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REVIEW

Myricetin: a potential plant-derived anticancer bioactive compound—an updated overview

Suneel Kumar[1] · Nitin Swamy[2] · Hardeep Singh Tuli[3] · Seema Rani[4] · Abhijeet Garg[2] · Deepa Mishra[5] · Hadi Sajid Abdulabbas[6] · Sardul Singh Sandhu[7]

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Abstract

The globe is currently confronting a global fight against the deadliest cancer sickness. Chemotherapy, hormonal therapy, surgery, and radiation therapy are among cancer treatment options. Still, these treatments can induce patient side effects, including recurrence, multidrug resistance, fever, and weakness. As a result, the scientific community is always working on natural phytochemical substances. Numerous phytochemical compounds, including taxol analogues, vinca alkaloids such as vincristine and vinblastine, and podophyllotoxin analogues, are currently undergoing testing and have shown promising results against a number of the deadliest diseases, as well as considerable advantages due to their safety and low cost. According to research, secondary plant metabolites such as myricetin, a flavonoid in berries, herbs, and walnuts, have emerged as valuable bio-agents for cancer prevention. Myricetin and its derivatives have antiinflammatory, anticancer, apoptosis-inducing, and anticarcinogenic properties and can prevent cancer cell proliferation. Multiple studies have found that myricetin has anticancer characteristics in various malignancies, including colon, breast, prostate, bladder, and pancreatic cancers. Current knowledge of the anticancer effects of myricetin reveals its promise as a potentially bioactive chemical produced from plants for the prevention and treatment of cancer. This review aimed to study the numerous bioactivities, mode of action, and modification of several cellular processes that myricetin possesses to impede the spread of cancer cells. This review also addresses the challenges and future prospects of using myricetin as a anticancer drug.

Keywords Bio-molecules · Cancer · Angiogenesis · Apoptosis · Proliferation · Antimalignant

✉ Sardul Singh Sandhu
ssandhu@rediffmail.com

[1] Department of Botany, Government Girls College Khargone, 451001 Khargone, Madhya Pradesh, India

[2] Fungal Biotechnology and Invertebrate Pathology Laboratory, Department of Biological Sciences, Rani Durgavati University, Jabalpur 482001, Madhya Pradesh, India

[3] Department of Biotechnology, Maharishi Markandeshwar (Deemed to Be University), Mullana, Ambala 133207, Haryana, India

[4] Department of Chemistry, Government M. H. College of Home Science & Science for Women, Autonomous, Jabalpur 482002, Madhya Pradesh, India

[5] Department of Biotechnology, Mata Gujri Mahila Mahavidyalaya Jabalpur, 482001 Jabalpur, Madhya Pradesh, India

[6] Continuous Education Department, Faculty of Dentistry, University of Al-Ameed, Karbala 56001, Iraq

[7] Bio-Design Innovation Centre, Rani Durgavati University, Jabalpur 482001, Madhya Pradesh, India

Abbreviations

PAL	Phenylalanine ammonia-lyase
4CL	4-Coumaryl-CoA ligase
CHS	Chalcone synthase
CHI	Chalconeisomerase
F3H	Flavanone-3-hydroxylase
F3′H	Flavonoid-3′-hydroxylase
FLS	Flavonol synthase

Introduction

Since the dawn of civilisation, people have used a variety of natural substances and their derivatives to treat terrible ailments. The use of secondary metabolites derived from plants to treat cancer is becoming more and more popular. Numerous studies have demonstrated the significance of phytochemicals in preventing this condition (Goyal et al. 2022; Khatoon et al. 2020; Shuaib et al. 2021). Therefore, the research community has identified an extensive range of

phytochemicals and their mechanism of anticancer activity (Abadi et al. 2021; Yeshi et al. 2022). To understand how phytochemicals can help fight cancer, we need to study how they interact with cellular targets. An effective cancer treatment strategy also requires studying the pharmacokinetics of these compounds. This involves determining the appropriate dose and course of treatment, assessing their acceptability and efficacy in physiological conditions. Additionally, we need to study the remedial index to understand the potential benefits and risks of using these compounds. Finally, it is important to investigate the metabolic mechanism of plant-derived molecules against cancer to develop effective treatments. Among the potent anticancer natural compounds isolated from plant parts, the phytochemical compound myricetin and its derivatives are some of the most promising molecules utilised against various cancer cells (Jan et al. 2022; Siddiqui et al. 2022; Khan et al. 2022). The majority of researchers have found that myricetin promotes apoptosis, the start of ROS-mediated stress, metastatic activity, and DNA damage in various cancer cell lines and animal models. In addition, it controls the expression of inflammatory factors, triggers autophagy, initiates cell cycle arrest, and prevents cell invasion and metastasis (Han et al. 2022a, b, ; Ji et al. 2022). Myricetin is a widely distributed flavonol obtained from various family members of the plants such as Myricaceae, Anacardiaceae, Polygonaceae, Pinaceae, and Primulaceae. Tea, berries, vegetables, fruits, and medicinal plants are all excellent sources of myricetin (Hou et al. 2018; Qu et al. 2020; Gervasi et al. 2022; Chua et al. 2011). Myricetin and its derivatives have shown unique therapeutic effects in vivo and in vitro conditions, including anticancer, antiphotoaging activity, antioxidant activity, antiallergic and analgesic activities, immunomodulatory activity, antihypertensive activity, and cardio-protective and neuro-protective activities (Sharma et al. 2021; Semwal et al. 2016; Hagenacker et al. 2010; Jung et al. 2010; Li et al. 2022a, b). Myricetin causes cancer cell apoptosis that is Bcl-2 family-dependent intrinsically and DR5-dependent extrinsically (Huang et al. 2015; Anwar et al. 2022). Previous research has suggested myricetin's role in inhibiting cell proliferation by regulating the S6 kinase 2 (RSK2) that increases the expression of Mad-1 and causes cell cycle arrest through ROS-dependent mitochondria-mediated mortality in the cancer cell (Rajendran et al. 2021; Feng et al. 2015). Myricetin increases BAX/BCL-2 and BAK caspase cascade expression in colon cancer, which leads to the induction of apoptosis (Rajabi et al. 2021; Xie et al. 2020; Kim et al. 2014). Myricetin plays a big part in deterring many pathways from occurring, such as PI3K/Akt/mTOR signalling, Akt/mTOR signalling pathway, and suppressing TGF-β1/Smad signalling, and also inhibits human breast cancer cell viability by controlling the PAK1/ ERK/MEK//GSK3β/Bax-caspase-3/β-catenin/cyclin D1/PCNA/surviving signalling (Sharma et al. 2022, Jiao and Zhang 2016). Myricetin reduces breast cancer MMP/2/9 and ST6GALNAC5 mRNA levels (Ci et al. 2018). Myricetin may also be able to block UVB-induced angiogenesis in SKH-1 hairless mouse skin by dramatically decreasing the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-9, and MMP-13 and suppressing factor-1α expression and phosphatidylinositol-3 (PI-3) kinase activity (Jung et al. 2012).

Hence, the review article has emphasised exploring the mechanism of action of myricetin bioactive compound that helps us understand the biology of neoplastic diseases and their regulation and cellular progression. Furthermore, it provides a detailed study of the molecules in cancer treatment, their chemical structure, chemopreventive properties, antioxidant and antiinflammatory activities, inhibitory role in angiogenesis and metastasis, and interactions of myricetin with other drugs. There has been discussion over the formulation of myricetin to include a comprehensive strategy for myricetin as a potential medicinal molecule.

