



DOSSIER · SUBSTANCE

Polydatin

Polydatin, a natural **resveratrol glycoside**, has been investigated in basic and clinical research for two decades. Controlled human studies reveal a narrow but methodologically sound field of application — primarily in **chronic inflammation** and **pain syndromes**. The most intriguing finding: most studies combine polydatin with palmitoylethanolamide (PEA), making it difficult to isolate the effect of the single substance.

279

STUDIES IN
TOTAL

25

IN HUMANS

3

OF WHICH
CONTROLLED

92

IN ANIMALS

57

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Polydatin at a glance

ORIGIN:

Polydatin (3,4',5-trihydroxystilbene-3-β-D-glucoside) is a plant-derived polyphenol from the stilbene group, a glycoside of resveratrol, primarily found in knotweed species (*Polygonum cuspidatum*), but also in grapes, peanuts and red wine. The glucose unit enhances its bioavailability and water solubility, while in the plant it acts as a phytoalexin against pathogens and oxidative stress. Industrially, it is mostly extracted from knotweed roots or synthesised, with metabolism in the gut by β-glucosidases of the microbiota yielding resveratrol.

EVIDENCE BASE:

279 reviewed studies · 3 controlled human trials · 22 observational studies · 5 review articles · 92 animal studies · 46 cell culture studies

STRONGEST EVIDENCE:

- **Gut and microbiome:** A 12-week, randomised, placebo-controlled trial in 54 IBS patients showed that a combination of polydatin (20 mg) and palmitoylethanolamide (PEA) significantly reduced mast cell numbers in the intestinal mucosa and normalised the endocannabinoid system (e.g., increase in oleoylethanolamide). The isolated effect of polydatin remains unclear.
- **Inflammation:** In women with chronic pelvic pain, co-micronised PEA/polydatin over three months led to a ≥3-point pain reduction in over 50 % of cases (scale), with a 19 % probability of good response. The contribution of polydatin alone was not assessed.
- **Oncology:** In an orthotopic metastasis model with tongue carcinoma cells, polydatin (100 mg/kg) inhibited glucose-6-phosphate dehydrogenase (G6PD), resulting in a 50 % apoptosis rate and 80 % reduction in lymph node metastases ($P < 0.005$). These findings are preclinical and require clinical validation.
- **Safety:** A controlled trial confirmed the tolerability of PEA/polydatin in IBS (adults and children), with no serious adverse events reported. The safety profile of polydatin alone is not established.
- **Viral infections:** Preclinical cell studies on SARS-CoV-2 showed that polydatin inhibited NLRP3-dependent pyroptosis by restoring lysosomal function, suggesting therapeutic potential in COVID-19. Clinical data are outstanding.

LIMITATIONS:

- **Combination effects:** All controlled human studies examine polydatin exclusively in combination with palmitoylethanolamide (PEA), leaving the isolated effect of the single compound unclear.
- **Dose-response:** The doses used range from milligrams to grams per day, with no clear relationship between dose and effect—dose-finding studies are lacking.
- **Preclinical dominance:** Many findings derive from cell and animal models (e.g., oxidative stress, oncology), while clinical data on metabolic diseases or viral infections remain outstanding.

ASSESSMENT:

Polydatin, a resveratrol glycoside with improved bioavailability, shows promising effects in combination with palmitoylethanolamide for inflammation and pain. Its isolated efficacy and clinical relevance in metabolism, oncology, and viral infections require systematic evaluation.

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1. What Polydatin Is

Polydatin (3,4',5-trihydroxystilbene-3-β-D-glucoside) is a **plant-derived polyphenol** from the stilbene group. It occurs in **knotweed species** (*Polygonum cuspidatum*), but also in grapes, peanuts and red wine. Chemically, it is the glycoside of the better-known resveratrol: the glucose unit increases **bioavailability** and **water solubility**, which is crucial for oral intake. In the plant, polydatin serves as a **phytoalexin**—a defence compound against pathogens and oxidative stress. Industrially, it is mostly extracted from knotweed roots, less commonly synthesised.

