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A REVIEW ON MYRICETIN AND ITS PHAMACOLOGICAL ACTIVITIES

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ABSTRACT

Often present in plants, myricetin is a flavonoid valued for its nutraceutical properties. It is an essential nutrient that helps to maintain excellent health and offers immune protection in the diet. Fruits, vegetables, tea, and wine all contain it. The families with the highest concentrations of myricetin include the Polygonaceae, Myricaceae, Primulaceae, Pinaceae, and Anacardiaceae. Myricetin demonstrates an extensive array of biological functions. It was proven to have antioxidant and antibacterial properties. Its neuroprotective activity, which has demonstrated preclinical effects on Huntington's, Parkinson's, and Alzheimer's illnesses as well as in amyotrophic lateral sclerosis, is one of its advantageous biological effects. Myricetin has also been shown to have additional biological effects, including antihypertensive, immunomodulatory, antidiabetic, anticancer, and cardiovascular effects. Myricetin hasn't, however, been the subject of many clinical research as a nutraceutical. Therefore, additional study is required to completely comprehend its possible therapeutic uses. Not to mention, myricetin has demonstrated potential in the prevention and treatment of cancer.

Keywords: Myrecitin; Flavonoid; Anti-oxidant; Anti-cancer; Immunomodulator; Anti-diabetic

1. INTRODUCTION

Polyphenols are a diverse range of compounds derived from plants that are widely distributed in the vegetable kingdom. They exhibit various activities, including defence against UV radiation, bacterial, viral, and fungal infections, regulation of plant hormones, inhibition of enzymes, and attraction of pollinators **[1]**. Numerous polyphenols found in nature fall into one of the following main classes: flavonoids, stilbenes, lignans, hydroxycinnamic acid derivatives (such as caffeic acid, p-coumaric, ferulic, and sinapic), simple phenolic acids (e.g., gallic, vanillic, syringic, and p-hydroxybenzoic). Flavonoids comprise the biggest prevalent type of polyphenols found in the diets of humans **[2, 3]**. Anthocyanidins, flavones, flavonols, and flavans are the several chemical classes of flavonoids **[4]**. Myricetin, a 3,3′,4′,5,5′,7-hexahydroxyflavone, is one of the flavonols with the most hydroxylated structures **(Figure 1)**. Myricetin's solubility in water is low (16.6 μg/mL), although it increases when deprotonated in acetone, tetrahydrofuran, dimethylformamide, and dimethylacetamide, as well as in several organic solvents **[5]**. Myricetin's chemical stability is temperature- and pH-dependent **[6]**. Myricetin can have both a strong antioxidant and a pro-oxidant effect in vitro, depending on the surroundings. Several structural components are responsible for its direct antioxidant effect, according to Buchter *et al*. **[7]**. However, Chobot and Hadacek showed how myricetin is pro-oxidative in relation to molecular oxygen reduction to reactive oxygen species (ROS) and iron (III) to iron (II) **[8]**. They also emphasized how myricetin can replace ascorbic acid, albeit less effectively. Myricetin is mostly found in plants, fruits, nuts, berries, vegetables, and tea, wine, as well as in the glycoside form (O-glycosides) in fruit and medicinal plants **[9–15]**. Numerous factors, including genetic and environmental ones, ripeness degree and germination, variety, seasonal variation, storage, processing, and cooking, can affect the amount of myricetin in plant foods. Since suitable dietary composition tables are currently unavailable, estimating total flavonoid intake is challenging. Nonetheless, accurate statistics on a population's daily flavonoid intake are required to create appropriate dietary guidelines and even to properly evaluate the results of intervention research. An average daily consumption of 2.2 ± 2.5 mg of myricetin was found using the M Flemish Dietetic Association database (Mullie *et al*.), **[9]**. Jun *et al*. **[10]** calculated an average daily consumption of 0.8 mg, or

roughly 1%–2% of the flavonol subclass, in an adult population in Korea, but Vogiatzoglou *et al*. **[11]** observed that the mean daily intake of myricetin in adults (18–64 years old) in the European Union ranged from 1 to 4 mg. Determining the potential impact of flavonoids on human health also requires an understanding of habitual flavonoid ingestion. Myricetin demonstrated the ability to scavenge free radicals and exhibit antioxidant qualities **[12]**. Numerous positive effects, such as those related to anti-platelet aggregation, antihypertensive, immunomodulatory, anti-inflammatory, anti-allergic, analgesic, and anticancer actions, appear to be supported by these activities **[6, 13–18]**. The primary objective of this study is to offer fresh perspectives on the preclinical pharmacological actions of myricetin and its function in particular clinical trials.

2. STRUCTURE

According to studies, one of the reasons myricetin is a powerful antioxidant is that it contains more hydroxyl groups. Its structure consists of two aromatic rings, A and B, which are joined by a three-carbon chain to form a cyclic ring, C **(Figure 1) [19]**.

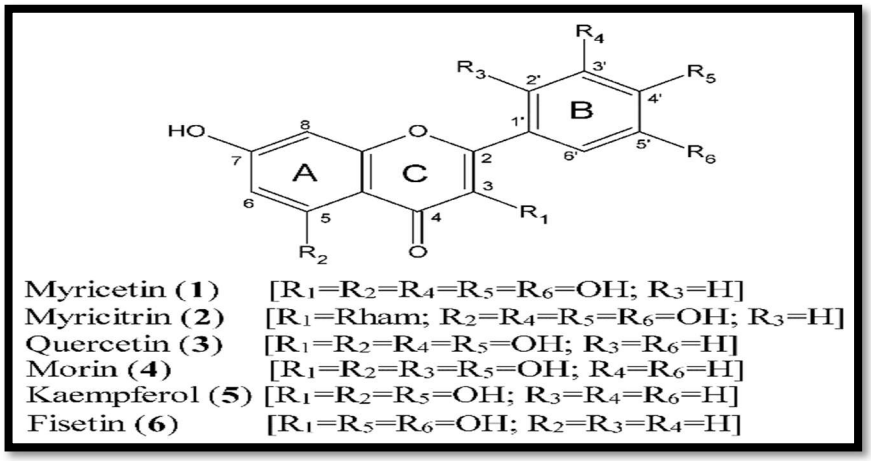

Figure 1: Chemical structure of Myricetin and its compound

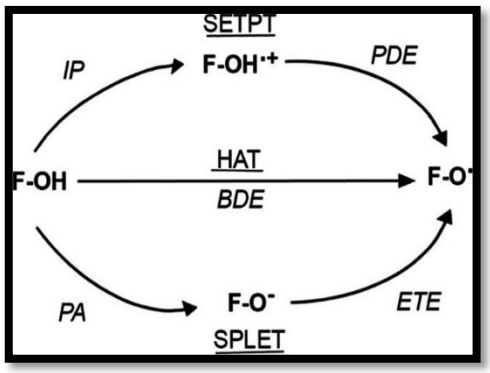

Figure 2: The example diagram illustrating myricetin's antioxidant properties

Myricetin and quercetin differ structurally in that myricetin has an additional hydroxyl at the 5'-OH of the phenyl moiety **[20]**. The presence of a 2,3-double bond in the C ring makes the molecule more stiff and planar. It also keeps the A and C rings coplanar, enabling the 3-OH/4-O and 5-OH/4-O groups to be closer together. With six hydroxyl groups—a catechol group in the B ring, a 3-hydroxyl group, a 2,3-double bond, and a 4-oxo group in the C ring—myricetin is a good reductant and its reducing activity is also influenced by these groups **[21]**. The metabolism or absorption of myricetin may be impacted by the presence of a 3-hydroxyl group on ring C and a 4-hydroxy group on ring B **[22]**. The presence of the 3-OH group, which activates the 2,3-double bond on the ring C, is the primary determinant influencing the chemical reactivity with 1O2, whereas the catechol moiety of the B ring mostly controls the effectiveness of the physical quenching. The quenching rate (kQ) value of myricetin is 5.12 1018 M-1 s-1 for 1O2 oxygen, which is higher than quercetin, rutin, and apigenin **[23]**. The 3-OH group at the C ring exhibits minimal reactivity. **Figure 1** depicts myricetin's two-dimensional structure.

