




Protective effects of polydatin against bone and joint disorders: the *in vitro* and *in vivo* evidence so far

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Abstract

Polydatin is an active polyphenol displaying multifaceted benefits. Recently, growing studies have noticed its potential therapeutic effects on bone and joint disorders (BJDs). Therefore, this article reviews recent *in vivo* and *in vitro* progress on the protective role of polydatin against BJDs. An insight into the underlying mechanisms is also presented. It was found that polydatin could promote osteogenesis *in vitro*, and symptom improvements have been disclosed with animal models of osteoporosis, osteosarcoma, osteoarthritis and rheumatic arthritis. These beneficial effects obtained in laboratory could be mainly attributed to the bone metabolism-regulating, anti-inflammatory, antioxidative, apoptosis-regulating and autophagy-regulating functions of polydatin. However, studies on human subjects with BJDs that can lead to early identification of the clinical efficacy and adverse effects of polydatin have not been reported yet. Accordingly, this review serves as a starting point for pursuing clinical trials. Additionally, future emphasis should also be devoted to the low bioavailability and prompt metabolism nature of polydatin. In summary, well-designed clinical trials of polydatin in patients with BJD are in demand, and its pharmacokinetic nature must be taken into account.

Keywords: Polydatin; Osteoporosis; Osteosarcoma; Osteoarthritis; Rheumatic arthritis

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Introduction

Polydatin, also known as piceid, is a natural polyphenol predominantly isolated from the root and rhizome of *Polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae)⁽¹⁾. Polydatin also exists in many plant species and processed foods, including grapes, peanuts, berries, wine and beer, in addition to Polygonaceae^(2,3). It is also a common component of the Mediterranean diet which is associated with a wide range of benefits for health⁽⁴⁾. Both *in vivo* and *in vitro* studies have revealed the multifaceted beneficial effects of polydatin, including anti-inflammatory, antioxidative, anticarcinogenic, neuroprotective, hepatoprotective and immunostimulatory effects^(1,5).

The skeletal system consists mainly of bones and joints, providing not only movement abilities and support for the human body but also cushion-like protection for other organs. Bone and joint disorders (BJDs) cover a range of diseases, including bone fracture, osteoarthritis, rheumatic arthritis (RA), cancer and osteoporosis. The prevalence of BJDs is high, as the former

three disorders alone affected 793 million people globally in 2019⁽⁶⁾. These disorders affect people across all ages, with high morbidity among the elderly^(7,8).

Polydatin has demonstrated multitarget and multisystem effects⁽⁹⁾. Since 2015⁽¹⁰⁾, the effects of polydatin against BJDs have been reported both *in vivo* and *in vitro*, suggesting a possible advantageous effects in humans. However, previous reviews of polydatin mainly concentrated on fields of atherosclerotic disease⁽⁹⁾, ischaemia–reperfusion injury⁽¹¹⁾ and the cardiovascular system⁽¹²⁾. Accordingly, the current review aims to systematically present the current progress on the beneficial effects of polydatin against different BJDs based on reported experiments in cell lines, cells isolated from animals and humans, and animals, and the underlying molecular mechanisms are also elucidated.

Characteristics of polydatin

Polydatin has the chemical structure of 3,4',5-trihydroxystilbene-3-β-D-glucoside (Fig. 1a). This structure is analogous to that of

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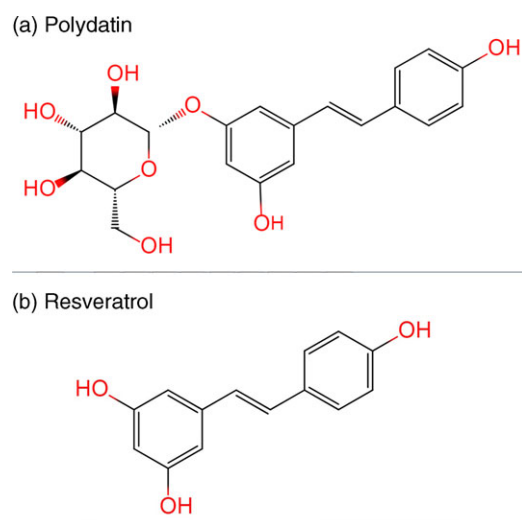


Fig. 1. Chemical structures of (a) polydatin and (b) resveratrol.

resveratrol, with a glucose group at position C-3 instead of the hydroxyl group of resveratrol (Fig. 1). Therefore, polydatin is considered the glycosylated resveratrol.

Pharmacokinetics of polydatin

As an essential factor determining the pharmacological efficacy and clinical safety of a drug, the pharmacokinetics of polydatin remain under investigation. The absorption of polydatin can be achieved through both passive diffusion and sodium-dependent glucose transporter-1 (SGLT-1)⁽¹³⁾. Detailed absorption mechanisms have been reviewed in a previous study⁽¹⁴⁾. Polydatin can be absorbed rapidly but is also eliminated promptly from the plasma⁽¹⁵⁾. With rats, a study reported the maximum plasma concentration (C_{max}) and the area under the concentration–time curve from dosing time 0 to t (AUC_{0-t}) values of $1.43 \pm 0.36 \mu\text{M}$ and $1.42 \pm 0.42 \mu\text{mol/h/L}$, respectively, at an oral administration dose of 100 mg/kg. A rapid decrease in concentration in the plasma was noticed with a terminal half-life ($t_{1/2}$) of $1.02 \pm 0.08 \text{ h}$ ⁽¹⁶⁾. In regard to human subjects, polydatin at a concentration of $65.07 \pm 6.81 \text{ nM}$ was detected in the plasma of volunteers 2 h after the oral administration of 75 mg polydatin⁽¹⁷⁾. Polydatin undergoes extensive first-pass deglycosylation and glucuronidation⁽¹⁸⁾. Upon intake, it is primarily distributed in the gastrointestinal tract and liver, and the intestine is the main organ where polydatin is hydrolysed into resveratrol, its aglycones^(15,19,20). The resulting resveratrol then undergoes further glucuronidation in the intestine and liver to form glucuronide and sulphate conjugates, which are excreted in urine and bile afterward^(15,20).

As reviewed above, polydatin displays high metabolism and excretion *in vivo*, whereas, in the *in vitro* tests reviewed, polydatin was applied directly on cells. This is a common conundrum for many polyphenols. A study with resveratrol detected the resveratrol at a concentration of about 2–10 nmol/g in tumour tissues in a mouse xenograft model at an oral administration dosage of 50 mg/kg for 5 weeks⁽²¹⁾. However, such evidence is not available with polydatin yet. Therefore, it remains unclear whether polydatin could reach the target tissues in the parent

form and at effective concentrations. Accordingly, cautions should be exercised regarding the reliability of *in vitro* outcomes throughout the review.

