Natural Flavonoids: Myricetin and Its Derivatives as Emerging Therapeutics, SAR and Molecular Target Analysis

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Abstract

Myricetin is a flavonol found naturally with a high degree of polyhydroxylation, with a very high antioxidant activity (ORAC 4.3 units). It has become a polypharmaceutical therapeutic candidate in cancer therapy, neurodegenerative, metabolic, and heart disease. The review is a synthesis of the structure-activity relationships (SAR) of myricetin and its derivatives, describing the key role of the pyrogallol B-ring moiety in the provision of a 60 % antioxidant ability enhancement. Specific structural changes, such as methylation, glycosylation, acylation, and semi-synthetic heterocyclic conjugation, result in compounds with 50-100-fold potency increases and better metabolic stability, though with a reduced antioxidant activity at orthodox assays. Molecularly, myricetin exhibits multitarget kinase engagement (PI3K, Akt, mTOR, JAK1, Src), context-dependent MAPK modulation, robust NF-κB/STAT3 suppression, and Nrf2/ARE antioxidant response activation. Mechanistically, myricetin induces bifocal cell cycle arrest (G0/G1 via cyclin D1 downregulation and p21/p27 accumulation; G2/M via cyclin B1 suppression), intrinsic and extrinsic apoptotic pathway activation, and ROS-dependent pro-death signaling in transformed cells. Preclinical studies show that it has great efficacy in triple-negative breast cancer (IC_{50} = 22.70-51.43 µg/mL; selectivity index = 63.64), hepatocellular carcinoma (92% tumour reduction), and Alzheimer's disease models, where tau phosphorylation is suppressed, and synaptic proteins are restored. However, myricetin has extremely low oral bioavailability (9.62-9.74%), chemical instability ($t_{1/2}$ = 0.55 hours), and extensive Phase II metabolism, which requires sophisticated delivery plans. Nano formulations have realized 4-25-fold enhancements in bioavailability. This review would make myricetin a scientifically proven natural lead compound with significant translational potential, provided that optimization of bioavailability and rational derivatives are done systematically.

Keywords - Myricetin, Structure activity relationships, Multitarget kinase inhibition, Nanoformulation strategies, Natural product therapeutics

1. Introduction

1.1 Overview of Natural Flavonoids

The most numerous dietary polyphenolic compounds are the flavonoids, which occur in over 10,000 different species, built on a typical C_6-C_3-C_6 carbon structure. The seven major subclasses of flavones, flavonols, flavanones, flavanols, anthocyanins, and isoflavones have a different pharmacological profile. Myricetin, a flavonol with unique polyhydroxylation (six phenolic hydroxyl groups), exhibits a greater antioxidant activity (ORAC 4.3 units). Regular intake of dietary flavonoids is epidemiologically linked with lower cardiovascular mortality, better metabolic outcomes, and slower development of neurodegenerative disease, as the examples in Mediterranean dietary trends. However, systemic flavonoids exist as Phase II metabolites (glucuronides, sulfates, methylated form, etc.) in the vast majority, which is why metabolite pharmacology research and bioavailability optimisation are required to obtain a therapeutic effect (Duarte et al., 2025; Wang et al., 2025).

1.2 Importance of Myricetin and Its Derivatives in Therapeutics

Myricetin (1A), with the molecular formula $C_{15}H_{10}O_8$ and a molecular weight of 318.24 g/mol, is chemically named 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one. Myricetin has become a versatile first-choice drug in a wide range of disease types. An increase in antioxidant capacity to 60% is conferred by the presence of the pyrogallol B-ring moiety (3 consecutive hydroxyl groups at 3', 4', and 5'). Myricetin exhibits strong anti-hepatocellular carcinoma, triple-negative breast cancer, Alzheimer's, Parkinson's, type 2 diabetes mellitus, and cardiovascular disease (Liu et al., 2020a; Mendes et al., 2015).

