Myricetin and its derivatives; potential therapeutic effect on human health: a review

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Abstract

Myricetin is the plant-based secondary metabolite belonging to flavonoids, a class of natural products. It is a simple structure, ubiquitously present in various fruits, vegetables and beverages. It is the oldest flavonols discovered with a polyphenolic structure as a yellow dye from the bark of *Myrica nagi* Thunb. also known as *Myrica esculenta* Buch.-Ham. ex D. Don (Myricaceae). Myricetin and its derivatives play multiple biological functions and crucial roles in the prevention, treatment and management of human diseases. This review explored the. sources of myricetin, its chemical structure, extraction, isolations, characterizations, biological activities and therapeutic effect of myricetin and its derivatives on human health

Keywords: Anticancer; Biological activities; Human health; Myricetin; Phytochemical.

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Introduction

Nature has an enormous number of plant-based bioactive compounds with significant therapeutic potential and if such compounds are included in our routine diet, they will prove to be a great beneficial impact on human health (Latani et al. 2019; Li et al. 2021; Satpute et al. 2021). In India, it is reported that 2500 species of plant are used by traditional healers and 100 species of plants serve as rich sources of medicine (Pie 2001; Samarth and Sinkar 2019, Hossain and Said 2021; Harouak and Jbijbijen 2022). The bioactive components such as flavonols, flavonoids, anthocyanins, terpenols, terpenoids, and steroids from plants are well investigated (Imrana and Asif 2020; Ahmad et al. 2021; Sinkar et al. 2022; Ali et al. 2022, Mohan and Arasi 2023). Heretofore, around thirteen thousand reports concerning these components are available (Mujeeb et al. 2014). Myricetin is an important member of the flavonoids group of plant-based secondary metabolites (Panche et al. 2016). It was as discovered as the yellow dye having a polyphenolic structure from the bark of *Myrica nagi* Thunb. also known as *Myrica esculenta* Buch.-Ham. ex D. Don of the Myricaceae family (Perkin et al. 1896). Myricetin is more often detected in various fruits, nuts, vegetables and beverages (Shahidi and Ambigaipalan 2015; Semwal et al. 2016). In the modern development of biological sciences have emerged several optimized methods of myricetin extraction and production from plants (Taheri et al. 2020). With the aid of modern techniques potential therapeutic applications of myricetin are reported for several diseases (Song et al. 2021; Wang et al. 2019). In this investigation, we are focusing on sources of myricetin, extraction, isolation, characterizations, biological activity and therapeutic effect of myricetin and its derivatives on human health.

Methodology

This study was initiated with a detailed search for literature relating to sources of myricetin, extraction, isolation, characterizations, biological activity and its therapeutic effect on human health. This review was written according to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 state (Fig. 1.). Related articles up to the year 2023 were identified through searching in Science Direct (https://www.sciencedirect.com/), Scopus (http://www.scopus.com), PubMed / (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://www.Googlescholar.com) and INFLIBNET Library (https://www.inflibnet.ac.in/). All the references of the studies were

screened to avoid any missing articles. The following keywords were used: “Myricetin” OR “3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one” AND “its derivatives” AND “plant source” AND “structure” AND “extraction” AND “isolation” AND “identification” AND “characterization” AND “cardiovascular diseases (CVD)” AND “fattyliver diseases” AND “cancer” AND “obesity” AND “bacterial diseases” OR “antibacterial properties” AND “viral diseases” OR “antiviral” AND “neurodegenerative diseases (NDDs)” in title or abstract. At the beginning, the search was conducted with no restrictions to find relevant articles, then, inclusion and exclusion criteria were applied to select most relevant articles. Here, all keywords related to the primary goals of the study were included to minimize any loss of studies. Entire selection and screening procedures are described in the PRISMA flowchart (Figure ١).

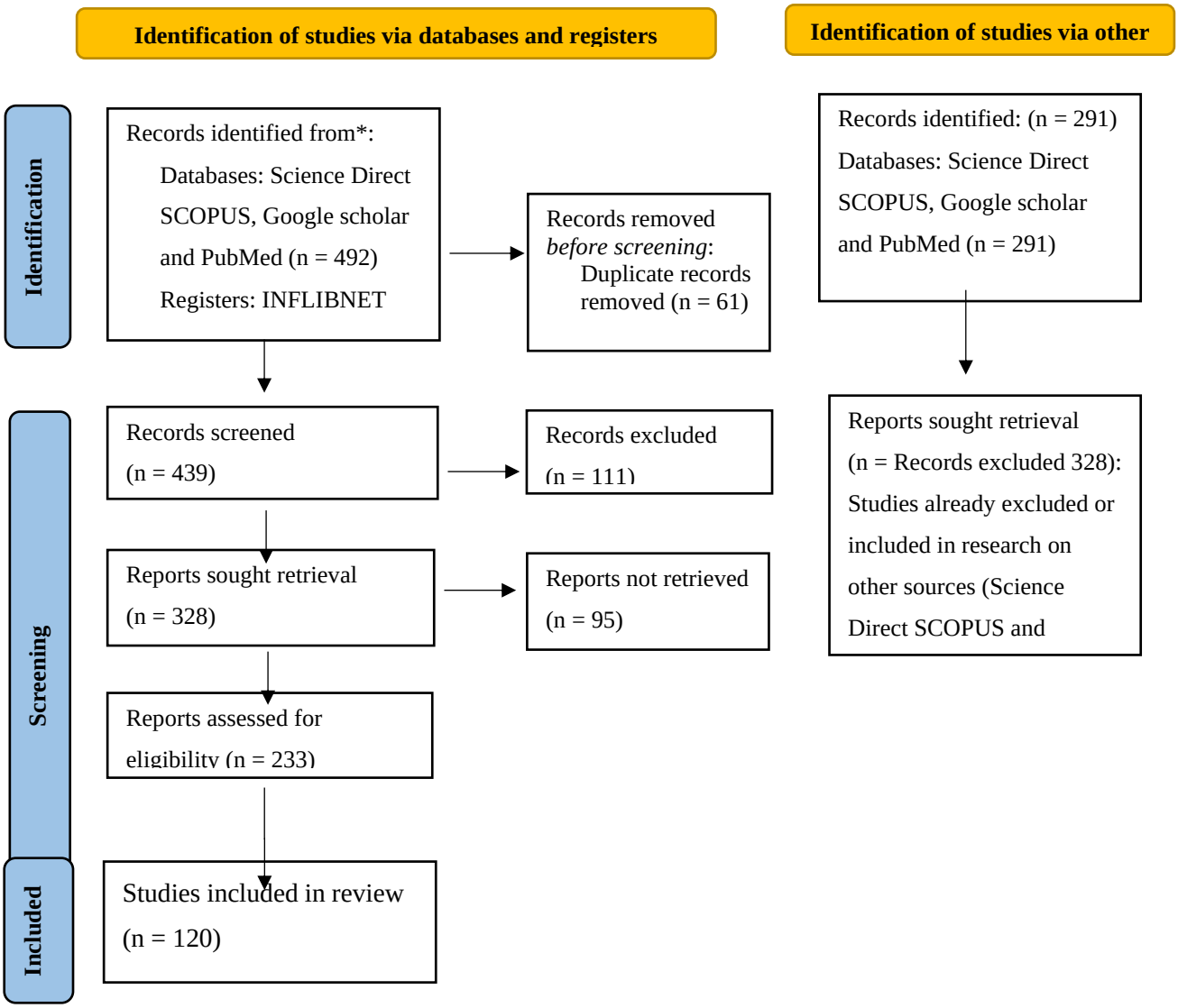
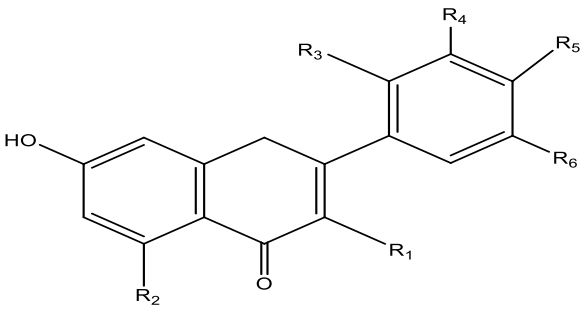


Figure ١: Entire selection and screening procedures are described in the PRISMA flowchart

Myricetin

Myricetin is a well-known flavonoid obtained from plants and their plant parts all over the globe and has significant therapeutic potential (Kumar and Pandey 2013; Panche et al. 2016). It is labelled as 3,5,7-Trihydroxy-2-(3,4,5-Tri-hydroxyphenyl)-4H-1-benzopyran-4-one with IUPAC system of nomenclature. Flavonoids are an important class of secondary metabolites present in plants having polyphenols in their chemical structures. They are more often present in fruits, vegetables and certain beverages. Myricetin is a nutraceutical-recognized flavonoid group of natural products (Taheri et al. 2020). Sometimes myricetin also referred to as hydroxy quercetin which is having structural similarities with quercetin (Semwal et al. 2016) (Figure ٢).