Interplay between polydatin and gut microbiota

The gut has the most diverse and abundant microbiota in the human body⁽²²⁾. The gut microbiota plays an indispensable role in mediating host metabolism and the effects of dietary compounds on the host. Accumulating evidence indicates that a series of polyphenols can be catabolised by gut microbiota and achieve improved oral bioavailability⁽²³⁾. Meanwhile, polyphenols can also modulate the microbial profile, suggesting an intimate interplay between polydatin and symbiotic bacteria⁽²⁴⁾. Owing to the inadequate absorption of glycosides by the small intestine, polydatin can persist to the colon and undergo metabolism by gut microbiota⁽²⁵⁾. *In vitro* tests with human intestinal bacteria (*Lactobacillus acidophilus*) and enzymes (*Bifidobacterium infantis*, *Bifidobacterium bifidum*, *Lactobacillus acidophilus* and *Lactobacillus plantarum*) revealed that polydatin can be deglycosylated into its aglycone, resveratrol^(26,27). Another two compounds, dihydro-polydatin and dihydro-resveratrol, were also identified as microbial degradation products by rat gut microbiota *in vitro*⁽²⁸⁾. While the gut microbiota regulates the metabolism of polydatin, polydatin also markedly influences microbial ecology. Polydatin markedly affects the abundance of the genera *Bifidobacterium*, *Butyricimonas*, *Desulfovibrio* and *Muribaculum* in mouse faeces. Such changes in microbiota lead to elevated faecal levels of valeric acid and caproic acid, which, in turn, enhance the effects of polydatin on improving lipid metabolism⁽²⁵⁾.

Low toxicity of polydatin

Polydatin has low toxicity to humans, animals and cells. In a phase II clinical trial treating both patients with irritable bowel syndrome and healthy controls with palmitoylethanolamide/polydatin at 200 mg/20 mg per day for 12 weeks, a safety profile similar to that of the placebo (cellulose) was obtained⁽²⁹⁾. A higher dosage (palmitoylethanolamide/polydatin at 400 mg/40 mg twice a day for 3 months) was tested in another clinical trial treating 21 patients with chronic pelvic pain related to endometriosis, and no significant side effects were reported⁽³⁰⁾. An intraperitoneal injection of 100 mg/kg polydatin caused neither death nor abnormal neurobehavior in mice⁽³¹⁾. Upon carrying out *in vitro* tests, it was found that polydatin did not cause observable cytotoxicity in human osteoarthritic chondrocytes at doses of up to 100 $\mu\text{g/mL}$ ⁽³²⁾. Similar results were reported for human neutrophils with polydatin concentrations up to 125 $\mu\text{g/mL}$ ⁽³³⁾. However, cytotoxicity was observed in nucleus pulposus cells upon increasing the polydatin concentration to 600 $\mu\text{g/mL}$ ⁽³⁴⁾.

Osteogenesis-potentiating effects of polydatin *in vitro*

Stem cells are a key element of bone metabolism, while *in vitro* studies have shown that polydatin regulated their behaviours (Fig. 2). The migration of stem cells to damaged or resorbed sites is a prerequisite for bone formation, and polydatin has been

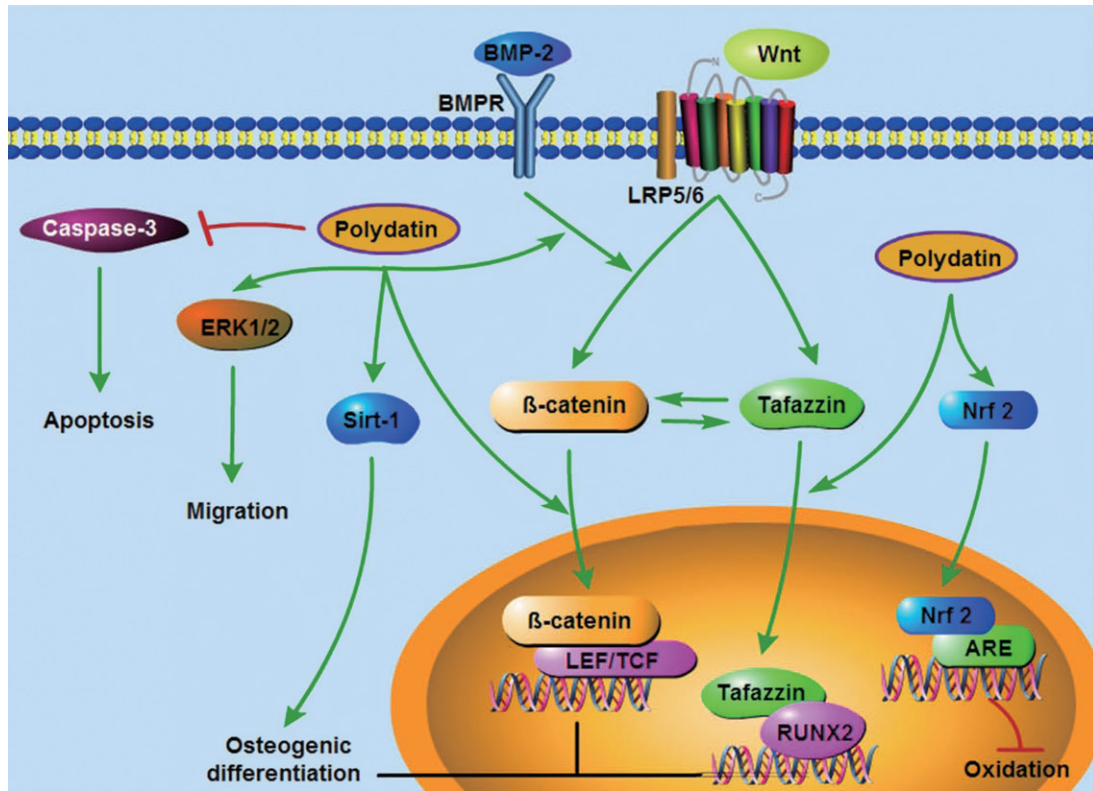


Fig. 2. Potential molecular mechanisms for the effects of polydatin on stem cells related to bone metabolism.

found to promote the migration of bone marrow stromal cells (BMSCs). It was found that the migration rate of rat BMSCs was elevated by approximately two-fold upon 30 μM polydatin treatment compared with that of the untreated group⁽³⁵⁾. This promotion function is achieved by activating extracellular signal-regulated kinase 1/2 (ERK1/2)⁽³⁵⁾, a cascade actively participating in the regulation of cell migration⁽³⁶⁾.

