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Ethnobotanical, Pharmacological And Phytochemical Assessment Of Myrica Rubra: A Review

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Abstract

This article provides a comprehensive overview of the historical cultivation, traditional usage, morphology, and various biological activities of the Chinese bayberry (Myrica rubra). Cultivated for more than two millennia, the Chinese bayberry is a subtropical fruit tree that has both culinary and commercial value. Conventional therapies have utilized their diverse components. This stone fruit is abundant in vitamins and yields a diverse range of products. The plant has a variety of biological functions, and its extracts have encouraging effects on heart health, cancer cell prevention, and metabolic issues linked to obesity. The fruit has a wonderful taste and several health advantages, such as demonstrating considerable antioxidant, anti-diabetic, anti-inflammatory, antibacterial, and anti-cancer capabilities. The chemical composition of bayberry was thoroughly assessed in this study, including its anthocyanins, flavonoids, diarylheptanoids, organic acids, amino acids, peptides, and sugar. To

comprehensively understand the mechanisms and structure-activity relationships of these natural compounds and to underscore their potential therapeutic applications for human health, further investigations are required.

Introduction

Originating in China, the Chinese bayberry (Myrica rubra Sieb. et Zucc.), a subtropical perennial tree that grows across Asia, including Japan, Korea, and China (Chen, 2004). In addition to its scientific name, Myrica rubra, it goes by several colloquial names, including yangmei, Chinese bayberry, and red bayberry (M. Wang, Ying Liu, Rui-Le Pan, Rui-Ying Wang, Shi-Lan Ding, Wan-Rui Dong, Gui-Bo Sun, Jing-Xue Ye, and Xiao-Bo Sun., 2019).

The cultivation of Chinese bayberry (Myricaceae) in the Chinese core dates back approximately two millennia.(Chen PingHong, 2017). The bayberry fruit is renowned for its mouthwatering flavor, richness, attractive hue, and significant economic worth. According to reports, Myrica rubra possesses antiviral, antioxidant, and antibacterial qualities(Liu HongBo, 2009). Various signs of this plant's ethnomedical use have been documented in herbal literature and folklore. It has been utilized to create wine and other drinks with antifungal and antioxidant qualities because of its pleasing sweet/sour flavor (Mo, 2024). According to reports, Myrica rubra is used to treat diarrhea, gastrointestinal ulcers, and a variety of skin disorders, including swelling and bruising (Masuda, 2010). According to traditional literature, it can be taken orally to treat diarrhea and duodenal ulcers. It has also shown healing effects in the case of a bone fracture (Chen PingHong, 2017). Extracts of M.rubra have shown diverse functions such as antioxidant, antifungal, anti-obesity, and inhibitor of melanin synthesis (MATSUDA, 1995), an antiviral such as an anti-influenza (Mochida, 2008) and antitumor (Yang, 2003).

Many active chemical components of this plant, such as anthocyanins and flavonoids, have been identified but a complete profile of its chemical constituents is yet to be given(Chen PingHong, 2017). All the parts of the plant contain important phytochemicals with great pharmacological activities; therefore, medicinal formulations involve its fruit, leaves, bark, seed, and roots. Particularly helpful for conditions including congestion, coughing, diarrhea, and digestive disorders are fruits and leaves. The bark is used to cure wounds, ulcers, skin conditions, and arsenic poisoning (He, 2004).

Taxonomical Classification of Myrica rubra:

Kingdom: Plantae
Subkingdom: Tracheobionta, Angiorspermea
Order: Fagales
Family: Myricaceae
Genus: Myrica
Specie: Rubra