According to **Figure 1**, myricetin (1) shares structural similarities with a number of well-known phenolic chemicals, including quercetin (3), morin (4), kaempferol (5), and fisetin (6). Because of its structural resemblance to quercetin, the molecule is frequently referred to as hydroxyquercetin qualities are highly prized. Claims that the molecule exhibits a range of pharmacological properties such as anti-inflammatory, analgesic, anti-tumour, hepatoprotective, and anti-diabetic effects are supported by scientific evidence **[24]**.

Table 1: IUPAC name

NAMES	
IUPAC name	**3,3′,4′,5,5′,7-Hexahydroxyflavone**
Systematic IUPAC name	**3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-1-benzopyran-4-one**
Other names	**Cannabiscetin, Myricetol, Myricitin**

Table 2: IUPAC name

PROPERTIES	
Chemical formula	**$C_{15}H_{10}O_8$**
Molar mass	**318.237 g·mol^{-1}**
Density	**1.912 g/mL**

3. SOURCES

Myricetin is a flavonoid found in a variety of foods. Here are some common sources:

- Vegetables
- Nuts
- Fruits
- Tea etc.

The exact concentration/amount (mg/100g) of Myricetin is given in **Table 3** as per USDA reports 2020.

Table 3: Concentration of Myricetin in different food sources (USDA, 2020) [25]

Sr. No.	FOODS	Amount (mg/100g)
1	Sweet potato leaves, raw	4
2	Rabbit-eye blueberry, raw	5
3	European black currant, raw	6
4	Fennel leaves, raw	20
5	Carob fiber	48
6	Parsley, fresh	15
7	Goji berry, dried	11
8	Bog blueberry, frozen	7
9	Carob flour	7
10	Cranberry	7
11	Crowberry	5
12	Blackberry	700
13	Rutabagas	2,100
14	Garlic	1,600
15	Dock	5,700
16	Broadbeans, immature seeds	2,600
17	Peppers, hot chili, green	1,200
18	Chard, swiss	3,100
19	Lemon	500
20	Lotus root	600

4. CHEMICAL SYNTHESIS

Myricetin production is crucial because it serves as a fundamental building block for the synthesis of several other advantageous substances, such as hibiscetin **[26, 27]**. In 1925, Dean and Nierenstein **[28]** made an unsuccessful attempt to synthesize myricetin by using the Kostanecki and Auwers method. Kalff and Robinson **[29]** succeeded in synthesizing myricetin from ω-methoxyphloroacetophenone in the same year. Using this process, the starting material, sodium trimethylgallate, and trimethylgallic anhydride were heated together. After the product was hydrolyzed, 5,7-dihydroxy-3,3′,4′,5′-tetramethoxyflavone was produced. Demethylation of this compound eventually produced myricetin **(Figure 3)**.

However, Rao and Seshadri **[30]** synthesized myricetin from quercetin by an ortho-oxidation process, employing a different method **(Figure 4)**. Through cyclization at the 4′ and 5′ positions, 3,5,7,3′-tetra-O-methylquercetin was transformed to the equivalent 5′-aldehyde in this technique. This 5′-aldehyde was then changed to 3,5,7,3′-

tetra-O-methylmyricetin, yielding 5-methoxykanugin. After 5-methoxykanugin was hydrolyzed and methylated, hexamethylmyricetin was generated. Demethylation of this compound resulted in myricetin.

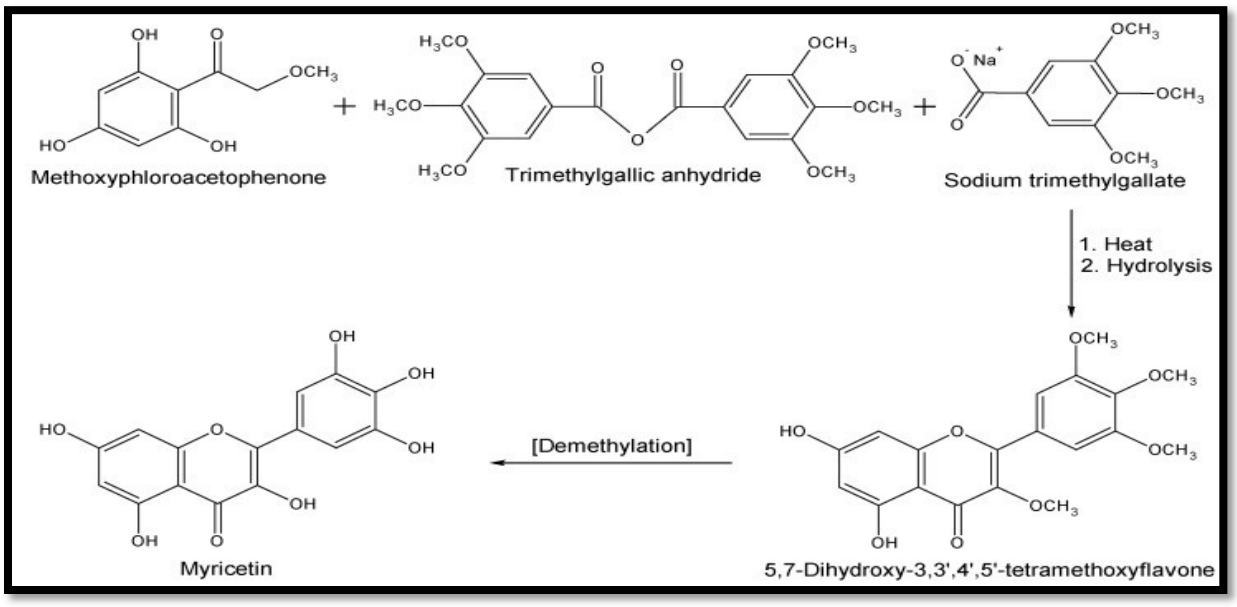

Figure 3: Synthesis of myricetin as proposed by Kalff and Robinson [29]

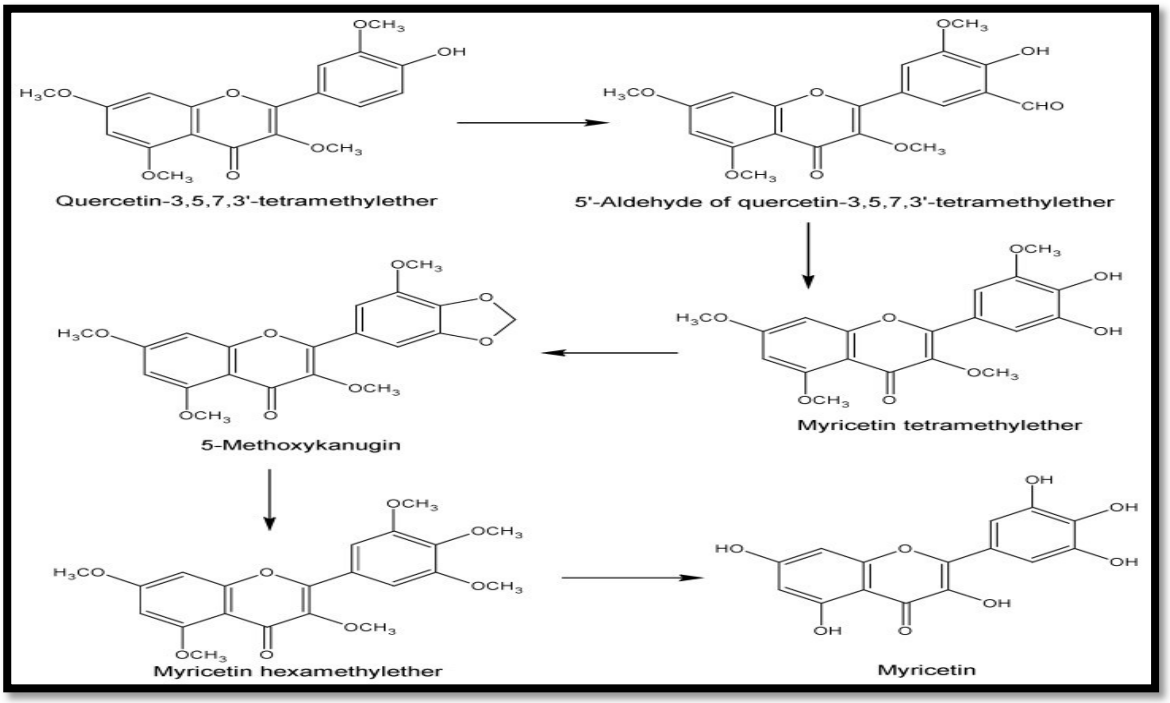

Figure 4: Route proposed by Rao and Seshadri for the synthesis of myricetin [30]

