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Letter to the editor:

RECENT STUDIES ON MYRICETIN AND ITS BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

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Flavonoids are compounds characterized by a 15-carbon skeleton structure (also abbreviated as C6-C3-C6) containing two aromatic ring systems (A and B rings) and a heterocyclic ring (C) (Kumar and Pandey, 2013; Dias et al., 2021). Among these, flavonols have an unsaturated C ring at the C2-C3 position, which is hydroxylated at C3 and oxidized at C4. The main flavonols are myricetin (MYR), quercetin, kaempferol, isorhamnetin, and fisetin (Kim et al., 2006; Spiegel et al., 2020).

MYR (3,3′,4′,5,5′,7-hexahydroxyflavone) is a flavonol (Ong and Khoo, 1997) derived from the parent compound taxifolin, which is turned into the (+)-dihydromyricetin intermediate and can be further chemically modified to produce laricitrin and then syringetin, both molecules in the flavonol class of flavonoids (Flamini et al., 2013).

MYR is present in various fruits, vegetables, tea, berries and red wine. MYR's augmented biological activity in comparison with other flavonols is due to the pyrogallol B-ring, and the more hydroxylated structure. MYR is found in the Myricaceae, Anacardiaceae, Polygonaceae, Pinaceae and Primulaceae families (Gupta et al., 2020; Taheri et al., 2020). MYR displays an array of biological and pharmacological activities such as antioxidant, anti-amyloidogenic, antibacterial, antiviral, antidiabetic, anticancer, anti-inflammatory, anti-epileptic and anti-ulcer (Imran et al., 2021; Pluta et al., 2021; Agraharam et al., 2022; Javed et al., 2022). Because of such a range of properties, MYR has been the object of great attention in recent years for its uses in the pharmaceutical, food, and cosmetic industries. The present letter summarizes recent key research on the biological and pharmacological properties of MYR (Table 1).

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Table 1: Recent research on the biological and pharmacological activities of myricetin

Key findings	Reference
MYR can lower the fibril load acting as a potent superoxide dismutase 1 (SOD1) aggregation inhibitor. MYR's structure can be a useful reference for the design of more powerful amyotrophic lateral sclerosis inhibitors that prevent the condition and reverse its symptoms.	Sharma et al., 2023
MYR relieves osteomyelitis by preventing biofilm formation. This activity is due to MYR inhibiting osteoblast growth markers alkaline phosphatase, osteopontin and type-I collagen via the Toll-like receptor-2 (TLR2) and mitogen-activated protein kinase (MAPK) pathways. In silico studies indicate that MAPK may be a potential MYR-binding protein.	Gao et al., 2023
MYR prevents HCoV-229E and SARS-CoV-2 replication ***in vitro***, deactivates SARS-CoV-2 virus entry facilitators, and eases inflammation via the RIPK1/NF-κB pathway. This indicates that MYR possesses the potential to become a therapeutic agent to treat COVID-19.	Pan et al., 2023
MYR has proved effective against experimental Alzheimer's disease (AD), suggesting its mechanism may be related to the inhibition of mitochondrial dysfunction, activation of the NLRP3 inflammasome, and neuroinflammation induced by the P38 MAPK pathway. Therefore, MYR could be an interesting drug candidate for AD treatment.	Liu et al., 2023
MYR exerts cardioprotective activity on cardiac injury caused by high-intensity exercise by downregulating PTGS2 and MAOB and upregulating MAP2K1 and EGFR, while controlling the complicated myocardial metabolic network.	Li et al., 2023
MYR can ease oxidative stress and apoptosis by targeting the nuclear factor erythroid 2–related factor 2 (NRF2) signallng pathway, hence exerting a therapeutic action on hypoxic-ischemic injury. This implies that MYR could become a future hypoxic-ischemic encephalopathy treatment.	Chen et al., 2023
MYR acts as an exogenous ligand for leukocyte mono-immunoglobulin-like receptor 3 (CD300f), thus downregulating MAS-related G protein-coupled receptor X2 (MRGPRX2)-mediated mast cells (MC) activation via CD300f. Therefore, MYR's activity prevents MC degranulation and pseudo-allergic reactions.	Dang et al., 2023
MYR can partly prevent arsenic-induced cardiac toxicity by lowering the oxidative stress and rehabilitating the antioxidant system.	Aminzadeh et al., 2023
MYR blocks the myocardium autoimmune response and monocyte chemoattractant protein-1 (MCP-1) expression in cardiomyocytes. These results imply that MYR can alleviate autoimmune myocarditis via modulation of the immune response and the expression of MCP-1. Hence, MYR could be an interesting candidate drug to treat autoimmune myocarditis.	Nie et al., 2023
MYR exhibits anti-inflammatory and antioxidant properties in atrazine (ATZ)-exposed rats by alleviating ATZ-mediated functional changes in their reproductive axis. MYR as a dietary supplement may be a valid chemoprotective agent against ATZ-induced reproductive dysfunction.	Ikeji et al., 2023
MYR can prevent acute liver failure by lowering inflammation and oxidative stress via NRF2 signaling. Therefore, MYR may be a promising agent to prevent liver damage.	Wang et al., 2023
MYR displays an hepatoprotective activity which may be attributed to its inhibition of oxidative, inflammatory, and apoptotic factors and promotion of antioxidants, in addition to its partial regulation of sirtuin 1 and the autophagic pathway.	Rostami et al., 2023
MYR may promote antioxidant activity and lower inflammation, lipotoxicity, and endoplasmic reticulum (ER) stress. These activities may be effective in reducing triacylglycerol accumulation in hepatocytes.	Yang et al., 2022
MYR ameliorates memory impairment due to its anti-inflammatory activity and regulation of the brain-derived neurotropic factor (BDNF) expression. MYR may be a promising agent to protect cognitive functions from sleep deprivation.	Sur and Lee, 2022b