Chemistry of myricetin

Myricetin is a naturally occurring flavone in fruits, vegetables, teas, and plant wines. Both the free and glycosidic bond forms of myricetin exist with hexahydroxyl substitutions at the 3,3′, 4′,5, 5′, and 7 positions (Zhou et al. 2022; Sun et al. 2012). It is less soluble in water but readily dissolves in organic solvents such as acetone, dimethylformamide, dimethylacetamide, tetrahydrofuran, and several primary aqueous media. The degradation of the compound is pH and temperature-dependent, and it is highly stable at pH2 (Yan et al. 2021; De Leo et al. 2006; Kong et al. 2014). The researchers initially isolated myricetin in light yellow crystal form from the bark of the plant Myrica nagi Thunb. (Myricaceae) hundreds of years ago in India. It was also isolated from the aerial part of the *Polygonumbellardii* All. Strawberry, spinach, *Euphorbia tirucalli* L., *Cyperusrotundus* L. rhizomes, and *Trigonella foenum-graecum* seed extract had the most amazing myricetin content among the Polygonaceae in methanol extract (Sultana and Anwar 2008; Yang et al. 2021; Jahan et al. 2013). It contains pyrogallol B-ring and hydroxylated structure, which is highly responsible for its various biological activities compared to other flavonols (Sato et al. 2013; Mendes et al. 2015; Kenouche et al. 2022; ONO et al. 1990). Myricetin has a linkage structurally to several phenolic chemicals, including quercetin, morin, kaempferol, and fisetin, and sometimes it is also called hydroxyquercetin due to its structural similarity with quercetin molecule (Lin 2012; Parvez et al. 2020). The dietary consumption of myricetin decreases the risk of cancer because of its numerous antitumour properties like antiproliferative, proapoptotic, and antimetastatic

activities in various cancers (Micek et al. 2021; Geybels et al. 2013; Marrero et al. 2022). The hexane/ethyl acetate/methanol/water extract of *Davillaelliptica* St. Hill. (Dilleniaceae) analysed by column chromatography and thin layer chromatography resulted in the isolation of myricetin and quercetin-3-*O*-a-L-rhamnopyranosid (Rinaldo et al. 2006). In another study, the initial extraction of myricetin compound comprises column chromatography over Sephadex LH-20 using a methanol fraction of *Davillaelliptica* St.-Hil. and finally characterised by preparative RP-HPLC (Campos et al. 2013). In one approach, a low-cost extraction process for myricetin, quercetin, luteolin, and kaemferol has been developed through a complex cap espresso machine using ethanol and water, and liquid chromatography determined chemical compounds (Corell et al. 2018) (Fig. 1).

Biosynthesis of myricetin

In myricetin biosynthesis, the plant typically follows the phenylpropanoid biosynthetic mechanism. The mechanism begins with converting phenylalanine to cinnamic acid, catalysed by the phenylalanine ammonia-lyase (PAL). The cinnamic acid was further catalysed by an enzyme cinnamate 4-hydroxylase (C4H) to generate *p*-coumaric acid and then 4-coumaroly-CoA. Natural phenylpropanoids, such as cumarins, stilbenes, and flavonoids, are formed by condensing three molecules of malonyl-CoA and one molecule of p-coumaroyl CoA that further changed into naringenin chalcone with the help of chalcone synthase (CHS). This enzyme is regarded as the initial enzyme in flavonoid biosynthesis. The chalcone isomerase (CHI) enzyme further converts the intermediate molecule, naringenin in chalcone, into naringenin. In the next step of myricetin biosynthesis, the enzyme flavone 3-hydroxylase (F3H) converts naringenin to pentahydroxyflavanone and dihydromyricetin. In the last stage of the biosynthesis of this compound, the flavonol synthase (FLS), an enzyme, finally transformed the dihydromyricetin into myricetin (Martens et al. 2010; Fogelman et al. 2015; Javed et al. 2022; Arafah et al. 2022) (Fig. 2).

Chemical synthesis of myricetin

For the chemical synthesis of myricetin, the first step was taken in 1925 by Dean and Nierenstein (Kalff and Robinson 1925) by using Kostanecki and Auwer's approach but failed to gain any success. However, one of Kalff and Robinson's other research groups synthesised myricetin from ω-methoxyphloroacetophenone that same year. The first stage of this process involves heating the starting material with trimethylgallic anhydride and sodium trimethylgallate, following the product's hydrolysis results in the formation of an intermediate known as 5,7-dihydroxy-3,31,41,51-tetramethoxyflavone, and following the demethylation of the intermediate, which results in the formation of myricetin. A series of myricetin analogues having a 1,3,4-thiadiazole scaffold was also synthesised chemically and observed the antibacterial activity against Xoo and Rs and the antiviral activity against the TMV (Zhong et al. 2017) (Fig. 3).

In a different method, myricetin was synthesised from quercetin by Rao and Seshadri (Rao and Seshadri 1948) by an ortho-oxidation reaction that transformed 3,5,7,3′-tetra-O-methylquercetin into 5′-aldehyde. In the next phase, 5′-aldehyde is transformed into 3,5,7,31-tetra-O-methylmyricetin, which yields 5-methoxykanugin followed by cyclisation at 41 and 51 positions. The subsequent methylation of 5-methoxykanugin produced hexamethylmyricetin that, after demethylation, failed myricetin (Tranchimand et al. 2006). One study designed a variety of myricetin analogues with a quinazolinone moiety and found the compound's in vitro antibacterial and in vivo antiviral activities (Liu et al. 2021).

Derivatives of myricetin

The derivatives of myricetin are also widely synthesised, designed, extracted, and tested for their anticancer properties against various cancer cell lines. In one study, different types of myricetin derivatives were synthesised by altering the original compounds' structures and observing their antitumour activity against human non-small cell lung

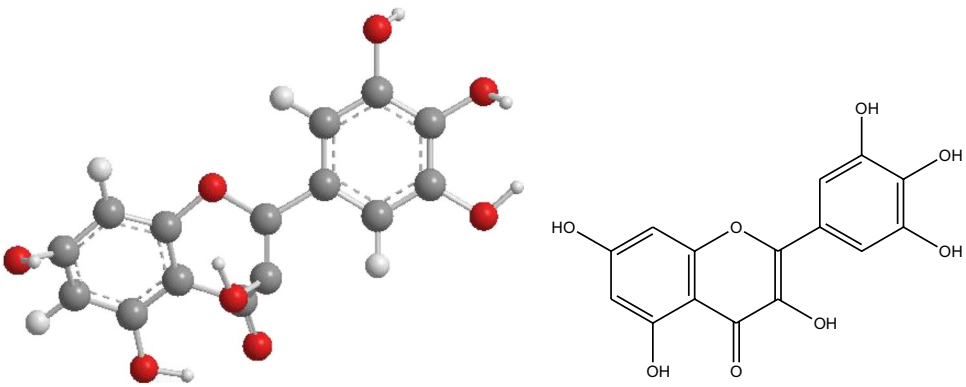

Fig. 1 Chemical structure of myricetin

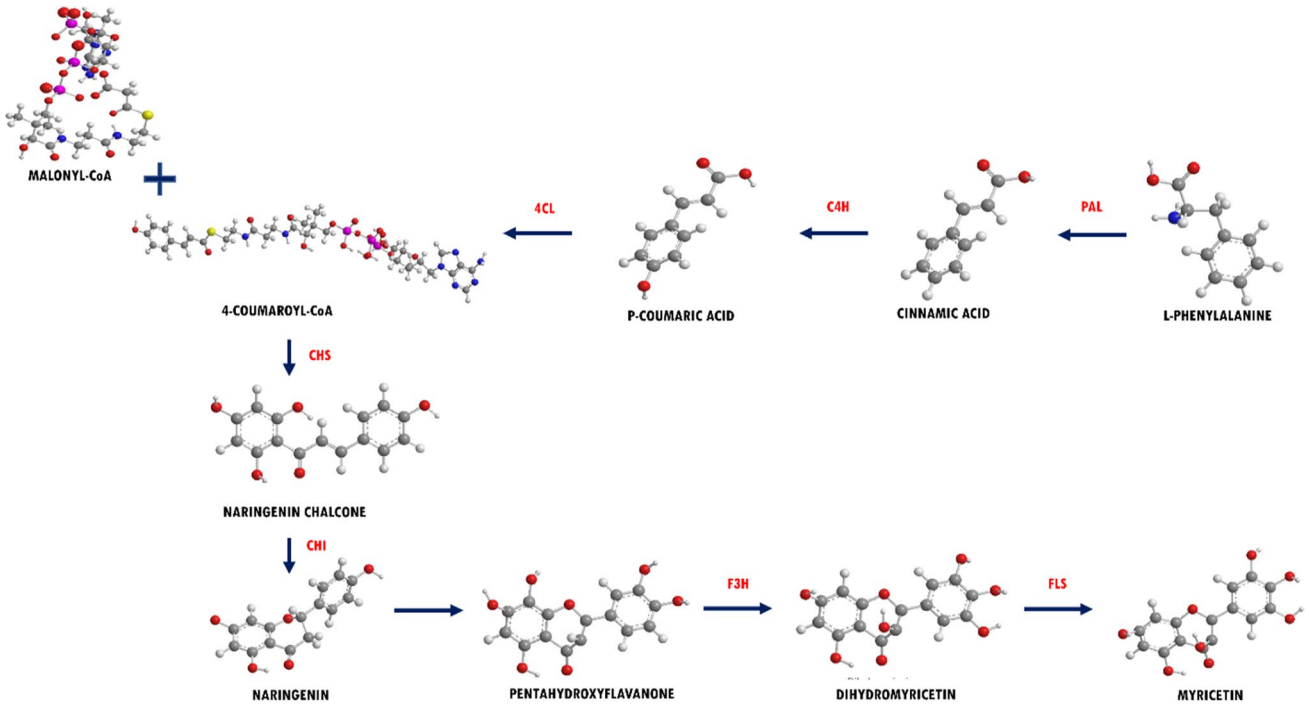

Fig. 2 The mechanism of phenylpropanoid biosynthetic pathway for myricetin. PAL, phenylalanine ammonia-lyase; 4CL, 4-coumaryl-CoA ligase; CHS, chalcone synthase; CHI, chalconeisomerase; F3H, flavanone-3-hydroxylase; F3′H, flavonoid-3′-hydroxylase; FLS, flavonol synthase

