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REVIEW

Exploring the Neuroprotective Potentials of Flavonoid Metabolites in *Syzygium aromaticum*: A Review with in-silico Insight to Therapeutic Potential

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Abstract: The worldwide occurrence of neurodegenerative diseases in Alzheimer's and Parkinson's patients is increasing owing to multiple disease mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and excitotoxicity. *Syzygium aromaticum* (clove) flavonoid metabolites show strong neuroprotective potential because they act as antioxidants, reduce inflammation and lipid peroxidation, and prevent apoptosis. The key *S. aromaticum* flavonoid metabolites, quercetin, kaempferol, kumatakenin, myricetin, ombuin 3-O-β-d-glucopyranoside, and tamarixetin 3-O-β-d-glucopyranoside, bind to various brain receptors implicated in disease propagation pathways and induce changes that support neuronal survival and decrease cognitive impairment. In vitro, in vivo, and molecular docking studies were reviewed. The SwissADME and ADMETlab 3.0 web servers demonstrated that these metabolites have favorable drug-like properties and absorption characteristics that follow Lipinski's Rule of Five, GSK, and Pfizer rules. The metabolites showed good gastrointestinal absorption and desirable physicochemical properties, suggesting safe oral use. The toxicological profile prediction generated from the pkCSM and ADMETlab 3.0 web servers indicated minimal liver, kidney, and brain damage risks; however, ombuin 3-O-β-d-glucopyranoside exhibited weak cardiac toxicity through hERG II blocking, whereas pachypodol requires additional research on long-term toxicity effects. The data from the reviewed studies indicate that *S. aromaticum* flavonoid metabolites show great promise as therapeutic agents for neurodegenerative diseases caused by oxidative stress, inflammation, apoptosis, and lipid peroxidation. Evidence suggests that their safety and effectiveness are positive, despite minimal risks. Further studies should focus on nanocarrier utilization to improve their Blood-Brain Barrier permeability and enhance therapeutic potential. Experimenting on primates before translating them to human clinical trials will be crucial.

Keywords: *Syzygium aromaticum*, metabolites, flavonoids, neuroprotective, therapeutic, botanical drugs, antioxidant, anti-inflammatory

Introduction

Neurodegenerative disorders (NDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD), and various cognitive impairments affect people on a global scale.[1] Neurological disorders are the primary cause of death and DALYs, particularly in low and middle-income countries.[2] A 2019 report indicated that 50 million people worldwide had NDs that led to dementia, which is projected to grow to 152 million by 2060.[3] Globally, the burden of AD and PD continues to increase, with increasing health disparities.[4] These disorders are characterized by progressive neuronal loss, oxidative stress, neuroinflammation, and mitochondrial dysfunction, ultimately leading to cognitive decline and motor impairment.[5,6] An increasing number of neurodegenerative disease cases has driven scientists to examine both natural

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therapeutic compounds and botanical medication candidates that could protect the nervous system.[7] Research has focused on flavonoids as secondary plant metabolites, owing to their antioxidant, anti-inflammatory, and neuroprotective effects.[8–15]

Most NDs are increasingly driven by interconnected processes such as oxidative stress, inflammation, apoptosis, altered synaptic plasticity, and neuroexcitotoxicity.[16,17] Botanical drugs and their metabolites, such as flavonoids, phenols, and tannins, demonstrate neuroprotective properties. These metabolites help protect the brain by controlling multiple biological pathways that reduce brain damage, thus providing promising therapeutic options.[18,19]

Plants contain natural polyphenolic compounds named flavonoids, which possess a C6-C3-C6 structure that connects two aromatic rings through a central three-carbon bridge to form a pyran ring.[20,21]

Syzygium aromaticum, commonly known as clove, is a medicinal plant widely utilized traditionally across Asia, Africa, and South America to treat various health problems requiring antioxidant, antimicrobial, analgesic, and anti-inflammatory remedies.[8,9,22] The most commonly used part of this plant, clove buds, contains bioactive compounds including flavonoids, which consist of quercetin, kaempferol, and myricetin that demonstrate various health benefits.[23,24] Earlier studies have identified emerging flavonoid metabolites in *Syzygium aromaticum* (*S. aromaticum*), including tamarixetin 3-O-β-d-glucopyranoside, ombuin 3-O-β-d-glucopyranoside, rhamnocitrin, kumatakenin, and pachypodol.[25] All of which exhibit significant pharmacological properties, particularly in mitigating oxidative stress and neuroinflammation.[26,27]

Numerous scientific studies have shown that botanical drugs derived from *S. aromaticum* and their bioactive metabolites can protect brain function through their influence on the crucial processes of oxidative stress, inflammation, apoptosis, and neurotoxicity.[5,8,9,28]

Flavonoid metabolites are active biological compounds that are formed when the plant compound class flavonoids undergo breakdown processes within the human body during digestion and metabolic activities.[29] These metabolites maintain or increase the therapeutic advantages of *S. aromaticum* botanical drugs by retaining refined properties, including antioxidant, anti-inflammatory, and neuroprotective properties. Flavonoid metabolites have better bioavailability because of their reduced size and modified chemical structure, which enable them to strongly affect brain cells and receptors for potential therapeutic use in neurological conditions.[30] These natural compounds offer advantages over synthetic drugs, owing to their lower toxicity, multi-target activity, and better biocompatibility.[31]

Drug development requires a thorough assessment of plant-derived metabolites to determine their ADME properties, drug-likeness characteristics, pharmacokinetic properties, and toxicity risks for therapeutic agent suitability.[32,33] Assessments conducted during this stage forecast absorption performance, distribution characteristics, metabolism patterns, drug-enzyme interactions, and toxicity risks. Early profiling enables researchers to identify promising drug candidates while lowering late-stage failure chances and guiding the development of optimized bioavailable solutions and adverse effect reduction strategies. Notably, some metabolites from botanical sources are blood-brain barrier (BBB) permeants that exert potent effects on specific brain regions and receptors, such as N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), and Transient Receptor Potential Vanilloid 1 (TRPV1), as well as receptors involved in inflammation and oxidative stress, such as Toll-like receptor 4 (TLR4), Nuclear factor erythroid 2-related factor 2 (Nrf2), and Nuclear Factor kappa B (NF-κB), which play crucial roles in modulating neuroinflammation and promoting neuronal survival.[34–36]

This review investigates the neuroprotective properties of flavonoid metabolites from S. aromaticum and highlights their mechanisms of action, enabling antioxidant defense, neuroinflammatory regulation, excitotoxicity blocking, and neuronal survival promotion. Secondly, we used an in-silico approach to provide insight into ADME, focusing on physicochemical, pharmacokinetic, drug-likeness, including Lipinski, Pfizer, and GSK rules, Blood-Brain Barrier (BBB) permeability (both categorical and numerical data), and toxicological profiles (AMES toxicity, hepatotoxicity, DILI, nephrotoxicity, and neurotoxicity) of the reviewed flavonoid metabolites using the SwisADME, ADMETlab 3.0, and pkCSM web servers.

By elucidating the neuroprotective properties of these bioactive compounds, this review aims to highlight their potential applications in managing and preventing neurodegenerative disorders and to unravel the therapeutic potential of these metabolites in *Syzygium aromaticum* plants.

Syzygium aromaticum: History and Traditional Uses

Syzygium aromaticum, commonly known as clove, is a member of the *Myrtaceae* family.[22] The name "clove" originates from the Latin word clavus, meaning "nail", referencing the bud's shape.[24] This aromatic plant is cultivated in the Indonesian Maluku Islands, but is now distributed in tropical regions, including Sri Lanka, Madagascar, Africa, Brazil, and India.[37] Clove trees are evergreen and can grow to 15 m in height under optimal conditions. The plant produces dried flower buds, which are the most commercially significant parts, and are highly valued for their pungent aroma and distinct taste.[37,38]

Historically, cloves were highly prized in the spice trade and were considered one of the most valuable commodities during the 16th and 17th centuries, with European explorers traveling long distances to obtain them.[39] They have been used in culinary applications worldwide, adding flavor to dishes, beverages, and baked goods, while also serving as a natural preservative, owing to their antimicrobial properties.[40]

Cloves are widely used in traditional medicine owing to their therapeutic effects. They have been used in Ayurvedic, Chinese, and Unani medicine to treat digestive disorders, toothaches, respiratory conditions, and infections.[41] The essential oil extracted from cloves is a well-known remedy for dental pain and is often used in oral care products, such as toothpaste and mouthwash.[42] Additionally, clove oil has been used as a topical analgesic for muscle pain and arthritis.[43] In Indonesia, clove is an essential ingredient in *kretek* cigarettes, which contain a mixture of tobacco and ground cloves and are believed to have a soothing effect on the respiratory system.[44]

Syzygium aromaticum has been widely used in traditional medicine across Africa for centuries, owing to its strong antimicrobial, anti-inflammatory, and analgesic properties.[22,38] This plant is widely used across Africa in traditional medicine, valued for its therapeutic properties in treating digestive issues, respiratory ailments, infections, pain, and reproductive health concerns.[22,45] In East Africa, especially Zanzibar, cloves are used to treat fever, dental pain, and wounds.[46] In West Africa, it is used for malaria, menstrual regulation, and reproductive vitality.[47,48] In other parts of Africa, it is utilized for oral health, respiratory issues, and menstrual cramps.[45,49]

Clove oil is commonly applied topically, whereas infusions and decoctions are used internally.[41] In addition to their medicinal uses, cloves play important cultural and religious roles, including incense, perfumes, and culinary spice blends.[50] Globally recognized, cloves have emerging scientific support for their antioxidant, antidiabetic, and anticancer properties, particularly because of their active compound eugenol.[23,24] Although traditional uses are being validated, further research is needed to clarify effective dosages and mechanisms, underscoring the continued significance of cloves in the health and food industries.

Phytochemistry and Biological Activities of Metabolites in Syzygium aromaticum

Syzygium aromaticum is a widely recognized medicinal plant with a complex phytochemical composition. It contains diverse bioactive metabolites, including flavonoids, tannins, terpenoids, alkaloids, and phenolic compounds, which contribute to its pharmacological properties.[51] Its most notable constituents are eugenol, β-caryophyllene, and acetyl eugenol, which are primarily responsible for its antimicrobial, antioxidant, anti-inflammatory, and analgesic activities.[38,52] Eugenol, the major active compound in clove essential oil, has been extensively studied for its potent free radical scavenging ability, role in modulating inflammatory pathways, and analgesic effects.[53] In addition, β-caryophyllene, a sesquiterpene, exerts strong anti-inflammatory and neuroprotective effects,[8,54] making *S. aromaticum* a promising candidate for treating neurodegenerative conditions.

