

Review

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Review

Role of Flavonoids in Sepsis: Advances and Future Prospects

Sara Osman Esmail * and Ahmad Zorin Sahlan

Department of Biomedical Sciences, Faculty Health Sciences, National University of Malaysia (UKM), 53100 Kuala Lumpur, Malaysia; ahmadzorinsahlan@ukm.edu.my

* Correspondence: osma.sara20@yahoo.com

Abstract: Due to the host immunological disease brought on by infection is flavonoids sepsis, multiple organ dysfunction syndrome (MODS), which has a high morbidity and mortality rate, could be the result. With advances in pathogen detection technologies, breakthroughs in anti-infection drugs, and the creation of organ function support, the clinical diagnosis and treatment of sepsis have advanced significantly. Pathogen-induced abnormal immunological responses, which can range from excessive inflammation to immunosuppression, are recognized to play a significant role in the high death rate. Unfortunately, no medications that are specifically intended to treat sepsis have been licensed. In order to offer a theoretical foundation for the management of flavonoids sepsis, we will now discuss current advancements in research on immunological responses in sepsis. The prognosis of sepsis patients may be improved by developing and optimizing a dynamic immune system treatment plan based on anti-infection therapy, fluid replacement, support for organ function, and timely application of immunomodulatory therapies.

Keywords: diagnosis; treatment; flavonoids; sepsis; inflammatory

1. Introduction

Sepsis is a dangerous and potentially fatal medical emergency that linked to dysregulated host immunological reactions to infection (Singer et al., 2016). It develops when your immune system overreacts to an infection. It produces widespread inflammation throughout your body, which can result in tissue damage, organ failure, and even death (Chen & Wei, 2021). Sepsis stands as a critical medical emergency characterized by dysregulated host immunological reactions to infection (Singer et al., 2016). Epidemiological data illuminates the extensive impact and seriousness of sepsis as a global health challenge.

The global Burden on the Sepsis affects over 30 million individuals worldwide annually, with approximately 6 million sepsis-related deaths reported globally each year (Fleischmann-Struzek & Rudd, 2023). In the United States alone, sepsis accounts for over 1.7 million hospitalizations annually, making it one of the most common reasons for hospital admission (Rhee et al., 2019).

Based on modeling studies or meta-analyses of prospective studies, global annual sepsis incidence was found to be 276–678/100,000 persons. Case fatality ranged from 22.5 to 26.7% (Fleischmann-Struzek & Rudd, 2023). The Mortality Rates recorded on Sepsis remains a leading cause of mortality in hospitals worldwide, with mortality rates varying widely but ranging from 15% to 55% in critically ill patients admitted to intensive care units (Singer et al., 2016). It significantly contributes to multiple organ dysfunction syndromes (MODS) in acute care settings, leading to substantial morbidity and mortality among affected individuals (Robba et al., 2020).

This call for the Public Health Concern on the burden of sepsis which extends beyond individual health outcomes to affect healthcare systems and public health infrastructure globally. It poses considerable challenges in terms of resource allocation, healthcare delivery, and patient management (Prescott & Angus, 2018). Despite advancements in critical care and sepsis management, sepsis-

related mortality remains a significant concern, particularly among vulnerable populations and in resource-limited settings (Fleischmann-Struzek & Rudd, 2023)

The Incidence and Prevalence on the epidemiological studies indicate a rising incidence of sepsis worldwide, attributed to factors such as an aging population, increased prevalence of chronic diseases, antimicrobial resistance, and healthcare-associated infections (Cristina et al., 2021). It imposes a substantial economic burden on healthcare systems and societies. The costs associated with sepsis-related hospitalizations, intensive care unit stays, and long-term sequelae contribute significantly to healthcare expenditures globally (Schlapbach et al., 2020).

The Geographical Disparities in sepsis incidence, outcomes, and access to care exist across different regions and populations, highlighting the need for targeted interventions and healthcare policy reforms to address these inequities (Brinkworth & Shaw, 2022). Some Studies have shown variations in sepsis incidence and outcomes based on geographical location, socioeconomic status, and access to healthcare services, emphasizing the need for tailored interventions and resource allocation strategies (Seymour et al., 2019; Fleischmann et al., 2016). These epidemiological insights underscore the urgent need for enhanced awareness, early recognition, and effective management strategies to mitigate the burden of sepsis on individuals, healthcare systems, and society as a whole.

According to the information provided in, the late-onset anti-inflammatory response establishes a link between sepsis and an immunosuppressive condition that may last for a long time (weeks or months) after the onset of SIRS (Figure 1) For patients with severe sepsis, maintaining a balance between the pro- and anti-inflammatory responses is essential (Sheth et al., 2019). Proinflammatory cytokines such IL-1, TNF- α and IL-6 are thought to be released in response to SIRS (Sheth et al., 2019). On the contrary, the pharmacological actions of anti-inflammatory mediators such as IL-1ra, IL10 and sTNFR-1 may be responsible for CARS (Sheth et al., 2019). The worst prognostic outcomes in septic patients are correlated with higher levels of IL-1 β , IL-6, IL-8 and TNF- α (Sheth et al., 2019)

The severity of the illness is consequently predicted by the anti-inflammatory chemicals that are produced in larger quantities during sepsis. In addition, it represents the overall clinical and survival results. As a result, the imbalance between pro-inflammatory and anti-inflammatory mediators in the septic state reveals how severe the body's defences against the infection were (Gabarin et al., 2021). In addition, it causes excessive cytokine production and stimulation, which can have negative consequences in individuals with serious and life-threatening illnesses.

Long before flavonoids were identified as the active ingredients, these natural products were well-known for their positive health effects (Panche et al., 2016). Flavonoids come in more than 4000 different types and many of them are what give flowers, fruits, and leaves their appealing hues (Perez-Vizcaino & Fraga, 2018). Red wine's flavonoids are at least partially to blame for this result (Antoce & Stockley, 2019). Furthermore, epidemiological research points to dietary flavonoids' preventive effects of dietary flavonoids against coronary heart disease (Micek et al., 2021). Up until about 50 years ago, nothing was known about how flavonoids functioned (Kumar & Pandey, 2013). When it was discovered that this substance was a flavonoid (rutin), a flurry of research was conducted to try and separate the different flavonoids and understand how they work. Early advances in floral genetics, according to Jorgensen (Jorgensen, 1995), were mainly the result of mutation techniques that have an effect on flower colours produced from flavonoids (Morita & Hoshino, 2018). It has been demonstrated that the subclass of plant polyphenols known as flavonoids has numerous physiological advantages that are health-promoting (Rupasinghe, 2020). It is clear that study advances our understanding of dietary flavonoids' beneficial physiological effects and their therapeutic potential. New information is provided regarding the potential use of flavonoid derivatives as potent therapeutics to treat specific cancers, in addition to their function as biologically active plant food molecules (Slika et al., 2022). Additionally, flavonoids show promise in the treatment of diseases linked to inflammation and obesity as well as the prevention and treatment of infectious diseases like COVID-19 (Berretta et al., 2020).

In clinical contexts, the term "nutrition evaluation" is frequently used and an human body serves as the evaluation object. There is a wide range of research on evaluating the nutritional qualities of foods, as well as on how the idea is understood and defined across disciplines. For example, food

scientists typically assess nutritional value based on the type and amount of nutrients it contains (De Souza et al., 2017; Hong et al., 2020; Nowak et al., 2016; Pereira et al., 2019; Popovi-Djordjevi et al., 2022; Shannon & Abu-Ghannam, 2019; Wang et al., 2022). Therefore, addressing the optimal dietary requirements of various groups while also taking into account the nutritional characteristics of foodstuffs will be a key area of nutrition development in the future. The precise food matrix in which a vitamin appears determines its true bioavailability, although nutrition science still pays little attention to this. It is beginning to become clear how flavonoids affect the gut microbiota and how their microbial metabolites affect optimal health. Flavonoid molecules' intricate physiological modulations are caused by the variety of their structures. However, some flavonoids are poorly absorbed, and the use of structural changes and nanotechnology uses, such as encapsulation, could increase their bioavailability (Zhao et al., 2019).

Whether or not ultra-processed foods (UPFs) play a significant role in the nutritional quality of modern diets is still up for debate (Martnez Steele et al., 2017). The primary focus of nutrition science is the impact of nutrients on human health. It breaks down complex dietary requirements into achievable suggestions in order to prevent disease. According to conventional nutrition, the type and quantity of nutrients in a food represent its nutritional value. Dietary components are correlated with one another and consumed in combination (Neelakantan et al., 2018). Today, nutrition provides us with more than just nutrients; it also offers the opportunity to combat illness and maintain good health. Consumers have a difficult time telling what food is actually healthy and nourishing (Ditlevsen et al., 2019). To assess the nutritional worth of meals, different specialists have adopted various points and methodologies. Following is the structure of flavonoids and its classes.