cancer (NSCLC) A549 cells (Li et al. 2021). One of the myriceitn derivatives known as S4-2–2 (5,7-dimethoxy-3-(4-(methyl(1-(naphthalen-2-ylsulfonyl)piperidin-4-yl)amino) butoxy)-2-(3,4,5-trimethoxyphenyl)-4H- chromen-4-one) has strongly inhibited the migration and invasion but induced the apoptosis in of non-small cell lung cancer A549 (Zhou et al. 2023). From all of the myricetin derivatives, the S4-10 has shown the maximum activity in cell migration, proliferation, invasion, induced apoptosis, and cell cycle arrest in A549 Cells. Myricetin derivatives, such as 2-(2′,6′-dimethyl-3′,4′,5′-alkyl or hydroxy alkyl substituted phenyl)-3-oxy-(alkyl or hydoxy alkyl)-5,7-dihydroxy-chromen-4-one, were isolated and characterised from the Mimosa pudica plant. These derivatives were tested for in vitro anticancer activity against human lung adenocarcinoma cell lines (A549) and human erythroleukaemic cells (K562). The tests utilised 3-(4,5-dimethylthiazol-2-yl)MTT assay-2,5-diphenyl tetrazolium bromide (Jose et al. 2016; Xianghui et al. 2018). Oral treatment of one of myricetin derivatives, M10, inhibited ulcerative colitis (UC) and colorectal tumours in the murine azoxymethane/dextran sodium sulfate model. The treatment was administered at 50–100 mg/kg daily for 12 weeks. The study discovered that M10 myricetin derivatives enhanced CD8 + T and CD4 + T cells in colorectal tissues while attenuating chronic inflammation and inhibiting the invasion of myeloid-derived suppressor cells. The M10 derivative of myricetin significantly decreased the pro-inflammatory factors IL-6, TNF-, and granulocyte–macrophage colony-stimulating factor, as well as the NF-B/IL-6/STAT3 pathways and colorectal carcinogenesis. (Wang et al. 2018). Two myricetin derivatives, 3,7,4,5-tetramethyl ether of myricetin and 3,5-diacetyl derivative, were also cytotoxic against human leukaemic cell lines when isolated from *Cistus monspeliensis* in hexane extract (Dimas et al. 2000).

Pharmacological utilisation of myricetin

Anticancer properties of myricetin

One of the crucial dietary components present in foods and beverages is the bioactive substance myricetin. Myricetin has potential antioxidant, antiinflammatory, and anticancer effects, according to numerous studies, as shown in Fig. 4. According to myricetin's biological characteristics, it is highly effective against many cancer cell lines, including those found in the liver, skin, bladder, pancreas, breast, and colon. It is also known to inhibit the activity of several molecular enzymes, such as DNA polymerases, RNA polymerases, reverse transcriptases, telomerase, kinases, and helicases (Awadelkareem et al. 2022; Jain et al. 2021). Myricetin and dihydromyricetin inhibited fibroblast proliferation

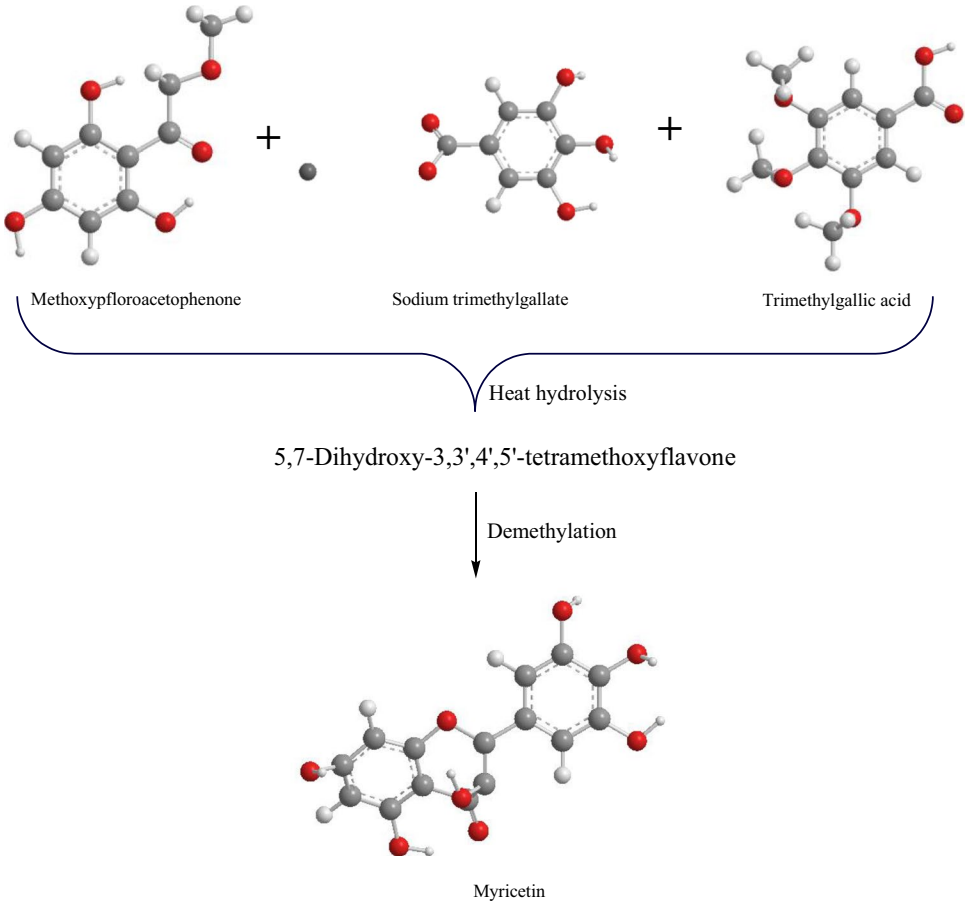

Fig. 3 Chemical synthesis of myricetin as proposed by Kalff and Robinson

in lung and breast cancer (MCF-7 and A549) via inducing apoptosis, inhibiting cell proliferation, and downregulating PDGFRβ signalling pathway and extracellular signal-regulated kinase (Erk) 1/2 and Akt expression (Fan et al. 2017). Myricetin inhibited the expression of MMP-2 and MMP-9 proteins in cancer cells. It also inhibited the phosphorylation of the FAK (focal adhesion kinase) signalling pathway and changed the F-actin/G-actin ratio in A549-IR cells (Kang et al. 2020). Another report involving the inhibition of cytokine-induced invasion and migration of KKU-100 cells treated with myricetin consists of the downregulation of STAT3, matrix metalloproteinase-9, inducible nitric oxide synthase, intercellular adhesion molecule-1, and cyclooxygenase 2 (COX-2). Similarly, treating myricetin on mouse skin epidermal JB6 P + cells indicated the role of UVB-induced cyclooxygenase (COX-2) expression (Senggunprai et al. 2018). Myricetin strongly suppressed UVB-induced start of activator protein-1, NF-κβ and Fyn kinase activity, MEK1 kinase activity, and transformation of JB6 P + mouse epidermal cells, as reported by the author (Jung et al. 2008). The combination of myricetin (MYR), methyl eugenol (MEG), and cisplatin (CP) significantly inhibited cancer cell growth, induction of cell apoptosis, loss of mitochondrial potential, and upregulation of caspase-3 activity, as well as increased the number of cells in the Go/G1 phase in human cervical cancer (Yi et al. 2015). One study reported that the myricetin induced apoptosis by serum deprivation in PCL-12 cell dose-dependently by expressing the tumour suppressor gene p53 and proapoptotic and antiapoptotic Bcl-2 family proteins Bax and Bcl-2 and induced the expression of caspase 3 and