Myricetin derivatives have a pharmaceutical use because of their ability to undergo strategic structural optimisation to give higher selective activity. Methylated analogs (isorhamnetin, laricitrin, syringetin) (fig. no. 1: 2A, 3A, 4A) have the opposite and paradoxically better metabolic stability and selective bioactivity curves, even though direct antioxidant potency is reduced in traditional in vitro tests. Semi-synthetic heterocyclic conjugate is 50-100-fold more potent (e.g., telomerase inhibitor compound 6d: IC_{50} = 0.91 μM vs. parent myricetin). Glycosylated derivatives (myricitrin) (fig. no 1: 5A) do not have direct antioxidant properties but ensure better bioavailability systemically due to transporter-mediated intestinal absorption and greater gastrointestinal stability (Xue et al., 2015).

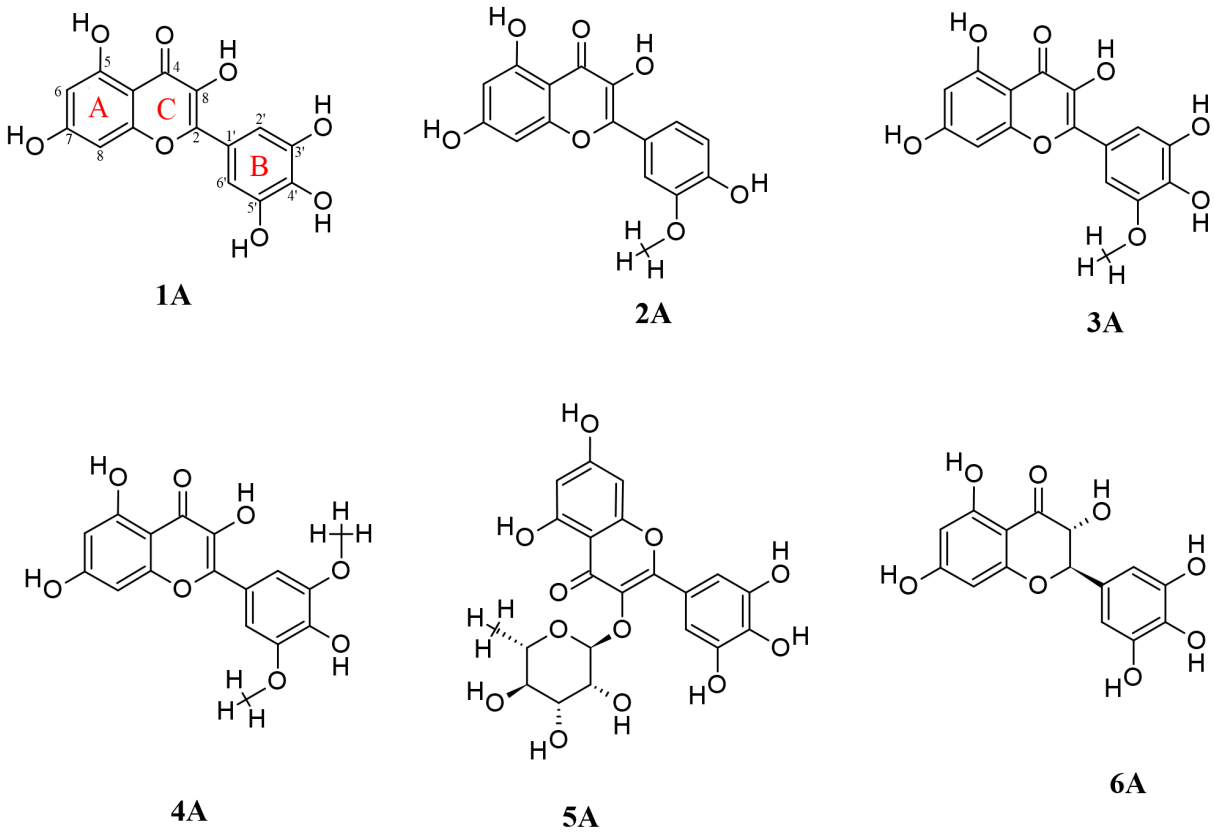

Fig. no. 1: Structure of Myricetin derivatives

1.3 Scope and Objectives of the Review

This is an in-depth review synthesising the structure activity relationship, molecular target, and therapeutic potential of myricetin in oncology, cardiovascular, metabolic, and neurodegenerative diseases. We combine SAR concepts with molecular docking, cellular validation, and clinical translation pathways with a focus on bioavailability improvement via nano formulations, derivative optimisation, and mechanistic combination therapies to take myricetin-based therapeutics to the clinic.

2. Chemical Structure and Properties of Myricetin

2.1 Flavonoid Backbone and Hydroxylation Pattern

Myricetin (fig. no. 1: 1A) is a flavonol subclass, which is characterised by a C_6-C_3-C_6 carbon framework. It consists of two phenolic rings of benzene (A and B) linked to each other through a three-carbon heterocyclic pyran ring (C ring). The highly essential critical 2,3-double bond conjugated to a 4-keto group enhances the planarity of the molecule, which makes the A-ring and C-ring well coplanar to each other, thereby making it biologically active (Myricetin CID 5281672 - PubChem, n.d.).

A-Ring (Resorcinol moiety): 5-OH and 7-OH
C-Ring: 3-OH (flavonol defining feature)
B-Ring (Pyrogallol moiety): 3'-OH, 4'-OH, 5'-OH (Myricetin CID 5281672 - PubChem, n.d.)

2.2 Structural Features Enabling Biological Activity

