

Myricetin: biological activity related to human health

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Abstract Myricetin (3,5,7,3',4',5'-hexahydroxyflavone) is one of the natural flavonols from fruit, vegetable, tea, and medicinal plants. A great deal of attention has been paid to this compound owing to its various health-promoting effects. In this review, we provide a comprehensive discussion of the therapeutic potential of myricetin by focusing on its biological activity and pharmacokinetic properties.

Keywords Biological activity · Health-promoting effect · Myricetin · Pharmacokinetics

Myricetin (3,3',4',5,5',7-hexahydroxyflavone, Fig. 1), together with quercetin and kaempferol, is a member of the class of flavonoids called flavonols, which are abundant in fruit, vegetables, tea, berries, and red wine. Myricetin is characterized by the pyrogallol B-ring, and the more hydroxylated structure is known to be responsible for its enhanced biological properties compared with other flavonols (Ono et al. 1990; Sato et al. 2013). Myricetin has been highlighted because of its various biological activities including antioxidant (Ong and Khoo 1997), anticancer (Holder et al. 2007; Phillips et al. 2011), anti-inflammatory (Tsai et al. 1999; Wang et al. 2010b), anti-amyloidogenic (Sato et al. 2013), antibacterial (Xu et al. 2001), antiviral

(Pasetto et al. 2014), and antidiabetic effects (Li and Ding 2012). Nevertheless, the therapeutic potential of myricetin for human diseases has not been well explored and documented. In this review, we summarize the biological activities and pharmacokinetic properties of myricetin.

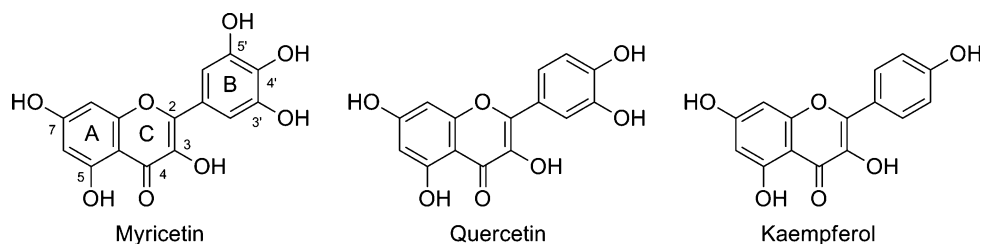
Natural sources

Generally, flavonoid content of plant materials is determined by extraction with organic solvents followed by high-performance liquid chromatography analysis. Myricetin mainly occurs in nature in the form of glycosides and can be detected in numerous nutritious foods such as blueberry leaves, rose petals (*Rosa damascena*), oranges, sea buckthorn, chia seeds, carob extract, pistachio extract (*Pistacia lentiscus*), grape seed extract, cruciferous vegetables, peppers, garlic, and black tea (*Camellia sinensis*). In 2008, Sultana and Anwar (Sultana and Anwar 2008) demonstrated the flavonol contents of 22 fruits, vegetables, and medicinal plants. In that study, myricetin was the second most abundant flavonol, and the total myricetin content in the plant species ranged from 146.2 to 1660.9 mg/kg of dry matter. Among the plants evaluated, spinach (1660.9 mg/kg), cauliflower (1586.9 mg/kg), carrot (525.3 mg/kg), turnip (457.0 mg/kg), and peas (146.2 mg/kg) were shown to have high content of myricetin while cabbage, onion, and garlic lacked myricetin. A more extensive list of myricetin aglycone content in foods, converted from glycoside values using conversion factors based on the molecular weight of the specific compounds, was composed by the United States Department of Agriculture (Table 1) (US Department of Agriculture 2003).

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Fig. 1 Structures of myricetin, quercetin, and kaempferol**Table 1** Myricetin content in selected foods (USDA 2003)

Food source	Myricetin content (mg/100 g)	Food source	Myricetin content (mg/100 g)
Carob fiber (Caromax)	47.74 ± 1.95	Sweet potato leaves, cooked, steamed, without salt	2.93 ± 0.28
Juice concentrate, blackberry	20.85	Cranberry sauce, canned, sweetened	2.7
Fennel, leaves, raw	19.8	Onions, red, raw	2.7 ± 0.61
Parsley, fresh (<i>Petroselinum crispum</i>)	14.84 ± 6.76	Broadbeans, immature seeds, raw (<i>Vicia faba</i>)	2.6
Carob kibbles	11.67	Cowpeas, common (blackeyes, crowder, southern), mature seeds, raw (<i>Vigna unguiculata</i>)	2.6
Goji berry (wolfberry), dried	11.4	Cranberries, dried, sweetened	2.4
Bog whortleberries, wild, frozen	7.3 ± 4.7	Rutabagas, raw (<i>Brassica napus var. napobrassica</i>)	2.13 ± 2.14
Carob flour (<i>Ceratonia siliqua</i>)	6.73 ± 1.12	Oregano, fresh	2.1
Cranberries, raw (<i>Vaccinium macrocarpon</i>)	6.63 ± 1.6	Turmeric, steamed (<i>Curcuma longa</i>)	2.04
Currants, european black, raw (<i>Ribes nigrum</i>)	6.18 ± 0.57	Cashew apple, raw	1.93 ± 0.73
Dock, raw (<i>Rumex spp.</i>)	5.7	Nalta jute, raw	1.93
Blueberries, rabbiteye, raw (<i>Vaccinium spp.</i>)	4.7 ± 1.01	Juice, black Currant	1.86 ± 0.66
Crowberries, raw	4.65 ± 0.25	Blueberries, frozen, unsweetened	1.76 ± 0.33
Juice, cranberry, raw	4.41	Garlic, raw (<i>Allium sativum</i>)	1.61
Sweet potato leaves, raw (<i>Ipomoea batatas</i>)	4.38 ± 2.9	Hartwort, leaves	1.6
Bayberries, raw	3.65 ± 0.71	Olive leaves, raw	1.43
Annual saw-thistle, leaves	3.6	Greek greens pie (prepared from wild greens)	1.4
Juice, crowberry	3.49 ± 0.03	Chard, swiss, raw (<i>Beta vulgaris subsp. vulgaris</i>)	1.35 ± 0.24
Pitanga, (surinam-cherry), raw (<i>Eugenia uniflora</i>)	3.36 ± 1.15	Blueberries, cultivated (highbush), raw (<i>Vaccinium spp.</i>)	1.26 ± 0.21
Bee Pollen	3.34 ± 1.13	Peppers, hot chili, green, raw (<i>Capsicum frutescens</i>)	1.2

