Plant-Derived Nutraceuticals in the Treatment of Tendinitis

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In tendinitis, as a very common and painful condition disabling musculoskeletal functionality and still lacking sustainable treatment, various plant-derived compounds have been demonstrated to affect inflammation and promote tissue healing, thus representing promising bio-active treatment agents in tendinitis therapy.

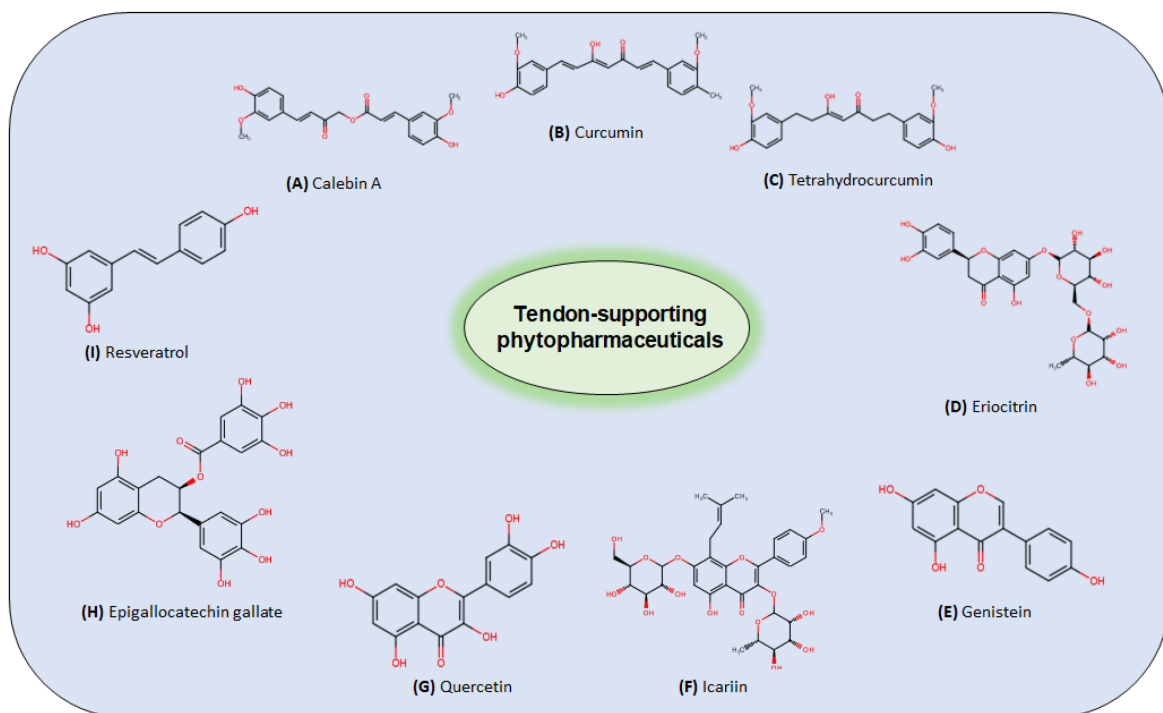tendinitis   tendinopathy   nutraceuticals   flavones   resveratrol   curcuminoids

polyphenols

1. Overview

Different natural compounds and polyphenols have been studied in the context of tendinitis, tendon tissue, and inflammation (**Table 1**). The chemical structures of some compounds are shown in **Figure 1**.

Figure 1. Chemical structures of tendon-supporting phytopharmaceuticals: curcuminoids (**A**–**C**), flavones/flavonoids (**D**–**G**), green tea extracts (**H**), and resveratrol (**I**).

Table 1. Tendon-supporting effects of phytopharmaceuticals.

