An Insight about Polydatin: Mechanism and Health Benefits

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Abstract

Polydatin is a bioavailable derivative of resveratrol and a powerful stilbenoid polyphenol found naturally. Specifically, polydatin may have biological effects by altering key signalling pathways associated with processes including inflammation, oxidative damage, and apoptosis. Anticancer, cardioprotective, anti-diabetic, gastroprotective, hepatoprotective, neuroprotective, anti-microbial, and health-promoting roles on the renal system, the respiratory system, rheumatoid diseases, skeletal system, and women's health are just some of the suggested essential biological activities for polydatin towards promising therapeutic effects. This assessment of polydatin's health advantages, biological activities, pharmacological mechanisms, and therapeutic targets informs future studies. New information may be gleaned through more clinical trials.
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Introduction:

Polydatin is a stilbenoid polyphenol and a monocrystalline natural compound [1,2,3]. The plant families *Vitaceae*, *Liliaceae*, and *Leguminosae* are prominent sources of polydatin extraction [4]. It is primarily isolated from the rhizome and root of *Polygonum cuspidatum* [5], traditionally used against inflammation, infection, jaundice, skin burns, and hyperlipemia [6]. *Reynoutria japonica* is an invasive plant from the Far East, and a main source of polydatin in industrial scale [7]. This plant source of polydatin is so invasive that it has reached even the most remote mountain areas where it unbalances the ecosystem including the agricultural potential of mountain areas, being advantaged by the context of climate change [8]. This phytochemical is also found in other plant sources such as red wine [9], nuts, vegetables, fruits [5], hop cones/pellets, and cocoa- and chocolate-containing products [10].

Polydatin is a glucoside derivative of resveratrol. Moreover, polydatin has a higher antioxidant [3] and anti-inflammatory [11] activity compared to resveratrol [1,12,13,14,15,16]. It possesses four leading derivatives in nature, including *trans*-polydatin, *trans*-resveratrol, *cis*-polydatin, and *cis*-resveratrol [10,17]. *trans*-polydatin, itself, can be produced from 4-coumaryol-CoA through a stilbene synthase reaction. Several methods have been developed for the isolation of resveratrol from other isomers in *P. cuspidatum*, including reflux extraction, filtering, hydrolyzing, liquid–

liquid extraction, eluting, and high-performance liquid chromatography coupled to an ultraviolet–visible diode array detector [18,19].

The therapeutic and protective effects of polydatin mainly originate from its anti-inflammatory, antioxidant, and anti-apoptotic activities [20]. Previous studies have shown a wide range of therapeutic effects of polydatin in the treatment of several pathological diseases such as cancer [21], cardiovascular diseases [22], diabetes [23], neurodegenerative diseases [24], hepatic/respiratory diseases [25,26], gastrointestinal diseases [27], infectious diseases [28], rheumatoid diseases [29], and skeletal/women disorders [30,31].

Previously, the protective effects of polydatin have been disclosed against neurodegenerative diseases [20,32,33], atherosclerosis [34,35], and multiple organ ischemia/reperfusion injury [36]. The protective effects of polydatin on damaged macrophages were also highlighted by Liu et al. [37]. A more recent study also reviewed the pharmacological effects of polydatin in some diseases [38]. In the current mechanistic review, the therapeutic targets, pharmacological mechanisms, biological activities, and health benefits of polydatin are highlighted for all related biological/pathological conditions. Moreover, the need to provide different novel delivery systems and clinical trials of polydatin is also considered to reveal new insights to researchers

Pharmacological Mechanisms of Polydatin

Considering the critical role of inflammation, oxidative stress, and apoptosis in the progression of several diseases, polydatin could play therapeutic roles by regulating associated signaling pathways.

Anti-Inflammatory Effects

As a protective mechanism, the initiation of inflammation is attributed to the involvement of immune system response against diverse factors such as pathogens, injured tissues, and infectious agents, which is generally attributed to favoring tissue repair and organ healing. This defense process is divided into two major categories known as acute and chronic inflammation. At present, chronic inflammation could be considered a vital cause of human diseases (e.g., atherosclerosis, arthritis, diabetes, neurodegenerative diseases, and cancer) [39,40]. In this context, chronic inflammation is induced via uncontrolled acute inflammatory responses through inflammatory mediators such as cytokine production and immune cell recruitment [39,41]. Reportedly, nuclear factor-kappa B (NF-κB) is considered as the key transcription factor in increasing inflammatory mediators/cascades, including tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), IL-6, and intercellular adhesion molecules (ICAMs) in various diseases. Such inflammatory mediators and interconnected pathways are mainly involved in the underlying mechanisms of the inflammatory state [42]. Several studies show that phytochemicals are multi-target agents that effectively represent their anti-inflammatory activities through underlying cellular mechanisms against different diseases associated with chronic inflammation [43]. In the phytochemical context, it has been reported that polydatin is a potent anti-inflammatory plant secondary metabolite [44], beneficially promoting miR-200a expression to regulate the Kelch-like ECH-associated protein 1