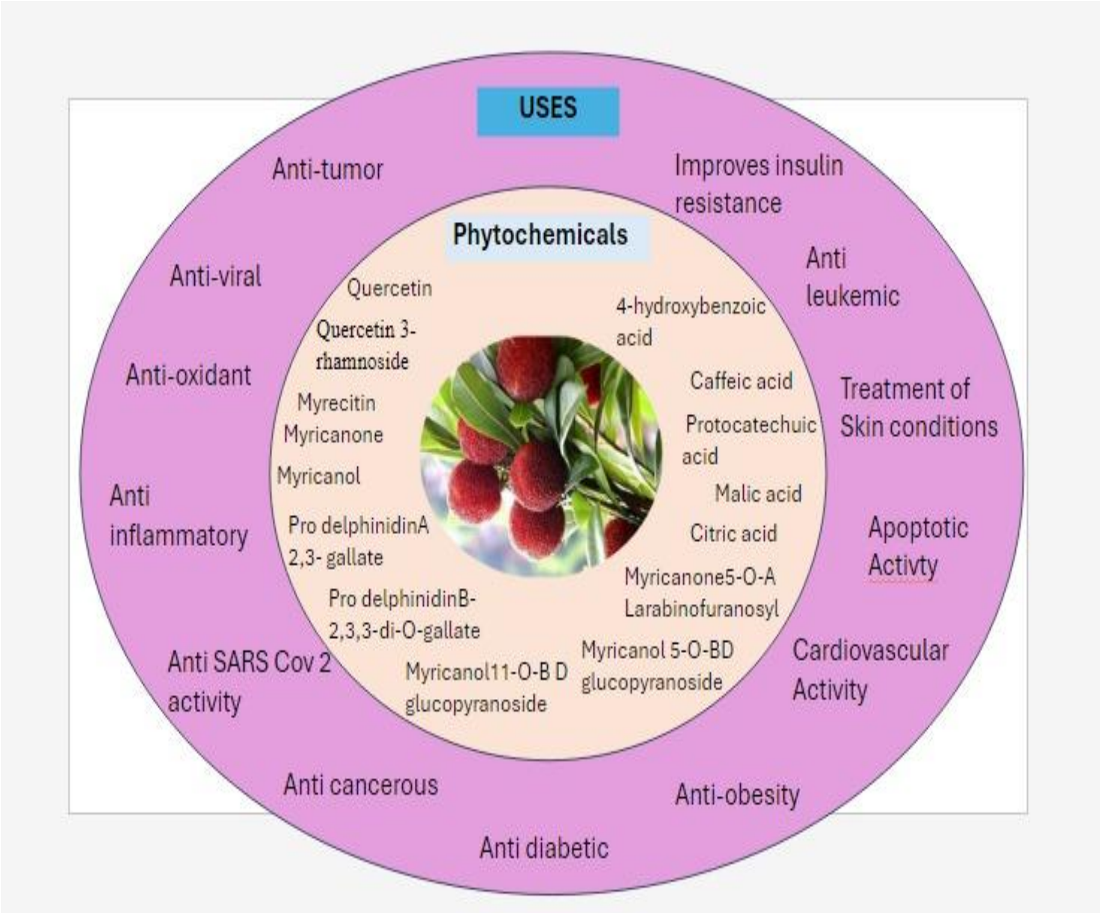
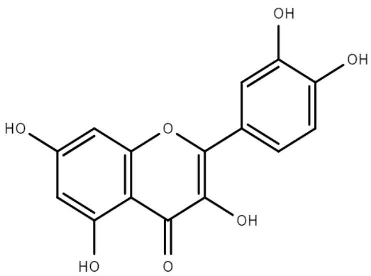
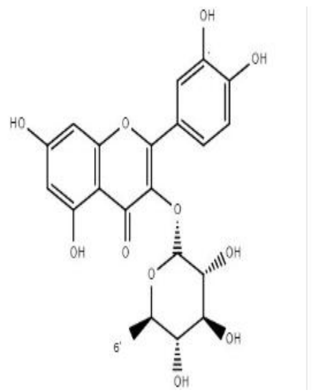
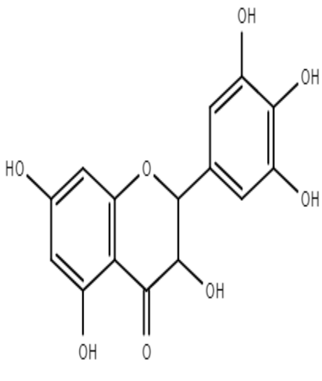