Key findings	Reference
MYR strongly inhibits the human glutathione transferase A1-1 (hGSTA1-1) and as such it can be employed to develop natural, safe, and effective cancer chemosensitizers that target glutathione S-transferases.	Alqarni et al., 2022
MYR eased the formaldehyde-enhanced Warburg effect in cancer cells by inhibiting hypoxia-inducible factor 1 subunit alpha (HIF-1α). Therefore, MYR could be developed into an effective drug to treat formaldehyde-induced carcinogenesis.	Li et al., 2022
MYR promotes lung cancer cell death via ER stress pathway-induced pyroptosis. Hence, MYR could be effectively used as a pyroptosis agonist to further develop new anticancer drugs.	Han et al., 2022
MYR has proved effective in normalizing the altered intestinal flora in mice affected by type 2 diabetes.	Zhao et al., 2022
A solid lipid nanoparticle MYR formulation effectively leads to colon cancer cell death via increased reactive oxygen species (ROS) formation and promotion of the apoptotic process.	Alidadi et al., 2022
MYR shows antidepressant and anxiolytic activity as a regulator of the hypothalamic-pituitary-adrenal axis and activator of the BDNF-extracellular signal-regulated kinase (ERK) signaling pathway. Hence, MYR may be helpful in the prevention of traumatic stress such as posttraumatic stress disorder.	Sur and Lee, 2022a
MYR successfully leads to apoptosis in hepatocellular carcinoma (HCC) cells by inducing ER stress. MYR also increases protective autophagy. Furthermore, inhibition of autophagy increases MYR's effectiveness against HCC. Therefore, MYR could become a valuable HCC treatment, particularly in combination with autophagy inhibitors.	Ji et al., 2022
MYR effectively inhibits amyloid aggregation in α-synuclein condensates by delaying the liquid-to-solid phase transition.	Xu et al., 2022
MYR, a pan-histone lysine demethylase family 4 (KDM4) inhibitor, is a potent cytotoxic agent against castration-resistant prostate cancer (CRPC) cells. In addition, the combination of poly lactic-co-glycolic acid (PLGA)-encapsulated MYR with enzalutamide is likely to be effective for CRPC.	Liu et al., 2022
MYR inhibits PAR1-mediated epithelial-endothelial transition, while blocking HCC cell invasion, metastasis, vasculogenic mimicry formation and angiogenesis by binding Leu258 and Thr261 in the PAR1 receptor.	Wang et al., 2022
Administering MYR can inhibit alcohol-induced hepatic injury via regulation of ethanol metabolism, reduction of the oxidative stress, control of the lipid profile, and suppression of inflammatory markers.	Ahmad et al., 2022
MYR ameliorates 5-Fluorouracil-induced cardiac impairment by regulating inflammation, oxidation levels, and cardiac-specific markers.	Arafah et al., 2022
MYR may reverse the mitochondrial impairment in N2a-SW cells, showing a potential neuroprotective activity for amyloid-precursor protein (APP)/amyloid-β (Aβ)-related illnesses, including AD.	Yao et al., 2022
MYR acts as an antiviral against infectious bronchitis virus (IBV) by downregulating the deubiquitinating activity of the papain-like protease. As such, MYR could be a potential tool to prevent and treat IBV.	Peng et al., 2022
MYR strongly blocks the proliferation of cancer cells MCF-7 and A549, also having an apoptotic effect. MYR could become a valid anticancer drug acting on microtubule-affinity regulating kinase-mediated diseases.	Anwar et al., 2022
MYR displays antioxidant activity and the ability to inhibit the mitochondrial permeability transition pore, which eases aluminum phosphide-induced toxicity in isolated cardiomyocytes and mitochondria. These results suggest that it may be worth examining MYR's ***in vivo*** activity.	Salimi et al., 2021
MYR is an orally available natural bruton tyrosine kinase inhibitor that effectively prevents lymphoma TMD-8 cell growth ***in vitro*** and ***in vivo***. Moreover, results from this study hint that MYR could be a promising novel drug for lymphoma treatment.	Song et al., 2021