The trihydroxylated B-ring aromatic structure forms an electron-rich environment with several hydrogen bonding positions and a decreased energy of dissociation of hydrogen atom abstraction, which explains excellent antioxidant activity directly. Intramolecular hydrogen bonding is what stabilises a near planar geometry of the molecules, which is essential in keeping the molecules planar to bind to target proteins and interact with radicals. The conjugation of the 2,3-double bond with the 4-carbonyl group is key to the best antioxidant activity, as demonstrated by the case of dihydromyricetin (6A) (saturated C2 -C3), which demonstrated severely reduced antioxidating ability despite an antioxidant capacity that is paradoxically increased (Semwal et al., 2016a).

2.3 Physicochemical Properties and Biopharmaceutical Barriers

Myricetin exhibits moderate lipophilicity (LogP = 1.21-1.34 at pH 7.4), the six polar hydroxyl groups of the compound equalizing its lipophilicity. Myricetin has a pKa of 6.63 ± 0.09, which means that about 50 % of myricetin molecules carry a negative charge at physiological pH, which has a strong influence on membrane permeability and protein binding. However, myricetin has disastrous chemical instability: 71.4 % loss of intensity in an hour at the UV irradiation ($t_{1/2}$ = 0.55 hours at pH 7.4), made worse by low aqueous solubility (less than 0.1 mg/mL at neutral pH) and low intrinsic dissolution rate (IDR = 11.66 ± 0.82 μg/min/cm²). These biopharmaceutical barriers present great challenges to oral bioavailability and thus require novel delivery systems and formulation methods (Myricetin CID 5281672 - PubChem, n.d.; Yao et al., 2014).

3. Structure Activity Relationship (SAR) of Myricetin

3.1 Role of hydroxyl groups in antioxidant and anti-inflammatory activity

The hierarchical importance of ring specific hydroxyl groups is outlined in the analysis, **B-ring pyrogallol moiety** is the primary determinant (97.4-97.6% LDL oxidation inhibition at 10-20 μM through the dominant 4'-OH group's hydrogen-bonding stabilization of phenoxyl radicals) due to its role as the primary strong hydrogen bond with the phenoxyl radical, **A-ring** 5,7-dihydroxyl resorcinol moiety is a moderate determinant, and **C -ring** 2,3-conjugation of the phenoxyl. The B-ring catechol moiety demonstrates unprecedented anti-inflammatory activity through NF-κB inhibition (IκBα stabilization, p65 nuclear translocation prevention) and suppression of STAT3 through JAK1 inhibition (Agraharam et al., 2022a; Kumamoto et al., 2009a).

