects. *In vivo* experiments using a rat model of RA showed that HA-M@PB@Ag@PD NPs significantly accumulated in arthritic joints and exhibited prolonged circulation time. The treatment led to marked suppression of joint inflammation, inhibition of synovial hyperplasia, and protection of cartilage and bone from destruction. Importantly, PD's activity in clearing ROS and promoting macrophage repolarization contributed to the restoration of the synovial microenvironment, reducing the number of RA-FLS and inflammatory macrophages in the affected joints (Zhaoli et al., 2024).

Collectively, these findings highlight polydatin's capacity to act on multiple inflammatory pathways and cellular processes, positioning it as a promising natural compound for the management of arthritis.

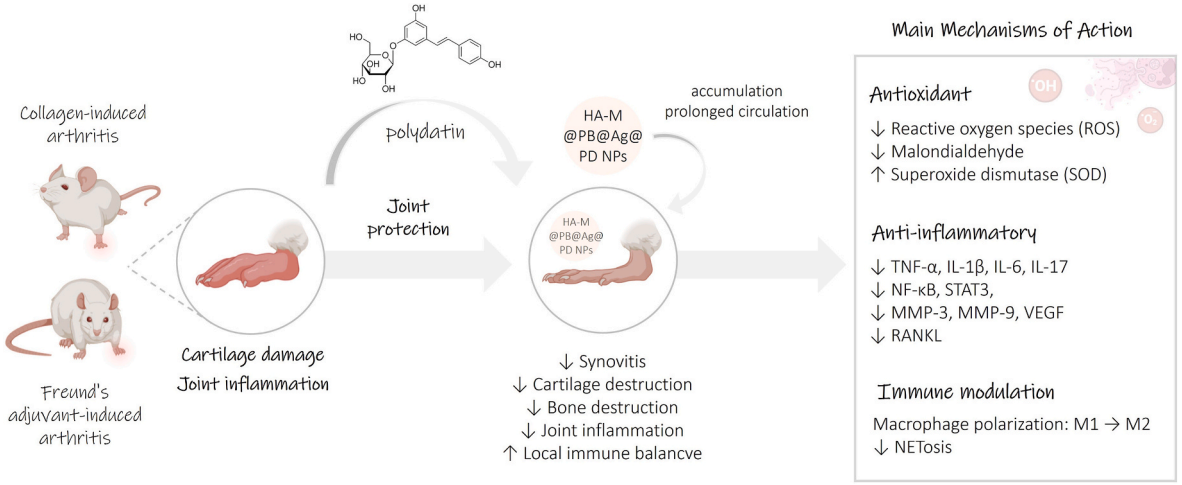

Fig. 2. Polydatin's therapeutic effects in rheumatoid arthritis.

5.2. Polydatin in osteoarthritis (OA)

As previously discussed, OA is the most prevalent joint disease worldwide. It is characterized by a subclinical inflammatory process leading to a deteriorative structural change in the cartilage, pain, loss of joint function, and disability. OA pathogenesis have been related to different molecular mechanisms eventually responsible of different phenotypes (e.g. post-traumatic vs. age-related vs. metabolic). Although PD's effects have not been specifically considered according to these phenotypes, the studies collectively establish PD as a potent chondroprotective and anti-osteoarthritic agent through distinct yet synergistic molecular mechanisms involving inflammation, autophagy, and bone/immune modulation (Fig. 3).

Post-traumatic OA is the most extensively studied phenotype in preclinical models. Using the cruciate ligament transection (ACLT) model, PD showed to effectively mitigate the severity and progression of OA after intra-articular administration in rats (Hu et al., 2022). PD significantly reversed the pathological changes associated with OA, such as reduced cartilage thickness, calcification, and destruction of superficial cartilage by regulating Wnt/β-catenin signaling. In this study rat chondrocytes were obtained to assess the effect of PD on the levels of inflammation-related mediators. PD showed to significantly suppresses the inflammatory cascade in IL-1β-stimulated chondrocytes through the downregulation of major pro-inflammatory mediators, including nitric oxide, prostaglandin E2, iNOS, COX-2, TNF-α, and IL-6. Furthermore, it exhibited a protective effect on the extracellular matrix balance, promoting anabolism by upregulating aggrecan and collagen II expression, while simultaneously inhibiting catabolism by downregulating the matrix-degrading enzymes.

A role of PD in modulating cellular homeostasis through the restoration of autophagy has been elucidated using the same post-traumatic OA model (Ye et al., 2024). The results showed that PD protects chondrocytes from degeneration by regulating the AMPK/mTOR signaling axis. In particular, PD has demonstrated to enhance cell viability, reduce the rate of apoptosis and promote autophagy flux. These findings, along with the inhibitory effect on chondrocyte apoptosis, suggest a protective role for PD in the age-related OA phenotype which is primarily driven by cellular senescence and accumulated oxidative stress.

A third study introduced a broader perspective showing that PD effectively delays the progression of OA in the ACLT mouse model, not only by limiting cartilage degradation and apoptosis but also by impacting the underlying bone and synovium (Sun et al., 2025). Specifically, PD was shown to maintain subchondral bone metabolic balance, suggesting a critical regulatory role in preventing pathological changes in the bone structure that contribute to joint failure. Furthermore, the study identified PD as a modulator of the local immune environment, demonstrating its ability to inhibit the polarization of macrophages towards the pro-inflammatory M1 phenotype. This anti-inflammatory shift is crucial, as M1 macrophages perpetuate synovitis and drive cartilage catabolism. Consistent with the study by Linyong Hu et al. (Hu et al., 2022), the mechanism for the anti-inflammatory and macrophage-regulating effects was attributed to the marked suppression of the NF-κB signaling pathway, positioning it as a central therapeutic target for PD.

A recent study further expanded the understanding of PD's anti-osteoarthritic activity by employing a high-content screening approach to identify bioactive polyphenols targeting chondrocyte inflammation. Using an IL-1β-stimulated primary chondrocyte model, the authors demonstrated that PD potently downregulated MMP-13 expression while promoting type II collagen synthesis, confirming its dual anabolic and anti-catabolic actions. RNA sequencing analyses revealed that PD's efficacy was partly mediated through inhibition of the Wnt signaling pathway, along with enrichment of IL-17 and peroxisome pathways, suggesting coordinated anti-inflammatory and antioxidative effects. In destabilization of the medial meniscus (DMM) and monosodium iodoacetate (MIA) mouse models, PD administration significantly reduced cartilage degradation, osteophyte formation, and synovial inflammation, without inducing systemic toxicity. Mechanistically, the study identified a novel mitochondria-centered pathway, showing that PD enhanced mitochondrial membrane potential and upregulated SIRT3 and SOD2 expression, thereby reducing mitochondrial reactive oxygen species (mtROS) production. This SIRT3/SOD2 axis was proposed as a key mediator of PD's antioxidant and chondroprotective effects, aligning with prior evidence linking PD to mitochondrial homeostasis in other tissues (Mao et al., 2025).

