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Review Article

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Unlocking the Health Benefits of Mulberry Fruit Pulp: Mitigating Sepsis Risk and Beyond

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Abstract

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, resulting in systemic inflammation and organ dysfunction. Despite advances in medical care, sepsis remains a major global health concern with high morbidity and mortality rates. As a result, there is an urgent need to explore novel preventive approaches to combat sepsis and improve patient outcomes. Mulberry fruit (*Morus* sp.) has gained attention in recent years for its diverse bioactive compounds and potential health benefits. This review aims to investigate the effect of mulberry fruit pulp on the prevention of sepsis. The bioactive compounds present in mulberry, including polyphenols, flavonoids, anthocyanins, and quercetin, possess antioxidant and immune-modulating properties that may play a critical role in modulating the inflammatory response and oxidative stress associated with sepsis. Additionally, we found mulberry compounds have been reported in various research to enhance immune function and mitigate tissue damage, which is significant valuable in preventing sepsis progression. The objective of the review is to find the potential mechanisms through which mulberry fruit pulp may exert its preventive effects on sepsis and highlights the need for further research to validate these findings. Through this review we found, the exploration of mulberry as a preventive measure against sepsis holds significant promise in developing natural and adjunctive therapies to combat this devastating condition with the help of different bioactive compounds present in mulberry, particularly cyanidin and anthocyanin found in mulberry.

Keywords

Morus nigra, Sepsis, Bioactive compounds, Inflammatory response, Natural therapy

Introduction

A serious health condition referred to as sepsis arises from the body's immune system reacting disproportionately to an infection. In the condition of sepsis, the immune system releases chemicals to fight against infection; but these chemicals lead to widespread inflammatory response, resulting in organ damage and failure. The tissues and organs of the body suffer harm because of the reaction. Anybody is vulnerable to sepsis, but those who are extremely young, older, pregnant, or suffering from other medical conditions are prone to be struck by sepsis. According to the scholars, Sepsis - a life-threatening condition resulting from the body's overwhelming response to infection, continues to be a significant global health challenge. Despite advancements in medical science, sepsis remains a leading cause of mortality and morbidity worldwide. However, the urgent need for effective preventive measures against sepsis has prompted researchers to explore the potential of natural compounds in mitigating its occurrence and severity. One such promising natural resource is the mulberry fruit pulp, known for its diverse bioactive constituents and health benefits [1]. The increased oxidative stress is considered as the prominent change during sepsis. The high mortality rates linked to several illnesses, including endotoxic shock, are significantly attributed to oxidative stress. Therefore, to prevent the negative effects of excessive reactive oxygen species (ROS) production and to maintain well-balanced redox homeostasis, immune cells require enough amounts of antioxidant defense mechanism [2].

Mulberry (*Morus* sp.) has been a part of traditional medicine systems in various cultures for centuries due to its antioxidant, anti-inflammatory, and antimicrobial properties. Recently, scientific interest in the therapeutic potential of mulberry fruit pulp has grown exponentially, and numerous studies have investigated its effects on various health conditions. Emerging evidence suggests that mulberry fruit pulp could play a crucial role in preventing sepsis and reducing its associated complications. However, the preventive effects of mulberry fruit pulp on sepsis are believed to be attributed to its rich nutritional composition. It contains an array of essential vitamins, minerals, and phytochemicals, including polyphenols, flavonoids, anthocyanins, and quercetin, which possess potent antioxidant and immune-modulating properties. While these bioactive compounds may act synergistically to develop the body's defense mechanisms, thereby conferring protection against microbial infections and the development of sepsis [3].

The black mulberry, commonly known as *M. nigra,* is a native of southwestern Asia. It has been growing for ages all over Europe and in the Mediterranean region. The analgesic and anti-inflammatory properties of the plants and some bioactive compounds identified in *M. nigra* have also been employed as herbal medicines for both humans and animals, even though their biological or pharmacological activities have been considerably less investigated than those of *M. alba*. Numerous studies have revealed that the antioxidant and anti-inflammatory properties of black mulberries are due to their high content of polyphenols, flavonoids, and anthocyanins [4].