3.2 Effects of modifications on A, B, and C rings

3.2.1 B-Ring Modifications: Three important derivatives of the paradoxical principle of SAR are isorhamnetin (2A) (3-5-fold superior oral bioavailability through Phase II resistance), syringetin (4A) (46.1 % lipofuscin reduction compared to 33.1 % with myricetin in anti-aging studies), and laricitrin (3A) (selective MCF-7 breast cancer enhancement with retained BCRP transporter inhibition).

3.2.2 A-Ring Modifications: The 5,7-dihydroxy-resorcinol motif is preserved and contributes to maintaining molecular planarity and controlling electronic dispersion. Modification of the compound’s hydrophilicity occurs through glycosylation, as seen in myricitrin (5A), or by acylation at the C7 position, which facilitates recognition by membrane transporters and consequently influences its bioavailability.

3.2.3 C-Ring Modifications: A 2,3-double bond in conjunction with a 4-carbonyl group is a structural nucleus that is necessary to maintain the conformation of the ring; any alterations of these characteristics are unfavourable to activity. On the other hand, the C3 hydroxyl group can be subjected to glycosylation, acylation, or methylation, which does not trigger constant loss of bioactivity. C-ring saturation, as in dihydromyricetin (fig. no. 1: 6A), has a significant antioxidant effect but can, under specific conditions, enhance specific treatment effects due to effects on metabolism (Chmiel & Stompor-Gorący, 2022; Rodriguez-Garcia et al., 2025).

3.3 SAR insights from synthetic and natural derivatives

Semi-synthetic myricetin analogs have been developed using systematic SAR studies to enhance the potency, selectivity, and pharmacokinetics. Introduction of nitrogen-based heterocycles like piperazine at the C-3' and C-5' positions provides 325-fold improvement in aqueous solubility, and a 22-96-fold enhancement in anticancer activity. Isoxazole derivatives with intrinsic bioactivity can be used to enhance drug-like parameters. Direct antioxidant capacity is sacrificed in naturally glycosylated myricitrin, which has non-inferior bioavailability in the system through recognition by the hexose transporters SGLT1/GLUT2. Phosphorylation metabolites, especially myricetin-3-O-sulfate, demonstrate a 4-7-fold better inhibition of hepatic transporters, which produces specific pharmacologically active species (Xue et al., 2015).

3.4 Impact of glycosylation, methylation, and other modifications

3.4.1 The Glycosylation Paradox: Myricitrin evidences significantly lower in-vitro DPPH radical scavenging but provides exceedingly high levels of myricetin equivalents in tissues due to increased gastrointestinal stability and transporter-mediated absorption through the SGLT1/GLUT2, providing excellent systemic bioavailability (Maronpot et al., 2015).

3.4.2 Phase II Metabolites as Active Compounds: Myricetin-3'-sulfate is a potent hepatic organic anion transporter inhibitor, suggesting the formation of different pharmacologically active products during metabolism (Almatroodi & Rahmani, 2025).

3.4.3 Acylation Strategy: Monopropionyl (LogP 2.21 ± 0.16) and monooctanoyl (LogP 2.76 ± 0.29) esters increase lipophilicity 7-26-fold at the cost of aqueous solubility, which positively impacts membrane permeability, transcellular absorption, and intracellular accumulation, a beneficial trade-off with poorly soluble compounds (Y. Chen et al., 2019).

3.4.4 Semi-Synthetic Heterocycle Conjugation: Isoxazoles, thiadiazoles, and quinazolinones increase the anti-tobacco mosaic virus, Xanthomonas oryzae (EC_{50} = 12.9-42.7 μg/mL) and antiviral activity, respectively. These alterations bring about 50-100-fold potency changes in the form of extra hydrogen-bonding and hydrophobic interactions, with the core myricetin pharmacophore being retained (Y. Chen et al., 2019).