(Keap1)/nuclear factor E2-related factor 2 (Nrf2) antioxidant axis. This pathway, in turn, suppresses nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome activation against diverse chronic inflammation-related diseases in vivo [25,45]. Furthermore, under inflammatory conditions, polydatin exhibited anti-inflammatory roles by improving AMP-activated protein kinase (AMPK)/sirtuin1 (Sirt1)/Nrf2 signaling expression, leading to the inhibition of the NF-κB/inhibitor of nuclear factor-kappa B α (IκBα)/NLRP3 pathway, as well as the reduction of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [31,46,47]. Meanwhile, polydatin treatment downregulated the expression of cerebral ischemia or spinal cord injury (SCI)-induced inflammatory mediators such as Toll-like receptor 4 (TLR4), NF-κB, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), nitric oxide (NO), and ICAM-1 [48,49,50]. In line with this, polydatin potentially plays a vital role in preventing the inflammatory action by reducing mitogen-activated protein kinases (MAPKs). This response is mainly orchestrated by extracellular-signal-regulated kinases (ERK1/2), c-Jun N-terminal kinase 1/2 (JNK1/2), and p38 protein kinases, and consequently inhibits NF-κB p65 phosphorylation and the release of inflammatory factors such as xanthine oxidase (XOD), prostaglandin E2 (PGE2), TNF-α, IL-1β, and COX-2 [51,52]. Another mechanism of the neuroprotective effect of polydatin is mediated by the CCAAT/enhancer-binding proteinβ (C/EBPβ)/metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/cAMP response element binding (CREB)/peroxisome proliferator-activated receptor gamma co-activator 1α (PGC-1α)/peroxisome proliferative-activated receptor γ (PPARγ) signaling pathway. This process results in silencing NF-κB-associated downstream inflammatory mediators, which could alleviate cerebral infarct volume and ameliorate the integrity of the blood–brain barrier (BBB) [53]. Numerous studies have confirmed that polydatin application could suppress phospholipase A2 (PLA2) against lipopolysaccharide (LPS)-induced lung injury [54], decreasing the serum levels of alanine transaminase (ALT) and aspartate aminotransferase (AST) against fulminant hepatic failure (FHF) [55]. Additional reports also revealed that polydatin downregulated the retinoic acid receptor-related orphan receptor gamma t (RORγt) and signal transducer and activator of transcription 3 (STAT3) gene expression, attenuated IL-17 production against CD3/DC28-induced peripheral blood mononuclear cells and arthritis [11,56], and ultimately reduced both the NF-κB and vascular endothelial growth factor (VEGF) as well as the circulating levels of the downstream inflammatory cascade including IL-6, TNF-α [56].

Antioxidant Effects

Oxidative stress is characterized by aberrant generation of the reactive oxygen species (ROS) and reactive nitrogen species (RNS) as byproducts of this metabolic process which leads to devastating effects on molecular intracellular signaling pathways and to the development of numerous diseases [57,58]. The antioxidant reaction of polydatin is presented via reducing lipid peroxidation while promoting antioxidant enzymatic activity against hepatotoxicity induction in vivo [59]. Polydatin has also shown modulatory roles on ROS and RNS in peripheral [60] and central diseases [49].