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Key findings	Reference
MYR has proved effective against nonalcoholic fatty liver disease via regulation of the expression of transcription factors of lipid metabolism in the liver, the antioxidant balance, and pro-inflammatory cytokines.	Choi et al., 2021
MYR has an inhibiting effect on acute gastric damage caused by ethanol, which is exerted by limiting injury by oxidative stress, upregulating prostaglandin E2 production, and downregulating NF-κB activation. Therefore, MYR may be a novel approach to treat alcohol-induced gastric injury.	Park et al., 2021
MYR exerts an anti-inflammatory and anti-EndMT effect on oxidized low-density lipoprotein (ox-LDL)-induced human umbilical vein endothelial cell (HUVEC) injury via regulation of GAS5/miR-29a-3p. Therefore, MYR could be useful for treating atherosclerosis.	Bai et al., 2021
Flavonoids like MYR inhibit liquid-liquid phase separation and abnormal aggregation of Tau in neuronal cells. Results also show that MYR may be an autophagy-related protein 5 (ATG5)-dependent autophagic activator, and therefore a potential alternative treatment for AD.	Dai et al., 2021
MYR inhibits neointimal hyperplasia and vascular smooth muscle cell expansion and migration by downregulating transforming growth factor-beta receptor 1 (TGFBR1) signaling. Therefore, MYR could become a new candidate drug to treat atherosclerosis and vascular restenosis.	Chen et al., 2021
MYR alleviates ***Staphylococcus aureus'*** pathogenicity ***in vivo***, also aiding the effectiveness of the traditionally employed antibiotic oxacillin on methicillin-resistant S. aureus (MRSA) infection and preventing the death of mice from MRSA-induced fatal lung infections. Therefore, MYR may become a promising therapeutic agent against ***S. aureus***-induced illnesses.	Jing et al., 2021
MYR decreases lipid synthesis and inflammation in the liver via modulation of fecal butyric-acid-related gut microbiota and protection of the gut barrier functionality. Such results could help understanding the action mechanism of low-bioavailability flavonoids.	Sun et al., 2021
MYR exerts a potent activity on bleomycin-induced lung inflammation by limiting inflammatory cell infiltration and the secretion of inflammatory cytokines IL-6, IL-1α, TNF-α, and IFN-γ. MYR could therefore be useful to treat COVID-19.	Xiao et al., 2021
MYR can greatly ameliorate mammary inflammation, probably due to its protective role exerted by inhibiting the phosphorylation level of P38 and ERK1/2 proteins.	Kan et al., 2021
MYR prevents high-molecular-weight Aβ oligomers (HMW-Aβo)-induced neurotoxicity via a number of antioxidant activities. Therefore, MYR could be further developed into an effective AD drug.	Kimura et al., 2021
MYR may protect natural killer cells from arsenite (As^{+3})-induced genetic damage by lowering oxidation levels and retaining poly (ADP-ribose) polymerase 1 (PARP-1) activity. This implies that MYR could prevent As^{+3}-induced toxicity in NK cells.	Ma et al., 2021
MYR can protect PC12 cells from cadmium-induced neurotoxicity, an activity related to MYR's antioxidant activity, suppression of lipid peroxidation, and inhibition of caspase-3 activation.	Aminzadeh and Salarinejad, 2021
MYR, as a potential type III secretion system (T3SS) inhibitor, shows a protective activity both ***in vitro*** and ***in vivo***. As such, MYR has the potential to become a new antibiotic capable of treating ***S. typhimurium*** infections.	Lv et al., 2021
MYR exerts a protective activity on rotenone-treated MES23.5 cells by strongly downregulating hepcidin expression which limits iron accumulation; this activity is related to a modification of STAT3 and SMAD1 signaling pathways.	Deng et al., 2021
MYR shows cytotoxic activity by blocking cell cycle progression and promoting ROS-dependent mitochondria-facilitated death in A549 lung cancer cells. Therefore, MYR could be a potential drug candidate for lung cancer treatment.	Rajendran et al., 2021
Molecular dynamics simulation studies hint that MYR acts on the human islet amyloid polypeptide (hIAPP) pentameric fibril model at the amyloidogenic core region, resulting in inhibited aggregation and distortion of the fibrils.	Dubey et al., 2020