Figure 1: Summary of phytochemicals and pharmacological activities of Myrica rubra

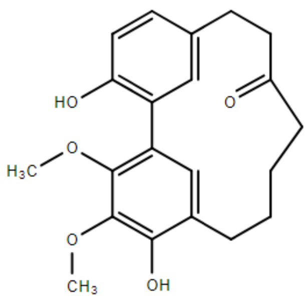
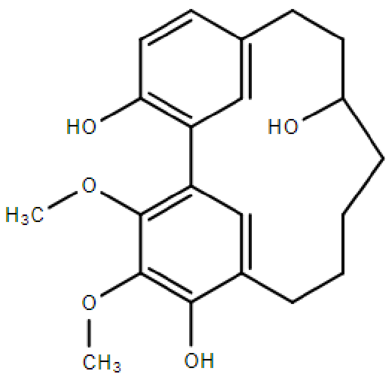
Phytochemical Classification of Myrica Rubra

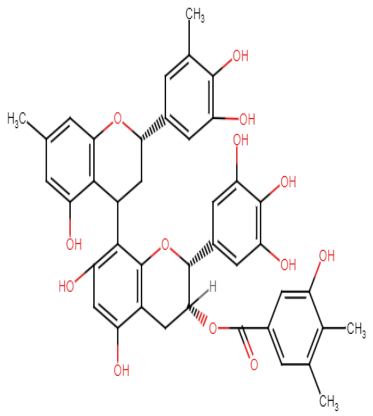
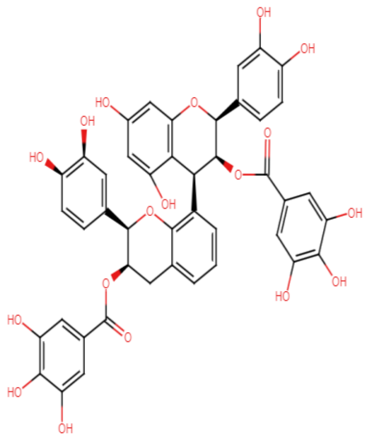
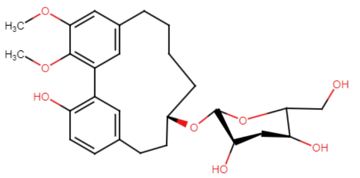
Major Classes	Compounds along with chemical structure	Use and Mechanism of Action	Properties	Reference
Flavanoids	Quercitin 	**Anti SARS Cov 2 activity:** Used as main ingredient to effectively treat and prevent COVID 19. It interferes with the SARS COV 2 replication theoretically and reduces inflammation and toxic effects. **Antioxidant:** It possesses antioxidant property due to presence of phenolic hydroxyl group and double bond in its structure. Some studies show that it interacts with DNA but are unsure whether it	Antioxidant, antitumor, antidiarrheal, antibacterial, cancer preventing agent.	(G. Wang, Wang, Y., Yao, L., Gu, W., Zhao, S., Shen, Z., ... & Yan, T., 2022) (Derosa G., 2021; Sun C, 2013) (Xu D., 2019) (Liu S., 2021) (Tsai C. F., 2021) (Rauf A., 2018; Zhu X., 2017)

