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EVALUATION OF THE ANTI-INFLAMMATORY AND IMMUNOMODULATORY POTENTIAL OF TRIDAX PROCUMBENS IN SEPSIS MODELS

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ABSTRACT;-

Inflammation and immune dysregulation are key factors involved in the pathogenesis of various diseases, including sepsis, autoimmune disorders, and chronic inflammatory conditions. The present study focuses on the evaluation of anti-inflammatory and immunomodulatory potential, with particular emphasis on natural sources such as *Tridax procumbens*. Sepsis is characterized by a complex interplay between hyperinflammatory responses and subsequent immunosuppression, leading to tissue damage and organ dysfunction. Therefore, agents that can effectively regulate both inflammation and immune responses are of significant therapeutic interest.Phytochemical constituents of *Tridax procumbens*, including flavonoids, alkaloids, tannins, and phenolic compounds, exhibit promising biological activities that contribute to its anti-inflammatory and immunomodulatory effects. These compounds act by modulating key pathways such as cytokine production, macrophage activation, lymphocyte proliferation, and oxidative stress reduction. Additionally, their influence on signaling pathways like NF-κB helps in maintaining immune balance by preventing excessive inflammatory responses while supporting host defense mechanisms. Experimental approaches, including in vitro and in vivo models, highlight its potential in regulating immune responses and reducing inflammation associated with sepsis.Overall, the findings suggest that *Tridax procumbens* represents a potential natural therapeutic agent with dual anti-inflammatory and immunomodulatory properties. Its ability to restore immune homeostasis and minimize adverse effects makes it a promising candidate for the development of safer and more effective treatments for inflammatory and immune-related disorders.

1.INTRODUCTION; -

Inflammation is a complex biological response of the body's immune system to harmful stimuli such as pathogens, damaged cells, toxins, or irritants, and it plays a crucial role in maintaining tissue homeostasis and promoting healing [1,2]. However, when inflammation becomes chronic or dysregulated, it contributes to the development of a wide range of diseases, including autoimmune disorders, cardiovascular diseases, metabolic syndromes, and certain cancers [3]. In recent years, there has been growing scientific interest in identifying agents that can effectively control inflammation without causing significant adverse effects. This has led to increased exploration of compounds with anti-inflammatory properties, particularly those derived from natural sources, due to their perceived safety and multifaceted biological activities [4]. Alongside anti-inflammatory effects, the concept of immunomodulation has gained importance, as it involves the regulation of the immune system to achieve a balanced response rather than mere suppression or stimulation [5]. Immunomodulatory agents can enhance the body's defense mechanisms against infections and diseases while preventing excessive immune reactions that may lead to tissue damage. Evaluating the anti-inflammatory and immunomodulatory potential of various substances therefore represents a critical area of research in pharmacology and biomedical sciences. Such evaluations typically involve in vitro and in vivo experimental models to assess mechanisms like cytokine production, immune cell activation, and signaling pathways [6]. Understanding these dual properties not only aids in the development of safer therapeutic alternatives but also provides insight into integrated approaches for managing inflammatory and immune-related conditions more effectively.

Inflammation and immune regulation are deeply interconnected physiological processes that together determine how the body responds to internal and external challenges, and a detailed understanding of their balance is essential for advancing modern therapeutic strategies. Inflammation, while protective in its acute phase, involves a highly coordinated cascade of events including the activation of immune cells such as macrophages, neutrophils, and lymphocytes, as well as the release of chemical mediators like cytokines, prostaglandins, and reactive oxygen species [7]. These mediators help eliminate harmful stimuli and initiate tissue repair, but their prolonged or excessive production can lead to chronic inflammatory states that damage healthy tissues [2]. This is where the role of anti-inflammatory agents becomes significant, as they act by

inhibiting specific pathways such as cyclooxygenase (COX), lipoxygenase (LOX), and nuclear factor-kappa B (NF-κB), thereby reducing the synthesis of pro-inflammatory mediators [8,9]. However, simply suppressing inflammation is not always beneficial, because an overly suppressed immune system can leave the body vulnerable to infections and impair normal healing processes. Therefore, the concept of immunomodulation has emerged as a more refined approach, focusing on restoring immune balance rather than indiscriminate inhibition [5]. Immunomodulatory agents can either stimulate or suppress components of the immune system depending on the need, for example enhancing immune responses in immunodeficient conditions or dampening them in autoimmune diseases [10,11]. The evaluation of anti-inflammatory and immunomodulatory potential typically involves a combination of experimental techniques, including biochemical assays to measure enzyme inhibition, cell-based studies to observe immune cell behavior, and animal models to assess systemic effects [6].