4. Molecular Targets and Mechanisms of Action

4.1 Kinase Interactions and PI3K/Akt/mTOR Pathway

4.1.1 Direct kinase inhibition: Direct kinase inhibition, Myricetin interacts with various kinases, such as PI3K, Akt, mTOR, MEK1, Raf, JAK1, and Src family members, through both ATP-competitive binding and

noncompetitive binding. Myricetin inhibited PI3K and Akt phosphorylation (10-25 μM concentrations) in dose dose-dependent manner in oncogenic cell lines, disrupting downstream mTOR signalling, decreasing anti-apoptotic protein translation (Bcl-2), increasing pro-apoptotic Bax/Bcl-2 ratios, and activating LC3-II -II/LC3-I autophagy markers of protective autophagy before apoptosis (Javed et al., 2022).

4.1.2 Nanoemulsion enhancement: Myricetin as a nanoemulsion (Myr-NE) achieves 2.5-fold lower IC_{50} values in triple-negative breast cancer cells and increases inhibition of phosphorylated Akt and mTOR, which is directly proportional to bioavailability and efficacy. Myr-NE (25 mg/kg) is found to induce the same tumour suppression as 50 mg/kg free myricetin in xenograft models, and this is the quantitative pharmacokinetic-pharmacodynamic evidence that formulation enhancements translate to better in vivo performance (Sharma et al., 2024).

4.2 MAPK and Transcription Factor Modulation

4.2.1 Context-dependent MAPK effects: Myricetin selectively activates or suppresses the MAPK cascade, inhibiting ERK1/2 and MEK1 in a noncompetitive manner, which is better than MEK1 inhibitor PD098059, and at the same time enhancing stress-responsive JNK and p38 phosphorylation. Myricetin also shows a cell-type-specific regulatory ability by paradoxically inhibiting the p38 MAPK in the Alzheimer's disease models (Javed et al., 2022).

4.2.2 NF-κB pathway suppression: NF-κB is expected to be activated by peptidoglycan and TNF-α via IκBα phosphorylation (Ser32/36), which translocates p65/p50 nuclear heterodimers. Myricetin (15 μM) prevents IκBα phosphorylation in cardiomyocytes and ensures cytoplasmic retention of NF-κB and prevents pro-inflammatory gene expression (TNF-α ↓89.4%, IL-6 ↓76.6%, COX-2, iNOS) (M. Chen et al., 2020).

4.2.3 STAT3 and JAK1 targeting: Myricetin (IC_{50} = 10.5 μM) is a superior direct inhibitor of JAK1 compared to quercetin (16 μM) and kaempferol (21.5 μM), and this prevents phosphorylation of STAT3 at Tyr705, thus inhibiting transcription of pro-survival proteins (Bcl2, Bcl-xl, Mcl-1) and pro-growth factors (cMyc, cyclinD1), and pro-angiogenic VEGF (Kumamoto et al., 2009b).

4.2.4 Nrf2/ARE antioxidant response pathway: Myricetin caused Nrf2 nuclear accumulation and phase II detoxifying enzymes under oxidative stress (heme oxygenase-1, NQO1, GCLC/GCLM, SOD1/SOD2), thus increasing the cellular antioxidant defence system (Imran et al., 2021).

4.3 Metabolic Enzyme Inhibition

4.3.1 α-Glucosidase and α-amylase: Myricetin is a competitive inhibitor of α-glucosidase (IC_{50} = 17.78 ± 1.75 μM) with a 58-fold potency in comparison with acarbose (1,037.6 ± 189.9 μM). This strength indicates the high concentration of hydrogen-bonding affiliations that its several hydroxyl groups offer, which block catalytic turnover, and consequently decrease post-prandial uptake of glucose (Imran et al., 2021; Semwal et al., 2016b).