Nrf2 could be the most vital antioxidative response-associated transcription factor and alleviates inflammation [**61**]. In this regard, polydatin strongly acts as an antioxidant agent on LPS-induced BV2 microglia cells in SCI-induced rat models via promoting the Nrf2/heme oxygenase-1 (HO-1) pathway activity, resulting in improved locomotor performance, suppressing spinal edema, and attenuating neurological deficits [**24**]. Additionally, the activation of protein kinase B (Akt) phosphorylation may be accelerated through the Nrf2/HO-1/NAD(P)H quinone dehydrogenase 1 (NQO1) expression-mediated antioxidant pathway after polydatin administration [**51**]. It has also been proposed that polydatin could significantly enhance Nrf2/thioredoxin (TRX) antioxidant signaling, and upregulate the Gli1/patched 1 (Ptch1)/superoxide dismutase 1 (SOD1) pathway, indicating its neuro/nephron-protective action against ischemic brain/renal injury-induced ROS generation [**62**,**63**,**64**]. Further in vivo studies have also indicated that polydatin supplementation provided an antioxidant ability through the Sirt1/Nrf2/antioxidant-responsive element (ARE) signaling pathway to reduce diabetes-induced renal dysfunction [**65**], as well as through the Notch1/Hes1-Pten/Akt axis to improve ischemic/reperfusion-injured diabetic heart disease [**66**,**67**]. Further, polydatin consumption is possibility beneficial against atherosclerosis and cardiovascular disease-induced oxidative stress via the scavenging of hydroxyl, oxygen free radicals, myeloperoxidase (MPO), and ROS [**56**,**68**,**69**], elevating enzymatic antioxidants such as SOD, glutathione peroxidase (GSH-Px), glutathione transferase (GST), catalase (CAT), and glutathione (GSH) [**70**]. Polydatin also induced protein kinase C (PKC) and the mitochondrial adenosine triphosphate (ATP)-sensitive-K^+ (mito-K_{ATP}) channel [**71**] towards the modulation of mitochondrial function and the Akt signaling pathway [**35**,**72**]. The body of this evidence strongly supports that the attenuation of Akt is associated to the antioxidant effect of polydatin [**50**]. In addition, polydatin attenuated the activity of hepatic stellate cells (HSCs) through its antioxidant activity on sphingosine kinase 1 (SphK1) signaling to ameliorate mice liver fibrosis induced by carbon tetrachloride (CCl4) [**73**].

Overall, polydatin employs several antioxidant mediators while suppressing oxidative pathways towards therapeutic responses in several disorders.

Apoptosis is defined as a programmed model of physiological cell death without the involvement of an inflammatory condition. Nonetheless, the uncontrolled regulation of this mechanism could be engaged in several diseases, including cancer, autoimmune diseases, and neurodegenerative disorders [**74**]. In this regard, polydatin significantly exhibited anti-apoptotic effects in a mice model of liver injury through the attenuation of Bcl-2-associated x (Bax) expression and enhancing B-cell lymphoma 2 (Bcl-2) expression [**59**]. In another experimental study, polydatin showed its anti-apoptotic activity by increasing Bcl-2 or D-cyclins and reducing caspase-3 or Bax levels in gastrointestinal injury. Such an effect is made by the activation of Gli1 transcription factor followed by the upregulation of the Sonic hedgehog (Shh) signaling pathway as the major component in repairing dextran sulfate sodium-induced colitis-related damaged tissues [**75**]. In another study, polydatin exerted its protective effects against acute lung injury-induced mitochondrial apoptosis by increasing Parkin-mediated mitophagy expression via inhibiting Bax, cytochrome c, and

caspase-3 activity as well as promoting Bcl-2 and mitochondrial membrane potential proteins [76]. Furthermore, polydatin administration could attenuate neuronal apoptosis through repressing p53/MAPK/JNK signaling activation in a rat model of ischemic brain injury [62]. Consequently, polydatin improved autophagy and apoptosis during osteoarthritis through suppressing the MAPK and phosphoinositide 3-kinases (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway [77]. Taken together, the described anti-apoptotic activities of polydatin indicate that this compound could be considered as a promising agent for apoptosis-induced tissue damage.

Biological Activities of Polydatin

As previously mentioned, polydatin exhibits significant pharmacological effects through its anti-inflammatory, antioxidant, and apoptosis-modifying activities. During different physiological/pathological conditions, the activity and expression of involved signaling pathways would change and polydatin plays a critical modulatory effect. We previously described near interconnections between the aforementioned signaling pathways during diseases which support each other [78,79]. Such effects make polydatin a potential therapeutic compound in the treatment of different pathological conditions.

Anticancer Effects

According to statistics from the World Health Organization, cancers leave the heaviest strain on the worldwide population based on the disability-adjusted life year (DALY) scale [80]. Radiotherapy, surgery, and chemotherapy are the main strategies in treating various cancer types [81,82]; however, associated resistance and side effects limit their applications. In addition, considering the multiple signaling pathways involved in cancer pathogenesis, there is an urgent need to provide novel alternatives and safe multi-target phytochemicals [83,84,85]. In this regard, the anticancer activity of polydatin has been elucidated against different cancer types [86].