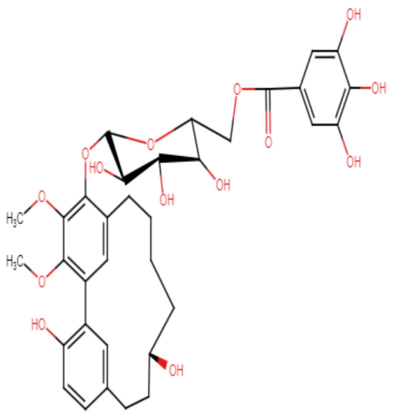
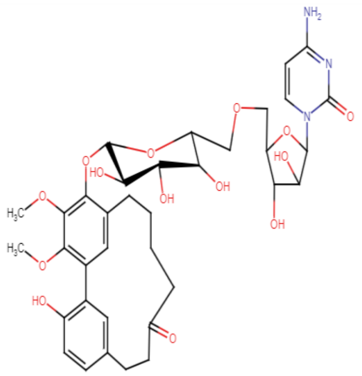
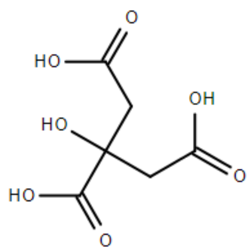
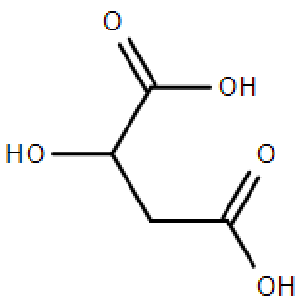
		heals DNA or protects it. It also inhibits lipid oxidation and reduces production of ROS. It inhibits ROS produced by ultraviolet b radiation and thus protects mitochondria. **Antitumor:** It has a suppressive effect on a number of tumor-forming pathways. It lowers the proliferation of cancer cells, inhibits the migration and invasion of cancerous cells by LM3 cells, triggers apoptosis, regulates metastasis, increases chemotherapy sensitivity, and lowers drug resistance. It is particularly useful in cases of glioblastoma multiforme and osteosarcoma. Moreover, it halts the spread of several human malignancies. **Antiviral activity:** It demonstrates effectiveness against a range of viruses, including the Mayar virus, poliovirus, influenza virus, and HIV. Its capacity to prevent viral infection in its initial stages, to inhibit proteases needed for viral replication, and to lessen inflammation account for its antiviral action. **Anti-inflammatory effect:** It reduces the impact of a lot of inflammatory		(Maleki Dana P., 2021; Tang S. M., 2020) (Liu M., 2020). (Luo X., 2022)

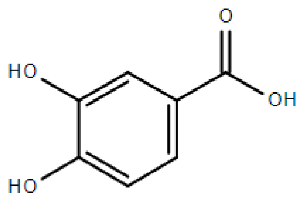
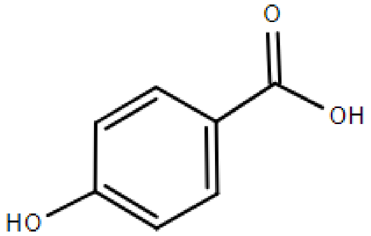
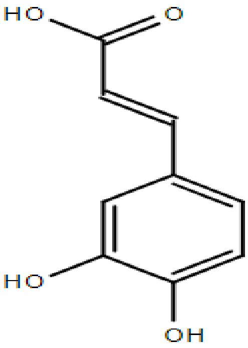
		reactions. Inhibiting the ROS/AMPK and TLR2/MyD88/NF-κB pathways, it lessens inflammation.		
	Quercetin-3- rhamnoside 	Has same mechanism of action of Quercitin as it is derivative of quercetin	Antioxidant. Anti-inflammatory, antiviral.	(Wu, 2021) (Sun C, 2013) (Septembre-Malaterre, 2022)
	Myricetin 	**Anticancerous effect:** Because matrix metalloproteinase activity is decreased, metastasis, invasion, and adhesion are decreased. To cause apoptosis, it increases the release of molecules that promote apoptosis, activates the caspase cascade, and upregulates the Bax: Bcl2 ratio. By inhibiting the formation of purine neocleotides and decreasing the catalytic activity of inosine 5'-monophosphate dehydrogenase (hIMPDH) one-half, antileukemic activity was shown. **Antidiabetic Effect:** It has a lowering effect on the activity of	Anti cancerous, antidiabetic, anti-inflammatory, Antiobesity	(Ci, 2018) (Ha, 2017) (Mondal, 2016) (Liao, 2017) (Li, 2017) (Meng, 2016) (Kandasamy, 2014) (Hu, 2018) (Chao, 2017) (Scarabelli, 2009; N. Zhang, Feng, H. , Liao, H. H. , Chen, S. , Yang, Z. , Deng, W. , & Tang, Q. Z., 2018) (Guo, 2015)

