DOI: https://doi.org/10.21323/2618-9771-2026-9-1-62-77

Received 10.09.2025
Accepted in revised 05.03.2026
Accepted for publication 10.03.2026

Available online at https://www.fsjour.com/jour
Review article
Open access

MYRICETIN AS A THERAPEUTIC AGENT: MOLECULAR RESEARCHES AND CLINICAL POTENTIAL

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KEYWORDS:
Myricetin, flavonoid, plant, medicine, human health

ABSTRACT

Myricetin is a polyphenolic flavonol that is commonly present in tea, grapes, fruits, vegetables, and a number of medicinal plants. It is known to have a number of biological actions that are important for human health. Myricetin stands out for its multifunctional potential in the prevention and treatment of different infectious and degenerative disorders, especially as interest in natural bioactive chemicals grows. The primary mechanism entails robust antioxidant action by scavenging reactive oxygen species (ROS) and inducing the endogenous enzymes like catalase and superoxide dismutase. Furthermore, myricetin has anti-inflammatory properties via inhibiting the activation of the MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathways, which lowers the synthesis of proinflammatory cytokines. Numerous *in vitro* and *in vivo* investigations have demonstrated its capacity to suppress the growth of cancer cells, trigger apoptosis, and stop metastasis in the context of oncology. Myricetin decreases cholesterol, promotes endothelial function, and guards against atherosclerosis in the cardiovascular system. Its neuroprotective benefits are also encouraging, especially in terms of protecting dopamine in Parkinson's disease and preventing β-amyloid buildup in Alzheimer's disease. Furthermore, myricetin is important for preventing diabetes and obesity because it regulates blood glucose, improves insulin sensitivity, and modifies lipid metabolism. Antimicrobial and antiviral activities have also been documented, although they are still limited to experimental studies. Nevertheless, two significant obstacles to its conversion to practical applications are the lack of extensive clinical trials and the limited oral bioavailability. Future studies will concentrate on developing novel formulations, investigating safe and efficient dosages, and conducting thorough clinical trials. All things considered, myricetin shows significant promise as a multipurpose natural therapeutic candidate that promotes human health.

FUNDING: This work was supported by the National Research and Innovation Agency (BRIN) and the Indonesia Endowment Fund for Education (LPDP) through the RIIM Program — Competitive Wave 7 (Decree No. 61/II.7/HK/2024). The funding body had no role in the design of the study, the collection, analysis or interpretation of data, or in writing of the manuscript.

ACKNOWLEDGEMENTS: The authors would like to express their sincere gratitude to the National Research and Innovation Agency (BRIN) and the Indonesia Endowment Fund for Education (LPDP) for financial support through the Research and Innovation for Advanced Indonesia (RIIM) Program — Competitive Wave 7, as stipulated in the Decree of the Deputy for Research and Innovation Facilitation of BRIN No. 61/II.7/HK/2024. The authors also acknowledge material and immaterial support from the Research Organization for Agriculture and Food (ORPP BRIN) and the valuable assistance of the Research Center for Mineral Technology, BRIN, in the preparation and completion of this manuscript. Collaborative contributions from Institut Teknologi Sumatera (ITERA) are gratefully appreciated.

FOR CITATION: **Pratama, B. P., Khairullah, A. R., Ma'ruf, I.F., Kurniasih, D. A. A., Sukmanadi, M., Mustofa, I.** et al. (2026). Myricetin as a therapeutic agent: Molecular researches and clinical potential. *Food Systems,* 9(1), 62–77. https://doi.org/10.21323/2618-9771-2026-9-1-62-77

ДЛЯ ЦИТИРОВАНИЯ: **Пратама. Б. П., Хайрулла. А. Р., Маруф И. Ф., Курниаси Д. А. А., Сукманади М., Мустофа И.** и др. (2026). Мирицетин как терапевтическое средство: молекулярные исследования и потенциал клинического применения. *Пищевые системы*, 9(1), 62–77. https://doi.org/10.21323/2618-9771-2026-9-1-62-77

Поступила 10.09.2025
Поступила после рецензирования 05.03.2026
Принята в печать 10.03.2026

https://www.fsjour.com/jour
Обзорная статья
Открытый доступ

МИРИЦЕТИН КАК ТЕРАПЕВТИЧЕСКОЕ СРЕДСТВО: МОЛЕКУЛЯРНЫЕ ИССЛЕДОВАНИЯ И ПОТЕНЦИАЛ КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ

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КЛЮЧЕВЫЕ СЛОВА: *Мирицетин, флавоноид, растение, лекарство, здоровье человека*

АННОТАЦИЯ

Мирицетин — полифенольный флавонол, широко распространенный в чае, винограде, фруктах, овощах и ряде лекарственных растений. Известно, что он обладает рядом биологических свойств, важных для здоровья человека. Мирицетин выделяется своим многофункциональным потенциалом в профилактике и лечении различных инфекционных и дегенеративных заболеваний, особенно в связи с ростом интереса к природным биоактивным веществам. Основной механизм его действия заключается в мощном антиоксидантном действии, которое выражается в нейтрализации активных форм кислорода (АФК) и индукции таких эндогенных ферментов, как каталаза и супероксиддисмутаза. Кроме того, мирицетин обладает противовоспалительными свойствами, ингибируя активацию сигнальных путей MAPK и NF-κB, что снижает синтез провоспалительных цитокинов. Многочисленные исследования *in vitro* и *in vivo* продемонстрировали его способность подавлять рост раковых клеток, запускать апоптоз и останавливать метастазирование в онкологии. Мирицетин снижает уровень холестерина, способствует улучшению функции эндотелия и защищает сердечно-сосудистую систему от атеросклероза. Его нейропротекторные свойства также весьма обещающие, особенно в плане защиты дофамина при болезни Паркинсона и предотвращения накопления β-амилоида при болезни Альцгеймера. Кроме того, мирицетин важен для профилактики диабета и ожирения, поскольку он регулирует уровень глюкозы в крови, улучшает чувствительность к инсулину и меняет липидный обмен. Также были зарегистрированы его антимикробные и противовирусные свойства, хотя они пока ограничены экспериментальными исследованиями. Тем не менее, двумя существенными препятствиями для практического применения являются отсутствие обширных клинических испытаний и ограниченная биодоступность при пероральном приёме. Будущие исследования будут сосредоточены на разработке новых формул, изучении безопасных и эффективных дозировок и проведении тщательных клинических испытаний. Учитывая всё это, мирицетин имеет возможность стать многоцелевым природным терапевтическим веществом, улучшающим здоровье человека.

ФИНАНСИРОВАНИЕ: Данная работа была поддержана Национальным агентством исследований и инноваций (BRIN) и Индонезийским фондом развития образования (LPDP) в рамках программы RIIM — Конкурсная волна 7 (Указ № 61/II.7/HK/2024). Финансирующая организация не принимала участия в разработке исследования, сборе, анализе или интерпретации данных, а также в написании данной статьи.

БЛАГОДАРНОСТИ: Авторы выражают искреннюю благодарность Национальному агентству исследований и инноваций (BRIN) и Индонезийскому фонду развития образования (LPDP) за финансовую поддержку в рамках Программы исследований и инноваций для передовой Индонезии (RIIM) — Конкурсная волна 7, предусмотренной Постановлением заместителя по научным исследованиям и содействию инновациям BRIN № 61/II.7/HK/2024. Авторы также выражают благодарность Научно-исследовательской организации сельского хозяйства и продовольствия (ORPP BRIN) за материальную и нематериальную поддержку, и Научно-исследовательскому центру минеральных технологий, BRIN за ценную помощь в подготовке и выполнении данной авторской работы. Мы выражаем благодарность Институту технологий Суматры (ITERA) за совместную работу.

1. Introduction

Flavonoids are a group of secondary plant metabolites that have an important role in maintaining human health [1]. This compound, which may be found in a wide variety of fruits, vegetables, tea, wine, and spices, has long been acknowledged for its anti-inflammatory, anti-cancer, and antioxidant biological benefits [2]. Flavonoids have garnered significant interest in the domains of pharmacology and nutraceuticals in recent decades due to their potential as preventive measures and supplementary treatments for a range of degenerative illnesses [3]. Myricetin is a significant member of the flavonol group and one of the flavonoids with the strongest antioxidant potential due to its polyhydroxy chemical structure and six hydroxyl groups [4].

Myricetin is found abundantly in berries, onions, spinach, green tea, and red wine [5]. Its inclusion into common dietary items suggests that people consume this compound in quite large quantities, so making research on its impact on health extremely pertinent [6]. Numerous studies have demonstrated that myricetin possesses a wider range of bioactivity than other flavonols, including anticancer properties and defense against the diseases of neurological, metabolic, and cardiovascular systems [7–10]. This function is strongly linked to its capacity to control cellular signaling pathways, neutralize free radicals, and alter the expression of genes linked to inflammation and oxidative stress [11].