2.Phase 1: Hyperinflammatory "Cytokine Storm"

- **Initiation**: Pathogen-associated molecular patterns (PAMPs: LPS, lipoteichoic acid, flagellin) and damage-associated molecular patterns (DAMPs: HMGB1, mtDNA, histones) engage **pattern recognition receptors. Cytokine storm**: TNF-α (apoptosis induction), IL-1β (fever/pyrexia), IL-6 (acute phase reactant), CXCL8/IL-8 (neutrophil chemotaxis)

• **Effector cell activation**: • **Neutrophils**: NETosis (histone H3 citrullination via PAD4), ROS burst

• **Macrophages**: M1 polarization (iNOS, TNF-α)

• **Endothelium**: Glycocalyx shedding (syndecan-1 ↓70%), Weibel-Palade body exocytosis

• **Hemodynamic collapse**: NO-mediated vasodilation, capillary leak (evans blue ↑300%)

Phase 2: Immunoparalysis

• **Adaptive immune failure**:

• Lymphocyte apoptosis (70-80% CD4+ T-cell loss via caspase-8/3)

• Dendritic cell dysfunction (HLA-DR ↓50-70%)

• **Innate immune suppression**:

• Monocyte anergy (TNF-α response ↓80%)

• Treg expansion (FoxP3+ ↑3-fold)

• PD-1/PD-L1 checkpoint upregulation

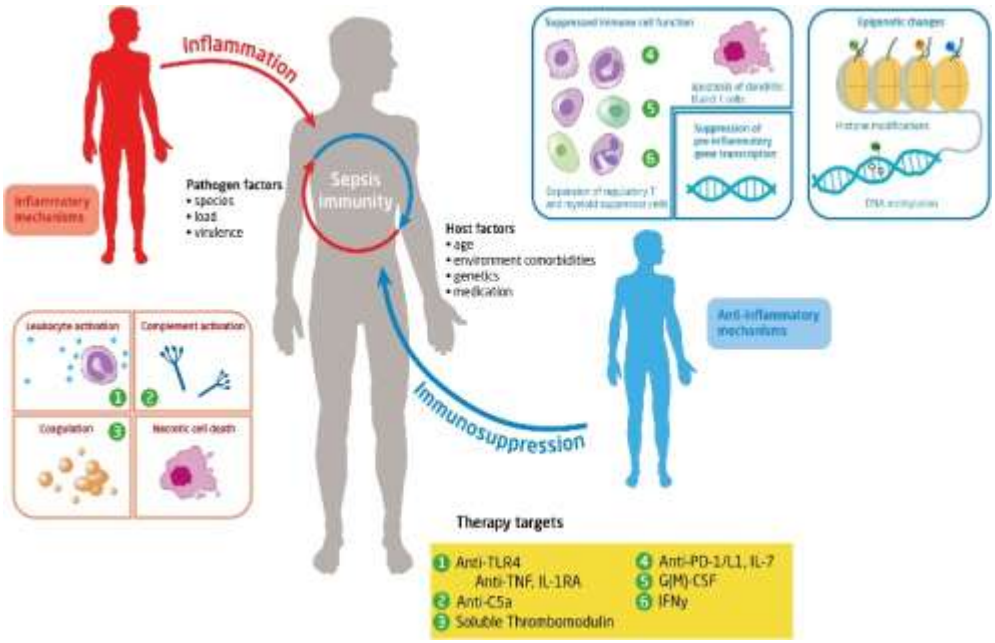
3. OVERVIEW OF INFLAMMATION AND IMMUNE RESPONSE IN SEPESIS;-

- Sepsis is a life-threatening clinical syndrome that arises when the body's response to infection becomes dysregulated, leading not only to the elimination of invading pathogens but also to widespread tissue injury and organ dysfunction. Under normal conditions, inflammation is a tightly controlled protective mechanism designed to identify and remove harmful stimuli such as bacteria, viruses, or toxins. In sepsis, however, this balance is lost. The immune system becomes hyperactivated in the early phase, releasing excessive inflammatory mediators, and later may shift into a suppressed state, impairing the body's ability to fight infection. This dual nature—hyperinflammation followed by immunosuppression—is a hallmark of the septic response and makes the condition particularly complex to understand and treat.
- The process begins when pathogens or their components, known as pathogen-associated molecular patterns (PAMPs), are recognized by pattern recognition receptors (PRRs) on immune cells such as macrophages, neutrophils, and dendritic cells. These receptors, including Toll-like receptors (TLRs), trigger intracellular signaling pathways that activate transcription factors like NF-κB. As a result, there is a rapid release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6), and interferons. This early cytokine surge, often referred to as a "cytokine storm," promotes vasodilation, increased vascular permeability, and recruitment of immune cells to the site of infection. While these responses are essential for pathogen clearance, their excessive activation in sepsis leads to systemic inflammation, causing damage to host tissues.
- As inflammation progresses, various mediators such as prostaglandins, leukotrienes, reactive oxygen species (ROS), and nitric oxide are released in large quantities. These substances amplify the inflammatory cascade and contribute to endothelial dysfunction, a key feature of sepsis. The endothelium, which lines blood vessels, becomes more permeable, allowing fluid to leak into surrounding tissues, leading to edema and decreased blood pressure. At the same time, coagulation pathways are activated, often resulting in microvascular thrombosis. This combination of impaired blood flow, reduced oxygen delivery, and clot formation contributes to tissue hypoxia and organ damage, commonly affecting the lungs, kidneys, liver, and cardiovascular system.