5. PHARMACOLOCIAL EFFECTS

5.1 Antioxidant activity

Numerous studies have demonstrated myricetin's ability to combat oxidative stress, which includes: (i) a lower O-H bond dissociation enthalpy (BDE), which facilitates H abstraction; (ii) an increased ionization potential (IP), which prevents the antioxidant from reducing oxygen; and (iii) enough solubility. The generated radicals and anionic species were taken into consideration in a study that used a PM6 Hamiltonian to conduct a semi-empirical experiment in the gas and waterphase of myricetin. Three mechanisms have been proposed to explain the structural and electronic features responsible for myricetin's antioxidant activity: (i) H atom abstraction (HAT); (ii) single electron transfer followed by proton transfer (SETPT); and (iii) sequential proton loss electron transfer (SPELT). In **Figure 2**, the mechanisms are displayed. Estimates were made for the proton dissociation enthalpy (PDE) from the cation radical and the BDE, proton affinity (PA), and electron transfer enthalpy (ETE) from the anion. The computations were carried out by determining the temperatures of formation (Hf) differences between the reactants and products **(Figure 2)**, where the radical (F-O•) and the anion (F-O-) derived from the antioxidant (F-OH) are represented, respectively. The three suggested antioxidant processes of myricetin become significant based on the results so obtained. The methods are as follows: (i) SETPT, which is determined by IP and PDE; (ii) HAT, which is quantifiable by BDE; and (iii) SPLET, which is quantifiable by the proton affinity and the ETE **(Figure 2) [31-35]**.

A lower quantity of myricetin (10 μm) was found to have the capacity to inhibit macrophage LDL oxidation, but a larger concentration of flavone and gossypin (100 μm) also demonstrated the same inhibiting action **[36]**. On plasmid pBR 322 DNA, myricetin demonstrated a protective effect against 1O2 caused DNA damage in vitro **[37]**. Lipid peroxidation mediated by divalent metal ions can also be inhibited by myricetin **[38]**. In brain neurons, myricetin significantly decreased Ca2+-dependent DCFH oxidation and DCF fluorescence **[39]**. According to a study, myricetin is the most effective of the 33 flavonoids and inhibited both the Ca2+-ATPase of damaged human erythrocyte plasma membranes **[40]** and the ATP-dependent Ca2+ uptake by the liver plasma membrane vesicles **[41]**. Using the DCF technique, an in vitro investigation on MCF-7 breast cancer cells also demonstrated the antioxidant qualities of myricetin. DCF's fluorescence activity was decreased by

myricetin, indicating a reduction in DCF oxidation and myricetin's ability to scavenge ROS **[42]**. Recent study revealed that myricetin encapsulated in nanoparticles increased the levels of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) in zebrafish embryos treated with hydrogen peroxide (unpublished data). This suggested that myricetin had antioxidant properties.

5.2 Anticancer activity

Worldwide, cancer ranks as the second leading cause of mortality **[43, 44]**. According to reports, the number of people who will die from this terrible illness by 2030 would exceed 13 million **[45, 46]**. According to research conducted in laboratories and clinics, myricetin derived from natural sources shows promise in treating different kinds of cancer **[47, 48]**. Additionally, the dietary ingredient myricetin may be able to block important enzymes that are involved in the development and spread of cancer.

Human colon cancer cells have demonstrated cytotoxic action towards myricetin. In a dose-dependent manner, Kim *et al*. **[48]** showed that myricetin greatly increases the Bcl2-associated X protein (BAX)/Bcl2 ratio and causes HCT-15 cells undergo apoptosis. (5 to 100 μM). According to this study, myricetin may be used in the development of therapeutic medicines to treat colon cancer in humans. Based on inhibitory mechanisms, molecular docking, and experiments using cancer cells, myricetin also exhibits a strong inhibitory effect on the human flap endonuclease 1 (hFEN1) protein (IC50 690 nM) **[49]**. A useful member of the 5′-nuclease superfamily is the hFEN1 protein. Chemically speaking, hFEN1 is a structure-specific, metal ion-dependent nuclease that is also involved in DNA replication and repair. The myricetin compound's ring A, which includes 4-keto and 5-OH, was shown to be stretched toward the two divalent metal ions, according to molecular docking experiments. Due to their apparent hydrogen bond interactions with the amino acids Lys93 and Arg100, both metal ions are essential.

The crucial interaction between these interacting residues and hFEN1 activity during human colon cancer is widely recognized. By inhibiting the angiogenesis of ovarian cancer cells, myricetin has also been demonstrated to offer protection against ovarian cancer [50]. Myricetin's (5 to 20 μM) anti-angiogenic properties were evaluated using in vivo (CAM) and in vitro (HUVEC) models, and the results showed that this chemical significantly suppresses angiogenesis that is caused by OVCAR-3 cells. Myricetin caused apoptosis in SKOV3

human ovarian cancer cells by inducing double-strand breaks in DNA and endoplasmic reticulum stress, with a time-dependent effect of 40 µg/mL **[51]**. According to Zheng *et al*. **[52]**, the dietary flavonoid myricetin significantly cytotoxicated OVCAR3 and A2780 ovarian cancer cells (IC50 = 25 µM). Myricetin has been shown in a recent study by Tavsan and Kayali **[53]** to decrease the development of ovarian cancer cells, cause apoptosis, halt the cell cycle, and perhaps inhibit cell invasion (IC50 = 184 µM A2780, 32 µM OVCAR-3, 3.3 µM SKOV3, and > 500 µM OSF). Therefore, it may be said that myricetin has sufficient potential to significantly treat ovarian cancer.

Strong anticancer-promoting effect of myricetin is seen against skin cancer. It was discovered to be able to suppress mitogen-activated protein kinase 1 (MEK1) activity (myricetin 1 or 5 µM) as well as the transformation of cancerous cells **[54]**. Myricetin and MEK1's molecular interaction reduced MEK1 activity, which in turn caused signaling to the ERK/p90RSK/AP-1 pathway downstream. Myricetin has been shown to be a powerful chemoprotective agent against skin cancer in another investigation **[55]**. Myricetin has the ability to bind directly to key kinases that control multiple cells signaling pathways in cancer cells, such as PI3-K, Akt, JAK1, Raf1, MEK1, MKK4, and Fyn. At 10 µM concentration, myricetin reduced the amount of 12-O-tetradecanoylphorbol-13-acetate (TPA) and epidermal growth factor (EGF)-induced cell transformation by 76% and 72%, respectively. According to a recent study by Sun *et al*. **[56]**, myricetin exhibits low toxicity and has anticancer effect against skin cancer A431 cell lines by causing apoptosis and cell cycle arrest.

Myricetin's antimetastatic action against human lung adenocarcinoma A549 cells was previously shown in vitro **[57]**. This study showed that myricetin (5 to 20 µM) inhibits the ERK pathway in a time-dependent manner, thereby suppressing the invasion and migration of adenocarcinoma A549 cells. Myricetin was shown to be accountable for augmenting the tumor radio-sensitivity of lung cancer A549 and H1299 cells by notably suppressing the cell-surviving fraction and proliferation in conjunction with a combo of radiotherapy **[58]**. According to Wang *et al*. **[59]**, myricetin plus 5-fluorouracil treatment may increase the tumor chemosensitivity of EC9706 cells that are used to treat esophageal cancer. According to research by Sun *et al*. **[60]**, myricetin is a phytochemical that functions against human T24 bladder cancer in a manner that is dependent on time and

dose. It has been found to strongly reduce the viability and proliferation of T24 cancer cells (IC50 = 85 μM).