The central point across all studies is **metabolism**: polydatin is hydrolysed to resveratrol in the gut by **β-glucosidases** of the microbiota. Only a small fraction enters the bloodstream unchanged. Measured plasma levels therefore **do not directly reflect the ingested dose**, but depend on individual gut flora. Moreover, polydatin and resveratrol compete for the same **transport proteins** (e.g., albumin) and **enzyme systems** (CYP450), which may lead to drug interactions. Most human studies use **micronised formulations** to enhance absorption.

2. What the Studies Show in Detail

The key controlled human studies and major reviews—grouped by application area, with population, duration, formulation, measurement and outcome as reported in the original papers. Numbers are included only where the study provides them.

Distribution of **controlled human trials** by application area — the numbers are not additive, as one study may cover multiple areas:

APPLICATION AREA	CONTROLLED TRIALS
Safety and tolerability	1
Gut and microbiome	1
Immune system	1

APPLICATION AREA	CONTROLLED TRIALS
Inflammation	1

Gut and Microbiome

Evidence: In a 12-week, randomised, double-blind, placebo-controlled multicentre trial with 54 IBS patients and 12 healthy controls, the combination of palmitoylethanolamide (200 mg) and polydatin (20 mg) twice daily was examined. The treatment significantly reduced mast cell numbers in the intestinal mucosa (5.3 ± 2.7 % vs. 3.2 ± 1.3 % in healthy controls, $P = 0.013$) and normalised endocannabinoid system expression (e.g., increase in oleoylethanolamide from 12.7 ± 9.8 to 45.8 ± 55.6 pmol/mg, $P = 0.002$). The study also assessed clinical symptoms, with pain reduction as the primary focus, but did not collect detailed microbiome composition data ¹.

Evidence: A paediatric multicentre trial with 70 children (10–17 years) with IBS according to Rome IV criteria compared the same combination (co-micronised PEA/PD, three times daily) over 12 weeks with placebo. The combination showed a significantly higher remission rate (IBS-SSS < 75 points) after 12 weeks ($P = 0.015$) and a reduction in abdominal pain frequency and improvement in stool consistency (Bristol Stool Scale). The study confirmed tolerability but provided no data on microbial changes or long-term effects ².

HYPOTHESIS The observed reduction in mast cell activation by polydatin may indirectly influence the microbiome, as mast cells act as an interface between the immune system and gut microbiota. Whether polydatin specifically modulates microbiome composition or function remains an open question. Metagenomic analyses and functional assays (e.g., short-chain fatty acids) would be required to clarify this.

Inflammation

Evidence: An observational study in cardiomyocytes and renal carcinoma cell lines (AC-16, H9C2, 769-P, A498) showed that the combination of polydatin and sunitinib significantly reduced oxidative stress (iROS, MDA, LTB4) and expression of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8) and the NLRP3 inflammasome ($P < 0.001$). The study suggests a protective effect in preclinical models against sunitinib-induced cardiotoxicity but did not evaluate clinical endpoints in humans ⁷.

Evidence: In women with chronic pelvic pain, co-micronised palmitoylethanolamide/polydatin over three months led to a ≥ 3 -point pain reduction in over 50 % of cases (scale). The study analysed individual patient data and identified a 19 % probability of good response in chronic pelvic pain. However, placebo controls and long-term data were lacking ³.

PLAUSIBLE Review articles highlight the pleiotropic anti-inflammatory potential of polydatin, particularly in atherosclerosis and ischaemia-reperfusion injury. Mechanistically, inhibition of NLRP3, modulation of cytokine profiles, and antioxidant effects are discussed.

HYPOTHESIS The anti-inflammatory effect of polydatin may be based on direct interaction with signalling pathways such as PI3K/AKT or HIF-1 α , as shown in preclinical models. However, whether these effects are dose-dependent and reproducible in clinical settings remains to be clarified. Of particular relevance would be testing in systemic inflammatory diseases (e.g., rheumatoid arthritis).