Polydatin also augments stem cell differentiation towards osteogenesis. This is exemplified by up-regulated expression of a series of osteogenic markers, from early to late, such as Runx2, collagen type I (COL-I), osteopontin (OPN), osteocalcin (OCN) and bone morphogenetic protein-2 (BMP-2)^(37–39). Especially for OCN and BMP-2, their expression in human BMSCs stimulated by polydatin (30 μM) can be seven- to eight-fold higher than those of the untreated groups^(38,39). The elevation of osteogenic differentiation is concentration dependent, with 0.1 and 30 μM polydatin showing the optimised effects for human dental bud stem cells (DBSCs) and BMSCs, respectively^(37–39). The activation of Wnt/β-catenin, BMP-2 and their crosstalk through Tafazzin is considered to mediate polydatin-induced differentiation^(31,38,39). Wnt/β-catenin signalling is indispensable for the differentiation of BMSCs towards osteoblast progenitors, and BMP signalling further induces their maturation into osteoblasts⁽⁴⁰⁾. Tafazzin, a target of the above two signalling pathways, also mediates osteogenic genes⁽³⁹⁾. Additionally, Di Benedetto *et al.*⁽³⁷⁾ observed a positive correlation between polydatin-induced cell differentiation and protein expression of Sirt-1, an important potential target gene of polydatin⁽⁴¹⁾.

In addition to enhancing migration and osteogenesis, polydatin also enhances the anti-apoptotic and antioxidative abilities of BMSCs. In a study on H₂O₂-induced apoptosis in BMSCs, the up-regulation of pro-apoptotic B-cell lymphoma-2 associated X protein (Bax) and cleaved caspase-3 was accompanied by a down-regulation of B-cell lymphoma-2 (Bcl-2)⁽¹⁰⁾. By pre-treating rat BMSCs with 30 μM polydatin, the apoptotic rate recovered to a level comparable to that of the untreated group, and the above apoptotic features were also reversed. Moreover, polydatin (30 μM) enhances the resistance of BMSCs to oxidative injuries with reduced reactive oxygen species via the activated nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf 2/ARE) pathway⁽¹⁰⁾.

In summary, polydatin modulates the behaviours of BMSCs, varying from migration to differentiation, apoptosis and oxidation. However, it should be noted that the above effects were obtained in *in vitro* experiments which neglected the influences of rapid metabolism in animals and humans. Therefore, *in vivo* tests and human trials are especially essential to confirm the beneficial effects for compounds with fast and extensive metabolism.

Dual effects of polydatin on osteoporosis

Osteoporosis is a metabolic bone disease that primarily affects Caucasians, elderly people and women. It is characterised by low bone mass, degraded bone tissue and defective bone micro-architecture⁽⁴²⁾. As a result of impaired bone strength, patients

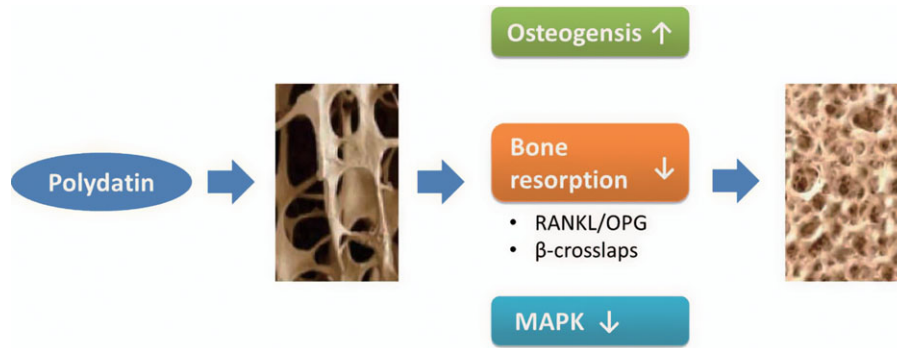


Fig. 3. Schematic illustration of the potential protective mechanisms of polydatin against osteoporosis.

with osteoporosis are susceptible to fractures⁽⁴³⁾. However, owing to a lack of clinical manifestations, awareness and diagnosis of this disease are deficient until fracture occurs⁽⁴²⁾. Current anti-osteoporosis pharmacological approaches mainly include oestrogen and bisphosphonates⁽⁴⁴⁾. Unfortunately, concerns regarding long-term efficiency and side effects have led to decreased patient compliance⁽⁴⁵⁾. Meanwhile, dietary components of calcium and vitamin D have been investigated extensively for bone health, while polyphenols have also been implicated in the bone metabolism regulation⁽⁴⁶⁾.

Excessive bone resorption and a failure of bone regeneration to maintain pace are considered the major pathogenetic factors of osteoporosis⁽⁴⁷⁾. As discussed above, *in vitro* studies have suggested benefits of polydatin for BMSCs. Attempts have also been made on exploring its anti-osteoporosis effects on cells and animals, and the possible mechanisms are summarised in Fig. 3.

Anti-osteoporosis *in vitro*

The *in vitro* anti-osteoporosis study of polydatin is limited. Lin *et al.*⁽⁴⁸⁾ established an osteoporosis model by treating MC3T3-E1 cells with dexamethasone (100 nM) and noticed that polydatin (20–80 μ M) promoted the differentiation of osteoporotic preosteoblasts. This finding indicates that the above-discussed osteogenesis-potentiating effect remains valid with osteoporotic cells. In the same study, a bioinformatic analysis was conducted to identify the potential molecular mechanisms. Upon screening pathways shared by osteoporosis and polydatin-targeted genes, mitogen-activated protein kinase (MAPK) signalling was identified. The *in vitro* experiment further confirmed that three major subfamilies of MAPK, namely ERK1/2, p38 α and c-Jun N-terminal kinase (JNK), were involved in polydatin-promoted cell differentiation *in vitro*.

Anti-osteoporosis *in vivo*

In vivo studies have demonstrated the repair of osteoporotic bones upon polydatin treatment. By intraperitoneally injecting (i.p.) polydatin (3 mg/kg, every 2 d) into ovariectomised mice, a prominent repair effect on the defective bone structures could be seen after 4 weeks, and the bone defects recovered to basal levels after 8 weeks, as characterised by computerised tomography. These defective structures included low bone volume per

tissue volume, low trabecular number and thickness, high trabecular separation, high trabecular structure model index and high bone surface area per bone volume⁽³⁹⁾. In the serum of ovariectomised animals, the levels of osteogenesis indices, including ALP, osteoprotegerin (OPG), calcium and phosphorus, were also augmented upon polydatin treatment (3–40 mg/kg, i.p.)^(31,39). In contrast, receptor activator of nuclear factor kappa B ligand (RANKL) and β -crosslaps, which are osteoclastic markers, declined to serum levels even lower than those of the sham group⁽³⁹⁾.