Physicochemical properties

It is only recently that the physicochemical properties of myricetin were reported (Yao et al. 2014) (Table 2). The average acid dissociation constant of myricetin ($pK_a = 6.63 \pm 0.09$) indicated that myricetin would be significantly ionized at physiological pH (7.4), but myricetin was only sparingly soluble in water ($16.60 \pm 0.92 \mu\text{g/mL}$). In addition, in buffered solutions, myricetin showed higher aqueous solubility at acidic pH (776.74 , 576.07 , and $149.75 \mu\text{g/mL}$ in acetate buffer

solutions of pHs 1.0, 2.0, and 3.0, respectively). In terms of solubility in organic solvents, myricetin was readily soluble in polar organic solvents ($317.23 \pm 21.41 \text{ mg/mL}$ in DMF) but strikingly less soluble in nonpolar ones ($0.74 \pm 0.30 \mu\text{g/mL}$ in chloroform). Typically, low solubility parallels low dissolution rates, and myricetin showed a low intrinsic dissolution rate ($\text{IDR} = 11.66 \pm 0.82 \text{ g/min/cm}^2$) at 37°C . Consistent with the low aqueous solubility, myricetin exhibited hydrophobicity (apparent partition coefficient, $\log P = 2.76 \pm 0.05$). Log P values of myricetin at different pHs (log D) were also determined,

Table 2 Physicochemical properties of myricetin (Yao et al. 2014)

pK_a	Solubility ($\mu\text{g/mL}$)			IDR	Lipophilicity		P_{app}	Stability, $t_{1/2}$ (h)			
	Water	pH 2	DMF		$\text{Log}D_{2.0}$	$\text{Log}D_{7.4}$		pH		Temp.($^{\circ}\text{C}$)	
								2.0	6.8	25	80
6.6	16.6	576.0	317.2 ^a	11.7 ^b	2.06	1.34	1.7 ^c	5.68	2.11	22.9	0.9

^a (mg/mL)^b (g/min/cm²)^c ($\times 10^{-6}$ cm/s)

and decreases in $\text{log}D_{\text{pH}}$ were observed at higher pH ($\text{log}D_{2.0} = 2.06 \pm 0.09$ versus $\text{log}D_{7.4} = 1.34 \pm 0.01$). The pH-dependent decrease in $\text{log}D$ indicates that myricetin might be better absorbed under acidic conditions, which is consistent with a previous report by Xue et al. This report showed that in rats, myricetin is most likely to be absorbed at the duodenum, a weakly acidic region in the small intestine (Xue et al. 2011). Noteworthy is the moderate membrane permeability of myricetin (apparent permeability coefficient, $P_{app} = 1.7 \times 10^{-6}$ cm/s) (Yee 1997), which, in combination with the favorable $\text{log}D_{7.4}$ value for absorption, suggests that the low solubility and slow dissolution rate of myricetin are the limiting factors in low absorption of myricetin. On the other hand, the stability of myricetin was dependent on both pH and temperature, as evidenced by facile decomposition upon increases in pH and temperature (Table 2).

Pharmacokinetic properties and bioavailability

It was not until recently that the pharmacokinetic properties of myricetin were evaluated as a single active principle. In 2014, Dang et al. developed a specific and sensitive ultra-performance liquid chromatography-tandem mass spectrometry method for myricetin quantification in rat plasma after oral and intravenous administrations (Dang et al. 2014). According to this study, owing to poor absorption, myricetin showed low oral bioavailability (9.62 and 9.74 % at oral doses of 50 and 100 mg/kg, respectively) (Table 3). Specifically, after oral administration, both C_{max} and AUC of myricetin increased in a dose-dependent manner, which can be attributed to the passive diffusion of myricetin in vivo. However, the relatively long T_{max} (6.4 h) to reach C_{max} (1488.75 ± 200.78 ng/mL) indicates that myricetin was only slowly absorbed, presumably owing to its poor aqueous solubility.