Oncology

Evidence: In a preclinical study using tongue carcinoma cells (orthotopic metastasis model in mice), polydatin (100 mg/kg) inhibited glucose-6-phosphate dehydrogenase (G6PD), a key enzyme of the pentose phosphate pathway. This resulted in a 50 % apoptosis rate in vitro, 60 % inhibition of invasion in vitro, and an 80 % reduction in lymph node metastases in vivo ($P < 0.005$). The study also confirmed tolerability in animal models, while a phase II trial (40 mg twice daily for 90 days) assessed safety in humans but did not investigate efficacy ²¹.

Evidence: The combination of polydatin with 2-deoxy-D-glucose (2-DG) in breast cancer cell lines (MCF-7, 4T1) reduced ROS levels, inhibited the PI3K/AKT signalling pathway, and suppressed the expression of hexokinase 2 (HK2), a key glycolytic enzyme. This led to significant tumour regression in vivo without morphological organ damage. The study indicates a synergistic effect of the combination therapy but provides no evidence for polydatin monotherapy ⁵.

PLAUSIBLE Network pharmacology analyses identified 15 potential target proteins of polydatin, including kinases such as ABL1, JAK1, and JAK2, which are involved in cancer, cell growth, and apoptosis. Molecular docking studies showed a stronger binding affinity of polydatin compared to curcumin.

HYPOTHESIS Inhibition of the pentose phosphate pathway by polydatin may represent a promising strategy for suppressing tumour metabolism. However, whether these effects are transferable to other cancer types or whether resistance mechanisms occur remains unclear. Clinical studies with biomarker analyses (e.g., G6PD activity) would be required.

Viral Infections

Evidence: In a cell study on SARS-CoV-2, polydatin inhibited NLRP3-dependent pyroptosis in lung epithelial cells triggered by the viral protein NSP6. The study suggests a possible *preclinical* therapeutic benefit in COVID-19 but did not investigate clinical endpoints or effects in humans ²⁷.

PLAUSIBLE Review articles summarise the potential of *various polyphenols, including polydatin*, in respiratory diseases, such as pulmonary fibrosis, acute lung injury, and COVID-19. The mechanisms of action include antioxidant, antimicrobial, and immunomodulatory effects. However, clinical studies confirming these effects *specifically for polydatin* in viral infections are lacking, as the reviews cover multiple compounds ³¹.

HYPOTHESIS The ability of polydatin to modulate autophagy and inhibit inflammatory signalling pathways may have a protective effect in viral infections. However, whether this leads to a clinically relevant reduction in symptoms or complications remains speculative. Randomised trials with viral infection models or patient cohorts would be necessary.

Oxidative Stress

Evidence: In a cell study using human mesenchymal stem cells (hBMSCs), polydatin (30 µM) promoted osteogenic differentiation by activating the BMP2-Wnt/β-catenin signalling pathway. This led to increased proliferation, alkaline phosphatase activity, and expression of osteogenic genes (Runx2, osteopontin, DLX5). The study provides *preclinical* evidence for a possible application in steroid-induced osteonecrosis but did not investigate clinical endpoints ⁴.

HYPOTHESIS The antioxidant properties of polydatin may be due to direct radical scavenging or activation of endogenous protective mechanisms (e.g., Sirt3). Of particular relevance would be testing in diseases with oxidative stress as a pathomechanism (e.g., neurodegenerative diseases).

Metabolism

Evidence: In a diabetic cardiomyopathy model (STZ-induced), polydatin improved cardiac function and increased autophagy in wild-type mice but not in Sirt3 knockout mice. Treatment led to an increase in mitochondrial function (citrate synthase activity, ATP content) and upregulation of autophagy markers (Beclin 1, Atg5, LC3). The study indicates a Sirt3-dependent effect in this preclinical model; clinical endpoints in humans were not investigated ⁶.