Earlier evidence also highlighted the pivotal role of the Nrf2 signaling pathway in mediating the protective effects of PD in osteoarthritis. In IL-1β-induced human osteoarthritic chondrocytes, PD markedly suppressed the production of major inflammatory mediators, including PGE_2, TNF-α, NO, COX-2, iNOS, and IL-6, and inhibited the

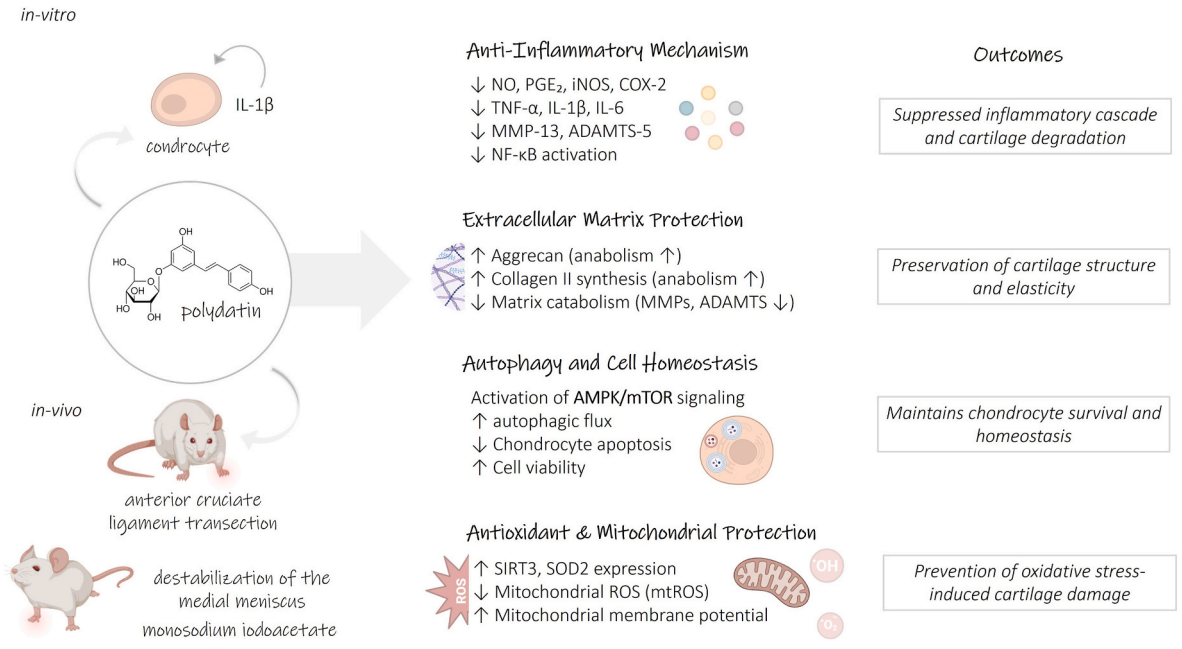

Fig. 3. Polydatin's protective actions in osteoarthritis.

expression of matrix-degrading enzymes such as MMP-13 and ADAMTS-5, thereby preserving the integrity of the extracellular matrix. The silencing of Nrf2 through siRNA completely abolished these anti-inflammatory and chondroprotective effects, confirming Nrf2 as a key molecular target of PD. Consistently, in DMM mouse model of OA, PD administration attenuated cartilage degeneration and mitigated joint inflammation, further substantiating its dual antioxidant and chondroprotective activity. Collectively, these findings position PD as a promising therapeutic agent capable of counteracting oxidative stress-driven cartilage degradation through Nrf2-dependent signaling (Tang et al., 2018).

5.3. Polydatin in crystal-induced arthritis

Crystal-induced arthritis is characterized by the deposition of monosodium urate (MSU) and calcium pyrophosphate (CPP) crystals in articular and periarticular tissues, leading to an intense inflammatory response. While hyperuricemia is a necessary condition to cause MSU precipitation and gout, CPP crystals may be found in different calcium crystal related arthropathies, and their formation is associated to a dysregulation of inorganic pyrophosphate homeostasis (Oliviero et al., 2012). *In vitro* models of MSU and CPP crystal-induced inflammation are widely used to investigate the beneficial effect of bioactive compounds towards the NLRP3/caspase-1/IL-1β axis. In one of this study both resveratrol and PD have shown to be effective in inhibiting crystal-induced inflammation by reducing the production of IL-1β, reactive oxygen species (ROS) and nitric oxide (NO). Of interest, these polyphenols almost completely abolished the inflammatory response after a pretreatment thus suggesting a preventive anti-inflammatory effect (Oliviero et al., 2019). This prophylactic benefit has been confirmed using a mouse model of local acute inflammation obtained through the intra-articular injection of CPP crystals (0.3 mg/20 μL) (Oliviero et al., 2021). In this case the oral pre-treatment with PD administered at 40 mg/kg significantly diminished ankle swelling after 48 h from crystal injection. Histological findings showed a decrease in leukocyte infiltration, necrosis, edema, and synovitis along with the reduction in IL-1β and CXCL1 tissue expression.

A recent study further elucidated the molecular mechanisms underlying the protective effects of PD in CPP crystal-induced arthritis. In this model, as reported in the previous study, prophylactic administration of PD prevented ankle swelling, leukocyte infiltration, edema, and synovitis, thereby preserving both articular and muscular structures, with an efficacy comparable to that of colchicine. In addition, histological analysis confirmed a reduction in inflammatory damage to joint and muscle tissues, along with the preservation of muscle strength.

Mechanistically, a protein array performed on joint tissues revealed that PD modulates pathways involved in leukocyte migration, angiogenesis, and inflammation, including the downregulation of VCAM-1, L-selectin, and BLC. *In vitro* experiments using CPP-stimulated human monocytes demonstrated that PD significantly reduced the release of key inflammatory mediators (IL-1β, IL-18, IL-6, TNF-α), chemokines (CCL-23, IL-8), and VEGF, indicating a strong suppression of both cytokine and angiogenic signaling.

Of particular relevance, PD's anti-inflammatory effects were associated with SIRT1 activation, as pharmacological inhibition of SIRT1 completely reversed its protective actions. Furthermore, PD reduced leukocyte chemotaxis toward synovial fluids from CPP arthritis patients, suggesting a role in limiting immune cell recruitment to inflamed tissues. The study also identified CCL-23/CCR1 signaling as a novel pathway involved in CPP-induced inflammation: PD and the CCR1 antagonist J-113863 each attenuated the production of inflammatory mediators and PBMC migration, with a synergistic effect when combined. Altogether, these findings establish that PD mitigates CPP crystal-induced inflammation through multitargeted mechanisms, including SIRT1 activation, CCR1 inhibition, and suppression of leukocyte migration, chemokine release, and VEGF-driven angiogenesis, reinforcing its potential as a preventive therapeutic strategy in acute pseudogout flares (Baggio et al., 2025).

A similar study using MSU crystals (0.2 mg/25 μL) in mice, showed that PD administered at 25-100 mg/kg according to a therapeutic protocol (i.e. after crystal injection) reduced ankle swelling, improved abnormal gait, and mitigated joint damage in a dose-dependent manner (Hu et al., 2022). These effects were mediated by the activation of the PPAR-γ pathway, the suppression of the NLRP3 inflammasome and ferritin activation (Du et al., 2023).

Pertaining gout, PD also showed a protective effect against gouty nephropathy in mice (Shi et al., 2023). It significantly ameliorated pathological changes in kidney tissue. It has been demonstrated that this nephroprotective action is linked to the inhibition of renal tubular cell pyroptosis, a type of programmed cell death. PD was shown to downregulate the expression of key proteins in this process, including NLRP3, caspase-1, and gasdermin D.

PD, along with resveratrol and other stilbenes, demonstrated antihyperuricemic activities in mice (Shi et al., 2012). Their therapeutic effects have been shown to be mediated by the regulation of renal organic ion transporters (Fig. 4).