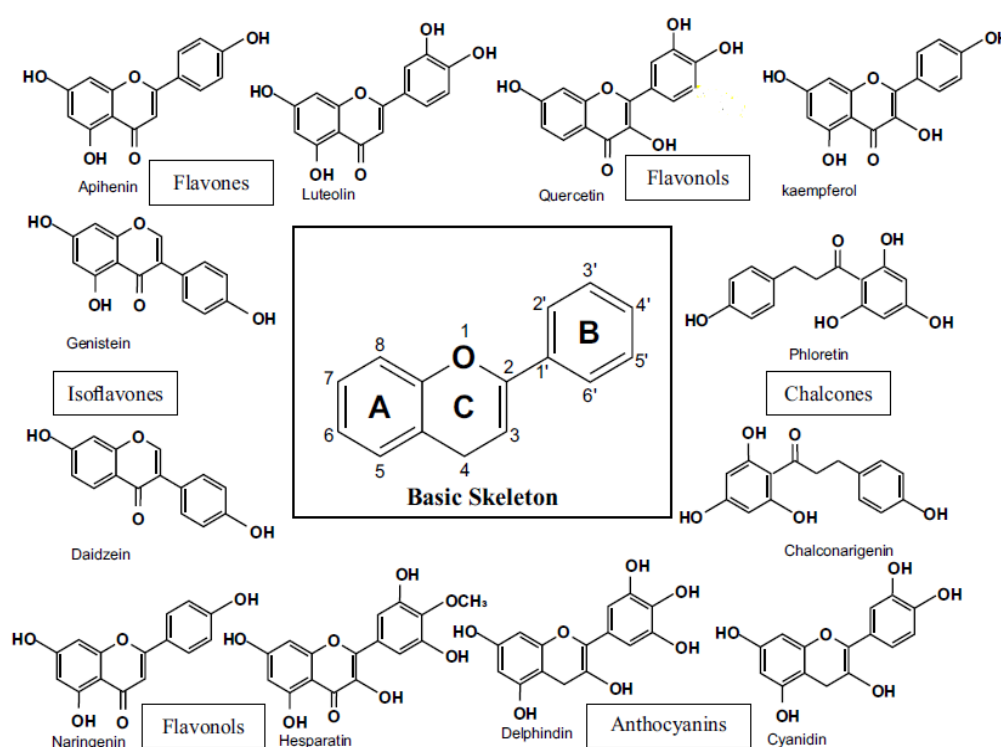


Figure 1. The Structure of Flavonoids and Classes.

1.1. The Study Inclusion/Exclusion Criteria

The literature review included randomised clinical trials, randomized quasi-trials in both people and animals, as well as in vitro and in vivo research. Research, such as unpublished theses, review newspapers, editorial documents, and memos, in which the data provided is insufficient to draw reliable conclusions, was excluded as shown in Figure 1.

2. Treatment of Sepsis Flavonoids

The potential use of various flavonoid classes in the treatment of sepsis is discussed in this section. The classification that is frequently used based on the kind and arrangement of substituents, flavones, flavonols, and flavanones, was investigated (DGI & Role, 2019; Kumar & Pandey, 2013).

2.1. Flavanoids

2.1.1. Baicalin

Baicalin (shown in Figure 2) is the primary flavonoid glucoside of *Scutellaria baicalensis* Georgi, a member of the Lamiaceae family, which exhibits antiviral, bacteriostatic, anticancer, and antioxidant properties (Lin et al., 2007; Shi et al., 2016). It is known for a Chinese herbal remedy, containing an active component (Deng et al., 2023). It functions as a non-steroidal anti-inflammatory drug, an inhibitor of the enzyme prolyl oligopeptidase, a prodrug, a plant metabolite, a ferroptosis inhibitor, a neuroprotective agent, an antineoplastic agent, a cardioprotective agent, an antiatherosclerotic agent, an antioxidant, an inhibitor of the enzyme RNA-directed RNA polymerase, an antibacterial agent, and an inhibitor of the enzyme (Dinda et al., 2017).

The main active component of baicalin (5,6,7-trihydroxyflavone), a common plant in traditional Chinese medicine used to cure fever, is produced from the dried root of *scutellaria* (Kumagai et al., 2007). Small-molecule monomer baicalin has antibacterial, anti-oxidant, anti-apoptotic, and anti-inflammatory effects (Bao et al., 2022). Baicalin reduced inflammation and preserved many organ functions. Baicalin suppressed the production of pro-inflammatory cytokines, nitric oxide (NO), nuclear factor-B (NF-B), caspase-3 activity, and reversed organ harm brought on by endotoxic shock in vivo while decreasing LPS-stimulated macrophage activation in vitro (Shahcheraghi et al., 2023). Additionally, baicalin can be used as an adjuvant therapy for both ex vivo methicillin-resistant *Staphylococcus aureus* (MRSA) and animal meningitis caused by *Escherichia coli* (*E. coli*) (Divyakolu et al., 2019; dos Santos Ramos et al., 2020; Rani et al., 2021).

Baicalin is viewed as the therapeutic chemical marker for *S. baicalensis* root quality control (Li et al., 2021). To create the TCM formula, many herbs are typically blended to enhance the medicinal effects. The pharmacokinetics may change due to interactions between the herbs in the prescription. *S. baicalensis* is frequently recommended with herbs such as *Bupleuri radix* and *Coptidis rhizoma* as a key ingredient in TCM formulae (Yin et al., 2021).

Many studies concentrating on baicalin's pharmacological properties have been conducted as awareness of its antiviral effects has grown (Song et al., 2020). We have outlined the mechanism of action of baicalin as it relates to several cytokines and cell pathways (Chen et al., 2020; K. Li et al., 2021). More discussion is also conducted on the pharmacological importance of baicalin for the creation of a broad-spectrum antiviral drug. Furthermore, pharmacologically, baicalin has been shown to protect against Sepsis. Induce liver damage and increase survival in mice suffering from polymicrobial sepsis (Achuthan & Werschler, 2022; Vo et al., 2019; von Knethen et al., 2020).

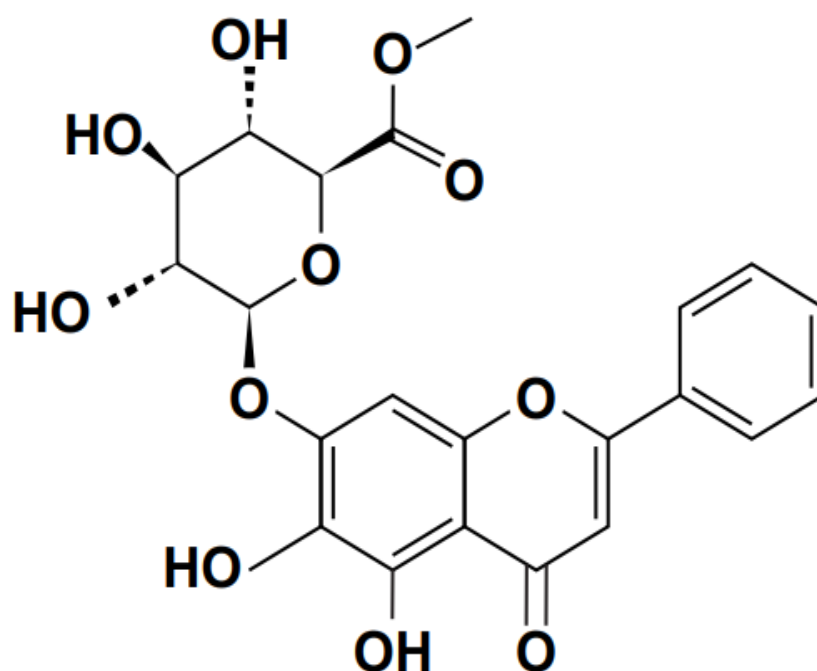


Figure 2. Structure of Baicalin.

2.1.2. Scutellarin

A flavone, or phenolic chemical compound, is scutellarin. *Scutellaria barbata* and *S. lateriflora*, two plants used in conventional medicine, contain it. Guido Goldschmiedt needed a lot of time to figure out the structure of scutellarin; after the first article on the subject was published in 1901, it wasn't until 1910 that he was able to gather enough information to begin more extensive research. Figure 3 shows its chemical structure. However, studies have demonstrated that scutellarin can provide neuroprotection by suppressing microglial activation induced by increased serum (TNF- α , IL- β , and IL-6), lactate dehydrogenase activities, and tissue glutathione levels. Scutellarin has been shown to cause ovarian and breast tumour cells to undergo apoptosis in vitro. Furthermore, scutellarin exhibits protective qualities for oestrogen-affected nerve cells (Zhu et al., 2007). It has been demonstrated by (Wang et al., 2014), that scutellarin may be used to cure diabetic retinopathy, hence preventing diabetic blindness.

Scutellarin has many pharmacological benefits, including anti-inflammatory (Chledzik et al., 2018; Niu et al., 2015; Peng et al., 2020; Tan et al., 2007) and antioxidant activity, anti-diabetic, anti-ischemic, anti-cancer impact, as demonstrated by systematic investigations in modern medicine (Peng et al., 2020; Wang et al., 2020). As a result, scutellarin's multifaceted effectiveness leads to the conclusion that it may have clinical uses for the treatment of a variety of illnesses, including tissues I/R injury. It is still unknown how scutellarin affects hepatic I/R damage. As a result, in the current investigation, we looked at how scutellarin affected in vitro hepatic hypoxia/reoxygenation (H/R) injury (Toklu et al., 2008).