HYPOTHESIS The metabolic effects of polydatin may be based on modulation of glucose metabolism and mitochondrial biogenesis. However, whether these effects lead to clinically relevant improvements in metabolic diseases (e.g., diabetes, fatty liver) remains to be clarified. Studies with metabolic parameters (e.g., HbA1c, insulin resistance) would be required.

Overall Picture

Polydatin shows broad pharmacological potential in preclinical and early clinical studies, particularly in the areas of anti-inflammation, oxidative stress, oncology, and metabolic regulation. The most robust evidence exists for its combination with palmitoylethanolamide in irritable bowel syndrome, where both mast cell activation and clinical symptoms were significantly reduced. In oncology, preclinical data suggest inhibition of the pentose phosphate pathway and potential synergistic effects with glycolysis inhibitors, while in viral infections, modulation of autophagy and pyroptosis is central. However, many effects have been investigated in combination with other active substances, so the specific contribution of polydatin alone often remains unclear.

Despite promising mechanisms, systematic clinical studies are still limited in many areas. Particularly in metabolic diseases, oxidative stress, and viral infections, the available evidence is predominantly preclinical or derived from cell models. Moreover, many effects have been investigated in combination with other active substances (e.g., 2-DG, PEA), so the specific effect of polydatin alone often remains unclear. Randomised, placebo-controlled trials with clear clinical endpoints are required.

Methodology of the evidence base

[The available studies on polydatin cover a wide range of designs, from randomised, placebo-controlled clinical trials (e.g., IBS in adults and children) to observational studies in cell lines and animal models, as well as review articles and molecular docking analyses. Typical intervention durations were 12 weeks (clinical studies), while preclinical models often covered shorter time periods (48 hours to 4 weeks). Endpoints ranged from biochemical markers (e.g., cytokines, ROS) to histological analyses (mast cell count) and clinical scores (IBS-SSS, pain scales).', 'Systematic gaps exist in the lack of standardisation of dosages (30 µM in vitro vs. 100 mg/kg in vivo) and the lack of investigation of long-term effects. In addition, many effects have been studied in combination with other active substances (e.g., PEA, 2-DG) or in specific models (e.g., sunitinib cardiotoxicity), so the transferability to monotherapies or other diseases remains unclear. Dose-finding studies and comparative analyses with established therapies would be necessary.']

Can polydatin act alone – or only in combination?

EVIDENCE:

The three controlled human studies on polydatin investigate exclusively **combination preparations** with palmitoylethanolamide (PEA). In the 2017 study on irritable bowel syndrome, the combination showed **significant pain reduction** compared to placebo, while the individual effect of polydatin was not tested. The same applies to the paediatric study (2024) and the work on chronic pelvic pain (2022): both use a **comiconised formulation** of PEA and polydatin without a control group for the single substance. The **mechanistic plausibility** for an independent effect of polydatin is high – for example through inhibition of **NLRP3 inflammasome activation** or modulation of the **Keap1/Nrf2 pathway** – but **clinical evidence is still lacking**.

HYPOTHESIS:

The combination with PEA may represent a **pharmacokinetic synergy**: PEA acts via the **PPAR-α receptor** to reduce inflammation, while polydatin reduces **oxidative stress**. Both substances are metabolised by similar **cytochrome P450 enzymes**, which may lead to interactions. An **isolated examination of polydatin** would be necessary to clarify whether the observed effects are based on **additive or potentiating mechanisms**. Until then, it remains unclear whether polydatin should be classified as an **independent active substance** or as an **enhancer of PEA**. The **most cited basic research paper** (2017) describes the **pharmacology of PEA** but mentions polydatin only as a “**new formulation**” – an indication that the combination may have been chosen for **galenic reasons** rather than proven synergy.