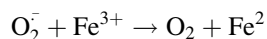
Myricetin is also known to enhance the bioavailability and pharmacokinetic properties of co-administered drugs through inhibition of drug-metabolizing cytochrome P450 s (CYP450 s) and/or drug efflux pumps such as P-glycoproteins (Pgps). Thus, Li et al. reported that myricetin

inhibits CYP450 s ($\text{IC}_{50} = 7.81 \mu\text{M}$ for CYP3A4 and $13.5 \mu\text{M}$ for CYP2C9) as well as Pgp (Li et al. 2011). As a result, upon combination with myricetin, both the $\text{AUC}_{0-\infty}$ and C_{max} of orally administered tamoxifen (10 mg/kg) increased by 41.8–74.4 and 48.4–81.7 %, respectively, with concurrent enhancement of the absolute bioavailability (29.0–35.7 %) when compared with a control group administered oral tamoxifen alone (20.4 %). The effect of myricetin as a metabolism-boosting drug was also demonstrated by co-administration with losartan (Choi et al. 2010). In that study, inhibition of CYP3A4, CYP2C9, and Pgp by myricetin was shown to increase the $\text{AUC}_{0-\infty}$ (31.4–61.1 %) and C_{max} (31.8–50.2 %) of losartan. The ratio of the losartan metabolite to the losartan parent also decreased by 20 %, presumably owing to inhibition of CYP450-mediated metabolism of losartan. However, other pharmacokinetic properties of losartan such as T_{max} , V_d , and $t_{1/2}$ were not affected by combination with myricetin.

Pharmacology

Antioxidant effects

In biological systems, reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical, hydrogen peroxide, and the nitrogen oxide radical play essential roles in homeostasis of physiological processes. However, imbalance of ROS and antioxidant enzyme activity causes several problems including protein aggregation, DNA degradation, and oxidation of membrane lipids. For example, superoxide anion radicals have been proposed to cause damage to cells and other components in bodily tissues by generating highly reactive hydroxyl radicals in a Fenton reaction (Halliwell 1978; McCord and Day 1978):



Flavonols are well known for effective reduction of free radical damage by providing antioxidant benefits, and quercetin is the most extensively studied flavonol

Table 3 Pharmacokinetic parameters of myricetin (Dang et al. 2014)

Parameters	Administration routes		
	<i>p.o.</i>		<i>i.v.</i>
Dose (mg/kg)	50	100	0.5
C_{\max} (ng/mL) ^a	1488.75 ± 200.78	2611.76 ± 1019.58	2232.16 ± 856.36
T_{\max} (h) ^b	6.4 ± 0.89	5.2 ± 3.03	0 (pre-dose)
$t_{1/2}$ (h)	2.78 ± 0.81	3.79 ± 0.75	6.99 ± 1.94
$AUC_{0-\infty}$ (ng·h/mL) ^c	13,731.13 ± 5,574.58	28,081.62 ± 10,982.45	1452.85 ± 170.30
CL (L/h/kg) ^d	–	–	0.35 ± 0.05
V_d (L/kg) ^e	–	–	4.12 ± 1.52
Bioavailability (%) ^f	9.62	9.74	–

^a The peak serum concentration of a drug after administration

^b The amount of time for which a drug is present at maximum concentration in serum

^c The total drug exposure over time

^d The rate at which the drug is cleared from the blood

^e Volume of distribution, a proportionality constant between total amount of drug in the body and plasma concentrations

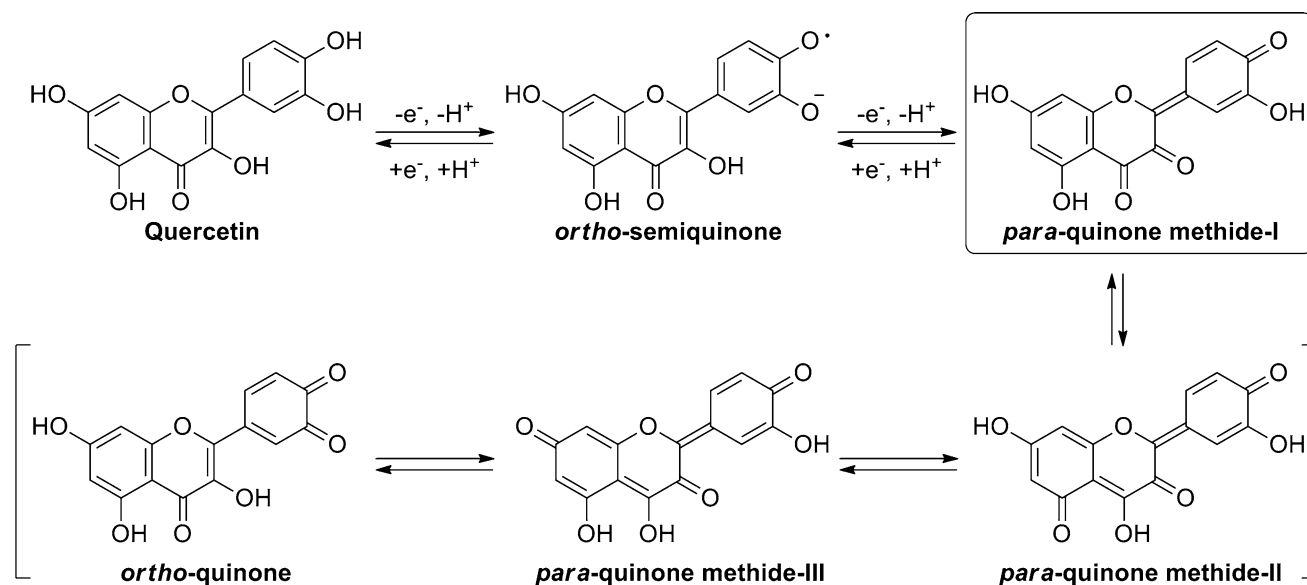
^f Fraction of drug that reaches the blood stream when compared with the amount of the drug that is administered