In the current review, the efficacy of the *M. nigra* leaf and pulp to prevent or reduce the redox and inflammatory imbalances brought on by sepsis is highlighted. Since *M. nigra* fruits and leaves have anti-inflammatory and antioxidant potential and that it is a strong therapeutic option to reduce systemic problems brought on by sepsis, it should have both anti-inflammatory and antioxidant properties. Furthermore, the sustainable approach to prevent and treat sepsis is being signified in this review [5].

Mulberry

Mulberry (*M. alba),* a member of the family *Moraceae* and the genus *Morus*, is widely planted throughout many temperate zones. Today, the mulberry is a common and cost-effective woody plant utilized in agriculture, the food industry, and pharmaceuticals. There are about 24 different species of mulberry, and more than 1,000 cultivars, most of which come from Southeast Asian nations. Mulberry fruits are dark purple in color. The three most popular mulberry species farmed worldwide are black (*M. nigra* L.), red (*M. rubra* L.), and white (*M. alba* L.) It is a salt-tolerant plant, grows tall to be 30-50 feet and can be cultivated with seeds. However, red mulberry trees can reach 35 to 50 feet with upright and spreading canopy whereas thrive in rich soil. While black mulberry trees can reach 35 feet height and are salt-tolerant in warm climates. The preferable soil for this tree is warm, moist, and well-drained [6].

In China, over 626,000 hectares of mulberry fruit are farmed, where they are historically consumed and used for biological purposes. Nearly, 280,000 hectares are grown in India. It is generally used in traditional Chinese medicine to treat fever, lower blood pressure, strengthen joints, prevent liver damage, and encourage urine excretion. However, the various parts of this plant including flowers, stems, bark, roots, and leaves, can be employed in herbal treatments to treat a variety of health issues. Mulberry fruit contains anti-bacterial, anti-alzheimer, anti-obesity, anti-tumor, and anti-cancer qualities. Though, it is helpful to treat intestinal worms, diarrhea, constipation, asthma, diabetes, kidney problems, headaches, depression, etc, due to these properties [7].

However, carbohydrates, proteins, lipids, minerals, and vitamins (thiamine, nicotinic acid, riboflavin, and ascorbic acid) contained within mulberry fruit make it the most nutrient-dense agricultural product available to consumers. The protein content of fruit is on par with the quality protein dense foods such as milk and fish. Furthermore, the mulberry fruit is a remarkable source of amino acids, containing 18 different amino acids. Whereas, out of these nine are essential in nature and are crucially required in the body. While, in comparison of total amino acids approximately 42% of essential amino acid is reported in mulberry fruit. Additionally, the fruit has important mineral components (macro and micro), both of which help to control metabolic processes. The key elements include potassium, calcium, magnesium, and sodium, as well as the micro-minerals such as iron, zinc, nickel, etc. [8].

Similarly, mulberries are an efficient source of polyphenols and represent a diverse family of compounds that include phenolic acids, flavonoids, tannins, stilbenes, and lignans, which are essential to life. However, during the developing phase the phenolic content substantially increases within the period of growth. Whereas, beta-carotene, anthocyanins, anthraquinones, glycosides, oleic acid, etc, are some of the compounds among the polyphenols, sufficiently found in mulberry fruit [9].

Sepsis

Sepsis is recognized by the World Health Organization as a global health priority. It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The word sepsis was first used in Homer's poems around 2700 years ago. It is a derivative of the Greek word for "decomposition" or "decay" and eventually turned up in the writings of Hippocrates and Galen in later times. The "Germ theory" of disease was introduced in the 1800s, and it was understood that harmful bacteria are blamed for sepsis. Heretofore, septicemia was the medical term used for sepsis, but nowadays different classifications are used according to the causative agents. These includes bacteremia (infection caused by bacteria), fungemia (infection caused by fungus), or viremia (infection caused by virus), which further triggers sepsis [10].