Fig. 4 Proposed mechanism of synthesis of myricetin by Route Rao and Seshadri

caspase 9 cascades (Tan et al. 2018). Mitogen-activated protein kinase (MAPK) and PI3/AKT signalling pathways are crucial for myricetin's ability to inhibit cell proliferation, regulate the cell cycle, and invade and promote angiogenesis [68]. Myricetin has also responsible for the initiation of apoptosis in breast cancer SK-BR3 cells via upregulation of PARP, Bax protein, expression of phosphorylated c-Jun N-terminal kinase (p-JNK) and phosphorylated mitogen-activated protein kinases (p-p38), and downregulation of Bcl2 and phosphorylated extracellular-regulated kinase (p-ERK) (Han et al. 2022a, b,). Another study found that myricetin caused breast cancer cells to undergo apoptosis through both intrinsic and extrinsic pathways, most notably the BRCA1-GADD45 pathway, which increased the expression of caspase-3, caspase-8 and caspase-9 as well as the proportion of BAX/Bcl-2, P53, BRCA1, GADD45, and annexin (Soleimani and Sajedi 2020). Myricetin caused apoptotic cell death in A431 human cancer cells in a dose-dependent manner by increasing the rate of reactive oxygen species (ROS) that leads to the disruption of outer mitochondria potential caused by discharged apoptotic triggering proteins and is also responsible for the alteration of Bcl and Bax expressions (Sun et al. 2018). Another study found that myricetin inhibits HCC cell growth by causing cell cycle arrest and autophagy by downregulating MARCH 1 mRNA but upregulating MARCH 1 mRNA in Hep3B cells. Furthermore, it suppressed p38 MAPK and Stat3 signalling by reducing MARCH 1 to suppress HCC proliferation in vitro and in vivo (Yang et al. 2021)**.**

Myricetin's proapoptotic activities in human hepatocarcinoma HepG2 cells are enhanced by reduced mitochondrial fragmentation and transmembrane potential. Furthermore, the author proposed that myricetin promoted apoptosis in HepG2 cells via the mitochondrial apoptotic route and the Akt/p70s6k1/Bad signalling pathways, which resulted in the production of proapoptotic proteins Bax and Bad in the mitochondria and the downregulation of Bcl-2 expression. Furthermore, the study discovered that myricetin boosted caspase-3 proteolytic activation and PARP protein degradation, which was followed by cytochrome C release in the cytoplasm (ZHAO et al. 2012). Similar to this report, another research reported that the induction of ERK1/2 and JNK signalling pathways supported the generation of ROS, increased apoptotic DNA fragmentation, lipid peroxidation, phosphorylation of AKT, p70S6K, and depolarisation of MMP in D-17 and DSN canine osteosarcoma cells (Li et al. 2019). Myricetin administration increased apoptosis-related genes caspase-3, caspase-8, and caspase-9, and the BAX/Bcl-2 ratio, as well as p53, BRCA1, and GADD45 in MCF-7 breast cancer cells (Park et al. 2018) (Fig. 5).

Myricetin affects the invasion and migration of radioresistant lung cancer cell A549IR. Similarly, dose- and time-dependent inhibitions of adhesion, migration, and invasion by matrix metalloproteinase-2 and urokinase plasminogen activator properties in A549 cells were also seen in specific investigations with myricetin. Myricetin-treated A549 cells inhibited nuclear factor kappa B c-Fos and c-Jun activation and phosphorylated extracellular signal-regulated 1 and 2 (Shih et al. 2009). Moreover, myricetin reduced the expression of Yes-associated protein (YAP) by promoting its phosphorylation and subsequent degradation via stimulating the LATS1/2 pathway that induced apoptosis and cell proliferation inhibition in hepatocellular carcinoma HepG2 and Huh-7 cells (Li et al. 2019).

Another study discovered that myricetin's role in the breakdown of mitochondrial membrane potential leads

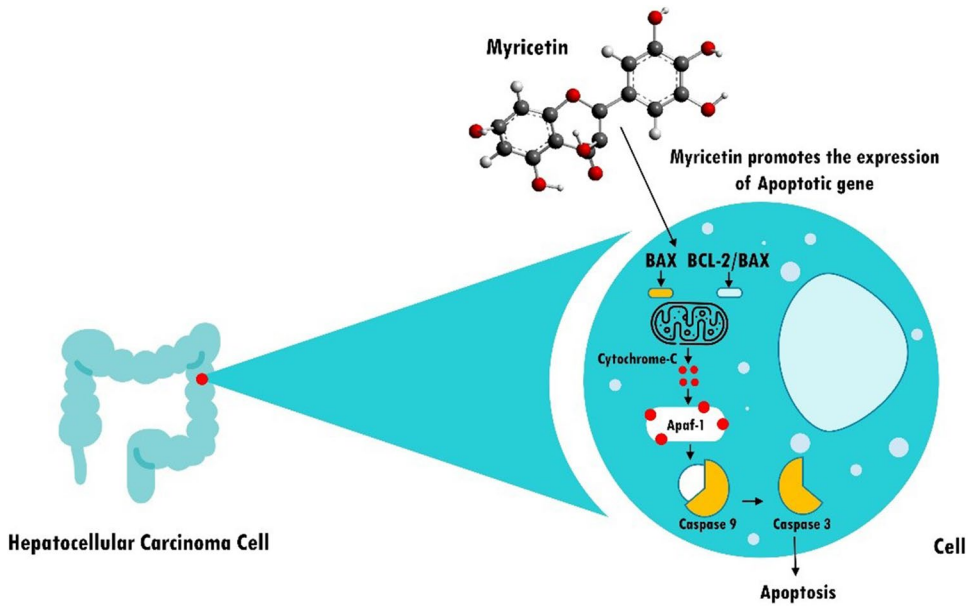

Fig. 5 Expression of an apoptotic gene by myricetin

to the release of cytochrome-C in the cytosol, which increases the proteolytic activation of caspase-3 and the degradation of PARP protein. The author hypothesised that myricetin caused the inactivation of Bcl-2 expression, the activation of proapoptotic protein Bad, and the translocation of Bax-induced death in HepG2 cells via the mitochondrial apoptotic route and the Akt/p70s6k1/Bad signalling pathway (Knickle et al. 2018).

Myricetin treatment of PC-3 and DU 145 prostate cancer cells reduced tumour potential by upregulating caspase-3 and caspase-9 activities and decreasing phosphorylation of ERK1/2 and Akt (Ma et al. 2019; Ye et al. 2018). Researchers evaluated myricetin's toxicity on a non-tumour cell and observed its effects on the growth, migration, and invasion of the SKVO3 cancer cell in one study. The data revealed that myricetin concentration from 0 to 40 µM increases apoptosis that inhibits oxidative stress reduces ROS levels and suppresses cancer cell growth by activating the p38/Sapla signalling mechanism (Li et al. 2022a, b). Myricetin has also induced apoptosis and autophagy in human colon cancer cells such asHT-29, HCT116, SW480, and SW620 by inhibiting the PI3K/Akt/mTOR signalling pathway (Zhu et al. 2020) (Fig. 6).

Myricetin has also been observed for its cytotoxicity, cell cycle inhibition, and DNA damage through a dose-dependent way in human papillary thyroid cancer (HPTC) cells by upregulating the caspase cascade and Bax/Bcl2 ratio and also initiated the apoptosis-inducing factor by changing the potential of mitochondria membrane (Ha et al. 2017). Apart from the above anticancer activities, the bio-molecules have diverse anticancer effects on the cell line as given in Table 1.

Antiinflammatory and antioxidant activities of myricetin

Myricetin, a natural bioactive component, controls numerous molecules involved in inflammatory reactions, such as cytokines and enzymes. The scientific community has done several investigations and observations to discover myricetin's antiinflammatory action. It can obstruct the production of pro-inflammatory mediators by initiating Nrf2 mediated HO-1 expression and suppressing the NF-κB and STAT1 in LPS-stimulated RAW264.7 macrophages (Oh et al. 2020; Gupta et al. 2020).