5.3 Immunomodulatory activity

Numerous studies conducted both in vitro and in vivo have demonstrated that myricetin can alter the immune response or immune system functioning by promoting the generation of antibodies or suppressing WBC activity in the model of the experiment. At a dosage of 10 μg/mL, it was discovered to modify the LPS-stimulated activation of mouse bone marrow-derived dendritic cells (DCs) without showing any harmful effects on DCs. Myricetin exposure reduced the production of TNF-α, IL-6, and IL-12 in LPS-stimulated DCs. The substance prevented LPS-stimulated DCs from endocytizing and migrating, and it also reduced the expression of CD40, CD86, and major histocompatibility class II on DCs. Furthermore, at a concentration of 10′5 M, it was discovered to inhibit the proliferation of lymphocytes caused by LPS. According to a study by Kang and colleagues **[61]** that aimed to clarify the mechanism of action, myricetin suppresses NF-κB binding activity in order to prevent LPS-induced IL-12 production in mouse primary macrophages and the RAW264.7 monocytic cell line. The substance, at 50 μM, increases the synthesis of cytosolic free calcium in cultured bovine endothelial cells and causes endothelium-dependent contractile responses in isolated rat aortic rings **[62]**.

Myricetin suppressed the immune system by preventing mouse EL-4 T cells that had been stimulated with PMA and Io from secreting the IL-2 protein. Furthermore, it inhibits the intracellular synthesis of IL-2 protein and decreases the expression of IL-2 mRNA that is triggered by PMA and Io **[63]**. Furthermore, the substance suppressed mouse CD3+T cell CD69 expression and mouse lymphocyte proliferation in vitro at doses ranging from 5 to 100 μM. Treatment with 100 μM myricetin caused mouse cells to completely stop expressing IL-2 mRNA **[64]**. Based on the aforementioned results, myricetin's ability to influence the immune system can be confirmed. Nevertheless, more study is required to establish it as an immunomodulatory medication.

5.4 Anti-diabetic activity

5.4.1 Inhibition of hIAPP aggregation: The development of type 2 diabetes is significantly influenced by the misfolding and aggregation of amyloid-β proteins and human pancreatic beta-amyloid polypeptides (hIAPP) **[65]**. According to recent research, MYR can stop amyloidosis by preventing hIAPP aggregation. It breaks down the produced fibrils into non-toxic species and interacts

with hIAPP in the amyloidosis core to stop fibrils from building up and twisting. Furthermore, MYR restores glucose-stimulated insulin secretion, hence reversing the functional loss of the islets exposed to hIAPP and aiding in the management of type 2 diabetes **[66]**.

5.4.2 Inhibition of α-Amy and α-Gls: Two enzymes that help break down starch into sugars and disaccharides and raise blood glucose levels are alpha-amylase (α-Amy) and alpha-glucosidase (α-Gls) **[67]**. Thus, the use of particular α-Amy and α-Gls inhibitors may also represent a viable treatment for obesity and type 2 diabetes. MYR is utilized to lower postprandial hyperglycemia in T2DM patients because it reversibly and competitively inhibits α-Amy activity and reversibly but not competitively inhibits α-Gls activity **[68]**.

5.4.3 Activation of GLP-1: Glucagon-like peptide-1 (GLP-1) is a possible target for the effective treatment of type 2 diabetes mellitus (T2DM) **[69]**, a condition that is a danger to public health **[70, 71]**. GLP-1 does this by stimulating insulin production and regulating blood sugar levels. MYR functions as an agonist of the GLP-1 receptor (GLP-1R) orally. In fact, when taken orally over an extended period of time, it slows the death of islet β cells and controls blood sugar levels. However, MYR has the ability to induce glucose-dependent insulin secretion in vivo as well as in vitro **[72]**. As a result, MYR may be used to treat and prevent hypoglycemia and type 2 diabetes.

5.4.4Inhibition of CDK5: β cell failure in type 2 diabetes is tightly associated with cyclin-dependent kinase 5 (CDK5) and ERS **[73, 74]**. By blocking CDK5-p66Shc signaling and ERS, MYR guards against thapsigargin-induced pancreatic β-cell failure. It also lessens mitochondrial dysfunction and prevents CDK5-induced myeloid cell leukemia sequence 1 degradation and phosphorylation of p66Shc serine 36. Additionally, MYR promotes the production of insulin and the mRNA expression of PDX-1 **[75]**, a transcriptional co-activator of β cells in the pancreas **[76]**. These findings demonstrate the therapeutic potential of MYR in lowering diabetes patients' β-cell ER stress.

5.4.5 Other: When streptozotocin (STZ)-cadmium-induced diabetic nephrotoxic rats are used, the expression of signaling molecules including insulin, hemoglobin, and glycogen synthase factors like GLUT-2, GLUT-4, IRS-1, IRS-2, and PKB is markedly downregulated. These rats' glucose utilization and renal function are improved when MYR therapy dramatically reverses the expression of these signaling molecules and improves carbohydrate metabolism **[77]**. Furthermore,

oxidative stress brought on by elevated glucose levels damages dermal fibroblasts and modifies the ratio of metalloprotease inhibitor-1 (TIMP-1) to MMP. MYR has a preventive effect against diabetic-related skin damage by balancing the TIMP1/MMP ratio and lowering the degree of oxidative stress in diabetic dermal fibroblasts **[78]**.

5.5 Other research: It is possible for MYR to prevent pulmonary fibrosis. Reports state that the transforming growth factor (TGF)-β/Smad signaling pathway and heat shock protein (HSP) isoforms HSP90β are important in the development of liver fibrosis **[79, 80]**. By blocking TGF-β1/Smad signaling by focusing on HSP90β, MYR can reduce bleomycin-induced lung fibrosis in mice and improve TGF-β1-induced lung fibroblast activation and EMT **[81]**. MYR is therefore a potentially effective anti-pulmonary fibrosis therapeutic substance.

MYR offers defense against hepatic injury. For instance, MYR protects the liver in fulminant hepatitis caused by LPS and D-galactosamine by controlling the MAPK-Nrf2/HO-1 signaling pathway, TLR4-NF-κB/-MAPK and NLRP3 inflammasomes, and proteins linked to apoptosis **[82]**. Through the down-regulation of TGF-β1 phosphorylation and the phosphorylation of its downstream protein SMAD2, the suppression of p38 MAPK increases the production of collagen and stress fibers **[83, 84]**. MYR alleviates liver fibrosis in the CCl4-induced animal model by inhibiting the deposition of type I collagen and α smooth muscle actin in mice, as well as reducing TGF-β1-induced hepatic stellate cell activation through the routes previously stated **[85]**. According to a different study, MYR increases the inhibitory effect of AMP-activated protein kinase phosphorylation and decreases ethanol-induced fatty acid synthase and sterol regulatory element-binding protein-1c mRNA expression, which in turn inhibits ethanol-induced lipid accumulation in liver cells **[86]**. In addition, one of the primary outcomes of oxidative damage brought on by free radicals is the synthesis of 8-hydroxy-2′-deoxyguanosine (8-OHdG) **[87]**. In order to prevent liver damage brought on by endosulfan and methotrexate, MYR lowers the quantity of 8-OHdG and the production of caspase-3, enhances the oxidative stress response, and returns liver enzyme levels to normal **[88, 89]**.

MYR can be used to treat gastric ulcers since it has the capacity to decrease the secretion of gastric acid. Members of the P2 type ATPase family, H+-K+-ATP, Na+-K+-ATP, and Ca2+-ATP, act as proton pumps in gastric parietal cells **[90]**. By preventing these three enzymes from functioning, MYR

dramatically lowers the amount of stomach acid secreted by mice in response to histamine. Furthermore, it has been observed that MYR's 3′- and 5′-hydroxyl groups are required to impede P2 type ATPase activity, whilst the 2′- and 6-hydroxyl groups enhance the inhibitory activity **[91]**. As a result, MYR might be taken into consideration as a supplement to lessen the production of stomach acid.