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
Avocado/Soybean unsaponifiables (ASU)	**avocado and soybean oils**	in vitro, horse tenocytes	IL-1β COX-2 PGE2	Avocado/soybean unsaponifiables significantly inhibited inflammation response, such as combination therapy with glucosamine and chondroitin sulfate.	8.3 µg/mL of ASU	[1]
Boswellia acid	*Boswellia serrata*	in vivo, Achilles tendinitis patients	-	Boswellia acid (as Casperome®) showed pain reduction on a visual analogical scale when Casperome® was administered in addition to physical therapy in patients with Achilles tendinitis.	250 mg of Casperome® for 15 and 30 days	[2]
		in vivo, joint inflammation patients	-	Boswellia acid (as Casperome®) supplementation accompanied by standard therapy reduced pain and inflammation in knee joints and tendon of rugby players.	500 mg of Casperome® for 5 days, then 250 mg for 23 days	[3]
		in vivo, supraspinatus injury patients	-	*Boswellia serrata* and *Curcuma longa* extracts (as Tendisulfur®) reduced pain after arthroscopic supraspinatus tendon repair compared to placebo treatment.	2 daily sachets Tendisulfur® for 15 days, then 1 daily sachet for 45 days	[4]
		in vivo, tendinopathy patients	-	*Boswellia serrata* and *Curcuma longa* extracts alleviated the symptoms (pain and functional limitation) of patients with tendon disease when applied	2 tablets twice a day for 1 month	[5]

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
				as combinational therapy.		
		in vivo, rotator cuff tendinopathy, Achilles tendinopathy, and lateral epicondylitis patients	-	*Boswellia serrata*, *Curcuma longa* and bromelain extracts (with methyl-sulfonyl-methane, hydrolysed collagen I and II, L-arginine, L-lysin, vitamin C, chondroitin sulfate, glucosamine, and myrrh as Tendisulfur® Forte), in combination with extracorporeal shock wave therapy, accelerated pain relief and remarkably reduced NSAID intake of patients.	2 daily tablets of Tendisulfur® Forte for 1 month, then once a day for a month	[6]
Bromelain	pineapple extracts, *Ananas cosmosus*	in vivo, Sprague–Dawley rats	MDA ROS	Pineapple flesh extract stimulated tenoblast proliferation and thus tendon healing after Achilles tendon injury.	30 mg/kg of pineapple flesh axtract for 14 days	[7]
		in vivo, Sprague–Dawley rats	ROS PAF	Pineapple extract bromelain shifted the thromboxane–prostacyclin ratio towards prostacyclin and increased the tenocyte population after Achilles tendon injury.	7 mg/kg of bromelain for 14 days	[8][9]
		in vivo, Achilles tendinopathy patients	-	Pineapple extract bromelain (as dietary supplement Tenosan with arginine, collagen, vitamin C, methyl-sulfonyl-methane, Vinitrox™) boosted the efficacy of extracorporeal shock wave therapy, resulting in better functional and	2 daily drug sachets containing 50 mg of bromelain for 60 days	[10]

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
				clinical outcome, compared to placebo treatment.		
		in vivo, rotator cuff tendinopathy patients	-	Pineapple extract bromelain (as dietary supplement Tenosan with arginine L-alpha-ketoglutarate, methyl-sulfonyl-methane and hydrolysed collagen I) reduced pain and improved repair integrity of rotator cuff repair.	2 daily drug sachets containing 50 mg of bromelain for 3 months	[11]
		in vivo, rotator cuff tendinopathy, Achilles tendinopathy, and lateral epicondylitis patients	-	Pineapple extract bromelain (with methyl-sulfonyl-methane, hydrolysed collagen I and II, L-arginine, L-lysin, vitamin C, chondroitin sulfate, glucosamine, *Curcuma longa, Boswellia serrata*, and myrrh as Tendisulfur® Forte), in combination with extracorporeal shock wave therapy, accelerated pain relief and remarkably reduced NSAID intake of patients.	2 daily tablets of Tendisulfur® Forte for 1 month, then once a day for an additional month	[6]
Curcuminoids	turmeric, *Curcuma longa*			Calebin A suppressed inflammation and exhibited potential as preventive and therapeutic treatment of tendinitis by suppressing down-regulation of tenomodulin and collagen I.		
		in vitro, canine tenocytes	NF-κB scleraxis TNF-α TNF-β		1–10 μM of calebin A	[12]
		in vitro, human tenocytes	NF-κB IL-1βPI3K/p85/Akt	Curcumin inhibited inflammation and apoptosis and showed	5 μM of curcumin	[13]