In one study, myricetin decreased the synthesis of interleukin-12 via lowering the macrophase's binding capabilities to nuclear kappa-B and preventing interleukin-1 (IL-β1) production in SW982 human synovial sarcoma cells (Lee and Choi 2010; Kang et al. 2005). By altering the gut microbiota associated with faecal butyric acid and preserving the integrity of the gut barrier, myricetin also aids in the reduction of hepatic lipid production and inflammation (Sun et al. 2021). Treating rat wounds with myricetin helps elevate the pro-inflammatory factors such as cytokines, IL-1β, TNF-α, and macrophage CD68, which are essential in promoting lesion healing (Elshamy et al. 2020).

Similarly, in TNF-α-activated ECV304 cells, the myricetin molecule inhibited the expression of TNF-α-mediated NF-κB by downregulating the inhibitor-κB kinase (IKK) (Tsai 1999). Myricetin treatment of HepG2 cells results in the downregulation of several inflammatory molecules such asiNOS, COX-2, IL-2 and IL-6, TNF-α, and IFN-γ in a dose-dependent manner (Zhou et al. 2019). In vivo research using mice treated with myricetin

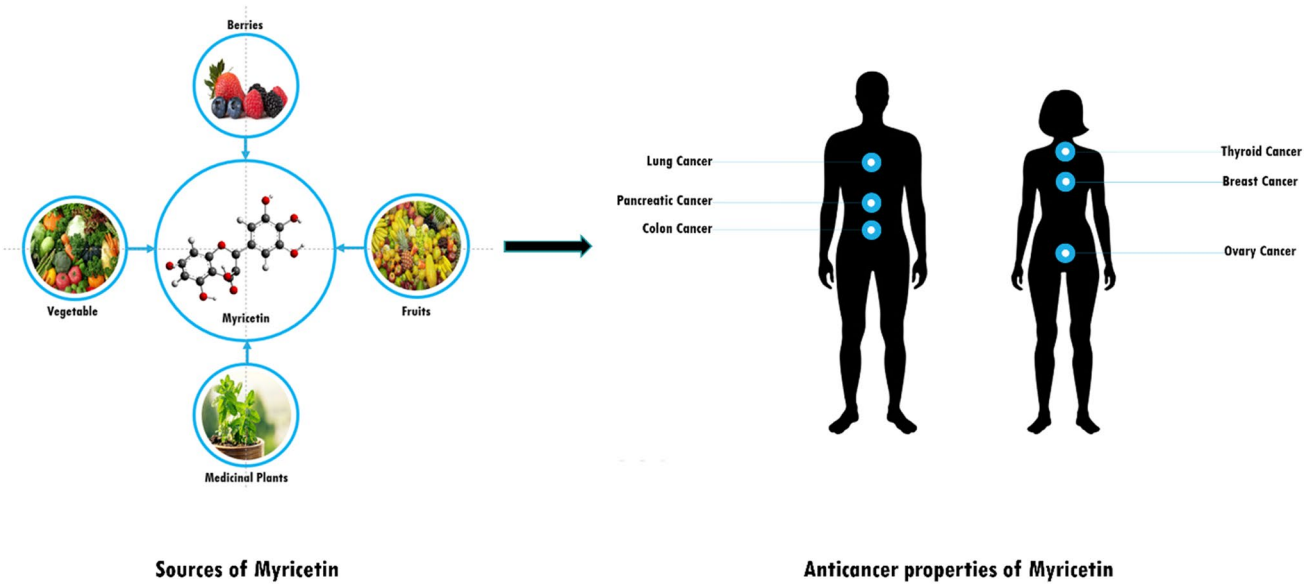

Fig. 6 Anticancer properties of myricetin against various cancers

Table 1 Effect of myricetin on various cancer cell line

Type of cancer	Cell line/animal model	Effects	Mechanism	Conc	In vitro/in vivo	Reference
Prostate cancer	Animal model (PC 3)	Cancer growth inhibition	Epithelial-to-mesenchymal transition inhibition	25 mg/kg every 2 days for 40 days	In vivo	Li et al. (2014)
Oesophageal cancer	EC9706	Induces apoptosis	The expression levels of survivin, cyclin D1, and Bcl-2 were downregulated to induce apoptosis which is further enhanced by upregulating the expression of caspase-3 and p53	Range of concentration of myricetin (0 µM, 25 µM, 50 µM, 100 µM)	In vitro	Wang et al. (2014)
Ovarian cancer	A2780, OVCAR3	Induces apoptosis	Induces apoptosis by upregulating proapoptotic regulating proapoptotic protein Bax and cleaved caspase-3 and downregulating antiapoptotic protein Bcl-2	50 µmol	In vitro	Xie and Zheng (2017)
Breast cancer	Wistar rat	Increased antioxidant level	Increased the antioxidant levels in plasma, erythrocyte lysate, and breast tissue and was effective in preventing the oxidative damage induced by the carcinogen DMBA	50–200 mg/kg	In vivo	Jayakumar et al. (2014)
Hepatocellular carcinoma	HepG2	Induces apoptosis	Myricetin decreases the cell viability by upregulating the ratio of BAX/BCL2 ratio, activation of caspase-3, caspase-9, and cytochrome C release	50 µM and 100 µM	In vitro	Kim et al. (2014)
Breast cancer	MCF-7	Induces apoptosis	It induces apoptosis by increasing Bax and caspase activation. Cell viability was suppressed via PAK1/MEK/ERK signalling pathway	80 µM	In vitro	Jiao and Zhang (2016)
Human BCBM	4T1	Induces apoptosis	Reduced the cell viability of MDA-Mb-231Br cells	20–40 µM	In vitro	Lee et al. (2012)
Prostate cancer	PC3, DU145	Induces apoptosis	Induces apoptosis by upregulating both cleaved caspase-3 and caspase-9 and by inhibiting ERK1/2 and Akt phosphorylation	47.6 µM and 55.3 µM	In vitro	Conley-LaComb et al. (2013) and Lee and Choi (2010)
Pancreatic cancer	MIA PaCa-2	Induces apoptosis	Induces apoptosis both in vitro and in vivo by releasing cyto-c and upregulating the and S2-013 expression of Cyt-3 and Cyt-9	12.5–200 µM	In vitro	Phillips et al. (2011)

Table 1 (continued)

Type of cancer	Cell line/animal model	Effects	Mechanism	Conc	In vitro/in vivo	Reference
Thyroid cancer	SUN-790 HPTC	Induces apoptosis	Induces apoptosis through mitochondrial disrupting mitochondrial function cells, which results in the release of AIF and activation of caspases (caspases 3, 8, 9 and PARP-1) change Bcl-2/Bax ratio and AIF release	Concentrations ranging from 25 to 100 µM	In vitro	Ha et al. (2017)
Skin cancer	A431	Induces apoptosis	Apoptotic induction is via a change in the expression of Bcl2/Bax ratio, apoptotic damage of cancer cells via increased production of ROS and reducing mitochondrial membrane potential	20 µM	In vitro	Sun et al. (2012)
Bladder cancer	T24	Induces apoptosis	Increases growth arrest at M-phase, downregulation of cyclin B1 and cyclin-dependent kinase cdc2, decreases proliferation, decreases cell migration	Various concentrations	In vitro	Sun et al. (2012)

revealed that the severity of inflammatory lesions and tumourigenesis, which were accountable for tumour inhibition in various ways, were less severe (Zhang et al. 2017). Myricetin suppresses acute and chronic inflammation in vivo in models of xylene-induced ear oedema, acetic acid–induced vascular permeability, carrageenan-induced paw oedema, and cotton pellet granuloma. Myricetin has dramatically elevated the serum level of SOD, decreased the serum level of MDA leukocyte count, and inhibited the formation of antiinflammatory granuloma tissue (Wang et al. 2010a, b). Myricetin can inhibit oxidative stress by enhancing the activities of SOD, glutathione peroxidase GPX, CAT, malondialdehyde, GSH, and hydrogen peroxide enzymes, reducing inflammation. Similarly, myricetin also decreases inflammation by regulating the production of oxidase-dependent ROS, NADPH, by inhibiting the JAK/STAT1 and NOX2/p47(phox) mechanism (Mao and Huang 2018; Hassan et al. 2017; Qi et al. 2017). Myricetin administration in lipopolysaccharide-stimulated RAW 264.7 cells and a lipopolysaccharide-induced lung damage model resulted in the downregulation of NF-κB p65 and the elevation of NF-κB pathway, JNK, p-ERK, and p38 in MAPK signalling pathway (Bai et al. 2021). Therefore, the initial results suggest that myricetin has the potential as an antiinflammatory chemical and could be employed as a medication in future in vivo trials.