The *S. aromaticum*-derived polyphenols, including gallic acid, ellagic acid, and flavonoids such as quercetin and kaempferol, exhibit significant antioxidant activity.[55,56] These compounds protect cells from oxidative stress and have been linked to anti-aging, anti-cancer, and cardioprotective effects.[57,58] Flavonoids in *S. aromaticum* exhibit broad antimicrobial activity against pathogens such as *Staphylococcus aureus, Escherichia coli, Candida albicans*, and *Aspergillus spp*.[59,60] Additionally, they protect neurons by preserving mitochondrial function, preventing apoptosis, and upregulating Brain-Derived Neurotrophic Factor (BDNF),[61,62] thereby contributing to overall neuroprotection. Tannins, including ellagitannins and gallotannins, are abundant in clove extracts and play a role in enhancing their antimicrobial and antiviral effects, particularly against influenza and herpes simplex viruses.[63]

The terpenoids present in *S. aromaticum* have been identified as the lead compounds responsible for their anti-inflammatory and analgesic properties. These include monoterpenes such as α-humulene, which modulate pro-inflammatory cytokine expression and inhibit cyclooxygenase (COX) enzymes, similar to non-steroidal anti-

inflammatory drugs (NSAIDs).[64,65] Eugenol is commonly used as a natural anesthetic and antimicrobial agent for the treatment of toothaches and gum infections.[66] The strong analgesic properties of clove oil have also been attributed to its ability to block voltage-gated sodium channels, similar to synthetic local anesthetics.[67]

Alkaloids and phenolic acids in *S. aromaticum* have demonstrated significant bioactivity, particularly in metabolic and cardiovascular health.[22,68] These compounds enhance insulin sensitivity and glucose uptake, aiding in type 2 diabetes management, whereas phenolic acids, such as chlorogenic and caffeic acids, support cardiovascular function by reducing blood pressure, lipid peroxidation, and endothelial dysfunction.[69,70] Eugenol and its derivatives improve lipid metabolism and inhibit low-density lipoprotein (LDL) oxidation, thereby lowering the risk.[71] Traditionally used dried cloves, oils, extracts, and clove preparations treat digestive, respiratory, and inflammatory conditions, with studies confirming their antimicrobial, gastroprotective, and hepatoprotective properties.[52]

The growing interest in natural therapeutics has led to the increased commercial production of *Syzygium aromaticum*-based products, including essential oils, botanical drug supplements, and functional foods. Thus, these products are promising alternatives to synthetic drugs. With rising concerns regarding antibiotic resistance, bioactive compounds found in *S. aromaticum* continue to be explored for their role in novel drug development and integrative medicine. With advances in research, the metabolite richness of cloves has highlighted their vast potential in modern pharmacology, reinforcing their long-standing use in traditional medicine.

Neuroprotective Mechanisms of Selected Flavonoid Metabolites in Syzygium aromaticum

Flavonoids are a diverse group of naturally occurring polyphenolic compounds that are abundant in fruits, vegetables, and medicinal plants. Chemically, they share a common structure consisting of two aromatic rings (A and B) connected by a three-carbon bridge that forms a closed pyran ring (C) typically arranged as a C6-C3-C6 skeleton.[20,21]

This structure allows them to be categorized into subclasses such as flavones, flavonols, flavanones, isoflavones, and anthocyanidins. Flavonoids possess important physicochemical properties, including strong antioxidant activity, metal ion chelation, and the ability to modulate cellular pathways and signaling.[55,56,72] These properties contribute to their biological activities, including their anti-inflammatory, antioxidant, antimicrobial, and neuroprotective effects. The general mechanisms of action of these *S. aromaticum* flavonoid metabolites are shown in Figure 1.

Flavonoids in *Syzygium aromaticum*, such as quercetin, kaempferol, myricetin, tamarixetin 3-O-β-d-glucopyranoside, rhamnocitrin, kumatakenin, ombuin 3-O-β-d-glucopyranoside, and pachypodol, show promising neuroprotective

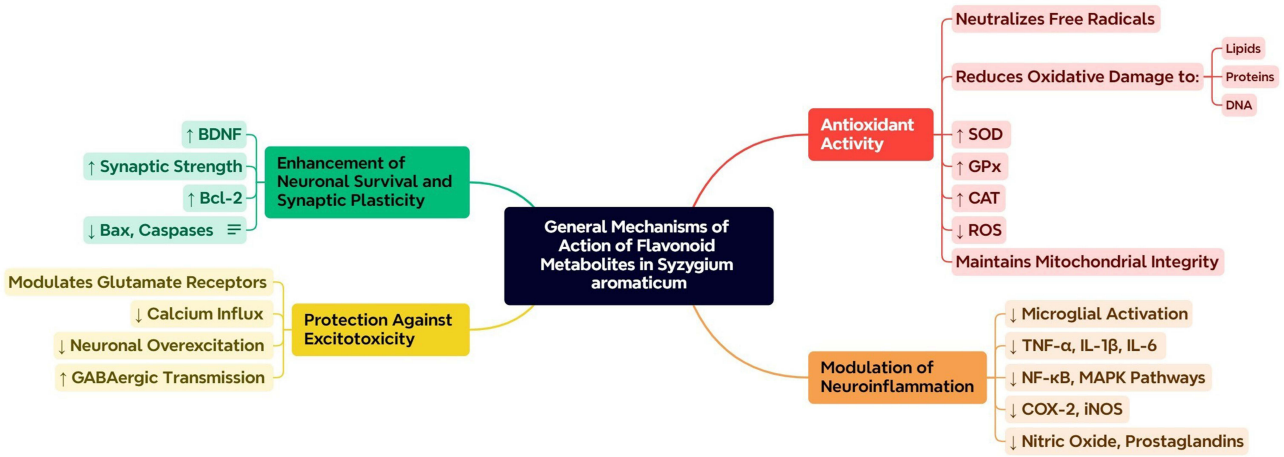

Figure 1 General mechanisms of action of flavonoid metabolites in Syzygium aromaticum. This ↑ Indicates Upregulation or increase; This ↓ Indicates Downregulation or decrease.

Abbreviations: SOD, Superoxide Dismutase; GPx, Glutathione Proxidase; CAT, Catalase; ROS, Reactive Oxygen Species; TNF-α, Tumor Necrosis Factor-alpha; IL-1β / IL-6, Interleukins 1-beta and 6; NF-κB, Nuclear Factor kappa-light-chain-enhancer; MAPK, Mitogen-Activated Protein Kinase; COX-2, Cyclooxygenase-2; iNOS, Inducible Nitric Oxide Synthase; BDNF, Brain-Derived Neurotrophic Factor; Bcl-2, Anti-apoptotic Protein; Bax, Caspases – Pro-apoptotic Proteins.

Table 1 Selected Flavonoid Metabolites Identified in Syzygium Aromaticum with Their Chemical Properties

S/N	Phytochemical Compound	Molecular Formula	Molecular Weight (g/mol)	PubChem CID	References
1	Quercetin	$C_{15}H_{10}O_7$	302.23	5280343	[8,74,75]
2	Kaempferol	$C_{15}H_{10}O_6$	286.24	5280863	[38,76,77]
3	Myricetin	$C_{15}H_{10}O_8$	318.23	5281672	[61,78,79]
4	Tamarixetin 3-O-β-d-glucopyranoside	$C_{16}H_{12}O_7$	316.26	5281699	[27,80,81]
5	Ombuin 3-O-β-d-glucopyranoside	$C_{23}H_{24}O_{12}$	249.4	44259621	[27,82,83]
6	Rhamnocitrin	$C_{16}H_{12}O_6$	300.26	5320946	[84,85]
7	Kumatakenin	$C_{17}H_{14}O_6$	314.29	5318869	[86,87]
8	Pachypodol	$C_{18}H_{16}O_7$	344.4		[88,89]

Notes: Molecular formula and molecular weight (g/mol) and PubChem Compound Identifiers (CID) were retrieved from the PubChem database, https://pubchem.ncbi.nlm.nih.gov/.[90]

properties. These bioactive compounds have antioxidant, anti-inflammatory, anti-excitotoxic, and neurotrophic effects, making them potential therapeutic candidates for neurodegenerative disorders, including AD and PD. The chemical formulae, molecular weights, and PubChem CIDs of these *S. aromaticum* metabolites are presented in Table 1. The Two-dimensional (2D) chemical structures of these selected metabolites are shown in Figure 2. The neuroprotective potential of the *S. aromaticum* metabolites is illustrated in Figures 3 and 4. Few studies provide reports on the neuroprotective outcomes of emerging *S. aromaticum* flavonoid metabolites such as tamarixetin 3-O-β-d-glucopyranoside, rhamnocitrin, kumatakenin, ombuin 3-O-β-d-glucopyranoside, and pachypodol using in vitro and in vivo experiments. Despite this gap, the neuroprotective mechanisms of quercetin, kaempferol, and myricetin have been greatly explored using in vitro and in *vivo* models (Table 2).