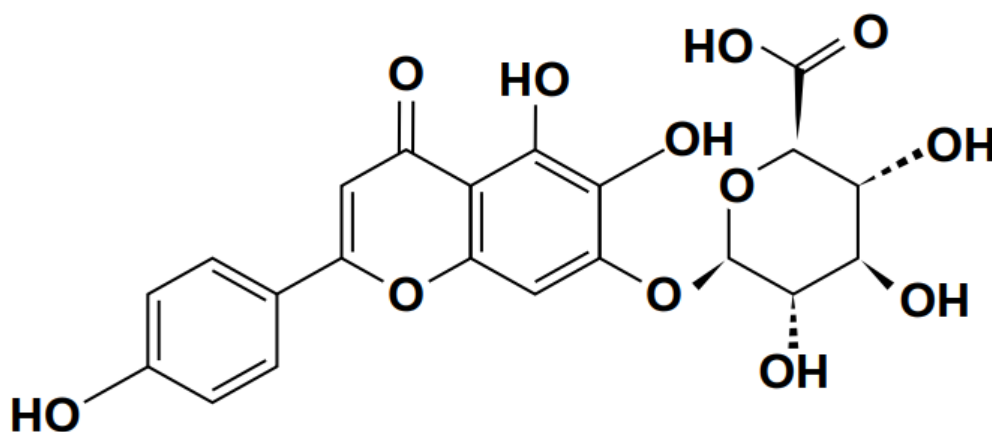


Figure 3. The Structure of Scutellarin.

3.1.3. Silymarin

Silymarin is a polyphenol that belongs to the flavone group. It is a natural herbal preparation derived from fruits and milky seeds. The milk thistle plant *Silybum marianum* L. Gaertn, which is widely cultivated in Europe and Asia, including India, produces silymarin, which is made up of many flavonoid-like substances. Kenguil seeds are small, hard fruits from which silymarin is extracted. The chemical, which belongs to the class of drugs known as flavonolignans. It is believed that silymarin, which is composed of the flavonolignan isomers silybin (70-80%), isosilybin (0.5%), silydianin (10%) and silychristin (20%) is what gives the extract its advantageous liver-protective qualities (Brent & Shao-Nong, 2013; Lee & Liu, 2003; Scott, 1998, p. 1). Clinical and pharmacotoxicological research on silybin, the main ingredient, is extensive (Fan et al., 2018; Q. Liang et al., 2015). The chemical structure of silymarin is shown in Figure 4. A chromone fragment in its chemical structure, which enables donor-acceptor interactions with base, gives it certain acidic characteristics. The molecule has a strong antioxidant activity because to the presence of polyphenol hydroxyls and its propensity to form complexes with other metal ions and transition metal ions at the 3,4, or 4,5-positions. Several studies have demonstrated that both people and animals can tolerate its active component at very high concentrations (Tvrd et al., 2021).

In fact, the oral 50% lethal dose for rats is 10,000 mg/kg, while the greatest tolerable dose for dogs is 300 mg/kg (Abenavoli et al., 2010). The exceptionally low water solubility of silybin (430 mg/L), which is symptomatic of its lipophilic nature, as evidenced by a logarithmic P value of 1.41 (Parveen et al., 2011), where P is the drug's partitioning coefficient, places certain restrictions on its therapeutic efficacy. Silymarin is classified as a compound in class II of the biopharmaceutical categorisation system (BCS), which includes chemicals that are totally or just very slightly soluble in water. Due to this, the drug has a low bioavailability in oral formulations and has poor GIT absorption (20–50%) (Wu et al., 2007). Chemical modifications that made silybin more water soluble often reduced its antioxidant (antiradical) (Gažák et al., 2004). Due to its antioxidant activity and ability to stabilise membranes, silymarin and its main component, silybin, have hepatoprotective qualities that prevent or slow the process of lipid peroxidation (Kurkin et al., 2009).

Because of its tendency to discourage neutrophil and ROS infiltration, silymarin treatment was observed to reverse the biochemical parameter and minimize damage to distant organs caused by sepsis. It also regulates the release of inflammatory mediators (Yang et al., 2014). As the study by (Chan et al., 2015) discovered that silymarin inhibits the formation of superoxide amino acid radicals and nitrates. Silymarin therapy also reduced the amount of serum segregated by sepsis. Silymarin was discovered in a study by (Al-Kadi et al., 2020) to protect against sepsis in laboratory mice using the cecal ligation and puncture method. In animal models induced by sepsis, silymarin antioxidants

and anti-inflammatory effects prevent liver and kidney damage and reduce levels of IL-6, NO and TNF- α levels.

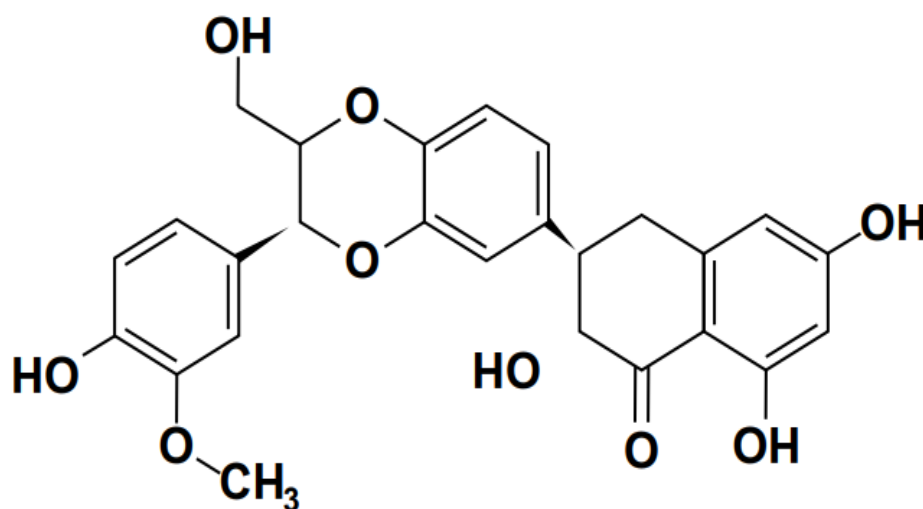


Figure 4. The Structure of Silymarin.

3.1.4. Luteolin

Luteolin is a member of the flavonoids class represented in Figure 5 and is mostly present in fruits, vegetables, and herbs. It has many therapeutic benefits, such as antioxidant, anti-inflammatory, and anticancer properties (Chuammitri et al., 2017). By enhancing contractile function and lowering apoptosis, it lowers ROS-activated MAPK pathways in ischemia healing in rats, works as an anti-inflammatory, and guards against excessive carbohydrate and fat consumption (Pan et al., 2022).

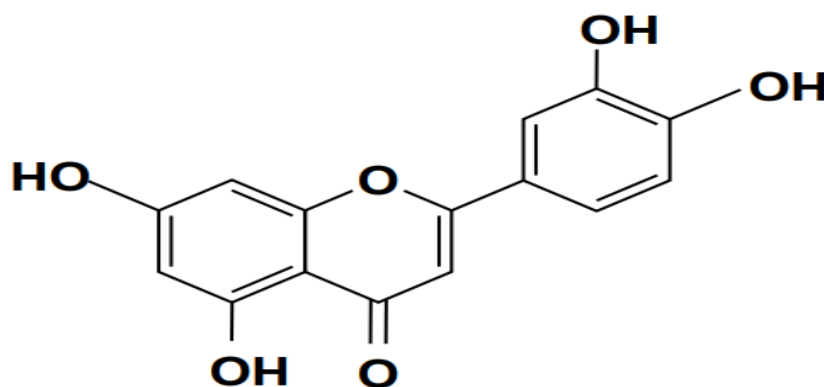


Figure 5. The Structure of Luteolin.

3.2. Flavonol

3.2.1. Quercetin

Quercetin is a flavonoid from the polyphenol flavonoid group, as shown in Figure 6. It has a wide range of pharmaceutical effects, including anti-tuberculosis (Hasan et al., 2022), anti-inflammatory (Lesjak et al., 2018), anti-proliferation, (Luo et al., 2016) and antioxidant protection (Karuppagounder et al., 2016). In RAW264.7 macrophages, it reduces LPS-induced TNF- release of

TNF- α induced by LPS and the production of IL-1 β , thereby reducing inflammatory reactions (Chuammitri et al., 2016; Yadav et al., 2012).

A study by (Huang et al., 2015) indicated the efficacy of quercetin pre-treatment on sepsis by lowering lung pathology, inflammatory cytokines, and increasing IL-10 secretions in LPS-Induced Acute Lung Injury. According to a study by (Maalik et al., 2014) research on the effects of quercetin on septic-induced mice, the antioxidant may be able to correct lung damage by lowering blood levels of NO and MDA and enhancing the activity of antioxidant enzymes. A similar finding has been revealed in (Gerin et al., 2016; Huang et al., 2015). A study by (Park et al., 2018) revealed that Quercetin suppresses the expression of HMGB1, greatly reduces oxidative stress, and activates the enzymatic antioxidant system, successfully healing sepsis and lung cells. According to study by (Cui et al., 2019) Quercetin lowers the possibility of tissue edema, boosts alveolar capacity, and safeguards the lungs of Septic Mice. Quercetin is discovered to suppress LPS-stimulated macrophages' production of TNF- α and IL-1 β as well as NF- κ B activation (Dai et al., 2013; Vickers, 2017). IKK and I κ B α phosphorylation is inhibited by quercetin, which prevents NF- κ B from activating.

A study by (Bharrhan et al., 2012) revealed that the induced animals had much lower levels of oxidative enzyme production, as did the inflammatory pathways. (NF- κ B) were negatively regulated. A study conducted by (Wang et al., 2014) revealed that Quercetin significantly reduces NOS, COX-2, NF- κ B p65 phosphorylation, malondialdehyde and HMGB1 levels and further suggested the lengthens lung life time.