Therefore, both *in vitro* and *in vivo* evidence has revealed the anti-osteoporosis action of polydatin. This could be attributed to its dual effect of promoting bone formation while blocking bone resorption as revealed *in vivo*. Unfortunately, clinical evidence has not been reported and, as a result, its potential in relieving osteoporosis in humans has not been confirmed.

Anticancer effects of polydatin on bones

Although primary bone tumours are rare, bones are susceptible to metastatic cancers⁽⁴⁹⁾. Osteosarcoma, chondrosarcoma and Ewing sarcoma are the most common types. Osteosarcoma, a frequent malignant bone tumour, has a bimodal age distribution. Specifically, adolescents aged 10–14 years and adults over the age of 65 are especially susceptible to osteosarcoma⁽⁵⁰⁾. This tumour predominantly affects the sites of femurs, tibias and humeri and causes pain and swelling in these areas^(51,52). Current systemic osteosarcoma therapy comprises multiagent chemotherapy and surgical resection⁽⁵³⁾. Methotrexate, doxorubicin, cisplatin and ifosfamide are the main agents that are currently employed for chemotherapy regimens in osteosarcoma⁽⁵¹⁾. However, these conventional agents were discovered over two decades ago, and the survival rate remains unimproved. Resistance to chemotherapy is another issue hindering the efficacy of current treatments⁽⁵⁴⁾.

Polydatin has showed anticancer effects against various tumours in laboratory, including breast cancer, liver cancer and renal cancer^(55–57). Efforts in the field of bone cancer are mainly devoted to osteosarcoma, and a broad spectrum of cell responses have been found to be involved in the anti-osteosarcoma process of polydatin (Fig. 4).

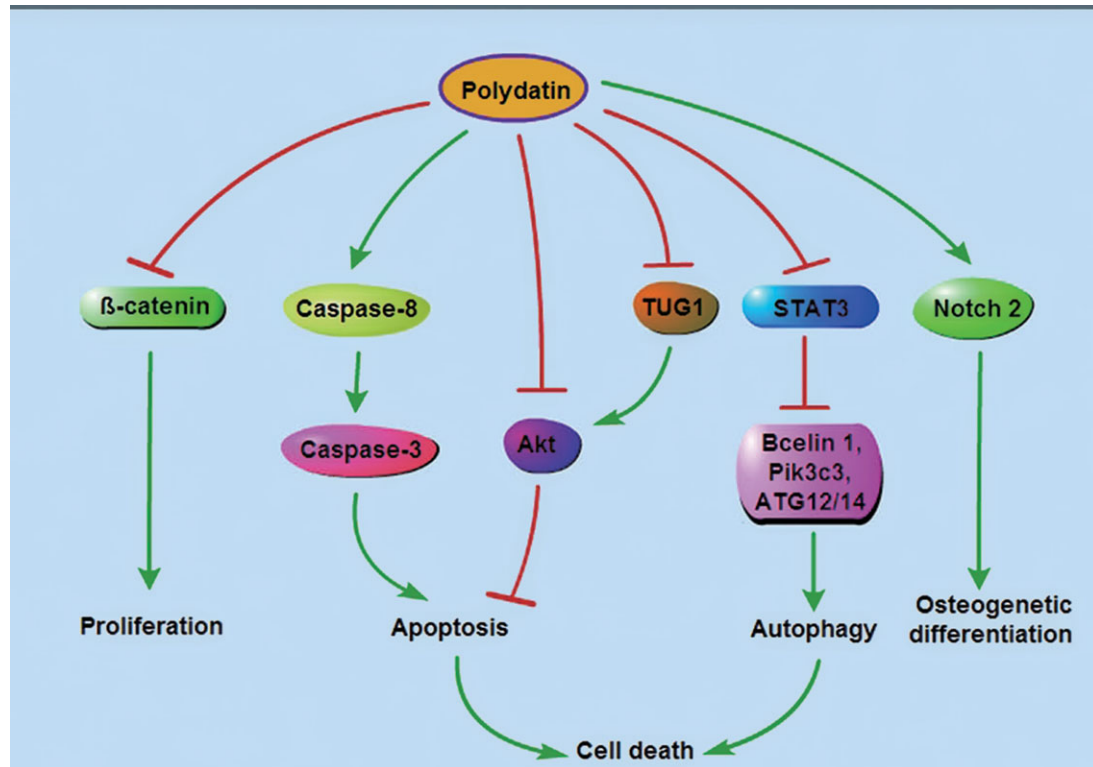


Fig. 4. Schematic representation of the potential effects of polydatin against osteosarcoma.

Anti-osteosarcoma effects *in vitro*

Aberrant cell proliferation is a defining hallmark of cancer⁽⁵⁸⁾, and polydatin shows a suppressing effect on the proliferation of osteosarcoma cells *in vitro*^(59–63). Such suppression is dose and time dependent, with a high polydatin dose (up to 400 μM) or long exposure duration (72 h) resulting in a cell viability rate lower than 10% of that of the control group⁽⁶¹⁾. This anti-proliferation effect is related to cell cycle arrest in the S phase and down-regulation of β-catenin signalling^(59,61,63). Additionally, β-catenin tends to be located in the plasma membranes of tumour cells under the influence of polydatin, corresponding to a compact cell layer morphology⁽⁶³⁾. This, together with the impaired cell migration, suggests a less invasive cell phenotype compared with that in the untreated group.

Polydatin also influences tumour cell proliferation via apoptosis⁽⁶¹⁾, an essential suppressor of tumour progression and chemoresistance⁽⁶⁴⁾. One study showed that, upon polydatin treatment (100 μM), the percentage of apoptotic cells increased considerably from approximately 5% to 26–40%, with a typical apoptotic morphology of apoptotic bodies, chromatin condensation, nuclear fragmentation and volume reduction⁽⁶¹⁾. Caspase-3 and Caspase-8 are implicated in polydatin-induced apoptosis, with increased pro-apoptotic Bax and decreased anti-apoptotic Bcl-2^(59,61,62). Hu *et al.*⁽⁶⁰⁾ and Zhao *et al.*⁽⁶¹⁾ also reported correlations between polydatin-induced apoptosis and protein kinase B (Akt). Osteosarcoma cells transfected with phosphorylated Akt showed a reduced apoptotic rate, whereas polydatin (100 μM for U-2OS, and 200 μM for MG-63) reversed this trend in cells with and without paclitaxel resistance⁽⁶¹⁾. The

long non-coding RNA (lncRNA) taurine up-regulated gene 1 (TUG1) is not only an oncogenic lncRNA in various cancers but also a regulator of the Akt pathway. Polydatin inhibits TUG1 expression in a dose-dependent manner. Moreover, in TUG1-overexpressing doxorubicin-resistant osteosarcoma cells, polydatin failed to block Akt phosphorylation, indicating an essential role of TUG1 in Akt-regulated apoptosis upon polydatin treatment⁽⁶⁰⁾.