Howsoever, proteins, acute-phase proteins, complement proteins, and cytokines are secreted by the immune system to fight infection. While sepsis occurs when these responses become out of control and cause substantial inflammation. Although, sepsis initiates with a minor cut which further becomes severe condition necessitating the surgery due to the increased proliferation [11]. Although sometimes the condition of sepsis is unidentifiable until turns worse. Individuals with an infection/a serious injury/a serious non-communicable disease can develop sepsis, but certain groups are more vulnerable. However, these groups chiefly include elderly, pregnant or recently pregnant women, new-born, hospitalized patients, intensive care unit patients, despite of these cases disease patients such as HIV/AIDS, liver cirrhosis, cancer, kidney disease, autoimmune diseases, and people without spleens.

Sepsis is classified into three stages, including systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock. SIRS, the first stage is difficult to recognize. However, it is frequently accompanied by extremely high or low body temperatures, along with rapid heartbeat, rapid breathing, a high or low white blood cell count, and known or suspected infection. SIRS only develops into sepsis when an infection is present and recognized by the symptoms. Although sepsis is only considered to be a subtype of SIRS, the term is more frequently used in some circles [12]. The progress of sepsis in the human body along with the symptoms that occur in different stages are depicted in figure 1.

Severe sepsis is a second stage and is identified when acute organ dysfunction starts. Howsoever, when sepsis coexists with hypotension (low blood pressure) or hypoperfusion, further develops the condition of severe sepsis. Additionally, the condition leads to decreased blood flow through an organ. While septic shock is the most serious, hazardous, and final stage of sepsis, it offers patients the lowest chances (almost 50%) of survival. Moreover, perfusion anomalies like high lactate levels pose the greatest risk of death, with estimates ranging from 30% to 50%.

According to the worldwide prevalence of around 8 million people die from sepsis each year, making it one of the world's deadliest conditions. Sepsis affects roughly 1.7 million adults in the United States each year and may be responsible for over 250,000 deaths. Whereas India has an estimated 11 million sepsis cases every year, with over 3 million deaths [13].

The prevalent risk factors for sepsis includes urinary tract infections, weakness, aging. While skin infections and urinary tract infections are the ubiquitous factors, further leads to greatest risk of developing sepsis at any age. However, sepsis can be treated by medication therapy that specifically targets the bacterium responsible for sickness. Vasopressors are highly recommended to lower blood pressure due to narrowing effect of blood vessels [14].

Pathogenesis of sepsis

Sepsis is not only a process of systemic inflammatory response or immune disorder but instead involves changes in the function of numerous organs in the body, at the cellular and molecular levels. The pathogenesis of sepsis is highly intricate, encompassing an array of factors imbalanced inflammatory responses, immune disturbances, mitochondrial impairment, coagulation abnormalities, neuroendocrine-immune network irregularities, and endoplasmic reticulum stress. However, it is essential to comprehend the complexity in pathogenesis of sepsis, as it comprises a dysregulated host reaction to infection. This further leads to a widespread inflammatory response that, if untreated, can progress to severe sepsis and septic shock. Having a comprehensive understanding of sepsis' pathogenesis is critical for formulating effective treatment approaches and enhancing patient outcomes. The interaction of immune system with sepsis and their caused effects are shown in figure 2.

Infection and immune response activation

Sepsis usually initiates following an infection caused by various pathogens like bacteria, viruses, or fungi, occurring in different parts of the body, such as the lungs, urinary tract, abdomen, skin, among others. While, in response to the infection, the body's immune system is activated, engaging immune cells like neutrophils, macrophages, and dendritic cells. These immune cells identify the invading pathogens and release signaling molecules known as pro-inflammatory cytokines and chemokines, which then initiate an immune response. The pathophysiology of sepsis involves a reduction in human leukocyte antigens (HLA-DR; marker of T cell activation), lymphocyte replication, induction of programmed cell death/apoptosis, overexpression of cell-associated co-suppres-

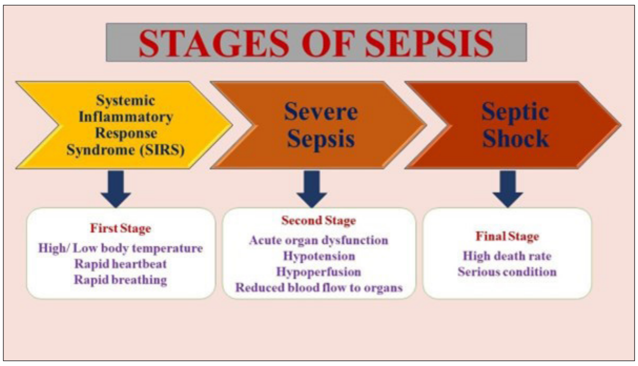

Figure 1: Sepsis continuum: an infographic of evolving stages.