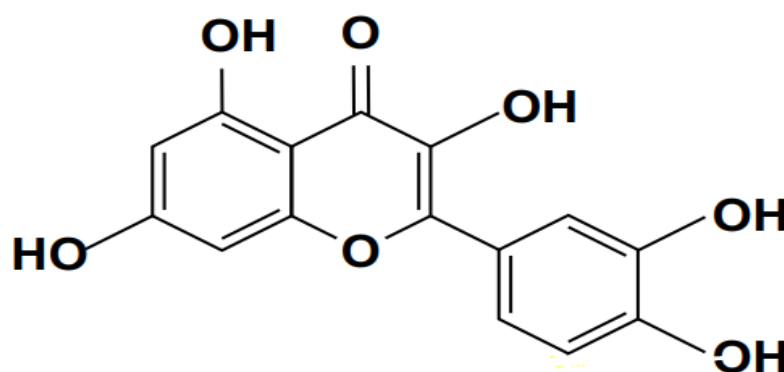


Figure 6. The Structure of Quercetin.

3.2.2. Isorhamnetin

Isorhamnetin, with the chemical structure illustrated in Figure 7, has been shown in research findings to have a broad spectrum of pharmaceutical impacts on cardiovascular disease (Zhao & Liu, 2008) and a wide range of tumors (Li et al., 2011), as well as the potential to protect cardiocerebral vessels and nerves (Gong et al., 2020) and neurodegenerative diseases (Ishola et al., 2019) such as Alzheimer's disease (Xu et al., 2021). It also exhibits antihyperuricemia and anti-pulmonary fibrosis pharmacodynamics (Adachi et al., 2019) and pulmonary fibrosis (Zheng et al., 2019). Several investigations have shown that Isomemtrin protects the heart and cerebrovascular system (Wang et al., 2014), prevents obesity (González-Arceo et al., 2022), is an antioxidant (Jiang et al., 2019), and has antitumor (Kim et al., 2011) and anti-inflammatory properties (Gong et al., 2020). Isorhamnetin significantly decreases AST, ALT, and BUN levels in mice with E-coli-induced sepsis. It has a pharmacological actions are connected to its control of NF- κ B, PI3K/ AKT, MAPK, and other signaling pathways and their downstream variables. The pharmacological activity and mechanism of isorhamnetin are currently being studied in depth. According to (Dong et al., 2015), isorhamnetin is cytotoxic for H9C2 cardiomyocytes and mouse primary hepatocytes (Liang et al., 2017) and promotes DNA damage in HepG2 cells (Grollino et al., 2017).

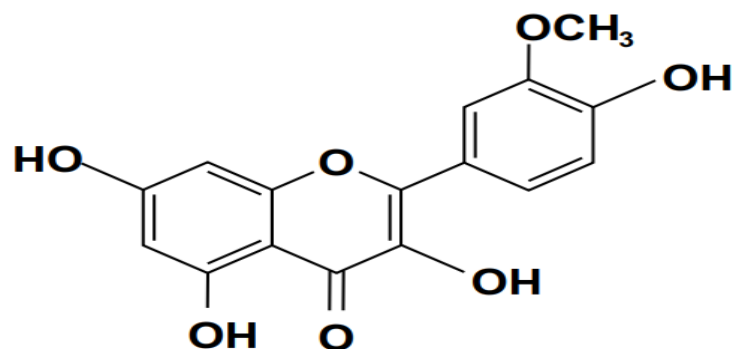


Figure 7. The Structure of Isorhamnetin.

3.2.3. Fisetin

Figure 8 demonstrates that strawberries, kiwi, onions, tea, grapes, oranges, peaches, and wine are high in fisetin, a flavonoid (Qian et al., 2019). Fisetin has the potential to cause apoptosis, carcinogenesis, antioxidant, anti-tumorigenic, anti-inflammation, antiangiogenic, antidiabetic and cardioprotective properties (Abotaleb et al., 2018; Mehta et al., 2018; Pal et al., 2016; Sharif et al., 2020; Yang & Yang, 2021; Yarla et al., 2016). It can be used in reducing the protein and mRNA expression of inducible iNOS, COX-2, and COX-2 (Proinflammatory mediators) in LPS-stimulated cells (Bak et al., 2012; Lee et al., 2016; Zhang et al., 2020). An Austrian chemist, (Herzig, 1891; Sahu et al., 2014) revealed its chemical formula for the first time. The biological activity of Fisetin has been examined in numerous laboratory experiments; like other polyphenols, it has a wide range of actions (Herzig, 1891; Lodyga-Chrusciska et al., 2018; Maher, 2015; Naeimi & Alizadeh, 2017).

A study by Lee et al. (2014) discovered that Fisetin can inhibit LPS-induced HMGB1 release and CAM expression, which reduce EPCR shedding significantly. The finding revealed as an effective in the treatment of vascular inflammatory diseases in sepsis-infected rats. It has been successfully in preventing action that successfully alleviates CLP-induced liver, kidney, and lung damage (H. Zhang et al., 2020). The finding of the study revealed that fisetin can be used to minimize lung damage in patients with sepsis. Fisetin was discovered to minimize lung damage in sepsis patients. It greatly reduces lung veridoperoxidase levels as well as cell proliferation for inflammatory cytokines. Many investigations have found that fisetin is a promising new antioxidant (Gryniewicz & Demchuk, 2019).

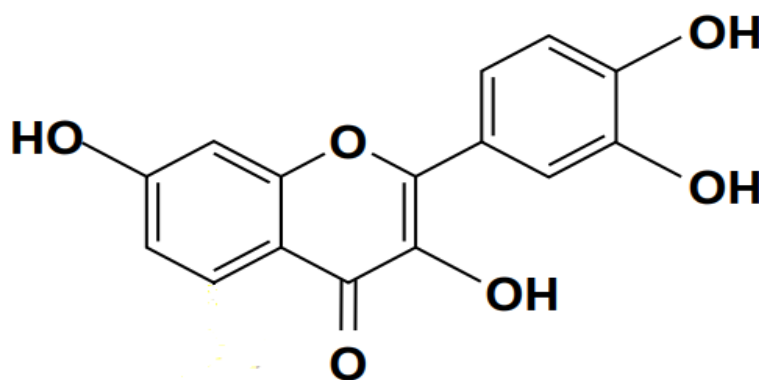


Figure 8. The Structure of Fisetin.

3.2.4. Myricetin

Myricetin is a polyphenolic molecule with antioxidant characteristics that belongs to the flavonoid class (Ong & Khoo, 1997). Typical food sources (Khan et al., 2021) include red wine, tea, nuts, berries, vegetables (including tomatoes), fruits (including oranges), tea, and nuts (Naeimi & Alizadeh, 2017). Fisetin, luteolin, and quercetin share structural similarities with myricetin, and both of these flavonoids are said to have many of the same properties (Hollman & Katan, 1999). Myricetin's reported daily average consumption varies depending on diet, although it has been shown to be 23 mg on average per day in the Netherlands (Hollman & Katan, 1999). Myricetin is created from the parent component taxifolin through the intermediate (+)-dihydromyricetin and it can then be processed to create laricitrin and syringetin, both of which are flavonoids that belong to the flavonol class (Nwachukwu et al., 2019). Dihydromyricetin is a supplement that is widely available for sale. It is used to treat alcohol use disorder and has a contentious role as a partial GABAA receptor potentiator (AUD). An alternative method is to make myricetin directly from kaempferol, a different flavonol (Felice et al., 2022).

Natural sources of the flavonoid myricetin include plants of the Primulaceae, Leguminosae, Rosaceae, Vitaceae, Ericaceae and Fagaceae families, as well as fruits, vegetables, tea, and honey (Taheri et al., 2020). Its chemistry is shown in Figure 9. Myricetin controls IB/NFB through reducing Nrf2 in NRCM. It has been shown by pharmacology studies that myricetin can serve as anti-diabetic potential (Gupta et al., 2020). It blocks the expression of the proteins protein kinase (PKB), GLUT-2 and GLUT-4, insulin receptors 1 and 2 as well as insulin receptor 3 (IRS-3) (Lalitha et al., 2020). A study by Ozcan et al. (2012), Myricetin can be used in decreasing the Malondialdehyde and protein carbonyl levels in diabetic erythrocytes. The study further revealed, it can also be used to reduce the amount of urine, BUN, and protein excretion in diabetic albinos. As anti-inflammatory, myricetin prevents the sepsis-induced animal from producing nitric oxide, iNOS, TNF- α , IL-6, or IL-12. Furthermore, it reduces the degradation of I κ B α , the translocation of the NF- κ B subunit p65, and DNA binding activity in RAW264.7 macrophages, which decreases NF- κ B stimulation (Imran et al., 2021). Moreover, it prevents the growth of leukemia-causing inosine 5'-monophosphate dehydrogenase and liver cancer cells (Jiang et al., 2019). Reduces PIM1 and interferes with interactions between PMI and CXCR4 to prevent the invasion of malignant prostate cancer (Huang et al., 2013; Imran et al., 2019; Song et al., 2021; Wang et al., 2019).