An important reason why myricetin deserves special attention is because of its pleiotropic properties, namely its ability to influence many molecular targets simultaneously [12]. This compound operates as a regulator of signaling pathways that control immunological responses, apoptosis, and cell proliferation in addition to acting as a direct antioxidant by absorbing reactive oxygen species (ROS) [13]. Therefore, myricetin holds significant promise for preventing multifactorial chronic diseases like cancer, Alzheimer's, type 2 diabetes, and atherosclerosis [14–17]. A reassessment of myricetin's potential in the health industry is also urgently needed, given the global trend towards a healthier lifestyle and the growing interest in functional foods and supplements made from natural ingredients [18].

Although much research has been done on flavonoids, comprehensive studies specifically on myricetin are relatively limited. The majority of the data that are currently available are still incomplete, concentrating primarily on specific elements, such as antioxidant or anticancer activities, without thoroughly connecting the molecular pathways to the potential therapeutic advantages attained [19]. However, there is still a shortage of clinical evidence in humans, and the majority of the data that is now accessible comes from *in vitro* and animal research [5]. This leads to a knowledge gap that must be filled by critical research in order to shift future research's focus more toward practical applications.

The limited bioavailability of myricetin is another significant obstacle to its use [20]. This compound is easily broken down in the liver and intestines, thus resulting in a comparatively low active concentration entering the bloodstream [4]. These elements bring up significant issues with relation to safe long-term use, ideal composition, and appropriate dosage. Examining the biological elements and health advantages is therefore important, but so is looking at the technical challenges and opportunities for its development as a medicinal agent or nutraceutical.

Based on this background, this review was prepared with the aim of summarizing the current scientific evidence regarding myricetin in the context of human health. The focus of discussion includes natural sources and bioavailability, key biological mechanisms, and documented health effects, ranging from cardiovascular, metabolic, and neuroprotective protection to anticancer and antimicrobial activities. This article also focuses on future development directions, research issues, and security aspects. Thus, there is hope that this review can provide a comprehensive overview of the potential of myricetin as a promising candidate bioactive agent, while also highlighting research gaps that still need to be addressed.

2. Data collection method

This review synthesized evidence identified through systematic searches of PubMed, Scopus, Web of Science, and Google Scholar covering publications through August 2025. Search strings combined controlled terms and free text (e.g., *myricetin* AND *flavonol* AND (*antioxidant* OR *anti-inflammatory* OR *anticancer* OR *neuroprotective* OR *cardioprotective* OR *antimicrobial* OR *bioavailability* OR *nanodelivery* OR *clinical*)), with Boolean operators and citation tracking (snowballing) from key papers. Eligible records were peer-reviewed articles in English, including *in vitro* and *in vivo* studies, clinical investigations, and critical reviews directly addressing myricetin's sources, chemistry, pharmacology, molecular mechanisms (e.g., NF-κB, Nrf2, MAPK, PI3K/AKT, AMPK), epigenetic regulation, safety/toxicity, drug–interaction potential, bioavailability, and formulation strategies. Exclusions consisted of conference abstracts, non-English works without reliable translation, editorials, non–peer-reviewed items, and studies lacking methodological clarity or having no direct relevance. After deduplication, titles/abstracts were screened followed by full-text assessment using predefined criteria; data were extracted on study design, model/system, exposure/dose/formulation, outcomes, and mechanistic readouts, and then narratively integrated across disciplines (biochemistry, pharmacology, nutraceuticals, and clinical sciences) to produce an updated, critical appraisal compliant with best practices for scoping reviews.

3. Sources and bioavailability of myricetin

To understand the health potential of myricetin, it is important to first review the basic aspects including its natural sources in food, its chemical structure characteristics and physicochemical properties, its bioavailability profile including digestion, absorption, metabolism, distribution, and elimination, and various factors that influence its stability and bioavailability.

3.1. Natural sources of myricetin

Myricetin is a polyhydroxy flavonol found widely in various plant foods [21]. It is typically found in the human diet from the ingestion of tea, wine, fruits, vegetables, and a number of herbal plants [5]. Myricetin is one of the significant flavonoids that frequently enters the body through daily meals because of its broad distribution [22]. Table 1 summarizes various natural sources of myricetin, ranging from fruits, vegetables, tea, wine, to herbal plants.

One of the primary sources of myricetin is fruit [4]. High levels of this compound are found in many berries, such as blueberries, cranberries, blackberries, and bilberries [23]. The high antioxidant content of berries has earned them the moniker "superfood," and myricetin is a key component in supplying these health benefits [24]. Furthermore, myricetin is available in considerable amounts in grapes, particularly red grapes [25]. Because of this, its fermented product, red wine, is frequently linked to cardioprotective advantages through the "French paradox" [26].

Myricetin has also been found in kiwis, oranges, pomegranates, and apples [27]. Similar to how other polyphenols are distributed, this compound is more prevalent in the skin of apples than in the meat [28]. This demonstrates how crucial it is to eat the entire fruit in order to maximize its bioactive effects.

Table 1. **Natural sources and characteristics of myricetin content**

Таблица 1. **Природные источники и характеристики уровней содержания мирицетина**

Category	Example source	Content/Distribution	Relevance description	References
Fruits	Blueberries, cranberries, blackberries, bilberries, red grapes, apples, pomegranates, oranges, and kiwis	High in fruit skin and red grapes are rich in flavonols	Acting as a major source of antioxidants and consuming whole fruit increases myricetin intake	[23–28]
Vegetables	Onions, tomatoes, spinach, broccoli, and cabbage	The content variation and red onions are relatively high	Supports antimicrobial properties and is protective against degenerative diseases	[29–31]
Tea	Green tea (*Camellia sinensis*) and black tea	High in green tea and lower in black tea due to fermentation	Regular consumption is associated with cardiovascular, antidiabetic, and anticancer protection	[32–35]
Wine and products	Red grapes (*Vitis vinifera*) and red wine	High concentration on the skin and increased through fermentation	It has been linked to the "French paradox" and heart protection, although the specific contribution of myricetin remains to be investigated	[36–38]
Herbal plants	*Myrica rubra* (bayberry), *Rhus verniciflua,* and *Ampelopsis* spp.	High concentration and the basis of traditional medicine	Provides anti-inflammatory, hepatoprotective, and immunomodulatory effects	[39–44]

In addition to fruit, myricetin can be found naturally in a variety of vegetables [5]. The flavonol content of red onions, which includes myricetin and quercetin, has been extensively researched in relation to its antibacterial and anti-inflammatory qualities [29]. Moderate levels of myricetin, which is frequently linked to a preventive effect against degenerative disorders, are also found in spinach and tomatoes [30]. According to reports, broccoli and cabbage, which belong to the *Brassicaceae* family, feature lesser levels of these flavonols but nevertheless contribute to daily consumption when frequently ingested [31].

One of the main sources of polyphenols consumed worldwide is tea, and green tea (*Camellia sinensis*) contains a notable quantity of myricetin [32]. The myricetin content in tea varies depending on the type, processing method, and brewing time [33]. Green tea tends to contain higher flavonols than black tea, because the fermentation process in black tea causes the degradation of some of the polyphenol compounds [34]. Myricetin is thought to be one of the primary bioactive components of green tea, which has been associated with a lower risk of diabetes, cardiovascular disease, and several types of cancer [35].

Red wine, which is made from fermented red grapes (*Vitis vinifera*), is a significant source of myricetin [36]. Red wine has a relatively high concentration of flavonols because the fermenting process uses the grape skin, which has a higher flavonoid content than the fruit's flesh [37]. Red wine consumption in moderation has been linked to heart and blood vessel protection, while further research is still needed to determine the precise role of myricetin [38].

There are also other traditional medicinal plants that are said to be high in myricetin [13]. One well-known example is the bayberry (*Myrica rubra*), which is also the compound's source of name and is utilized in East Asian traditional medicine [39]. High levels of myricetin have also been found in plants like tea (*Camellia sinensis*), *Rhus verniciflua*, and a number of Ampelopsis species [4]. In addition to these sources, myricetin is also present in several species of the genus *Syzygium*. For instance, a myricetin derivative-rich fraction from *Syzygium malaccense* leaves, particularly containing myricitrin, has been reported to account for approximately 48.48 % of the total flavonoid content based on HPLC analysis [40]. Moreover, *Syzygium polyanthum*, a widely used culinary and medicinal plant in Southeast Asia, has also been found as a natural source of myricetin, further supporting the nutritional and pharmacological importance of this genus [41–44]. These compounds are thought to support the herb's anti-inflammatory, hepatoprotective, and immunomodulatory properties, among other therapeutic benefits, in traditional medical practices [11,43].

It should be mentioned that a number of factors, including plant variety, growth conditions, harvesting techniques, and storage, affect the amount of myricetin in food [6]. For instance, it has been noted that berries cultivated in conditions with high light intensity featured higher flavonoid contents [45]. Myricetin levels are also impacted by processing; for instance, prolonged heating may degrade it, but some fermentations may actually make it more bioavailable [46].

Myricetin is found in many fruits, vegetables, tea, wine, and herbs, thus it can be naturally incorporated into a regular diet [47]. Consuming foods high in flavonoids, such as myricetin, has been linked in epidemiological studies to a lower chance of developing chronic illnesses like cancer, diabetes mellitus, and atherosclerosis [48]. Consequently, adding natural myricetin sources to the diet is one possible nutrition-based disease preventive tactics [49].