Myricetin: $R_1 = R_2 = R_4 = R_5 = R_6 = OH$, $R_3 = H$,
Myricitrin: $R_1 = Rham$, $R_2 = R_4 = R_5 = R_6 = OH$, $R_3 = H$,
Quercetin: $R_1 = R_2 = R_4 = R_5 = OH$, $R_3 = R_6 = H$,
Morin: $R_1 = R_2 = R_3 = R_5 = OH$, $R_4 = R_6 = H$,
Kaempferol: $R_1 = R_2 = R_5 = OH$, $R_3 = R_4 = R_6 = H$,
Fisetin: $R_1 = R_5 = R_6 = OH$, $R_2 = R_3 = R_4 = H$

Figure ٢: Structure of myricetin and other structurally similar compounds (Semwal et al. 2016).

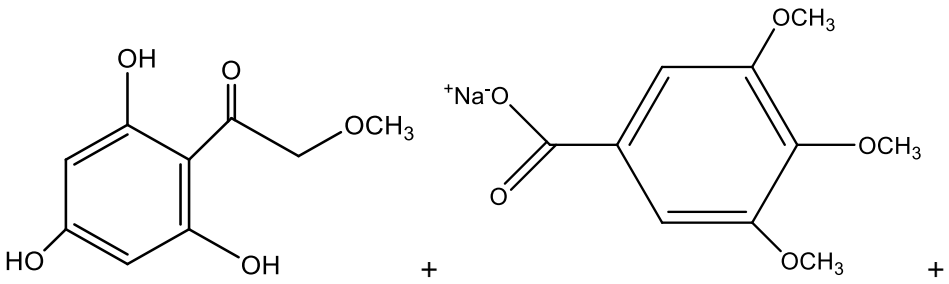
The myricetin is abundant in plant sources and available in free and derived forms with glycosidic linkages such as; myricetin-3-O-(3”-acetyl)--L-arabinopyranoside,myricetin-3-O-(4”-acetyl)--L-arabinopyranoside,myricetin-3-O--L-rhamnopyranoside,myricetin-3-O-D-galactopyranoside, myricetin-3-O- (6”-galloyl)--D-galactopyranoside,myricetin-3-O-D-xylopyranoside,myricetin-3-O--L- arabinofuranoside, myricetin-3-O-(2”-O-galloyl)-L-rhamnoside, myricetin-3-O-(3”-O-galloyl)-L-rhamnoside and myricetin-3-O-L-rhamnoside (De Leo et al. 2006; Kong et al. 2014). The reported biological activity of myricetin and its derivatives on several diseases like Parkinson’s disease (Ara et al. 2017), Alzheimer’s disease (Wang et al. 2017), brain neurodegeneration caused by ischemia (Pluta et al. 2021), Atherosclerosis (Meng et al. 2019), Fatty Liver diseases (Sukkasem et al. 2021), Cancer (Zhou et al. 2023).

Biosynthesis

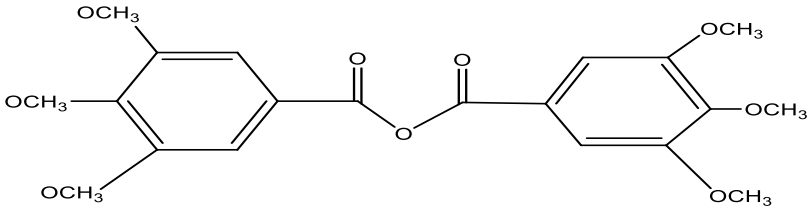
The plant system contains numerous enzymes responsible for the synthesis of secondary metabolites like flavonoids. Enzymes responsible for the synthesis of flavonoids or members of flavonoids are located in between the cytosol and the membrane of the endoplasmic reticulum. Flavonoids are biosynthesized through the phenylpropanoid pathway commenced with the conversion of L-Phe to 4-coumaroyl CoA (Falcone-Ferreyra et al. 2012; Chouhan et al. 2017). Enzymes involved in catalysis are phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (4CH), and 4-coumaroyl CoA ligase. In the case of bacteria, it prefers L-tyrosine as a precursor for heterologous biosynthesis and there is no use of 4CH activity as L-tyr presents hydroxylated form at the position of our interest. For biosynthesis of polyphenolic compounds like flavonoids, bacteria use tyrosine ammonia-lyase (TAL) for heterologous biosynthesis (Kyndtet al. 2002; Watts et al. 2004). The basic structural skeleton for around 9000 members of flavonoids is naringenin chalcone which is formed by the condensation of 4-coumaroyl-CoA with malonyl-CoA (Wang et al. 2011; Falcone-Ferreyra et al. 2012; Chouhan et al. 2017). The precursor for a sort of flavanol is flavanone obtained by the closure reaction of heterocycle C catalyzed by chalcone isomerase (CHI). In some biosynthetic pathways of myricetin, kaemferol is transformed into myricetin. Biosynthesis of Kaempferol is done, by the conversion of naringenin to dihydrokaempferol (aromadendrin) catalyzed by chalcone isomerase (CHI), further this intermediate transform into kaempferol with the help of flavonol synthase 1 (FLS1). Myricetin as the end product is formed by the catalysis reactions of flavonoid 3',5'-hydroxylase (F3'5'H) using kaempferol as the substrate (Marı´n et al. 2018).

Chemical Synthesis of Myricetin

Synthetically myricetin can be produced by using omega-methoxyphloroacetophenone as the precursor of it (Kalff and Robinson 1925) (Figure ٣).