antioxidant (Metodiewa et al. 1999; Awad et al. 2000). The proposed antioxidant mechanism of quercetin includes single electron transfer followed by hemolytic cleavage of the phenolic OH bonds in the B-ring, resulting in successive formation of the *ortho*-semiquinone and *para*-quinone methide (Fig. 2). The potent antioxidant effect of quercetin was attributed to stabilization of these intermediates by the 3',4'-catechol moiety (Boots et al. 2008).

According to Chobot et al., the mechanism of myricetin's antioxidant effect also includes inactivation of superoxide anion radicals through single electron transfer

to form an aryloxy radical (Fig. 3A) (Chobot and Hadacek 2011). In contrast, by tracing the oxidized products of myricetin by mass spectrometry, Ghidouche et al. identified a myricetin dimer linked through a C2'–C2' covalent bond (Fig. 3B), and therefore proposed a different antioxidant mechanism of myricetin, wherein an alkoxy radical is initially generated at the 3-position and then rapidly isomerizes to a C2' radical that is stabilized by three phenolic hydroxyl groups (Ghidouche et al. 2007).

It is noteworthy that stabilization of the aryloxy radical in the B-ring is anticipated to increase the antioxidant

**Fig. 2** Antioxidant mechanism of quercetin

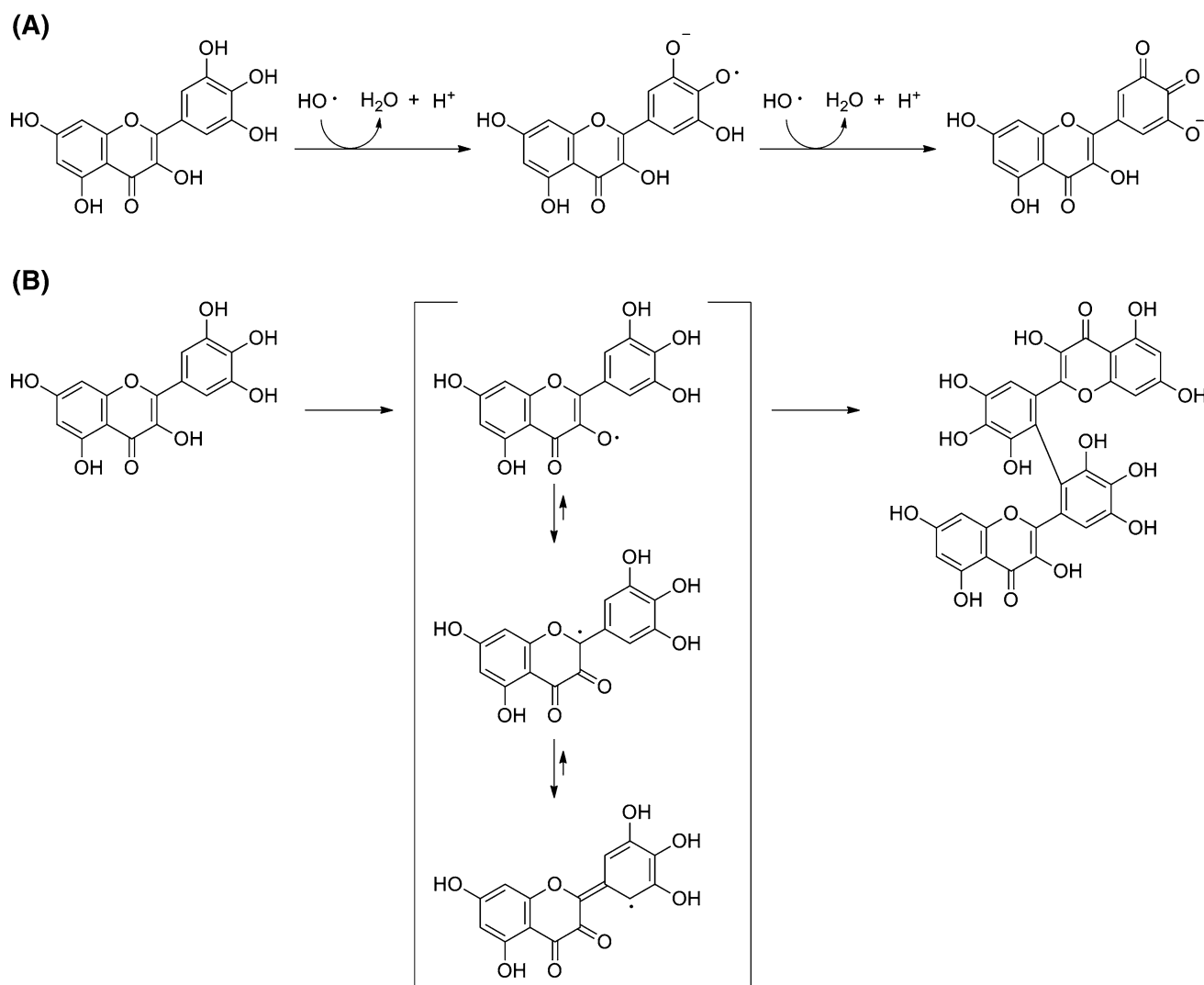


Fig. 3 Proposed antioxidant mechanisms of myricetin

activity of the flavonols because a pyrogallol moiety with a 3',4',5'-trihydroxy-substituted phenyl group is a better radical scavenger than a catechol moiety (Furuno et al. 2002). Thus, myricetin has been proposed as a stronger antioxidant than quercetin (Oyama et al. 1994; Gordon and Roedig-Penmann 1998). This has been demonstrated by myricetin's effective radical scavenging activity in various radical generating systems. These systems include the superoxide anion (O_2^-) generated by phenazine methosulfate-NADH (Robak and Gryglewski 1988); hydroxyl radical ($HO\cdot$) generated either by hydrogen peroxide (Hussain et al. 1987) or *tert*-butyl hydroperoxide (Fraga et al. 1987), and DPPH (2,2-diphenyl-1-picrylhydrazyl) radical (Khanduja and Bhardwaj 2003).

The antioxidant effect of myricetin was demonstrated in various cell-based assays. In Chinese hamster lung fibroblast cells (V97-4), myricetin showed a protective

effect through inactivation of H_2O_2 -induced radicals as well as regulation of apoptosis (Kang et al. 2010). Similarly, myricetin protected yeast cells from H_2O_2 -induced oxidative stress that leads to a reduction in intracellular oxidation and protein carbonylation (Mendes et al. 2015). In the case of vascular endothelial dysfunction, myricetin regulated the amount of oxidized low-density lipoprotein (oxLDL), which is crucial for disease development, to increase the viability of EA.Hy926 cells (Yi et al. 2011). Myricetin was also effective in preventing methylmercury (MeHg)-induced mitochondrial dysfunction by blocking ROS generation as well as lipid peroxidation (Franco et al. 2010).

Antioxidant effect of myricetin was also observed in animal models. Myricetin decreased the generation of nitric oxide, myeloperoxidase, and malondialdehyde (MDA) while increasing the activity of superoxide