From the mechanistic point, polydatin modulates oxidative stress to decrease carcinogenesis and mutagenesis [87]. It is reported that polydatin inhibits tumor growth [88] and improves radiosensitivity via inducing apoptosis in colorectal cancer models [89]. Polydatin also plays therapeutic roles in the treatment of leukemia alone or in combination with Janus kinase (JAK) inhibitors [86,90]. Moreover, it is revealed that polydatin is efficacious in the treatment of laryngeal cancer [91], nasopharyngeal cancer [92], ovarian cancer [93], lung cancer [94,95,96], glioblastoma multiforme [97], multiple myeloma [98], and cervical cancer [99,100]. Consequently, polydatin exerts therapeutic effects against such cancers employing different mechanisms, including the inhibition of proliferation/migration [97]. Several pre-clinical studies demonstrated that polydatin exerted therapeutic effects against an orthotopic metastatic tongue cancer model via inhibiting glucose 6 phosphate dehydrogenase (G6PD), and reduced tumor size and lymph node size and metastases [1]. In another study, the inhibition of G6PD by polydatin reduced tyrosine kinase inhibitor (TKI) resistance in breast cancer models [21]. In addition, polydatin suppressed the growth of MDA-MB-231 and MCF-7 breast cancer cell lines in vitro

[**101**]. This secondary metabolite also induced apoptosis and inhibited cell proliferation/migration in breast cancer cell lines when used in combination with 2-deoxy-D-glucose [**102**].

Osteosarcoma is a malignant bone tumor; however, its etiology and pathogenesis remain unclear [**103**]. Prevailing in vitro studies showed that polydatin inhibited cells' migration [**103**] and proliferation [**103,104,105**]. In this regard, inhibition of the β-catenin signaling pathway by polydatin is associated with its anti-proliferative effects [**105**]. Polydatin also induced apoptosis [**103,104**] via different mechanisms such as reducing the expression/phosphorylation of STAT3, increasing autophagy-related gene expression [**104**], and caspase-3 activity [**105**] in vitro. Polydatin also exerted therapeutic effects against doxorubicin-resistant osteosarcoma by suppressing TUG1/Akt signaling, promoting apoptosis and suppressing cell proliferation. In addition, polydatin reduced tumor size in animal models [**106**]. On another point, chronic liver disease and cirrhosis lead to hepatocellular carcinoma (HCC). HCC is a common malignancy of the liver and is classified as the third leading cause of cancer-related deaths in the world [**107**]. Similarly, polydatin showed positive effects against HCC through the inhibition of the Akt/STAT3–forkhead box protein O1 (FOXO1) signaling pathway towards apoptosis induction [**108**]. It also inhibited proliferation/invasion/migration of cell lines [**107**], and reduced tumor growth by increasing caspase-3 expression and terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling (TUNEL) activity in animal models of HHC [**107**].

On the other hand, it is worth mentioning that polydatin could remarkably induce apoptosis against acute monocytic leukemia cell proliferation via modulating cyclin D1, Bcl-2, cyclin A, and Bax, accompanied by cell cycle arrest at the S phase [**90**]. Additionally, polydatin induced apoptosis in human nasopharyngeal carcinoma CNE cells through ROS-mediated mitochondrial dysfunction and endoplasmic reticulum stress. Thus, polydatin might be a promising anti-tumor agent through inducing apoptosis [**92**]. Additionally, polydatin inhibited the progression of doxorubicin-resistant osteosarcoma by regulating the taurine-upregulated gene 1 (TUG1)/Akt signaling pathway [**106**]. Furthermore, suppressing the phosphorylation of CREB and cyclin D1 gene expression might be associated with the apoptotic effect of polydatin on human breast cancer cells [**101**]. Moreover, extensive studies have demonstrated that the suppression of platelet-derived growth factor (PDGF)/Akt signaling [**91**], stimulation of cytochrome c release, and activation of poly (ADP-ribose) polymerase (PARP) fragmentation [**109**] could induce cell cycle arrest and apoptosis on polydatin-treated laryngeal/cervical cancer and oral squamous cell carcinoma.

Not only is polydatin efficacious in the treatment of various cancer types, it also reduces adverse effects of some chemotherapeutic agents such as cisplatin [**110**] and doxorubicin [**111**]. Polydatin plays a protective role against cisplatin-induced toxicity via improving antioxidant mechanisms and tissue regeneration [**110**]. It is reported that polydatin attenuated the cardiotoxicity of doxorubicin by increasing heart rate, arterial pressure, and GSH-Px activity while reducing myocardial injury. In addition, polydatin decreased ST, QT, and QRS intervals in an electrocardiogram. Antioxidant effects and the enhancement of metabolism were also associated with the protective effects of polydatin [**111**].