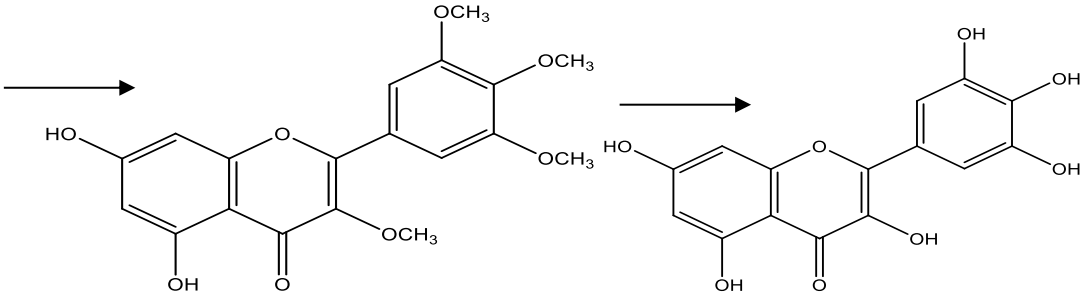


Methoxyphloroacetophenone Sodium trimethylgallate



1. Heat
2. Hydrolysis

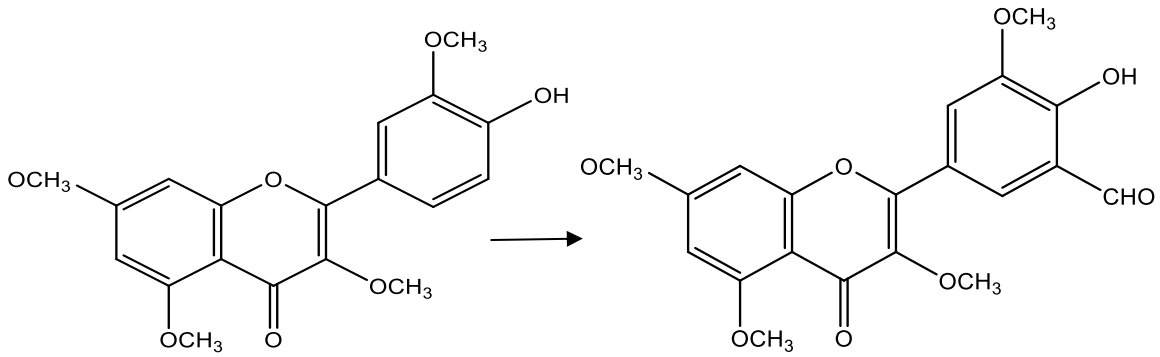
Trimethylgallic anhydride



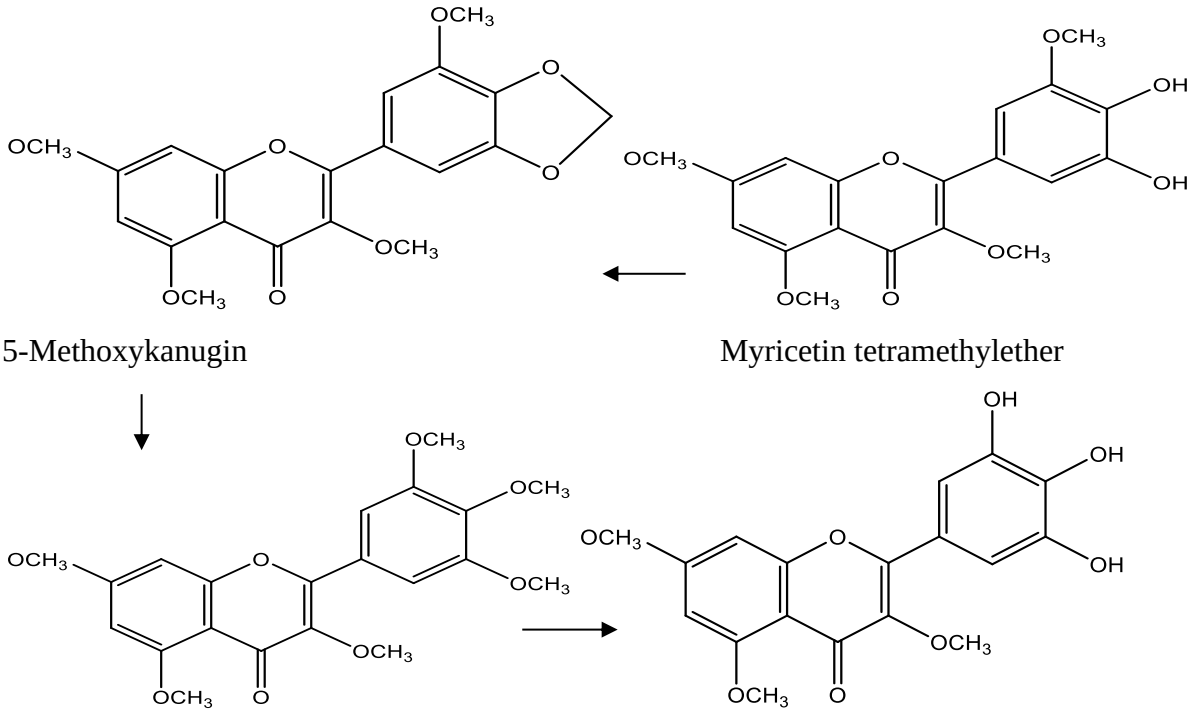
5,7-dihydroxy, 3,3', 4', 5'-tetramethoxyflavone Myricetin

Figure ٣: Synthesis mechanism of myricetin proposed by Kalff and Robinson

The reaction started by heating omega-methoxyphloroacetophenone with trimethyl gallic anhydride and sodium trimethylgallate and further hydrolysis yields an intermediate product 5,7-dihydroxy-3,3',4',5'-tetramethoxyflavone. This intermediate product converts into myricetin by demethylation reaction. Myricetin can also be produced in an alternative way by using quercetin as the starting material and processed by ortho-oxidation reaction (Rao and Seshadri 1948). This synthesis reaction can convert 3,5,3'-tetra-O-methylquercetin to 3,5,7,3'-tetra-O-methoxymyricetin through the aldehydic intermediate further producing to 5-methodykanugin. The cyclizationof 5-methodykanugin at the 4' and 5' positions with immediate hydrolysis and methylation intermediate product formed is hexamethylmyricetin. Subsequent demethylation of this intermediate product yields myricetin (Figure ٤).



Quercetin-3,5,7,3'-tetramethylether 5'-Aldehyde of quercetin-3,5,7,3'-tetramethylether



5-Methoxykanugin Myricetin tetramethylether

Myricetin hexamethylether Myricetin

Figure ٤: Mechanisms of myricetin synthesis proposed by Rao and Seshadri (1948).

Molecular mechanisms of Biosynthesis of Myricetin

The biosynthetic pathways for the synthesis of flavonoids are highly conserved in a diverse group of plant species (Martens et al. 2010). The biosynthesis of flavonoids can be done by catalysis of chalcone synthase (CHS). Chalcone is transformed into 4′OH-flavanone naringenin with the help of enzymes Chalcone isomerase (CHI), which acts as the precursor for diverse members of flavonoids such as flavones, flavonols, flavonols, anthocyanins, and proanthocyanidins (Martens et al. 2010). Biosynthesis of flavonols as the core of montbretinA (MbA) takes place by using hydroxylation of naringenin to 4'OH-dihydroflavonol dihydrokaempferol (DHK) catalyzed by flavanone 3-hydroxylase (F3H). It can also catalyze the conversion of 3′4′OH-flavanone eriodictyol into dihydroquercetin (DHQ) and the 3′4′5′-OH flavanone pentahydroxyflavanone (PHF) into dihydromyricetin (DHM) (Irmisch et al. 2019). Myricetin is not a common sort of flavonoid in all sorts of plant species because of the limited occurrence of its part F3′5′H e.g. Arabidopsis (*Arabidopsis thaliana*) and rice (*Oryza sativa*) (Tohge et al. 2013). DHM is the poor substrate for the synthesis of FLS, hence reports have documented the biosynthesis of myricetin by using DHM as a precursor e.g. *Solanum*

lycopersicum or *S. tuberosum* (Bovy et al. 2002; Tanaka et al. 2008). Fewer reports are available regarding the biosynthesis of myricetin. Derivatives of myricetin are formed as the intermediate product for the synthesis of montbretin. The pathway for the synthesis of montbretin catalyzed by two UDP-dependent glycosyltransferases (UGTs), CcUGT1 and CcUGT2, leads to the formation of myricetin 3-O-rhamnoside and myricetin 3-O-glucosyl rhamnoside (Irmisch et al. 2019). In one of the studies, biosynthesis of myricetin was investigated in plant species *Nicotiana benthamiana* and observed that dihydromyricetin can be transformed into myricetin by the enzyme Montbretia flavonol synthase. In *N. benthamiana,* myricetin is supposed to be a precursor for the biosynthesis of montbretin, and the availability of myricetin is detected in the expression of montbretia flavonol biosynthesis genes and a montbretia MYB transcription factor. Myricetin derivative i.e. myricetin 3-O-glucosyl rhamnoside generated for the biosynthesis of montbretin through the combined expression of montbretia flavonol biosynthesis genes along with CcUGT1 and CcUGT2 (Irmisch et al. 2019).

Sources and therapeutic potential of Myricetin

The leaves and the bark extract of *Myrica rubra* (Lour.) Siebold & Zucc. can be used for the isolation of myricetin and myricetin 3-O-rhamnoside (Wang et al. 2010; Kim et al. 2013). These compounds have the potency to inhibit hyperpigmentation which can be used as a natural skin whitening agent (Matsuda et al. 1995; Pillaiyar et al. 2017). The plant extract obtained from Nigerian native plant *Chrysophyllum albidum* G. has been widely used to treat yellow plague, malaria, diarrhea, and other infections like vaginal and skin infections and has active components as myricetin rhamnoside (Ogunleye et al. 2020; Park and Lee 2021). The herb, *Bidens alba* L. var. minor, rich in myricetin and its derivative, has anti-oxidative potential and prevents DNA damage (Othman et al. 2012; Lin et al. 2013). In one of the studies, conducted in Bangladesh, a scientific group collected mono-floral honey from different regions and found that it contains flavonoids and phenolic acid constituents and the major components were myricetin and naringenin (Moniruzzaman et al. 2014). The leaves of *Leucenia leucocephala* Lam. contain a novel myricetin derivative, myricetin 3-O-(2',3'4'-tri-O-galloyl)-α-L-rhamnopyranoside having a potential antioxidant activity (Haggag et al. 2011). The plant extract was taken from flowers of *Rhododendron mucronulatum* for. *albiflorum* contains myricetin along with other flavonoid contents having anti-diabetic properties like inhibition of aldose reductase (Mok and Lee 2013). Ethyl acetate extract of *Chamaecyparis obtusa* var *formosana* showing antioxidant properties contains myricetin-3-O-α-rhamnopyranoside along