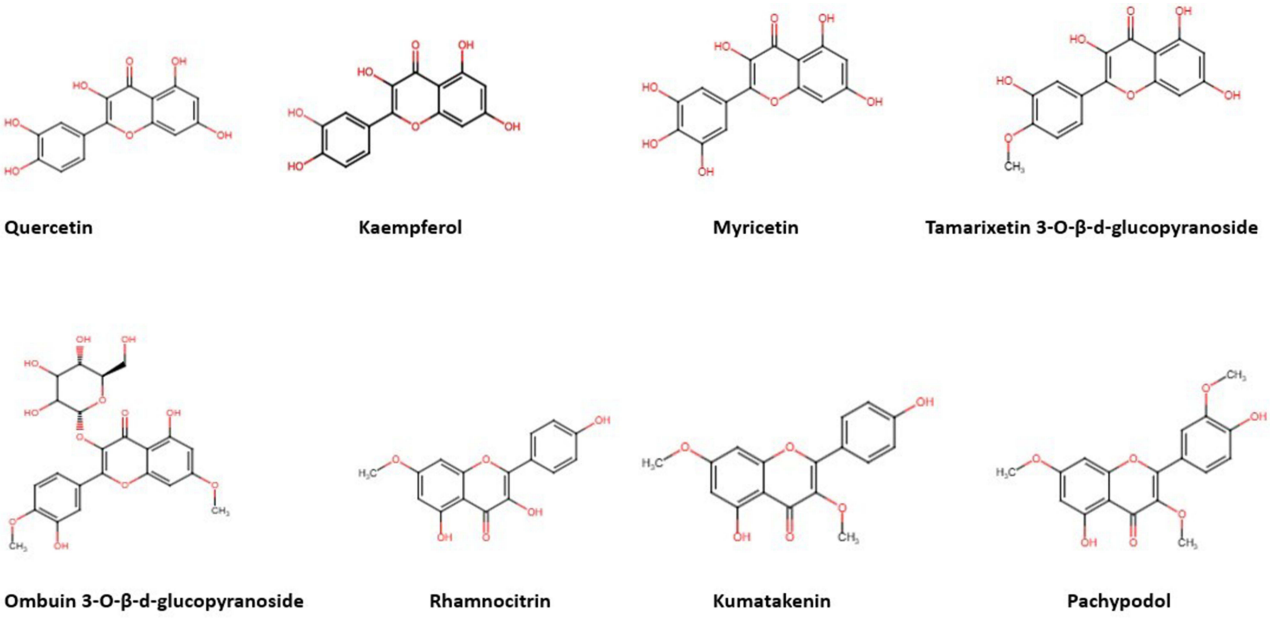

Figure 2 Two-dimensional (2D) Chemical Structures of *S. aromaticum* metabolites as retrieved from the SwissAdme web server, http://www.swissadme.ch/index.php via the Marvin JS using ChemAxon software.[73]

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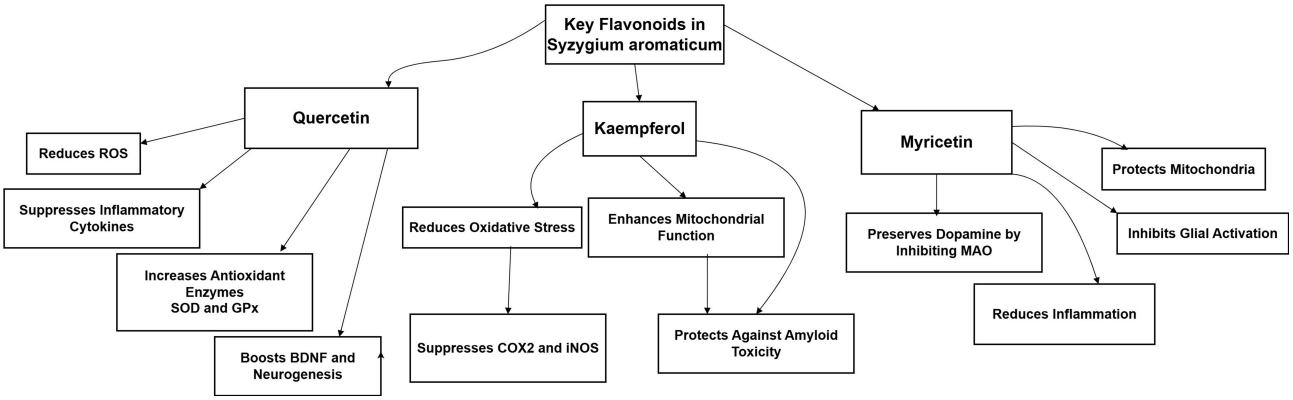

Figure 3 Specific neuroprotective mechanisms of Key flavonoid metabolites in *Syzygium aromaticum*.
Abbreviations: SOD, Superoxide Dismutase; GPx, Glutathione Peroxidase; ROS, Reactive Oxygen Species; BDNF, Brain-Derived Neurotrophic Factor; COX2, Cyclooxygenase-2; iNOS, Inducible Nitric Oxide Synthase; MAO, Monoamine Oxidase.

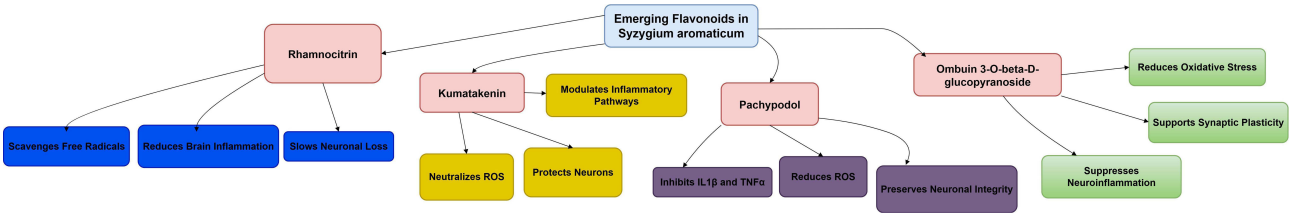

Figure 4 Specific neuroprotective mechanisms of emerging flavonoid metabolites in *Syzygium aromaticum*.
Abbreviations: ROS, Reactive Oxygen Species; IL1β, Interleukin 1 beta; TNFα, Tumor Necrosis Factor alpha.

Quercetin

Quercetin is a well-known flavonoid with strong antioxidant, anti-inflammatory, and neuroprotective effects.[8,74,75] It exerts neuroprotective effects by upregulating intrinsic antioxidant defenses, including superoxide dismutase (SOD) and glutathione peroxidase (GPx).[121] Quercetin has been shown to decrease lipid peroxidation and prevent neuronal cell death.[122,123]

Studies have demonstrated that quercetin mitigates neuroinflammation by modulating microglial activation and inhibiting pro-inflammatory cytokines, such as TNF-α, IL-1β, and Interleukin 6 (IL-6).[75,124] Additionally, quercetin modulates the activation of microglial cells, which are central to neuroinflammation, thereby protecting neurons from inflammatory damage.[75]

Table 2 Selected Syzygium Aromaticum Flavonoid Metabolites and Their Neuroprotective Mechanisms Reported in vitro and in vivo

S/N	Metabolite	PubChem CID	In vitro	In vivo	Reference
1	Quercetin	5280343	- Scavenges ROS in neuronal cells; and upregulates SOD, CAT, GSH via Nrf2 activation - Reduces IL-1β, TNF-α in lipopolysaccharide (LPS)-stimulated RAW264.7 cells - ↓ Caspase-3 activity and Bax/Bcl-2 ratio - Inhibits fibril formation via Aβ/α-syn modulation - ↑ BDNF and neurite outgrowth (PC12 cells)	- Reverses scopolamine-induced memory deficits (neurobehavioral tests) and inhibits NLRP3 inflammasome activation - ↓ MDA and ↑ SOD/GSH and significant differences in inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α) in brain tissue - ↑ Dopaminergic neuron survival, modulates the PI3K/Akt/GSK-3β signaling pathway and prevents ferroptosis in MPTP mice - ↓ IL-1β, TNF-α in LPS models - Reduces lesion volume in hippocampus (MCAO model)	[91–97] [98–104]

(*Continued*)

Table 2 (Continued).

S/N	Metabolite	PubChem CID	In vitro	In vivo	Reference
2	Kaempferol	5280863	- ↓ Intracellular ROS, upregulates Nrf2 (SH-SY5Y cells) - ↓Bcl-2, ↑ Bax in HepG2 cells - Blocks excitotoxicity and protects fibroblast-induced neurons from mitochondrial dysfunction - Suppress LPS-induced neuroinflammation in microglial cells through inhibition of ROS, pro-inflammatory mediators (NO, iNOS, COX-2, PTGES2, IL-6, TNF-α), MAPKs, and NF-κB pathways, while activating the Nrf2/HO-1 antioxidant pathway	- Improves Y-maze performance in LPS-induced model while reducing inflammation and oxidative stress - Prevents dopaminergic loss in MPTP-flies - ↓ TNF-α, IL-1β in AD mice - Improves depression-like behavior by regulating microglia polarization while suppressing NLRP3 - ↓ MDA in the brains of rats	[105–115]
3	Myricetin	5281672	- Inhibits SOD 1 aggregation - ↓ Tau phosphorylation in neuronal SH-SY5Y cells - Protected PC12 cells from $CoCl_2$-induced cytotoxicity, with 200 μM optimally restoring cell viability and alleviating morphological damage	- Improved memory and novel object recognition outcome - ↑ GSH and ↓ ROS in 6-OHDA rats - Suppresses microglial activation (Iba-1 ↓)	[78,116–120]

Notes: ↑ Indicates Upregulation or increase; ↓ Indicates Downregulation or decrease.
Abbreviations: ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; CAT, Catalase; GSH, Reduced Glutathione; Nrf2, Nuclear Factor Erythroid 2–Related Factor 2; NLRP3, NOD-; LRR- and Pyrin Domain-Containing Protein 3 (inflammasome); IL-1β, Interleukin-1 beta; TNF-α, Tumor Necrosis Factor alpha; LPS, Lipopolysaccharide; RAW264.7 cells, Murine Macrophage Cell Line RAW264.7; MDA, Malondialdehyde; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; PI3K, Phosphoinositide 3-Kinase; Akt, Protein Kinase B; GSK-3β, Glycogen Synthase Kinase 3 beta; Aβ, Amyloid beta; α-syn, Alpha-synuclein; BDNF, Brain-Derived Neurotrophic Factor; MCAO, Middle Cerebral Artery Occlusion; SH-SY5Y cells, Human Neuroblastoma Cell Line SH-SY5Y; AD, Alzheimer's Disease; NO, Nitric Oxide; iNOS, Inducible Nitric Oxide Synthase; COX-2, Cyclooxygenase-2; PTGES2, Prostaglandin E Synthase 2; MAPKs, Mitogen-Activated Protein Kinases; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; HO-1, Heme Oxygenase-1; 6-OHDA, 6-Hydroxydopamine; $CoCl_2$, Cobalt(II) Chloride; Iba-1, Ionized Calcium-Binding Adapter Molecule 1.

Quercetin has also been implicated in the promotion of neurogenesis and the enhancement of synaptic plasticity. It activates the brain-derived neurotrophic factor (BDNF) pathway, which is essential for neuronal survival and cognitive function.[62] In addition, it enhances synaptic plasticity and reduces amyloid-beta (Aβ) aggregation, a hallmark of disease pathology.[125] This suggests a potential role for quercetin in the prevention and treatment of cognitive disorders such as Alzheimer's disease.