5.4. Polydatin in spondyloarthritis

SpA encompasses different chronic inflammatory diseases that primarily affect the spine and peripheral joints, often involving the entheses. This heterogeneous group of disorders, which includes ankylosing spondylitis (AS) and psoriatic arthritis (PsA), shares clinical, genetic, and pathogenic features. AS, in particular is characterized by an aberrant and excessive proliferation of fibroblasts, particularly those residing in the synovium and entheses, which drives the chronic inflammatory and structural remodeling processes. The potential therapeutic role of PD has been investigated in fibroblasts isolated from AS patients demonstrating that PD significantly suppressed cell proliferation in a concentration- and time-dependent manner without substantially affecting normal human fibroblasts (Ma et al., 2019). Mechanistically, PD was shown to induce apoptosis by modulating key proteins in the intrinsic pathway, specifically by upregulating the pro-apoptotic factors active caspase-3 and Bax, while concurrently decreasing the expression of the anti-apoptotic factor Bcl-2. Furthermore, PD enhanced cellular autophagy, which was confirmed by a significant increase in the expression levels of autophagic markers, as well as by direct evidence of autophagosome formation. The crucial interplay between these two processes was established when co-treatment with an autophagy inhibitor significantly reversed both the polydatin-induced apoptosis and the increase in autophagy markers (Ma et al., 2019). These findings indicate that PD promotes apoptosis and autophagy in AS fibroblasts, suggesting its potential as adjuvant therapeutic agent for AS (Fig. 5).

5.5. Polydatin in systemic lupus erythematosus (SLE)

The beneficial effect of resveratrol was observed in lupus mice models by attenuating proteinuria, serum autoantibodies, glomerulonephritis and affecting T and B cell proliferation (Jhou et al., 2017; Wang et al., 2014).

To date, there's only one study investigating the therapeutic potential of PD in SLE, providing mechanistic insight into its immunomodulatory effects (Fig. 6) (Liao et al., 2018). The research focused on the compound's effect on neutrophil extracellular trap (NET) formation (NETosis), a process closely implicated in SLE pathogenesis.

NETs represent a major source of autoantigens, promote immune complex formation, activate type I interferon pathways, and contribute directly to renal inflammation and tissue injury. Liao et al. demonstrated that PD markedly inhibited phorbol 12-myristate 13-acetate (PMA)-induced NET formation in neutrophils from both SLE patients and healthy donors by suppressing intracellular ROS generation, without

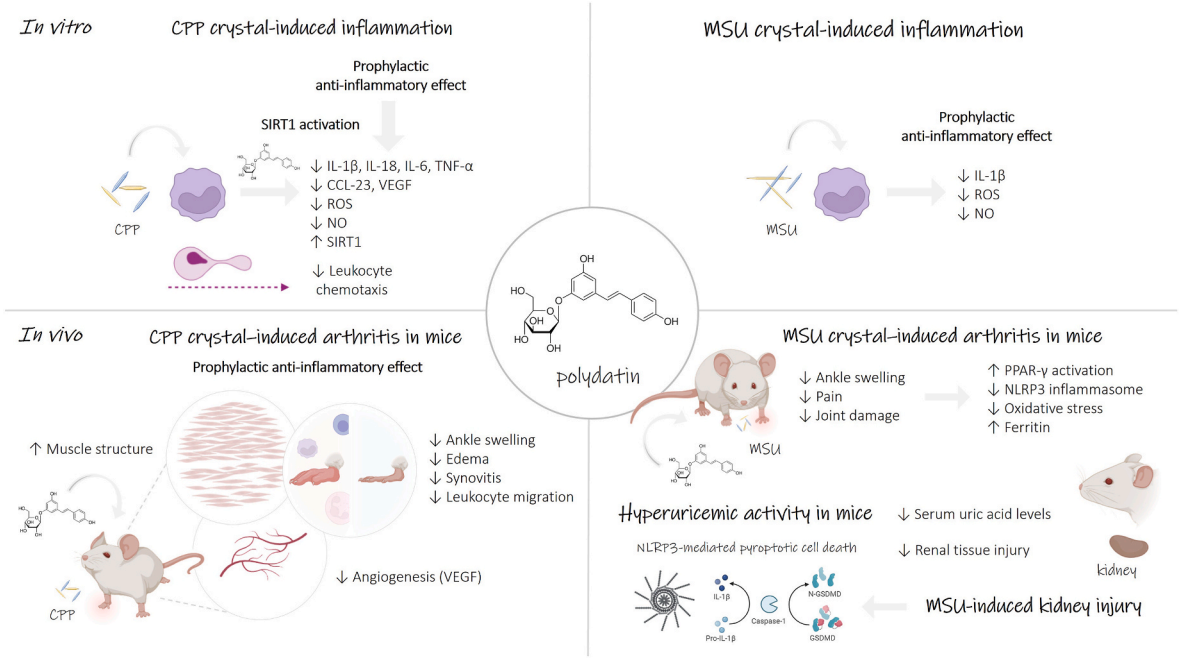

Fig. 4. Polydatin's protective actions in crystal induced arthritis.

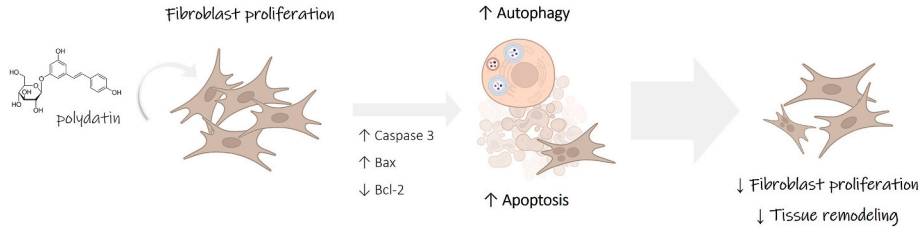

Fig. 5. Polydatin effects on fibroblasts in ankylosing spondylitis.

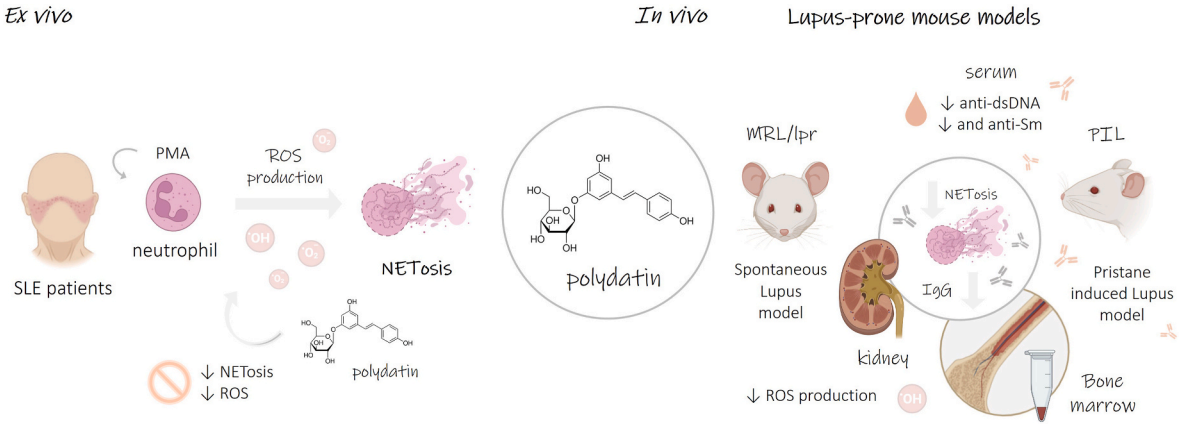

Fig. 6. Polydatin in systemic lupus erythematosus.

affecting neutrophil viability.

In vivo, PD was evaluated in two lupus-prone mouse models: MRL/lpr mice, which spontaneously develop severe lupus-like disease, and pristane-induced lupus (PIL) mice, an environmentally triggered model of SLE. In both models, PD treatment significantly reduced proteinuria, circulating autoantibodies (anti-dsDNA and anti-Sm), renal Austin activity scores, and IgG deposition within glomeruli. Notably, PD treatment markedly decreased NET deposition in renal tissue, indicating effective inhibition of intrarenal NETosis.