with other secondary metabolites; catechin, quercetin, quercetin-3-O-α-rhamnopyranoside, vanillic acid, and 4-hydroxybenzoic acid (Cheng et al. 2014). The plant extract obtained from *Limonium tetragonum* (Thunb.) having a role in the inhibition of melanin production through melanogenesis-regulating pathways contains the major components as myricetin 3-galactoside and quercetin 3-o-beta-galactopyranoside (Lee et al. 2017). The popular ornamental plant *Rhododendron pseudochrysanthum* contains a myricetin derivative as Myricetin 3-O- β -d-glucopyranoside (Tripathi et al. 2009; Lin et al. 2014). Plant extract of *Nelumbo nucifera* obtained from stamens having anti-oxidative properties possess a myricetin derivative as the major bioactive component (Jung et al. 2003). Leaves extract of *Memecylon edule* Roxb. contains several compounds which shows anti-inflammatory activity, among them one of the active components is myricetin-3-O-α-l-rhamnopyranoside along with 4-O-β-d-glucopyranoside and epigallocatechin-3-O-gallate (EGCG) (Srinivasan et al. 2017; Nualkaew et al. 2017).*Premnaresinosa* (Hochst.) Schauer is a shrub, which has anti-oxidative and anti-proliferative properties majorly it contains myricetin 3,7,3′-trimethyl ether as a bioactive compound (Albadawi et al. 2017). The plant extract was obtained from the leaves of *Miconia albicans* (Sw.) Steud having PTP1B (protein-tyrosine phosphatases) inhibition and anti-diabetic properties contains the principal component as myricetin 3-O-α-l-rhamnopyranoside along with other flavonoids (De Cássia et al. 2018). The ethyl acetate and water fractions obtained from *Dioscorea bulbifera* L. (Dioscoreaceae) having antiviral activity against HIV-1, contains the major bioactive components as myricetin (Chaniad et al. 2016).

Extraction, Isolation and characterization

Maceration, percolation, hydro-distillation, boiling, reflux, soaking, and Soxhlet are just a few of the methods that have been employed to extract flavonoids. To get over the limits of traditional methods for extracting these flavonoids, advanced techniques and strategies are continuously being developed. Recent advances in extraction techniques include enzyme-assisted extraction, pressurized liquid extraction (PLE or accelerated solvent extraction—ASE), extraction assisted by pulsed electric field (PEF), supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), solid-phase extraction (SPE), and ultrasound-assisted extraction (UAE) (Chaves et al. 2020).

The dried leaves of *Inga laurina* (Sw.) Willd. containing myricetin-3-O-rhamnose-3’-O-rhamnoside obtained by liquid-liquid extraction in 90% methanol against hexane,

chloroform, ethyl acetate, and n-butanol can be qualitatively detected and analyzed by UV Spectrophotometer (shown λ_{max} 258 and 353 nm), NMR [(doublets at δ 6.20 and δ 6.37, singlets in δ 6.89 attributed to hydrogens H-2' and H-6' of ring B, other singlets at δ 12.00 corresponds to the hydroxyl hydrogen of carbonyl C-5, δ 5.2 (1H, d, J = 1.2Hz), anomeric carbon (δ 101.94, C-1) of rhamnose] and High-Performance Liquid Chromatography–Electrospray Ionization–Tandem Mass Spectrometry (m/z 609) (HPLC–ESI-MS-MS) (Martins et al. 2019). The methanolic leaf extract of *Betula* species contains myricetin 3-O-galactoside can be detected and characterized by HPLC with photodiode arrayand mass spectrometry (MS) (Germanò et al. 2013). Similarly, methanolic of air-dried bark *Eucalyptus* globules containing myricetin rhamnoside can be characterized and analyzed by HPLC-UV, ESI-QqQ-MS analysis, and ESI-IT-MS-MS analysis (Santos et al. 2011). In one of the experiments looking for myricetin glycoside in the Black Jampa bean (*Phaseolus vulgaris* L.), two methods were employed and it was observed that the methanolic extract contains flavonoid components while extraction done with aqueous acetone contains non-flavonoid components (Aparicio-Fernandez et al. 2005). Similarly, the active components present in *Cochlospermum regium* (Mart. ex Schrank) Pilg., a Brazilian plant like myricetin, and its derivative, and further analysis can be done by HPLC using a reversed-phase C18 column and a UV detection at 280 nm (Arunachalam et al. 2019). A variety of plant sources can be used for the extraction and isolation of myricetin like *Dioscorea alata* L. (tubers) (Deyet al. 2016), *Cuphea spp*. (leaves) (Santos et al. 2020), etc. The extraction and purification of myricetin can be done with the help of molecularly imprinted polymers which has a specific binding capacity with myricetin (Zhong et al. 2014), the affinity of these polymers with myricetin varies with changing the solvent (Wan et al. 2018). Hadjmohammadi and Sharifi (2012) repurposed Derringer's desirability function (method uses multiple scales for decision-making) for analysis and resolution of flavonoids in reverse-phase HPLC. The ultrasound treatment can be combined with a solid-liquid extraction method for time-efficient degradations and extractions of flavonoid compounds like myricetin, rutin and quercetin (Novak et al. 2008).

The technique used for the extraction of myricetin belongs to both conventional and advanced. The conventional techniques are cost-effective but also come with lower yields and lesser purity of the compound. The conventional techniques include maceration, percolation, hydro-distillation, boiling, reflux, soaking and Soxhlet while the advanced which give pure

compounds in higher concentrations but are more expensive such as enzyme-assisted extraction, pressurized liquid extraction (PLE or accelerated solvent extraction—ASE), extraction assisted by a pulsed electric field (PEF), supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), solid-phase extraction (SPE) and ultrasound-assisted extraction (UAE) (Chaves et al. 2020) (Table ١).

Table ١: **Comparison of techniques used in the extraction of Myricetin**

Sr. No.	Name of Technique	Type of technique	Yield	Purity	Time	Cost
1.	Maceration	Conventional	Low	Less	Consuming	Low
2.	Percolation	Conventional	Low	Less	Consuming	Low
3.	Distillation	Conventional	Low	Less	Consuming	Low
4.	Boiling	Conventional	Low	Less	Consuming	Low
5.	Reflux	Conventional	Low	Less	Consuming	Low
6.	Soxhlet	Conventional	Low	Less	Consuming	Low
7.	Enzyme-Assisted Extraction	Advanced	High	High	Saving	High
8.	Pressurized-Liquid Extraction	Advanced	High	High	Saving	High
9.	Extraction Assisted by Pulsed Electric Field	Advanced	High	High	Saving	High
10.	Supercritical Fluid Extraction	Advanced	High	High	Saving	High
11.	Microwave-Assisted Extraction	Advanced	High	High	Saving	High
12.	Solid-Phase Extraction	Advanced	High	High	Saving	High
13.	Ultrasound Assisted Extraction	Advanced	High	High	Saving	High

Once the compound is extracted from the natural source, no single technique is enough to identify the obtained compound. Each analysis technique gives some parameters which help in the identification of compounds. Some of the techniques are interdependent. In HPLC the yield or purity of the compound directly depend on the solvent used for the extraction and analysis. The UV-Spectrometer will show the purity of the compound with higher precision at specific wavelengths. The NMR technique will give the structure of the compound with greater precision as the HPLC and UV-spectrometer have the chances of contamination and misinterpretation, but in the case of NMR, it will give a specific orientation of functional groups, spatial arrangement of atoms on the molecule and their distance from the central

molecule. Mass spectrophotometry or tandem mass spectrophotometry is specifically used for the determination of molecular weight. In the case of techniques like HPLC-UV, ESI-QqQ-MS the techniques are interdependent, the compound is purified through the HPLC and confirmed by UV further analyzed through MS or MS/MS. The purified compound through chromatography can be directly analyzed through other techniques like ESI-IT-MS-MS which helps in the detection of compounds but these latter two techniques come with higher precision barely are highly expensive (Table ٢). The conventional techniques are more often used to obtain the crude product from the biomass or extracellular components. These obtained crude products further process with the modern techniques to get more purified products. The modern and advanced techniques can be used are Enzyme-Assisted Extraction, Pressurized-Liquid Extraction, Extraction Assisted by Pulsed Electric Field, Supercritical Fluid Extraction, Microwave-Assisted Extraction, Solid-Phase Extraction and Ultrasound Assisted Extraction

Table ٢: Comparative analysis of techniques used in the identification of Myricetin

Sr. No.	Technique	Precision	Time	Cost
1.	UV-Spectrophotometer	Double beam ± 0.0015 A Single beam ± 0.003 to 0.005 A	10-60 Sec/min	50-100 Rs/sample
2.	NMR	± 0.01%	1 – 5 Sec/Sample	300-500Rs/sample
3.	HPLC-ESI-MS/MS	± 0.01%	a couple of minutes to hours/sample	10000-15000 Rs/Sample
4.	HPLC-UV	± 0.01%	a couple of minutes to hours/sample	2000Rs/Sample
5.	ESI-QqQ-MS	± 0.01%	one hour or less/sample	2000Rs/Sample
6.	ESI-IT-MS-MS	± 0.01%	a couple of minutes to hours/sample	2000-6000/ Sample