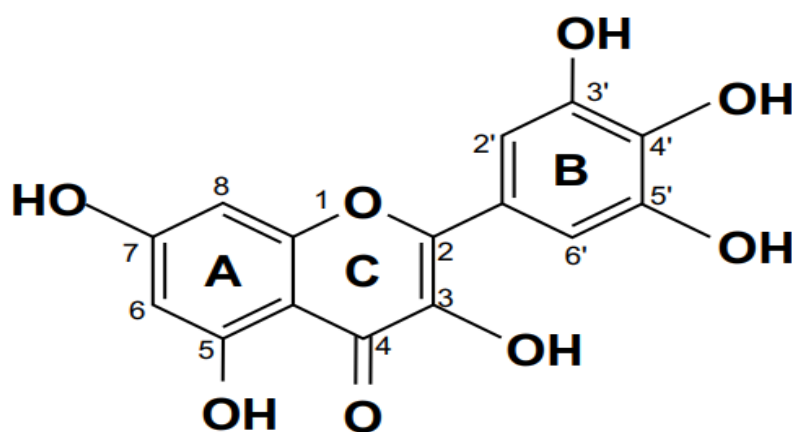


Figure 9. The Composition of Myricetin.

3.3. Flavan

3.3.1. Epigallocatechin-3-gallate (EGCG)

Green tea extracts contain EGCG, a powerful catechin that is widely distributed. Its chemistry is shown in Figure 10. It has cancer prevention, bacterial resistance, anti-inflammatory, and immune stimulating qualities (Almatroodi et al., 2020). According to reported by Wheeler et al. (2007) , supported by Xin et al. (2016), revealed that, EGCG can improved the hemodynamics via lowering CL2P activity and NOS2 gene expression. When used in rodent models of polymicrobial sepsis, it increases survival rates. A drop in ALT, AST, MDA, and TNF-, as well as an improvement in hepatic expression of Nrf-2 and HO-1, were linked to a rise in survival rates in sepsis rats given EGCG taken as a pill or capsule (Yang et al., 2017). Similarly, Hu et al. (2018) recommended that daily EGCG intake be 338 mg, although drinking tea is safe at 704 mg. Green tea has approximately 70.2 mg of EGCG per 100 mL. (about 165 mg per cup). EGCG, a potent and widely used catechin, is present in green tea extracts. In Figure 10, its chemistry is displayed. It has anti-inflammatory, antibacterial, anticancer, and immune-stimulating properties (Almatroodi et al., 2020). By reducing CL2P activity and NOS2 gene expression, EGCG improved hemodynamics. Improves survival rates in rodent models of polymicrobial sepsis. In sepsis rats fed EGCG, a decrease in ALT, AST, MDA, and TNF-, as well as an improvement in Nrf-2 and HO-1 liver expression, was associated with a rise in survival rate.

The most prevalent catechin in tea, EGCG, is a polyphenol that is being investigated for its potential to impact health and disease in people. A variety of dietary supplements contain EGCG. Even with a daily intake of 8 to 16 cups of green tea, orally administered EGCG has limited absorption, which could result in unpleasant side effects such as nausea or heartburn (Chow et al., 2003). Within 1.7 hours of intake, EGCG blood levels reach their peak (Lee et al., 2002). Although most unmodified EGCG is eliminated from the urine over a period of 0 to 8 hours, the half-life of plasma absorbed is 5 hours. Methylated metabolites are present in plasma at levels 8–25 times higher than those of unmetabolized EGCG and seem to have longer half-lives (Williamson & Manach, 2005). EGCG has a wide range of biological effects in laboratory experiments and is well researched in basic science (Furst & Zündorf, 2014; Granja et al., 2017; Riegsecker et al., 2013; Wu et al., 2012). According to study by the European Food Safety Authority, in 2011, there is no evidence of a causal connection between tea catechins and the preservation of normal blood LDL cholesterol levels (Prawira-Atmaja et al., 2022). Similarly, in the 2016 assessment, human individuals that took high daily doses (107 to 856 mg/day) for four to 14 weeks saw a slight decrease in LDL cholesterol. According to a 2018 review, consuming too much EGCG can be harmful to the liver (Momose et al., 2016).

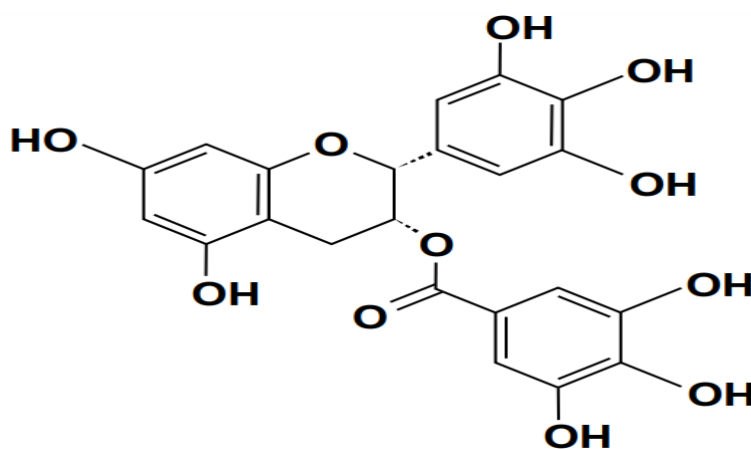


Figure 10. The Structure of Epigallocatechin-3-gallate (EGCG).

Table 1. Table of review.

Year	Author(s)	Title	Purpose/Objectives	Methods	Findings/Results
2016	Panche et al.	Flavonoids: An overview	To provide an overview of flavonoids, including their health benefits and potential therapeutic applications.	Review of existing literature	Flavonoids offer preventive effects against coronary heart disease, anti-inflammatory properties, and therapeutic potential for cancer and infectious diseases.
2018	Perez-Vizcaino & Fraga	Flavonoids in cardiovascular health: A review	To review the role of flavonoids in cardiovascular health, including their effects on endothelial function, blood pressure, and oxidative stress.	Review of existing literature	Flavonoids exhibit cardiovascular benefits by improving endothelial function, reducing blood pressure, and mitigating oxidative stress.
2019	Antoce & Stockley	The role of polyphenols in cardiovascular disease risk factors: A review	To examine the role of polyphenols, including flavonoids found in red wine, in mitigating cardiovascular disease risk factors.	Review of existing literature	Polyphenols, including flavonoids, found in red wine, contribute to the reduction of cardiovascular disease risk factors such as inflammation and oxidative stress.
2021	Micek et al.	Flavonoids - A Review of Their Potential Role in the Treatment of Diabetes Mellitus	To evaluate the potential role of flavonoids in the treatment of diabetes mellitus, including their effects on glucose metabolism and insulin sensitivity.	Review of existing literature	Flavonoids demonstrate potential in managing diabetes mellitus by improving glucose metabolism and enhancing insulin sensitivity.
2017	De Souza et al.	Methods for evaluation of food and nutrient intake	To review methods for evaluating food and nutrient intake, with a focus on different approaches used in nutrition research.	Review of existing literature	Various methods, such as dietary recalls, food frequency questionnaires, and biomarkers, are employed to evaluate food and nutrient intake in nutrition research.
2020	Hong et al.	Nutritional evaluation of food: A review	To provide an overview of nutritional evaluation methods used in assessing the nutritional quality of food products.	Review of existing literature	Nutritional evaluation methods include assessing nutrient content, bioavailability, and bioactivity to determine the overall quality of food products.
2016	Martnez Steele et al.	Ultra-processed foods and added sugars in the US diet: Evidence from a nationally representative cross-sectional study	To investigate the consumption of ultra-processed foods and added sugars in the US diet and their impact on health outcomes.	Cross-sectional study using national dietary data	Consumption of ultra-processed foods and added sugars is associated with poor dietary quality and increased risk of obesity and chronic diseases.
2019	Neelakantan et al.	Association between ultra-processed food consumption and risk of mortality among middle-aged adults in France	To examine the association between ultra-processed food consumption and risk of mortality among middle-aged adults in France.	Prospective cohort study using dietary data and mortality records	Higher consumption of ultra-processed foods is associated with an increased risk of mortality among middle-aged adults in France.
Year	Author(s)	Title	Objectives	Methods	Findings/Results
2007	Lin et al.	Baicalin: A natural compound with potent pharmacological activities	To investigate the pharmacological activities of baicalin, the primary flavonoid glucoside of Scutellaria baicalensis Georgi.	Review of existing literature	Baicalin exhibits antiviral, bacteriostatic, anticancer, and antioxidant properties, and functions as a non-steroidal anti-

			inflammatory drug and neuroprotective agent.
			Baicalin demonstrates anti-cancer effects in hepatocellular carcinoma
2016	Shi et al.	Baicalin: A review of its anti-cancer effects and mechanisms in hepatocellular carcinoma To review the anti-cancer effects and mechanisms of baicalin in hepatocellular carcinoma.	Review of through various mechanisms, including inhibition of cell proliferation and induction of apoptosis. Baicalin exhibits a wide range of pharmacological properties, including anti-inflammatory, neuroprotective, and anticancer effects, contributing to its therapeutic potential.
2023	Deng et al.	Pharmacological Properties of Baicalin: A Review To provide an overview of the pharmacological properties of baicalin, including its role as an anti-inflammatory, neuroprotective, and anticancer agent.	Review of existing literature neuroprotective, and anticancer effects, contributing to its therapeutic potential.
2022	Bao et al.	Baicalin as a natural product: Anti-oxidant, anti-apoptotic, and anti-inflammatory properties To investigate the antioxidant, anti-apoptotic, and anti-inflammatory properties of baicalin.	Review of and anti-inflammatory properties, indicating its potential therapeutic value in various conditions. Baicalin possesses antioxidant, anti-apoptotic, and anti-inflammatory properties, indicating its potential therapeutic value in various conditions.
2023	Shahcheraghi et al.	Therapeutic potential of Baicalin in inflammation and organ damage To explore the therapeutic potential of baicalin in inflammation and organ damage.	Review of damage by suppressing pro-inflammatory cytokines, nitric oxide production, and caspase-3 activity.
2019	Divyakolu et al.	Baicalin as an adjuvant therapy for methicillin-resistant Staphylococcus aureus infection To investigate the adjuvant therapy potential of baicalin in methicillin-resistant Staphylococcus aureus animal models	Experimental an adjuvant therapy for methicillin-resistant Staphylococcus aureus infection. Baicalin shows promise as an adjuvant therapy for methicillin-resistant Staphylococcus aureus infection.
2020	Song et al.	Baicalin: A potent compound with multiple pharmacological activities To explore the pharmacological activities of baicalin and its potential as a broad-spectrum antiviral drug.	Review of including antiviral effects, suggesting its potential as a broad-spectrum antiviral drug.