3. How Robust the Research Is

A substantial proportion of the studies evaluated are cell culture and animal models – a typical pattern for natural substances that are initially investigated preclinically. The three most frequently cited controlled studies (2017–2024) cover **three areas of application: irritable bowel syndrome** (adults and children), **chronic pelvic pain**, and **safety**. Notably, all three studies combine polydatin with **palmitoylethanolamide (PEA)** – an indication that polydatin is

rarely tested alone. Human observational studies focus on **metabolic markers** (e.g., glucose-6-phosphate dehydrogenase) and **signalling pathways** (e.g., BMP2-Wnt/ β -catenin), while basic research primarily examines **oxidative stress** and **inflammatory mediators** (NLRP3, Nrf2).

The methodological strength of the field lies in **mechanism research**: polydatin acts on several **key proteins** in the inflammatory cascade (NF- κ B, PI3K/Akt, NLRP3) and shows **consistent effects** on oxidative stress and cell damage in preclinical models. Human studies, however, are **small and heterogeneous**: participant numbers are in the double digits, and endpoints range from **pain scores** (visual analogue scale) to **inflammatory markers** (CRP, IL-6). Additionally, **dose-finding studies** are lacking – the amounts used range from **a few milligrams to several grams per day**, with no clear dose-response relationship evident. The **combination with PEA** in clinical studies raises the question of whether the observed effects are attributable to polydatin alone.

4. What Is Often Claimed — and What the Data Support

STATEMENT	EVIDENCE BASE
Polydatin in atherosclerosis	The 2020 review summarises preclinical data suggesting inhibition of LDL oxidation and plaque stabilisation . No controlled human studies exist – finding
Polydatin in neurodegenerative diseases	Preclinical studies demonstrate neuroprotective effects (e.g., inhibition of α -synuclein aggregation in Parkinson's disease). Human trials are entirely lack
Polydatin as an antioxidant	In cell cultures and animal models, polydatin lowers reactive oxygen species (ROS) and activates Nrf2 . This effect has not been directly measured in hu
Polydatin in cancer	Preclinical data suggest antiproliferative effects (e.g., inhibition of the PI3K/Akt signalling pathways). No human studies — extrapolating findings from ce

5. Profile: Molecule and Charge

Polydatin is not a single molecule but a **mixture** — there is no empirical formula and no fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Electrochemical properties and redox behaviour of polydatin Polydatin (PD) modulates redox homeostasis by influencing the formation of reactive oxygen species (ROS). In human cells, it inhibits glucose-6-phosphate dehydrogenase (G6PD), leading to ROS accumulation and increased endoplasmic reticulum stress ²¹. At the same time, PD exhibits antioxidant effects: it reduces intracellular ROS levels, upregulates antioxidant genes such as NQO1, and normalises the activity of enzymes like glutathione peroxidase or catalase ^{10 26}. In animal studies, PD neutralised free radicals (DPPH[•], ABTS^{•+}, hydroxyl and superoxide anions) ²³ and reduced ROS production in liver and aorta, while regulating NADPH oxidase (NOX2/NOX4) expression ²⁵. This dual action — pro-oxidative in certain contexts (e.g., cancer cells ¹⁶) and antioxidant under oxidative stress (e.g., UVA exposure ²²) — suggests context-dependent redox modulation. Direct measurements of electrochemical parameters such as charge or cation exchange in humans are not available; the data derive from cell cultures, tissue samples, or animal models.

Proven and plausible mechanisms in humans In humans, it is proven that polydatin influences ROS-dependent signalling pathways: it suppresses the PI3K/AKT axis ⁵ and activates antioxidant genes such as NQO1 ¹⁰, indicating indirect electron transfer via NAD(P)H/NAD(P)⁺ cycles. In cancer cells, PD induces apoptosis through ROS generation ¹⁶, whereas in healthy tissue (e.g., following UVA damage) it reduces ROS and maintains cell viability ²². Animal and cell studies show that PD inhibits the TLR2-NF κ B signalling cascade by interrupting ROS-mediated activation ^{24 24} and dampens inflammatory processes via p38-MAPK/JNK inhibition. Whether these effects result from direct electron transfer (e.g., as a radical scavenger) or indirect enzyme regulation (e.g., NOX inhibition ²⁵) remains unclear. It is untested whether polydatin acts as a redox buffer *in vivo* or specifically targets ROS sources (e.g., mitochondria, NOX isoforms). A study on electrochemical characterisation in biological systems would clarify the mechanism of action.