In vitro, quercetin protected neuronal cells by reducing oxidative stress, suppressing inflammation, regulating apoptosis-related proteins, inhibiting toxic protein aggregation, and promoting neuronal growth.[91–97] Animal studies reveal that quercetin improved memory, reduced oxidative stress and inflammation, protected dopaminergic neurons by modulating PI3K/Akt/GSK-3β signaling and preventing ferroptosis, and lessened brain damage in disease models.[98–104] (Table 2)

Kaempferol

Kaempferol exerts strong neuroprotective effects by reducing oxidative stress and preventing neuronal apoptosis.[76,126] It enhances antioxidant defenses and preserves mitochondrial function, maintaining membrane potential and ATP production.[38,127] It also modulates survival pathways, such as PI3K/Akt and MAPK, while inhibiting neurotoxic signaling linked to amyloid-beta and alpha-synuclein, which are key drivers of Alzheimer's and Parkinson's disease.[77,128]

Kaempferol suppresses the production of pro-inflammatory mediators [cyclooxygenase2 (COX-2) and inducible nitric oxide synthase (iNOS)], thereby reducing neuroinflammation.[105] Inhibition of the NF-κB pathway limits excessive activation of microglial cells, which is known to contribute to neuronal damage in neurodegenerative diseases.[129] These properties indicate their therapeutic potential in neurodegenerative disorders. In vitro, kaempferol reduced oxidative stress, regulated apoptosis-related proteins, protected neurons from mitochondrial damage, and suppressed neuroinflammation by inhibiting pro-inflammatory pathways while activating antioxidant defenses.[105–109] In vivo studies reveal that kaempferol improved cognitive and behavioral outcomes, protected dopaminergic neurons, reduced neuroinflammation and oxidative damage, and modulated microglial activity in neurodegenerative and inflammatory models[110–115] (Table 2).

Myricetin

Myricetin is a potent flavonoid known for its strong antioxidant, anti-inflammatory, and neuroprotective effects.[61,78,79] Antioxidant activity reduces lipid peroxidation, mitochondrial dysfunction, and ROS-induced neuronal apoptosis.[130] Research has shown that myricetin attenuates neuroinflammation by suppressing microglial activation and downregulating the expression of inflammatory cytokines TNF-α, IL-6, and IL-1β.[131,132]

Myricetin has been shown to modulate dopamine levels in the brain, which is particularly relevant in Parkinson's disease.[78] It prevents dopamine depletion by inhibiting monoamine oxidase (MAO), which is an enzyme responsible for dopamine breakdown.[78,130] Additionally, myricetin enhances synaptic plasticity and learning ability, making it a promising candidate for the treatment of neurodegenerative diseases.[116,130] Furthermore, it protects against oxidative stress-induced neuronal damage and inhibits tau phosphorylation and amyloid-beta (Aβ) accumulation, contributing to the prevention of neurodegenerative processes, particularly Alzheimer's disease.[132,133]

Specifically, in vitro studies report that myricetin inhibited protein aggregation, reduced tau phosphorylation, and protected neuronal cells from oxidative and hypoxic damage, restoring viability and morphology.[116–118] This was supported by findings from in vivo experiments showing that myricetin enhanced memory performance, boosted antioxidant defenses, reduced oxidative stress, and suppressed microglial activation in neurodegenerative models[78,119,120] (Table 2).

Tamarixetin 3-O-β-d-Glucopyranoside

Tamarixetin, 3-O-β-d-glucopyranoside, is a glycosylated flavonol derivative with strong anti-inflammatory and antioxidant properties. Neutralizing reactive oxygen species (ROS) reduces oxidative stress, which is a major contributor to neuronal damage in neurodegenerative diseases.[27,80,81] Studies have suggested that tamarixetin derivatives can inhibit neuroinflammation by downregulating pro-inflammatory cytokines, such as TNF-α and IL-6, thereby protecting neurons from inflammation-induced damage.[81,134] Additionally, it enhances mitochondrial function, reduces oxidative stress, and improves neuronal energy metabolism, which are crucial for neurodegenerative conditions.[134] These properties suggest that tamarixetin is a promising candidate for neuroprotective intervention.

Ombuin 3-O-β-d-Glucopyranoside

Ombuin 3-O-β-d-glucopyranoside is a methylated flavonol that exerts neuroprotective effects by modulating oxidative stress pathways in tissues, including the brain.[82,135] It scavenges free radicals, enhances superoxide dismutase (SOD) activity, and reduces lipid peroxidation, which helps maintain neuronal integrity.[82,136] Furthermore, ombuin derivatives have been reported to inhibit acetylcholinesterase (AChE),[27,83] supporting synaptic plasticity and neuronal survival, which are key factors in maintaining cognitive function and preventing neurodegeneration. This suggests potential applications in treating memory-related disorders such as Alzheimer's disease.

Rhamnocitrin

Rhamnocitrin is a flavonol with potent anti-inflammatory and neuroprotective effects. It suppresses microglial activation, thereby reducing the release of neurotoxic mediators such as nitric oxide (NO) and reactive oxygen species (ROS).[75,137] Its antioxidant activity is particularly relevant in AD and PD, where oxidative stress accelerates neuronal loss.[84,137] By reducing chronic inflammation in the brain, rhamnocitrin contributes to neuronal protection and may help slow the progression of neurodegenerative disorders.[138]

Kumatakenin

Kumatakenin is a flavonoid with potent antioxidant and antiapoptotic properties.[139,140] Additionally, kumatakenin has been shown to enhance neurotransmission by modulating NMDA and GABA receptors and reducing lipid peroxidation-induced demyelination, which is essential for cognitive function and neuronal survival.[38,141] These combined actions may protect neurons from degeneration and contribute to long-term brain health.

Pachypodol

Pachypodol is a flavone with significant anti-inflammatory, antioxidant, antiapoptotic, and neuroprotective properties.[88,142,143] It inhibits the activation of NF-κB, a key regulator of neuroinflammation, and reduces the expression

of inflammatory mediators such as COX-2 and iNOS.[88] Additionally, pachypodol has been reported to enhance autophagy,[143] which is essential for clearing damaged proteins and organelles in neurodegenerative disorders, such as Parkinson's disease.

Additionally, pachypodol inhibits the expression of key inflammatory mediators, IL-1β and TNF-α, both of which are strongly associated with neuroinflammatory processes in conditions such as Alzheimer's and Parkinson's diseases.[88,89] By counteracting oxidative stress, apoptosis, and inflammation, this flavonoid metabolite helps maintain neuronal integrity, making it a promising natural compound for the prevention and management of neurodegenerative diseases.

Molecular Interactions of Key Syzygium aromaticum Flavonoid Metabolites with Receptors Implicated in Neurodegenerative Diseases

The neuroprotective mechanisms of *Syzygium aromaticum* metabolites are further validated by findings from molecular docking studies. These studies show that they exhibit potent neuroprotective effects through strong molecular interactions with critical receptors implicated in neurodegenerative diseases. The reviewed examples included Quercetin, kaempferol, and myricetin.

These key metabolites (ligands) showed high and varied molecular interactions, indicating neuroprotective potential. The docking scores, tools used, and the reported molecular docking outcomes are presented in Table 3.

Quercetin has a strong binding affinity to antioxidative enzymes (glutathione reductase, glutathione peroxidase, superoxide dismutase) and neurotransmission-related receptors (acetylcholinesterase, GABA receptor subunits), which exert the modulating activities of oxidative stress and synaptic activity in the pathology of Alzheimer's and Parkinson's diseases. Kaempferol is a potent inhibitor of neuroinflammatory and apoptotic signaling by forming strong interactions with Toll-Like Receptor 4 (TLR4), RAC-alpha serine/threonine-protein kinase 1 (Akt1), and tyrosine hydroxylase, which explains its applications in decreasing inflammation, inhibiting apoptosis, and sustaining dopamine production in models of Parkinsonism (Table 3). Myricetin demonstrates strong inhibition of pathological protein aggregation in Amyotrophic Lateral Sclerosis (ALS) by binding to different forms of superoxide dismutase 1 (SOD1), interferes with the activity of signal transducer and activator of transcription 1 (STAT1) to decrease neuroinflammation, and potently regulates LIM domain kinase 1 (LIMK1), a modifier of cytoskeletal dynamics, which could be therapeutic in a variety of neurodegenerative situations (Table 3). All of these flavonoids exhibit multitarget binding properties with antioxidative, anti-inflammatory, anti-apoptotic, and anti-amyloidogenic effects, which justify their potential as neurodegenerative disease intervention agents.

In-silico ADME and Toxicological Profiles of the Selected Flavonoid Metabolites in Syzygium aromaticum

After reviewing the *Syzygium aromaticum* flavonoid metabolites with neuroprotective potential, an in-silico Absorption, Distribution, Metabolism and Excretion (ADME), toxicological profiling was carried out using the SwissADME, ADMETlab 3.0, and pkCSM web servers to provide insight into the ability of these metabolites to be potential drug-like agents, considerably bioavailable, highly absorbed in the gastrointestinal tract, not violating more than one Lipinski's rule, and having other promising therapeutic profiles.

The rationale for using the SwissADME web server was to explore its ability to predict absorption, distribution, metabolism, and drug-likeness based on physicochemical properties. The pkCSM web server was employed for accurate toxicological profile prediction, presenting both categorical and numerical data to enable comprehensive and comparative evaluation of compound safety and efficacy. We used both web servers to ensure scientific rigor and a less biased data presentation.

This provided more insight, which will stir actionable future directions for identifying and further developing or designing these *S. aromaticum* flavonoid metabolites as promising neuroprotective agents.