Regarding antioxidant characteristics, the low concentration of myricetin inhibits the synthesis of reactive oxygen species and shields cells from the cytotoxic action of peroxide molecules. (Barzegar 2016; Taheri et al. 2020). In a dose-dependent manner, myricetin suppressed the activity of XOD up to 50% at a concentration of $(8.66 \pm 0.03) \times 10^{-6}$ molL^{-1} showed that myricetin could inhibit the synthesis of superoxide anion (Zhang et al. 2017). Myricetin can also control hydrogen peroxide-induced DNA damage at a concentration of 100 µM in human lymphocytes (Duthie et al. 1997). Myricetin also inhibits oxidative stress-induced apoptosis via modulating PI3K/Akt and MAPK signalling pathways. It also increases the production of SOD, catalase (CAT), and glutathione peroxidase (GPx), which are all lowered by H_2O_2 treatment (Wang et al. 2010b). Myricetin treatment caused triple-negative breast cancer (TNBC) cells to undergo early and late apoptosis and necrosis caused by oxidative stress. H_2O_2 and myricetin autooxidation produce oxidative stress. In human colonocyte Caco-2 cells, myricetin also prevented the oxidative effect of H_2O_2 and protected DNA strand breaks (Duthie and Dobson 1999) (Fig. 7).

Angiogenesis and metastasis effects of myricetin

Angiogenesis is the process by which new blood cells are formed from preexisting vessels, and it plays an essential role in cancer cell proliferation in cells and organs. Therefore, considerable work is going on the natural bioactive

compound that can help inhibit the angiogenesis of the cancer cell (Huang et al. 2015; Marrero et al. 2022; Birbrair et al. 2014). In human umbilical vascular endothelial cells, myricetin activated reactive oxygen species, causing apoptosis and the cleavage of procaspase-3, which reduced cell migration, PI3K/Akt/mTOR, and tube formation (Kim 2017). In the case of hepatocellular carcinoma cell lines (HCC), myricetin plays a substantial role in the reversion of PAR1-mediated EET that inhibited the invasion, migration, vasculogenic mimicry (VM) formation, and angiogenesis by targeting Leu258 and Thr261 of PAR1 involved in VM and angiogenesis (Wang et al. 2022) (Fig. 8).

In the case of SKH-1 hairless mouse skin carcinogenesis, myricetin is critical in suppressing UV-induced B-angiogenesis. It inhibited the expression of MMP-9, MMP-13, and vascular endothelial growth factor and the activity of phosphatidylinositol-3 (PI-3) kinase (Jung et al. 2010). Similarly, myricetin downregulated the tumour promoter-induced cancer cell formation by inhibiting the direct activity of MEK, JAK1, Akt, and MKK4 kinases in skin carcinogenesis. Myricetin dramatically attenuated the ultraviolet B-induced COX-2 expression and skin tumour formation by controlling the Fyn (Kang et al. 2011). Myricetin also helps to reduce cell proliferation in JAR and JEG-3 choriocarcinoma cells by increasing apoptosis and trophoblast cell attenuation via the MAPK and PI3/AKT signalling pathways. Myricetin also increases reactive oxygen species (ROS), lipid peroxidation, glutathione depletion, and mitochondrial membrane potential loss (Yang et al. 2021). A nucleoside diphosphate kinase encoded by NM23 is essential in suppressing metastasis. As a result, myricetin reduced the expression of Bcle-2, Parp, and caspase-related proteins in a human colon cancer cell line while increasing the expression of nucleoside diphosphate kinase, PARPs, caspase-3, and caspase-9 cleavage (Attwood and Muimo 2017; Tan and Chang 2018). Myricetin also decreased the activity of the epithelial-mesenchymal transition (EMT), which is essential for metastasis, by increasing E-cadherin and decreasing vimentin (Ye et al. 2018). In the 4T1 mouse lung metastasis model, myricetin molecules at 50 mg/kg concentration reduce the size and number of tumour nodules compared to vehicles (Lee et al. 2012) (Fig. 9).

Effect of myricetin on miRNA and mRNA

Myricetin's interaction with RNAs opens new avenues for targeting various cancer cells. Micro-RNAs (miRNA) play a wide range of roles in human biological processes, illnesses, and metabolic disorders. A dysregulated miRNA impacts various signalling pathways (Lee et al. 2015). By downregulating miR-29a-3p, myricetin can provide an antiinflammatory impact against ox-LDL-induced HUVEC (Bai et al. 2021). In one study, it was observed that myricetin significantly downregulated the level of IL-1β mRNA. However, no effect was observed in the synthesis of IL-1β protein in RAW 264.7 macrophages through inhibiting gene transcription (Blonska et al. 2003). Similarly, in one of the investigations, myricetin interacted with telomere G-quadruplex TTAGGG 3 DNA in the MCF-7 human breast cancer cell line in a concentration-dependent way. It inhibited the activity of human telomerase reverse transcriptase mRNA and telomerase (Mondal et al. 2016).

Effect of myricetin on autophagy

Myricetin has a significant role in the induction of apoptosis and autophagy in the various cancer cells alone or in adjuvant form. In colon cancer cells, myricetin initiates apoptosis and autophagy by inhibiting PI3K/Akt/mTOR signalling pathway (Zhu et al. 2020). Similarly to the previous observation, myricetin affected autophagy-related proteins. It enhanced the stimulation of microtubule-associated protein 1A/1B light chain 3 (LC 3) and Beclin 1. This stimulation occurred in human breast cancer SK BR 3 cells. The apoptosis rate increased when myricetin and 3 methyladenine (3 MA) were administered simultaneously to cancer cells. The subsequent treatment of a JNK inhibitor to the cells reduced cell viability, triggered the expression of Bax, and decreased the expression of p-JNK, Bcl 2, and LC 3 II/I. Hence, these actions revealed that myricetin triggered and controlled apoptosis and autophagy in SK BR 3 cells via the MAPK pathway and JNK-mediated autophagy (Han et al. 2022a, b,). A research group observed the protective autophagy of myricetin on hepatocellular carcinoma (HCC) cells. The molecule directly linked the activation of endoplasmic reticulum stress, which boosted autophagy, as shown by the result indicating that it induced apoptosis. AGS gastric cancer cell myricetin induced apoptosis and autophagy by inhibiting the PI3K/Akt/mTOR pathway that leads to cell-protective autophagy and inhibition of cancer cell proliferation (Han et al. 2022a, b,). Researchers investigated myricetin's antihepatocellular carcinoma (anti-HCC) mechanism in one study. The researchers observed that inhibiting the expression of MARCH 1 induced autophagy and cell cycle arrest in the G2/M phase. They utilised this effect to inhibit the growth of HCC cells. In Hep3B cells, myricetin increased MARCH1 mRNA levels, whereas, in HepG2 cells, it lowered them. Thus, knocking down MARCH1 by siRNAs (small interfering RNAs) downregulates phosphorylated p38 MAPK (p-p38 MAPK) and Stat3 (p-Stat3). This downregulation reduces the viability of HCC cells. Myricetin and the autophagy inhibitor bafilomycin A1 (BafA1) significantly reduced the development of HCC cells (Yang et al. 2021).