3.2. Chemical structure and physicochemical properties of myricetin

Myricetin Myricetin belongs to the flavonoid subgroup and is a polyphenol component of the flavonol group [4]. This compound has the molecular formula $C_{15}H_{10}O_8$ with a molecular mass of approximately 318.24 g/mol [12]. The basic structure is a C6–C3–C6 flavonoid skeleton, which is composed of two aromatic rings (A and B) connected by an oxygenated heterocyclic ring (ring C) [1]. Myricetin differs from other flavonols, such as quercetin or kaempferol, in that it has six hydroxyl groups (–OH) at positions C-3, C-5, C-7, C-3′, C-4′, and C-5′ [50]. Myricetin is a flavonoid with a very strong antioxidant capacity because of its extensive dispersion of hydroxyl groups [51].

The hydroxyl groups in ring A (5 and 7) contribute to the transition of metal ion chelating activity, whereas the groups in ring B (3′, 4′, and 5′) are generally in charge of the free radical scavenging capacity [52]. The stability of flavonoid radicals is another benefit of the -OH group at position 3 of the C ring, which enhances myricetin's antioxidant properties [53]. Therefore, myricetin's hydroxyl-rich chemical structure allows neutralizing reactive oxygen species (ROS) by donating hydrogen and electrons [54].

Myricetin has physicochemical characteristics as a pale yellow crystalline powder. Strong internal hydrogen bonding and the planarity of its aromatic structure limit this compound's solubility in water, despite the fact that it has several hydroxyl groups, which make it relatively polar [55]. In contrast, myricetin is more soluble in polar organic solvents such as ethanol, methanol, and dimethyl sulfoxide (DMSO) [56]. According to reports, this compound's melting point ranges from 357 to 360 °C, demonstrating the resilience of polyphenols' aromatic structure [57].

There are a number of outside variables that affect myricetin stability. This compound is highly stable in acidic pH environments (like the stomach environment), but it readily undergoes oxidative degradation and isomerization in neutral to alkaline pH environments (like the small intestine environment) [58]. Degradation is also accelerated by exposure to light and high temperatures, which can reduce biological activity by generating oxidation products [59]. This explains why pure myricetin typically loses stability when food is processed or stored.

The utilization of myricetin is significantly hampered by its physicochemical characteristics from a pharmacokinetic point of view. The quantity of active aglycone that enters the systemic circulation is decreased by quick phase II metabolism (glucuronidation, sulfatation, and methylation), and intestine absorption is restricted by its poor water solubility [60]. Consequently, myricetin's oral bioavailability is comparatively poor in comparison to other flavonols [20]. Thus, contemporary research focuses on attempts to improve bioavailability by altering physicochemical features, such as via derivatization or complex formation.

Furthermore, myricetin's chemical characteristics enable its interactions with biomolecules. The hydroxyl group and its aromatic conjugation system can intercalate to DNA and bind to proteins via hydrophobic and hydrogen interactions [61]. Metal chelating activity is crucial in stopping the Fenton reaction, which generates hazardous hydroxyl radicals, particularly with regard to Fe^{2+} and Cu^{2+} ions [62]. However, this ability also has the potential to disrupt mineral homeostasis when consumed in very high concentrations [30].

Myricetin has a higher antioxidant activity than quercetin or kaempferol when compared to other flavonols, mostly because it possesses an extra hydroxyl group on the B ring [4]. Nevertheless, this additional hydroxyl group also decreases its chemical stability by increasing its susceptibility to oxidation [63]. In other words, the primary constraint on the use of myricetin is its superior chemical structure.

3.3. Myricetin bioavailability: Absorption, metabolism, distribution, and elimination

Absorption: Myricetin is typically found as glycosides attached to sugar groups after being ingested from plant sources [5]. This compound must be hydrolyzed by the β-glucosidase enzyme in the small intestine or by the colonic microbiota to become a more easily absorbed aglycone form [64]. However, the bioavailability of myricetin is highly limited because its polyhydroxyl chemical nature makes it poorly soluble in fat so that the passive diffusion process in the enterocyte membrane becomes inefficient [65]. Furthermore, myricetin stability in the gastrointestinal tract is limited; exposure to digestive enzymes and the neutral pH of the intestines might cause its breakdown [66]. As a result, very little of the oral intake makes it into the bloodstream.

Metabolism: Myricetin promptly goes through first-pass metabolism in the liver and enterocytes upon effective absorption [11]. These metabolic activities include glucuronidation, sulfatation, and O-methylation, which are mediated by transferase enzymes such catechol-O-methyltransferase (COMT), sulfotransferase (SULT), and UDP-glucuronosyltransferase (UGT) [67]. Therefore, conjugated metabolites of myricetin are more prevalent in plasma than free aglycones [68]. Certain metabolites, such as antioxidants or cell signal modulators, have their own biological function even when this metabolism lowers the quantity of the parent chemical [55]. However, a significant factor limiting myricetin's bioeffectiveness at target tissues is still substantial conjugation [19].

Distribution: Myricetin's distribution profile demonstrates that it can reach a variety of tissues, with a particular predisposition to the brain, liver, kidney, and lungs [13]. According to experimental animal research, myricetin has a restricted capacity to cross the blood-brain barrier, which may contribute to its ability to prevent neurodegenerative diseases [69]. Myricetin and its metabolites are crucial for regulating detoxification enzymes and preventing oxidative stress in the liver [70]. However, the dosage form, timing of administration, and dose all have a significant impact on tissue concentrations [11].

Elimination: The main ways that myricetin is evacuated through are bile and urine [71]. The metabolites resulting from glucuronidation and sulfatation are water-soluble and therefore easily excreted by the kidneys [72]. A comparatively minor portion is eliminated in the bile and may go through enterohepatic cycle [13]. Myricetin typically has a short elimination half-life, which could account for the low plasma levels following oral dosing [57]. Although it is uncommon for these compounds

to accumulate, long-term ingestion of natural foods can keep the body's levels at a specific baseline [73].

3.4. Factors affecting the stability and bioavailability of myricetin

The bioavailability of myricetin is one of the main determinants of its biological effectiveness in humans [74]. Despite the fact that these compounds are known to possess neuroprotective, anti-inflammatory, anticancer, and antioxidant properties, their efficacy is frequently limited because of the low plasma concentrations attained upon oral ingestion [20]. The chemical characteristics of myricetin, the surrounding environment, and bodily biological interactions are some of the interconnected elements that contribute to this [75]. Figure 1 provides an overview of myricetin, highlighting its main dietary sources, core chemical structure, and the principal factors that affect its stability and bioavailability.

Myricetin is extremely reactive due to its polyhydroxyl structure, which contains six hydroxyl groups [52]. This property makes it easily oxidized when exposed to light, oxygen, or neutral to alkaline pH such as in the small intestine [59]. Food processing techniques like boiling or baking can drastically lower the quantities of this chemical because of its limited heat stability [76]. Therefore, the amount of myricetin that is still available for the body to absorb depends in large part on physicochemical variables and food preparation [77].

Bioavailability is also influenced by biological circumstances in the digestive tract in addition to chemical considerations. Myricetin in the form of glycosides should be hydrolyzed by the enzyme β-glucosidase or intestinal microbiota to become an absorbable aglycone form [78]. Individual differences in microbiota makeup result in wide variations in absorption rates. Myricetin is subjected to a rigorous first-pass metabolism in the liver upon absorption, which includes glucuronidation, sulfatation, and methylation [79]. The quantity of myricetin in free form that circulates in the plasma is greatly decreased by this mechanism, however some of its conjugated metabolites still have some biological activity [80].

Stability and bioavailability are also influenced by interactions with other dietary ingredients. For instance, myricetin can undergo oxidative degradation due to complex formation from metal ions like Fe^{2+} and Cu^{2+} [59]. Conversely, absorption can be facilitated by increasing their solubility in the intestinal micelle phase through its co-consumption together with lipids or phospholipids [81]. Myricetin oxidation during gastrointestinal transit may be prevented by other antioxidants, such as vitamin C, which may also have a protective effect [82]. These factors suggest that overall dietary patterns may modulate the effectiveness of myricetin.

Myricetin's low bioavailability has prompted the creation of several formulation techniques for use in clinical and nutraceutical purposes [83]. Several strategies have been shown to be successful, such as complexation with cyclodextrins to enhance stability, liposomes and micelles to boost solubility, and polymer- or lipid-based nanoencapsulation to prevent myricetin from degrading [84]. This method has the potential to be improved in people and has continuously demonstrated elevated plasma myricetin concentrations in animal studies [85].

4. Biological mechanisms of myricetin

Myricetin's biological effects on health are mediated by a number of interconnected molecular pathways. This compound not only demonstrates antioxidant action by scavenging reactive oxygen species (ROS) and altering endogenous defense enzymes, but it also contributes to the regulation of the NF-κB pathway and proinflammatory enzymes like COX and iNOS [86]. Furthermore, myricetin affects important intracellular signals that are involved in metabolism, apoptosis, and cell division, such as AMPK, PI3K/AKT, and MAPK [87]. Additionally, this compound may have long-term impacts on cellular homeostasis and the prevention of degenerative diseases through its potential in epigenetic control and gene expression [54].