			To elucidate the mechanisms of		Baicalin modulates various
					cytokines and cell
2020	Chen et al.	Mechanisms of actionaction of baicalin, particularlyReview	of baicalin: A review its effects on cytokines and cellexisting literatureits pharmacological effects		ofpathways, contributing to
			pathways.		and potential as a
					therapeutic agent.
					Baicalin demonstrates
2021	Li et al.	Baicalin as a potentialTo investigate the potential	therapy for sepsis:therapeutic effects of baicalinReview		potential as a therapy for
		Mechanisms andin sepsis and its underlyingexisting literatureagainst liver damage and	implications mechanisms.		ofsepsis by protecting
					increasing survival in mice
					with polymicrobial sepsis.
Year	Author(s)	Title	Purpose/Objectives	Methods	Findings/Results
				Suppressed	
				microglial	Scutellarin suppresses
				activation,	microglial activation,
				measured serum	reduces serum levels of
2007	Zhu et al.	Neuroprotective	Investigate neuroprotection(TNF- α , IL- β , IL-inflammatory	cytokines,	
		Effects of Scutellarin	mechanisms of Scutellarin	6), lactateand enhances tissue	
				dehydrogenase glutathione levels,	
				activities, tissueindicating neuroprotective	
				glutathione potential.	
				levels.	
				Experimental	
				studies on	Scutellarin shows promise
				diabetic animalin treating diabetic	
		Scutellarin as a		models, retinopathy by mitigating	
2014	Wang et al.	Potential TreatmentAssess efficacy of Scutellarin in	Diabeticdiabetic retinopathy treatment	evaluation ofretinal histopathological	
		for		retinal changes and biochemical	
		Retinopathy		histopathology markers associated with	
				and biochemicalthe condition.	
				markers.	
				In vitro and in	Scutellarin demonstrates
				vivo studies,	significant anti-
		Anti-inflammatory	Examine anti-inflammatory	assessment ofinflammatory effects both	
2018	Chledzik et al.	Properties of	effects of Scutellarin	inflammatory in vitro and in vivo by	
		Scutellarin		markers, modulating inflammatory	
				histological markers and improving	
				analysis. tissue histology.	
				In vitro assays	Scutellarin exhibits potent
2015	Niu et al.	Antioxidant ActivityInvestigate	antioxidantevaluating	antioxidant activity by	
		of Scutellarin	potential of Scutellarin	antioxidant scavenging ROS, reducing	
				capacity, lipid peroxidation, and	

					measurement of enhancing cellular ROS levels, antioxidant defenses.
					assessment of lipid peroxidation.
				In vitro cell culture	Scutellarin induces apoptosis in ovarian and breast tumor cells through caspase activation, suggesting potential as an anticancer agent.
2007	Tan et al.	Apoptotic Effects of Scutellarin on Ovarian and Breast Tumor Cells	Explore apoptotic mechanisms induced by Scutellarin in cancer cells	sexperiments, in assessment of apoptosis markers, caspase activation assays.	
				Animal models of liver injury, evaluation of hepatoprotective effects by preserving liver histology, reducing biochemical markers of liver injury, and inhibiting neutrophil infiltration.	
2013	Brent & Nong	Shao-Hepatoprotective Effects of Silymarin	Investigate hepatoprotective qualities and mechanisms of Silymarin	liver histology, biochemical analysis of liver function parameters.	
				Pharmacokinetic studies in animals, favorable	
2018	Fan et al.	Pharmacotoxicological Research on Silybin	Examine of Silybin, a major component of Silymarin	pharmacotoxicological aspects assessment of toxicity profiles, indicating high evaluation of tolerability and low drug tolerance toxicity levels in animals.	
				In vitro assays measuring ROS levels, inflammatory effects by scavenging ROS, reducing inflammatory mediator levels, and protecting animal models against sepsis-induced organ damage.	
2015	Chan et al.	Antioxidant and Anti-inflammatory Effects of Silymarin	Investigate antioxidant and anti-inflammatory properties of Silymarin	assessment of inflammatory mediators, levels, and protecting animal models against sepsis.	
				Silymarin protects against sepsis-induced liver and kidney damage by reducing inflammatory cytokine levels and preserving organ function in animal models.	
2020	Al-Kadi et al.	Protective Effects of Silymarin Against Sepsis	Explore protective effects of Silymarin against sepsis-induced organ damage	assessment of liver and kidney function, measurement of	

				inflammatory cytokines.
				In vitro and animal studies,
				assessment of
				antioxidant Luteolin exhibits diverse
		Investigate therapeutic		therapeutic properties,
		benefits of Luteolin, including		including antioxidant, anti-
2017	Chuammitri et al.	Therapeutic Properties of Luteolin	antioxidant, anti-inflammatory, and anticancer properties	evaluation of inflammatory, and anticancer effects, suggesting potential in various disease conditions.
				measurement of tumor growth inhibition.
				Animal models of Luteolin protects against ischemia, ischemia-induced tissue
		Protective Effects of Luteolin Against Ischemia Injury	Evaluate protective effects of Luteolin against ischemia-induced tissue damage	assessment of damage by reducing ROS levels, mitigating tissue damage markers, and measurement of improving tissue function ROS levels. in animal models.
				In vitro assays
				Quercetin exhibits anti-
		Anti-Tuberculosis Effects of Quercetin	Investigate the anti-tuberculosis properties of Quercetin	evaluating tuberculosis effects by inhibiting the growth of Mycobacterium tuberculosis.
				In vitro studies
				using RAW264.7 macrophages,
		Anti-inflammatory Properties of Quercetin	Examine the anti-inflammatory effects of Quercetin	Quercetin reduces LPS-induced inflammatory responses by suppressing TNF- α release and IL-1 β production in RAW264.7 macrophages.
2018	Lesjak et al.			assessment of inflammatory marker expression, cytokine production.
				In vitro cell
		Anti-proliferative Effects of Quercetin	Investigate the proliferative effects of Quercetin on cancer cells	Quercetin inhibits cancer cell proliferation and induces apoptosis in cancer cells.
2016	Luo et al.			of experiments, assessment of cell viability,

				proliferation assays.
				In vitro and in vivo assays
				Quercetin demonstrates measuring potent antioxidant activity
				antioxidant by enhancing antioxidant enzyme levels and
2016	Karuppagounder et al.	Antioxidant Protection Quercetin	Evaluate the antioxidantenzyme activity, protective effects of Quercetin lipid	reducing oxidative stress peroxidation markers in vitro and in vivo.
				scavenging activity.
				Animal models of sepsis, evaluationQuercetin pre-treatment
				of lungattenuates lung pathology, reduces inflammatory
2015	Huang et al.	Quercetin treatment in Sepsis	Assess the efficacy of Pre-Quercetin pre-treatment in sepsis-induced lung injury	measurement ofcytokine levels, and inflammatory increases IL-10 secretion in cytokines, IL-10sepsis-induced lung injury. secretion levels.
				Animal models of sepsis, Quercetin reduces lung
				assessment ofdamage in septic mice by lung attenuating lung
2014	Maalik et al.	Quercetin Effects on Septic-induced Lung Damage	Investigate the effects of Quercetin on lung damage in septic-induced mice	histopathology, histopathological changes, measurement oflowering NO and MDA blood NO, MDAlevels, and enhancing levels, evaluationantioxidant enzyme of antioxidantactivity.
				enzyme activity.
				In vivo studies using sepsis-induced animalQuercetin suppresses
				models, HMGB1 expression, Quercetin suppresses
2018	Park et al.	Quercetin Suppresses HMGB1 Expression in Sepsis	Examine the effects of Quercetin on HMGB1expression and oxidative stressHMGB1 in sepsis	assessment ofreduces oxidative stress, and improves survival expression, outcomes in sepsis-measurement ofinduced animal models. oxidative stress markers.
				Quercetin AlleviatesInvestigate the protectiveAnimal models ofQuercetin alleviates lung
2019	Cui et al.	Lung Damage in Septic Mice	ineffects of Quercetin on lungdamage in septic mice of lung edema,	reducing lung edema,