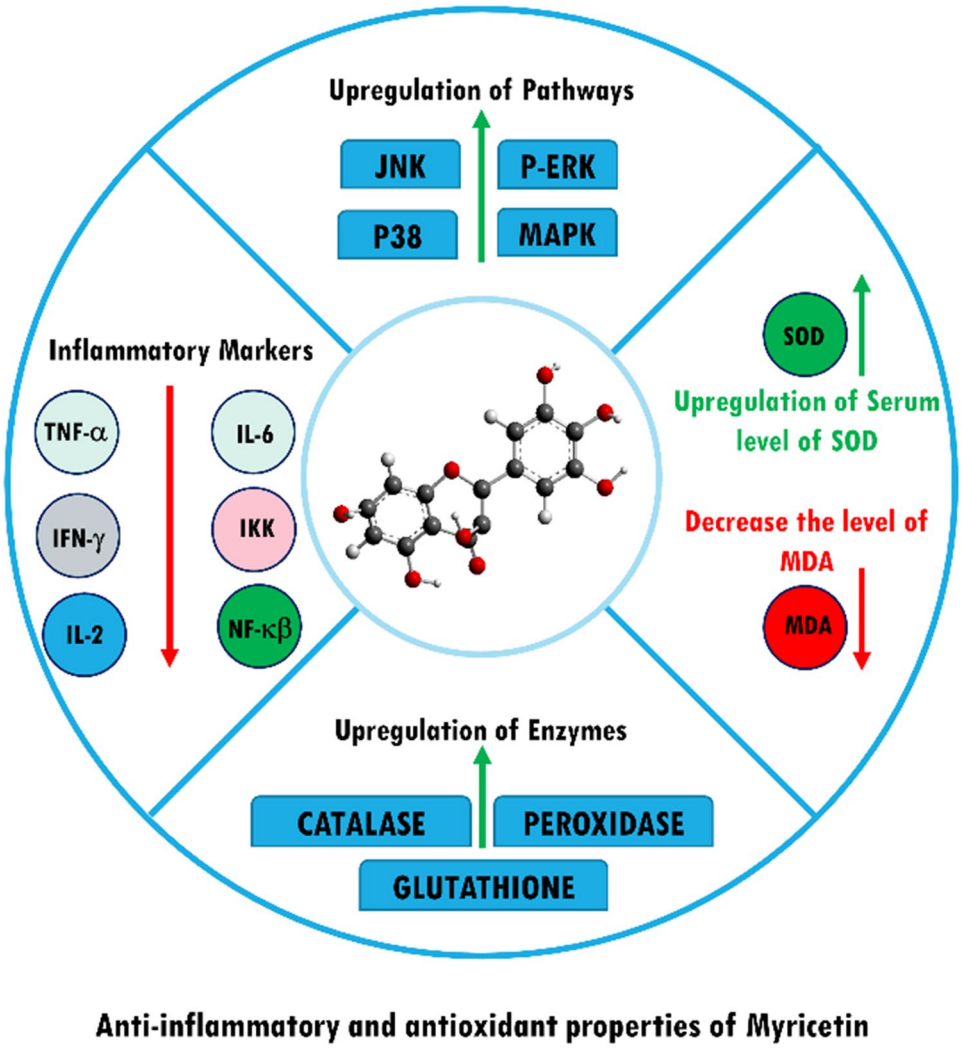

Fig. 7 Antiinflammatory and antioxidant properties of myricetin

Cucurbitacin E (CuE) and myricetin (Myr) of *Citrullus colocynthis* (L.) Schrad are essential in inhibiting cell proliferation and colony formation but increases apoptosis and cell cycle arrest in the G0/G1 phase. Moreover, the CuMy-12 combination leads to the inhibition of autophagy and commencement of the PI3K/AKT/mTOR signalling mechanism that was differentiated by a reduction in Beclin 1, AKT, and phospho-AKT, exhibiting a synergistic effect. Furthermore, CuMy-12 caused a decrease in Beclin 1, AKT, and phospho-AKT proteins, indicating inhibition of autophagy and activation of the PI3K/AKT/mTOR signalling pathway (Zhang et al. 2023).

Synergistic effect of myricetin

Myricetin is essential in various human foods, including vegetables, beverages, fruits, and other natural foods. Myricetin is well-known for its antioxidant, antiinflammatory, and antitumour properties. Numerous studies have found that cancer cells generally resist the anticancer drug cisplatin, which causes degeneration. However, myricetin exhibits more significant cell toxicity than cisplatin in cisplatin-resistant cancer cell lines, such as OVCAR-3 and A2780/CP70, while exhibiting minimal toxicity effects on the normal cell IOSE-364. Myricetin promoted intrinsic and extrinsic apoptosis and Bcl-2 family protein pathways in the standard cell line but did not initiate the cell cycle arrest. The combination of 5-fluorouracil and myricetin inhibited cell proliferation and function, initiated apoptosis, increased caspase-3 and P53 expression levels, and decreased survivin, cyclin D, and Bcl-2 expression levels, according to research on the chemosensitisation activity of the two drugs in the EC9706 cancer cell line (Wang et al. 2014).

One study found that cervical cancer cells were impacted by myricetin, methyl eugenol (MEG), and cisplatin (CP). These three medications were found to promote cell death, cell cycle arrest, and caspase-3 activity, all of which suppressed the growth of cancer cells. Combining these

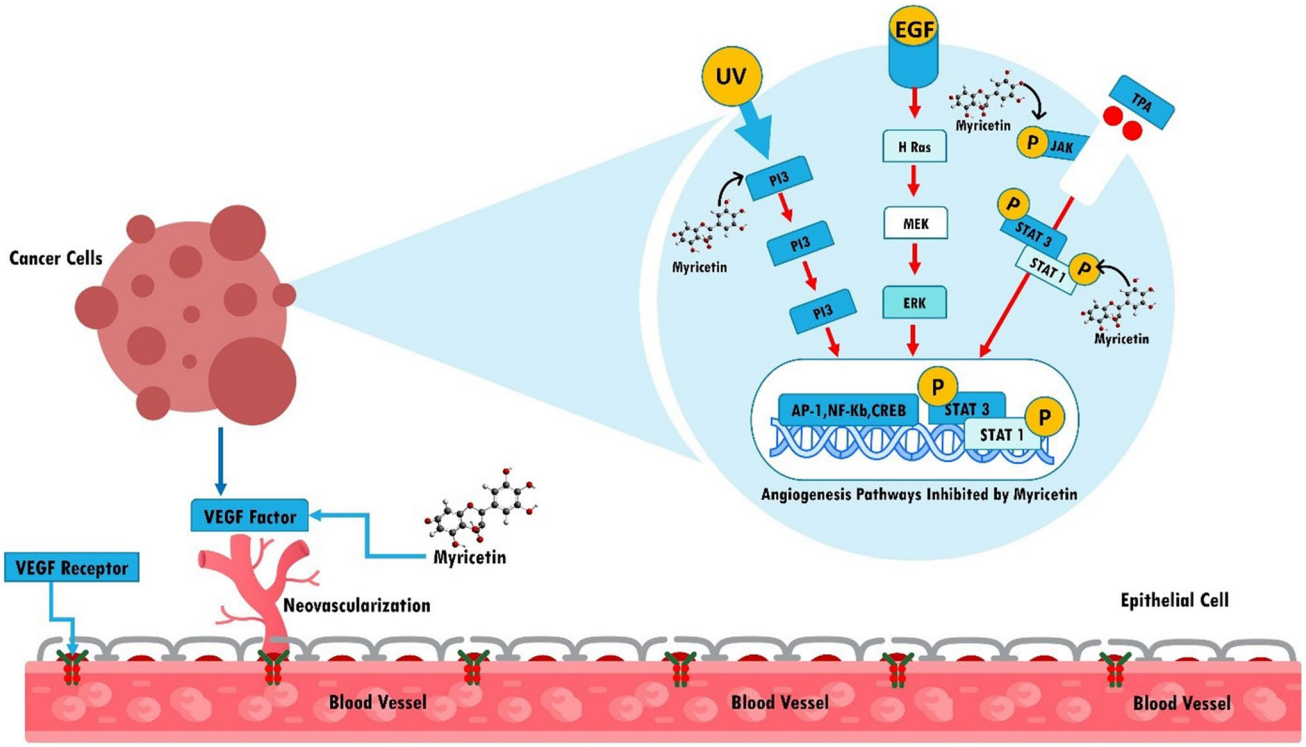

Fig. 8 Effect of myricetin on angiogenesis and vascularization process

chemicals also decreases mitochondrial membrane potential and increases the proportion of cells in the G0/G1 phase of the cell cycle (Yi et al. 2015). The prophylactic treatment of rats with myricetin for 21 days lowered the markers of inflammation, apoptosis, cardiac toxicity, and oxidative stress in the context of 5-fluorouracil's reduced cardiotoxicity. It increased the antioxidative activity (Arafah et al. 2022). In a previous study, through an MTT assay, researchers detected the apoptosis-inducing mechanisms of myricetin, myricitrin, and quercitrin in the human prostate cancer cell line PC-3. At concentrations ranging from 37.5 to 300 mol/L, the combination of myricetin and myricitrin had a strong inhibitory effect on the proliferation of cancer cells (Xu 2013). Myricetin and temozolomide decreased the