Neuroprotective Effects

Neurological diseases are known as the second leading cause of death globally. Such disorders are the first cause of severe long-term disability worldwide [112]. Oxidative stress and inflammatory and apoptotic processes play essential roles in the pathogenesis of neurological diseases [112]. Regarding the previously described antioxidant, anti-inflammatory, and anti-apoptotic activities of polydatin, it can be a potential agent in the treatment of neurological diseases. Studies revealed therapeutic and protective effects of polydatin against Parkinson's disease (PD) [112], intracranial hemorrhage (ICH) [113], cerebral ischemia [5], hemorrhagic shock [114,115], SCI [24], dementia [116], and traumatic brain injury [117].

Oxidative stress and mitochondrial dysfunction are two critical factors involved in PD pathogenesis [112]. It is shown that polydatin has neuroprotective effects against PD through various mechanisms [9,112,118,119]. Polydatin attenuated motor dysfunction in animal models of PD via lowering pro-inflammatory cytokine and microglial suppression. Inhibition of microglial activation leads to the decrement of dopaminergic neurodegeneration. Consequently, polydatin regulated the Akt/glycogen synthase kinase-3β (GSK-3β)/Nrf2/NF-κB signaling axis towards such effects [118]. In addition, polydatin improved cell viability and Sirt1 expression. It also decreased mitochondrial dysfunction and ROS level [119]. Moreover, it was revealed that polydatin exerted therapeutic and protective effects in animal models of PD, including decreasing dopaminergic neuronal degeneration, neural apoptosis, and improving motor function via enhancement of glucose metabolism in neurons [120]. Polydatin also has the ability to pass through the blood–brain barrier [112]. Taken together, polydatin can be a potential therapeutic agent for treatment of PD.

Neurological I/R conditions due to oxygen and glucose deprivation lead to the occurrence of neurotoxicity and apoptosis [53,121]. Production of ROS and the inflammatory process are some of the main factors that contribute to neurological damages of I/R conditions. It has been demonstrated that polydatin, through its antioxidant, anti-inflammatory, and anti-apoptotic activities, exerts neuroprotective effects [53,62,63,116,121,122,123]. It is reported that polydatin improved neurological dysfunction and reduced infarcted area in animal models through inhibition of various CAMs, ameliorating mitochondrial dysfunction and decreasing ROS and pro-inflammatory factors [122,123,124]. Moreover, polydatin causes an enhancement in behavioral scores, reducing brain edema and hemiplegia in animal models [125].

Polydatin can improve cognitive function in conditions such as dementia [116], ethanol toxicity [126], and doxorubicin-induced cognitive impairment [81] via antioxidant [81,116], anti-inflammatory, and anti-apoptotic effects in the hippocampus [116]. Upregulation of the Nrf2/ARE signaling pathway plays an essential role in this polydatin effect [81]. In addition, polydatin ameliorated memory impairment in animal models via upregulation of brain-derived neurotrophic factor (BDNF) [127].

It is reported that polydatin has protective and therapeutic effects on SCI, such as improving motor function, reducing apoptosis, and enhancing neuron and bone marrow stromal cell (BMSC) viability [24,49,128]. Mitochondrial injury plays an essential role in SCI. Polydatin also attenuates mitochondrial dysfunction via activation of the Nrf2/ARE signaling pathway [24,129]. In addition, it is revealed that activation of the Nrf2/ARE signaling pathway by polydatin administration and BMSC transplantation led to the improvement of neuronal regeneration in animal models of SCI, facilitating BMSC differentiation and reducing glial scar formation in glial cells [130]. The reduction in inflammatory factors is another mechanism associated with polydatin's protective and therapeutic effects against SCI [49].

It is demonstrated that polydatin has therapeutic effects against intracranial hemorrhage (ICH) and its complication [113,131]. Polydatin improved neuronal function [113] and inhibited brain edema in animal models [131]. Regulation of the Nrf2/ARE signaling pathway and downstream genes are mechanisms that are associated with the antioxidant activity of polydatin against ICH [113]. In addition, increasing levels of excitatory amino acids by polydatin may be associated with the protective and therapeutic effects of polydatin against ICH [131].

As mentioned in , activation of Nrf2-related signaling is one of the primary mechanisms involved in polydatin's therapeutic effects against neurological diseases such as ICH, PD, and cognitive impairment. Moreover, the anti-apoptotic effects play essential roles in this field. Polydatin can be a suitable choice in the treatment of neurological diseases

Conclusions

As such, the broad therapeutic potential of polydatin urges the need for finding potential sources to promote the application of polydatin in industrial, commercial, and research sectors. Of polydatin sources, Reynoutria japonica is a useful highly invasive plant and a rich source in the pharmaceutical industry. However, to better improve the bioavailability and efficacy of polydatin in clinical trials, investigating appropriate delivery systems in order to solve the pharmacokinetic limitation is of great importance.

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