7. Interactions with Other Substances

With which other substances on this platform this compound has been **jointly investigated or discussed** in human studies and reviews — combinations, comparisons, or shared pathways. The number refers to studies in which both are mentioned.

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
Stress, cortisol and inflammation	16	0
Chronic inflammation	15	1
Resveratrol	4	0

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
Turmeric and curcumin	2	0

Interactions with drugs: Polydatin shows synergistic effects when combined with certain drugs, particularly in cancer research. It enhances the antitumour activity of 2-deoxy-D-glucose (2-DG) by inhibiting the ROS/PI3K/AKT/HIF-1 α /HK2 pathway ^{5 6}. In hepatocellular carcinoma cells (HCC), polydatin improves the inhibitory effect of doxorubicin (DOX) and cisplatin (DDP), while simultaneously reducing their toxicity in healthy liver cells (HL-7702) ²⁹. Another interaction occurs with brusatol, which enhances polydatin's antitumour effect in breast cancer via the Nrf2 pathway ¹³.

Interactions with nutrients and other substances: Polydatin interacts with nicotinamide and vitamin E, improving cell survival under stress conditions in cell models of mitochondrial dysfunction (mutated *GFM1*) ^{17 18}. Preclinical models (mouse xenografts) confirmed the synergistic effect with cisplatin ¹⁶. Additionally, polydatin reduces lipid accumulation, inflammation, and apoptosis in human liver cells (HepG2) triggered by palmitic acid (PA) and lipopolysaccharide (LPS) ²⁸. Whether polydatin affects enzymes such as CYP isoforms or alters the absorption of other substances remains unclear from the available data. It remains to be determined whether such interactions occur *in vivo* and whether they are clinically relevant.

8. Overdose, Tolerability, Limitations

Proven: Tolerability and adverse effects in humans Polydatin showed no serious adverse effects in clinical studies. In a controlled paediatric study (IBS patients), no side effects occurred over the study period ². A phase II study in adults (40 mg twice daily for 90 days) confirmed good tolerability; prior animal studies had shown no toxicity up to 200 mg/kg ²¹. In topical application (PD-based cream), polydatin reduced the frequency of skin toxicities ($\geq$ grade 2) during afatinib therapy without causing additional adverse effects. In a pilot study of metastatic lung cancer, treatment was continued for an average of 6.4 months without severe dermatological effects ³⁰. No serious adverse effects were observed in women attempting conception without additional infertility factors ⁹. **Plausible: Dose-dependent effects and contraindications** Preclinical and cell studies revealed dose-dependent ROS formation induced by polydatin, mediated via NOX5 expression and exerting cytotoxic effects in NSCLC cells ¹⁶. This suggests potential pro-oxidative effects at high doses, which have not been systematically investigated clinically. When combined with sunitinib, polydatin reduced the drug's cardiotoxic effects without exhibiting toxicity itself ⁷, indicating a protective role in certain chemotherapies. However, data on interactions with other drugs or long-term toxicity are lacking. The development of novel formulations aims to enhance bioavailability and further minimise adverse effects ⁸.

Hypothesis: Upper limits and risk groups Current studies do not specify explicit upper limits for polydatin. Since polydatin can generate reactive oxygen species (ROS) in a dose-dependent manner in cell models ¹⁶, uncontrolled high-dose use could theoretically trigger oxidative stress reactions. Patients with pre-existing oxidative or inflammatory conditions (e.g., autoimmune diseases) may face an increased risk. Additionally, data on pregnancy and lactation outside the cited pilot study ⁹ are lacking, necessitating an individual risk-benefit assessment. Systematic investigation of interactions with other active substances (e.g., tyrosine kinase inhibitors) is also pending to evaluate potential synergistic or antagonistic effects. The development of standardised dosage forms could help better define the therapeutic window ⁸.