As elucidated above, apoptosis plays a vital role in the anticancer function of polydatin *in vitro*. However, Jiang *et al.*⁽⁶²⁾ noticed that a pancaspase inhibitor only partially blocked the cell death caused by polydatin. With an in-depth investigation, the indispensable role of autophagy was revealed. In particular, polydatin (80 μM) elicits autophagy in tumour cells by suppressing the expression and phosphorylation levels of signal transducer and activator of transcription 3 (STAT3). As a result, a series of autophagy-associated genes (Beclin 1, class III phosphatidylinositol 3-kinase (Pik3c3), and autophagy-related 12/14 (ATG12/14)) are augmented, leading to increased autophagic flux in tumour cells after polydatin treatment⁽⁶²⁾.

Recent oncological studies have found that a deficit in cell differentiation can lead to osteosarcoma development and progression⁽⁶⁵⁾. The treatment strategy based on this concept is called differentiation therapy. Luce and Lama⁽⁶³⁾ reported that polydatin at 48 μM stimulated the differentiation of osteosarcoma cells with elevated OPN and Notch 2 expression (by almost two-fold). Such an effect is more prominent in conjunction with radiotherapy, as polydatin treatment with a radiation dose of 2 Gray induced approximately 23- and 14-fold increases in the

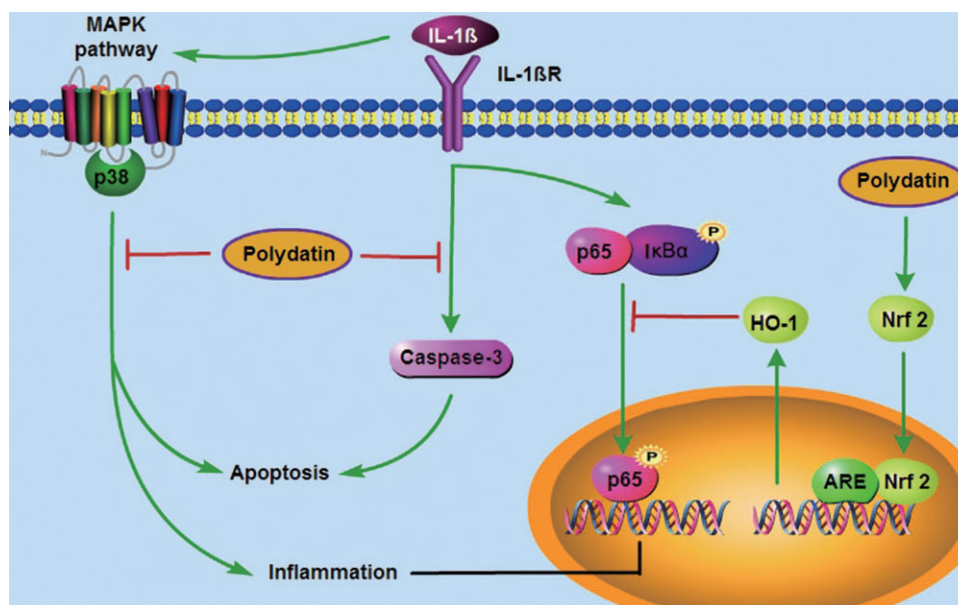


Fig. 5. Potential signalling pathways for protective effects of polydatin against osteoarthritis.

OPN and Notch 2 expression compared with those in the untreated group.

The chemo- and radioresistance of tumour cells are two main obstacles to high treatment efficacy and low side effects of cancer remedies. Notably, the antiproliferation and proapoptotic properties of polydatin have been verified in doxorubicin- and paclitaxel-resistant tumour cells *in vitro*^(60,61). Moreover, Luce and Lama⁽⁶³⁾ found that pre-treating osteosarcoma Saos-2 cells with polydatin at 48 μM significantly increased the cell sensitivity to ionising radiation, resulting in reduced cell viability (by 51%) and clonogenic survival rate (by 40%) even under a low radiation dose of 2 Gray.

Anti-osteosarcoma effects *in vivo*

It has been demonstrated with a xenograft mouse model with doxorubicin-resistant MG-63 cells that mice in the polydatin group showed significantly reduced tumour growth. Upon polydatin treatment (150 mg/kg/d, *i.p.*), the tumour volume and weight of the experimental group were reduced to 9.6% and 8.5% of those of the control group, respectively⁽⁶⁰⁾. Corresponding to the *in vitro* test, a positive correlation was also noticed between low tumour progression and the down-regulation of TUG1/Akt signalling.

Polydatin inhibits osteosarcoma both *in vitro* and *in vivo*. This effect has been found to be associated to its pro-apoptosis and pro-autophagy activities and regulations in cell survival, proliferation, differentiation, migration, etc. Most importantly, the anticancer effects remain valid with drug-resistant cell models. The polydatin-enhanced sensitivity of osteosarcoma cells to radiation also enables polydatin as an adjuvant for radiotherapy. Notably, the above outcomes were derived from laboratory tests; human clinic trials confirming the above effects are warranted.

Protective effects of polydatin against osteoarthritis

Although osteoarthritis can occur in all joints, it primarily occurs in knees, hips and hand joints⁽⁶⁶⁾. Osteoarthritis is manifested by clinical features of pain, joint stiffness, loss of movement and function, and even disability⁽⁶⁶⁾. Osteoarthritis is a multifactorial disease, and its aetiology is complicated by various contributing factors, such as age, genetics, anatomy and weight⁽⁶⁷⁾. Pathologically, osteoarthritis mainly manifests as cartilage damage, subchondral sclerosis, osteophyte formation and synovial inflammation⁽⁶⁸⁾. Current pharmacological management mainly aims to relieve pain and swelling with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, glucosamine sulphate, etc. Unfortunately, limited efficacy and cardiovascular and gastrointestinal risks are the main concerns regarding the use of paracetamol and NSAIDs, respectively⁽⁶⁶⁾. Although controversy remains, dietary components and supplements, including fatty acids, glucosamine and chondroitin sulphate, have been investigated for their potential anti-osteoarthritis function^(69,70). Meanwhile, growing *in vitro* and *in vivo* evidence is now available regarding the possible benefits of polydatin against osteoarthritis (Fig. 5).