			alveolar capacity,preserving alveolar histological capacity, and protecting analysis. lung tissues.
			In vitro studies using LPS-stimulated Quercetin inhibits NF-κB macrophages, activation and reduces the assessment ofproduction of NF-κB activation,inflammatory mediators in measurement ofLPS-stimulated inflammatory macrophages. mediator production.
2013	Dai et al.	Quercetin Inhibition of NF-κB Activation	Examine the inhibitory effects of Quercetin on NF-κB activation
			In vivo studies using animalQuercetin regulates oxidative enzyme production and suppresses NF-κB signaling pathways levels, NF-κBin vivo, reducing oxidative expression stress and inflammation. analysis.
2012	Bharrhan et al.	Quercetin Regulation of Oxidative Enzymes and NF-κB	Investigate the regulatorymodels, effects of Quercetin onassessment ofproduction and suppresses oxidative enzymes and NF-κBoxidative enzymeNF-κB signaling pathways
			Animal models of sepsis, Quercetin reduces lung damage and inflammatory markers in sepsis-induced animals, improving histological survival outcomes and analysis of lunglung function. tissues.
2014	Wang et al.	Quercetin Reduces Lung Damage and Inflammatory Markers	Evaluate the effects ofQuercetin on lung damage andinflammatory markers inmarkers, animals, improving sepsis-induced animals histological survival outcomes and analysis of lunglung function. tissues.
			In vitro and in vivo studies, Myricetin reduces oxidative stress and improves kidney function in diabetic erythrocytes, suggesting potential therapeutic benefits in diabetes. parameters.
2012	Ozcan et al.	Myricetin Effects onDiabetic Erythrocytes and kidney function in diabeticerythrocytes	Investigate the effects ofMyricetin on oxidative stressoxidative stress markers, measurement of therapeutic benefits in kidney function diabetes. parameters.
			In vitro and in vivo studiessepsis-induced inflammation by using sepsis-induced animalssuppressing NF-κB signaling and reducing assessment ofinflammatory mediator
2021	Imran et al.	Anti-inflammatory Effects of Myricetin	Examine the anti-vivo studiesinflammatory effects ofMyricetin on sepsis-inducedinduced animalssuppressing NF-κB inflammation models, signaling and reducing assessment ofinflammatory mediator

				inflammatory production in vitro and in markers, NF-κBvivo.
				signaling
				analysis.
				In vivo studies
				using animal
				Fisetin inhibits HMGB1
				models of release, reduces vascular
				inflammation, and
				improves vascular function
				measurement of in animal models of
				HMGB1 levels, vascular inflammation.
				assessment of
				vascular function.
				Animal models of
				sepsis, evaluation Fisetin protects against
				CLP-induced organ
				of organ damage in sepsis by
				attenuating organ
				measurement of pathology, reducing
				inflammatory inflammatory markers,
				assessment of and alleviating oxidative
				oxidative stress.
				In vitro assays
				evaluating
				antioxidant Fisetin exhibits potent
				antioxidant activity by
				capacity, scavenging ROS, reducing
				measurement of lipid peroxidation, and
				ROS levels, enhancing cellular
				assessment of antioxidant defenses.
				lipid
				peroxidation.
				In vitro and inEGCG demonstrates
				vivo studies,diverse pharmacological
				assessment ofactivities including anti-
				anti-inflammatory,
				inflammatory, antibacterial, and
				antibacterial, anticancer effects in vitro
				anticancer effects.and in vivo.

3.4. Immune Response in Sepsis

3.4.1. Natural Killer (NK)

Sepsis is a life-threatening condition marked by a dysregulated immune response to infection, resulting in widespread inflammation, tissue damage, and organ dysfunction(Nedeva, 2021). This

complex syndrome poses a significant challenge to healthcare providers worldwide due to its high mortality rates and profound impact on patient outcomes (Van Der Poll et al., 2021).

To grasp the intricacies of sepsis pathophysiology and devise effective treatment strategies, it is imperative to explore the intricate interplay of various components of the immune system. Among these components, natural killer (NK) cells, T cells, B cells, and cytokines play pivotal roles in orchestrating the immune response to infection and modulating inflammation levels within the body (Gálvez et al., 2020; Y. Wu et al., 2017).

Natural killer (NK) cells, an integral component of the innate immune system, play a pivotal role in the body's defense against pathogens and tumors. NK cells are known for their ability to recognize and eliminate infected cells and tumor cells without the need for prior sensitization (Pahl & Cerwenka, 2017). This unique capacity allows them to act as the first line of defense against invading pathogens.

However, in the context of sepsis, the function of NK cells can become compromised, leading to significant immune dysregulation and impairment of host defense mechanisms (Nedeva, 2021). Studies have shown that during sepsis, there is a reduction in NK cell numbers and altered NK cell phenotype and function (Guo et al., 2018). These alterations in NK cell activity contribute to the dysregulated immune response observed in septic patients, making them more susceptible to secondary infections and worsening clinical outcomes (Cao et al., 2023).

Therefore, understanding the role of NK cells in sepsis pathophysiology is crucial for developing targeted therapies aimed at restoring NK cell function and bolstering host immunity during sepsis management.

Available treatments for targets such as NK cells in sepsis are currently under investigation and development. Some potential therapeutic strategies aim to modulate NK cell function and restore immune balance during sepsis (Guo et al., 2018; van der Poll et al., 2017)

1. Cytokine Therapy: Administration of cytokines such as interleukin-15 (IL-15) and interleukin-2 (IL-2) may help enhance NK cell activity and promote their proliferation and function in sepsis (Carson et al., 1995).
2. Immunomodulatory Agents: Drugs that target immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, could potentially enhance NK cell-mediated immune responses during sepsis (Chen et al., 2013).
3. Adoptive NK Cell Therapy: Infusion of ex vivo expanded and activated NK cells may offer a promising approach to augment NK cell function and improve immune surveillance in septic patients (Romee et al., 2016).
4. Targeted Immunotherapy: Monoclonal antibodies directed against inhibitory receptors on NK cells, such as killer cell immunoglobulin-like receptors (KIRs), may unleash the cytotoxic potential of NK cells and enhance their antitumor and antiviral activities (Vey et al., 2012).
5. Immunomodulatory Strategies: Adjunctive therapies that modulate the balance between pro-inflammatory and anti-inflammatory cytokines, such as interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α), could help restore immune homeostasis and improve outcomes in septic patients (Hotchkiss et al., 2013).

Further research is needed to evaluate the safety, efficacy, and optimal dosing strategies of these treatments in clinical settings.

Therapeutic interventions to enhance NK cell function in sepsis remain an area of active research. While no specific NK cell-targeted therapies are currently approved for sepsis management, strategies such as cytokine therapy (e.g., interleukin-15) and adoptive NK cell transfer show promise in preclinical studies (Alrubayyi et al., 2020; Godfrey et al., 2018).

3.4.2. T Cells

T cells, fundamental constituents of the adaptive immune system, wield significant influence over immune responses and inflammation regulation. In the context of sepsis, T cell dysfunction and exhaustion frequently manifest, precipitating immune suppression and heightened vulnerability to subsequent infections (ElTanbouly & Noelle, 2021). Gaining insights into the intricate dynamics of T

cell responses during sepsis is paramount for devising precise immunomodulatory interventions aimed at reinstating immune equilibrium.

Research indicates that T cell dysfunction in sepsis often involves impaired effector functions and dysregulated cytokine production, contributing to immune paralysis and prolonged critical illness (Boomer et al., 2011; Hotchkiss et al., 2013). Additionally, sepsis-induced T cell exhaustion, characterized by the upregulation of inhibitory receptors like programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), further exacerbates immune dysregulation and compromises host defense mechanisms (Chang et al., 2014; Hotchkiss et al., 2013).

Given the multifaceted role of T cells in orchestrating immune responses, therapeutic strategies aimed at restoring T cell function hold significant promise in mitigating sepsis-associated morbidity and mortality. Targeted immunomodulatory approaches, such as checkpoint blockade therapy targeting PD-1 and CTLA-4, have shown potential for rejuvenating T cell responses and augmenting host immunity in preclinical and clinical studies (Chang et al., 2014; Hotchkiss et al., 2013; Matsuo et al., 2021).

Furthermore, emerging immunotherapeutic modalities, including adoptive T cell transfer and cytokine-based therapies, offer novel avenues for bolstering T cell-mediated immune surveillance and combating sepsis-induced immune dysfunction (Jackie Oh et al., 2016; Napolitano, 2018; Vellani et al., 2023). However, comprehensive understanding of the complex interplay between T cell subsets, cytokine signaling pathways, and immunoregulatory networks in sepsis remains pivotal for the development of efficacious and targeted therapeutic interventions (Bhan et al., 2016; van der Poll et al., 2017; Y. Zhang & Ning, 2021).