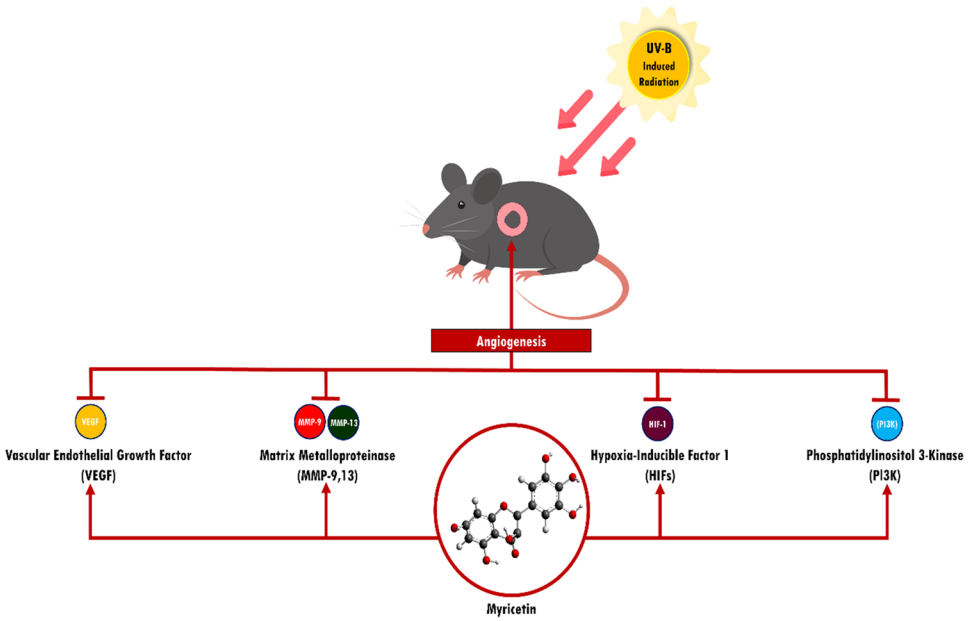

Fig. 9 Myricetin inhibiting the main angiogenesis factors

proliferation, migration, and invasion of U-87MG glioblastoma cells. However, combining myricetin and temozolomide did not demonstrate any beneficial effects. Myricetin inhibited the development of lamellipodia, focal adhesions, membrane ruffles, vasculogenic mimicry, and the phosphorylation of the ROCK2, paxillin, cortactin, PI3K/Akt, and JNK signalling pathways (Zhao et al. 2018).

Bioavailability of myricetin

Only after evaluating their efficacy, novelty, and minimum detrimental effects on organisms could the vast treasury of natural materials be utilised as pharmaceutical medications. Therefore, the solubility of biomolecules through diverse physiological processes is crucial for their efficacy. Myricetin is less hydrophilic yet significantly soluble in organic solvents such as acetone, dimethylformamide, tetrahydrofuran, and dimethylacetyl chloride (Chang et al. 2012). Various strategies, such as nanotechnology, are now being developed to enhance the bioavailability of myricetin (Xia et al. 2020). In one study, rats were given myricetin orally and intravenously in dose-dependent ways. It evaluated the bioavailability in the blood, and myricetin was found less orally due to inadequate absorption of the molecule (Dang et al. 2014). Solid lipid nanoparticles with about 30 µmol of myricetin were used against HT-29 cells, and colony formation, expression of Bax, Bcl2, and apoptosis-inducing factor were measured. In the HT-29 cells, the nano-loaded myricetin significantly boosted apoptosis, Bax, and AIF expression and decreased Bcl2 and MMP (Alidadi et al. 2022). The liposomal nanoformulation of myricetin not only increases the molecules' bioavailability but also decreases the pro-oxidant properties. Accordingly, the zebrafish embryo showed an effect of nanocapsulated myricetin formulation, in which the chemical increased antioxidant activity against oxidative stressors (Agraharam et al. 2021). Myricetin microemulsion (MYR-ME) is a mixture of myricetin, Cremphor, Tween-80, Transcutol, WL1349, and distilled water that improves the molecule's bioavailability by more than 1225 times compared to water, allowing for greater oral efficacy. The MYR-ME has potentially enhanced the antioxidative and antiproliferative activity against HepG2 human cancer cells and further increased 14.43 fold oral bioavailability of myricetin after oral administration of the emulsion to Sprague Dawley rats (Guo et al. 2016). The TPGS-modified liposome nanocarriers also have the potential to deliver myricetin via the oral route and increase the pharmaceutical efficacy of the molecules (Thant et al. 2021). Mesoporous silica nanoparticles treated with folic acid and filled with myricetin were utilised to treat non-small cell lung cancer. (NSCLC). Under in vitro environments, FA-conjugated nanocarriers improve the absorption of myricetin in lung cancer, thereby decreasing colony formation cell viability, dramatically enhancing apoptosis, and upregulating the expression of caspase-3 and PARP (Song et al. 2020). Myricetin-loaded NLCs and DXT induce apoptosis in MDA-MBA231 breast cancer cells by decreasing survivin, cyclin B1, and Mcl1 antiapoptotic genes and augmenting Bax and Bid proapoptotic proteins (Maroufi et al. 2020).

Challenges in using myricetin as a drug

Plant metabolites have a vast contribution to the progress of pharmaceutical cancer drug development. However, most bio-products always have challenges in using as safe drugs and optimise their optimisation. In the case of the bioactive molecule myricetin, it has shown a wide variety of anticancer activity against several cancer cell lines. However, it also poses a challenge for utilisation as a drug due to its pleiotropic nature and variability. Myricetin has multiple targets in signalling pathways. These targets can encumber tumour progression. They can also prevent metastasis and induce cell cycle inhibition. Additionally, myricetin can have other effects. The main challenge of the molecules is their poor bioavailability and solubility. This decreases their chemotherapeutic application. This is particularly true for large-scale utilisation in aqueous solutions. Furthermore, bio-molecule sensitivity against various abiotic factors, such as light and heat, can lead to their degradation and, consequently, the loss of their bioactivities (Albuquerque et al. 2021). Some studies have also limited the use of myricetin due to its toxic nature towards the biological cell. One of the reports observed that molecules above 450 µM lead to cellular damage in isolated guinea pig enterocytes (Semwal et al. 2016; Canada et al. 1989). Another limitation of the clinical use of myricetin is the lack of research on aspects of their route for administration, exact formulation, and doses for various types of cancer. It combines the administration of this drug with other bioactive compounds (Imran et al. 2021). The clinical trial research on myricetin molecules is minimal. However, some clinical survey suggests that the consumption of these molecules assist in the low incidence of prostate cancer, and regular consumption of myricetin with other flavonoids bio-molecule by menopausal females helps to reduce the risk of coronary heart disease.

Future perspective

Future research on myricetin for cancer treatment could concentrate on addressing its current limits and downsides and expanding its potential therapeutic applications. Some possible research areas are enhancing bioavailability, targeted delivery, clinical trials, combination therapy, and mechanisms of action. New formulations and administration

methods may improve myricetin's solubility, bioavailability, and efficacy. Researchers could investigate using targeted delivery systems for myricetin to increase specificity and decrease the likelihood of non-specific targeting of healthy cells (Afroze et al. 2020). Large-scale clinical trials are required to examine the safety and efficacy of myricetin in people, particularly in connection to specific forms of cancer. Researchers could investigate the potential benefits of combining myricetin with other cancer treatments, such as chemotherapy or radiation therapy, to improve their efficacy and lessen side effects (Albuquerque et al. 2021). Myricetin's mechanisms of action on cancer cells, including its impact on specific signalling pathways and biological processes, require additional research.

Conclusion

Cancer is a multifaceted disease, and the genesis and progression of the disease involve simultaneous modulation of multiple biological pathways responsible for the growth, survival, and proliferation of cells. The treatment of cancer must target signalling cascades. Myricetin is a plant flavonoid. It is present in wine, tea, and medication. Myricetin affects cancer cell processes. Since it blocks several proteins and signalling pathways that promote cell proliferation and inhibit apoptosis, myricetin has been a promising cancer chemopreventive in numerous cancer models. It has remarkable antitumour efficacy since it also causes cell cycle arrest, prevents cell invasion and migration, and triggers autophagy and necroptosis. However, it has limited bioavailability, non-specific targeting, lack of clinical data, potential side effects, and interactions with other drugs. More research is needed to understand its safety and effectiveness and address its potential limitations and drawbacks. Future research on myricetin for cancer treatment could concentrate on bioavailability enhancement, targeted delivery, clinical trials, combination therapy, and action mechanisms. These investigations will aid in advancing knowledge of the compound's potential and identifying methods for overcoming its current limits.

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Data availability All the generated data is summarised in the form of supporting references.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no competing interests.

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