4.3.2 Xanthine oxidase inhibition: Myricetin causes competitive binding to xanthine oxidoreductase, which suppresses uric acid formation and ROS production. Myricetin is not as potent as quercetin, but as an XOR inhibitor, it is also functionally important in the prevention of gout and the reduction of hyperuricemia (Agraharam et al., 2022b; Imran et al., 2021; Semwal et al., 2016b).

4.3.3 COX-2 and iNOS suppression: NF-κB and AP-1-mediated transcriptional suppression, enhanced by post-translational stabilisation, inhibits COX-2 expression, resulting in a decrease in prostaglandin E2 production and production of inflammatory mediators. Simultaneously silencing iNOS inhibits the formation of nitric oxide and the nitrosative stress (Lee & Lee, 2016).

4.4 Downstream Cellular Effects

4.4.1 Cell cycle arrest and proliferation suppression: Myricetin induces G0/G1 arrest by inhibiting cyclin D1 downregulation expression by inducing NF-κB/STAT3 inhibition, up-regulating CDK inhibitors $p21^{WAF1/CIP1}$ and $p27^{KIP1}$, and inhibiting retinoblastoma phosphorylation. It also enhances G2/M arrest through cyclin B1, Cdc2-inhibitory phosphorylation of Cdk2 and p53/p21 cascade (Javed et al., 2022; Kumamoto et al., 2009a).

4.4.2 Apoptosis induction: Bax up-regulation and Bcl-2 down-regulation activate intrinsic mitochondrial apoptosis, causing an outer mitochondrial membrane permeabilisation with release of cytochrome c, formation of Apaf-1/caspase-9 apoptosomes, and cleavage of substrates by caspase-3, including PARP, fragmentation of DNA, and apoptotic bodies. Sensitisation to TRAIL or Fas ligand stimulates extrinsic pathways that augment caspase-8 in a downstream apoptotic commitment (Kumamoto et al., 2009a; Lotito & Frei, 2006).

4.4.3 Autophagy activation: mTOR inhibition causes autophagic repression, enhanced conversion of Beclin-1, LC3-II/LC3-I, and Atg5 expression, and p62 turnover via the lysosomal degradation cascade. Protective autophagy indeed suppresses apoptosis, but too much autophagy or the inhibition of lysosome fusion (e.g., chloroquine co-inhibitor) actually increases apoptotic commitment (Kumamoto et al., 2009a; Lotito & Frei, 2006).

4.4.4 Context-dependent ROS modulation: In normal or healthy cells, myricetin is a potent antioxidant because of direct radical scavenging and antioxidant enzyme up-regulation by Nrf2/ARE. Conversely, myricetin enhances the generation of ROS by amplifying the pro-death signalling pathways by stimulating mitochondrial dysfunction, activation of NADPH oxidase, and redox cycling in malignant cells (Imran et al., 2021; Lotito & Frei, 2006; Semwal et al., 2016b).

5. Therapeutic Potential and Preclinical Applications

5.1 Oncology: TNBC and Hepatocellular Carcinoma

5.1.1 Triple-negative breast cancer (TNBC): Myricetin has significantly better potency (IC_{50} = 22.70-51.43 μg/mL) and a remarkable selectivity index (SI = 63.64 versus cisplatin's 0.23), which means it has much less normal cell toxicity. Myricetin (25mg/kg) formulated as nano nanoemulsion shows tumor suppression comparable to 50 mg/kg of the free form of myricetin in mouse xenografts via multifactorial effects, which include impeding PI3K/Akt/mTOR cascade, enhancing the reactive oxygen species in transformed cells, activating G0/G1 phase arrest by p53/p21, and preventing NF-κB signaling (Knickle et al., 2018).