dismutase (SOD) and glutathione peroxide in a mice model of dextran sulfate sodium (DSS)-induced colitis (Zhao et al. 2013). Protective effects of myricetin on hypoxia-induced mitochondrial impairments were reported, and myricetin treatment attenuated acute hypoxia-induced mitochondrial impairment in rats (Zou et al. 2015). In 7,12-dimethyl benzanthracene (DMBA)-induced breast cancer in female Wistar rats (Jayakumar et al. 2014) and in a sickle cell anemia model, myricetin was effective in preventing oxidative damage (Henneberg et al. 2013). However, according to Duthie et al., the *in vivo* protective effects of myricetin are limited by poor bioavailability (Duthie and Morrice 2012).

Anti-inflammatory effects

Anti-inflammatory effects are closely linked with antioxidants effect because one of the main effects of inflammation is oxidative stress. Wang et al. evaluated the *in vivo* anti-inflammatory effect of myricetin in both acute and chronic models of inflammation and reported a significant inhibition of xylene-induced ear edema, carrageenan-induced hind paw edema, and acetic acid-induced capillary permeability (Wang et al. 2010a). In the carrageenan-induced paw edema model, myricetin treatment resulted in a significant decrease in MDA, increased levels of SOD, and a concurrent decrease in leukocyte count. Myricetin was also effective in preventing chronic inflammation, which inhibited formation of granuloma tissue. Taken together, myricetin showed potent anti-inflammatory activity for both acute and chronic inflammation, which might be associated with its antioxidant activity (Wang et al. 2010b).

Inhibition of specific anti-inflammatory target enzymes by myricetin was also demonstrated. Myricetin inhibited 5-lipoxygenase (5-LOX) with an IC_{50} of 4.02 μ M. This is of importance because 5-LOX is related to the production of leukotriene B₄ (LTB₄), a mediator of several inflammatory diseases including atherosclerosis (Yamada et al. 1999). Others have also reported stimulation of cyclooxygenases 1 and 2 (COX-1 and COX-2) by myricetin; upon co-incubation with myricetin, the catalytic activity of COX-2 increased by 124.5 % compared with control. This result was attributed to tight binding of myricetin to the peroxidase active site of COX-2, resulting in re-activation of its catalytic activity (Wang et al. 2010b). However, *in vivo* exposure of Sprague–Dawley rats to myricetin showed a unique biphasic pattern in the catalytic activity of COX-2. At low myricetin doses (<0.3 mg/kg), COX-2 was stimulated to convert prostaglandin G₂ (PGG₂) to prostaglandin E₂ (PGE₂), while at high doses of myricetin (>0.3 mg/kg), stimulation of COX-2 decreased (Bai and Zhu 2010).

Myricetin also showed regulatory effects on the production of cytokines involved in inflammatory responses. In lipopolysaccharide-stimulated primary macrophages and RAW264.7 macrophages, myricetin was shown to inhibit the production of interleukin-12 (IL-12) via downregulation of the binding activity of macrophages to nuclear factor kappa-B (NF- κ B) (Kang et al. 2005). Production of interleukin-1 β (IL-1 β) in SW982 human synovial sarcoma cells was also shown to be inhibited by myricetin (Lee and Choi 2010).