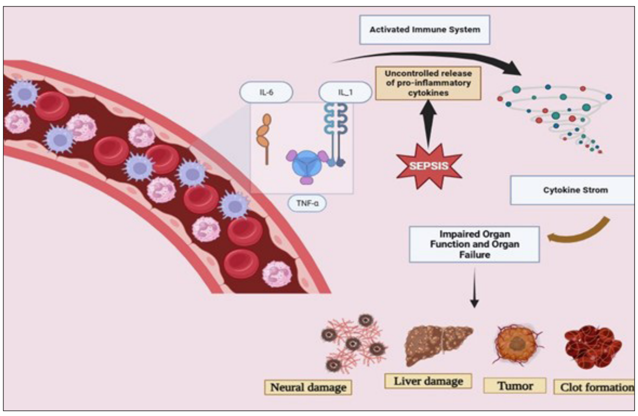

Figure 2: Pathogenesis roadmap: unravelling the development of sepsis.

sor receptors and ligands, and increases in the production of anti-inflammatory molecules [15].

One of the primary responses initiated by the immune system involves the secretion of pro-inflammatory cytokines and chemokines. While these signaling molecules act as messengers, facilitating communication among various immune cells and orchestrating an inflammatory response to control and eliminate the infection. Pro-inflammatory cytokines, namely interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), play essential roles in recruiting additional immune cells to the site of infection, promoting inflammation, and enhancing the immune response. While, during the initial stages of sepsis, the immune system becomes activated in response to an infection. Immune cells recognize the presence of pathogens and trigger the release of pro-inflammatory cytokines and chemokines, which work together to coordinate the body's defense mechanisms. When sepsis causes inflammation, neutrophils engage with endothelial cells and go toward the inflammatory site under the influence of chemokines [16].

Furthermore, mononuclear/macrophage cells become activated while stimulated by cytokines (such as GM-CSF, TNF, and INF) or by pathogenic microorganisms, chemical mediators, immune complexes, etc. The activated cells kill the numerous pathogens as well as present antigens via the process of phagocytosis. Effector T cells have undergone the differentiation aid in the activation of macrophages and release a significant amount of active medium to harm fibrous tissues. Whereas sepsis also hinders the maturation process of dendritic cells of the spleen lymph nodes. Activation of dendritic cells during sepsis also causes a rapid accumulation of innate immune cells such as monocytes, natural killer cells, and granulocytes. Monocytes play an important role in the pathophysiology of sepsis. Abnormalities in monocyte metabolism in sepsis patients lead to immunosuppression, which is characterized by a marked reduction in metabolic processes such glycolysis, fatty acid oxidation, and oxidative phosphorylation [17].

Systemic inflammatory response

Inflammatory imbalance is the most important basis of sepsis pathogenesis and continues throughout the process of sepsis. The innate immune system can be activated by the initial acute reaction of host to invasive pathogens, which often results in the engulfing of the pathogens via macrophages produces a variety of pro-inflammatory cytokines and chemokines into the bloodstream, triggering a systemic inflammatory response. Though, these signaling molecules are intended to activate the immune system and limit the spread of the infection. Furthermore, pattern-recognition receptors, start a cascade of activation in immune cells by detecting damage-associated molecular patterns or pathogen-associated molecular patterns, undoubtedly play a role in the activation of the innate immune system. Lipopolysaccharide, an exogenous pathogen-derived factor, and high-mobility group box-1 protein, an endogenous factor released by injured cells, are both involved in the interaction of different pattern-recognition receptors during the immune response to sepsis. However, sepsis disrupts this regulation, leading to an overwhelming and uncontrolled inflammatory reaction. The immune response becomes imbalanced, resulting in an excessive release of pro-inflammatory molecules. This phenomenon, commonly referred to as a "cytokine storm," can cause extensive tissue damage, impair organ function, and even lead to organ failure [18].