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
			MMPs COX-2 caspase-3 Bax/Bcl-2	potential for treatment of tendon inflammation.		
		in vivo, diabetic rats	ROS AGE	Curcumin reduced oxidative stress by inhibiting lipid peroxidation and prevented glycation and crosslinking of advanced glycated collagen in tail tendon and skin.	200 mg/kg of curcumin for 8 weeks	[14]
		in vivo, Sprague–Dawley rats	MDA HOPro SOD	Curcumin improved the healing quality of tendon ruptures by promoting well-organized collagen filaments and biomechanical traits.	100 mg/kg of curcumin for 14 days	[15]
		in vivo, Sprague–Dawley rats	adhesion of inflammatory products	Curcumin (as loaded nanoparticle) promoted the healing process of Achilles tendon rupture.	1 injection containing 0.44 mg of curcumin/kg	[16]
		in vivo, Wistar albino rats	-	Curcumin showed biomechanical and histological healing (collagen I and III) promotion after surgically treated Achilles tendon ruptures.	200 mg/kg of curcumin for 28 days	[17]
		in vivo, rats	AP	Curcumin prevented tendon calcification and improved tendon regeneration by tendon stem/progenitor cells.	3 µg of curcumin every 3 days for up to 4 weeks	[18]
		in vivo, Sprague–Dawley rats	ROS IL-1β TNF-α MMPs	Curcumin showed anti-oxidative and anti-inflammatory properties as part of	1 injection with 50 µL of hydrogel	[19]

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
				Cur&Mg-QCS/PF hydrogel application.		
		in vivo, diabetic rats	AGE HOPro	Curcumin's metabolite tetrahydrocurcumin reduced accumulation and crosslinking of advanced glycated collagen.	80 mg/kg of tetrahydrocurcumin for 45 days	[20]
		in vivo, tendinopathy patients	-	*Curcuma longa* and *Boswellia serrata* extracts alleviated the symptoms (pain and functional limitation) of patients with tendon disease as combinational therapy.	2 tablets twice a day for 1 month	[5]
		in vivo, rotator cuff tendinopathy, Achilles tendinopathy, and lateral epicondylitis patients	-	*Curcuma longa*, *Boswellia serrata* and bromelain extracts (with methyl-sulfonyl-methane, hydrolysed collagen I and II, L-arginine, L-lysin, vitamin C, chondroitin sulfate, glucosamine, and myrrh as Tendisulfur® Forte), in combination with extracorporeal shock wave therapy, accelerated pain relief and remarkably reduced NSAID intake of patients.	2 daily tablets of Tendisulfur® Forte for 1 month, then once a day for an additional month	[6]
		in vivo, supraspinatus injury patients	-	*Curcuma longa* and *Boswellia serrata* extracts (as Tendisulfur®) reduced pain after arthroscopic supraspinatus tendon repair compared to placebo treatment.	2 daily sachets of Tendisulfur® for 15 days and 1 daily sachet for the next 45 days	[4]

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
EGCG (epigallocatechin gallate)	green tea extracts	in vitro, human tendon-derived fibroblasts	IL-1β MMPs p54/JNK/SAPK collagenases/ gelatinases/ aggrecanases	Green tea's epigallocatechin gallate targeted extracellular matrix breakdown.	2.5–25 µM of epigallocatechin gallate	[21]
		in vivo, diabetic rats	AGE	Green tea extract reduced collagen glycation and crosslinking in the tail tendon.	300 mg/kg of green tea extract for 4 weeks	[22]
		in vivo, Wistar rats	MMPs HOPro	Green tea promoted the synthesis of ECM components and glycosaminoglycans, and thus the recovery process after Achilles tendinitis in combination with a glycin diet.	700 mg/kg of green tea extract for 21 days	[23]
		in vivo, Wistar rats	IL-1β MMPs	Green tea modulated inflammatory action and promoted synthesis of recovery elements after Achilles tendinitis, in combination with a glycin diet.	700 mg/kg of green tea extract for 7 days	[24]
		in vivo, C57BL/6 mice	ROS	Green tea extract slowed collagen aging by inhibiting crosslinking.	21.2 mL (young mice) and 27.2 mL (adult mice) of green tea extract for 14 days	[25]
Echinaceae angustifolia extracts	*Echinaceae angustifolia*	in vivo, carpal tunnel syndrome patients	-	*Echinaceae angustifolia* extract (as a dietary supplement mainly composed of alpha lipoic acid and conjugated linoleic acid) showed significant improvement in pain,	2 capsules containing 250 mg of echinacea extract for 40 days, then 1 capsule for 80 days	[26]

[40][41][42][43]

combination therapy with GLU and CS (**Table 1**) [1]. However, because of the small number of studies conducted with ASU in the context of tendinitis, these results must be considered as an only vague hint of ASU's potential in tendinitis treatment and further research has to be carried out.