Myricetin also controlled inflammation in JB6 P+ mouse epidermal cells via signaling pathways such as TNF- α -induced VEGF (vascular endothelial growth factor) upregulation by inhibition of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase kinase 1 (MEK1), as well as MAPK kinase 4 (MKK4) (Kim et al. 2009). In another study in TNF- α -activated ECV304 cells, myricetin suppressed the activity of TNF- α -mediated NF- κ B through downregulation of inhibitor- κ B kinase (IKK) (Tsai et al. 1999). Ding et al. also reported that myricetin protects from cytokine-induced cell death. It also decreased cell apoptosis induced by the cytokine mixture of TNF- α (10 ng/mL), IL-1 β (5 ng/mL), and IFN- γ (1000 IU/mL) in insulin-secreting RIN-m5f β cells (Ding et al. 2012).

Anti-diabetes effects

Zamora-Ros et al. (2014) reported the statistical relationship between dietary intake of flavonoids and type II diabetes in a European population through statistical analysis. Among various flavonoids, myricetin showed an inverse association with the risk of type II diabetes, which indicates that myricetin has potential anti-diabetes activity (Zamora-Ros et al. 2014).

Diabetes is a metabolic disorder resulting hyperglycemia and development of diabetes-specific complications such as macrovascular and microvascular diseases. Diabetes is closely related to inflammation and oxidative stress. Chronic inflammatory responses, including production of cytokines, result in insulin and β -cell dysfunction, and ultimately diabetes (Hotamisligil 2006). Therefore, balancing the generation and elimination of ROS is important for pathogenesis of diabetes (Cheng et al. 2011). As described above, myricetin has antioxidant as well as anti-inflammatory effects and as a result, myricetin can be useful in preventing diabetic complications (Pandey et al. 2009).

Additionally, myricetin directly affects glycogen metabolism and insulin resistance. In a mouse model of diabetes, treatment with myricetin for 2 days (3 mg/12 h) resulted in 50 % reduction of hyperglycemia compared with control along with normalization of hypertriglyceridemia (Ong and

Khoo 2000). Myricetin was also reported to lower plasma glucose levels in streptozotocin-induced diabetes in rats (Liu et al. 2005) and in a rat model of insulin resistance (Tzeng et al. 2011). In the insulin resistant rat model in particular, myricetin reduced insulin resistance by increasing endogenous production of β -endorphins followed by activation of μ -opioid receptors, which ameliorated defective post-receptor insulin signaling (Tzeng et al. 2011). In mice that fed a high-fat and high-sucrose diet, 0.12 % myricetin supplementation significantly improved hypertriglyceridemia and hypercholesterolemia, which suggests that myricetin may have a protective effect against diet-induced obesity and insulin resistance (Choi et al. 2014a).

Myricetin was found to inhibit glucose uptake in isolated rat adipocytes through direct interaction with glucose-transporter subtype 4 (GLUT4) (Strobel et al. 2005). Myricetin was found to block the uptake of methylglucose by inhibiting GLUT4. However, phosphorylation of insulin receptor substrate 1 via insulin receptor tyrosine kinase was not affected by myricetin in insulin-stimulated rat adipocytes (Strobel et al. 2005).

Aggregation of islet amyloid polypeptide (IAPP) results in pancreatic β -cell death in type II diabetes. IAPP has thus been considered as a potential target for type II diabetes. According to Zelus et al., myricetin not only strongly inhibits the formation of IAPP, but also protects from the neurotoxic effect of IAPP in PC12 cells (Zelus et al. 2012).

Protective effects against Alzheimer's disease

Major hallmarks of Alzheimer's disease are amyloid beta ($A\beta$) fibrils and neurofibrillary tangles (NFTs) that are composed of highly phosphorylated forms of the microtubule-associated protein tau. Myricetin showed therapeutic potential against Alzheimer's disease by inhibiting the formation of both $A\beta$ fibrils and NFTs.

$A\beta$ peptides result from cleavage of the amyloid precursor protein (APP) catalyzed by β -secretase (BACE) and γ -secretase, and myricetin is known to inhibit BACE-1 (Shimmyo et al. 2008a). Upon exposure to stress, $A\beta$ peptides are aggregated to $A\beta$ fibrils. The formation of $A\beta$ fibrils results in neurotoxicity by producing ROS. Myricetin showed neuroprotective effects by scavenging radicals induced by $A\beta$ fibrils (Choi et al. 2014b).

Myricetin was found to have a higher binding affinity for $A\beta$ fibrils than for $A\beta$ monomer, and it was claimed that oxidized myricetin shows higher binding affinity for $A\beta$ fibrils than un-oxidized myricetin (Hirohata et al. 2007). It was also demonstrated that myricetin inhibited the formation of $A\beta$ fibrils (Bartolini et al. 2011). Sato et al. reported the half-maximal inhibitory concentration (IC_{50}) of myricetin against $A\beta$ fibril formation to be 15.1 μ M (Sato et al. 2013). Shimmyo et al. proposed that the underlying

molecular mechanism for inhibition of $A\beta$ fibrillogenesis by myricetin includes preventing a conformational change of $A\beta$ to a toxic β -sheet structure (Shimmyo et al. 2008b). A molecular docking study of myricetin to $A\beta$ fibrils was performed to show the binding mode of myricetin (Keshet et al. 2010).