In PIL mice, PD treatment ameliorated lupus-like features to a degree comparable to the positive control drugs mycophenolate or cyclophosphamide.

Mechanistically, PD prevented spontaneous NET formation and ROS production by bone marrow–derived neutrophils *in vivo* and reduced neutrophil necrotic cell death, further supporting its role in suppressing NETosis. These effects suggest that PD indirectly modulates autoantibody production and renal injury by limiting the availability of NET-derived autoantigens and immune complex deposition in target organs

(Liao et al., 2018).

Collectively, these findings indicate that PD exerts immunomodulatory effects in SLE primarily through inhibition NETosis, thereby attenuating systemic autoimmunity and lupus nephritis. By targeting a pathogenic mechanism that links innate immune activation, autoantibody generation, and renal involvement, PD emerges as a promising candidate for the modulation of SLE disease activity.

6. Conclusion

Rheumatological diseases share common pathogenic mechanisms, including chronic inflammation, oxidative stress, immune dysregulation, and progressive tissue remodeling, that collectively drive joint damage and systemic complications.

In this context, this review highlights the promising therapeutic potential of PD, a natural polyphenolic derivative of resveratrol, in the treatment of various rheumatological diseases, thanks to its ability to modulate multiple biological pathways involved in disease progression. Owing to its unique chemical structure and favorable pharmacokinetic properties, PD exhibits multiple mechanisms of action, including antioxidant, anti-inflammatory, anti-angiogenic, and immunomodulatory effects. Importantly, the growing body of evidence on PD-based delivery systems indicates that improvements in bioavailability and therapeutic efficacy are highly formulation-dependent. While certain approaches, such as liposomal or polymeric nanoparticle formulations, can enhance systemic exposure or prolong drug release, others primarily favor tissue-specific targeting or merely preserve biological activity without increasing circulating levels. This heterogeneity underscores the need for a rational selection and rigorous pharmacokinetic characterization of PD formulations tailored to the specific rheumatological condition and route of administration.

Numerous preclinical studies have demonstrated polydatin's efficacy in counteracting chronic inflammation, joint damage, and altered bone metabolism in models of RA, OA, CIA, SpA, and SLE. PD appears to modulate multiple molecular and cellular pathways that regulate inflammation, oxidative stress, angiogenesis, apoptosis, autophagy and tissue remodeling. Furthermore, PD has shown protective effects on articular cartilage and a role in maintaining bone homeostasis and immune balance.

Despite these promising findings, there is a notable scarcity of clinical trials specifically investigating PD in rheumatological conditions. Nevertheless, the translational potential of PD - often administered in combination with palmitoylethanolamide (PEA) - is supported by several randomized controlled trials (RCTs) involving other human inflammatory and pain-related disorders.

Specifically, the PEA-PD association has demonstrated significant clinical efficacy in reducing pain and symptoms associated with chronic inflammation. Evidence from RCTs in patients with irritable bowel syndrome (IBS) (Cremon et al., 2017; Di Nardo et al., 2024) showed a marked reduction in abdominal pain and symptom severity. Furthermore, the clinical benefits of this association extend to gynecological inflammatory conditions including endometriosis (Cobellis et al., 2011), primary dysmenorrhea (Tartaglia et al., 2015), and vestibulodynia (Murina et al., 2013). These clinical data underscore PD's ability to effectively modulate mast cell activation and neuro-inflammatory pathways in humans, providing a robust rationale for its potential application in the management of chronic rheumatological diseases. However, the transition from preclinical models to clinical practice in rheumatology requires caution. Future research must focus on dedicated clinical trials to validate the chondroprotective effects, long-term safety, and optimal dosage of PD, while also exploring its potential as an adjuvant therapy alongside standard pharmacological treatments.

CRediT authorship contribution statement

Chiara Baggio: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Paolo Sfriso:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Amelia Carmela Damasco:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Giacomo Cozzi:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Giampietro Ravagnan:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Roberta Ramonda:** Writing – review & editing, Writing – original draft, Visualization, Supervision. **Francesca Oliviero:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the revision of this work the authors used Lucrez-IA ChatUnipd in order to improve english language. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Open access publishing was supported by Univerity of Padova.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Abd El-Hameed, A. M., Yousef, A. I., Abd El-Twab, S. M., El-Shahawy, A. A. G., & Abdel-Moneim, A. (2021). Hepatoprotective effects of polydatin-loaded chitosan nanoparticles in diabetic rats: Modulation of glucose metabolism, oxidative stress, and inflammation biomarkers. Biochemistry. *Biokhimiia, 86*(2), 179–189. https://doi.org/10.1134/S0006297921020061

Aboul-Enein, H. Y., Kruk, I., Kładna, A., Lichszteld, K., & Michalska, T. (2007). Scavenging effects of phenolic compounds on reactive oxygen species. *Biopolymers, 86*(3), 222–230. https://doi.org/10.1002/bip.20725

Amalraj, A., Varma, K., Jacob, J., Divya, C., Kunnumakkara, A. B., Stohs, S. J., & Gopi, S. (2017). A novel highly bioavailable curcumin formulation improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, Double-Blind, placebo-Controlled, Two-Dose, Three-Arm, and parallel-group Study. *Journal of Medicinal Food, 20*(10), 1022–1030. https://doi.org/10.1089/jmf.2017.3930

Askarizadeh, F., Karav, S., & Sahebkar, A. (2025). Phytochemicals as modulators of NETosis: A comprehensive review on their mechanisms and therapeutic potential. *Phytotherapy Research, 39*(8), 3545–3577. https://doi.org/10.1002/ptr.70025

Baggio, C., Galozzi, P., Damasco, A., Lazzarin, V., Ravagnan, G., Sfriso, P., Ramonda, R., Punzi, L., Pennelli, G., Doria, A., Luisetto, R., & Oliviero, F. (2025). Multitargeted biological actions of polydatin in preventing pseudogout acute attack. *Frontiers in Molecular Biosciences, 12*, Article 1553912. https://doi.org/10.3389/fmolb.2025.1553912

Bashmil, Y. M., Dunshea, F. R., Appels, R., & Suleria, H. A. R. (2025). Bio-Accessibility of phenolic compounds from Green banana-fortified bread during simulated digestion and colonic fermentation. *Molecules, 30*(18), 3743. https://doi.org/10.3390/molecules30183743

Basta-Kaim, A., Ślusarczyk, J., Szczepanowicz, K., Warszyński, P., Leśkiewicz, M., Regulska, M., Trojan, E., & Lasoń, W. (2019). Protective effects of polydatin in free and nanocapsulated form on changes caused by lipopolysaccharide in hippocampal organotypic cultures. *Pharmacological Reports: PR, 71*(4), 603–613. https://doi.org/10.1016/j.pharep.2019.02.017

Bavetta, M., Silvaggio, D., Campione, E., Sollena, P., Formica, V., Coletta, D., Graziani, G., Romano, M. C. P., Roselli, M., Peris, K., & Bianchi, L. (2021). The effects of Association of topical polydatin improves the preemptive systemic treatment on EGFR inhibitors cutaneous adverse reactions. *Journal of Clinical Medicine, 10*(3), 466. https://doi.org/10.3390/jcm10030466

Binke, W., Xinyu, Q., Ruping, Y., Xu, X., Shiyao, L., Chunli, Z., & Haitao, Y. (2025). Cubosome-based co-delivery of doxorubicin and polydatin for targeted cancer therapy. *Chemical Engineering Journal, 524*, Article 168855. https://doi.org/10.1016/j.cej.2025.168855

Biswas, P., Dellanoce, C., Vezzoli, A., Mrakic-Sposta, S., Malnati, M., Beretta, A., & Accinni, R. (2020). Antioxidant activity with increased endogenous levels of vitamin C, E and A following dietary supplementation with a combination of glutathione and resveratrol precursors. *Nutrients, 12*(11), 3224. https://doi.org/10.3390/nu12113224

Buhrmann, C., Brockmueller, A., Mueller, A. L., Shayan, P., & Shakibaei, M. (2021). Curcumin Attenuates environment-derived osteoarthritis by Sox9/NF-kB signaling axis. *International Journal of Molecular Sciences, 22*(14), 7645. https://doi.org/10.3390/ijms22147645

Cerezo, A. B., Winterbone, M. S., Moyle, C. W., Needs, P. W., & Kroon, P. A. (2015). Molecular structure-function relationship of dietary polyphenols for inhibiting VEGF-induced VEGFR-2 activity. *Molecular Nutrition & Food Research, 59*(11), 2119–2131. https://doi.org/10.1002/mnfr.201500407

Chen, X. X. (2004). In A. Hypogaes (Ed.), *The content of resveratrol, piceid in Polygonum Cuspidatum and resveratrol* (2004). Shuo Shi Lun Wen: Fujian Normal University.