Key findings	Reference
MYR induces apoptosis in T47D breast cancer cells by acting on extrinsic and intrinsic apoptotic pathways, probably by inducing the BRCA1-GADD45 pathway.	Soleimani and Sajedi, 2020
MYR suppresses *S. aureus'* virulence by acting on Hla and lowering the inflammatory response in host cells. As such, together with traditional antibiotics, MYR could be a novel drug to treat *S. aureus* infections.	Wang et al., 2020
MYR has the ability to trap methylglyoxal in mice. This suggests that administrating MYR-containing foods could lead to scavenging of MGO (methylglyoxal) ***in vivo*** and prevent MGO-induced dangerous effects on human health.	Zhang et al., 2020
MYR activates apoptotic and autophagic processes in colon tumor cells, and for this reason it could be a valid candidate for chemotherapy, by inhibiting tumor growth alone or as an adjuvant agent to induce autophagy.	Zhu et al., 2020
MYR may lower blood pressure either in the form of a dietary supplement or as a natural product suitable for the development of novel antihypertensive drugs.	Berköz et al., 2020
MYR displays potent anti-schistosome activity both ***in vitro*** and ***in vivo***, and therefore could serve as the base for the development of a new therapeutic agent effective against ***S. japonicum***.	Huang et al., 2020
MYR ameliorates myocardial damage and lethality in heat stroke via upregulation of the heat shock protein 72 and could be further developed into a novel agent to prevent heat stroke.	Lin et al., 2020
MYR effectively inhibits A549-IR radioresistant lung cancer cell migration by blocking MMP-2 and MMP-9 expression via inhibition of the focal adhesion kinase (FAK)-ERK signaling pathway.	Kang et al., 2020
The cellular uptake and antitumor activity of MYR in lung carcinoma are enhanced by nano encapsulated phospholipidic complexes. Therefore, a formulation of inhalable microparticles could become an effective therapy for lung carcinoma.	Nafee et al., 2020
MYR exhibits great inhibitory activity against dipeptidyl peptidase-4 (DPP-4) both ***in vitro*** and ***in vivo***, resulting in increased circulating glucagon-like peptide 1 (GLP-1) and insulin levels, hence ameliorating diabetic symptomatology. However, even if MYR and horsegram protein individually ease the diabetic condition, their dietary combination shows a diminished efficiency.	Lalitha et al., 2020
MYR exerts a protective effect on monoclonal gammopathy of unknown significance (MGUS) and its nutritional supplement may also protect against cancer development in patients affected by MGUS.	Akhtar et al., 2020
A polyphenol-rich extract and its most abundant flavonoid MYR display strong inhibition of platelet function. Moreover, MYR has proved effective in inhibiting ERp5 and protein disulfide isomerase (PDI), therefore showing potential as a novel therapeutic agent for thrombotic disorders.	Gaspar et al., 2020
MYR lowers BV2 microglial neuroinflammation via inhibition of the MAPK signaling pathway and the production of proinflammatory modulators and cytokines. Hence, MYR could be useful as a treatment for neuroinflammatory diseases.	Jang et al., 2020
MYR can suppress amyloid formation: therefore, it could be further developed into new anti-amyloid drugs.	Prajapati et al., 2020
MYR ameliorates streptozotocin-induced abnormal bone metabolism in rats and could therefore become a new therapeutic agent to treat diabetic bone disease.	Ying et al., 2020
MYR has proved effective in easing inflammation in acute ulcerative colitis, greatly improving the condition. MYR induces higher expression of IL-10 and transforming growth factor β. Moreover, the number of regulatory T cells is noticeably higher in mice treated with MYR.	Qu et al., 2020
MYR likely protects HUVECs from high glucose-induced oxidative stress by improving cell total antioxidant capacity and lowering Bax/Bcl-2 protein ratio, as well as lowering caspase-3 expression.	Aminzadeh and Bashiri, 2020

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Conflict of interest

The authors declare no conflict of interest.

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