Recently, $A\beta$ oligomers have been suggested as more important in Alzheimer's disease pathogenesis than $A\beta$ fibrils. Interestingly, myricetin was also found to be an effective inhibitor of formation of $A\beta$ oligomers (Ono et al. 2012). Necular et al. determined the IC_{50} value of myricetin (106.87 μ M) against $A\beta$ oligomerization using an oligomer-specific antibody (A11) (Necula et al. 2007). In a transgenic mouse model (Tg2576) of Alzheimer's disease, myricetin was shown to decrease $A\beta$ oligomers by inhibition of oligomerization (Hamaguchi et al. 2009).

Myricetin treatment also reduced abnormal fibrillation ($IC_{50} = 1.2 \mu$ M), as well as oligomerization, of the tau protein (Taniguchi et al. 2005). This result was supported by molecular dynamics calculation of the binding energy of myricetin to the VQIVYK oligomer fragment of tau (Berhanu and Masunov 2015).

Anticancer effects

Myricetin shows anticancer activity against various kinds of cancers through different molecular mechanisms. Due to the structural similarity with ATP (Fig. 4), myricetin is able to mimic ATP. Thus, protein kinases and ATPases are anticancer targets of myricetin.

There have been numerous reports regarding competitive or noncompetitive inhibition of protein kinases by myricetin. For example, Phillips et al. suggested that myricetin would show anticancer activity in pancreatic cancer by acting as an inhibitor of phosphatidylinositol 3-kinase. This was confirmed by tumor regression and decreased metastatic spread in vivo (Phillips et al. 2011). The serine/threonine kinase PIM1, an oncogenic protein that has been implicated in the development of leukemias, lymphomas, and prostate cancer, was also shown to be inhibited by

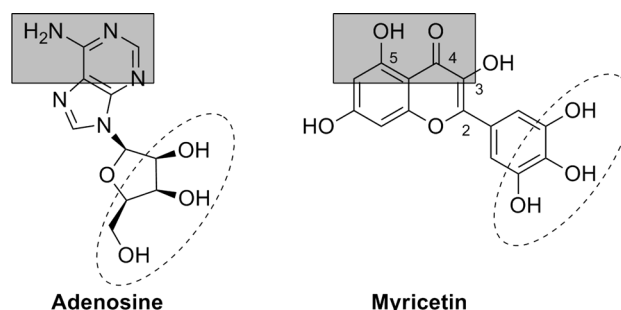


Fig. 4 Structural comparison of adenosine and myricetin

myricetin with an IC_{50} value of 0.78 μM (Holder et al. 2007). Zhang et al. reported that myricetin inhibits proliferation of human hepatoma HepG2 cells by arresting the cell cycle at the G2/M phase through inhibition of cyclin-dependent kinase 1 (Zhang et al. 2011). MKK4, another anti-tumor target, was shown to be inhibited by myricetin in an ATP-competitive manner (Kim et al. 2009). Receptor tyrosine kinase is another target for myricetin. The tyrosine kinase Met, a receptor of hepatocyte growth factor (HGF), has been proposed as an attractive target for prevention and treatment of human medulloblastoma. Labbé et al. observed that myricetin (5 $\mu\text{mol/L}$) inhibited HGF/Met signaling in a medulloblastoma cell line (Labbé et al. 2009).

Similar to kinases, ATPases also use ATP for their catalytic activity, and several ATPases such as Hsp70 ATPase (Koren et al. 2010) have been reported to be inhibited by myricetin.

Other molecular targets of myricetin for cancer have been reported. In colorectal carcinoma cells, myricetin showed inhibitory activity against matrix metalloproteinase-2, with an IC_{50} of 7.82 $\mu\text{mol/L}$ (Ko et al. 2005). Lu et al. reported inhibition of thioredoxin reductase (TrxR), a potential anticancer target, by myricetin ($IC_{50} = 0.63 \mu\text{mol/L}$) in TrxR-overexpressed A549 cells and suggested that the oxidized form of myricetin is utilized as both inhibitor and substrate (Lu et al. 2006).

Myricetin has been shown to have maximal chemoprotective effects in a mouse model of skin tumorigenesis induced by PAHs and *N*-methyl-*N*-nitrosourea (Mukhtar et al. 1988). In this model, myricetin afforded significant protection against skin tumorigenicity by delaying the onset and the subsequent development of skin tumors (Mukhtar et al. 1988).

Several reports suggest that myricetin can also be used as a chemosensitizer for cancer. Myricetin increased the radiosensitivity of lung cancer cells (A549 and H1299 cells), resulting in increased apoptosis of cancer cells after radiotherapy. This was indicated by monitoring the expression levels of caspase-3 (Zhang et al. 2014). In esophageal cancer EC9706 cells, myricetin enhanced chemosensitivity of 5-fluorouracil, and the combination therapy of myricetin and 5-fluorouracil resulted in suppression of tumor growth in tumor-bearing nude mice (Wang et al. 2014).