5.1.2 Hepatocellular carcinoma and liver cancer stem cells (LCSCs): Controlled-adverse-event (CAM)-models show a dose-dependent tumor decrease (92%→21% at 200 μg) and a reduction in tumor diameter (5.44 ± 1.56 mm → 2.17 ± 0.29 mm) Myricetin, in its mechanist action, targets the stemness markers (Sox2, Oct4, Nanog, ALDH1A1) and reverses the process of epithelial-mesenchymal transition

(down-regulation of SLUG/TWIST1 and the restoration of the E-cadherin), and activates two apoptotic pathways. Ironically, the autophagic blockage increases the apoptosis process with the introduction of chloroquine (Li et al., 2019).

5.2 Neurodegenerative diseases

5.2.1 Alzheimer's disease: Myricetin inflicts a dramatic cognitive boost in 3xTg transgenic mice, which is credited to the inhibition of tau phosphorylation through the inhibition of GSK-31/ERK1/2, reinstatement of synaptic proteins (SNAP25, synaptophysin, PSD95), mitochondrial rehabilitation (enhanced Mfn1 and Mfn2), and alleviation of oxidative stress indicators (reduced ROS, 4-HNE) (Liu et al., 2020b).

5.2.2 Parkinson's disease: MPTP-induced models demonstrate the recovery of motor function, which is confirmed by the protection of dopamine neurons, the restoration of neurons with tyrosine hydroxylase plus (MO) that has been developed in the substantia nigra, inactivation of GSK-3β (Ser9), reduction of /α-synuclein accumulation through ferroptosis inhibition, and maintenance of dopaminergic markers (TH, VMAT2) (Gu et al., 2024).

5.2.3 Cerebral ischemia-reperfusion: Pretreatment with myricetin-3-glucoside decreases the volume of infarcts and neurological severity scores through Bax/Bcl-2 anti-apoptotic pathway remodelling, inhibition of pro-inflammatory cytokines, and preservation of blood-brain barrier integrity (preservation of ZO-1, claudin-5, β-catenin) and BDNF/TrkB signalling (Liu et al., 2020c).

5.3 Metabolic and Cardiovascular Disorders

5.3.1 Type 2 diabetes mellitus: Myricetin is a selective, glucose-dependent insulin secretagogue that uses the cAMP-PKA-Epac2 pathway and is independent of ATP, which reduces the risk of hypoglycaemia. Isolated mouse islets exhibit tripled insulin secretion when glucose levels are high (16.7 mM). A decrease in serum glucose levels is seen in streptozotocin diabetic rats with up-regulation of GLUT-2/GLUT-4 expression and IRS-1 (Agraharam et al., 2022b; Semwal et al., 2016b).

5.3.2 Cardiovascular disease: Myricetin inhibits oxidised LDL-induced apoptosis in human umbilical vein endothelial cells (HUVECs) by regulating the GAS5/miR-29a-3p axis. Systolic and diastolic blood pressure in spontaneously hypertensive rats is decreased under chronic flavonol administration, which can be explained by the fact that it stimulates endothelial autophagy and increases the bioavailability of nitric oxide (M. Chen et al., 2020; Imran et al., 2021).

6. Drug Development and Clinical Translation

6.1 Molecular Docking and Computational Approaches

Myricetin binding modes to kinase ATP sites and allosteric sites are predicted with molecular docking complemented with simulations over 100+ nanoseconds of molecular dynamics, which predicts binding to kinase active sites. The interaction between PDK3 and myricetin is represented by PDK3-myricetin complexes, which have stable binding with sustained intramolecular hydrogen bonds over the course of the simulation. ADME computational prediction determines optimisation goals: TPSA should be reduced by 151.59 to <130 Ų

by methylation, LogP should be optimised to the 1.21→1-5 range by acylation/derivatization, and TPSA should be optimised by selective methylation to reduce 151.59 to <130 Ų (Farias et al., 2023; Liu et al., 2020d).