		antioxidant enzymes including SOD and GPx and increases the Nrf2/HO−1 pathway. It lessens the inflammatory impact of cytokines such as TNF-α, IL-6, and IL-1β. It lowers blood glucose, increasing insulin sensitivity. Along with regulating the levels of urea, plasma glucose, uric acid, urine albumin, blood urea nitrogen, glucose-6-phosphatase, glycosylated hemoglobin, glycogen phosphorylase, hexokinase, glycogen synthase, and glycogen with insulin signaling molecule expression, it also suppresses the rise of amylase and glucosidase. **Anti-obesity:** It causes weight reduction along with improving liver steatosis and insulin resistance. It enhances and modulates thermogenic protein infection. It also regulates endorphins and adropin levels. **Cardiovascular Effect:** It inhibits the nuclear translocation of p65 and IκBα, reduces pro-inflammatory cytokines, and stops cell death. It suppresses overexpression of nitric oxide and oxidoreductase activity. Prior studies have also demonstrated that myricetin inhibits the activity of the signal		

		transducer and activator of transcription 1 (STAT1). It decreases the size of infarcts and restores normal levels of nitric oxide, prostaglandin 12, endothelin nitric oxide synthase, and high-density lipoprotein cholesterol in the blood. **Antiinflammatory:** Same mechanism of action as of quercitin		
	Myricanone 	By reducing the cytokines and by the mechanism same as myrecitin	Anti-inflammatory& anti-allergic activity	(Sun C, 2013)
	Myricanol 	It has same mechanism of action as of myrecitin.	Anti-inflammatory & anti-allergic activity	(Sun C, 2013)
Anthocyanin	• Pro delphinidin A 2,3O-gallate	By reducing toxic effects, metastasis, invasion, and inflammation Also, by inducing apoptosis	Anti-cancer activity	(Sun C, 2013)

	 • Pro delphindin B-2 3,3-di-O-gallate 			
Diarylhopanoids	• Myricanol11-O-B D glucopyranoside  • Myricanol 5-O-BDglucopyranoside	By same mechanism as other constituents	Anticancer activity	(Sun C, 2013)

	 • Myricanone 5-O-aLarabinofuranosyl 			
Organicacid	1. Citric acid  2. Malic acid  3. Protocatechuic acid	It causes contraction of skin and cures many skin conditions.	As astringent and as dyeing & tanning agent	(Sun C, 2013)

	 4. 4-hydroxybenzoic acid  5. Caffeic acid 			

Methods

Several articles from electronic scientific databases, including Google, Google Scholar, PubMed, Science Direct, and Web of Science, as well as journals accessed by citations or straight from their websites, were used in a thorough literature search. Distribution, morphology, ethnobotanical, phytochemistry, nutritional content, toxicity, and pharmaceutical activity were among the search terms employed. To evaluate the importance of the peels, we have studied the constituents and their action so that they should not be wasted and should be used for beneficial purposes in daily life, as they are economically efficient and commercially available.

Evaluation of Myrica Rubra:
Macroscopic evaluation:
Organoleptic evaluation:

Taste: sweet sour
Odor: characteristic
Color: Red or purple
Shape: wedge at the base, tapered or pointed at the apex, and serrated on the top half or margin

Morphology:
Fruit:

This stone fruit, resembling a berry, has an edible part composed of numerous radially arranged pulpous columns. Various varieties exist, differing in size, color, and ripening time. Cultivated varieties usually weigh 10 to 15 grams, are either brilliant red or black, and mature between mid-June and early July. The fruit's mild acidity, well-balanced high sugar content, and abundant juice are all responsible for its wonderful flavor. It is versatile and full of vitamins, and may be eaten fresh or processed into cans of syrup, jam, juice, or wine.(Zai-long, 1991)