MYR possesses anti-obesity properties. Generally speaking, SIRT3 is required to control lipid and glucose metabolism **[92]**, and obesity and the function of brown adipose tissue (BAT) are intimately associated **[93]**. According to some research, MYR can fend off obesity by upregulating mitochondrial metabolism and Sirt3 expression in adipose tissue **[94, 95]**. It can also fend off insulin resistance by triggering BAT and boosting adiponectin levels in BAT. Furthermore, peroxisome proliferator-activated receptor (PPAR) and CCAAT enhancer binding protein α (C/EBPα) regulate glucose homeostasis and energy metabolism **[96, 97]**. By suppressing the expression of PPARγ, C/EBPα, and adipogenic transcription factor (SREBP-1c), MYR controls lipid metabolism and prevents obesity **[98]**. Furthermore, MYR alleviates hepatic steatosis brought on by a high-fat diet by down-regulating PPARγ, increasing hepatic nuclear Nrf2 translocation, and increasing the expression of HO-1 and NQO1 proteins **[99]**. These actions reduce lipid accumulation in the liver.

MYR has the power to increase resistance to exercise and strengthen bones. According to certain research, MYR prevents diabetic osteoporosis by boosting bone mineral density and preventing the blockage of osteocalcin and alkaline phosphatase **[100]**. It also lessens the effects of dexamethasone-induced osteoporosis by encouraging osteogenic differentiation and matrix mineralization through the ERK signaling pathway **[101]**. An osteoinductive growth factor is Bone Morphogenetic Protein 2 (BMP-2) **[102]**. By triggering the BMP-2/Smad and ERK/JNK/p38 MAPK pathways, MYR improves the osteogenic differentiation of human periodontal ligament stem cells **[103]**. Furthermore, MYR has the ability to upregulate the expression of miR-499 and downregulate the expression of the downstream gene Sox6, which facilitates the reprogramming of fast-slow muscle fiber-type switches and improves exercise endurance. These effects are critical for improving the health of individuals who lead sedentary lifestyles and suffer from muscle disorders **[104]**.

6. CONCLUSION

A common dietary flavonoid, myricetin has been demonstrated in multiple studies to have biological activity and may have use in nutraceuticals. It has a well-established antibacterial and antioxidant role, and multiple studies have demonstrated its neurobiological activity as well as a possible positive effect on AD, PD, HD, and ALS. Preclinical research has also shown antihypertensive, analgesic, immunomodulatory, anti-cardiovascular, and antidiabetic properties. These research looked on the effects of myricetin, either as a pure substance or as an extract from plants high in this substance. Myricetin-rich plant extracts are invariably accompanied by other flavonoids that have demonstrated antioxidant action on their own. However, more thorough research is required to examine all of the biological impacts previously mentioned. Additionally, preclinical studies contrasting myricetin's effects with those of other flavonoids and phytochemicals must be conducted. Further comprehensive research are needed to demonstrate the pre-clinical outcomes in neurological illnesses.

7. ACKNOWLEDGEMENT

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Conflict of interest:

NO

REFERENCE

[1] Matilla MA. Chapter 10 - metabolic responses of plants upon different plant–pathogen interactions. In: Ahmad P, Ahanger MA, Singh VP, Tripathi DK, Alam P, Alyemeni MN, editors. Plant metabolites and regulation under environmental stress. Cambridge: Academic Press; 2018. p. 195–214.

[2] Imran M, Salehi B, Sharifi-Rad J, Gondal TA, Saeed F, Imran A, Shahbaz M, Fokou PVT, Arshad MU, Khan H, *et al*. Kaempferol: a key emphasis to its anticancer potential. Molecules. 2019;24(12):2277.

[3] Sharifi-Rad J, Sharifi-Rad M, Salehi B, Iriti M, Roointan A, Mnayer D, SoltaniNejad A, Afshari A. In vitro and in vivo assessment of free radical scavenging and antioxidant activities of Veronica persica Poir. Cell Mol Biol. 2018;64(8):57–64.

[4] Rauter AP, Ennis M, Hellwich K-H, Herold BJ, Horton D, Moss GP, Schomburg I. Nomenclature of flavonoids (IUPAC Recommendations 2017). Pure Appl Chem. 2018;90(9):1429.

[5] Yao Y, Lin G, Xie Y, Ma P, Li G, Meng Q, Wu T. Preformulation studies of myricetin: a natural antioxidant flavonoid. Pharmazie. 2014;69(1):19–26.

[6] Yao Y, Lin G, Xie Y, Ma P, Li G, Meng Q, Wu T. Preformulation studies of myricetin: a natural antioxidant flavonoid. Pharmazie. 2014;69(1):19–26.

[7] Buchter C, Ackermann D, Havermann S, Honnen S, Chovolou Y, Fritz G, Kampkotter A, Watjen W. Myricetin-mediated lifespan extension in Caenorhabditis elegans is modulated by DAF-16. Int J Mol Sci. 2013;14(6): 11895–914.

[8] Chobot V, Hadacek F. Exploration of pro-oxidant and antioxidant activities of the flavonoid myricetin. Redox Rep. 2011;16(6):242–7.

[9] Mullie P, Clarys P, Deriemaeker P, Hebbelinck M. Estimation of daily human intake of food flavonoids. Plant Foods Hum Nutr. 2007;62(3):93–8

[10] Jun S, Shin S, Joung H. Estimation of dietary flavonoid intake and major food sources of Korean adults. Br J Nutr. 2016;115(3):480–9.

[11] Vogiatzoglou A, Mulligan AA, Lentjes MA, Luben RN, Spencer JP, Schroeter H, Khaw KT, Kuhnle GG. Flavonoid intake in European adults (18 to 64 years). PLoS One. 2015;10(5):e0128132

[12] Semwal D, Semwal R, Combrinck S, Viljoen A. Myricetin: a dietary molecule with diverse biological activities. Nutrients. 2016;8(2):90.

[13] Yang Z-J, Wang H-R, Wang Y-I, Zhai Z-H, Wang L-W, Li L, Zhang C, Tang L. Myricetin attenuated diabetes-associated kidney injuries and dysfunction via regulating nuclear factor (erythroid derived 2)-like 2 and nuclear factor-κBsignaling. Front Pharmacol. 2019;10:647.

[14] Kim ME, Ha TK, Yoon JH, Lee JS. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. Anticancer Res. 2014; 34(2):701–6.

[15] Kang BY, Kim SH, Cho D, Kim TS. Inhibition of interleukin-12 production in mouse macrophagesvia decreased nuclear factor-κB DNA binding activity by myricetin, a naturally occurring flavonoid. Arch Pharm Res. 2005;28(3): 274–9.

[16] Giglio RV, Patti AM, Cicero AF, Lippi G, Rizzo M, Toth PP, Banach M. Polyphenols: potential use in the prevention and treatment of

cardiovascular diseases. Curr Pharm Des. 2018;24(2):239–58.

[17] Tong Y, Zhou X-M, Wang S-J, Yang Y, Cao Y-L. Analgesic activity of myricetin isolated from Myrica rubra Sieb. Et Zucc. Leaves. Arch Pharm Res. 2009;32(4):527–33.

[18] Borde P, Mohan M, Kasture S. Effect of myricetin on deoxycorticosterone acetate (DOCA)-salt-hypertensive rats. Nat Prod Res. 2011;25(16):1549–59.

[19] Devi KP, Rajave T, Habtemariam S, Nabavi SF, Nabavi SM. Molecular mechanisms underlying anticancer effects of myricetin. *Life Sci.* 2015;142:19–25. [PubMed] [Google Scholar]

[20] Walker EH, Pacold ME, Perisic O, Stephens L, Hawkins PT, Wymann MP, Williams RL. Structural determinants of phosphoinositide 3-kinase inhibition by wortmannin, LY294002, quercetin, myricetin, and staurosporine. *Mol Cell.* 2000;6:909–
919. [PubMed] [Google Scholar]

[21] Mira L, Tereza Fernandez M, Santos M, Rocha R, Helena Florêncio M, Jennings KR. Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity. *Free Radic Res.* 2002;36:1199–
1208. [PubMed] [Google Scholar]

[22] Ueda H, Yamazaki C, Yamazaki M. A hydroxyl group of flavonoids affects oral anti-inflammatory activity and inhibition of systemic tumor necrosis factor-α production. *BiosciBiotechnolBiochem.* 2004;68:119–125. [PubMed] [Google Scholar]

[23] Nagai S, Ohara K, Mukai K. Kinetic study of the quenching reaction of singlet oxygen by flavonoids in ethanol solution. *J Phys Chem B.* 2005;109:42344240.[PubMed] [Google Scholar]

[24] Lin, G.B.; Xie, Y.; Li, G.W. Research advances of myricetin. J. Int. Pharm. Res. 2012, 39, 483–487.