The overabundance of inflammation and unregulated release of inflammatory mediators can disturb the intricate equilibrium of the body's immune and coagulation systems. This disruption may result in endothelial dysfunction, heightened vascular permeability, and the formation of tiny blood clots. Therefore, impaired blood flow and tissue oxygen deficiency contribute to organ dysfunction and potential failure. The identification and effective management of this dysregulated immune response hold paramount importance in the treatment of sepsis. Present therapies aim to modulate the immune response, control inflammation, and restore homeostasis to prevent further deterioration and enhance patient outcomes [19].

Immune dysregulation and cytokine storm

The immune response of the body experiences dysregulation, resulting in an imbalance between pro-inflammatory and anti-inflammatory signals. This disruption leads to an excessive release of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha, which is commonly known as a "cytokine storm". While, the cytokine storm can have severe consequences, as the excessive inflammation causes widespread tissue damage and disrupts the normal functioning of organs. During the cytokinestorm, the immune system's efforts to fight the infection can inadvertently harm healthy tissues. This uncontrolled inflammatory response, coupled with endothelial dysfunction and coagulation abnormalities, contributes to the development of multiple organ dysfunction and failure in sepsis patients [20].

The cytokine storm plays a crucial role in the severity of sepsis, driving the progression from mild sepsis to severe sepsis and septic shock. Effectively recognizing and addressing this dysregulated immune response is vital in sepsis treatment to minimize the detrimental effects of the cytokine storm and enhance patient outcomes. Therefore, ongoing endeavors focus on pinpointing specific therapies that can modulate the immune response and regulate the cytokine storm, aiming to advance sepsis management and decrease mortality rates [21].

Endothelial dysfunction

The immune system becomes overly activated, leading to an excessive release of pro-inflammatory mediators, disrupting the delicate balance between inflammation and immune regulation. This uncontrolled inflammatory response causes dysfunction in the endothelial cells that line the blood vessels. Consequently, the integrity of the endothelial barrier is compromised, leading to an increase in vascular permeability. However, this heightened permeability allows fluid, proteins, and immune cells to leak into the surrounding tissues, causing tissue edema and impeding the delivery of oxygen and nutrients to vital organs. Additionally, the disrupted endothelial function hinders the regulation of blood flow, resulting in irregularities in microcirculation. Therefore, specific areas of the body may experience inadequate blood supply, leading to tissue hypoxia and subsequent organ dysfunction [22].

The interplay of heightened vascular permeability and compromised blood flow regulation also plays a role in the creation of tiny blood clots within the vessels, termed micro thrombosis. These micro clots obstruct blood circulation, exacerbating tissue oxygen deprivation. Furthermore, microthrombi may contribute to the depletion of clotting factors, potentially leading to bleeding complications. The cumulative impact of endothelial dysfunction, encompassing increased vascular permeability, impaired blood flow, and micro clot formation, collectively contributes to the progression of multiple organ failure in cases of severe sepsis [23].

Coagulation abnormalities

The activation of the inflammatory response may induce coagulation irregularities, culminating in disseminated intravascular coagulation (DIC), a critical state marked by abnormal clot formation. While, in DIC, the body's innate coagulation mechanisms become hyperactive, giving rise to the development of minute blood clots dispersed throughout the circulatory system. These microclots can further impede the proper blood flow to vital organs, resulting in organ impairment and dysfunction. As DIC advances, the excessive clotting process can deplete crucial clotting factors, heightening the likelihood of bleeding complications.

The simultaneous occurrence of both clotting and bleeding in DIC presents a precarious equilibrium that can swiftly escalate into a life-threatening situation. The formation of micro clots consumes vital clotting factors, potentially leading to uncontrolled bleeding in other parts of the body. As a result of microclots, organs face compromised blood supply, significantly raising the risk of organ failure. This intricate interplay between coagulation and bleeding adds complexity to managing sepsis, necessitating immediate and targeted interventions to restore coagulation balance and preserve organ function. Early detection and aggressive treatment of DIC are crucial for enhancing sepsis outcomes and reducing mortality rates [24].