6.2 Target Validation: Nano BRET and Cell-Based Assays

Nano BRET intracellular target engagement assays measure the binding of compounds to their targets in whole cells that include cellular penetration and target expression. Cellular phosphorylation detection. Cellular phosphorylation is measured by using phospho-specific antibodies and immunoblotting to measure downstream substrate phosphorylation (p-Akt, p-ERK, p-JNK, p-STAT3, p-IκBα). In the MTT/MTS viability assay, dose response curves are obtained, and IC 50 values are obtained. Flow cytometric BrdU/EdU incorporation assays can be used to establish cell-cycle distribution and proliferation rates, but Annexin V/PI flow cytometry can also quantitatively measure apoptotic populations simultaneously. Executioner proteins are tested through the use of caspase activity assays (Agraharam et al., 2022b; M. Chen et al., 2020; Kumamoto et al., 2009b; Soorya et al., 2021).

6.3 Rational Derivative Design

Heterocyclic conjugation into hydroxyl positions (semi-synthetic) increases compound potencies by 50-100-fold, such as with the telomerase inhibitor 6d (IC_{50} =0.91 μM). Conjugation between piperazine/pyrrolidine increases aqueous solubility 325-fold and anticancer efficacy at the same time. Selective bioactivities are not lost during strategic methylation to enhance metabolic stability, but acylation increases lipophilicity (LogP 2.21-2.76) and membrane permeability (Massi et al., 2017; Zhang et al., 2021).

7. Clinical Translation Challenges and Future Perspectives

The drug Myricetin is defined by tremendously low oral bioavailability (9.62-9.74% oral bioavailability in rats), which is explained by aqueous insolubility (<0.1 mg/mL), chemical instability ($t_{1/2}$ = 0.55 hours), high phase II metabolism, and P-glycoprotein efflux. The following barriers are overcome by nanoformulation strategies: casein nanomicelles have a four-fold enhancement of absorption, and PLGA nanoparticles and cyclodextrin complexes have an increase in solubility by 25 and 4 times, respectively. A twelve-subject Phase 1 clinical trial of dihydromyricetin (NCT05623501) is conducted using dose-escalation (300 to 900mg DHM) in the FDA Botanical Drug Development Totality of the Evidence pathway. A precedent has been set by the approval of 19 flavonoid-based drugs, the majority of which are natural products (52.6% natural). Some of the emerging approaches include compulsory nanoformulation, site-specific targeting, mechanistic combination therapy (synergy between chemotherapy, immunotherapy, and tyrosine-kinase inhibitors), (stratifying pharmacogenomics), pharmacogenomic stratification (CYP450 polymorphisms in 20-30 % populations), and integration of metabolite pharmacology. It has been realised that glucuronidated and sulphated derivatives have different activities; therefore, the development of these two types of metabolites should be done independently (Dang et al., 2013; NCT05623501 | Phase I, ClinicalTrials.Gov, n.d.; Ye et al., 2024).

8. Conclusion

The translation of systematic SAR analysis, accurate characterisation of molecular targets, and novel formulation technologies into clinical therapies based on natural products in the diet is best illustrated by

Myricetin. It has a particularly remarkable polyhydroxylation pattern, which gives it multitarget engagements in key disease pathways, such as PI3K/Akt/mTOR signalling, NF-κB-inflammation, and oxidative stress pathways, and produces reproducible biological activity in models of triple-negative breast cancer, hepatocellular carcinoma, Alzheimer's disease, and Parkinson's disease. The paradoxical nature of methylation or glycosylation to decrease direct antioxidant activity and increase therapeutic activity is indicative of the need to assess natural products beyond the conventional in vitro tests. These difficulties, however, can be overcome with a nanoformulation platform that provides 4-25-fold improvements in bioavailability despite oral bioavailability being established as critically low and a chemical instability induced by solubility as a correlation to polarization and, consequently, solubility loss. Combined nanoformulation, rational derivative design, mechanistic combination therapies, and metabolite pharmacology recognition of myricetin-based therapeutics make them scientifically rigorous, leading to speedy clinical development in precision oncology, neurology, and treatment of metabolic diseases.

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