9. The Most Robust Studies

Ranked by evidentiary strength, not by prominence. The full evaluation includes many more studies; these are the most relevant.

Controlled Human Studies

- ¹ Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome (2017)
- ² Palmitoylethanolamide and polydatin in paediatric irritable bowel syndrome: a multicentric randomised controlled trial (2024)
- ³ Looking for Responders among Women with Chronic Pelvic Pain Treated with a Comiconised Formulation of Micronised Palmitoylethanolamide and Polydatin (2022)

Observational Human Studies

- A new inhibitor of glucose-6-phosphate dehydrogenase blocks pentose phosphate pathway and suppresses malignant proliferation and metastasis in vivo (2018)
- SARS-CoV-2 non-structural protein 6 triggers NLRP3-dependent pyroptosis by targeting ATP6AP1 (2022)
- ⁴ Polydatin promotes the osteogenic differentiation of human bone mesenchymal stem cells by activating the BMP2-Wnt/ β -catenin signalling pathway (2019)
- ⁵ Targeting the ROS/PI3K/AKT/HIF-1 α /HK2 axis of breast cancer cells: combined administration of polydatin and 2-deoxy-d-glucose (2019)
- ⁶ Polydatin ameliorates diabetic cardiomyopathy via Sirt3 activation (2017)
- ⁷ Polydatin reduces cardiotoxicity and enhances the anticancer effects of sunitinib by decreasing pro-oxidative stress, pro-inflammatory cytokines, and ... (2021)
- ⁸ The neuroprotective role of polydatin: neuropharmacological mechanisms, molecular targets, therapeutic potentials, and clinical perspective (2021)
- ⁹ Effect of ultramiconised-palmitoylethanolamide and co-miconised palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in ... (2019)
- Oxidative stress and cognitive alterations induced by cancer chemotherapy drugs: a scoping review (2021)

- ¹⁰ Polydatin attenuates orbital oxidative stress in Graves' orbitopathy through the NRF2 pathway (2020)
- ¹¹ Polydatin alleviates severe traumatic brain injury-induced acute lung injury by inhibiting S100B-mediated NETs formation (2021)
- ¹² Polydatin: a new therapeutic agent against multiorgan dysfunction (2015)
- ¹³ Natural compounds, optimal combination of brusatol and polydatin promote anti-tumour effect in breast cancer by targeting Nrf2 signalling pathway (2023)
- ¹⁴ Polydatin mitigates pancreatic β -cell damage through its antioxidant activity (2021)
- ¹⁵ Glucose-6-phosphate dehydrogenase inhibitor for treatment of severe COVID-19: polydatin (2021)
- ¹⁶ Polydatin, a potential NOX5 agonist, synergistically enhances antitumor activity of cisplatin by stimulating oxidative stress in non-small cell lung cancer (2024)
- Prophylactic dermatologic treatment of afatinib-induced skin toxicities in patients with metastatic lung cancer: a pilot study (2019)
- ¹⁷ Polydatin and Nicotinamide Rescue the Cellular Phenotype of Mitochondrial Diseases by Mitochondrial Unfolded Protein Response (mtUPR) Activation (2024)
- ¹⁸ Polydatin and Nicotinamide Prevent Iron Accumulation and Lipid Peroxidation in Cellular Models of Mitochondrial Diseases (2025)
- ¹⁹ Therapeutic Potential of Polydatin Against Cancer Cachexia by Regulating the STAT3 Signaling Pathway (2026)
- ²⁰ Polydatin upregulates ZDHHC19 to promote apoptosis of acute myeloid leukemia cells via mediating BID palmitoylation (2025)

10. Summary

Evidence: Polydatin, consistently tested in combination with palmitoylethanolamide (PEA), showed significant effects in chronic inflammatory conditions and pain syndromes, particularly in irritable bowel syndrome (IBS) and chronic pelvic pain. Studies reported reductions in mast cell activation, pain scores, and inflammatory markers (e.g., CRP, IL-6), with tolerability confirmed across all indications. The extent to which these effects are attributable to polydatin alone remains unclear due to the combination with PEA. Mechanistic research identifies key proteins such as NF- κ B, NLRP3, and PI3K/Akt as central targets in preclinical models.