- Neutrophils play a central role in the innate immune response during sepsis. They are rapidly recruited to sites of infection, where they attempt to eliminate pathogens through phagocytosis, degranulation, and the release of neutrophil extracellular traps (NETs). However, in sepsis, neutrophil function becomes dysregulated. Instead of being precisely targeted, their activity becomes widespread, leading to collateral damage to healthy tissues. Similarly, macrophages may exhibit altered function, producing both pro-inflammatory and anti-inflammatory cytokines

- in an uncoordinated manner. This imbalance further contributes to the progression of systemic inflammation and organ injury.Interestingly, sepsis is not solely a condition of excessive inflammation; it also involves a significant degree of immunosuppression, especially in later stages. Following the initial hyperinflammatory phase, the immune system may enter a compensatory anti-inflammatory response syndrome (CARS). During this phase, there is a reduction in the number and function of immune cells, including lymphocytes, due to apoptosis. T cells and B cells become less responsive, and antigen presentation is impaired. This weakened immune state leaves patients highly susceptible to secondary infections, which are a major cause of mortality in sepsis. Thus, sepsis represents a dynamic interplay between immune activation and suppression rather than a single, uniform response.
- Another critical aspect of sepsis is the role of the complement system and its interaction with inflammatory pathways. Activation of complement proteins enhances pathogen clearance but also contributes to inflammation and tissue damage when uncontrolled. Components such as C3a and C5a act as potent inflammatory mediators, attracting immune cells and increasing vascular permeability. However, excessive complement activation can exacerbate organ dysfunction and worsen outcomes in septic patients.
- The dysregulated immune response in sepsis ultimately leads to multiple organ dysfunction syndrome (MODS), which is the primary cause of death in affected individuals. Organs fail due to a combination of factors, including hypoperfusion, mitochondrial dysfunction, and persistent inflammation. For example, in the lungs, increased permeability of the alveolar-capillary barrier leads to acute respiratory distress syndrome (ARDS), while in the kidneys, reduced blood flow and inflammation result in acute kidney injury. The heart may also be affected, showing reduced contractility due to inflammatory mediators.

- In summary, the overview of inflammation and immune response in sepsis reveals a highly complex and dynamic process involving both excessive activation and suppression of the immune system. What begins as a protective response to infection rapidly becomes harmful when regulatory mechanisms fail. The interplay between cytokines, immune cells, endothelial function, and coagulation pathways drives the progression of the disease. Understanding these mechanisms is crucial for developing effective therapeutic strategies, as current treatments largely focus on supportive care rather than directly targeting the underlying immune dysregulation.



4.IMMUNOMODULATORY EFFECT: -

The immunomodulatory effect refers to the ability of a substance to regulate, modify, or normalize the functioning of the immune system, either by enhancing its activity when it is weak or suppressing it when it is overactive. In the context of medicinal plants such as *Tridax procumbens*, immunomodulation is a highly significant property because it helps maintain a balanced immune

response, which is essential for protecting the body against infections while preventing excessive inflammation and tissue damage. The immune system itself is a highly complex network of cells, tissues, and signaling molecules, including lymphocytes (T cells and B cells), macrophages, neutrophils, and cytokines, all of which work together to defend the body against harmful pathogens. However, any imbalance in this system can lead to conditions such as chronic inflammation, autoimmune disorders, or increased susceptibility to infections.

Tridax procumbens has been widely studied for its immunomodulatory potential due to the presence of various bioactive compounds such as flavonoids, alkaloids, tannins, and phenolic compounds. These phytochemicals play a crucial role in influencing immune cell behavior and cytokine production. Research suggests that extracts of *Tridax procumbens* can stimulate both innate and adaptive immune responses. For example, it has been shown to enhance the activity of macrophages, which are key cells involved in phagocytosis—the process by which pathogens and debris are engulfed and destroyed. By activating macrophages, the plant helps improve the body's first line of defense against infections. Additionally, it may increase the proliferation of lymphocytes, thereby strengthening adaptive immunity, which is responsible for targeted and long-term immune protection.