Plant:
This perennial tree maintains an evergreen presence, standing at a height of 5 to 10 meters and displaying a consistently rounded canopy. With separate male and female catkins on distinct plants, it undergoes flowering in spring, relying on wind for pollination. Its ability to thrive in less fertile soils is attributed to the presence of mycorrhizae on its root system. The red bayberry, a tropical and subtropical fruit, has acclimated to warm and humid conditions. Its primary distribution includes regions south of the Yangtze River, such as Taiwan and Hainan.(Zai-long, 1991) Chinese bayberry (CB) has a cultivation history spanning a remarkable 7,000 years. Its enduring shrubs typically reach an average height of 2–3 meters, with a maximum height of six meters. They feature waxyor shiny single alternating leaves, which are elliptic or oblanceolate in shape. The leaves measure 8–13 cm in length, and newly emerged leaves display an emerald green hue with yellow gland spots on the back (X. Zhang et al., 2015)

Flower:
Chinese bayberry (CB) is a diecious plant, following the ZW sex-determination system and featuring catkin inflorescence of flowers. The female inflorescence, typically around 1.5 cm in length, is elongated and commonly found in solitary leaf axils. In contrast, the male inflorescence is cylindrical, approximately 3 cm long, and forms clusters in leaf axils, exhibiting various colorations such.

Microscopic Evaluation:
Electron microscope study indicated that particles have following sub structures:
Stain impenetrable central "core"
Stain penetrable middle part
Floccule like outer space structure(Fang, 2006; Zhongxiang Fang, 2009)

Physical Evaluation:
Length: 5-14cm
Width: 1-4cm
Temperature: 20-22° C for 3 days and for 9-12 days stored at 0-2° C temperature(Yan, 2011)

Chemical Evaluation:

Chemicals	**Tests**
Anthocyanin	The anthocyanins were detected by HPLC using a photo diode array detector and linking it with MS. GC is utilized to determine the anthocyanin's sugar moiety. The HPLC-DAD-ESIMS method is used to identify the anthocyanins in bayberries. (Fang, 2006)
Flavonoids	Flavonoids were identified by HPLC with diode array detector and with MS(Kim, 2013)

Diaryl heptanoids	It was identified by m/z ratio of different fragments in mass spectrometry.(Chen P, 2017)
Organic acid	Organic acids were analyzed by HPLC assay (2695 pump; Waters). Individual organic acids were separated in an ODSC18column(4.6mm×250mm) at 25 °C, isocratically eluted with 50mmol/L (NH4)2HPO4 buffer (pH = 2.7) as the mobile phase at a flow rate of 0.5 mL/min. The compounds were detected at 210m (2996) diode array detector
Aminoacids and Peptides	Based on high-resolution mass spectrometry and MS fragment data, the protein molecule was inferred to be monascumicacidorits isomers. With the chemical formula C16H28O10N2, they display a pseudomolecular ion [M+H] at m/z 409. N-(1-deoxyfructopyranos1-yl) isoleucyl aspartic acid or its isomers are responsible for the fragment ion at m/2 230 that results from these compounds' tendency to remove the $C_2H_{13}NO$ group. The MS fragmentation spectra of the peptides that were studied indicate fragment ions from peptide bond breakage, along with additional neutral losses of NH3, H2O, and CO_2, which help forecast. (Chen P, 2017)
Sugars	A sugar solution underwent concentration, drying, and derivatization with hydrochloric hydroxylamine, pyridine, and aceticanhydride. Gas chromatography analysis using a Shimadzu 14A instrument was employed, equipped with a DB-1701 quartz capillary column. Standard sugars like rhamnose, arabinose, xylose, mannose, glucose, and galactose were used for comparison. The process involved specific temperature settings, flow rates of gases, and a programmed temperature gradient during chromatography(Fang, 2006).