Cobellis, L., Castaldi, M. A., Giordano, V., Trabucco, E., De Franciscis, P., Torella, M., & Colacurci, N. (2011). Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: A pilot study. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 158*(1), 82–86. https://doi.org/10.1016/j.ejogrb.2011.04.011

Cremon, C., Stanghellini, V., Barbaro, M. R., Cogliandro, R. F., Bellacosa, L., Santos, J., Vicario, M., Pigrau, M., Alonso Cotoner, C., Lobo, B., Azpiroz, F., Bruley des Varannes, S., Neunlist, M., DeFilippis, D., Iuvone, T., Petrosino, S., Di Marzo, V., & Barbara, G. (2017). Randomised clinical trial: The analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome. *Alimentary pharmacology & therapeutics, 45*(7), 909–922. https://doi.org/10.1111/apt.13958

Dai, X., Fan, Y., & Zhao, X. (2025). Systemic lupus erythematosus: Updated insights on the pathogenesis, diagnosis, prevention and therapeutics. *Signal Transduction and Targeted Therapy, 10*(1), 102. https://doi.org/10.1038/s41392-025-02168-0

De Souza Andrade, M. M., Leal, V. N. C., Fernandes, I. G., Gozzi-Silva, S. C., Beserra, D. R., Oliveira, E. A., Teixeira, F. M. E., Yendo, T. M., Sousa, M. D. G. T., Teodoro, W. R., Oliveira, L. M., Alberca, R. W., Aoki, V., Duarte, A. J. S., & Sato, M. N. (2022). Resveratrol downmodulates Neutrophil Extracellular Trap (NET) generation by neutrophils in patients with severe COVID-19. *Antioxidants, 11*(9), 1690. https://doi.org/10.3390/antiox11091690

Di Nardo, G., Bernardo, L., Cremon, C., Barbara, G., Felici, E., Evangelisti, M., Ferretti, A., Furio, S., Piccirillo, M., Coluzzi, F., Parisi, P., Mauro, A., Di Mari, C., D'Angelo, F., & Mennini, M. (2024). Palmitoylethanolamide and polydatin in pediatric irritable bowel syndrome: A multicentric randomized controlled trial. *Nutrition, 122*, Article 112397. https://doi.org/10.1016/j.nut.2024.112397

Du, Q. H., Peng, C., & Zhang, H. (2013). Polydatin: A review of pharmacology and pharmacokinetics. *Pharmaceutical Biology, 51*(11), 1347–1354. https://doi.org/10.3109/13880209.2013.792849

Du, K., Zhou, Q., Wang, Z., Mo, C., Dong, W., Wei, N., Zhong, W., You, Y., Wang, Y., & Wang, Z. (2023). Polydatin ameliorates inflammation and oxidative stress associated with MSU-induced gouty arthritis in mice by regulating PPAR-γ and ferritin activation. *Life Sciences, 326*, Article 121766. https://doi.org/10.1016/j.lfs.2023.121766

Fabris, S., Momo, F., Ravagnan, G., & Stevanato, R. (2008). Antioxidant properties of resveratrol and piceid on lipid peroxidation in micelles and monolamellar liposomes. *Biophysical Chemistry, 135*(1-3), 76–83. https://doi.org/10.1016/j.bpc.2008.03.005

Ferrari, I. V., De Gregorio, A., Fuggetta, M. P., Ravagnan, G., Ali, W., Perrella, F., Coppola, F., Di Mario, M., Patrizio, P., & Abdalla, M. (2023). Focus on polydatin interaction with sirtuins family: A comparative computational analysis. *Int. J. Sci. Res. Biol. Sci., 10*(3), 1–8.

Fuggetta, M. P., Migliorino, M. R., Ricciardi, S., Osman, G., Iacono, D., Leone, A., Lombardi, A., Ravagnan, G., Greco, S., Remotti, D., & Romano, M. C. P. (2019). Prophylactic dermatologic treatment of afatinib-induced skin toxicities in patients with metastatic lung cancer: A pilot Study. *Scientifica, 2019*, Article 9136249.

GBD 2021 Other Musculoskeletal Disorders Collaborators. (2023). Global, regional, and national burden of other musculoskeletal disorders, 1990-2020, and projections to 2050: A systematic analysis of the global Burden of Disease Study 2021. *The Lancet. Rheumatology, 5*(11), e670–e682. https://doi.org/10.1016/S2665-9913(23)00232-1

He, Y., Li, Z., Alexander, P. G., Ocasio-Nieves, B. D., Yocum, L., Lin, H., & Tuan, R. S. (2020). Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. *Biology, 9*(8), 194. https://doi.org/10.3390/biology9080194

Henry, C., Vitrac, X., Decendit, A., Ennamany, R., Krisa, S., & Mérillon, J. M. (2005). Cellular uptake and efflux of trans-piceid and its aglycone trans-resveratrol on the apical membrane of human intestinal Caco-2 cells. *Journal of Agricultural and Food Chemistry, 53*(3), 798–803. https://doi.org/10.1021/jf048909e

Henry-Vitrac, C., Desmoulière, A., Girard, D., Mérillon, J. M., & Krisa, S. (2006). Transport, deglycosylation, and metabolism of trans-piceid by small intestinal epithelial cells. *European Journal of Nutrition, 45*(7), 376–382. https://doi.org/10.1007/s00394-006-0609-8

Hu, L., Luo, D., Zhang, H., & He, L. (2022). Polydatin inhibits IL-1β-mediated chondrocyte inflammation and ameliorates cartilage degradation: Involvement of the NF-κB and Wnt/β-catenin pathways. *Tissue and Cell, 78*, Article 101865. https://doi.org/10.1016/j.tice.2022.101865

Hu, W. H., Wang, H. Y., Kong, X. P., Xiong, Q. P., Poon, K. K., Xu, L., Duan, R., Chan, G. K., Dong, T. T., & Tsim, K. W. (2019). Polydatin suppresses VEGF-induced angiogenesis through binding with VEGF and inhibiting its receptor signaling. *The FASEB Journal, 33*(1), 532–544. https://doi.org/10.1096/fj.201800750R

Hurst, W. J., Glinski, J. A., Miller, K. B., Apgar, J., Davey, M. H., & Stuart, D. A. (2008). Survey of the trans-resveratrol and trans-piceid content of cocoa-containing and chocolate products. *Journal of Agricultural and Food Chemistry, 56*(18), 8374–8378. https://doi.org/10.1021/jf801297w

Indraccolo, U., Indraccolo, S. R., & Mignini, F. (2017). Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: A meta-analysis. *Annali dell'Istituto superiore di sanita, 53*(2), 125–134. https://doi.org/10.4415/ANN_17_02_08