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Table 3 Key Syzygium Aromaticum Flavonoid Metabolites and Their Neuroprotective Molecular Mechanisms (Reported in Docking Studies)

S/N	Ligand	Target Receptor	Docking/ Visualization Tool Used	Docking Scores (kcal/mol)	Amino Acid Residues with Strong Binding	Number of Conventional Hydrogen Bonds	Reported Outcome/Summary	Reference
1	Quercetin	GR, GPx, GST, SOD, CAT	SwissDock	GR: −19.75; GPx: −14.66; GST: −12.94; SOD: Fullfitness −2431.18 (ΔG −7.76); CAT: −16.60	GR: Ser30, Asp331, Lys66; GPx: Thr143, Arg179, Gln82; GST: LysB102 (2), LysA44 (2), TrpA38 (1); CAT: ArgB354, AspD65, TyrB358, PheB153	GR: 4; GPx: 3; GST: 5; SOD: Not specified; CAT: 2	Quercetin showed strong to moderate affinity to all tested antioxidative stress enzymes, generally higher than or close to cocrystallized ligands, forming multiple H-bonds and additional interactions (arene-cation, arene-arene) depending on target.	[144]
2	Quercetin	Human acetylcholinesterase (AChE) – PDB ID: 4EY7	Discovery Studio 4.5 (CDOCKER algorithm)	−8.8	Asp74, Glu202, Gly120, Tyr133, Trp86, Tyr337, Phe338, Trp117, Tyr119, Gly121, Tyr124, Ser125, Gly126, Ser203, Tyr341, His447, Ile451, Gly448, Phe338	4	Quercetin binds to both the peripheral aromatic site (PAS) and catalytic active site (CAS) of AChE, forming hydrogen bonds with Asp74, Glu202, Gly120, and Tyr133, and π–π stacking with Trp86, Tyr337, and Phe338. Van der Waals interactions involve multiple residues along the gorge. Binding may disrupt the catalytic triad stability, alter PAS allosteric structure, and block substrate access, leading to inhibition of AChE activity.	[145]
3	Quercetin	Interleukin-1 beta (IL-1β) – PDB ID: 1UNQ	CB-Dock2 webserver, Discovery Studio	−6.2	VAL4, LEU6, LEU28, LYS30, THR34, ILE36, TYR38, ARG48, GLU49, ALA50, PRO51, ASN54	2	Quercetin showed strong binding affinity to IL-1β active site residues, indicating potential to modulate inflammatory responses in AD.	[146]
4	Quercetin	PI3K, AKT1, GSK-3β	AutoDock, visualisation with PyMOL	−6.44 (PI3K), −5.32 (AKT1), −5.24 (GSK-3β)	Not specified	Not specified	Quercetin binds strongly to PI3K, AKT1, and GSK-3β, contributing to activation of the PI3K/Akt/GSK-3β pathway, supporting cell survival signalling, suppressing neuroinflammation, and inhibiting apoptosis, thereby reducing PD pathology and highlighting its multitarget neuroprotective potential.	[101]
5	Quercetin	GABA α5, β1, β2 subunits	AutoDock Vina, PyMol, Discovery Studio 4.5	QUR: −6.8 (α5), −8.5 (β1), −8.1 (β2); DZP: −6.2 (α5), −7.0 (β1), −6.4 (β2)	QUR: Thr59 (H-bond), Pro281, Asp58 (pi-anion) (α5); Thr271, Tyr220 (C–H bonds), Glu92 (pi-anion) (β1); Glu436, Lys427 (2 H-bonds), Lys353, Pro287 (pi–alkyl) (β2)	QUR: 1 (α5), 0 (β1), 2 (β2)	Quercetin showed strong multi-bond interactions with GABA receptor subunits, especially β1 and β2. Diazepam and flumazenil exhibited moderate binding via hydrogen bonds and hydrophobic interactions across all subunits, supporting their known pharmacological effects on GABA receptors.	[147]
					DZP: Asn192 (2 H-bonds), Lys225 (2 H-bonds), Try228 (pi-alkyl) (α5); Gly254 (C–H bonds), Trp381 (pi–pi), Val304, Ala276, Cys232 (pi–alkyl) (β1); Lys397 (H-bond), Val396 (C–H bond), Arg394, Pro245 (pi–alkyl) (β2)	DZP: 2 (α5), 0 (β1), 1 (β2)		
				FLU: −6.0 (α5), −6.4 (β1), −7.9 (β2)	FLU: Asn278 (carbon–hydrogen bonds), Tyr228 (pi–pi) (α5); Ser233 (2 H-bonds), Trp168, Trp381 (pi–pi and pi–alkyl) (β1); Cys690, Tyr620 (2 H-bonds), Ser691 (C–H bond), Ala526, Cys662, ILE68 (pi–alkyl) (β2)	FLU: 2 (α5), 2 (β1), 2 (β2)		

6	Kaempferol	Toll-Like Receptor 4 (TLR4)	AutoDockTools 1.5.6, AutoDock Vina, Deepsite (binding site prediction), visualisation with PyMOL	−7.5	ASP100, ASP99, GLU229	3	Kaempferol showed tight binding to TLR4, forming three hydrogen bonds, indicating potential modulation of TLR4-mediated inflammatory responses.	[148]
7	Kaempferol	RAC-alpha serine/threonine-protein kinase 1 (Akt1)	AutoDock Tools (v1.5.6), PyMOL (v2.5.2)	−5.72	Not specified	Not specified	KPL binds to Akt1, inducing phosphorylation at Ser-473, which inhibits mitochondrial apoptosis in H_2O_2-exposed PC12 cells. It increases cell viability, upregulates Bcl-2, and reduces cleaved caspase-3, Cyt C, and Bax expression. Effect is reduced by Akt1 inhibitor MK2206.	[149]
8	Kaempferol	Tyrosine hydroxylase	AutoDock with Cygwin Terminal software	−7.84 (Leu346), −7.61 (Leu384), −8.55 (Leu387), −8.10 (Phe404), −7.70 (Leu525)	Leu346, Leu384, Leu387, Phe404, Leu525	Not specified	In silico molecular docking confirmed strong binding of kaempferol to tyrosine hydroxylase, with the highest affinity at Leu387 (−8.55 kcal/mol), suggesting potential neuroprotective effects by preventing tyrosine hydroxylase loss in Parkinson's disease models.	[150]
9	Myricetin	Native SOD1 dimer, Non-native SOD1 trimer, Full-length fibril of apo SOD1	AutoDock 4.2	−6.0 (Native dimer), −5.91 (Non-native trimer), −4.39 (Full-length fibril)	Val7(A), Val148(A), Lys9(B), Gly10(B), Asp11(B), Asn53(B), Gly56(B), Cys57(B), Lys146(B), Gly147(B), Val148(B) (Native dimer); Asp52(A), Thr54(A), Gly138(A), Asn139(A), Ala140(A), Lys275(B), Asp358(C), Asn359(C), Phe370(C) (Non-native trimer); Leu42(B), His43(B), Gly44(B), Phe45(B), Ile18(C), Asn19(C), Phe20(C), Gln22(C), Leu42(C), His43(C), Gly44(C), Phe45(C) (Fibril)	Not specified	Myricetin binds stably to native dimer, non-native trimer, and fibril forms of SOD1 with decreasing affinity, stabilizing protein interfaces, destabilizing preformed fibrils, inhibiting aggregation dose-dependently, and reducing fibril load, suggesting its potential as a potent anti-amyloidogenic agent against ALS.	[117]
10	Myricetin	STAT1 (three conformations: dimer 1YVL chain A/B and monomer 1BF5)	Smina (Vina scoring function), Chimera 1.14 (visualization)	Not specified but STAT1 pockets near CYS324 and CYS492.	Cluster A binding site: GLN243, ALA246, ILE248, GLY249, ASN253, ALA254, LEU256, GLN322, CYS324, PRO252, PRO332, ARG346; Cluster B site: ARG241, SER245, ILE248, ASN475, MET476, ARG494, ALA496, GLN497, GLU500	Not specified	Myricetin (MYR) directly interacts with STAT1, impairing its S-glutathionylation and phosphorylation by binding near key cysteine residues (CYS324 and CYS492). Blind docking revealed two main binding pockets where MYR likely prevents glutathione binding, thus inhibiting STAT1 activation and microglia M1 polarization. This supports MYR's anti-inflammatory and neuroprotective effects by targeting STAT1 in neurodegeneration.	[151]
11	Myricetin	LIM domain kinase 1 (LIMK1)	Schrödinger Suite (Glide docking), Maestro 12.7.161, ChemDraw Ultra 20.0, LigPrep	Myricetin: −12.22; BMS-5 (standard): −5.05	Myricetin: ILE416 (H-bond with carbonyl of C ring and hydroxyl of A ring), LYS368 (pi-cation with phenyl ring B), ASP478 (H-bond with hydroxyl of phenyl ring B); BMS-5: LYS368 (single H-bond with carbonyl of amide group)	Myricetin: Multiple (at least 2); BMS-5: 1	Myricetin exhibits significantly higher binding affinity than BMS-5 by forming multiple strong interactions, indicating effective binding and potential modulation of LIMK.	[152]

Abbreviations: GR, Glutathione Reductase; GPx, Glutathione Peroxidase; GST, Glutathione S-Transferase; SOD, Superoxide Dismutase; CAT, Catalase; AChE, Acetylcholinesterase; IL-1β, Interleukin-1 beta; PI3K, Phosphoinositide 3-Kinase; AKT1, RAC-alpha serine/threonine-protein kinase 1; GSK-3β, Glycogen Synthase Kinase-3 beta; TLR4, Toll-Like Receptor 4; SOD1, Superoxide Dismutase 1; STAT1, Signal Transducer and Activator of Transcription 1; LIMK1, LIM domain kinase 1.

ADME Prediction

ADME and drug-likeness profiling are essential in drug design and development as they help predict the absorption, distribution, metabolism, and excretion of a compound in the body.[153] By evaluating properties like solubility, permeability, and stability, researchers can identify promising drug candidates early, reduce development costs, and improve the chances of success in clinical trials.[154] These assessments provide information on adequate bioavailability, minimize toxicity risks, and support the design of safe, effective, and orally available medications.

The ADME, drug-likeness, and pharmacokinetic profiles of *S. aromaticum* flavonoid metabolites are presented in Tables 4 and 5.

In this review, the ADME profiling of eight *Syzygium aromaticum* flavonoid metabolites retrieved from the SwissADME web server highlights promising drug-likeness and oral bioavailability characteristics. Key parameters, such as molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), rotatable bonds, topological polar surface area (TPSA), molar refractivity (MR), and iLOGP, were analyzed, along with bioavailability scores (Table 4).

Table 4 Drug-Likeness of the *S. aromaticum* Flavonoid Metabolites from the SwissADME Web Server (Swiss Drug Design)

PubChem CID	#Heavy Atoms	Aromatic Heavy Atoms	Fraction Csp3	Rotatable Bonds	H-bond Acceptors	H-bond donors	MR	TPSA (Å²)	iLOGP	Bioavail. Score	MW (g/mol)
5280343	22	16	0.00	1	7	5	78.03	131.36	1.63	0.55	302.23
5280863	21	16	0.00	1	6	4	76.01	111.13	1.70	0.55	286.24
5281672	23	16	0.00	1	8	6	80.06	151.59	1.08	0.55	318.23
5281699	23	16	0.06	2	7	4	82.50	120.36	2.24	0.55	316.26
44259621	35	16	0.35	6	12	6	119.10	188.51	2.67	0.17	492.4
5320946	22	16	0.06	2	6	3	80.48	100.13	2.31	0.55	300.26
5318869	23	16	0.12	3	6	2	84.95	89.13	2.81	0.55	314.29
5281677	25	16	0.17	4	7	2	91.44	98.36	3.26	0.55	344.4

Note: http://wwwswissadme.ch/index.php.
Abbreviations: CID, Compound Identifier; TPSA, topological polar surface area; Log P, octanol-water partition coefficient; MW, Molecular Weight; MR, Molar Refractivity; Bioavail Score, Bioavailability Score.