4.1. Antioxidant activity of myricetin

A pathological state known as oxidative stress is defined by an imbalance between the body's ability to defend itself against oxidative stress and the generation of reactive oxygen species (ROS) [88]. Overproduction of ROS can harm proteins, lipids, and DNA, which can aid in the ethiology of a number of chronic degenerative illnesses, including diabetes mellitus, cancer, cardiovascular disease, and neurodegenerative diseases [89]. Accordingly, myricetin, a flavonol that is widely present in fruits, vegetables, tea, and red wine, has a high potential for antioxidant activity through both direct and indirect action mechanisms [90].

Scavenging ROS: Myricetin's direct neutralization of ROS is the primary mechanism behind its antioxidant action [91]. Because myricetin has a lot of hydroxyl groups (–OH) at positions 3, 5, 7, 3', 4', and 5' in its chemical structure, it can act as an electron or proton donor and change ROS into a more stable and innocuous form [13]. For instance, myricetin can lower the known highly reactive and biomolecule-damaging hydroxyl

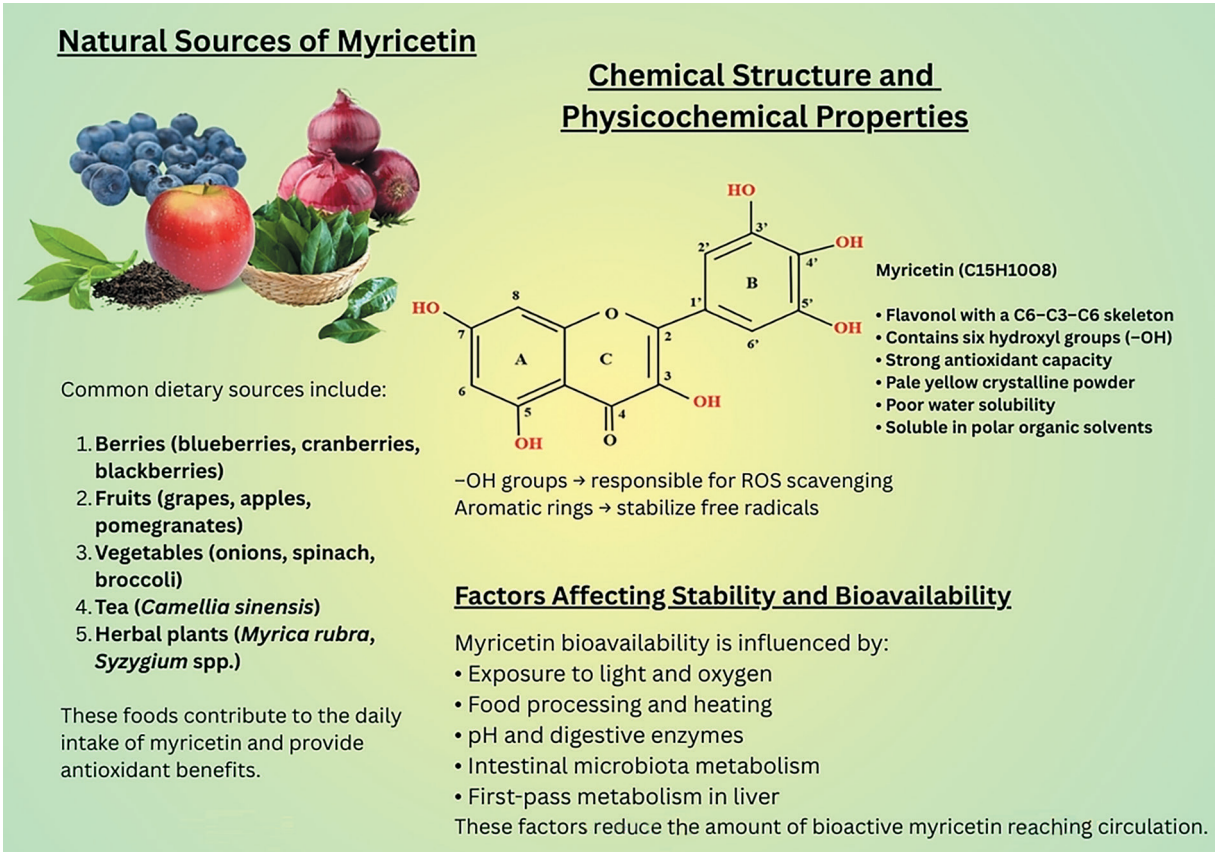

Figure 1. **Natural sources, chemical structure, and factors influencing the stability and bioavailability of myricetin**
Рисунок 1. **Природные источники, химическая структура и факторы, влияющие на стабильность и биодоступность мирицетина**

radicals (•OH), superoxide (O_2^-), and peroxyl radicals (ROO•) [4]. Furthermore, electron resonance is supported by the conjugated double bond system in the aromatic ring, which makes the myricetin radical that results from the reaction with ROS comparatively stable [92]. This mechanism of scavenging radicals efficiently interrupts the series of oxidative events that might lead to lipid peroxidation and cell membrane damage [93].

Modulation of endogenous antioxidant enzymes: Furthermore, myricetin affects molecular pathways that control the expression of endogenous antioxidant enzymes in addition to its direct role as a radical scavenger [22]. Research shows that myricetin can activate the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) [94]. The translocation of Nrf2 into the cell nucleus upon activation results in its binding to the DNA's antioxidant response element (ARE), which raises the transcription of several defensive genes [95]. These target genes include those that encode vital enzymes like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) [96]. Myricetin increases the ability of cells to defend against oxidative stress by activating the Nrf2-ARE pathway [97].

Increased SOD expression allows converting superoxide to hydrogen peroxide (H_2O_2), which is further degraded to water and oxygen by catalase and GPx [98]. Myricetin thereby improves the enzymatic ability that sustains long-term redox equilibrium in addition to immediately removing ROS [99]. Myricetin differs from simple antioxidants that merely act chemically and don't alter cellular signalling pathways because of its dual action [11].

Biomedical implications: Myricetin's ability to scavenge reactive oxygen species (ROS) and modulate antioxidant enzymes makes it a highly relevant supplement for the prevention and treatment of disorders linked to oxidative stress [100]. Protecting the vascular endothelium can lower the risk of atherosclerosis in the cardiovascular system [101]. Myricetin may be able to decrease the progression of neurodegenerative disorders like Parkinson's and Alzheimer's by reducing the accumulation of ROS in the central nervous system [102]. However, myricetin may also help prevent carcinogenesis by lowering DNA damage caused by free radicals [103].

4.2. Anti-inflammatory activity of myricetin

The body uses inflammation as a physiological defense against infection and tissue damage, but excessive or persistent inflammation can lead to the development of a number of degenerative diseases, including as cancer, atherosclerosis, arthritis, and neurological diseases [104]. The main molecular pathways involved in the regulation of inflammation are nuclear factor-kappa B (NF-κB), cyclooxygenase (COX) enzymes, and inducible nitric oxide synthase (iNOS) [105]. Myricetin, a flavonol found in abundance in fruits, vegetables, tea, and red wine, has been demonstrated in numerous studies to have a strong anti-inflammatory effect by influencing these three targets [106–108].

NF-κB pathway inhibition: NF-κB is a central transcription factor that regulates the expression of various proinflammatory mediators, including cytokines (TNF-α, IL-1β, IL-6), chemokines, COX-2, and iNOS [109]. NF-κB activation is typically brought on by proinflammatory cytokines or inflammatory signals like lipopolysaccharide (LPS) [110]. Translocation of the NF-κB component into the cell nucleus is made possible by the breakdown of the IκB inhibitor [111]. According to reports, myricetin prevents NF-κB from translocating to the nucleus by inhibiting the phosphorylation and degradation of IκB [112]. This lowers the synthesis of inflammatory mediators by suppressing the expression of pro-inflammatory genes. Myricetin suppresses the inflammatory response's amplification, which frequently causes tissue damage, by this mechanism [113].

COX enzyme modulation: COX is a key enzyme in the biosynthesis of prostaglandins, lipid mediators involved in vasodilation, pain, and edema during inflammation [114]. The COX-2 isoform is a key target of non-steroidal anti-inflammatory drug (NSAID) therapy and is markedly increased during inflammation [115]. According to research conducted both in vitro and in vivo, myricetin can decrease the synthesis of prostaglandin E2 (PGE2) and inhibit COX-2 expression at both the transcriptional and translational stages [116,117]. Given that flavonoid modulation is typically more selective and has no influence on COX-1, which is crucial for physiological function, this action implies that myricetin may behave similarly to NSAID mechanisms, but with a lower risk of adverse effects [118].

Suppression of iNOS expression: an enzyme called iNOS is in charge of producing a lot of nitric oxide (NO) when inflammation occurs [119]. Despite the fact that NO plays crucial physiological roles in neurotransmission and vasodilation, excessive synthesis brought on by iNOS activation can result in nitrosative stress and cell damage [120]. It is well known that myricetin can reduce the buildup of NO in inflammatory tissues by transcriptionally suppressing iNOS expression [121]. Therefore, myricetin not only lessens oxidative damage caused by NO, but it also lessens chronic inflammation, which frequently makes tissue damage worse [6].