Javadi, F., Ahmadzadeh, A., Eghtesadi, S., Aryaeian, N., Zabihiyeganeh, M., Rahimi Foroushani, A., & Jazayeri, S. (2017). The effect of Quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: A Double-Blind, randomized controlled trial. *Journal of the American College of Nutrition, 36*(1), 9–15. https://doi.org/10.1080/07315724.2016.1140093

Jhou, J. P., Chen, S. J., Huang, H. Y., Lin, W. W., Huang, D. Y., & Tzeng, S. J. (2017). Upregulation of FcγRIIB by resveratrol via NF-κB activation reduces B-cell numbers and ameliorates lupus. *Experimental & molecular medicine, 49*(9), Article e381. https://doi.org/10.1038/emm.2017.144

Kamel, K. M., Gad, A. M., Mansour, S. M., Safar, M. M., & Fawzy, H. M. (2018). Novel anti-arthritic mechanisms of polydatin in complete freund's adjuvant-induced arthritis in rats: Involvement of IL-6, STAT-3, IL-17, and NF-κB. *Inflammation, 41*(5), 1974–1986. https://doi.org/10.1007/s10753-018-0841-4

Kanzaki, N., Saito, K., Maeda, A., Kitagawa, Y., Kiso, Y., Watanabe, K., Tomonaga, A., Nagaoka, I., & Yamaguchi, H. (2012). Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee osteoarthritis: A randomized, double-blind, placebo-controlled study. *Journal of the Science of Food and Agriculture, 92*(4), 862–869. https://doi.org/10.1002/jsfa.4660

Karami, A., Fakhri, S., Kooshki, L., & Khan, H. (2022). Polydatin: Pharmacological mechanisms, therapeutic targets, biological activities, and health benefits. *Molecules, 27*(19), 6474. https://doi.org/10.3390/molecules27196474

Karim, A., Khan, H. A., Ahmad, F., & Qaisar, R. (2025). Resveratrol treatment increases sirtuin 1 levels and alleviates frailty phenotype in knee osteoarthritis patients: A randomised placebo-controlled clinical trial. *International Journal of Food Sciences & Nutrition, 76*(7), 748–758. https://doi.org/10.1080/09637486.2025.2563670

Khojah, H. M., Ahmed, S., Abdel-Rahman, M. S., & Elhakeim, E. H. (2018). Resveratrol as an effective adjuvant therapy in the management of rheumatoid arthritis: A clinical study. *Clinical Rheumatology, 37*(8), 2035–2042. https://doi.org/10.1007/s10067-018-4080-8

Kocatürk, B., Balık, Z., Pişiren, G., Kalyoncu, U., Özmen, F., & Özen, S. (2022). Spondyloarthritides: Theories and beyond. *Frontiers in Pediatrics, 10*, Article 1074239. https://doi.org/10.3389/fped.2022.1074239

Lanzilli, G., Cottarelli, A., Nicotera, G., Guida, S., Ravagnan, G., & Fuggetta, M. P. (2012). Anti-inflammatory effect of resveratrol and polydatin by *in vitro* IL-17 modulation. *Inflammation, 35*(1), 240–248. https://doi.org/10.1007/s10753-011-9310-z

Li, S., Du, J., Gan, H., Chen, J., Zhou, Y., Tian, J., Ling, G., & Li, F. (2021). Resveratrol promotes apoptosis and G2/M cell cycle arrest of fibroblast-like synoviocytes in rheumatoid arthritis through regulation of autophagy and the serine-threonine kinase-p53 axis. *Archives of Medical Science: AMS, 20*(1), 280–288.

Li, B., & Wang, X. L. (2016). Effective treatment of polydatin weakens the symptoms of collagen-induced arthritis in mice through its anti-oxidative and anti-inflammatory effects and the activation of MMP-9. *Molecular Medicine Reports, 14*(6), 5357–5362. https://doi.org/10.3892/mmr.2016.5903

Li, P., Wang, X., Zhao, M., Song, R., & Zhao, K. S. (2015). Polydatin protects hepatocytes against mitochondrial injury in acute severe hemorrhagic shock via SIRT1-SOD2 pathway. *Expert Opinion on Therapeutic Targets, 19*(7), 997–1010. https://doi.org/10.1517/14728222.2015.1054806

Liao, P., He, Y., Yang, F., Luo, G., Zhuang, J., Zhai, Z., Zhuang, L., Lin, Z., Zheng, J., & Sun, E. (2018). Polydatin effectively attenuates disease activity in lupus-prone mouse models by blocking ROS-mediated NET formation. *Arthritis Research and Therapy, 20*(1), 254. https://doi.org/10.1186/s13075-018-1749-y

Lin, L., Gong, H., Li, R., Huang, J., Cai, M., Lan, T., Huang, W., Guo, Y., Zhou, Z., An, Y., Chen, Z., Liang, L., Wang, Y., Shuai, X., & Zhu, K. (2020). Nanodrug with ROS and pH dual-sensitivity ameliorates liver fibrosis via multicellular regulation. *Advanced science, 7*(7), Article 1903138. https://doi.org/10.1002/advs.201903138

Liu, S., Wang, Y., Ying, L., Li, H., Zhang, K., Liang, N., Luo, G., & Xiao, L. (2024). Quercetin mitigates lysophosphatidylcholine (LPC)-Induced neutrophil extracellular traps (NETs) Formation through inhibiting the P2X7R/P38MAPK/NOX2 pathway. *International Journal of Molecular Sciences, 25*(17), 9411. https://doi.org/10.3390/ijms25179411

Long, Z., Xiang, W., He, Q., Xiao, W., Wei, H., Li, H., Guo, H., Chen, Y., Yuan, M., Yuan, X., Zeng, L., Yang, K., Deng, Y., & Huang, Z. (2023). Efficacy and safety of dietary polyphenols in rheumatoid arthritis: A systematic review and meta-analysis of 47 randomized controlled trials. *Frontiers in Immunology, 14*, Article 1024120. https://doi.org/10.3389/fimmu.2023.1024120

Lopresti, A. L., Smith, S. J., Jackson-Michel, S., & Fairchild, T. (2021). An investigation into the effects of a curcumin extract (Curcugen®) on osteoarthritis pain of the knee: A randomised, Double-Blind, placebo-controlled Study. *Nutrients, 14*(1), 41. https://doi.org/10.3390/nu14010041

Ma, C., Wen, B., Zhang, Q., Shao, P., Gu, W., Qu, K., Shi, Y., & Wang, B. (2019). Polydatin regulates the apoptosis and autophagy of fibroblasts obtained from patients with ankylosing spondylitis. *Biological & pharmaceutical bulletin, 42*(1), 50–56. https://doi.org/10.1248/bpb.b18-00522

Mao, A., Fu, Y., Zhang, M., Wu, J., & Wu, M. (2025). Phenotypic screening identified polydatin alleviating cartilage degeneration by modulating SIRT3-dependent mitochondrial dysfunction. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 144*, Article 156948. https://doi.org/10.1016/j.phymed.2025.156948

Mikulski, D., & Molski, M. (2010). Quantitative structure-antioxidant activity relationship of trans-resveratrol oligomers, trans-4,4'-dihydroxystilbene dimer, trans-resveratrol-3-O-glucuronide, glucosides: Trans-piceid, cis-piceid, trans-astringin and trans-resveratrol-4'-O-beta-D-glucopyranoside. *European Journal of Medicinal Chemistry, 45*(6), 2366–2380. https://doi.org/10.1016/j.ejmech.2010.02.016