In vitro protective effects against osteoarthritis

Inflammation is a key feature of osteoarthritis⁽⁷¹⁾. For osteoarthritic chondrocytes, a variety of inflammatory mediators are released and cause a cascade of adverse effects. For example, nitric oxide (NO) is a detrimental factor hampering extracellular matrix (ECM) synthesis⁽⁷²⁾. NO suppresses the production of collagen type II and aggrecan, the main components of the ECM⁽⁷³⁾, while up-regulating the release of destructive matrix metalloproteinase-13 (MMP-13) and a disintegrin and metalloproteinase with thrombospondin motifs 5^(72,74). As an anti-inflammatory agent, polydatin (40 μM) blocked more than 50% of NO release

from IL-1 β -treated rat chondrocytes *in vitro*⁽⁷⁵⁾. In addition to NO, polydatin was also observed to inhibit TNF- α , IL-1 β /6/8, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2) and inducible nitric oxide synthase in a dose-dependent manner^(32,75,76). Both the nuclear factor-kappa B (NF- κ B) and Nrf 2/haem oxygenase-1 (HO-1) pathways are involved in the anti-inflammatory process of polydatin⁽³²⁾. The latter pathway is supported by the observation that reduced inflammatory factor release and ECM degradation induced by polydatin treatment (100 μ g/mL, approximately 258 μ M) were abolished in Nrf 2-siRNA human chondrocytes⁽³²⁾. MicroRNAs (miRNAs) are non-coding RNAs that play important roles in regulating gene expression, and miR-125b adjusts a series of key inflammatory genes in different cell types. In chondrogenic ATDC5 cells with lipopolysaccharide-induced osteoarthritis injuries, polydatin (20 and 50 μ M) up-regulated miR-125b (approximately 154% and 246%, respectively) and, as a result, suppressed its binding target, Rho-associated coiled-coil containing protein kinase 1⁽⁷⁶⁾.

In addition to inhibiting inflammation, polydatin also blocks the apoptosis of osteoarthritic chondrocytes *in vitro*. Similar to the case in BMSCs discussed above, the down-regulation of apoptosis is associated with suppressed caspase-3 activities, leading to an increased Bcl-2/Bax ratio in osteoarthritic chondrocytes^(75,76). Notably, Yang *et al.*⁽⁷⁵⁾ also noticed that the p38 MAPK inhibitor showed a similar reducing effect to that of polydatin apoptosis in osteoarthritic chondrocytes. Such an effect is also observed with the inflammatory factors TNF- α , IL-1 β /8 and COX-2, and could be a result of an intimate relationship between apoptosis and inflammation in osteoarthritis.

In vivo protective effects against osteoarthritis

Polydatin also displayed an anti-osteoarthritis effect in an animal model. Upon polydatin treatment, the osteoarthritis features of mice with surgical destabilisation of the medial meniscus were relieved, varying from joint space narrowing, osteophyte formation and calcification of the cartilage surface to cartilage erosion of mouse knee joints. Quantitative analyses of the Osteoarthritis Research Society International Scores and synovitis scores were also evaluated. Upon polydatin treatment (100 mg/kg/d, *i.p.*), the former score decreased from 8.6 to 4.9, while the latter decreased from 3.9 to 2.3, demonstrating an anti-osteoarthritis function of polydatin *in vivo*⁽³²⁾.

Accordingly, anti-inflammatory and anti-apoptotic functions of polydatin are the main contributors to its anti-osteoarthritis effects *in vitro*. Although improvements in symptoms have been noticed in an osteoarthritic mouse model, the corresponding *in vivo* mechanism has not been elucidated.

Anti-RA activities of polydatin

RA is a common autoimmune disease found mostly in the small diarthrodial joints of the hands and feet. Patients with RA usually suffer from joint swelling and stiffness, synovial inflammation and cartilage and bone destruction, which may lead to activity limitations and disabilities⁽⁷⁷⁾. RA is a systemic disease. Secondary conditions such as cardiovascular illness, severe infections and respiratory diseases are common

comorbidities that cause higher mortality than RA *per se*⁽⁷⁸⁾. Although the aetiology of RA has not been fully elucidated, it is considered an interplay of susceptible genotype, activation of innate immunity, and adaptive immune response against autologous antigens⁽⁷⁹⁾. The potential role of diet and nutrition in RA prevention and management has attracted the attention of researchers, though the results are still inconclusive. Diet and nutrients with anti-inflammatory and antioxidative properties have been suggested to be beneficial for subjects of and at risk for RA, including the Mediterranean diet, which is high in omega-3/6⁽⁸⁰⁾.

Anti-RA activities *in vivo*

RA is primarily characterised by the infiltration of inflammatory cells into the synovium and synovial hyperplasia (swelling), which ultimately leads to the destruction of bones and cartilage. As indicated by *in vivo* experiments, polydatin could improve the conditions of RA. Polydatin treatment (45 mg/kg/d, *i.p.*) delayed the onset of arthritis, as the time taken to reach 100% incidence of collagen-induced mouse joint arthritis extended from 30 to 43 d⁽³³⁾. Moreover, a decrease in arthritis score in a dose-dependent manner was also noticed with the collagen-treated mice, with 15 and 45 mg/kg polydatin inducing approximately 20% and 66% decreases, respectively⁽⁸¹⁾. Additionally, histopathological changes as a result of complete Freund's adjuvant-induced arthritis in rats were significantly improved after treatment (200 mg/kg/d, oral administration). These changes varied from inflammatory cell infiltration in the dermal layer, periosteum thickening, and hyperplasia of synovial membranes to resorption and osteoporosis of bone trabeculae of knee joints⁽⁸²⁾.

Although the aetiology of RA remains unclear, its pathogenesis is characterised by inflammatory infiltration of the synovium and synovial fluid⁽⁸³⁾. Similar to the case of osteoarthritis, this inflammation is also mainly mediated by cytokines such as TNF- α and IL-6. Biological agents targeting these cytokines have achieved satisfactory therapeutic effects⁽⁸⁴⁾. Polydatin has been shown to reduce the release of TNF- α and IL-1 β /6/17 *in vivo*, and this anti-inflammatory function was considered to be achieved through STAT3 and NF- κ B^(81,82). The oral administration of polydatin (200 mg/kg/d) also induced a substantial drop in MMP-3 and RANKL expression (to approximately 60% of those of the control group, respectively) in a Freund's adjuvant-induced arthritis rat model⁽⁸²⁾. However, it is interesting to note that Li and Wang⁽⁸¹⁾ observed the opposite trend, as the administration of polydatin at 45 mg/kg reversed the decrease in MMP-9 to a level more than two times higher than that of the control in mice with collagen-induced arthritis. An explanation for this discrepancy was not given; therefore, further studies are in demand to address the controversy.