Biomedical implications: Myricetin's modulation of NF-κB, COX, and iNOS signaling has wide-ranging therapeutic effects [122]. Inhibiting vascular inflammation may help stop atherogenesis in cardiovascular disease [123]. Suppression of the microglia inflammatory pathway can reduce the rate of neuronal damage in neurodegenerative disorders [124]. In contrast, myricetin's anti-inflammatory properties help lower the proinflammatory milieu that promotes tumor cell growth and dissemination in cancerous situations [125]. This demonstrates myricetin's potential as a pleiotropic, naturally occurring anti-inflammatory agent [19].

4.3. Modulation of cellular signaling pathways by myricetin

Intracellular signals are crucial for controlling energy balance, differentiation, apoptosis, and proliferation [126]. Deregulation of these signalling pathways has a role in the pathophysiology of a number of chronic illnesses, such as diabetes, cancer, cardiovascular problems, and neurodegenerative diseases [127]. A polyphenolic flavonoid that is common in tea, fruits, and vegetables, myricetin has been demonstrated to alter a number of molecular signalling pathways [11]. Regarding the biological effects of myricetin, the three primary pathways that have been most thoroughly investigated are AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and mitogen-activated protein kinase (MAPK) [128].

MAPK path regulation: The MAPK pathway, which controls how cells react to oxidative stress, inflammation, and proliferation, is made up of ERK, JNK, and p38 MAPK [129]. Chronic inflammation or pathological apoptosis may result from excessive activation of MAPK pathways, especially JNK and p38 [130]. According to numerous studies, myricetin can prevent JNK and p38 from becoming phosphorylated, which lowers the production of proinflammatory cytokines like TNF-α and IL-1β and lessens oxidative stress-induced apoptosis [131,132]. On the other hand, myricetin can sometimes trigger ERK to promote healthy tissue regeneration or cell division [133]. According to this selective modulation, myricetin functions contextually, adjusting its effects to the cell's microenvironmental circumstances [12].

Modulation of the PI3K/AKT pathway: One important signalling pathway that controls angiogenesis, metabolism, cell growth, and survival is PI3K/AKT [134]. Many malignancies have abnormal PI3K/AKT activation, which results in unchecked growth and resistance to apoptosis [135]. It has been demonstrated that myricetin inhibits AKT phosphorylation and PI3K activation, which lowers the expression of anti-apoptotic proteins (survivin, Bcl-2) and increases the expression of proapoptotic proteins (caspase, Bax) [136]. Furthermore, myricetin can improve glucose transport in metabolic disorders like insulin resistance by altering the PI3K/AKT pathway in muscle and adipose cells, which in turn increases insulin sensitivity [137]. This demonstrates myricetin's dualistic effects, which include promoting metabolic balance and inhibiting pathogenic PI3K/AKT activity in cancer [13].

AMPK pathway activation: A cellular energy sensor called AMPK is crucial for preserving the equilibrium of energy metabolism [138]. AMPK activation promotes glucose absorption, suppresses lipid production, and boosts fatty acid oxidation [139]. According to reports, myricetin causes AMPKα phosphorylation and increases the AMP/ATP ratio, activating AMPK [140]. This activation has beneficial effects on preventing non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and obesity [141]. Furthermore, myricetin-induced AMPK activation has the ability to block mTOR, a crucial regulator of cell growth and proliferation, indicating anticancer potential [19].

Biomedical implications: Furthermore, myricetin-induced AMPK activation has the ability to block mTOR, a crucial regulator of cell growth and proliferation, indicating anticancer potential [142]. Myocardial protection in the circulatory system is facilitated by both AMPK activation and MAPK-mediated oxidative stress suppression [143]. PI3K/AKT modulation and AMPK stimulation enhance glucose and lipid balance in a metabolic setting [144]. In contrast, myricetin inhibits PI3K/AKT and p38 MAPK in cancer to decrease growth and trigger apoptosis [14]. Thus, myricetin addresses several important molecular pathways in human health, acting as a multifunctional modulator [19].

4.4. Epigenetic effects and gene regulation by myricetin

Heritable changes to gene expression that do not alter the DNA sequence are known as epigenetics. These changes are mostly caused by DNA methylation, histone modifications, and the control of non-coding RNAs (miRNAs/lncRNAs) [145]. According to a number of preclinical investigations, the polyphenolic flavonol myricetin can contextually alter all three levels of control, impacting a network of signalling pathways linked to inflammation, oxidative stress, metabolism, and carcinogenesis [146]. Figure 2 shows the interconnected molecular mechanisms of

myricetin, including its antioxidant effects through ROS scavenging and Nrf2 activation, anti-inflammatory activity via NF-κB, COX-2, and iNOS suppression, modulation of AMPK, PI3K/AKT, and MAPK signaling pathways, and epigenetic regulation, which together contribute to cardiovascular protection, neuroprotection, and anticancer effects.

DNA methylation (DNMT-centric): Many important genes, such as antioxidant, tumor suppressor, and anti-inflammatory genes, have their «on/off» status determined by their promoter methylation patterns [147]. In a number of cell models, myricetin has been shown to inhibit DNA methyltransferase (DNMT1/3A/3B) production and activity. This is linked to the hypomethylation of protective gene promoters and the transcriptional restoration of those promoters [148]. Functionally, this can boost the transcription of genes that regulate the cell cycle and apoptosis, as well as those that are antioxidant and anti-stress. Large-scale methylome analysis is necessary to confirm generalizations across tissues because demethylation patterns vary by locus and are impacted by exposure duration and dose [149].

Histone modifications (HDAC/HAT/HMT/HDM): Chromatin accessibility is controlled by the ratio of histone acetylation to methylation [150]. Myricetin is known to alter histone methyltransferase/demethylase and HDAC/HAT, two enzymes that erase and write histones [151]. H3/H4 acetylation can be increased, chromatin can be loosened, and the transcription of cytoprotective genes (such as antioxidant pathways) can be encouraged by inhibiting specific HDACs [152]. However, myricetin can reduce the transactivation of proinflammatory genes (COX-2, iNOS) via suppressing the activity of p300/CBP HAT against NF-κB in the context of inflammation [116]. There are signs that myricetin either enhances active marks (H3K4me3) or decreases repressive marks like H3K27me3 (for example, by suppressing HMTs like EZH2) or H3K9me2/3 in specific models [153]. In the end, gene expression is reprogrammed to steer cells toward a less proliferative and proinflammatory state.

Regulation of non-coding RNAs (miRNA/lncRNA): Additionally, myricetin alters miRNA profiles that target important pathways [154]. Increases in anti-inflammatory/anti-proliferative miRNAs can inhibit genes in the cell cycle factor, PI3K/AKT, or NF-κB axes [14]. It is possible to downregulate pro-survival/pro-angiogenic miRNAs, which would reduce the expression of targets that promote angiogenesis, migration, and proliferation [155]. The downstream consequences of these miRNA alterations are frequently explained by enhanced glucose transporter and fatty acid oxidation genes in metabolic contexts, or decreased Bcl-2/survivin, increased Bax/caspase, and VEGF/MMP suppression in cancer models [156]. Although the evidence is still being gathered, interactions with certain lncRNAs have also been documented, providing support for chromatin regulation and mRNA stability [157].

Crosstalk with key transcription factors: Myricetin epigenetics is linked to NF-κB, AP-1, p53, and Nrf2-ARE regulation [54]. Chromatin relaxing at target promoters frequently precedes Nrf2 activation, which promotes transcription of HO-1, NQO1, GCLC, and other redox genes [158]. NF-κB suppression is dual in nature: Limitation of acetyltransferase co-activator (p300/CBP) and chromatin accessibility at NF-κB response elements [159]. Modification in p53 acetylation or activity in response to DNA damage or stress might cause a cell to choose between planned apoptosis or DNA repair [160].

Biomedical implications: Myricetin epigenetics can improve fatty acid oxidation through the AMPK–SIRT1–PGC-1α axis, which is likewise reliant on the histone/PGC-1α acetylation status, and decrease the production of lipogenic genes (e.g. downstream of SREBP-1c) in cardiometabolic [161]. Silencing repressive histone marks and selectively demethylating suppressor gene promoters in oncology slows EMT/angiogenesis, decreases cancer cells proliferation, and initiates their death [162]. The foundation for neuroprotective effects in neurology is the normalization of neuroprotective miRNAs and the improvement of the antioxidant-anti-inflammatory program (Nrf2↑/NF-κB↓) [163].

5. Health effects of myricetin

Various studies have shown that myricetin has a broad spectrum of health benefits through complex biological mechanisms. This compound not only provides protection to the cardiovascular system through vasodilatory effects and improved endothelial function, but also plays a role in metabolic regulation by increasing insulin sensitivity and controlling lipid metabolism [5]. Myricetin has a neuroprotective effect by slowing the progression of neurodegenerative illnesses including Parkinson's and Alzheimer's and preventing damage to neurons [164]. Furthermore, its antiproliferative, pro-apoptotic, and angiogenesis and metastasis-inhibiting properties demonstrate its potential in oncology and even provide support to its usage as an adjuvant in cancer therapy [19]. Furthermore, myricetin has antibacterial and antiviral properties, and its hepatoprotective, photoprotective, and immunomodulatory properties, which fortify the body's defenses, offer extra protection [11].