[25] "USDA Database for the Flavanoid Content of the selected Foods, Release3". U.S. Department of Agriculture. 2011.

[26] Rao, K.V.; Seshadri, T.R. Nuclear oxidation in the flavone series—Part IV. New synthesis of herbacetin and hibiscetin. Proc. Indian Acad. Sci. A 1948, 25, 444–448.

[27] Tranchimand, S.; Tron, T.; Gaudin, C.; Iacazio, G. First chemical synthesis of three natural depsides involved in flavonol catabolism and related to

quercetinase catalysis. Synth. Commun. 2006, 36, 587–597. [CrossRef]

[28] Dean, H.F.; Nierenstein, M. Attempts to synthesize myricetin. J. Am. Chem. Soc. 1925, 47, 1676–1684. [CrossRef]

[29] Kalff, J.; Robinson, R. XXVIII.-A synthesis of myricetin and of a galangin monomethyl ether occurring in galanga root. J. Chem. Soc. Trans. 1925, 127, 181–184. [CrossRef]

[30] Rao, K.V.; Seshadri, T.R. Nuclear oxidation in flavones and related compounds—Part XVI. A new synthesis of myricetin. Proc. Indian Acad. Sci. A 1948, 28, 210–215.

[31] Fiorucci S, Golebiowski J, Cabrol-Bass D, Antonczak S. DFT study of quercetin activated forms involved in antiradical, antioxidant, and prooxidant biological processes. *J Agric Food Chem.* 2007;55:903911. [PubMed] [Goo gle Scholar] [Ref list]

[32] Justino GC, Vieira AJSC. Antioxidant mechanisms of quercetin and myricetin in the gas phase and in solution – a comparison and validation of semi-empirical methods. *J Mol Model.* 2010;16:863876. [PubMed] [Go ogle Scholar] [Ref list]

[33] Klein E, Lukeš V, Ilčin M. DFT/B3LYP study of tocopherols and chromans antioxidant action energetics. *Chem Phys.* 2007;336:5157. [GoogleScholar] [Ref list]

[34] Litwinienko G, Ingold KU. Solvent effects on the rates and mechanisms of reaction of phenols with free radicals. *Acc Chem Res.* 2007;40:222–230. [PubMed] [Google Scholar] [Ref list]

[35] Zhang H-Y, Sun Y-M, Wang X-L. Substituent effects on O-H bond dissociation enthalpies and ionization potentials of catechols: a DFT study and its implications in the rational design of phenolic antioxidants and elucidation of structure-activity relationships for flavonoid antioxidants. *Chem Eur J.* 2003;9:502–508. [PubMed] [Google Scholar] [Ref list]

[36] De Whalley CV, Rankin SM, Hoult JRS, Jessup W, Leake DS. Flavonoids inhibit the oxidative modification of low density lipoproteins by macrophages. BiochemPharmacol. 1990 ;39:1743–1750. [PubMed] [Google Scholar] [Ref list]

[37] Devasagayam TPA, Subramanian M, Singh BB, Ramanathan R, Das NP. Protection of plasmid pBR322 DNA by flavonoids against single-strand breaks induced by singlet molecular oxygen. *J*

PhotocPhotobiol B. 1995;30:97–103. [PubMed] [Google Scholar] [Ref list]

[38] Ramanathan L, Das NP. Inhibitory effects of some natural products on metal-induced lipid oxidation in cooked fish. *Biol Trace Elem Res.* 1992;34:35–44. [PubMed] [Google Scholar] [Ref list]

[39] Oyama Y, Fuchs PA, Katayama N, Noda K. Myricetin and quercetin, the flavonoid constituents of *Ginkgo biloba* extract, greatly reduce oxidative metabolism in both resting and Ca^{2+}-loaded brain neurons. *Brain Res.* 1994;635:125129. [PubMed] [Goog le Scholar] [Ref list]

[40] Thiyagarajah P, Kuttan SC, Lim SC, Teo TS, Das NP. Effect of myricetin and other flavonoids on the liver plasma membrane Ca^{2+} pump/ kinetics and structure-function relationships. BiochemPharmacol. 1991; 41:669675. [PubMed] [Google Scholar] [Ref list]

[41] Teo TS, Thiyagarajah P, Wong ZZ, Das NP. Does calmodulin mediate inhibition of human erythrocyte Ca*'- pumping ATPase by myricetin? *Biochem Med Metab Biol.* 1991;45:209–215. [PubMed] [Google Scholar] [Ref list]

[42] Barzegar A. Antioxidant activity of polyphenolic myricetin in vitro cell-free and cell-based systems. *Mol Biol Res Commun.* 2016;5:87–95. [PMC free article] [PubMed] [GoogleScholar] [Ref list]

[43] Haick H, Broza YY, Mochalski P, Ruzsanyi V, Amann A. Assessment, origin, and implementation of breath volatile cancer markers. Chem Soc Rev. 2014; 43(5):1423–49.

[44] MohanáAgarwal S. VOCC: a database of volatile organic compounds in cancer. RSC Adv. 2016;6(115):114783–9.

[45] White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med. 2014; 46(3):S7–S15.

[46] Mishra AP, Salehi B, Sharifi-Rad M, Pezzani R, Kobarfard F, Sharifi-Rad J, Nigam M. Programmed cell death, from a Cancer perspective: an overview. Mole Diagn Ther. 2018;22(3):281–95.

[47] Semwal D, Semwal R, Combrinck S, Viljoen A. Myricetin: a dietary molecule with diverse biological activities. Nutrients. 2016;8(2):90.

[48] Kim ME, Ha TK, Yoon JH, Lee JS. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. Anticancer Res. 2014; 34(2):701–6.

[49] . Ma L, Cao X, Wang H, Lu K, Wang Y, Tu C, Dai Y, Meng Y, Li Y, Yu P. Discovery of Myricetin as a potent inhibitor of human flap endonuclease 1, which potentially can be used as sensitizing agent against HT-29 human Colon Cancer cells. J Agric Food Chem. 2019;67(6):1656–65.

[50] Huang H, Chen AY, Ye X, Li B, Rojanasakul Y, Rankin GO, Chen YC. Myricetin inhibits proliferation of cisplatin-resistant cancer cells through a p53- dependent apoptotic pathway. Int J Oncol. 2015;47(4):1494–502

[51] Xu Y, Xie Q, Wu S, Yi D, Yu Y, Liu S, Li S, Li Z. Myricetin induces apoptosis via endoplasmic reticulum stress and DNA double-strand breaks in human ovarian cancer cells. Mol Med Rep. 2016;13(3):2094–100.

[52] Zheng AW, Chen YQ, Zhao LQ, Feng JG. Myricetin induces apoptosis and enhances chemosensitivity in ovarian cancer cells. Oncol Lett. 2017;13(6): 4974–8.

[53] Tavsan Z, Kayali HA. Flavonoids showed anticancer effects on the ovarian cancer cells: involvement of reactive oxygen species, apoptosis, cell cycle and invasion. Biomed Pharmacother. 2019;116:109004

[54] Lee KW, Kang NJ, Rogozin EA, Kim H-G, Cho YY, Bode AM, Lee HJ, Surh Y-J, Bowden GT, Dong Z. Myricetin is a novel natural inhibitor of neoplastic cell transformation and MEK1. Carcinogenesis. 2007;28(9):1918–27.