Available treatments for targeting T cells in sepsis are an area of active research and development. Some potential therapeutic strategies aim to modulate T cell function and mitigate immune dysfunction during sepsis. These treatments include:

1. **Immune Checkpoint Inhibitors:** Drugs targeting immune checkpoint molecules such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) may help alleviate T cell exhaustion and restore their effector functions in sepsis (Hotchkiss et al., 2013).
2. **Cytokine Therapy:** Administration of cytokines such as interleukin-7 (IL-7) and interleukin-15 (IL-15) can promote T cell proliferation, survival, and effector functions, potentially enhancing immune responses in septic patients (Zagorulya, 2023).
3. **Adoptive T Cell Therapy:** Infusion of ex vivo expanded and activated T cells, such as cytotoxic T lymphocytes (CTLs) or T cell receptor (TCR)-engineered T cells, may augment T cell-mediated immune responses and improve host defense mechanisms during sepsis (Lynn et al., 2019).
4. **Targeted Immunomodulation:** Therapies targeting specific T cell subsets, such as regulatory T cells (Tregs) or memory T cells, could help rebalance the immune response and mitigate excessive inflammation in sepsis (Duffy & Crown, 2019).
5. **Immunomodulatory Agents:** Small molecules or biologics that modulate T cell signaling pathways, such as Janus kinase (JAK) inhibitors or nuclear factor-kappa B (NF- κ B) inhibitors, may offer novel approaches to regulate T cell activation and function in septic patients (Angioni et al., 2021).
6. **Supportive Therapies:** Supportive care measures, including early and appropriate antibiotic therapy, fluid resuscitation, and organ support, remain crucial in managing sepsis and preventing further T cell dysfunction and immune compromise (Shankar-Hari et al., 2016).

Immunomodulatory therapies aimed at restoring T cell function in sepsis include cytokine-based therapies, such as interleukin-7 (IL-7) administration, which has shown potential in preclinical and early clinical studies to reverse T cell depletion and improve immune function in septic patients (Francois et al., 2018; Venet et al., 2008).

3.4.3. B Cells

B cells, crucial components of the adaptive immune system, play a pivotal role in antibody production and antigen presentation. In sepsis, dysregulation of B cell function can lead to abnormal

antibody production and compromised humoral immunity, exacerbating the inflammatory response and tissue damage (Romero-Ramírez et al., 2019).

Studies have highlighted the significance of B cells in sepsis pathophysiology. For instance, research by Boomer et al. (Boomer et al., 2011) demonstrated alterations in B cell phenotypes and functions in septic patients, suggesting impaired B cell responses during the disease course. Additionally, a study by Venet et al. (2008) revealed reduced B cell counts and dysfunctional antibody production in septic shock patients, correlating with disease severity and poor outcomes.

Furthermore, B cell dysfunction in sepsis has been associated with impaired pathogen clearance and increased susceptibility to secondary infections. Studies by Pene et al. (2008) and Xiao et al. (2011) highlighted the role of B cell depletion in exacerbating sepsis progression and impairing host defense mechanisms against microbial pathogens.

Understanding the intricate role of B cells in sepsis pathogenesis is critical for developing targeted therapeutic interventions. Strategies aimed at modulating B cell responses, such as B cell-targeted therapies and immunomodulatory agents, hold promise in mitigating immune dysregulation and improving patient outcomes in sepsis (Shankar-Hari et al., 2016; Singer et al., 2016; Venet et al., 2008). Unraveling the complexities of B cell-mediated immunity in sepsis offers insights into potential therapeutic targets and treatment strategies to attenuate the detrimental effects of immune dysregulation in this life-threatening condition.

Available treatments targeting B cells in sepsis remain an area of active research and development. While specific therapies directly targeting B cells in sepsis are limited, several strategies aim to modulate B cell responses and mitigate immune dysregulation in this condition.

1. **Immunomodulatory Therapies:** Immunomodulatory agents, such as corticosteroids, intravenous immunoglobulins (IVIG), and monoclonal antibodies, are being investigated for their potential to modulate B cell function and attenuate the inflammatory response in sepsis. For example, IVIG therapy has shown promise in improving outcomes in septic patients by enhancing antibody-mediated immunity and mitigating immune dysregulation (Alejandria et al., 2013).
2. **B Cell-Targeted Therapies:** Emerging therapies targeting B cells, such as anti-CD20 monoclonal antibodies (e.g., rituximab), aim to deplete B cell populations and suppress aberrant antibody production in sepsis. These targeted approaches hold potential for modulating B cell responses and restoring immune homeostasis in septic patients (Fowler et al., 2014).
3. **Cytokine Modulation:** Therapies aimed at modulating cytokine levels and inflammatory signaling pathways may indirectly influence B cell function and immune responses in sepsis. For instance, agents targeting pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), may attenuate B cell activation and dampen the systemic inflammatory response associated with sepsis (Cohen et al., 2015).
4. **Supportive Care:** In addition to targeted therapies, supportive care measures play a crucial role in managing sepsis-associated complications and optimizing patient outcomes. Supportive interventions, including fluid resuscitation, vasopressor therapy, and mechanical ventilation, aim to stabilize hemodynamics, maintain organ perfusion, and support vital organ function during the acute phase of sepsis (Rhodes et al., 2017).

Currently, no specific B cell-targeted therapies are approved for sepsis treatment. However, strategies to restore B cell function and antibody production, such as intravenous immunoglobulin (IVIG) therapy, have been explored in septic patients with mixed results (Netea et al., 2017; Stawicki et al., 2020).

While ongoing research continues to explore novel therapeutic approaches targeting B cells and immune dysregulation in sepsis, the current treatment strategies primarily focus on mitigating systemic inflammation, restoring immune function, and providing supportive care to improve patient survival and outcomes.

3.4.4. Cytokines

Cytokines, pivotal signaling molecules produced by diverse immune cells, orchestrate immune responses and regulate inflammation. In the context of sepsis, dysregulated cytokine production can precipitate a phenomenon termed cytokine storm, characterized by uncontrolled inflammation and tissue damage. Addressing specific cytokines implicated in sepsis pathogenesis presents a promising avenue for ameliorating the adverse effects of hyperinflammation and enhancing patient outcomes (Reddy et al., 2024).

Studies have underscored the significance of cytokine modulation in sepsis management (Schulte et al., 2013). For instance, research by Tanaka et al., (2016) highlighted the role of interleukin-6 (IL-6) blockade in attenuating cytokine storm and improving survival outcomes in septic patients. Additionally, trials investigating the use of tumor necrosis factor-alpha (TNF- α) inhibitors, such as infliximab and etanercept, have shown potential in dampening inflammatory responses and mitigating organ dysfunction in sepsis (A. K. Mehta et al., 2018; Saad et al., 2008) (Mehta et al., 2018).

Moreover, targeted therapies aimed at interleukin-1 (IL-1) blockade have demonstrated efficacy in modulating inflammatory cascades and improving clinical outcomes in septic patients. Clinical studies by Shakoory et al., (2016); Tisoncik et al., (2012) evaluated the use of IL-1 receptor antagonists, such as anakinra, in attenuating cytokine storm and reducing mortality rates among septic individuals.

Furthermore, emerging immunomodulatory agents, including toll-like receptor (TLR) antagonists and Janus kinase (JAK) inhibitors, hold promise for selectively modulating cytokine responses and restoring immune homeostasis in sepsis (Davis et al., 2020; van der Poll et al., 2017) (van der Poll et al., 2017; Riva et al., 2020). These innovative therapeutic approaches target key components of the cytokine signaling pathway, offering potential avenues for precision medicine in sepsis management.

Available treatments targeting the immune system components involved in sepsis pathophysiology aim to modulate immune responses and mitigate inflammation, thereby improving patient outcomes. Here are some treatment approaches targeting specific immune system components:

Targeted cytokine therapies represent a promising approach for managing cytokine storm in sepsis. Anti-cytokine agents, including monoclonal antibodies targeting interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF- α), have shown efficacy in dampening hyperinflammatory responses and improving clinical outcomes in septic patients (Alhazzani et al., 2020; Remy et al., 2020).

While progress has been made in understanding the immune response in sepsis and developing targeted therapies, further research is needed to optimize treatment efficacy, safety, and clinical applicability. By elucidating the complex mechanisms underlying immune dysregulation in sepsis, researchers and clinicians can pave the way for innovative treatment strategies aimed at restoring immune balance and improving patient survival.

4. Conclusions and Future Prospects

This study review into the diverse biological functions of flavonoids, aiming to illuminate their potential health benefits. Flavonoids, organic compounds abundant in fruits, vegetables, tea, and wine, have garnered significant attention since the emergence of the French paradox, which highlighted the intriguing cardiovascular benefits associated with red wine consumption despite a high saturated fat diet in Mediterranean populations. Subsequent research has unveiled additional therapeutic properties of flavonoids, prompting an exploration of their mechanisms of action, functions, and potential applications.

Evidence from numerous studies has underscored the anti-inflammatory, anticancer, antituberculosis, antidiabetic, antibacterial, and neuroprotective effects of flavonoids. Human participation in clinical trials has corroborated the efficacy of flavonoids in managing various inflammatory conditions such as metabolic syndrome, rheumatoid arthritis, urosepsis, and tuberculosis. However, it's noteworthy that the majority of studies relied on animal models,

indicating a gap in clinical research. While animal models offer insights, they may not fully replicate human sepsis, highlighting the necessity for more robust clinical investigations.

The pharmacological profile and safety profile of flavonoids position them as promising candidates for clinical studies across diverse therapeutic areas. However, further research is imperative to elucidate their full potential and establish their efficacy and safety in human subjects. Continued exploration of flavonoids' pharmaceutical applications holds promise for the development of novel therapeutic interventions to prevent and treat chronic diseases. Thus, future endeavors should prioritize clinical investigations to harness the therapeutic potential of flavonoids for the benefit of human health.

Conflicts of Interest: We certify that the publication of this material does not involve conflicts of interest.

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