Table 5 Druglikeness Insight on Natural Product Score, Lipinski, Pfizer, GSK Rules, and Golden Triangle from the ADMETlab 3.0 Web Server

PubChem CID	NP Score	Lipinski Rule (#)	Pfizer Rule	GSK Rule (*)	Golden Triangle	SMILES
5280343	1.70	Accepted (0)	Accepted	Accepted (0)	Accepted	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
5280863	1.55	Accepted (0)	Accepted	Accepted (0)	Accepted	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
5281672	1.70	Accepted (0)	Accepted	Accepted (0)	Accepted	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
5281699	1.55	Accepted (0)	Accepted	Accepted (0)	Accepted	COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
44259621	1.85	Accepted (1)	Accepted	Accepted (1)	Accepted	COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)OC)O)O[C@@H]4C(C([C@@H]([C@H](O4)CO)O)O)O)O
5320946	1.33	Accepted (0)	Accepted	Accepted (0)	Accepted	COC1=CC(=C2C(=C1)OC(=C(C2=O)O)C3=CC=C(C=C3)O)O
5318869	1.24	Accepted (0)	Accepted	Accepted (0)	Accepted	COC1=CC(=C2C(=C1)OC(=C(C2=O)OC)C3=CC=C(C=C3)O)O
5281677	1.21	Accepted (0)	Accepted	Accepted (0)	Accepted	COC1=CC(=C2C(=C1)OC(=C(C2=O)OC)C3=CC(=C(C=C3)O)OC)O

Notes: # = Number of Lipinski Violations, * = Number of GSK Violations. https://admetlab3.scbdd.com/.
Abbreviations: NP score, Natural product-likeness score; SMILES, Simplified Molecular Input Line Entry System.

Physicochemical properties of a compound can be used to assess its drug-likeness in drug discovery. This is about their potential to become orally active drugs in human beings.[155,156] Important parameters like molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), rotatable bonds, topological polar surface area (TPSA), molar refractivity (MR), and iLOGP are all checked regularly.[153] Such properties have a direct impact on the absorption, distribution, metabolism, and excretion (ADME) profile of a compound. The molecular weight (MW) can influence the capacity of a drug to pass through biological membranes. The Lipinski Rule of Five states that a compound with an MW of 500Da or less has a higher probability of being orally bioavailable.[157,158] Bigger molecules are not easily absorbed and have a bad membrane permeability. Hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) affect the capacity of a drug to form hydrogen bonds with biologic targets or transport proteins. The most favorable drug-likeness is related to HBD 5 and HBA 10. The excessive number of hydrogen bonds may cause a compound to become impermeable to lipid membranes. Molecular flexibility depends on rotatable bonds. Less than 10 rotatable bonds are typically good when it comes to oral bioavailability, because highly flexible molecules can have difficulties in traversing membranes or can be unable to bind to receptors stably. Topological polar surface area (TPSA) is the surface area of atoms that are polar (typically oxygen and nitrogen, and their bonded hydrogens). TPSA 140 Å² or less is generally desirable to have good intestinal absorption, and 90 Å² or less is desirable to cross the blood-brain barrier (relevant in neurotherapeutics). Molar refractivity (MR) is associated with the size and polarizability of a compound and assists in the interpretation of receptor interactions. The optimal MR should be between 40 and 130. Divergences can indicate inefficient contact with biological targets. Lipophilicity is key when considering membrane permeability and solubility, and is predicted by iLOGP. An iLOGP of 0–5 is desirable and is considered balanced. Very lipophilic drugs can be insoluble, and very hydrophilic drugs can have difficulty crossing membranes. These properties are summarized by the Lipinski Rule of Five: a compound is likely to have good oral bioavailability when it does not exceed more than one of the following: MW 500 Da, HBD 5, HBA 10, iLOGP 5. Two or more violation compounds tend to have poor absorption or permeation. Bioavailability score makes a prediction (typically on a scale of 0 to 1) of the likelihood that a compound will enter systemic circulation in the event of oral administration. A score of 0.55 and above is acceptable and indicates a moderate-to-high probability of oral effectiveness.[159] Such parameters serve as a first-line screening method to determine potential drug candidates before more expensive in vitro and in vivo testing.

In our review, most *S. aromaticum* flavonoid metabolites, including quercetin (PubChem CID: 5280343), kaempferol (PubChem CID: 5280863), myricetin (PubChem CID: 5281672), rhamnocitrin (PubChem CID: 5320946), kumatakenin (PubChem CID: 5318869), and pachypodol (PubChem CID: 5281677), showed no Lipinski violations, indicating strong potential for oral bioavailability. These compounds also fell within the optimal range for hydrogen bonding and molecular weight, reinforcing their drug-likeness. Tamarixetin 3-O-β-d-glucopyranoside (PubChem CID: 5281699) also complied with Lipinski's rules, supporting its potential as a drug-like molecule despite its glycosylated structure. However, ombuin 3-O-β-d-glucopyranoside (PubChem CID: 44259621) had two violations (high MW and excessive HBA count), suggesting challenges in its oral absorption. Its high TPSA (188.51 Å²) and six HBDs may improve aqueous solubility but could hinder passive membrane permeability. All compounds except ombuin had a bioavailability score of 0.55, which is considered acceptable for oral drugs. Ombuin scored 0.17, aligning with its reduced permeability profile and Lipinski violations. This score represents the likelihood of the compound reaching the systemic circulation when administered orally.

TPSA values of less than 140 Å² are generally favorable for cell membrane permeability.[160,161] Most compounds, such as Rhamnocitrin (100.13 Å²), Kaempferol (111.13 Å²), and Kumatakenin (89.13 Å²), are within this range, indicating efficient membrane penetration.

The iLOGP values ranged from 1.08 (Myricetin) to 3.26 (Pachypodol), demonstrating a well-balanced hydrophilic-lipophilic profile suitable for oral drugs. Pachypodol showed the highest lipophilicity. This suggests strong potential for membrane permeability,[162] which is a desirable characteristic of neuroprotective agents.

Overall, ADME profile prediction revealed that Quercetin, Kaempferol, Myricetin, Rhamnocitrin, Kumatakenin, Tamarixetin 3-O-β-d-glucopyranoside, and pachypodol demonstrated favorable drug-likeness, permeability, and oral bioavailability profiles.

To provide a deeper insight into the druglike properties of these selected *S. aromaticum* flavonoids, in silico prediction was carried out using the ADMETlab 3.0 database (https://admetlab3.scbdd.com/). The ADME screening plugin was explored, and the data on parameters concerning druglikeness, such as the Natural Product-likeness Score (NP Score), Lipinski Rule, Pfizer Rule, GSK Rule, and the Golden Triangle, were extracted from the medicinal chemistry option. This was enabled after the Simplified Molecular Input Line Entry System (SMILES) of these *S. aromaticum* metabolites retrieved from the PubChem database were input into the ADMETlab 3.0 database. The results concerning the druglike parameters and the SMILES of these metabolites are presented in Table 5.

The Lipinski Rule, the Pfizer Rule, the GSK Rule, and the Golden Triangle are all straightforward rules in drug discovery to determine whether a substance has a good chance of becoming an effective oral drug. These rules are used to determine druglikeness in terms of size, solubility, and permeability. The Lipinski Rule permits compounds whose molecular weight is less than or equal to 500, logP is less than or equal to 5, number of hydrogen bond donors is less than or equal to 5, and the number of hydrogen bond acceptors is less than or equal to 10 (ADMETLab 3). A compound is rejected when it breaks more than one of these rules. The Pfizer Rule identifies compounds with logP greater than 3 and tPSA less than 75 Å² as being at high risk of being toxic. The GSK Rule favors drugs with a molecular weight of less than 400 and logP less than 4, in the hope of obtaining superior safety and solubility. The Golden Triangle is a combination of logP and molecular weight that is used to enhance potency and clearance by creating a suitable spot, most commonly between MW 200 and 500, and logP of −0.4 to +5.6. In ADMETLab, the compounds that fall into these ranges are commonly highlighted as accepted (green), and the outliers are rejected (red), in order to help the researcher prioritize safer, more effective drug candidates.

The druglikeness analysis of ADMETlab 3.0 indicates that all eight metabolites of *Syzygium aromaticum* have good drug-like properties. Their Natural Product (NP) scores are between 1.21 and 1.85, which is a good indication that they are similar to known natural bioactive compounds. All of the compounds passed Lipinski, Pfizer, GSK, and Golden Triangle rules, which are major filters in medicinal chemistry used to assess oral bioavailability and safety, and physicochemical suitability. It is worth noting that the majority of compounds possessed zero Lipinski and GSK violations, which is indicative of a favorable molecular weight, hydrogen bonding capacity, and lipophilicity in terms of drug development. The compound with only one Lipinski and one GSK violation (CID: 44259621) also passed the rest of the rules, which means that the violation is not significant. These findings suggest that the chosen *S. aromaticum* flavonoid metabolites have favorable pharmacokinetic properties and can be considered as potential new neuroprotective agents to be further formulated and tested in vivo.

Their compliance with Lipinski's rules, appropriate TPSA and iLOGP values, and high bioavailability scores make them promising candidates for neuroprotection studies. Notably, Ombuin 3-O-β-d-glucopyranoside, which is potentially pharmacologically active, may face limitations owing to its high polarity and molecular weight, necessitating formulation optimization to enhance its oral absorption and systemic bioavailability. This challenge can be addressed through nanoformulation techniques using nanoemulsions or liposomes, prodrug strategies to reduce polarity, or the use of permeation enhancers to improve membrane transport and oral absorption.[163,164]

The pharmacokinetic profile predictions of *Syzygium aromaticum* flavonoid metabolites revealed key insights into their gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-glycoprotein (Pgp) substrate status, and interactions with cytochrome P450 (CYP) enzymes (Tables 6 and 7).