[55] Kang NJ, Jung SK, Lee KW, Lee HJ. Myricetin is a potent chemopreventive phytochemical in skin carcinogenesis. Ann N Y Acad Sci. 2011;1229(1):124–32.

[56] Sun W, Tao Y, Yu D, Zhao T, Wu L, Yu W, Han W. Myricetin exerts potent anticancer effects on human skin tumor cells. Trop J Pharm Res. 2018;17(6): 1067–72

[57] Shih Y-W, Wu P-F, Lee Y-C, Shi M-D, Chiang T-A. Myricetin suppresses invasion and migration of human lung adenocarcinoma A549 cells: possible mediation by blocking the ERK signaling pathway. J Agric Food Chem. 2009;57(9):3490–9.

[58] Zhang S, Wang L, Liu H, Zhao G, Ming L. Enhancement of recombinant

myricetin on the radiosensitivity of lung cancer A549 and H1299 cells. DiagnPathol. 2014;9(1):68.

[59] Wang L, Feng J, Chen X, Guo W, Du Y, Wang Y, Zang W, Zhang S, Zhao G. Myricetin enhance chemosensitivity of 5-fluorouracil on esophageal carcinoma in vitro and in vivo. Cancer Cell Int. 2014;14(1):71.

[60] Sun F, Zheng XY, Ye J, Wu TT, Wang JL, Chen W. Potential anticancer activity of myricetin in human T24 bladder cancer cells both in vitro and in vivo. Nutr Cancer. 2012;64(4):599–606

[61] Kang, B.Y.; Kim, S.H.; Cho, D.; Kim, T.S. Inhibition of interleukin-12 production in mouse macrophages via decreased nuclear factor-kappaB DNA binding activity by myricetin, a naturally occurring flavonoid. Arch. Pharm. Res. 2005, 28, 274–279. [CrossRef] [PubMed]

[62] Jimenez, R.; Andriambeloson, E.; Duarte, J.; Andriantsitohaina, R.; Jiménez, J.; Pérez-Vizcaino, F.; Zarzuelo, A.; Tamargo, J. Involvement of thromboxane A2 in the endothelium-dependent contractions induced by myricetin in rat isolated aorta. Br. J. Pharmacol. 1999, 127, 1539–1544. [CrossRef] [PubMed]

[63] Cho, Y.C.; Yoon, G.; Kwang, Y.L.; Hyun, J.C.; Bok, Y.K. Inhibition of interleukin-2 production by myricetin in mouse EL-4 T cells. Arch. Pharm. Res. 2007, 30, 1075–1079. [CrossRef] [PubMed]

[64] Yu, Y.; Zeng, Y.Y.; Liu, L.; Ji, Y.H.; Xing, F.Y.; Zhao, J.X. The effects of myrictin on inhibition of mouse lymphocytes activated in vitro. Chin. Pharmacol. Bull. 2006, 22, 63–66.

[65] J. Xu, C. Zhao, X. Huang, W. Du, Regulation of artemisinin and Its derivatives on the assembly behavior and cytotoxicity of amyloid polypeptides hIAPP and Aβ, ACS Chem. Neurosci. 10 (11) (2019) 4522–4534, https://doi.org/10.1021/acschemneuro.9b00385.

[66] R. Dubey, S.H. Kulkarni, S.C. Dantu, R. Panigrahi, D.M. Sardesai, N. Malik, *et al*., Myricetin protects pancreatic β-cells from human islet amyloid polypeptide (hIAPP) induced cytotoxicity and restores islet function, Biol. Chem. (2020), https://doi.org/10.1515/hsz-2020-0176. Advance online publication

[67] M. Saeedi, A. Hadjiakhondi, S.M. Nabavi, A. Manayi, Heterocyclic compounds: effective α-amylase and α-glucosidase inhibitors, Curr. Top. Med.

Chem. 17 (4) (2017) 428–440,https://doi.org/10.2174/1568026616666160824104655.

[68] Y. Meng, A. Su, S. Yuan, H. Zhao, S. Tan, C. Hu, *et al*., Evaluation of total flavonoids, myricetin, and quercetin from Hovenia dulcis Thunb. as inhibitors of α-amylase and α-glucosidase, Plant Foods Hum. Nutr. 71 (4) (2016) 444–449, https://doi.org/10.1007/s11130-016-0581-2.

[69] B. Jones, S.R. Bloom, T. Buenaventura, A. Tomas, G.A. Rutter, Control of insulin secretion by GLP-1, Peptides 100 (2018) 75–84, https://doi.org/10.1016/j.peptides.2017.12.013.

[70] S.H. Kwak, K.S. Park, Recent progress in genetic and epigenetic research on type 2 diabetes, Exp. Mol. Med. 48 (3) (2016) e220, https://doi.org/10.1038/emm.2016.7.

[71] T.R. Einarson, A. Acs, C. Ludwig, U.H. Panton, Economic burden of cardiovascular disease in type 2 diabetes: a systematic review, Value Health 21 (7) (2018) 881–890, https://doi.org/10.1016/j.jval.2017.12.019.

[72] Y. Li, X. Zheng, X. Yi, C. Liu, D. Kong, J. Zhang, M. Gong, Myricetin: a potent approach for the treatment of type 2 diabetes as a natural class B GPCR agonist, FASEB J. 31 (6) (2017) 2603–2611, https://doi.org/10.1096/fj.201601339R.

[73] S.K. Rad, A. Arya, H. Karimian, P. Madhavan, F. Rizwan, S. Koshy, G. Prabhu, Mechanism involved in insulin resistance via accumulation of β-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease, Drug Des. Devel. Ther. 12 (2018) 3999–4021, https://doi.org/10.2147/DDDT.S173970.

[74] X. Wei, N. Gu, N. Feng, X. Guo, X. Ma, Inhibition of p38 mitogen-activated protein kinase exerts a hypoglycemic effect by improving β cell function via inhibition of β cell apoptosis in db/db mice, J. Enzyme Inhib. Med. Chem. 33 (1) (2018) 1494–1500,https://doi.org/10.1080/14756366.2018.1477138.

[75] U. Karunakaran, J.E. Lee, S. Elumalai, J.S. Moon, K.C. Won, Myricetin prevents thapsigargin-induced CDK5-P66Shc signalosome mediated pancreatic β-cell dysfunction, Free Radic. Biol. Med. 141 (2019) 59–66, https://doi.org/10.1016/j.freeradbiomed.2019.05.038.

[76] H. Li, Z. Wang, Y. Li, R. Fang, H. Wang, H. Shi, *et al*., Hepatitis B X-interacting protein promotes the formation of the insulin gene-transcribing protein complex Pdx-1/Neurod1 in animal pancreatic β-cells, J. Biol. Chem. 293 (6) (2018) 2053–2065, https://doi.org/10.1074/jbc.M117.809582.

[77] N. Kandasamy, N. Ashokkumar, Protective effect of bioflavonoid myricetin enhances carbohydrate metabolic enzymes and insulin signaling molecules in streptozotocin-cadmium induced diabetic nephrotoxic rats, Toxicol. Appl. Pharmacol. 279 (2) (2014) 173–185, https://doi.org/10.1016/j.taap.2014.05.014.

[78] Z. Wu, X. Zheng, M. Gong, Y. Li, Myricetin, a potent natural agent for treatment of diabetic skin damage by modulating TIMP/MMPs balance and oxidative stress, Oncotarget 7 (44) (2016) 71754–71760, https://doi.org/10.18632/oncotarget.12330.

[79] P.S. Bellaye, C. Shimbori, T. Yanagihara, D.A. Carlson, P. Hughes, C. Upagupta, *et al*., Synergistic role of HSP90α and HSP90β to promote myofibroblast persistence in lung fibrosis, Eur. Respir. J. 51 (2) (2018), 1700386, https://doi.org/10.1183/13993003.00386-2017.

[80] Z. Sibinska, X. Tian, M. Korfei, B. Kojonazarov, J.S. Kolb, W. Klepetko, *et al*., Amplified canonical transforming growth factor-β signalling via heat shock protein 90 in pulmonary fibrosis, Eur. Respir. J. 49 (2) (2017), 1501941, https://doi.org/10.1183/13993003.01941-2015.