Biological activity of Myricetin

As per the reports available on flavonoids, it is having proven beneficial to use human beings as a vital part of drugs and necessary dietary ingredients (Fig. ٥) (Perkin et al. 1896; Semwal et al. 2016; Vernarelli et al. 2017). It has emerged as a potential therapeutic agent for many human diseases and reports on its novel functions are revealed every day. According to a recent report, myricetin and its derivative dihydromyricetin, isodihydromyricetin inhibit SARS -CoV-2-3CL^{pro} proteases, which is a key molecule for viral replication (Xionget al. 2021). The commercial products of myricetin and their derivatives are known by several synonymic names such as Cannabiscetin, Myricetol, Myricitin, 3,5,7-Trihydroxy-2-(3,4,5-

trihydroxyphenyl)-4H-chromen-4-one, 3,3',4',5,5',7-Hexahydroxyflavone, 3,5,7,3',4',5'-Hexahydroxyflavone, delphidenolon 1575 and 3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one. No other trade names for the myricetin or myricetin derived products are reported by researchers. Significant applications of myricetin and its derivatives for several pathological diseases are mentioned in Figure ٥

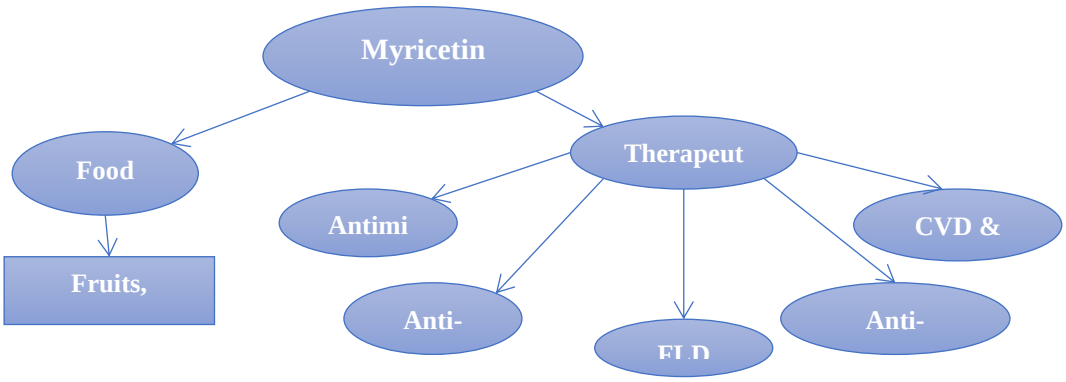


Figure ٥: Diverse applications of myricetin in foods and therapeutics

Cardiovascular Diseases (CVD)

The development of novel drugs and treatment therapies is a rapidly growing field of research. The role of myricetin in the treatment of cardiovascular diseases has been reported in the last few years (Table ٤) (Song et al. 2021). Myricetin plays an important role in CVD by inhibiting the up-regulation of lactate dehydrogenase and creatine kinase (marker enzymes for the detection of myocardial cell injury in isolated Rat Heart), also, it maintains the normal level of superoxide dismutase and oxidized/reduced glutathione (Qiu et al. 2017). Inflammation, oxidative stress and injury to endothelial cells lead to ischemia/reperfusion injury which further leads to tissue injury. States of higher inflammations are responsible for up-regulations of phosphorylation of JNK, TNF-α, IL-1β, IL-6. Myricetin has inhibited the activity of these marker proteins and plays a protective role concerning tissue injury (Sun et al. 2018). Since lipopolysaccharide and streptozocin were found to have an adverse effect on the mouse heart, myricetin was found to have a protective effect against these effects. As a result, it may be used as an adjuvant therapy or as a potential therapeutic approach for malignant cardiac hypertrophy (Liao et al. 2019).

Fatty Liver diseases

Deposition of excess fats in the liver, infections of the hepatitis C virus, over-consuming alcohol and poor dietary lifestyle may lead to conditions of Fatty liver disease (FLD). More than 50 reports are documented on therapeutic applications of myricetin and its derivative in the treatment of FLD (Guo et al. 2019). In an experiment where mice are treated with a high-fat diet and treated with ethanol develops the symptoms, after the treatment of myricetin it was observed that the hepatic histo-morphology attributes were improved along with the expression of metabolic genes like NfKb and TNF-α also retained to normal (Sukkasem et al. 2021). Sun et al. (2021) reported myricetin modulates gut microbiota which lessens hepatic lipid synthesis and inflammation in non-fatty liver diseases (Table ٤) (Sun et al. 2021).

Anti-cancer

Myricetin has the potential role in the treatment of cancer (Xie et al. 2020), it helps in the down regulations of several marker enzymes and inhibits MMP-2 and MMP-9 activity (MMPs are responsible for disrupting the extracellular matrix and tissue remodeling) and also inhibits the activity of inflammatory cytokines like IL-2 and IL-6, TNF α, and IFN-γ and scavenges more than 50% of the reactive oxygen species (ROS) (Afroze et al. 2020). A study showed that myricetin has an anti-metastatic effect in human adenocarcinoma A549 cells *in vitro* conditions, therefore, can be a powerful candidate for developing preventive agents for cancer (Shih et al. 2009). The research provided evidence that myricetin can enhance the radio-sensitivity of tumours in pulmonary carcinoma A549 and H1299 cells in both *in vitro* and *in vivo* settings, suggesting that myricetin may have potential as a radio-sensitizer for the treatment of lung cancer (Zhang et al. 2014). A derivative of S4-2-2 was shown to act as a potential molecular inhibitor of A549 cells. Myricetin has a potential to prevent human placental choriocarcinomas (Yang et al. 2017). Studies revealed myricetin may inhibit the migration and invasion of hepatocellular carcinoma MHCC97H cells (Ma et al. 2019). Myricetin in the treatment of MCF-7 and T47D breast cancer cells has shown enhanced activity apoptosis by increasing the expression of caspase-3, caspase-8, caspase-9, P53, BRCA1, GADD45 (Sajedi et al. 2020; Soleimani et al. 2020). Myricetin can inhibit the migrations and invasion of radio-resistant lung cancer cells (A549-IR) through the FAK-ERK pathway and also inhibits the expression of MMP-2 & MMP-9 (Kang et al. 2020). Myricetin inhibits oxidative DNA damage and mutagenic DNA adduct formation which makes myricetin the protective agent against the

carcinogenic activity of Benzo-[a]-pyrene (Jee et al. 2020). Also, some of the reports documented the biological activity of myricetin against ovarian cancer cells in mice models (Varela-Rodríguez et al. 2020). Wang et al. (2018) noticed that myricetin derivative M10 as a chemoprevention of ulcerative colitis and colorectal tumours in mice. Zhou et al. (2020) reported that myricetin derivative M10 prevents chronic ulcerative colitis by inhibiting necroptosis and therefore, in further clinical trials it is revealed that M10 could be developed as a promising drug for the treatment of chronic ulcerative colitis. The myricetin derivative, S4-10 has the highest anti-tumour efficacy against human non-small cell lung cancer (NSCLC) A549 cells. The anti-tumour potential of the myricetin derivative S4-10 against human non-small cell lung cancer (NSCLC) A549 cells were studied and it was found that derivatives may be used as a promising treatment agent for NSCLC (Zhou et al. 2023).

Anti-obesity

In an experiment to find lipogenesis and body weight increase in the nematode *Caenorhabditis elegans*, Aranaz et al. (2020) studied the role of myricetin along with other phenolic compounds including kaempferol, naringin, hesperidin, epicatechin and found that these molecules are having anti-obesity properties and also protects the organisms from oxidative stress. They also studied the role of myricetin along with other phenolic compounds including kaempferol, naringin, hesperidin and epicatechin for their effect on lipogenesis and body weight increase in the nematode *Caenorhabditis elegan*, study showed the anti-obesity effect of these compounds and also protective actions against oxidative stress and cellular stress like the stress of the endoplasmic reticulum leading to the release of unfolded proteins (Table ٤). If the investigations of myricetin on different animal models for the metabolic pathways that lead to lipogenesis and lipolysis may reveal more significant aspects (Akindehin et al. 2018).

Antibacterial

Myricetin and its derivatives displayed antibacterial activities against several human diseases-causing pathogenic microorganisms (Table ٤). A promising antibacterial activity (20 µg/mL) of myricetin was reported against the Gram-negative anaerobic periodontal pathogens, *Porphyromonas gingivalis* and *Prevotella intermedia* (Cai and Wu 1996). Souza et al. (2010) reported the antimicrobial activity on *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Shigella flexneri, Staphylococcus aureus, Vibrio cholerae* and myricetin showed the significant activity against *P. aeruginosa* (MIC 1.5 µg/mL).