2. Bromelain

Bromelain is a natural complex of proteolytic enzymes that are derived from fruit or stem of the *Ananas cosmosus* (pineapple). It has been used as another phytopharmaceutical in folk medicine for centuries due to its anti-inflammatory, anti-cancer, immune-modulating, as well as anti-thrombotic properties, to name just a few, as well as its safety for administration [44][45][46]. In musculoskeletal injuries or disorders, it is also known to reduce acute pain and swelling [7]. In a study by Aiyegbusi et al., the effects of aqueous extracts of different parts of the

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
				symptoms, and functionality.		
Flavones/Flavonoids	celery, parsley, red peppers, chamomile, mint and gingko bilboa, citrus fruit	in vitro, rat tenofibroblast	ROS ERK1/2 JNK	Flavonoid anthocyanin acted as an anti-apoptotic and showed the therapeutic potential of rotator cuff tendon.	10–200 µg/mL of anthocyanins	[27]
		in vitro, tendon stem cells	caspase-3	Flavonoid eriocitrin inhibited apoptosis and scar formation (biglycan, fibronectin, COMP) and improved woundhealing by stimulating proliferation and migration of tendon stem cells.	25–75 of µM eriocitrin	[28]
		in vivo, Sprague–Dawley rats	-	Flavone genistein protected ovariectomy-induced collagen reduction in Achilles tendon.	300 mg/kg of genistein for 6 weeks	[29]
		in vivo, Sprague–Dawley rats	Pcna Timp1	Flavone genistein enhanced tendon function at an estrogen-deficit through the modulation of tenomodulin.	6 mg/kg of genistein for 6 weeks	[30]
		in vivo, Sprague–Dawley rats	AP CD31 VEGF	Flavonoid icariin supported healing and angiogenesis after rotator cuff reconstruction through promoting collagen I/II.	0.125 mg/g of icariin for 2 and 4 weeks	[31]
		in vivo, Wistar rats	ROS MDA SOD GPX	Flavonoid quercetin prevented the adhesion of tendon tissue.	50–100 mg/kg for 4 weeks	[32]
		in vivo, Sprague–Dawley rats	MMPs ICAM-1	Flavonoid quercetin prevented collagenase-induced	25–50 mg/kg for 7 days	[33]

promoted by curcumin, suggesting the polyphenol as an effective treatment option for tendinitis as well as for prophylaxis by its modulation of pro-inflammatory NF-κB signaling [13]. The strong anti-inflammatory effect of curcumin was also found in a recent in vivo study by Chen et al., demonstrating the down-regulation of pro-inflammatory ROS, TNF-α, IL-1β and MMPs in rats during curcumin treatment in the form of curcumin/Mg^{2+} hydrogels as well [19].

In addition, in a study by Sajithlal et al. investigating the preventive and therapeutic potential of curcumin in tail tendon of diabetic rats, it has been demonstrated that curcumin treatment significantly reduced oxidative stress by the suppression of lipid peroxidation and even more, prevented increased accumulation of advanced glycation end products and collagen crosslinking in tendon as an issue coming along with diabetes [14]. In another study, of diabetic rats similar observations were made using tetrahydro-curcumin (a metabolite of curcumin) for treatment [20], showing curcumins potential in tendon-associated therapy as an effective anti-oxidant [14][20]. Besides its anti-