Muñoz-Sánchez, G., Godínez-Méndez, L. A., Fafutis-Morris, M., & Delgado-Rizo, V. (2023). Effect of antioxidant supplementation on NET Formation induced by LPS *In Vitro*; the roles of vitamins E and C, glutathione, and N-acetyl cysteine. *International Journal of Molecular Sciences, 24*(17), Article 13162. https://doi.org/10.3390/ijms241713162

Murina, F., Graziottin, A., Felice, R., Radici, G., & Tognocchi, C. (2013). Vestibulodynia: Synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. *Journal of Lower Genital Tract Disease, 17*(2), 111–116. https://doi.org/10.1097/LGT.0b013e3182652316

Ohinata, H., Phimarn, W., Mizuno, M., Obama, T., Fukuhara, K., Makiyama, T., Watanabe, Y., & Itabe, H. (2024). Suppressive effect of resveratrol, catechin and their conformationally constrained analogs on neutrophil extracellular trap formation by HL-60-derived neutrophils. *Journal of Clinical Biochemistry & Nutrition, 75*(1), 17–23. https://doi.org/10.3164/jcbn.23-80

Oliviero, F., Galozzi, P., Scanu, A., Galuppini, F., Lazzarin, V., Brocco, S., Ravagnan, G., Sfriso, P., Ramonda, R., Spinella, P., Punzi, L., Pennelli, G., & Luisetto, R. (2021). Polydatin prevents calcium pyrophosphate crystal-induced arthritis in mice. *Nutrients, 13*(3), 929. https://doi.org/10.3390/nu13030929

Oliviero, F., Scanu, A., & Punzi, L. (2012). Metabolism of crystals within the joint. *Reumatismo, 63*(4), 221–229. https://doi.org/10.4081/reumatismo.2011.221

Oliviero, F., Scanu, A., Zamudio-Cuevas, Y., Punzi, L., & Spinella, P. (2018). Anti-inflammatory effects of polyphenols in arthritis. *Journal of the Science of Food and Agriculture, 98*(5), 1653–1659. https://doi.org/10.1002/jsfa.8664

Oliviero, F., Sfriso, P., Scanu, A., Fiocco, U., Spinella, P., & Punzi, L. (2013). Epigallocatechin-3-gallate reduces inflammation induced by calcium pyrophosphate crystals *in vitro*. *Frontiers in Pharmacology, 4*, 51. https://doi.org/10.3389/fphar.2013.00051

Oliviero, F., Zamudio-Cuevas, Y., Belluzzi, E., Andretto, L., Scanu, A., Favero, M., Ramonda, R., Ravagnan, G., López-Reyes, A., Spinella, P., & Punzi, L. (2019). Polydatin and resveratrol inhibit the inflammatory process induced by urate and pyrophosphate crystals in THP-1 cells. *Foods, 8*(11), 560. https://doi.org/10.3390/foods8110560

Pace, M. C., Passavanti, M. B., Aurilio, C., Sansone, P., Aurilio, R., DE Maria, S., Lama, S., Federico, A., Ravagnan, G., Caraglia, M., & Stiuso, P. (2015). Polydatin administration improves serum biochemical parameters and oxidative stress markers during chronic alcoholism: A pilot study. *In vivo, 29*(3), 405–408.

Pandey, S. N., Babu, M. A., Goyal, K., Menon, S. V., Ray, S., Kaur, M., Sharma, S., Rana, M., Rekha, A., Ali, H., Singh, S. K., & Gupta, G. (2025). Targeting NLRP3 inflammasome with curcumin: Mechanisms and therapeutic promise in chronic inflammation. *Inflammopharmacology, 33*(10), 5667–5687. https://doi.org/10.1007/s10787-025-01926-4

Pascart, T., Filippou, G., Lioté, F., Sirotti, S., Jauffret, C., & Abhishek, A. (2024). Calcium pyrophosphate deposition disease. *The Lancet. Rheumatology, 6*(11), e791–e804. https://doi.org/10.1016/S2665-9913(24)00122-X

Perez-Moral, N., Needs, P. W., Moyle, C. W. A., & Kroon, P. A. (2019). Hydrophobic interactions drive binding between vascular endothelial growth Factor-A (VEGFA) and polyphenolic inhibitors. *Molecules, 24*(15), 2785. https://doi.org/10.3390/molecules24152785

Potdar, S., Parmar, M. S., Ray, S. D., & Cavanaugh, J. E. (2018). Protective effects of the resveratrol analog piceid in dopaminergic SH-SY5Y cells. *Archives of Toxicology, 92*(2), 669–677. https://doi.org/10.1007/s00204-017-2073-z

Ramonda, R., Cozzi, G., & Oliviero, F. (2025). Nutritional guidance in spondyloarthritis: Confronting the evidence gap. *Current Opinion in Rheumatology, 37*(4), 269–275. https://doi.org/10.1097/BOR.0000000000001090

Romero-Pérez, A. I., Lamuela-Raventós, R. M., Andrés-Lacueva, C., & de La Torre-Boronat, M. C. (2001). Method for the quantitative extraction of resveratrol and piceid isomers in grape berry skins. Effect of powdery mildew on the stilbene content. *Journal of Agricultural and Food Chemistry, 49*(1), 210–215. https://doi.org/10.1021/jf000745o

Rudrapal, M., Khairnar, S. J., Khan, J., Dukhyil, A. B., Ansari, M. A., Alomary, M. N., Alshabrmi, F. M., Palai, S., Deb, P. K., & Devi, R. (2022). Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism(s) of action. *Frontiers in Pharmacology, 13*, Article 806470. https://doi.org/10.3389/fphar.2022.806470

Scherer, H. U., Häupl, T., & Burmester, G. R. (2020). The etiology of rheumatoid arthritis. *Journal of Autoimmunity, 110*, Article 102400. https://doi.org/10.1016/j.jaut.2019.102400

Shi, Y. W., Wang, C. P., Liu, L., Liu, Y. L., Wang, X., Hong, Y., Li, Z., & Kong, L. D. (2012). Antihyperuricemic and nephroprotective effects of resveratrol and its analogues in hyperuricemic mice. *Molecular Nutrition & Food Research, 56*(9), 1433–1444. https://doi.org/10.1002/mnfr.201100828

Shi, X., Zhuang, L., Zhai, Z., He, Y., & Sun, E. (2023). Polydatin protects against gouty nephropathy by inhibiting renal tubular cell pyroptosis. *International journal of rheumatic diseases, 26*(1), 116–123. https://doi.org/10.1111/1756-185X.14463

Şöhretoğlu, D., Baran, M. Y., Arroo, R., & Kuruüzüm-Uz, A. (2018). Recent advances in chemistry, therapeutic properties and sources of polydatin. *Phytochemistry Reviews, 17*, 973–1005. https://doi.org/10.1007/s11101-018-9574-0

Stochino Loi, E., Pontis, A., Cofelice, V., Pirarba, S., Fais, M. F., Daniilidis, A., Melis, I., Paoletti, A. M., & Angioni, S. (2019). Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: An open-label pilot study. *International Journal of Women's Health, 11*, 443–449. https://doi.org/10.2147/IJWH.S204275

Sun, Q., Nan, X. Y., Wang, H., Pan, S., Ji, G., Guo, Y. F., Zhao, Y. H., Li, G. C., Guo, S. S., Lin, L. F., Jin, Y. J., Zhang, X. L., Liu, C. C., & Liu, G. B. (2025). Polydatin retards the progression of osteoarthritis by maintaining bone metabolic balance and inhibiting macrophage polarization. *Frontiers in Bioengineering and Biotechnology, 12*, Article 1514483. https://doi.org/10.3389/fbioe.2024.1514483