Phytochemical Analysis:

Groups	**Concentration**	**Subgroups**	**Components**	**Reference**
Essential oils	0.12%~0.13 %	Sesquiterpenes	1.Betacaryophyllene 2.Alphahumulene 3.Valencene	(Langhasova, 2014)

			4.Betacaryophyllene oxide 5.TransNerolidol 6.Aromadenrene	
		Other compound	1. Humuleneepoxide 2. Epi-a-selinene	
Soluble sugars	60%	Sucrose	1. Fructose 2. Glucose	(X. Zhang, et,al., 2015)
Organic acid	80%		1.Citric acid 2.Malic acid 3.Protocatechuic acid 4.Hydroxybenzoic acid 5.Caffeic acid	(Chen P, 2017; X. Zhang, et,al., 2015)
Flavonoids	50%	Glycoside	1. myricetin- 2. rhamnoside 3. myricetin-3deoxyhexosidegallate	(X. Zhang, et,al., 2015)
	50%	Quercetin Glycoside	1.quercetin- 3O-galactoside 2.quercetin- 3O-glucoside 3.quercetin- 3O-rhamnoside	
		Kaempferol glycosides	1. kaemferol- 3O-glactoside 2. kaemferol- 3O-glucoside	Reference?
Anthocyanins		Glycoside of delphinidin	Delphinidinhexoside	(X. Zhang, et,al., 2015)
	68%-95%	Cyaniding	1. Cyanidin-3-Oglucoside 2. cyanidin-3-Ogalactoside	
		Pelargonidin	Pelargonidin-3O-glucoside	
		Peonidin	Peonidin-3- Oglucoside	
Phenols		Other phenolic compound	1. Gallic acid 2. protocatechuic acid 3. phydroxybenzoic acid 4.p-coumaricacid 5.caffeicacid 6.ferulic acid	(Sun C, 2013)
		1.+S-Myricanol 2.myricanone	1.+-s-myricanol5- O-B-Dglucopyranoside 2.myricanone5O- B-Dglucopyranoside	(Sun C, 2013)

		3.myricanol 4.myricanene 5.myricaneneB 6.myricanane	3.myricanol glucoside 4.myricaneneA5- O-a-Larabinofuranosyl (1-6)-B-D glucoside	
Alkaloids	50%	Ethanol		(Sun C, 2013)
Aminoacids & peptides		Primary amines Secondary amines peptides	Tyrosine Phenylalanine Tryptophan	(Chen P, 2017)
Other constituents			Naphthoquinones Terpenoids Polysaccharides Steriods	(Chen P, 2017)

Discussion:

Flavonoids, due to their antioxidant qualities, flavonoids which are abundant in traditional Chinese herbal treatments like M. rubra help to prevent cardiovascular disease. For example, the antioxidant potential of Ginkgo biloba leaf extracts is well known around the world. Oriental medicine makes use of M. rubra bark for a number of purposes. Myricitrin and quercetin 3-rhamnoside, two flavonoids found in M. rubra, have been proven to have anti-inflammatory, antioxidant, and anti-hyperlipidemic properties, which help prevent cardiovascular illnesses. A study showing the cardioprotective benefits of M. rubra extract (MRF) treatment showed that it protected oxidative damage by increasing antioxidant activities and lowering ROS levels during hypoxia/reoxygenation (H/R).

Under circumstances such as ischemia/reperfusion (I/R), oxidative stress plays a critical role in cardiac myocyte apoptosis, resulting in mitochondrial malfunction and eventual cell death. According to the study, MRF therapy significantly maintained the health of the mitochondria by lowering the number of apoptotic cells and preventing the activation of caspase-3 during hypoxia/reoxygenation (H/R). MRF also had a major effect on the Bcl-2/Bax ratio, which is an important determinant of the cellular apoptotic threshold. This suggests that because MRF can regulate intracellular ROS levels and change the apoptotic cascade, it may help prevent heart injury. The fact that cancer cells frequently develop resistance to DOX emphasizes the need to identify substances that can inhibit this resistance. Due to their capacity to improve medication absorption through enhanced membrane permeability, these molecules may be found among sesquiterpenes. Furthermore, it has been demonstrated that some sesquiterpenes themselves have anti-proliferative properties in cancer cells and work in concert with traditional cytostatics. Myrica rubra (Chinese bayberry) essential oil and its sesquiterpene components, humulene (HUM), caryophyllene oxide (CAO), nerolidol (NER), and valencene (VAL), were shown in a prior study to be able to inhibit the growth of colon cancer cell lines and to improve the effectiveness of doxorubicin (DOX) treatment. This impact was caused by these cells producing more reactive oxygen species (ROS) and accumulating more DOX intracellularly. Rat hepatocytes, on the other hand, showed no cytotoxic impact or decrease in DOX-induced toxicity. However, rat hepatocytes, a model of noncancerous cells, showed no cytotoxic impact or reduction in DOX toxicity.