[81] X. Li, H. Yu, L. Liang, Z. Bi, Y. Wang, S. Gao, *et al*., Myricetin ameliorates bleomycin-induced pulmonary fibrosis in mice by inhibiting TGF-β signaling via targeting HSP90β, Biochem. Pharmacol. 178 (2020), 114097 https://doi.org/10.1016/j.bcp.2020.114097.

[82] H. Lv, B. An, Q. Yu, Y. Cao, Y. Liu, S. Li, The hepatoprotective effect of myricetin against lipopolysaccharide and D-galactosamine-induced fulminant hepatitis, Int. J. Biol. Macromol. 155 (2020) 1092–1104, https://doi.org/10.1016/j.ijbiomac.2019.11.075.

[83] J.L. Granadillo, W.K. Chung, L. Hecht, N. Corsten-Janssen, D. Wegner, S. Nij Bijvank, *et al*., Variable cardiovascular phenotypes associated with SMAD2 pathogenic variants, Hum. Mutat. 39 (12)

(2018) 1875–1884, https://doi.org/ 10.1002/humu.236277.

[84] B. Kojonazarov, T. Novoyatleva, M. Boehm, C. Happe, Z. Sibinska, X. Tian, *et al*., p38 MAPK inhibition improves heart function in pressure-loaded right ventricular hypertrophy, Am. J. Respir. Cell Mol. Biol. 57 (5) (2017) 603–614, https://doi. org/10.1165/rcmb.2016-0374OC.

[85] Y. Geng, Q. Sun, W. Li, Z.M. Lu, H.Y. Xu, J.S. Shi, Z.H. Xu, The common dietary flavonoid myricetin attenuates liver fibrosis in carbon tetrachloride treated mice, Mol. Nutr. Food Res. 61 (4) (2017), 1600392, https://doi.org/10.1002/ mnfr.201600392.

[86] C. Guo, G. Xue, B. Pan, M. Zhao, S. Chen, J. Gao, *et al*., Myricetin ameliorates ethanol-induced lipid accumulation in liver cells by reducing fatty acid biosynthesis, Mol. Nutr. Food Res. 63 (14) (2019), e1801393, https://doi.org/ 10.1002/mnfr.201801393.

[87] G.V. Martins, A. Tavares, E. Fortunato, M. Sales, Paper-based sensing device for electrochemical detection of oxidative stress biomarker 8-Hydroxy-2'-deoxyguanosine (8-OHdG) in point-of-Care, Sci. Rep. 7 (1) (2017), 14558, https://doi.org/10.1038/s41598-017-14878-9.

[88] M. Shokrzadeh, H. Ebrahimnejad, A. Zear, A. Chabra, F. Naghshvar, A. Ahmadi, In vivo protective effect of Myricetin on liver biochemical damage induced by endosulfan, J. Mazandaran Univ. Med. Sci. 26 (143) (2016) 28–36.

[89] F.N. EkiNci-Akdemir, S. Yildirim, R.F.M. Kandemir, ˙ I. Gülçin, S. Küçükler, Y. S. Saglam, ˘ S. Yakan, The effects of casticin and myricetin on liver damage induced by methotrexate in rats, Iran. J. Basic Med. Sci. 21 (12) (2018) 1281–1288, https://doi.org/10.22038/ijbms.2018.29922.7217.

[90] F. Tadini-Buoninsegni, S.A. Mikkelsen, L.S. Mogensen, R.S. Molday, J. P. Andersen, Phosphatidylserine flipping by the P4-ATPase ATP8A2 is electrogenic, Proc. Natl. Acad. Sci. U.S.A. 116 (33) (2019) 16332–16337, https:// doi.org/10.1073/pnas.1910211116.

[91] Y. Miyazaki, A. Ichimura, S. Sato, T. Fujii, S. Oishi, H. Sakai, H. Takeshima, The natural flavonoid myricetin inhibits gastric H+, K+-ATPase, Eur. J. Pharmacol. 820 (2018) 217–221,

https://doi.org/10.1016/j.ejphar.2017.12.042.

[92] W. Sun, C. Liu, Q. Chen, N. Liu, Y. Yan, B. Liu, SIRT3: a new regulator of cardiovascular diseases, Oxid. Med. Cell. Longev. 2018 (2018), 7293861, https://doi.org/10.1155/2018/7293861.

[93] F. Villarroya, R. Cereijo, J. Villarroya, M. Giralt, Brown adipose tissue as a secretory organ. Nature reviews, Endocrinology 13 (1) (2017) 26–35, https://doi.org/10.1038/nrendo.2016.136.

[94] S. Akindehin, Y.S. Jung, S.N. Kim, Y.H. Son, I. Lee, J.K. Seong, *et al*., Myricetin exerts anti-obesity effects through upregulation of SIRT3 in adipose tissue, Nutrients 10 (12) (2018) 1962, https://doi.org/10.3390/nu10121962.

[95] T. Hu, X. Yuan, G. Wei, H. Luo, H.J. Lee, W. Jin, Myricetin-induced brown adipose tissue activation prevents obesity and insulin resistance in db/db mice, Eur. J. Nutr. 57 (1) (2018) 391–403, https://doi.org/10.1007/s00394-017-1433-z.

[96] V. Dubois, J. Eeckhoute, P. Lefebvre, B. Staels, Distinct but complementary contributions of PPAR isotypes to energy homeostasis, J. Clin. Invest. 127 (4) (2017) 1202–1214, https://doi.org/10.1172/JCI88894.

[97] J. Bindhu, A. Das, An edible fungi Pleurotus ostreatus inhibits adipogenesis via suppressing expression of PPAR γ and C/EBP α in 3T3-L1 cells: in vitro validation of gene knock out of RNAs in PPAR γ using CRISPR spcas9, Biomed. Pharmacother. 116 (2019), 109030, https://doi.org/10.1016/j.biopha.2019.109030.

[98] H.M. Su, L.N. Feng, X.D. Zheng, W. Chen, Myricetin protects against diet-induced obesity and ameliorates oxidative stress in C57BL/6 mice, J. Zhejiang Univ. Sci. B 17 (6) (2016) 437–446, https://doi.org/10.1631/jzus.B1600074.

[99] S.F. Xia, G.W. Le, P. Wang, Y.Y. Qiu, Y.Y. Jiang, X. Tang, Regressive effect of myricetin on hepatic steatosis in mice fed a high-fat diet, Nutrients 8 (12) (2016) 799, https://doi.org/10.3390/nu8120799.

[100] X. Ying, X. Chen, T. Wang, W. Zheng, L. Chen, Y. Xu, Possible osteoprotective effects of myricetin in STZ induced diabetic osteoporosis in rats, Eur. J. Pharmacol. 866 (2020), 172805, https://doi.org/10.1016/j.ejphar.2019.172805.

[101] S. Fan, X. Gao, P. Chen, X. Li, Myricetin ameliorates glucocorticoid-induced osteoporosis through the ERK signaling pathway, Life Sci. 207 (2018) 205–211, https://doi.org/10.1016/j.lfs.2018.06.006.

[102] A.W. James, G. LaChaud, J. Shen, G. Asatrian, V. Nguyen, X. Zhang, *et al*., A review of the clinical side effects of bone morphogenetic Protein-2, Tissue Eng. Part B Rev. 22 (4) (2016) 284–297, https://doi.org/10.1089/ten.TEB.2015.0357.

[103] H.Y. Kim, S.Y. Park, S.Y. Choung, Enhancing effects of myricetin on the osteogenic differentiation of human periodontal ligament stem cells via BMP-2/ Smad and ERK/JNK/p38 mitogen-activated protein kinase signaling pathway, Eur. J. Pharmacol. 834 (2018) 84–91, https://doi.org/10.1016/j.ejphar.2018.

[104] L. Wu, L. Ran, H. Lang, M. Zhou, L. Yu, L. Yi, *et al*., Myricetin improves endurance capacity by inducing muscle fiber type conversion via miR-499, Nutr. Metab. (Lond) 16 (2019) 27, https://doi.org/10.1186/s12986-019-0353-8.