Modulation of ion channels

Ca^{2+} channels are important for various cellular functions including contraction of vascular smooth muscle and modulation of intracellular Ca^{2+} concentration for pain signals. There are many reports demonstrating that

myricetin has a stimulatory effect on Ca^{2+} channels, which might be useful for the treatment of hypertension and stroke. In rat tail artery myocytes, myricetin stimulated vascular Ca_v 1.2 channels in a concentration- and voltage-dependent manner with an EC_{50} value of 16 μM (Saponara et al. 2011). In rat aorta rings, myricetin induced contractile responses in vascular smooth muscle L-type Ca^{2+} channels with a pEC_{50} value of 4.43 ± 0.03 . A functional study observed that myricetin induced vasoconstriction by activating L-type Ca^{2+} channels with similar efficacy but at a site of action different than that of the Ca^{2+} channel agonist, (S)-(-)-Bay K 8644 (Fusi et al. 2003). Interestingly, the stimulatory effect of myricetin was exerted only on the L-type, but not on the T-type, Ca^{2+} channel (Fusi et al. 2005). In neurons of hypothalamic paraventricular nucleus (PVN), myricetin increased Ca^{2+} currents and intracellular Ca^{2+} concentration through T- and L-type Ca^{2+} channels to enhance GABA_A receptor activity (Zhang et al. 2012).

Behavioral studies indicated a potential analgesic effect of myricetin in a neuropathic pain model of spinal nerve ligation (SNL) in rats. Injection of myricetin (0.1–10 mg/kg i.p.) reduced SNL-induced mechanical allodynia and thermal hyperalgesia (Hagenacker et al. 2010).

Anti-infectious activity

Antiviral activity of myricetin against several viruses, including the human immunodeficiency virus (HIV) and human papillomaviruses (HPVs), has been reported. Pasetto, et al. tested the antiviral activity of myricetin against several HIV-1 strains. Myricetin showed potent inhibitory activity, as indicated by IC_{50} values, in several cells lines: 20.43 μM (HIV-1 BaL-infected TZM-b1 cells), 22.91 μM (HIV-1 MN-infected H9 cells), 1.76 μM (HIV-1 89.6-infected H9 cells), 4.49 μM (HIV-1 MN-infected PBMC cells), and 3.23 μM (HIV-1 89.6-infected PBMC cells) (Pasetto et al. 2014).

HPVs cause cervical as well as head and neck cancers, which might be attributed to two on coproteins (E6 and E7). In particular, binding of E6 to a Fas-associated protein containing a death domain and caspase-8 can prevent apoptosis of infected cells. However, the HPV-induced apoptotic blockade was shown to be prevented or reversed by myricetin with an IC_{50} of 850 nM (Yuan et al. 2012).

Myricetin showed antibacterial effects against methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Burkholderia cepacia*, vancomycin-resistant enterococci, and other medically important organisms such as *Klebsiella pneumoniae* and *Staphylococcus epidermidis* with minimum inhibitory concentrations (MIC) of 32–256 $\mu\text{g/mL}$ (Xu and Lee 2001).

The bacterial replicative helicase DnaB helicase was shown to be the major target enzyme for antibacterial activity of myricetin. Myricetin noncompetitively inhibited *Escherichia coli* DnaB helicase ($IC_{50} = 11.3 \mu\text{M}$) which, along with primase, plays a central role during DNA replication and elongation (Griep et al. 2007). Myricetin regulated *K. pneumoniae* DnaB helicase (KpDnaB) activity to decrease its ssDNA-stimulated ATPase activity (59 %) as well as its dsDNA-unwinding activity (Lin and Huang 2012).

Myricetin has found additional usefulness in prevention of bacterial/viral infection by stimulating epithelial Cl^- secretion (Sun et al. 2014). In contrast to quercetin, which stimulated epithelial Cl^- secretion only under basal conditions in epithelial A6 cells, myricetin was able to stimulate epithelial Cl^- secretion even under cAMP-stimulated conditions (Sun et al. 2014).

Other biological activities

Myricetin showed the anti-obesity effects in a rat model of diet-induced obesity. In this model, myricetin reduced not only body weight, visceral fat-pad weight, and plasma lipid levels but also decreased triglycerides and cholesterol. These effects were achieved by upregulation of peroxisome proliferator-activated receptor α and downregulation of sterol regulatory element binding proteins (SREBPs) expression (Chang et al. 2012).

Lifespan was prolonged (32.9 %) by myricetin in *C. elegans* through nuclear translocation of DAF-16. This was confirmed by a complete loss of myricetin-induced lifespan expansion in a DAF-16 loss-of-function mutant strain (CF1038). Myricetin also decreased the formation of lipofuscin, a biomarker of aging (Buchter et al. 2013).

Inhibition of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) zipper by myricetin was also reported (Yang et al. 2010). Neuronal SNARE proteins facilitate the synaptic fusion of vesicles to the presynaptic plasma membrane and mediate neurotransmitter release. Myricetin intercalated into the hydrophobic inner core near the middle of the SNARE complex to stop SNARE zipper.

Myricetin has been suggested to interfere with the intestinal folate transport system, and Furumiya et al. demonstrated that myricetin inhibited proton-coupled folate transporter in a noncompetitive manner both in Caco-2 ($K_m = 0.407 \mu\text{M}$, $K_i = 61 \mu\text{M}$) and MDCK cells ($K_m = 1.246 \mu\text{M}$, $K_i = 130 \mu\text{M}$) (Furumiya et al. 2014).

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