Agent	Origin	Type of Trial	Presumed Modulation	Mode of Action	Concentration/Dose Range	Reference
[16]		[15]		tendon damage[16][17] Achilles tendinopathy.		
		in vivo, rats	-	Flavonoid quercetin, kaempferol, and isorhamnetin (*Hippophae rhamnoides'* flavones) improved fibre alignment, collagen deposition, healing, and recovery after patellar tendon injury.	1 injection with 0.1 mg of *Hippophae rhamnoides'* flavones	[34]
Resveratrol	red grapes, *Vitis vinifera*	in vitro, human tenocytes	NF-κB p53 Sirt-1 IL-1β COX-2 MMPs Akt/scleraxis Bax/caspase-3	Resveratrol regulated tenocytes homeostatic and inhibited inflammation of cascades and apoptosis.	5 µM of resveratrol	[35]
		in vitro, human tenocytes	Sirt-1	Resveratrol averted dexamethasone-induced senescence despite glucocorticoid treatment.	30 µM of resveratrol	[36]
		in vitro, human tenocytes [12]	NF-κB PI3K IL-1β scleraxis	Resveratrol inhibited inflammation cascades; prevented apoptosis; and promoted collagen I, collagen III, and tenomodulin expression.	0.1–20 µM of resveratrol	[37]
		in vitro, Wistar rat tail tendon	ROS	Resveratrol's derivate [12] polydatin protected from advanced glycation as an anti-oxidant property.	50–500 µg of polydatin	[38]
		in vivo, Sprague–Dawley rats	-	Resveratrol promoted the collagens and the healing process of Achilles tendinopathy, despite diabetic condition. [58][59][60]	10 mg/kg of resveratrol for 14 days	[39]

3.2. Calebin A

in a study investigating human tendon-derived fibroblasts in vitro, in which EGCG administration suppressed IL-1β-stimulated collagenase and stromelysin, as well as the expression of MMPs, and simultaneously reduced the stimulation of p54/JNK/SAPK phosphorylation. Altogether, these outcomes suggest ECM breakdown as an important target for EGCG and other green tea polyphenols, thus proposing a potential target for EGCG therapy in tendon injury [21]. In addition to that, green tea extract has also been shown to remarkably reduce glycation, i.e., the resulting formation of advanced glycation end products (AGE), as well as crosslink collagen in the tail tendon of diabetic rats. These outcomes demonstrate the therapeutic potential of green tea extracts in treating diabetes-related tendon glycation, since the formation of glycation and AGE in tendon finally leads to impaired tendon turnover, making it even more vulnerable to tendinitis [22]. Furthermore, in an in vivo study by Rutter et al., it has been demonstrated that green tea polyphenols could prevent collagen aging markers from rising and to even delay collagen crosslinking by anti-oxidant mechanisms in rats, further supporting green tea extract as a promising anti-

glycation agent. These effects could be even enhanced by the concomitant supplementation of vitamin C and E [25]. Besides their anti-oxidant mechanisms, green tea polyphenols are able to stimulate recovery processes during tendinitis, as shown by the promotion of ECM components and glycosaminoglycans, among other recovery elements after Achilles tendinitis in rats, in combination with a glycine diet. In addition, the synthesis of collagen I as a crucial constituent of tendon was remarkably enhanced by green tea treatment. Simultaneously, inflammatory pathways were modulated in the form of decreased MMP-9 levels, which is important for the remodeling of tissue, whereas MMP-2 and IL-1β, both involved in the active remodeling process, remained elevated during green tea treatment, indicating the potential of green tea polyphenols to accelerate tendon tissue remodeling and the regeneration after tendinitis [23][24]. Altogether, several studies indicate that green tea extracts and EGCG represent promising agents when it comes to fighting ROS and inflammation-triggering stimuli, as well as inflammation itself in tendon tissue (**Table 1**). However, further research and clinical trials have to be conducted in the future for validation purposes.

5. Flavonoids/Flavones

Flavonoids and flavones (**Figure 1**) comprise a group of secondary metabolites that are present in a variety of plants, such as celery, parsley, red pepper, chamomile, mint or *gingko bilboa*, and citrus fruit, and are known to exhibit anti-inflammatory and associated properties in a wide range of chronic diseases [61][62][63][64].