5.1. Cardiovascular

Myricetin has shown protective potential for the cardiovascular system through several mechanisms. This compound can reduce blood pressure by enhancing the generation of nitric oxide (NO), which is crucial for vasodilation, by raising the activity of the endothelial nitric oxide synthase (eNOS) enzyme [165]. It also has vasoprotective benefits by lowering endothelial cell oxidative stress and inhibiting monocyte adhesion,

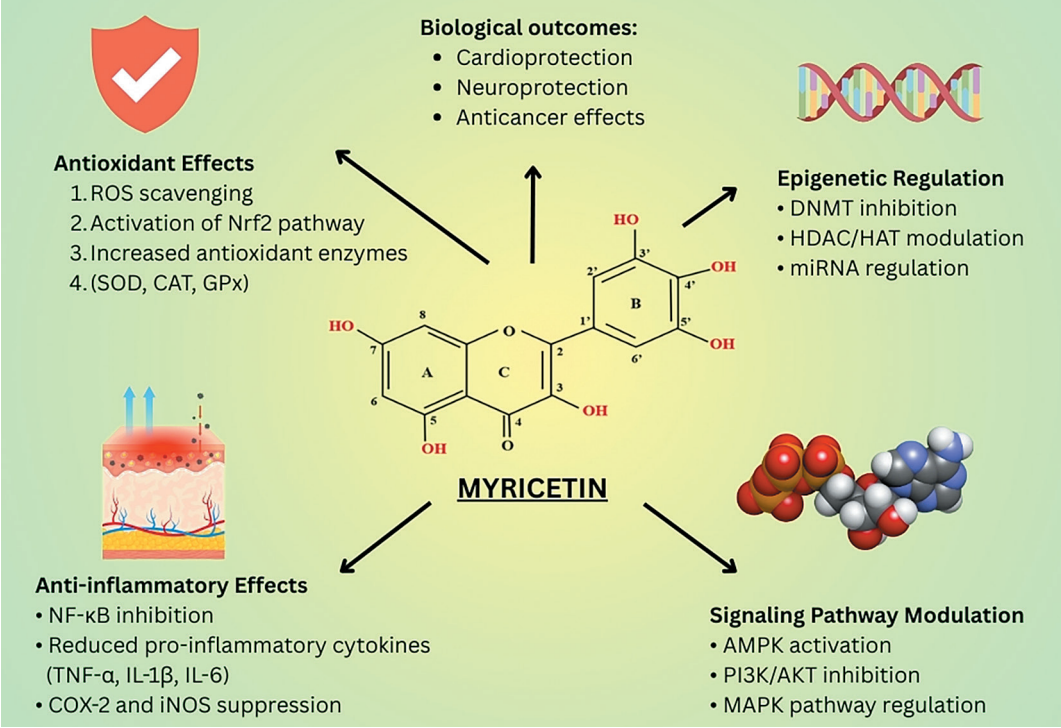

Figure 2. **Antioxidant, anti-inflammatory, signaling, and epigenetic mechanisms of myricetin in promoting cardiovascular protective, neuroprotective, and anticancer effects**

Рисунок 2. **Антиоксидантные, противовоспалительные, сигнальные и эпигенетические механизмы мирицетина, способствующие кардиозащитному, нейропротекторному и противораковому действию**

a precursor to atherosclerosis [166]. Myricetin is also helpful in reducing dyslipidemia and atherosclerosis since it helps to increase HDL fractions and decrease total cholesterol and triglyceride levels [17].

5.2. Metabolic

Myricetin exhibits strong antidiabetic effects in a metabolic setting [167]. This compound raises insulin sensitivity by activating the AMPK pathway, which causes the liver to produce less glucose and muscle and fat cells to absorb more glucose [168]. Furthermore, myricetin can slow down the intestinal absorption of glucose by blocking the action of the enzyme α-glucosidase [169]. Its effects are also shown in the regulation of lipid metabolism, where myricetin may help avoid obesity and metabolic syndrome problems by suppressing lipogenesis and stimulating fatty acid oxidation [170].

5.3. Neuroprotective

Myricetin's capacity to prevent the aggregation of neurotoxic proteins and lessen the buildup of oxidative stress is intimately linked to its neuroprotective properties [171]. Myricetin has been demonstrated to prevent the development of β-amyloid fibrils and lessen the neurotoxicity they produce in Alzheimer's disease [172]. This compound can maintain mitochondrial activity and shield dopaminergic neurons from oxidative stress in Parkinson's disease [173]. Furthermore, myricetin boosts the brain's natural antioxidant capacity, preserving cognitive function and halting neuronal deterioration [15].

5.4. Anticancer

Myricetin plays a wide range of roles in both cancer prevention and treatment [14]. Molecularly, this compound can restrict the growth of cancer cells by blocking the cell cycle in the G2/M phase and causing death by activating caspase-3 and raising the Bax/Bcl-2 ratio [174]. Moreover, myricetin inhibits angiogenesis by lowering VEGF expression and stops metastasis via altering cell adhesion molecules [175]. Interestingly, myricetin exhibits synergistic effects when combined with traditional chemotherapy medicines, suggesting that it could be used as an adjuvant in cancer treatment [175].

5.5. Antimicrobial

Apart from its anticancer and antioxidant qualities, myricetin also demonstrates broad-spectrum antimicrobial action, which includes antifungal, antiviral, and antibacterial qualities [11]. Myricetin has been shown to have antibacterial properties against a variety of harmful bacteria, including both Gram-positive and Gram-negative ones [176]. For instance, the mechanisms of myricetin sensitivity in *Staphylococcus aureus* and *Escherichia coli* include enhanced permeability, inhibition of important metabolic enzymes, and loss of cell membrane integrity [177]. Myricetin may also prevent the production of bacterial biofilms, which is a major contributor to antibiotic resistance, according to a number of studies [178–180]. As a result, myricetin may be utilized as an adjuvant to treat bacterial infections that are resistant to antibiotics.

5.6. Antivirus

Myricetin's antiviral qualities include the ability to inhibit the growth of different DNA and RNA viruses [113]. According to reports, this compound targets viral DNA polymerase and interferes with viral gene expression in the early stages of infection, hence inhibiting the replication of herpes simplex viruses (HSV-1 and HSV-2) [181]. Myricetin also exhibits antiviral efficacy against RNA viruses, including influenza A, hepatitis C virus (HCV), and SARS-CoV-2, by inhibiting the viral protease and RNA-dependent RNA polymerase (RdRp) enzymes, which are critical for reproduction [182–184]. This demonstrates that myricetin has the potential to be used directly as a treatment for some viral infections in addition to its preventive advantages through immunomodulatory actions [185].

5.7. Antifungi

Meanwhile, there has also been interest in myricetin's antifungal properties. According to in vitro experiments, myricetin can stop the growth of harmful fungus like *Aspergillus niger*, *Candida albicans*, and *Cryptococcus neoformans* [186–188]. The mechanism involves disrupting the biosynthesis of ergosterol, a key component of fungal cell membranes, thereby increasing membrane permeability and causing leakage of cellular contents [189]. Furthermore, myricetin triggers the accumulation of reactive oxygen species (ROS) in fungal cells, leading to oxidative stress and apoptosis [171]. Remarkably, this substance can also prevent the growth of *Candida* biofilms, which is frequently the primary source of resistance to traditional antifungal medications [187]. Therefore, myricetin may be created as an adjuvant or as a stand-alone medication to improve the efficacy of current antifungal therapies [6].

5.8. Other effects

Apart from the aforementioned primary advantages, myricetin also exhibits hepatoprotective properties by decreasing lipid peroxidation and boosting the activity of liver antioxidant enzymes, which may help avoid hepatocellular damage brought on by toxins or oxidative stress [79]. This compound has anti-aging and photoprotective properties in dermatology; it can prevent collagen degradation and decrease UV-induced DNA damage [190]. Not to be overlooked, myricetin also functions as an immunomodulator, specifically by regulating the innate and adaptive immune responses [113]. This prevents excessive inflammation and offers protection against infection. Figure 3 illustrates the diverse health effects of myricetin, including cardiovascular, metabolic, neuroprotective, anticancer, antimicrobial, and other protective benefits.

6. Safety and toxicity of myricetin

Safety and toxicity aspects are important considerations in evaluating the therapeutic potential of a bioactive compound, including myricetin. Although these flavonoids are generally considered safe as part of daily dietary consumption through fruits, vegetables, and tea, toxicological studies in animal models and pharmacological interaction data are still needed to ensure their safe use in pharmacological doses [11].

6.1. Toxicological data on experimental animals

Toxicological studies are an important aspect in assessing the safety of a bioactive compound, including myricetin, before its widespread application in humans [191]. A number of studies on experimental animals have been conducted to evaluate the potential acute, subchronic, and chronic toxicity of this compound. In general, myricetin exhibits a relatively low toxicity profile in various animal models, although some limitations still need to be considered. Table 2 describes the main results of myricetin toxicology tests in experimental animals, including acute, subchronic, reproductive, genotoxicity, and chronic toxicity.