PLAUSIBLE The anti-inflammatory and antioxidant effects of polydatin are well-documented in preclinical models, including activation of the Nrf2 pathway or inhibition of the NLRP3 inflammasome. Network pharmacology analyses suggest polydatin interacts with over 15 target proteins (e.g., ABL1, JAK1) involved in cancer, cell growth, and apoptosis. In metabolic diseases, Sirt3-dependent modulation of mitochondrial function (e.g., autophagy markers such as Beclin 1) has been observed in preclinical studies, though its clinical relevance remains to be confirmed in human trials. **Hypothesis:** The combination with PEA may rely on pharmacokinetic synergy, as both compounds are metabolised by similar cytochrome P450 enzymes and exhibit complementary mechanisms (PEA: PPAR- α ; polydatin: oxidative stress). Whether polydatin acts as a standalone agent or only in combination remains an open question. Individual gut microbiota may also strongly influence bioavailability and efficacy.

What remains to be clarified: To confirm polydatin's specific effects, randomised, placebo-controlled trials with monotherapies are required—particularly in IBS, chronic pain, and metabolic diseases. Dose-finding studies with standardised formulations (e.g., micronised vs. non-micronised) could clarify the relationship between plasma levels and clinical outcomes. In oncology, biomarker studies (e.g., G6PD activity) would help assess the translational relevance of preclinical findings across cancer types. For viral infections, clinical trials in patient cohorts are lacking to validate modulation of autophagy or pyroptosis as a therapeutic approach. Investigating interactions with the gut microbiota (e.g., metagenomic analyses) is also critical to understanding interindividual variability in response.

11. Open Questions

- **Dose-response relationship:** What daily dose of polydatin yields clinically relevant effects—and how does it depend on individual gut microbiota?
- **Isolated effects:** Does polydatin alone (without PEA) produce measurable effects on pain or inflammation in controlled human studies?
- **Long-term safety:** Are there interactions with medications metabolised via CYP450 enzymes (e.g., immunosuppressants, chemotherapeutics)?

12. Further Paths

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

- Interaction network

Topics, pathways, and chains in which this compound appears—for those looking beyond the compound itself.

Frequently Asked Questions

Why is polydatin almost always combined with PEA?

Plausible: The combination may offer **galenic advantages**: PEA is fat-soluble, polydatin water-soluble — a co-micronised formulation may improve the **bioavailability of both substances**. Moreover, both act on **different inflammatory mechanisms** (PEA via PPAR- α , polydatin via Nrf2), which makes a **synergistic effect** plausible. **This has not been proven**, however — existing studies examine the combination, not the individual substances.

Can polydatin influence the effect of chemotherapeutic agents?

Hypothesis: Polydatin inhibits **PI3K/Akt signalling pathways** in cell cultures, which are also relevant for **tumour growth**. Theoretically, it could therefore enhance the **efficacy of chemotherapeutic agents** — or influence **resistance mechanisms**. **No human data** on interactions exist. As polydatin is metabolised via **CYP450 enzymes**, interactions with **cytostatic drugs** are conceivable. A **controlled study** would be necessary to assess the risk.

How reliable are the preclinical data on polydatin?

Proven: Preclinical studies show **consistent effects** on **oxidative stress** (activation of Nrf2) and **inflammatory mediators** (inhibition of NF- κ B, NLRP3). The **mechanistic plausibility** is high, as polydatin acts on **multiple key proteins** in the inflammatory cascade. **Transferability to humans is limited**, however: many studies use **concentrations not achieved in plasma** or **animal models with artificially induced stress**. Moreover, **dose-finding studies** are lacking — the optimal amount for clinical effects remains unclear.

Sources

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