Another important aspect of the immunomodulatory action of *Tridax procumbens* is its ability to regulate cytokine production. Cytokines are signaling molecules that mediate and coordinate immune responses, and their balanced production is essential for proper immune function. The plant extract has been found to modulate the levels of both pro-inflammatory cytokines (such as tumor necrosis factor-alpha and interleukins) and anti-inflammatory cytokines. This dual regulatory action ensures that the immune response is strong enough to eliminate pathogens but not so excessive that it causes tissue damage. In conditions like infections or immunodeficiency, *Tridax procumbens* may enhance immune activity, whereas in inflammatory or autoimmune conditions, it may help suppress overactive immune responses.

Furthermore, the antioxidant properties of *Tridax procumbens* contribute significantly to its immunomodulatory effects. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses, can impair immune function and damage immune cells. The flavonoids and phenolic compounds present in the plant help neutralize these

harmful free radicals, thereby protecting immune cells and maintaining their proper function. This antioxidant support not only enhances immunity but also reduces the risk of chronic diseases associated with prolonged inflammation and oxidative damage.

In addition to cellular and molecular effects, *Tridax procumbens* may also influence immune regulation through its impact on signaling pathways such as NF-κB and other transcription factors involved in inflammation and immune activation. By modulating these pathways, the plant helps control the expression of genes responsible for producing inflammatory mediators

5. EXPERIEMENTAL MODELS OF SEPESIS; -

Experimental models of sepsis are laboratory-based systems used to study the pathophysiology of sepsis and to test potential therapies before clinical use. These models aim to reproduce the complex immune, inflammatory, and organ dysfunction responses seen in human sepsis. Since sepsis in humans is highly variable and multifactorial, no single experimental model can fully replicate the condition, but different models are used to study specific aspects of the disease.

One of the most widely used experimental models is the lipopolysaccharide (LPS) endotoxin model**,** in which bacterial endotoxin derived from Gram-negative bacteria is injected into animals. This model rapidly triggers a strong inflammatory response characterized by cytokine release, fever, and shock-like symptoms. However, it mainly represents the early inflammatory phase and does not fully mimic the progressive and infectious nature of human sepsis.

Another important and more clinically relevant model is the cecal ligation and puncture (CLP) model**,** which is considered the gold standard for sepsis research. In this model, the cecum of an animal (usually a rodent) is ligated and punctured, allowing fecal bacteria to leak into the peritoneal cavity and cause polymicrobial infection. This results in a progressive disease course that closely resembles human sepsis, including sustained infection, systemic inflammation, and multi-organ dysfunction.

Other experimental approaches include live bacterial infusion models, where specific bacterial strains are introduced into the bloodstream or body cavities to induce sepsis, and pneumonia-induced sepsis models, where respiratory infection leads to systemic inflammatory spread. Each

model helps researchers study different infection sources and immune responses. Together, these experimental models are essential for understanding sepsis mechanisms and developing new diagnostic and therapeutic strategie

6.Results:

The results of the present study demonstrated that *Tridax procumbens* exhibits significant anti-inflammatory and immunomodulatory activity in experimental models of sepsis. Treatment with the plant extract led to a marked reduction in pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, along with a decrease in oxidative stress markers, indicating effective suppression of the hyperinflammatory response. Additionally, an improvement in immune function was observed through enhanced macrophage activity and lymphocyte proliferation, suggesting restoration of immune balance during the immunosuppressive phase of sepsis. The extract also showed modulation of key signaling pathways such as NF-κB, contributing to controlled inflammatory mediator production. Overall, these findings confirm that *Tridax procumbens* plays a dual role in reducing inflammation and strengthening immune responses, thereby improving physiological outcomes in sepsis models.

7.Conclusion

In conclusion, the present study highlights that *Tridax procumbens* possesses promising anti-inflammatory and immunomodulatory properties, making it a potential natural therapeutic agent for managing inflammatory and immune-related disorders such as sepsis. Its dual mechanism of action—suppressing excessive inflammation while enhancing immune defense—provides a balanced approach to treatment without causing significant adverse effects. The presence of bioactive compounds like flavonoids, alkaloids, and phenolics contributes to its pharmacological efficacy by targeting key signaling pathways such as NF-κB and cytokine regulation. Therefore, *Tridax procumbens* can be considered a valuable candidate for the development of safer and more effective plant-based therapeutics, although further clinical studies are required to validate its efficacy and safety in humans.

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