Yadav et al. (2013) reported that myricetin displayed antibacterial activity against *Mycobacterium tuberculosis* with MIC of 50 µg/mL further structure–activity relationship study showed that their anti-tubercular potential due to the presence of hydroxy (-OH) groups in their structure. Myricetin-3,7,3′,4′-tetramethyl ether established antibiotic activity against major human pathogens such as quinolone-resistant *Staphylococcus aureus* (Morimoto et al. 2015). Cetin-Karaca and Newman (2015) reported antibacterial activity against foodborne pathogens.The minimum inhibitory concentration (MIC, mg/mL) showed <15.0, <15.0, < 20.0, <10.0 at 24 h and <20.0, <20.0, <15.0, <5.0 at 60 h incubation for foodborne pathogens *E. coli, S. paratyphi, S. cholerasuis* and *S. enteritidis* respectively. Recently, Wang et al. (2020) reported that Myricetin acts as an α-Hemolysin inhibitor for controlling *Staphylococcus aureus* infection.

Anti-viral

The role of myricetin as an anti-viral drug well established (Table ٤) (Park et al. 2016) and also more than 25 reports are documented on the anti-viral properties of myricetin against SARS. Myricetin-3-rhamnoside extracted from leaves of *Guiera senegalensis* had shown anti-viral activities against Hepatitis B viral (Parvezet al. 2020). Infections of Hepatitis B are responsible for life-threatening chronic liver diseases like liver failure, cirrhosis and hepatocarcinoma. Myricetin has anti-viral activity against the Herpes simplex virus, type-1, and type-2, it can interfere with gD protein (an envelope glycoprotein that binds to the host receptor for entering into) Herpes simplex virus (HSV) type-1 and type-2 and prevents viral activity concerning host (Li et al. 2020). Antiviral properties against African swine fever (ASF) were confirmed by determining the binding capacity of the flavonoid to the viral proteases using FRET (Jo et al. 2020). ASF infections are responsible for high fever, inactivity and bleeding of the skin and internal organs and can lead to death within 2–10 days of infections (Patil et al. 2020). Bourbon virus, a tick-borne virus characterized as a complex syndrome disease with an increased level of aspartate aminotransferase and alanine aminotransferase and its 90% endonuclease activity is inhibited by binding of NS1N specifically to B19V ori, similarly Hao et al. (2020) hypothesized that the myricetin could be a potent inhibitor of Bourbon virus. A molecular docking study shows that the compounds present in Kabasura kudineer (A Siddha medicine churnam; one of the active compounds in this churnam was myricetin) inhibit a protease, 3CL pro of SARS-CoV-12; this finding was based on a binding energy score (Vincent et al. 2020). Myricetin-3-o-rhamnoside obtained from plant extractions is also effective against

Influenza A responsible for diarrhea and other diseases, though it requires thorough study to establish antiviral properties of myricetin and its derivative against Influenza A (Motlhatlego et al. 2021). Myricetin is also reported to reduce inflammatory cytokines like IL-6, IL-α, TNF-α, IFN-γ in bleomycin treated mice and helps in the inhibitions of SARS-CoV-2 M^{pro} (Song et al. 2021; Xiao et al. 2021).

Neurodegenerative diseases (NDDs)

Worldwide, neurodegenerative illnesses like Alzheimer's, Parkinson's, Huntington's, Multiple Sclerosis and Ischemic stroke have emerged as serious health issues. The role of myricetin in the treatment and management of neurodegenerative diseases (NDDs) is mentioned in Table ٤. Myricetin is a potential multifunctional drug for Alzheimer'sdisease (Wang et al. 2017), Parkinson's disease (Ara et al. 2017). The preclinical activities study revealed that myricetin acts as a neuro-protective in Huntington's disease and amyotrophic lateral sclerosis (Taheri et al. 2020). Myricetin showed promising effects in the prevention and treatment of brain neurodegeneration caused by ischemia (Pluta et al. 2021).

There are other flavonols other than myricetin showing significant biological activities such as Quercetin, Epigallocatechin gallate, Kaempferol, Luteolin, Hesperidin, Apigenin, Cyanidin, Genistein, etc. are known for their significant properties like anti-oxidative, anti-inflammatory and anti-cancerous activities. Some of the flavonoids in addition to these activities are also showing significant activity such as antiviral activity (e.g. Quercetin), Neuroprotective activity (e.g. Epigallocatechin gallate) and strengthening blood vessels (e.g. Hesperidin). Above mentioned properties makes these flavonoids most demanding in industries as the major food supplements and health products. Lastly, the sources of Myricetin in different parts of the plant, type of extraction and reported biological activity health benefits of Myricetin and its derivatives are mentioned and summarized in Table ٣ and ٤

Table ٣- Presence of Myricetin in different parts of the plant, type of extraction and reported biological activity of Myricetin and its derivatives

Plant name	Plant part (s)	Type Extraction/Yield	Analysis/ identification techniques	Myricetin/its derivatives	Biological activity	References
Myrica rubra (Lour.) Siebold &Zucc.	Leaves	Ethanolic extraction at room temperature for 24 h.Final yield of myricetin was 2.05 g and myricetin 3-O-rhamnoside 910 mg obtained from 11.5kg of leaves.	Bioassay guided fractionation using column chromatography on silica gel.	Myricetin and myricetin 3-O-rhamnoside	Myricetin Conc. of 10µg/mL and 50µg/mL respectively showed 12.3% and 21.2 % Inhibitory effects on tyrosinase activity. Myricetin 3-O-rhamnoside conc. of 10µg/mL and 50µg/mL respectively showed 4.3% and 21.6 % inhibitory effects on tyrosinase activity.	(Matsuda et al.1995)
Nelumbo nucifera Gaertn.	Stamens	Refluxed with methanol for 3h. The final yield was 25 mg from 3.4 kg dried stamens.	Silica gel and Sephadex LH-20 column chromatography.	Myricetin 3',5'-dimethylether 3-O-beta-D-	Antioxidant activity,	(Jung et al. 2003)

				glucopyranoside	with 50% inhibition concentration (IC50) values of 13.5µg/mL.	
*Leucenialeucocephala*Lam.	Leaves	Hot methanolic extraction under reflux. The final yield was 40 mg from 1kg of dried leaves.	Fractionated on Sephadex LH-20 column (Ø 3.5 × 100 cm).	Myricetin 3-O-(2',3'4'-tri-O-galloyl)-α-L-rhamnopyranoside	Antioxidant activity (SC50=2.49 µg/ml). High cytotoxic activity (IC_{50}=2.41).	(Haggag et al. 2011)
Bidens alba L. Var. Minor and *Centella asiatica* L.	Whole plant	Extracted into distilled deionized (dd)H_2O, then heated to 90°C in a steam bath and refluxed for 2 h. Then sonicated for 5 min.	High-performance liquid chromatography (HPLC)	Myricetin	Antioxidant activity *Bidens alba* L. Var. Minor Samples (100 µg/mL) TEAC (mM Trolox) 184.61 *Centella asiatica* L. Samples (100 µg/mL) TEAC (mM Trolox)132.80	(Lin et al. 2013)
*Rhododendron mucronulatum*for. *Albiflorum*	Flowers	Extracted with MeOH for 3 h under reflux at 65–75 C. MeOH extract (255.1 g) was collected.	Bioassay guided fractionation using column	Myricetin	Inhibitory activities against aldose reductase 2.67µg/mL.	(Mok and Lee 2013)

			chromatography on silica gel.			
*Rhododendron aberconwayi*cowan	Leaves	Ultrasound-assisted extraction for 30 min at room temperature.	Semipreparative HPLC using a PU-2080 pump.	Myricetin 3-O-β -d-glucopyranoside	Antioxidant activity	(Lin et al. 2014)
Chamaecyparisobtusa var. Formosana	Leaves	Boiling double-distilled water and allowed to infuse for 6 h. crude extract (579 g) was fractionated.	Semipreparative HPLC.	Myricetin-3-O-α-rhamnopyranoside	Antioxidant activity myricetin-3-O-α-rhamnopyranoside (4) contents (mg/ g of crude)6.79 ± 0.2 IC50 (μM) DPPH radica7.2 ± 0.2 c *C. elegans* survival (%)70.1 ± 0.7 c	(Cheng et al. 2014)
Etlingera elatior (Jack) R.M.Sm.	Flowers	Extraction with hydroethanolic refluxed for 2 h at 65 °C.	Ultra-high performance liquid	Myricetin	Antioxidant and anticancer activity	(Ghasemzadeh et al. 2015)