5.1. Anthocyanin

In an in vitro study model of rotator cuff-derived tenofibroblasts, the effect of flavonoid anthocyanin extracted from the black soybean (*Glycine max* (L.) MEER) as anti-oxidants was observed, thus reducing apoptosis in oxidation-stressed tenofibroblasts. Moreover, the suppression of activation of ERK1/2 and JNK accompanied by decreased ROS levels has been assumed to be an important mechanism in the effect of anthocyanins, as, in contrast, ERK1/2 and JAK were up-regulated in H_2O_2-induced apoptotic tenofibroblast cultures without anthocyanin treatment, indicating anthocyanins therapeutic potential in rotator cuff tendon that is exposed to oxidative stressors (**Table 1**) [27].

5.2. Eriocitrin

In previous research by Shang et al., eriocitrin, as another flavonoid derived from lemon and limes, was investigated for its potential as a bio-active reagent in tendon stem cells in vitro. Eriocitrin that has been described as the most potent anti-oxidant in citrus fruits was found to stimulate tendon stem cell proliferation and to enhance their migration activity, as an important feature of tissue healing and regeneration [28][65][66]. In addition, not only could pro-apoptotic caspase-3 activity be reduced in a concentration-dependent manner, but also the extent of scar formation, determined by scar-formation-related markers fibronectin and biglycan, could be markedly reduced in tenocyte stem cells when treated with eriocitrin, making it another promising plant-derived agent in tendinitis therapy (**Table 1**) [28].

5.3. Genistein

In the context of estrogen deficiency, as experienced in menopause, which consequently promotes a loss of collagen and increases the risk of tendinopathies, the flavone and phyto-oestrogen genistein was investigated on collagen synthesis and Achilles tendon in ovariectomized rats in previous research [29][30][67]. Ramos et al. found evidence that genistein was able to prevent collagen loss in the Achilles tendon of rats in a postmenopausal state, underlining its potential for reducing tendinitis risk in women undergoing estrogen deficiency [29]. Moreover, it has been recently demonstrated that genistein improved functional features of Achilles tendon in estrogen-deficient rats, mostly by modulating proliferation-related gene expression (tenomodulin, proliferating cell nuclear antigen (Pcna)), as opposed to collagen remodeling (**Table 1**) [30]. However, further studies have to be conducted in the future to verify this hypothesis.

5.4. Icariin

Icariin is the most abundant flavonoid in horny goat weed (*Epimedium grandiflorum*) and has been demonstrated to positively affect bone metabolism, regeneration, and density [68][69]. In a study by Ye et al., flavonoids have been shown to also support the healing and repair of tendon after rotator cuff reconstruction in rats in vivo, mainly by stimulating the synthesis of collagen type I and II. Moreover, the inhibition of bone loss and the promotion of osteogenesis and angiogenesis, as shown by vascular staining, clearly demonstrating enhanced CD31 (platelet endothelial cell adhesion molecule) and VEGF expression as a sign for intrinsic neovascularization around the tendon insertion site through icariin treatment, are assumed to be crucial components for tendon-bone healing (**Table 1**) [31]. On this background, icariin represents another flavonoid with therapeutic potential when it comes to tendinitis and tendon-associated issues, but still, cellular and molecular mechanisms have to be investigated in the future.

5.5. Quercetin

The polyphenolic flavonoid quercetin that is found in fruit and vegetables shows unique bio-active properties, such as anti-cancer, anti-inflammation, anti-oxidant, and anti-viral effects, which thus might play a role in health promotion and disease prevention, as well as in treatment [70][71][72]. Interestingly, previous studies have demonstrated that anti-oxidation methods reducing ROS could reduce the extent of tendon adhesion [73][74]. Furthermore, in a recent in vivo study by Liang et al., it has been demonstrated that quercetin treatment of rat tendon adhesion models can lead to increased anti-oxidant enzyme activity, as shown by enhanced levels of glutathione peroxidase and superoxide dismutase, while MDA levels were reduced in a concentration-dependent manner. In addition, histological analysis showed a lower extent of tendon adhesion in the rats treated with higher concentrations of quercetin, and no side effects or toxicity of quercetin therapy were observed [32].