Tang, K. S., & Tan, J. S. (2019). The protective mechanisms of polydatin in cerebral ischemia. *European Journal of Pharmacology, 842*, 133–138. https://doi.org/10.1016/j.ejphar.2018.10.039

Tang, S., Tang, Q., Jin, J., Zheng, G., Xu, J., Huang, W., Li, X., Shang, P., & Liu, H. (2018). Polydatin inhibits the IL-1β-induced inflammatory response in human osteoarthritic chondrocytes by activating the Nrf2 signaling pathway and ameliorates murine osteoarthritis. *Food & Function, 9*(3), 1701–1712. https://doi.org/10.1039/c7fo01555k

Tang, D., Zhang, Q., Duan, H., Ye, X., Liu, J., Peng, W., & Wu, C. (2022). Polydatin: A critical promising natural agent for liver protection via antioxidative stress. *Oxidative Medicine and Cellular Longevity, 2022*, Article 9218738. https://doi.org/10.1155/2022/9218738

Tartaglia, E., Armentano, M., Giugliano, B., Sena, T., Giuliano, P., Loffredo, C., & Mastrantonio, P. (2015). Effectiveness of the Association N-Palmitoylethanolamine and transpolydatin in the treatment of primary dysmenorrhea. *Journal of Pediatric and Adolescent Gynecology, 28*(6), 447–450. https://doi.org/10.1016/j.jpag.2014.12.011

Walle, T. (2011). Bioavailability of resveratrol. *Annals of the New York Academy of Sciences, 1215*, 9–15. https://doi.org/10.1111/j.1749-6632.2010.05842.x

Wang, H. Y. (2017). Effect of GA3 treatment on quality of two TableGrape varieties. *Northwest A & F University, Shuo Shi LunWen, 2017*.

Wang, X., Guan, Q., Chen, W., Hu, X., & Li, L. (2015). Novel nanoliposomal delivery system for polydatin: Preparation, characterization, and *in vivo* evaluation. *Drug Design, Development and Therapy, 9*, 1805–1813. https://doi.org/10.2147/DDDT.S77615

Wang, D. G., Liu, W. Y., & Chen, G. T. (2013). A simple method for the isolation and purification of resveratrol from Polygonum cuspidatum. *Journal of pharmaceutical analysis, 3*(4), 241–247. https://doi.org/10.1016/j.jpha.2012.12.001

Wang, Z. L., Luo, X. F., Li, M. T., Xu, D., Zhou, S., Chen, H. Z., Gao, N., Chen, Z., Zhang, L. L., & Zeng, X. F. (2014). Resveratrol possesses protective effects in a pristane-induced lupus mouse model. *PLoS One, 9*(12), Article e114792. https://doi.org/10.1371/journal.pone.0114792

Wang, Q., Ye, C., Sun, S., Li, R., Shi, X., Wang, S., Zeng, X., Kuang, N., Liu, Y., Shi, Q., & Liu, R. (2019). Curcumin attenuates collagen-induced rat arthritis via anti-inflammatory and apoptotic effects. *International Immunopharmacology, 72*, 292–300. https://doi.org/10.1016/j.intimp.2019.04.027

Wang, L., Zhao, B., Wang, J., Zhang, D., Ma, R., Zhang, T., Qi, Y., Sheng, Y., Hu, B., & Jin, T. (2025). Epigollatecatechin gallate alleviates rheumatoid arthritis through PI3K-Akt pathway by inhibiting FLT1. *International Immunopharmacology, 160*, Article 114958. https://doi.org/10.1016/j.intimp.2025.114958

Wang, Y. S., Zhu, G. H., & Wang, B. (2020). Influences of ancient processing method steaming with black bean and drying and pharmacopoeia processing method continuous steaming with black bean decoction on 12 components of Polygoni Multiflori Radix. *Chinese Traditional and Herbal Drugs, 51*(19), 4972–4982.

Xiao, J., Wang, F., Liu, J., Wang, L., Kai, G., & Yu, X. (2011). Effect of ZnO#ZnS QDs heterojunctures on the stilbenes-plasma proteins interactions. *Molecular BioSystems, 7*(8), 2452–2458. https://doi.org/10.1039/c1mb05087g

Yang, F., Luo, X., Luo, G., Zhai, Z., Zhuang, J., He, J., Han, J., Zhang, Y., Zhuang, L., Sun, E., & He, Y. (2019). Inhibition of NET formation by polydatin protects against collagen-induced arthritis. *International Immunopharmacology, 77*, Article 105919. https://doi.org/10.1016/j.intimp.2019.105919

Ye, Z., Lin, J., He, C., Yu, P., Cao, G., Shen, Q., & Wang, C. (2024). Polydatin protects against articular cartilage degeneration by regulating autophagy mediated by the AMPK/mTOR signaling pathway. *Histology & Histopathology, 39*(11), 1505–1515. https://doi.org/10.14670/HH-18-739

Zeng, Z., Chen, Z., Li, T., Zhang, J., Gao, Y., Xu, S., Cai, S., & Zhao, K. S. (2015). Polydatin: A new therapeutic agent against multiorgan dysfunction. *Journal of Surgical Research, 198*(1), 192–199. https://doi.org/10.1016/j.jss.2015.05.041

Zhang, S. L., Chen, Z. H., Lin, D. T., Yan, Q., Gao, F., & Lin, H. (2021). Epigallocatechin gallate regulates inflammatory responses and new bone formation through Wnt/β-Catenin/COX-2 pathway in spondyloarthritis. *International Immunopharmacology, 98*, Article 107869. https://doi.org/10.1016/j.intimp.2021.107869

Zhang, X. H., & Li, J. (2018). The clinical efficacy of polydatin in the treatment of elderly coronary heart disease and its influence on patients NF-κB and inflammatory factors. *Chinese Journal of Integrative Medicine on Cardio-Cerebrovasc Diseases, 16*, 2352–2354.

Zhao, K., Su, Z. R., Yang, B. W., Tan, F., & Deng, J. (2010). Determination of resveratrol and polydatin in mulberry. *Food Science, 31*(14), 241–244.

Zhaoli, S., Yuanyuan, T., Gejing, L., Junping, Z., Yini, H., Junlan, Z., Feng, Z., Ye, L., Bin, L., & Xiong, C. (2024). Polydatin and chitosan-silver co-loaded nanocomplexes for synergistic treatment of rheumatoid arthritis via repolarizing macrophages and inducing apoptosis of fibroblast-like synoviocytes. *Materials & Design, 245*, Article 113287. https://doi.org/10.1016/j.matdes.2024.113287

Zhou, Z., Deng, Z., Liu, Y., Zheng, Y., Yang, S., Lu, W., Xiao, D., & Zhu, W. (2021). Protective effect of SIRT1 activator on the knee with osteoarthritis. *Frontiers in Physiology, 12*, Article 661852. https://doi.org/10.3389/fphys.2021.661852

Zhou, C. S., Xiang, Y. H., Xiao, J. B., & Lei, Q. F. (2005). Quantitative determination of resveratrol and piceid in Polygonum Cuspidatum Sieb.et Zucc.by HPLC. *Chinese Journal of Pharmaceutical Analysis, 25*(5), 534–536.

Zhu, W., Tang, H., Cao, L., Zhang, J., Li, J., Ma, D., & Guo, C. (2022). Epigallocatechin-3-O-gallate ameliorates oxidative stress-induced chondrocyte dysfunction and exerts chondroprotective effects via the Keap1/Nrf2/ARE signaling pathway. *Chemical Biology & Drug Design, 100*(1), 108–120. https://doi.org/10.1111/cbdd.14056

Zong, N., Hu, Y. Q., & Liu, D. L. (2002). Study on the biological activity of resveratrol glycosides. *Acta Academiae Medicinae, 11*(4), 298–300.