			chromatography (UHPLC)			
Dioscoreabulbifera L.	Bulbil	Macerated with ethanol at room temperature. and concentrated under reduced pressure to obtain the ethanol extract (258.0 g) and fractionation with ethyl acetate.	A bioassay-guided isolation by vacuum liquid chromatography (VLC) using silica gel and Sephadex LH-20	Myricetin	Anti-HIV-1 integrase activity most potent activity with an IC50value of 3.15mM	(Chaniad et al. 2016)
Premnaresinosa (Hochst.)	Aerial parts	Methanolic extraction by using Soxhlet apparatus For 4 h. give a crude methanol extract (90 g). (myricetin 3,7,30 -trimethyl ether, 10 mg) was obtained from this fraction.	A bioassay-guided fractionation.	Myricetin 3,7,3'-trimethyl ether	Antimicrobial activity against Acinetobacter baumannii and S. flexneri with MIC values of 0.01–0.25 mg/mL Myricetin 3,7,30 -trimethyl ether showed interesting	(Albadawi et al. 2017)

					cytotoxic activity with IC50 values of 7.0 lg/mL. Antioxidant activity was revealed by myricetin 3,7,30 -trimethyl ether (80.9%)	
Memecylon edule Roxb	Leaves	Macerated at room temperature.	separated by preparative RP-HPLC.	Dihydromyricetin-4'-β-d-glucopyranoside, myricetin-3-O-α-l-rhamnopyranoside	Anti-inflammatory activity, myricetin-3-O-α-l-rhamnopyranoside at 100 µM showed inhibition of 19.46 ± 0.84%	(Nualkaew et al. 2017)
Limoniastrumguyoni anum	The aerial parts	Infusions preparationat room temperature for 5 min	Characterized by HPLC-DAD-ESI/MSn	Myricetin-3-O-glucoside and myricetin-O-rhamnoside	Antibacterial activity Antibacterial activity 34 of the infusions ranged between 2.5 and 20 mg/mL (MIC values)	(Ziani et al. 2018)

Miconia albicans (Sw.) Steud.	Leaves	Sonication. Yielding a crude defatted extract (4.0 g).	HPLC-HRMS-SPE-NMR.	Myricetin 3-O-α-l-rhamnopyranoside	Antidiabetic activity	(De Cássia et al. 2018)
Inga laurina(Sw.) Willd.	Leaves	Maceration at room temperature with ethanol (95%) for 48h and Liquid-liquid extraction. Final yield was 500.0 mg.	Column Chromatography with Sephadex LH20	Myricetin-3-O-rhamnoside	Antifungal activity	(Martins et al. 2019)
Chrysophyllumcainito L.	Leaves	Extracted with 70% aqueous methanol evaporated under reflux at 40–50 °C. The solvent was evaporated to dryness and the yield was 16 and 90 g for chloroform and methanol extracts, respectively. The final yield was 17mg.	Column chromatography on cellulose and Sephadex LH-20 with 20–60% aqueous MeOH as an eluent.	Myricetrin, myrecetrin 3``-O-gallate	The extract reduces the liver and kidney toxicity induced by exposure to gamma radiation.	(Sayed et al. 2019)
Tecomaria capensis v. aurea	Shoots	Hydroalcoholic extraction for 3 days at room temperature.	Chromatography -Sephadex LH-20 and identified	Myricetin	Improving wound curing in Rats	(Elshamy et al. 2020)

	Crude extract fractionated on silica gel flash CC (5 × 60 cm). Final yield was 123.4 mg.	with 1H NMR (Bruker, 500 MHz) and 13C NMR (125 MHz) and mass spectroscopy.

Table ٤: Biological Activities and health benefits of Myricetin and its derivatives

Source of Myricetin	Name of Myricetin or Myricetin derivatives	Human Diseases	Biological Activities and health benefits of Myricetin and its derivatives	**Reference**
Chengdu Must Bio-Technol Co., LTD. (Chengdu, China).	Myricetin	Cardiovascular Diseases (CVD)	Protective in cardiovascular diseases.	(Qiu et al. 2017)
Aladdin.	Myricetin		Inhibition of marker proteins (JNK, TNF-α, IL-1β, IL-6) activity.	(Sun et al. 2018)
Shanghai Winherb Medical Science Co., Ltd. (Shanghai, China).	Myricetin		Potentially effective as an adjuvant or a treatment for malignant cardiac hypertrophy.	(Liao et al. 2019)

Myricetin source not mentioned	Myricetin	Fatty Liver diseases	AMP-activated protein kinase (AMPK) phosphorylation is inhibited by myricetin.	(Guo et al. 2019)
Chengdu Biopurify (Chengdu, China).	Myricetin		Improves hepatic histomorphology, restores the expression of metabolic genes (NfKb and TNF), strengthens the antioxidant system, and suppresses inflammatory pathways.	(Sukkasem et al. 2021)
Myricetin supplements, source not mentioned	Myricetin		Reduces hepatic lipid production and inflammation in non-fatty liver disorders by modifying the gut microbiome.	(Sun et al. 2021)
Sigma-Aldrich (St. Louis, MO)	Myricetin	Cancer	*in vitro* Antimetastatic effect in human adenocarcinoma A549 cells.	(Shih et al. 2009)
Sigma-Aldrich.	Myricetin		Radiosensitizer for the treatment of lung cancer	(Zhang et al. 2014)
Sigma Aldrich.	Myricetin		Myricetin has structural similarity with ATP hence it is able to mimic ATP and acts as an anticancer agent.	(Park et al. 2016)
SigmaeAldrich, Inc (St. Louis, MO, USA).	Myricetin		Act as potentially preventive in human placental choriocarcinomas	(Yang et al. 2017)
Chengdu PushiBiotechnology Co., Ltd.; purity, 98%),	Myricetin		Inhibit the migration and invasion of hepatocellular carcinoma MHCC97H cells	(Ma et al. 2019)

Originally isolated *from Myrica nagi*	Myricetin	Anticancer effect	(Xie et al. 2020)
Extrasynthese (Lyon Nord, France).	Myricetin	Inhibits the activity of inflammatory cytokines like IL-2 and IL-6, TNF α, and IFN-γ and scavenges more than 50% of the reactive oxygen species (ROS)	(Li et al. 2019; Afroze et al. 2020)
Sigma, USA.	Myricetin	Myricetin was effective in treatment of MCF-7 and T47D breast cancer.	(Sajedi et al. 2020; Soleimani et al. 2020)
Dietary flavonoid myricetin	Myricetin	Inhibit the migrations and invasion of radioresistant lung cancer cells (A549-IR).	(Kang et al. 2020)
Sigma-Aldrich Chemical (St. Louis, MO, USA).	Myricetin	Inhibits oxidative DNA damage and mutagenic DNA adduct formation.	(Jee et al. 2020)
Sigma-Aldrich© Chemical Co. (St. Louis, Missouri, EE.UU.)	Myricetin and its derivative	Protective action against ovarian cancer cells in mice models	(Varela-Rodríguez et al. 2020)
Myricetin derivative provided by Dr Li in Marine (Biomedical Research Institute of Qingdao).	Myricetin derivative M10	Exerts chemoprevention of ulcerative colitis and colorectal tumor in mice.	(Wang et al. 2018)

M10 derivative was provided by Dr. Li in Marine (Biomedical Research Institute of Qingdao).	Myricetin derivative M10		Prevents chronic ulcerative colitis.	(Zhou et al. 2020)
The original myricetin was p urchased from Macklin, Shanghai, China and the derivative was synthesized.	Myricetin derivative S4-10		Antitumor potential against human non-small cell lung cancer (NSCLC) A549 cells	(Zhou et al. 2023)
Myricetin analytical standard obtained from SIGMA Aldrich (St. Louis, MO, USA).	Myricetin	Obesity	Anti-obesity properties and also protects the organisms from oxidative stress.	(Aranaz, et al. 2020)
A crude Methanolic extract of flower buds of *Syzygiumaromaticum* (clove)	Myricetin	Bacterial diseases	Myricetin showed the significant activity against *P. aeruginosa, Mycobacterium tuberculosis* (MIC 1.5 µg/mL), (MIC of 50 µg/mL) respectively.	(Cai and Wu 1996; Souza et al. 2010; Yadav et al. 2013)
Not mentioned	Myricetin-3,7,3′,4′-		Antibiotic activity against quinolone-resistant S*taphylococcus aureus*	(Morimoto et al. 2015)

	tetramethyl ether			
Sigma-Aldrich, St Louis, MO, USA	Myricetin		Antibacterial activity against foodborne pathogens.	(Cetin-Karaca and Newman 2015)
Herbpurify (Chengdu, China)	Myricetin		Acts as an α-Hemolysin inhibitor for controlling *Staphylococcus aureus* infection.	(Wang et al. 2020)
Myricetin-3-rhamnoside was isolated from *Guiera senegalensis* n-bu-tanol fraction	Myricetin-3-rhamnoside	Viral diseases	Anti-viral activities against Hepatitis B viral	(Parvez et al. 2020)
Purchased from Topscience Co., Ltd. (Shanghai, China).	Myricetin		Anti-viral activity against the Herpes simplex virus, type-1, and type-2, it can interfere with gD protein.	(Li et al. 2020)
A flavonoid library	Myricetin		Antiviral activity against African swine fever (ASF)	(Jo et al. 2020)
Sigma-Aldrich, St Louis, MO, USA	Myricetin		Potent inhibitor of Bourbon virus	(Hao et al. 2020)
The source of Myricetin was *Syzygium aromaticum* (plants included in Kabasurakudineer)	Myricetin		Inhibit a protease, 3CL pro of SARS-CoV-12.	(Vincent et al.2020)