Furthermore, Semis et al. found proof of quercetin exhibiting anti-inflammatory, anti-apoptotic, and anti-oxidant activity on rat tendon in vivo after collagenase-induced tendinitis. Moreover, inflammatory markers such as MMPs, ICAM-1, and STAT3 were activated by tendinitis induction, whereas all of them could be remarkably suppressed by quercetin administration, making it a promising agent for tendon damage protection [33]. In a study by Fu et al.,

quercetin has been investigated in combination with kaempferol and isorhamnetin as total flavones of sea buckthorn (*Hippophae rhamnoides*) for the healing of patellar tendon in rats. Within the study, it has been observed that the administration of the flavones not only improved the stress of healing tendons, especially at early stages, but also fiber alignment, collagen deposition, healing, and the recovery of the patellar tendon, suggesting that they could be effective for the improved recovery of tendon injuries (**Table 1**) [34].

6. Resveratrol

Resveratrol (**Figure 1**) is a polyphenolic compound that is found in a variety of plants, including grapes, peanuts, or mulberries. It has been reported as a health-beneficial agent with pharmacological activity positively affecting inflammation, ROS, cancer, diabetes, obesity, and other chronic diseases [75][76][77][78][79][80][81][82]. Moreover, resveratrol has been found to play a role in the modulation of a wide range of cellular mechanisms and pathways, including growth inhibition, proliferation and differentiation, apoptosis, and inflammation cascades [35][37][83][84]. In addition, resveratrol, although its mode of action is not completely understood yet, is known to be a potent activator of Sirt-1; thus, it has a modulatory impact on the Sirt-1 signaling pathway [83][85][86] and acts as NF-κB inhibitor [87][88][89]. Furthermore, in the context of tendinitis, the potential of resveratrol to inhibit the NF-κB signaling pathway, induced by IL-1β and pro-inflammatory gene end products linked with it, has been observed in human tenocytes in vitro. Similarly, IL-1β-promoted PI3K activation has also been described to be suppressed in a dose-dependent manner by resveratrol treatment in tenocytes, comparable to the effects of PI3K inhibitors, suggesting PI3K as a main target signaling pathway of resveratrol in order to suppress NF-κB [37]. These anti-inflammatory effects of resveratrol in tenocytes are assumed to be partly associated with the linkage of Sirt-1 and scleraxis, as well as the deacetylation of NF-κB and PI3K [35][37]. In the same context, it has been demonstrated that resveratrol not only exhibited anti-inflammatory properties, but also stimulated the synthesis of collagens, tenomodulin, and tendon-specific transcription factor scleraxis, which is necessary for tissue vitality and regeneration [37]. The healing capabilities of resveratrol in tendon tissue have also been revealed in diabetic rats in vivo suffering from poor wound healing, following enhanced collagen production, vascular proliferation, and higher fibroblast density, which supported the healing process of Achilles tendinitis despite diabetic conditions [39]. Interestingly, in another in vitro study by Busch et al., the previously mentioned target of resveratrol, Sirt-1, was down-regulated in human tenocytes, leading to the expression of apoptotic proteins (Bax, caspase-3), the acetylation of p53 tumor suppressor Akt activation, and scleraxis suppression. Resveratrol could only inhibit IL-1β-induced NF-κB activation to down-regulate inflammatory mediators, such as COX-2 and MMP-9 in tenocytes, when Sirt-1 was expressed [35]. The role of Sirt-1 in association with resveratrol's anti-inflammatory effects has also been demonstrated in an in vivo study by Poulsen et al. whereby resveratrol prevented dexamethasone-induced senescence of tenocytes triggered by Sirt-1 inhibition [36]. As glucocorticoids are known to promote tendon senescence and collagen attenuation, the effect of resveratrol to activate Sirt-1, thus inhibiting inflammatory and tendon degrading processes, despite glucocorticoid treatment, is of great potential [90][91][92].

Moreover, in a recently conducted study, polydatin, a derivate of resveratrol, was found to exhibit anti-glycation effects in rat tail tendon in vitro. Glycation leads to AGE formation that causes molecular cross-linking of collagen,

making it develop resistance to MMPs, leading to strongly reduced collagen turnover, in turn making collagen and tendon less flexible, and increasing the risk of tendinitis. AGE formation has been found to be accelerated by ROS; hence, resveratrol as a plant-derived anti-oxidant could be a potential natural anti-glycation agent for diabetes and could help to prevent diabetes accompanying disorders, such as tendinitis (**Table 1**) [38].

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