According to acute toxicity testing, giving rats and mice large doses of myricetin did not result in any appreciable fatal side effects. The OECD classification of this chemical as relatively safe is supported by the stated LD_{50} value of more than 2,000 mg/kg of body weight. High dosages often only cause minor gastrointestinal problems, like diarrhea and appetite loss, that don't seriously harm any organs [192].

According to subchronic toxicity tests, myricetin did not significantly alter hematological parameters, liver function (AST, ALT), or renal function (urea, creatinine) when administered repeatedly over a period of 28–90 days. Major organ histopathology, including those of the liver, kidneys, spleen, and heart, similarly revealed no notable structural anomalies. However, some publications have indicated symptoms of oxidative stress in the liver at very high dosages (⩾ 1,000 mg/kgBW/day), suggesting a potential safe limit for long-term usage [193].

Furthermore, myricetin is comparatively harmless for the reproductive system, as evidenced by reproductive toxicology tests conducted on rats, which reveal that it has no effect on fertility, embryo development, or reproductive organ parameters [194]. The micronucleus assay and the Ames test yielded negative mutagenicity data, suggesting that this chemical is not genotoxic at physiological quantities [195].

Even though animal toxicology test results indicate a good safety profile, there are still a number of areas that require more investigation. First, there is currently a dearth of information regarding long-term chronic toxicity effects. Second, different animal species, dosage routes, and myricetin formulations may produce different outcomes. Furthermore, if delivery technologies that improve absorption are employed, the toxicity profile may change since pharmacokinetic and metabolic evidence indicate that limited bioavailability may decrease systemic exposure [196].

6.2. Safe daily consumption limits

The No Observed Adverse Effect Level (NOAEL) value from preclinical experiments is typically used to determine the safe limit for daily ingestion of a natural bioactive molecule. This value is then translated into an Acceptable Daily Intake (ADI) for humans by accounting for the safety factor [197]. According to the OECD guidelines, myricetin is classified as a chemical with a low toxicity level since toxicological investigations have demonstrated that it has a reasonably excellent safety profile with an oral LD_{50} > 2000 mg/kgBW confirmed in experimental animals [198]. Table 3 describes toxicological data and estimates of safe limits for myricetin consumption based on experimental research and interspecies calculations.

Although there were signs of mild liver oxidative stress at the highest dose, subchronic investigations in rats given myricetin at doses up to 1000 mg/kgBW/day for 90 days did not reveal any appreciable changes in hematological parameters, liver function, kidney function, or histology [199]. The NOAEL in animal models is predicted to be between 500 and 1000 mg/kgBW/day based on these studies [200].

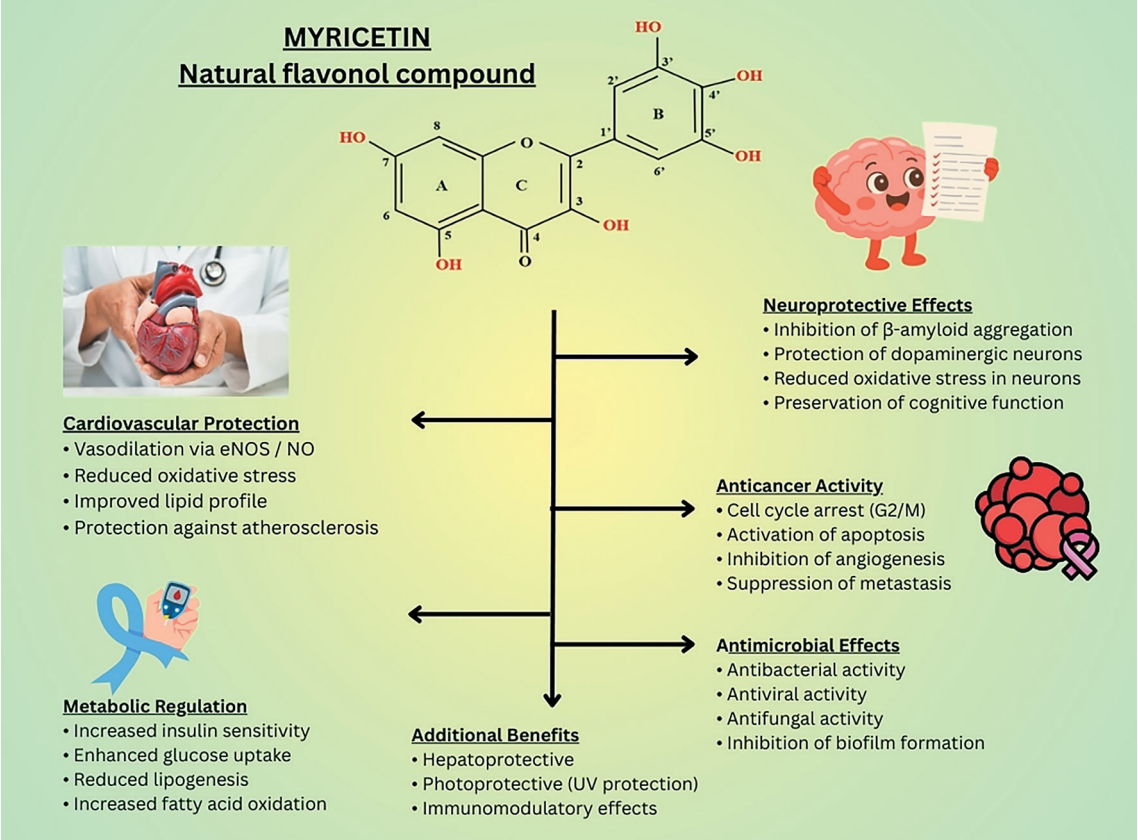

Figure 3. **Overview of the health effects and biological mechanisms of myricetin**
Рисунок 3. **Обзор влияния на здоровье и биологических механизмов действия мирицетина**

Table 2. **Toxicological data of myricetin in experimental animals**
Таблица 2. **Токсикологические данные по мирицетину в экспериментах над животными**

Types of toxicology tests	Species/ Test	Tested dose	Key results	Infor-mation	Reference
Acute toxicity	Rats and mice	Up to > 2,000 mg/kgBW (oral)	There were no deaths, mild symptoms such as diarrhea and decreased appetite	LD_{50} > 2,000 mg/kgBW → considered safe (OECD)	[187]
Subchronic toxicity (28–90 days)	Rats	100–1,000 mg/ kgBW/day	There were no significant changes in hematology, liver and kidney function; histopathology was normal	Doses ⩾ 1,000 mg/kgBW/day trigger mild liver oxidative stress	[188]
Reproductive toxicity	Rats	Up to 500 mg/kgBW/ day	Does not affect fertility, embryonic development, or reproductive organs	Safe for the reproductive system	[189]
Mutagenicity/Genotoxicity	Ames test and micronucleus assay	Physio-logical concentration	Negative result → not mutagenic/genotoxic	Supporting long-term security	[190]
Chronic (long-term) toxicity	Limited data	–	There have been no consistent reports of chronic toxicity effects	Needs further research	[191]

Table 3. **Toxicological data and estimated safe daily consumption limits for myricetin**
Таблица 3. **Токсикологические данные и расчетные безопасные суточные нормы потребления мирицетина**

Parameter	Scientific findings	Reference
LD_{50} oral (animal experiments)	> 2000 mg/kgBW → included in the low toxicity category according to the OECD	[193]
Subchronic studies in mice	90 days, doses up to 1000 mg/kgBW/day → no significant changes in hematology, liver, kidney, histopathology; the highest dose induces mild oxidative stress in the liver	[194]
NOAEL (rats)	500–1000 mg/kgBW/day	[195]
Conversion to human (HED)	≈ 50–100 mg/kgBW/day (based on body surface area)	[196]
Estimated ADI (with safety factor 100)	2–5 mg/kgBW/day → around 120–300 mg/day for adults weighing 60 kg	[13]
Official regulations	There has been no official ADI determination from FAO/WHO JECFA or EFSA	[190]
Natural diet intake	Usually < 10–20 mg/day from consumption of vegetables, fruit, tea, and other natural sources	[197]

The estimated ADI for humans is between 2 and 5 mg/kgBW/day, or 120 to 300 mg/day for an adult weighing 60 kg, if the NOAEL value of 500 mg/kgBW/day in rats is converted to humans using an interspecies conversion factor (based on body surface area) and a conservative safety factor of 100 is added [13,201]. Since international health organizations (FAO/WHO JECFA or EFSA) have not formally determined the safe limit for daily consumption of myricetin, this number is merely a conservative estimate [195].

In addition to supplements, myricetin can be found in a variety of natural foods, including tea, berries, spinach, kale, and onions. Consumption through a regular diet is regarded as safe because the average daily dietary intake of flavonoids (including myricetin) from the consumption of fruits and vegetables is typically significantly lower than the toxic dose in animals [202]. However, the use of myricetin in high-dose supplement form still requires caution due to the lack of long-term clinical trials in humans.

6.3. Potential drug interactions

Myricetin is a polyhydroxy flavonoid found in many fruits, vegetables, teas, and herbs [4]. Apart from its anti-inflammatory, anti-cancer, and antioxidant properties, this compound may interact with medications due to its effects on membrane transporters, pharmacodynamic pathways, and enzymes involved in drug metabolism, particularly the cytochrome P450 system [203]. It's critical to comprehend these interactions

in order to lower the possibility of side effects or decrease the efficacy of treatment. Table 4 shows that myricetin can interact with various drugs through pharmacokinetic and pharmacodynamic mechanisms.