The BBB permeability was of utmost interest in this current review; hence, we compared the results on BBB permeability retrieved from the SwissADME web server (Categorical) with the BBB permeability results from the ADMETlab 3.0 web server (Numerical) to strengthen our findings further (Tables 6 and 7).

For clarity, in ADMETlab 3.0, blood-brain barrier (BBB) permeability is predicted as a classification endpoint, with confidence scores represented by six symbols: - (0.0–0.1), – (0.1–0.3), - (0.3–0.5), + (0.5–0.7), ++ (0.7–0.9), and +++ (0.9–1.0). These symbols reflect the probability that a compound can cross the BBB. A prediction score of ++ or +++ (above 0.7) is considered favorable and indicates a high likelihood of BBB penetration, which is essential for central nervous system (CNS)-active drugs (Table 7). In contrast, scores below + suggest poor permeability and limited CNS access, which may limit the therapeutic potential of such compounds for neurological conditions. The results of the validated numerical values of BBB permeability from the ADMETlab 3.0 web server are presented in Table 7.

Table 6 Pharmacokinetics Properties of the *S. aromaticum* Flavonoid Metabolites from SwissADME Web Server (Swiss Drug Design)

PubChem CID	GI Absorption	BBB Permeant	Pgp Substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
5280343	High	N	N	Y	N	N	Y	Y
5280863	High	N	N	Y	N	N	Y	Y
5281672	Low	N	N	Y	N	N	N	Y
5281699	High	N	N	Y	N	Y	Y	Y
44259621	Low	N	Y	N	N	N	N	Y
5320946	High	N	N	Y	N	N	Y	Y
5318869	High	N	N	Y	N	Y	Y	Y
5281677	High	N	N	Y	N	Y	Y	Y

Notes: Quercetin (PubChem CID: 5280343), Kaempferol (PubChem CID: 5280863), Myricetin (PubChem CID: 5281672), Tamarixetin 3-O-β-d-glucopyranoside (PubChem CID: 5281699), Ombuin 3-O-β-d-glucopyranoside (PubChem CID: 44259621), Rhamnocitrin (PubChem CID: 5320946), Kumatakenin (PubChem CID: 5318869), and Pachypodol (PubChem CID: 5281677). http://www.swissadme.ch/index.php.
Abbreviations: GI, gastrointestinal; BBB, blood-brain barrier (Categorical); Pgp, P-glycoprotein; CYP, cytochrome P; N, No; Y, Yes.

Table 7 Predicted BBB Permeability and Liver, Kidney, and Brain Toxicity of the *S. aromaticum* Flavonoid Metabolites in ADMETlab 3.0 Web Server

PubChem CID	vBBB	DILI	Human Hepatotoxicity	Drug-Induced Nephrotoxicity	Drug-Induced Neurotoxicity
5280343	0.00044529	0.782596	0.337382317	0.010642405	0.008593749
5280863	0.00095131	0.702867	0.386179209	0.018629327	0.038668543
5281672	0.00045408	0.839328	0.325381398	0.003110142	0.000876808
5281699	0.00038262	0.742716	0.392908126	0.039236177	0.037996754
44259621	0.00000727	0.786135	0.519109607	0.159253448	0.038186584
5320946	0.00073408	0.848478	0.403131634	0.047232695	0.068723217
5318869	0.00418202	0.829917	0.413502187	0.057172313	0.108579345
5281677	0.00079488	0.838962	0.403881848	0.112569705	0.091039792

Notes: Thresholds for DILI, human hepatotoxicity, drug-induced nephrotoxicity and neurotoxicity: 0.0–0.1 (-): Very low risk (good indicator), 0.1–0.3 (–): Low risk, 0.3–0.5 (-): Moderate risk, 0.5–0.7 (+): Elevated risk, 0.7–0.9 (++): High risk, 0.9–1.0 (+++): Very high risk (poor indicator). BBB permeability probability: 0.0–0.1 (-) is Very unlikely, 0.1–0.3 (–) is Unlikely, 0.3–0.5 (-) is Low possibility, 0.5–0.7 (+) is Moderate, 0.7–0.9 (++) is Likely, and 0.9–1.0 (+++) is Highly likely to permeate the BBB. https://admetlab3.scbdd.com/.
Abbreviations: vBBB, Validated numerical blood-brain barrier permeability; DILI, Drug-induced Liver Injury.

The BBB results from the ADMETlab 3.0 toxicity predictions indicate that all examined metabolites from *Syzygium aromaticum*, including Quercetin (CID: 5280343), Kaempferol (CID: 5280863), Myricetin (CID: 5281672), Tamarixetin 3-O-β-d-glucopyranoside (CID: 5281699), Ombuin 3-O-β-d-glucopyranoside (CID: 44259621), Rhamnocitrin (CID: 5320946), Kumatakenin (CID: 5318869), and Pachypodol (CID: 5281677), exhibit very low predicted BBB permeability (vBBB < 0.005), suggesting limited passive entry into the CNS.

When doing comparative analysis, none of the flavonoid metabolites were predicted to permeate the BBB by both the SwissADME (categorical) and ADMETlab 3.0 (numerical) web servers. This may limit these metabolites' direct central nervous system (CNS) effects, although peripheral neuroprotection or delivery system modification may still offer therapeutic advantages.

The permeability of the blood-brain barrier (BBB) is important in assessing the capacity of therapeutic agents to reach the central nervous system (CNS). The BBB is a very selective and highly regulated barrier made up of endothelial cells,

astrocyte end-feet, and tight junctions, which limit the movement of most molecules. A compound BBB permeability is usually predicted by computational models and in silico tools, including logP, topological polar surface area (TPSA), and molecular weight. The likelihood of drugs to cross the BBB is higher when it has a low molecular weight (<400 500 Da), moderate lipophilicity (logP 1–3), low hydrogen bonding potential, and TPSA <90 Å². The precise forecasts can be used to make the CNS drug development process more streamlined by selecting only the candidates with high brain bioavailability and weeding out the poorly penetrating compounds, and the final outcome is the enhanced design of neurotherapeutic agents.

Notably, BBB impermeability is not the total write-off of the neuroprotective mechanisms. Metabolites that cannot cross the blood-brain barrier (BBB) can still exert indirect neuroprotective effects through peripheral mechanisms. They may reduce systemic inflammation and oxidative stress or modulate gut microbiota, which in turn influences brain health via the gut-brain axis. Additionally, these metabolites can trigger the release of signaling molecules such as anti-inflammatory cytokines, neurotrophic factors, and short-chain fatty acids, which can cross the BBB and positively affect brain function and neuronal survival. The reviewed *S. aromaticum* flavonoid metabolites have been reported by many authors to reduce ROS, lipid peroxidation, and neuroinflammation, all of which are involved in neuroprotection. Ombuin 3-O-β-d-glucopyranoside was the only compound predicted to be a P-gp substrate, indicating a potential efflux from intestinal cells.[165,166]

From our findings, most compounds, including quercetin (PubChem CID: 5280343), kaempferol (PubChem CID: 5280863), tamarixetin 3-O-β-d-glucopyranoside (PubChem CID: 5281699), rhamnocitrin (PubChem CID: 5320946), kumatakenin (PubChem CID: 5318869), and pachypodol (PubChem CID: 5281677), exhibited high GI absorption, suggesting good oral uptake potential. In contrast, myricetin (PubChem CID: 5281672) and ombuin 3-O-β-d-glucopyranoside (PubChem CID: 44259621) showed low GI absorption (Table 5), which could limit their oral bioavailability and necessitate formulation enhancement.

Regarding cytochrome P 450 (CYP) enzyme inhibition, several compounds, such as Quercetin, Kaempferol, Kumatakenin, and Pachypodol, were predicted to inhibit key CYP enzymes like CYP1A2, CYP2D6, and CYP3A4. This suggests possible drug-drug interaction risks.[167,168] However, compounds, such as Myricetin and Ombuin 3-O-β-d-glucopyranoside, showed minimal CYP inhibition, which may reduce such risks. This implies that most *S. aromaticum* flavonoid metabolites demonstrated favorable GI absorption and manageable metabolic profiles. However, the low GI absorption and efflux potential of ombuin 3-O-β-d-glucopyranoside and myricetin may require optimization of the drug delivery. The CYP interactions must be considered during its co-administration with other therapies.

Toxicological Profile Prediction

The toxicological profile screening of plant metabolites is crucial in drug development and design because it helps to identify potential safety risks early in the discovery process.[32,169] This helps determine safe dosage ranges and predict interactions with critical systems, such as liver enzymes (CYPs) or cardiac ion channels (hERG). This ensures that only compounds with acceptable safety margins advance to preclinical and clinical stages, reducing the risk of failure, saving time and resources, and protecting human health.[170,171]

Additionally, the toxicological profiling of parameters of drug-induced liver injury (DILI), human hepatotoxicity, nephrotoxicity, and neurotoxicity will allow predicting the possible adverse effects at the initial stages of development, minimizing the chances of late-stage failures. Plant metabolites are natural, but they are not always safe and can have bioactivity that is harmful to vital organs or metabolic processes. Toxic liabilities can be identified early so that structural optimization can be performed, dosage planning can be informed, and safer and more effective drugs can be developed.

Therefore, in silico toxicity profiling, which can be performed with the aid of free web tools, can increase the translational potential of phytochemicals in contemporary drug discovery with minimal financial implications.

In this current review, the toxicity profiles of *Syzygium aromaticum* flavonoid metabolites, predicted via the pkCSM and ADMETlab 3.0 web servers, indicated an overall favorable safety profile with minimal adverse effects expected in therapeutic contexts (Tables 7 and 8).