It has been suggested that the inflammation of RA can also trigger oxidative reactions, a pathological factor for RA due to potential damage to proteins, lipids, DNA, etc.⁽⁸⁵⁾. A high malondialdehyde (MDA) level in the serum, plasma and synovial fluid of RA subjects is closely associated with oxidative lipid damage⁽⁸⁵⁾. Additionally, a low glutathione (GSH) level, a non-enzymatic antioxidant, corresponds to an impaired antioxidative

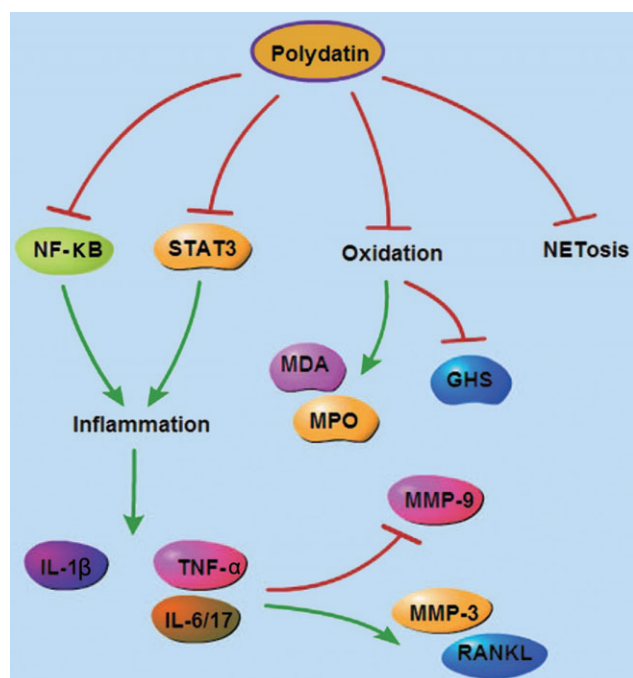


Fig. 6. Schematic illustration of the protective effects of polydatin against rheumatic arthritis (RA).

system⁽⁸⁶⁾. As an antioxidative compound, polydatin effectively reduced MDA concentrations (by 64% for rats and 51% for mice) while increasing GSH levels (by 274% for rats and 100% for mice)^(81,82). Additionally, myeloperoxidase (MPO) activity, a marker of oxidative damage, was also reduced (by 59%) by polydatin (200 mg/kg/d, oral administration)⁽⁸²⁾. The above evidence indicates that polydatin could decrease oxidative stress and repair the antioxidative defence system.

In vitro and *in vivo* anti-NETosis effects

Neutrophil extracellular trap (NET) formation has recently been implicated in the development of autoimmune diseases, including RA. NETosis refers to a cell death process in which the mixture of antimicrobial substances stored in neutrophils and the chromatin inside neutrophils is released as a network of chromatin and antimicrobial peptides⁽⁸⁷⁾. An increase in NET deposition was found in patients with RA and animals with RA both *in vivo* and *in vitro*⁽⁸⁸⁾. In contrast, polydatin at 100 µg/mL (approximately 258 µM) suppressed phorbol 12-myristate 13-acetate-induced NET formation by more than 30% in neutrophils from both patients and mice with RA *in vitro*. This trend was also verified in ankle joints of mice with collagen-induced arthritis *in vivo*⁽³³⁾. As elucidated above, the interruption of NETosis by polydatin provides a new explanation for its anti-RA effects. However, more evidence is needed to further reveal the underlying mechanisms.

In conclusion, the relief of symptoms by polydatin has been confirmed with animal models. Polydatin reduced pro-inflammatory cytokine release and oxidative stress, and enhanced the antioxidative ability of RA cells *in vivo*. NETosis, a pathogenesis factor of RA, is also reduced by polydatin both *in vitro* and

in vivo, while the underlying mechanisms remain largely unclear (Fig. 6). Moreover, the mediation of MMPs by polydatin remains inconclusive, together with a lack of human clinical trials, more studies reporting the benefits of polydatin against RA are warranted.

Discussion and future perspectives

As documented in this review, *in vitro* and *in vivo* evidence has revealed that, for different BJDs, the action of polydatin contains a broad spectrum of regulatory mechanisms primarily via its pro-osteogenesis, anti-inflammatory, apoptosis regulation and autophagy regulation functions. Owing to the proteins and protein complexes in specific pathways, the above mechanisms show crosstalk. For example, PD inhibits the inflammatory factors of TNF-α and IL-1β/6/17 via pathways of both STAT3 and NF-κB *in vivo*. Moreover, the regulating effect of polydatin remains valid with different cell lineages and tissues. As reviewed above, the mediation of apoptosis through caspase-3 was observed with BMSCs, bone tumour cells and osteoarthritic chondrocytes. Therefore, polydatin displays a multi-target and multi-system feature.

Polydatin, like other polyphenolic compounds, has low absolute bioavailability (2.9%⁽⁸⁹⁾) and fast metabolism. The rapid clearance of polydatin and its metabolites could lead to low accumulation of effective compounds in targeted tissues⁽²⁰⁾. Take the example of resveratrol. A low concentration was noticed in neuroblastoma tumours and normal tissues of mice after extended oral treatment regimens (2, 10 and 50 mg/kg/d of resveratrol for 5 weeks), whereas peritumour injection (5, 10 and 20 mg of resveratrol, five injections over 16 d) increased the drug level, resulting in rapid tumour regression⁽²¹⁾. Therefore, active compounds of low bioavailability and rapid metabolism warrant more efficient delivery approaches to the targeted tissues to avoid rapid metabolism and/or clearance. Advances have been achieved in nanodrug delivery systems for polydatin. For example, polydatin-loaded chitosan nanoparticles were prepared for safe and efficient type 2 diabetes therapy⁽⁹⁰⁾. Moreover, polydatin-loaded micelles possessing a liver-targeted function have also been reported⁽⁹¹⁾. Of course, studies on the bioavailability and metabolism of polydatin at different dosages are also necessary. A thorough understanding of the pharmacokinetic properties is fundamental for translating the laboratory effects to clinical efficacy.

To the best of our knowledge, there has been no clinical trial of polydatin in patients with BJD. Therefore, the main aim of this review is to present evidence of therapeutic benefits from *in vitro* and animal studies, and to encourage future clinical trials that can lead to early identification of clinical efficacy of polydatin. Secondly, it should also be noted that action outcomes and mechanisms obtained *in vitro* cannot simply be extrapolated to the *in vivo* and clinic studies for polydatin showing fast metabolism. The limited use of polydatin metabolites in cell models may not fully mimic the actions of polydatin in animals and humans. Thirdly, although low toxicity has been reported in human subjects, a detailed record of hepatic, cardiac and neurological