Organ dysfunction and failure

As the inflammatory reaction and coagulation irregularities advance, several organs can be impacted, leading to dysfunction. Commonly affected organs encompass the lungs, kidneys, liver, and heart. Whereas, without prompt intervention, this chain of events may culminate in multiple organ failure and septic shock, a life-threatening state characterized by severe hypotension and inadequate tissue perfusion.

The pathogenesis of sepsis involves a dysregulated and exaggerated immune response to an infection, leading to systemic inflammation, endothelial dysfunction, coagulation abnormalities, and organ dysfunction. However, the management of sepsis requires early recognition, appropriate antimicrobial therapy, and supportive care aimed at controlling the inflammatory response and restoring organ function. Ongoing research is essential to further elucidate the intricate mechanisms underlying sepsis pathogenesis and to develop targeted therapies to improve patient outcomes [25].

Therapeutic use of mulberry in sepsis

The bioactive components found in mulberry, including polyphenols, flavonoids, anthocyanins, and quercetin, have been associated with their antioxidant and anti-inflammatory properties. While these compounds have demonstrated the capability to scavenge free radicals and reduce oxidative stress. Furthermore, this could be advantageous in mitigating the adverse consequences of systemic inflammation caused by sepsis. By restraining excessive inflammation and oxidative harm, the bioactive constituents in mulberry might potentially regulate the immune response, halting the progression of sepsis. Additionally, the immunomodulatory properties of mulberry could have a crucial role in preventing sepsis. Mulberry extracts can enhance the function of immune cells, such as macrophages and lymphocytes, and stimulate the production of anti-inflammatory cytokines [26].

The potential influence of mulberry on the gut microbiota is an intriguing aspect related to sepsis prevention. A well-balanced gut microbiota is crucial for a strong immune system and defense against infections. Recent studies suggest that mulberry consumption may have a positive impact on the composition of gut microbiota, fostering the growth of beneficial bacteria while restraining the proliferation of harmful microorganisms [27]. However, by promoting a healthy gut microbiota, mulberry could indirectly boost the body's ability to defend against infections and potentially lower the risk of sepsis occurrence.

While the direct correlation between mulberry and sepsis prevention is still undergoing scientific investigation, available research indicates the promising potential of this fruit in promoting immune health and combating inflammation. It is crucial to note that mulberry, like any natural product, should not replace standard medical care for sepsis. Instead, it could serve as a complementary approach to overall sepsis management. Further studies, including human clinical trials, are necessary to validate these findings and determine the optimal dosage and specific compounds responsible for the potential protective effects of mulberry against sepsis. Mulberry contains various bioactive compounds with antioxidant, anti-inflammatory, and immune-modulating properties, suggesting a possible link to sepsis prevention. Its ability to mitigate excessive inflammation, support a healthy gut microbiota, and enhance immune responses may contribute to reducing the severity and occurrence of sepsis [28].

Metabolic changes in sepsis

Sepsis triggers a cascade of complex metabolic changes that significantly impact overall physiology. These alterations play an important role in the pathogenesis and progression of sepsis, contributing to organ dysfunction and mortality. However, one of the metabolic changesin sepsis is the disruption of energy metabolism. As the body fights off the infection, it undergoes a shift from aerobic to anaerobic metabolism. Cellular oxygen utilization becomes impaired due to microcirculatory dysfunction, leading to a preference for anaerobic glycolysis. This shift results in increased lactate production, leading to lactic acidosis, a key indicator of sepsis severity. Furthermore, the inadequate production of adenosine triphosphate, the primary energy currency of cells, further contributes to cellular dysfunction and organ damage. Sepsis induces insulin resistance, impairing glucose uptake and utilization by cells, despite elevated blood glucose levels. This condition, known as sepsis-induced hyperglycemia, can lead to cellular energy deficits and exacerbate organ dysfunction. Hyperglycemia is associated with worse outcomes in septic patients, and controlling blood glucose levels is an important aspect of sepsis management [15].