Chinese bayberry leaves (BLPs) contain proanthocyanidins that, when activated through the AMPK pathway, reduce lipid accumulation in HepG2 cells induced by oleic acid (Zhang, Phytochemical characterization of Chinese bayberry (Myrica rubra Sieb. et Zucc.) of 17 cultivars and their antioxidant properties. 2015). BLPs improved obesity and associated metabolic problems in mice fed a high-fat diet by dramatically lowering body weight, blood glucose, insulin levels, and the AUC of OGTT ($p < 0.01$) (Zhang et al., 2022). The molecular process is still unknown, though. In IR-HepG2 cells, the additional hypoglycemic mechanism of BLPs was examined in this work. Plant PR protein is associated with defence against insects and diseases. **Ethylene** treatment induces MaPR expression in immature banana fruit, but 1-MCP treatment can inhibit MaPkla expression. STR is crucial in alkaloid biosynthesis, catalyzing the formation of strictosidine, a precursor of terpenoid indole alkaloids (TIAs). ERF and MAPK cascade regulate TIA gene expression, with MPK influencing STR gene expression in response to ethylene. Flavin adenine dinucleotide (FAD) is vital for glutathione reductase, involved in antioxidative stress reduction. Riboflavin kinase (RFK) activates riboflavin, catalyzed by FAD synthetase (FADS)(Zhu et al., 2015).

Additionally, exploring breeding and genetic studies of bayberry to enhance the accumulation of pharmaceutically active compounds for human health could open new avenues for bayberry research and industry. This holistic approach can pave the way for a more comprehensive understanding of bayberry's potential in promoting health and its applications in various domains.

The study concludes by emphasizing that MRF holds promise for further development as a cardiovascular disease treatment. However, it underscores the need for additional research, particularly in understanding the detailed mechanisms underlying MRF's anti-apoptotic effects. The authors also highlight the necessity for investigating the active flavonoids within MRF and their synergistic mechanisms against ischemic heart disease. Overall, the findings provide a foundation for considering MRF in future preclinical developments for cardiovascular therapies.

Conclusions:

As the identification of bioactive compounds from bayberry extracts continues to grow, there is a growing interest in studying their in vivo metabolism, bioavailability, synergies, competitive effects, and potential toxicity in animal models. Further, there is a need for extensive research on structure-activity relationships to understand various activities.

In conclusion, the discussed studies highlight the diverse therapeutic potential of natural compounds, particularly focusing on Myrica rubra and Chinese bayberry leaves. By lowering oxidative damage, maintaining mitochondrial integrity, and modifying apoptotic pathways during hypoxia/reoxygenation, extracts from Myrica rubra exhibit cardioprotective properties. Sesquiterpenes from Myrica rubra essential oil also have the potential to improve the effectiveness of doxorubicin treatment by preventing the growth of colon cancer cells.

Additionally, Chinese bayberry leaves' proanthocyanidins show promise in lowering cholesterol buildup, enhancing metabolic problems linked to obesity, and stimulating the AMPK system. More research is necessary to understand the molecular mechanisms behind these effects.

Given the circumstances, these results emphasize how crucial it is to investigate natural substances for their medicinal qualities, which can range from potential anticancer effects to cardiovascular protection. The molecular mechanisms and therapeutic uses of these natural substances for human health can be further clarified by future studies.

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