Newtonia buchananii plant	Myricetin		Anti-viral activity Influenza A	(Motlhatlego et al. 2021)
Myricetin-3-o-rhamnoside (myricitrin), isolated using acetone and methanol-dichloromethane as solvent from leaf and stem of *Newtonia buchananii*	Myricetin		Reduce inflammatory cytokines (IL-6, IL-α, TNF-α, IFN-γ).	(Song et al. 2021; Xiao et al. 2021)
Source of myricetin not mentioned.	Myricetin	Neurodegenerative diseases (NDDs)	Potential multifunctional drug for Alzheimer's and Parkinson's disease	(Wang et al. 2017; Ara et al. 2017)
Fruits and vegetables.	Myricetin		Prevention and treatment of brain neurodegeneration caused by ischemia	(Pluta et al. 2021)

Structure-activity relationships (SARs) and Mechanism

Myricetin is structurally related to phenolics compounds (Fig. 2) such as quercetin, morin, kaempferol and fisetin (Semwal et al. 2016). It is sometimes referred to as hydroxyquercetin resulting from its structural similarity to quercetin. Semwal et al. (2016) studied SARs and suggested that the strongest inhibitors of COX-2 expression are thought to be the double-bond at C2-C3 and the keto group at C-4. Park et al. (2016) reported that due to its structural resemblance to ATP and ability to mimic ATP, myricetin serves as an anticancer drug against many cancers through a variety of molecular mechanisms. Myricetin's anticancer targets are therefore protein kinases and ATPases. A hydrophilic group is added to myricetin to create the M10 derivatives. This hydrophilic group gives M10 good water solubility (>0.1 g/ml) and a median fatal dose (LD50 was >5 g/kg in mice) due to its potent effects. M10 derivatives of myricetin appear to have an excellent safety profile as an oral chemoprevention drug (Wang et al. 2018; Zhou et al. 2020).

The pure myricetin compound helps in the reduction of malondialdehyde which is generated because of UV-B irradiations and helps in the reduction of UVB-induced keratinocyte death (Huang et al. 2010).

Conclusion and Future prospective:

This investigation focus on methods of extractions, isolations, characterizations, biological activity and therapeutic effect of myricetin and its derivatives on human health, reported during last few decades (Table ٤ & ,٣ ,٢ ,١). Our findings showed that myricetin is a simple structure belongs to naturally occurring flavonoids (Panche et al. 2016; Kumar and Pandey 2013). It has wide sources including vegetables, fruits, nuts, berries and tea, it is well-recognized for its nutraceutical value (Shahidi and Ambigaipalan 2015; Semwal et al. 2016; Taheri et al. 2020).

The methods employed for extraction includes both conventional (Maceration, Digestion, Infusion and percolation, Decoction, Soxhlet extraction) as well as non-conventional method (Accelerated solvent extraction (ASE), Ultrasound-assisted extraction, UAE (sonication extraction) (Chaves et al. 2020), Supercritical fluid extraction (SFE), Enzyme-assisted extraction (EAE), Pressurized hot water extraction (PHWE) of extraction. Conventional extraction methods use simple and low-cost equipment, large amounts of solvent

and extended extraction times working at atmospheric pressure and at relatively higher temperatures. Whereas, unconventional, which are modern and uses more expensive and sophisticated equipment that saves extraction time and generally can work at higher pressure and temperature values. The solvents methanol, hexane, chloroform, ethyl acetate and n-butanol have been used (Martins et al. 2019). It is found that Bioassay-guided fractionation is a widely used method for the identification of myricetin and its derivatives in crude plant extracts, despite it is laborious and time-consuming (Table ٣ &١).

In the characterization, various techniques have been reported such as UV Spectrophotometer, Nuclear Magnetic Resonance (NMR), High-Performance Liquid Chromatography–Electrospray Ionization–Tandem Mass Spectrometry (HPLC–ESI-MS-MS) (Martins et al. 2019), High-Performance Liquid Chromatography (HPLC) with photodiode array and Mass Spectrometry (MS) (Germanò et al. 2013), High-Performance Liquid Chromatography with Ultra Violet detection (HPLC–UV), ESI-QqQ-MS analysis and ESI-IT-MS-MS analysis, HPLC using a reversed-phase (C18 column) and a UV detection (at 280 nm) (Arunachalam et al. 2019)(Table ٢).

Myricetin and its derivatives play multiple biological functions and crucial roles the prevention, treatment and management of human diseases (Table ٤). These diseases include cardiovascular diseases (CVD)(Qiu et al. 2017; Sun et al. 2018; Liao et al. 2019), fatty Liver diseases (Guo et al. 2019; Sukkasem et al. 2021), anti-cancer (Zhang et al. 2014; Park et al. 2016; Yang et al. 2017; Ma et al. 2019; Xie et al. 2020; Afroze et al. 2020; Sajedi et al. 2020; Soleimani et al. 2020; Kang et al. 2020; Jee et al. 2020; Varela-Rodríguez et al. 2020; Wang et al. 2018; Zhou et al. 2020; Zhou et al. 2023), anti-obesity(Aranaz, et al. 2020), antibacterial (Cai and Wu 1996; Souza et al. 2010; Yadav et al. 2013; Morimoto et al. 2015; Cetin-Karaca and Newman 2015; Wang et al. 2020)and anti-viral diseases (Jo et al. 2020; Hao et al. 2020; Vincent et al.2020; Motlhatlego et al. 2021; Song et al. 2021; Xiao et al. 2021). It is also found that it has antioxidant (Haggag et al. 2011;Chenget al. 2014)and anti-inflammatory properties (Srinivasan et al. 2017; Nualkaew et al. 2017; Afroze et al. 2020, Song et al. 2021; Xiao et al. 2021). Moreover, myricetin is a promising molecule in the prevention and treatment of neurodegenerative diseases like Parkinson's disease (Ara et al. 2017), Alzheimer's disease (Wang et al. 2017), Huntington's disease and Amyotrophic Lateral Sclerosis (ALC) (Taheri et al. 2020), brain neurodegeneration caused by ischemia (Pluta et al. 2021) which of course set a

trail for the exploration and establishment of nature-derived medicines for human society (Table ٤).

The modern time after the discovery of novel instrumentation and techniques, our scientific society has a solid base to identify more indigenous plant sources, discover their role in human health care and hence share the medical burden either at the level of the globe or at the level of the country. The available literature on myricetin sources points out that scientists need to identify more indigenous sources of flavonoids and other necessary secondary metabolites, especially in India as it is having greater biodiversity and is a great resource for various vegetation which differs from north to south to east to west. The findings of indigenous sources and their thorough study from different regions will surge sustainability and will pave the path for alternative health care.

In conclusion, we observed in our present investigation, myricetin is having major significant therapeutic potentials such as anti-inflammatory, anti-cancerous and anti-oxidative activity. Myricetin can be also used in the treatment of cardiovascular diseases, fatty liver diseases, anti-obesity, anti-bacterial, anti-viral and neurodegenerative diseases, etc. Other than myricetin there are other flavonoids, that can also easily obtained from our food supplements such as Quercetin, Epigallocatechin gallate, Kaempferol, Luteolin, Naringenin, Hesperidin, Apigenin, Cyanidin and Genistein, etc. with similar effective significant therapeutic potentials. These flavonoids are most demanding for their potential activity in industries and healthcare sector. Along with the conventional techniques modern techniques are also available for the extraction of such a vital component and more compounds needs to be reveal with such available techniques.

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