During sepsis, the body enters a catabolic state, resulting in increased protein breakdown and reduced protein synthesis. Pro-inflammatory cytokines released during the immune response contribute to muscle wasting and proteolysis. The loss of proteins, especially in vital organs, can impair their function and exacerbate sepsis-induced organ dysfunction. Lipid metabolism, leading to increased lipolysis (breakdown of stored fats) and elevated levels of free fatty acids. These fatty acids can contribute to insulin resistance and impair mitochondrial function, further compromising cellular energy production. Additionally, altered lipid metabolism may affect the immune response and contribute to immune cell dysfunction [29].

Mitochondrial dysfunction is a central feature of sepsis-induced metabolic changes. Sepsis can lead to mitochondrial damage and impaired oxidative phosphorylation, reducing adenosine triphosphate synthesis and increasing the production of ROS. This mitochondrial dysfunction exacerbates cellular energy deficits and contributes to tissue injury and organ dysfunction. Sepsis induces oxidative stress through the excessive production of ROS and impaired antioxidant defenses. The imbalance between ROS generation and antioxidant capacity leads to cellular damage and amplifies the inflammatory response, further contributing to organ dysfunction. The metabolic changes in sepsis, particularly the accumulation of lactic acid, can lead to disturbances in acid-base balance. The resulting metabolic acidosis can impair cellular processes and negatively impact cardiovascular function, perpetuating the vicious cycle of sepsis [30].

Effect of bioactive compounds on sepsis

The bioactive compounds found in mulberry include various polyphenols, flavonoids, anthocyanins, quercetin, and other phytochemicals, each possessing unique properties with potential immunomodulatory and antioxidant effects. However, these compounds have been shown to exert anti-inflammatory actions, inhibit the release of pro-inflammatory cytokines, and modulate immune cell responses, thus dampening the exaggerated immune response associated with sepsis. Moreover, the antioxidant properties of mulberry's bioactive compounds could help mitigate oxidative stress, reducing cellular damage and organ dysfunction observed in sepsis. Furthermore, studies have suggested that these compounds might aid in restoring endothelial function, ameliorating vascular dysfunction, and improving microcirculation, thus potentially contributing to improved tissue perfusion and organ recovery during sepsis [31]. Figure 3 depicts the efficiency of mulberry fruit pulp in treating sepsis.

Based on various studies, the anthocyanins demonstrate the ability to counteract oxidative stress, as well as act as antimicrobial substances, and prevent the onset and progression of a wide range of noncommunicable diseases, including neurodegenerative, cardiovascular, metabolic, and cancer diseases. While, these are also well known for protecting visual function, along with vitamin A and carotenes. It has been theorized that anthocyanins act by scavenging free radicals, activating enzymes such as cyclooxygenase and mitogen-activated protein kinase, and signaling inflammation through cytokines. Whereas the most abundant anthocyanin found in mulberry is cyanidin-3-O-glucoside, followed by cyanidin-3-O-rutinoside. In comparison to the other two varieties of mulberry fruit, *M. alba* L. contained the highest concentration of cyanidin-3-O-glucoside (8.65 mg/g dry weight) [32].

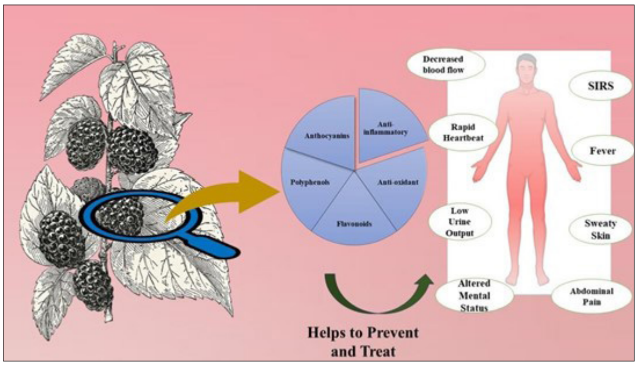

Figure 3: Mulberry fruit pulp: mitigating risk of sepsis.