Research on the pharmacokinetics of myricetin has demonstrated that it inhibits a number of CYP450 isoenzymes, specifically CYP3A4, CYP2C9, and CYP2C19 [204–206]. This has consequences for elevated plasma levels of medications that are processed by this enzyme, including phenytoin, warfarin, cyclosporine, and statins, which may result in clinical toxicity. Furthermore, myricetin has an impact on P-glycoprotein (P-gp), a crucial membrane transporter involved in drug excretion [207]. P-gp inhibition may raise the bioavailability of substrate medications like doxorubicin or digoxin, which could raise the risk of nephrotoxicity or cardiotoxicity [207]. Figure 4 shows the safety and interactions of myricetin, indicating general safety from dietary sources with defined LD_{50}, NOAEL, ADI values, and potential interactions via CYP450, P-glycoprotein, and drug synergy.

Myricetin has antidiabetic effects (reducing blood glucose, increasing insulin sensitivity) that can work in concert with other antidiabetic medications, thus raising the risk of hypoglycemia from a pharmacodynamic standpoint [208]. Additionally, the anticoagulant and antiplatelet actions may intensify the effects of clopidogrel, aspirin, or warfarin, this way raising the risk of bleeding [209]. Furthermore, the effects of benzodiazepines and SSRI antidepressants might be amplified by the modulatory actions of neurotransmitters (GABA, serotonin), leading to excessive sedation or mood swings [210].

7. Challenges and future prospects of myricetin

Numerous studies have demonstrated myricetin's promise in terms of health advantages, but before this substance can be widely used in the pharmaceutical and functional food industries, a number of obstacles must be addressed. One of the main limitations is the lack of research continuity from *in vitro* to *in vivo* scale and clinical trials. Studies of cultured cells or animal models continue to provide the majority of the molecular evidence for antioxidant, anti-inflammatory, neuroprotective, and anticancer properties [54]. It is currently insufficient to establish safe and effective dosage recommendations because human clinical evidence is still scarce in terms of amount, sample size, and intervention duration [73]. This suggests that in order to prove the advantages of myricetin in human populations, controlled clinical trials with sound methods are required.

Another significant challenge is the low oral bioavailability of myricetin [211]. This compound has limited solubility in water and is susceptible to presystemic metabolism in the intestine and liver, thus resulting in low systemic concentrations after ingestion [11]. Its stability is further diminished by metabolism via glucuronidation and sulfatation, which frequently prevents biological effects on target tissues from occurring

Table 4. **Potential drug interactions of myricetin based on mechanism**

Таблица 4. **Возможные взаимодействия мирицетина с лекартсвенными средствами на основе механизма его действия**

Interaction mechanism	Potentially involved drugs	Possible effects	Reference
CYP3A4 enzyme inhibition	Statins (simvastatin and atorvastatin), calcium channel blockers, and cyclosporine	Increased plasma drug concentration → risk of toxicity	[198]
CYP2C9 & CYP2C19 Inhibition	Warfarin, phenytoin, and NSAIDs (ibuprofen and diclofenac)	Potential for bleeding (warfarin), increased sedation or toxicity of other drugs	[199–201]
P-glycoprotein (P-gp) inhibition	Digoxin, doxorubicin, and some antiretrovirals	Increased bioavailability → risk of cardiotoxic or nephrotoxic side effects	[202]
Pharmacodynamic interactions with antidiabetics	Metformin, insulin, and sulfonylureas	Additive effect of lowering blood glucose → hypoglycemia	[203]
Interactions with anticoagulant/ antiplatelet agents	Warfarin, aspirin, and clopidogrel	Potential increased risk of bleeding	[204]
Interactions with neuroactive agents	Benzodiazepines and SSRI antidepressants	Additive effects on neurotransmitter modulation (e.g. GABA, serotonin) → sedation or mood interactions	[205]

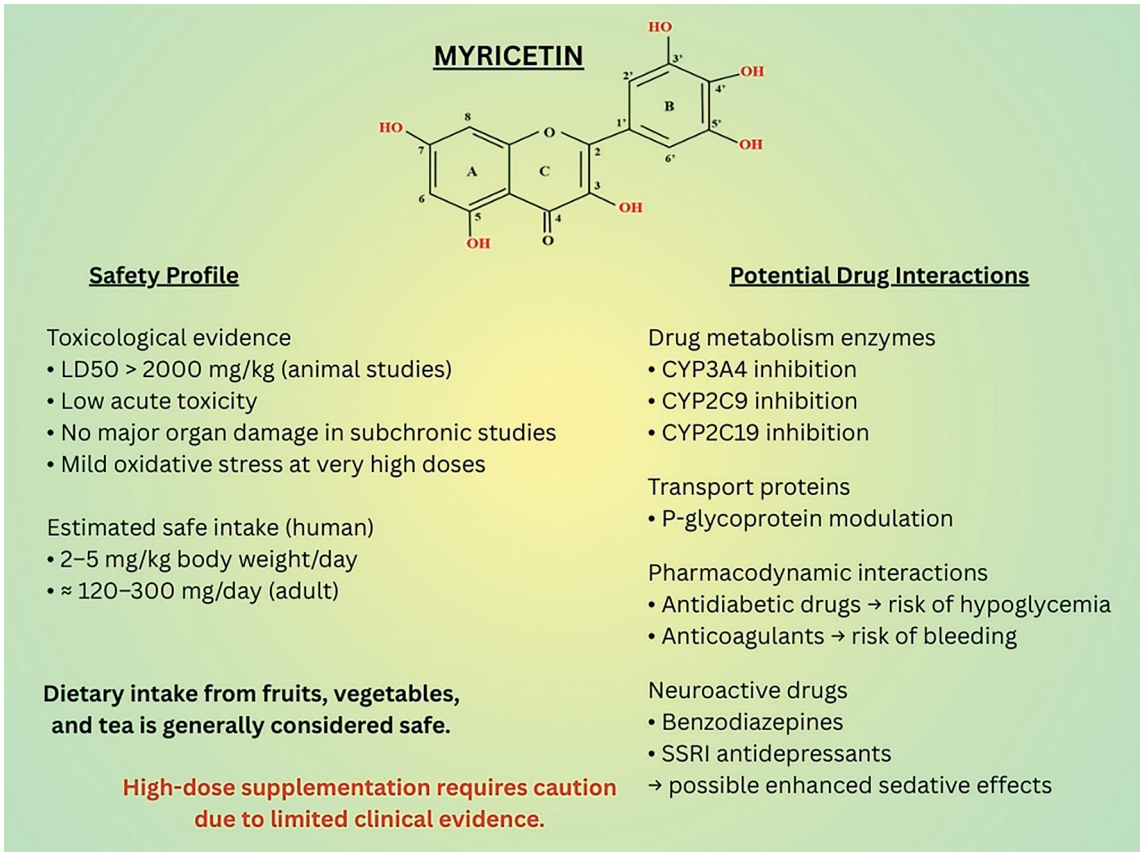

Figure 4. **Safety, toxicity profile, and potential drug interactions of myricetin**

Рисунок 4. **Безопасность, профиль токсичности и потенциальное взаимодействие мирицетина с лекарственными средствами**

at physiological levels [118]. Novel formulation techniques have been created to address this issue, such as complexation with cyclodextrins, liposome-based delivery systems, nanocapsules, and polymeric nanoparticles [212]. It has been demonstrated that this endeavour improves its intestine absorption, stability, and solubility, which may enhance myricetin's biological efficacy [6].

Future possibilities show that myricetin has a lot of potential for development in a variety of applications. This compound can be utilized in the food industry as a bioactive ingredient in functional food items, such as fermented goods, health drinks, or fortified snacks [213]. Myricetin can be prepared as a supplement in powder or capsule form with defined dosages to promote neuroprotective, cardiovascular, and metabolic health [79]. In the pharmaceutical industry, this compound shows promise as a candidate for adjuvant or supplementary medications, particularly in the treatment of cancer, neurological illnesses, and metabolic syndrome [214]. Advances in molecular identification techniques continue to play an important role in biomedical and veterinary research, enabling more accurate detection and characterization of pathogenic organisms and supporting improved disease management strategies [215]. Future research directions should focus on developing formulations that improve bioavailability, exploring synergistic combinations with other bioactive compounds, and conducting large-scale clinical trials to ensure safety and effectiveness in humans.

8. Conclusion

Myricetin is a flavonoid that has many health advantages, including antibacterial, cardioprotective, neuroprotective, anti-inflammatory, antioxidant, and anticancer properties. It works by influencing metabolic and epigenetic processes, controlling cellular signalling, and modifying oxidative stress. However, its application is severely hampered by low dosage guidelines, inadequate absorption, and deficit of extensive clinical data. Further research, particularly controlled clinical trials and the development of delivery technologies that enhance stability and bioavailability, is essential to ensure the safety and effectiveness of myricetin so that it can be optimized as a bioactive agent in functional foods and pharmaceutical therapies in the future.

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