All the reviewed *S. aromaticum* flavonoid metabolites, except pachypodol (PubChem CID: 5281677), tested negative in the AMES Test for Mutagenicity (AMES), suggesting low mutagenic risk. AMES is a biological assay that is used to

Table 8 Predicted Toxicity Profile of the *S. aromaticum* Flavonoid Metabolites in pkCSM Web Server

PubChem CID	AMES Toxicity	hERG I Inhibitor	hERG II Inhibitor	Hepatotoxicity	Skin Sensitization
5280343	No	No	No	No	No
5280863	No	No	No	No	No
5281672	No	No	No	No	No
5281699	No	No	No	No	No
44259621	No	No	Yes	No	No
5320946	No	No	No	No	No
5318869	No	No	No	No	No
5281677	Yes	No	No	No	No
PubChem CID	**MTD (Human) Log (mg/kg/day)**	**LD50 (Mol/Kg)**	**LOAEL Log (mg/kg_bw/day)**	**T.pT (Log ug/L)**	**MT Log (Mm)**
5280343	0.499	2.471	2.612	0.288	3.721
5280863	0.531	2.449	2.505	0.312	2.885
5281672	0.51	2.497	2.718	0.286	5.023
5281699	0.577	2.407	2.476	0.299	2.289
44259621	0.587	2.578	4.656	2.285	5.845
5320946	0.305	2.297	2.047	0.393	1.050
5318869	−0.045	2.273	2.122	0.419	0.877
5281677	0.438	2.482	13.324	0.285	7.233

Notes: Quercetin (PubChem CID: 5280343), Kaempferol (PubChem CID: 5280863), Myricetin (PubChem CID: 5281672), Tamarixetin 3-O-β-d-glucopyranoside (PubChem CID: 5281699), Ombuin 3-O-β-d-glucopyranoside (PubChem CID: 44259621), Rhamnocitrin (PubChem CID: 5320946), Kumatakenin (PubChem CID: 5318869), and Pachypodol (PubChem CID: 5281677). pkCSM web server: https://biosig.lab.uq.edu.au/pkcsm/prediction.

Abbreviations: hERG, human ether-a-go-go gene; MTD, maximum tolerated dose; LD50, oral rat acute toxicity; LOAEL, Lowest Observed Adverse Effect Level oral rat chronic toxicity; T.pT, T. pyriformis toxicity; MT, Minnow Toxicity.

assess the mutagenic potential of chemical compounds. A compound that tests positive in the AMES test may cause genetic mutations and is carcinogenic.[172,173]

Notably, Ombuin 3-O-β-d-glucopyranoside (PubChem CID: 44259621) was the only compound predicted to inhibit hERG II (Table 4), which may indicate a minor potential for cardiotoxicity,[174] although it is not a hERG I inhibitor. All other compounds, including quercetin (PubChem CID: 5280343), kaempferol (PubChem CID: 5280863), myricetin (PubChem CID: 5281672), rhamnocitrin (PubChem CID: 5320946), kumatakenin (PubChem CID: 5318869), and tamarixetin 3-O-β-d-glucopyranoside (PubChem CID: 5281699) showed no hepatotoxicity or skin sensitization (Table 4), further supporting their safety.

Toxicity thresholds such as minimum tolerated dose (MTD), median lethal dose (LD_{50}), and lowest observed adverse effect level (LOAEL) suggest that these flavonoid metabolites are well tolerated at standard dosages. Ombuin 3-O-β-d-glucopyranoside had a relatively high LOAEL log value (4.656), indicating a greater threshold before chronic toxicity was manifested. However, Pachypodol exhibited a high LOAEL (13.324), which may reflect a unique toxicological profile of chronic exposure that warrants further in vivo evaluation.

Minnow toxicity (MT) and *Tetrahymena pyriformis* toxicity (T. pT) were assessed. MT refers to the predicted acute aquatic toxicity of a compound to fathead minnows (a standard model organism), which is often used as a measure of environmental toxicity, whereas *Tetrahymena pyriformis* toxicity (T.pT) refers to the toxic effect of a compound on the protozoan *Tetrahymena pyriformis*, a widely used single-celled organism in ecotoxicology studies.[175,176] T. pT serves as a model for assessing the general cytotoxicity of chemicals in simple eukaryotic organisms. A lower T.pT value (log μg/L) indicates higher toxicity, indicating that the compound is toxic at lower concentrations. This helps to evaluate the environmental safety and

potential biological hazards of plant-derived or synthetic compounds.[177,178] The pT predictions indicated that all *Syzygium aromaticum* flavonoid metabolites exhibited low toxicity to this protozoan model, with log T. pT values ranging from 0.285 to 0.419.

These MT values varied among the reviewed metabolites, with pachypodol exhibiting the highest MT (7.233), suggesting potential aquatic toxicity at higher concentrations. Kumatakenin and Rhamnocitrin displayed the lowest MT values, indicating a diminished environmental toxicity.

Compounds such as Quercetin, Kaempferol, and Pachypodol showed the lowest toxicity, whereas Rhamnocitrin and Kumatakenin displayed slightly higher but still safer profiles. These findings suggest minimal environmental toxicity, supporting the biosafety of these compounds and their suitability for drug development.

Overall, the reviewed *S. aromaticum* flavonoid metabolites generally exhibited low toxicity risks across standard predictive endpoints. However, Pachypodol and Ombuin 3-O-β-d-glucopyranoside may require further assessment because of their mutagenicity and potential interactions with cardiac channels, particularly in the context of long-term or high-dose use.

To provide a deeper insight into the toxicological profiles of these eight *S. aromaticum* flavonoid metabolites, we utilized the ADMETlab 3.0 to assess some parameters such as Drug-induced liver injury (DILI), human hepatotoxicity, drug-induced nephrotoxicity, and drug-induced neurotoxicity (Table 7).

In ADMETlab 3.0, toxicity classification endpoints like DILI (Drug-Induced Liver Injury), human hepatotoxicity, drug-induced nephrotoxicity, and neurotoxicity are predicted based on probability scores ranging from 0 to 1. The confidence thresholds are categorized as follows: 0.0–0.1 (-): Very low risk (good indicator), 0.1–0.3 (–): Low risk, 0.3–0.5 (-): Moderate risk, 0.5–0.7 (+): Elevated risk, 0.7–0.9 (++): High risk, 0.9–1.0 (+++): Very high risk (poor indicator). Scores closer to 0 are desirable, indicating a low probability of causing organ-specific toxicity, while scores approaching 1 suggest a higher likelihood of adverse effects.

In this current review, most of the reviewed *S. aromaticum* flavonoid metabolites showed a high likelihood for Drug-Induced Liver Injury (DILI), with notably elevated scores for Rhamnocitrin (CID: 5320946; 0.848) and Myricetin (CID: 5281672; 0.839) (Table 7). Human hepatotoxicity predictions span a moderate range (0.32–0.52), with Ombuin 3-O-β-d-glucopyranoside (CID: 44259621) having the highest estimated potential (0.519) (Table 7). On the other hand, nephrotoxicity and neurotoxicity scores remain low (< 0.2) across all compounds, suggesting good renal and neurological safety. Slightly higher neurotoxicity risks were observed for Kumatakenin (CID: 5318869; 0.108) and Pachypodol (CID: 5281677; 0.091), but these remain within tolerable thresholds for early-phase therapeutic consideration.

Conclusion

Flavonoid metabolites present in *Syzygium aromaticum*, such as quercetin, kaempferol, and myricetin, demonstrate significant neuroprotective effects through their antioxidant, anti-inflammatory, and cellular protective properties. Their ability to mitigate oxidative stress, suppress neuroinflammation, and enhance synaptic function makes them promising agents for the prevention and treatment of neurodegenerative disorders such as AD and PD, as evident in reported studies exploring in vitro, in vivo, and in silico molecular docking approaches. Tamarixetin 3-O-β-d-glucopyranoside, ombuin 3-O-β-d-glucopyranoside, Rhamnocitrin, Kumatakenin, and Pachypodol are among the understudied and emerging *S. aromaticum* flavonoid metabolites with significant neuroprotective potential. Although these metabolites are not BBB permeants, as predicted by the SwissAdme and ADMETlab 3.0 web servers, their antioxidant, anti-inflammatory, and cellular protective properties make them promising candidates for the prevention and treatment of neurodegenerative diseases. Most of the studies reviewed utilized rodent models, thereby posing a limitation in the extrapolation of these findings to humans. This indicates the necessity for conducting studies on primates and advancing to clinical trials in humans because these metabolites showed favorable pharmacokinetic and toxicological profiles. However, dosage optimization is vital.

The eight reviewed *Syzygium aromaticum* flavonoid metabolites generally exhibited favorable ADME and drug-likeness profiles, with most showing high gastrointestinal absorption, compliance with Lipinski's rule, Pfitzer and GSK rules, and good oral bioavailability. Toxicological evaluations indicated a low risk of mutagenicity, cardiotoxicity,

hepatotoxicity, drug-induced liver injury, nephrotoxicity, and neurotoxicity. Despite this, minor concerns such as potential skin sensitization or P-gp substrate activity were noted in a few compounds, warranting further investigation.

Future Directions and Prospects

To advance the therapeutic applications of these flavonoid metabolites in *S. aromaticum*, future research should focus on in vivo and clinical studies to validate their neuroprotective efficacy and safety in humans. Emerging S. *aromaticum* flavonoid metabolites from *S. aromaticum* show promise for neuroprotection and warrant further investigation. Future studies should involve isolating the key metabolites and testing them in models (in vivo and in vitro) of neurodegeneration. All eight reviewed *S. aromaticum* flavonoid metabolites were impermeable to the BBB; therefore, efforts should be directed toward optimizing their permeability through nanoparticle-based delivery systems or novel drug formulations to enhance their pharmacokinetic properties. Nanocarrier systems as liposomes, solid lipid nanoparticles, polymeric nanoparticles (including poly-lactic-co-glycolic acid-PLGA), and nanoemulsions, may enhance stability, solubility, and controlled release. The BBB penetration can be increased by ligand modification of the surface, using transferrin or lactoferrin, to facilitate receptor-mediated transport. Exosome-based delivery is biocompatible and has good brain targeting properties, whereas intranasal administration partially avoids the BBB, making it possible to enter the CNS directly. Also, stimuli-responsive systems (for example, ROS- or pH-sensitive) can be applied to guarantee their release only in inflamed or oxidative conditions, maximizing the neuroprotective effect and reducing the side effects on the whole system. All these strategies will be beneficial towards the creation of flavonoid-based treatment of neurodegenerative disorders.

Further studies should prioritize the comprehensive toxicity profiling and dose optimization of *S. aromaticum* flavonoid metabolites to ensure their safety for human use in the treatment of neurodegenerative disorders.

Additionally, future studies should investigate the potential synergistic effects of these flavonoid metabolites with existing neuroprotective drugs to develop combination therapies. Public health initiatives and nutraceutical development should consider integrating *S. aromaticum*-derived flavonoids into dietary interventions for neuroprotection.

Furthermore, interdisciplinary collaboration among neuroscientists, pharmacologists, and traditional medicine practitioners could facilitate translational research, ensuring that this botanical drug and its flavonoid metabolites move from bench to bedside as viable neuroprotective agents.

Disclosure

The authors report no conflicts of interest in this work.

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