In general, the intestinal absorption of flavonoids is mediated by 2 processes. Vegetables contain flavonoids as glycoside conjugates, which can be deglycosylated by gut microflora enzymes or endogenous glycosidase (lactase phlorizin hydrolase), and further absorbed by passive diffusion of the aglycone form. While, as second mechanism includes the direct interaction of hexose transport pathway with the absorption of the glycosidic form. Anthocyanins easily get absorbed in the stomach and small intestine [33]. Although, the exact process of anthocyanin absorption in the stomach is unknown but the involvement of the gastric epithelium-expressed anion translocator Bili translocase is hypothesized. While plasma mainly contains anthocyanins in their undamaged form, with lesser amounts in methylated and conjugated forms with glucuronic acid, during enterocyte absorption, other compounds are produced in the liver and kidney. Like quercetin, anthocyanins may or may not be absorbed by the Na^+ dependent glucose transporter (SGLT1).

While research is still ongoing, the bioactive compounds present in mulberry hold promising potential as adjunctive therapeutic agents in the management of sepsis, and their exploration opens new avenues for the development of novel interventions to improve patient outcomes in this life-threatening condition. Table 1 depicts the effect of bioactive compounds present in mulberry to eliminate the health complications occurring in sepsis.

Conclusion

The purpose of this review is to confirm the ability of *M. nigra* leaf and fruit pulp to preventor minimize redox and in-

Table 1: Sepsis response altered by bioactive compounds.

Bioactive compound	Role	Ref.
Flavonoid and cyclosporine	Helps in prevention of atherosclerosis; lowers the concentration of nitric oxide that is being produced by activated macrophages.	[33]
Butyl pyroglutamate, quercetin 3-O-D-glucoside, kaempferol 3-O-D-rutinoside, 2-phenylethyl D-rutinoside and rutin	Showed protective effect for cisplatin-induced nephrotoxicity by fading the phosphorylation of Jun N-terminal kinase, extracellular signal-regulated kinase, mitogen activated protein kinase, p38 and caspase-3. This in turn helped to prevent kidney cell damage.	[34]
Polyphenolics and alkaloids	Improve brain functioning, cognitive abilities and reduces the risk for development of neuro-degenerative diseases.	[35]
Resveratrol	Anti-inflammatory, anti-carcinogenic and promotes heart health. It suppresses the proliferation process of tumor (especially in pancreas, stomach, colon, prostate, breast, and ovary).	[36]
Quercetin, gallocatectingallate and naringenin	Lowers the risk of atherosclerosis by inhibiting lipid peroxidation.	[37]
Flavonoids and secondarymetabolites	Antioxidant and anti- inflammatory properties were shown when the septic animal models (male C57BL/6 mice) were being treated for 21 days with mulberry extracts or pulp. Moreover, there was reduction in TNF and leukocytes serum levels.	[38]
Anthocyanins	It is well known that the liver is one of the immune modulating organs in the body and plays an important role in metabolic processes. Sepsis negatively impacts liver functioning and can lead to severe liver complications. Hence, studies reveal that ingestion of anthocyanins has protective effect on liver and prevent the condition of non- alcoholic fatty liver. When rats were being ingested with mulberry fruit marc (anthocyanin rich); anthocyanin acted on carbon tetrachloride induced liver fibrosis and in turn lowered the levels of hydroxyproline, aspartate amino transferase, collagen type-III hyaluronidase acid and alanine amino transferase.	[39]

flammatory imbalances brought on by sepsis. The findings show the intricacy of sepsis and demonstrated that this condition can impair the function of several organs and illustrate favorable effects on the modulation of significant parameters that are typically affected in sepsis when using *M. nigra* leaf and pulp extracts as a therapy, also the review reveals that different compounds of mulberry prevent some part of sepsis. It revealed that different bioactive compounds present in mulberry, particularly cyanidin, an anthocyanin, played a crucial role in the observed effects. However, these compounds demonstrate the ability to regulate and counteract the harmful consequences induced by sepsis, at least in part. Notably, the research underscored the immunomodulatory and antioxidant properties of *M. nigra* extracts, which helped in reducing the exaggerated immune response and oxidative stress seen in sepsis. However, further research and clinical trials are needed to validate these findings and explore the specific mechanisms of action involved. The utilization of mulberry compounds in sepsis management could hold significant promise in improving patient outcomes and shedding light on novel therapeutic strategies to combat this complex and life-threatening condition.

Acknowledgements

None.

Conflict of Interest

None.

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