Table 1. *In vitro* studies of the effects of polydatin on BJDs

Bone or joint disorder	Cell	Main dosage (μM)	Major action	References
Osteogenesis-potentiating	Rat BMSCs	30	<ul style="list-style-type: none"> • \downarrowApoptosis rate with caspase-3 • GHS (\uparrow) and ROS (\downarrow) via Nrf 2/ARE signalling 	(10)
	Rat BMSCs	10 and 30*	<ul style="list-style-type: none"> • \uparrowMigration via ERK1/2 	(35)
	Human dental bud stem cells	0.1* and 1.0	<ul style="list-style-type: none"> • \uparrowOsteogenesis via Sirt-1 and BMP2-Wnt/β-catenin signalling 	(37)
Osteoporosis	Human BMSCs	10, 30*, and 100	<ul style="list-style-type: none"> • \uparrowOsteogenesis via MAPK 	(38,39)
	MC3T3-E1 cells treated with 100 mM dexamethasone	20, 40 and 80*	<ul style="list-style-type: none"> • \uparrowOsteogenesis via MAPK 	(48)
Osteosarcoma	Saos-2 and MG-63 cells with and without doxorubicin resistance	50, 150, 200 and 250*	<ul style="list-style-type: none"> • \downarrowCell viability • \uparrowApoptosis rate with caspases via TUG1/ Akt signalling 	(60)
	U-2OS and MG-63 cells with and without paclitaxel-resistance	100 μM for U-2OS and 200 μM for MG-63	<ul style="list-style-type: none"> • \downarrowCell-cycle arrest in the S phase • \downarrowCell migration • \uparrowApoptosis with caspase via Akt 	(61)
	MG-63 cells	20, 40 and 80*	<ul style="list-style-type: none"> • \downarrowCell viability • \uparrowAutophagy factor via STAT3 • \uparrowApoptosis rate with caspases 	(62)
	Saos-2 cells	48	<ul style="list-style-type: none"> • \downarrowProliferation • \uparrowOsteogenesis through Notch 2 	(63)
Osteoarthritis	Osteoarthritis cartilage chondrocytes from human	Approximately 64, 129 and 258* (25, 50, 100* $\mu\text{g}/\text{mL}$)	<ul style="list-style-type: none"> • \downarrowInflammatory factors of NO, iNOS, TNF-α, IL-6 and cyclooxygenase-2 via Nrf 2/HO-1 • \downarrowMMP-13 and a disintegrin and metalloproteinase with thrombospondin motif 5 	(32)
	Articular chondrocytes from the rat knee joints	Approximately 51, 77, and 103* (20, 30, 40* $\mu\text{g}/\text{mL}$)	<ul style="list-style-type: none"> • \downarrowApoptosis rate with caspase-3 • \downarrowInflammatory factors of NO, iNOS, TNF-α, IL-1β/8, and cyclooxygenase-2 	(75)
	Murine chondrogenic ATDC5 cell line	10, 20 and 50	<ul style="list-style-type: none"> • \uparrowViability • \downarrowInflammatory factors of TNF-α and IL-6/1β with miR-125b • \downarrowApoptosis rate with caspase-3 	(76)
RA	Neutrophils from patients with RA and mice treated with phorbol 12-myristate 13-acetate	Approximately 258 (100 $\mu\text{g}/\text{mL}$)	<ul style="list-style-type: none"> • \downarrowNetosis 	(33)

* : optimal polydatin dosages.

Table 2. *In vivo* studies of the effects of polydatin on BJDs

Bone or joint disorder	Animal model	Dosage (mg/kg) and administration	Major action	Reference
Osteoporosis	Ovariectomised mouse model	10, 20 and 40*, i.p.	<ul style="list-style-type: none"> • \uparrowWeight of thigh bone • \uparrowCalcium and phosphorus levels in serum 	(31)
		3, i.p., every 2 d	<ul style="list-style-type: none"> • Improved bone volumes and structures • \downarrowOsteoclastic markers 	(39)
Osteosarcoma	Xenograft mouse model with doxorubicin-resistant MG-63 cells injected into the left flank of mice	150, i.p., per day	<ul style="list-style-type: none"> • \downarrowTumour volume and weight • Pro-apoptosis via TUG1/Akt signalling 	(60)
Osteoarthritis	Surgical destabilisation of medial meniscus mouse osteoarthritis models	100, i.p., per day	<ul style="list-style-type: none"> • Symptom relief • \downarrowOA scores 	(32)
RA	Collagen-induced arthritis mouse model	45, i.p., per day	<ul style="list-style-type: none"> • \downarrowIncidence • \downarrowArthritis scores • \downarrowSerum autoantibodies • \downarrowNetosis 	(33)
		15, 30 and 45*, i.p.	<ul style="list-style-type: none"> • \downarrowArthritis scores • \downarrowHind-paw thickness • \downarrowInflammatory factors of TNF-α and IL-1β • Oxidation-related factors of MDA (\downarrow) and GHS (\uparrow) 	(81)
	Complete Freund's adjuvant-induced arthritis rat model	200, oral administration, per day	<ul style="list-style-type: none"> • Symptom relief • \downarrowPaw and ankle diameters • \downarrowInflammatory factors of TNF-α and IL-6/17 via IL-6/STAT-3/IL-17/NF-κB cascade • Oxidation-related factors of MDA (\downarrow), MPO(\downarrow), and GHS (\uparrow) 	(82)

* : optimal polydatin dosages.

toxicity has yet to be reported. Therefore, a more thorough understanding of the adverse effects of polydatin is also needed in future studies.

Conclusion

Emerging *in vitro* and *in vivo* evidence has revealed a potential therapeutic effect of polydatin on BJDs of osteoporosis, osteosarcoma, osteoarthritis and RA. This therapeutic benefit is primarily associated with the functions of pro-osteogenesis, anti-inflammation, antioxidation, apoptosis regulation and autophagy regulation.

In vitro studies disclose that polydatin could affect the migration, differentiation, apoptosis and oxidation of BMSCs. Its *in vivo* anti-osteoporosis outcome could contribute to both the promotion of bone formation and blockage of bone resorption. With a recognised anticancer effect, polydatin suppresses osteosarcoma development and progression via multiple cell responses. More importantly, its anticancer effect remains effective in drug-resistant cell models. In terms of osteoarthritis and RA, polydatin constrains the secretion of inflammatory factors which are risk factors for bone and cartilage degradation. Polydatin also blocks apoptosis to arrest chondrocyte death related to osteoarthritis. In RA, polydatin suppresses NET formation and oxidative damage while repairing the impaired antioxidative system. However, since clinical trials disclosing the benefits of polydatin against BJDs are not available, the results obtained from basic science would serve as a starting point, rather than an interpreting from a human perspective.

Nevertheless, the inherently low bioavailability and prompt metabolic nature of polydatin remain major issues for its high therapeutic efficacy in animals and humans. New technologies of drug delivery are promising strategies to address the above issue. Moreover, trials revealing the therapeutic effects of polydatin on human subjects with BJDs have not yet been reported. Additional studies, as well as those on clinical adverse events, are warranted (Tables 1 and 2).

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